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Editors

Jay Y. Gillenwater MD

Hovey S. Dabney Professor
Department of Urology, University of Virginia Medical School; Professor of Urology, University of Virginia Hospital, Charlottesville, Virginia

John T. Grayhack MD

Professor
Department of Urology, Northwestern University Medical School; Attending, Department of Urology, Northwestern Memorial Hospital, Chicago, Illinois

Stuart S. Howards MD

Professor
Departments of Urology and Physiology, University of Virginia, Charlottesville, Virginia

Michael E. Mitchell MD

Professor
Department of Urology, University of Washington; Chief, Division of Pediatric Urology, Children's Hospital and Regional Medical Center, Seattle, Washington

Secondary Editors

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CONTRIBUTING AUTHORS

Mark C. Adams MD

Associate Professor
Department of Urologic Surgery, Department of Pediatrics, Vanderbilt University Medical Center; Division of Pediatric Urology, Vanderbilt Children's Hospital, Nashville, Tennessee

Vaseem Ali MD, MRCOG

Associate Professor
Department of Obstetrics and Gynecology, University of Texas Medical School at Houston, Herman Hospital, Houston, Texas

Beth Andersen MD
Children's Hospital and Regional Medical Center, University of Washington, Seattle, Washington

Jeffrey C. Applewhite MD
Department of Urology, Wake Forest University School of Medicine, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina

Anthony Atala MD

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

David M. Barrett MD

Clinical Professor
Department of Urology, Tufts University School of Medicine, Boston, Massachusetts; Chief Executive Officer, Lahey Clinic, Burlington, Massachusetts

Georg Bartsch MD

Chief and Professor of Urology
Department of Urology, University of Innsbruck, Innsbruck, Austria

Laurence S. Baskin MD

Chief, Pediatric Urology
Department of Urology, University of California–San Francisco, San Francisco, California

Mark F. Bellinger MD

Clinical Professor
Department of Surgery/Urology, University of Pittsburgh; Attending Physician, Department of Pediatric Urology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

George S. Benson MD

Medical Officer
Food and Drug Administration, Rockville, Maryland

David A. Bloom MD

Professor of Surgery; Chief of Pediatric Urology
Department of Urology, University of Michigan, Ann Arbor, Michigan

Bernard Bochner MD

Attending Physician
Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York

Michel A. Boileau MD

Bend Urology Associates
Bend, Oregon

John W. Brock III MD

Professor
Departments of Urologic Surgery and Pediatrics; Director, Pediatric Urology, Vanderbilt University Medical Center, Nashville, Tennessee

Wade Bushman MD, PhD

Assistant Professor
Department of Urology, Northwestern University Medical School; Consultant, Rehabilitation Institute of Chicago, Chicago, Illinois

Douglas A. Canning MD

Associate Professor
Department of Urology, Hospital of the University of Pennsylvania; Chief, Division of Urology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Michael C. Carr MD, PhD

Assistant Professor
Department of Urology, University of Pennsylvania; Attending Surgeon, Department of Urology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Patrick C. Cartwright MD

Associate Professor
Departments of Surgery and Pediatrics, University of Utah; Attending Surgeon, Division of Pediatric Urology, Primary Children's Medical Center, Salt Lake City, Utah

Marc Cendron MD, FAAP

Associate Professor
Departments of Surgery (Urology) and Pediatrics, Dartmouth Medical School, Hanover, New Hampshire; Director, Pediatric Urology Services, Section of Urology, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire

Samuel Chacko DVM, PhD

Professor of Pathobiology
Director of Basic Urologic Research, Department of Pathobiology, University of Pennsylvania, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Queena Chou MD, FRCSC

Assistant Professor
Department of Obstetrics and Gynecology, University of Western Ontario; Staff Physician, Department of Obstetrics and Gynecology, St. Joseph's Health Care London, London, Ontario, Canada

Peter L. Choyke MD

Professor of Radiology
Department of Radiology, Uniformed Services University of the Health Sciences; Chief of MRI, Department of Radiology, National Institutes of Health, Bethesda, Maryland

Ralph V. Clayman MD

Professor of Urology and Radiology; Co-director
Division of Minimally Invasive Surgery, Department of Surgery and Radiology, Washington University, Barnes-Jewish Hospital, St. Louis, Missouri

J. Quentin Clemens MD

Assistant Professor
Department of Urology, Northwestern University Medical School, Northwestern Memorial Hospital, Chicago, Illinois

Clare E. Close MD

Assistant Professor
Department of Surgery and Pediatrics, University of Nevada School of Medicine, Las Vegas, Nevada

Christopher S. Cooper MD

Assistant Professor
Department of Urology, University of Iowa College of Medicine; Assistant Professor, Department of Urology, Children's Hospital of Iowa, Iowa City, Iowa

Douglas E. Coplen MD

Assistant Professor
Department of Surgery, Division of Urology, Washington University-St. Louis; Director of Pediatric Urology, Division of Pediatric Urology, St. Louis Children's Hospital, St. Louis, Missouri

John M. Corman MD

Assistant Clinical Professor
Department of Urology, University of Washington; Staff Urologist, Section of Urology, Virginia Mason Medical Center, Seattle, Washington

Joseph N. Corriere Jr. MD

Professor of Surgery
Department of Surgery, Division of Urology, The University of Texas, Houston, Texas

Barbara Y. Croft PhD

Program Director
Biomedical Imaging Program, National Cancer Institute, Bethesda, Maryland

Jean B. deKernion MD

Chairman
Department of Urology, UCLA School of Medicine; Attending Urologist, UCLA Medical Center, Los Angeles, California

Michael E. DiSanto PhD

Research Assistant Professor
Division of Urology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Jack S. Elder MD

Professor of Urology and Pediatrics
Case Western Reserve University; Director of Pediatric Urology, Rainbow Babies & Children's Hospital, Cleveland, Ohio

R. Sherburne Figenshau MD

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

Stuart M. Flechner MD
Section, Renal Transplantation, Urological Institute and Cleveland Clinic Foundation; Transplant Center, Cleveland Clinic Hospital, Cleveland, Ohio

Indiber S. Gill MD, MCh

Head
Section of Laparoscopic and Minimally Invasive Surgery, Cleveland Clinic Urological Institute, Cleveland Clinic Foundation, Cleveland, Ohio

Jay Y. Gillenwater MD

Hovey S. Dabney Professor
Department of Urology, University of Virginia Medical School; Professor of Urology, University of Virginia Hospital, Charlottesville, Virginia

Meidee Goh MD, MPH

Lecturer, Section of Urology
Department of General Surgery, University of Michigan, Ann Arbor, Michigan

Richard W. Grady MD

Assistant Professor
Department of Urology, The University of Washington Medical Center; Attending, Section of Pediatric Urology, Children's Hospital and Regional Medical Center, Seattle, Washington

John T. Grayhack MD

Professor
Department of Urology, Northwestern University Medical School; Attending, Department of Urology, Northwestern Memorial Hospital, Chicago, Illinois

Kenneth E. Greer MD

Chair and Professor
Department of Dermatology, University of Virginia, Charlottesville, Virginia

Marko Gudziak MD
Department of Urology, Royal Melbourne Hospital, Melbourne, Victoria, Australia

Faruk Hadziselimovic MD

Professor
Department of Pediatrics, University Basel, Basel, Switzerland; Chief, Department of Pediatrics, Kindertagesklinik, Liestal, Switzerland

M. Craig Hall MD

Associate Professor, Director, Urologic Oncology
Department of Urology, Wake Forest University School of Medicine; Staff, Department of Urology, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina

Terry W. Hensle MD

Professor of Urology
Department of Urology, Columbia University College of Physicians and Surgeons; Director, Pediatric Urology, Children's Hospital of New York, New York, New York

James R. Herman MD, PhD

Assistant Professor
Department of Surgery/Urology, University of Kentucky Chandler Medical Center, Lexington, Kentucky

Stuart S. Howards MD

Professor
Departments of Urology and Physiology, University of Virginia, Charlottesville, Virginia

Robert Huben MD

Associate Professor
Department of Urology, State University of New York at Buffalo; Chief, Urologic Oncology, Roswell Park Cancer Institute, Buffalo, New York

Dale Huff MD

Senior Pathologist
Department of Pathology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Douglas A. Husmann MD

Professor
Department of Urology, Mayo Clinic, Rochester, Minnesota

Alan D. Jenkins MD

Associate Professor of Urology
Department of Urology, University of Virginia, Charlottesville, Virginia

Judith M. Joyce MD

Associate Chief, Nuclear Medicine
Western Pennsylvania Hospital, Pittsburgh, Pennsylvania

Edward D. Kim MD

Associate Professor
Departments of Urology and Urologic Surgery, The University of Tennessee Graduate School of Medicine, Knoxville, Tennessee

Stephen A. Koff MD

Professor of Surgery
Department of Surgery, The Ohio State University College of Medicine and Public Health; Chief, Section of Pediatric Urology, Children's Hospital, Columbus, Ohio

Stanley J. Kogan MD

Clinical Professor of Urology
Department of Urology, Weil Medical College, New York Medical College, Cornell University; Attending Pediatric Urologist, Department of Urology, New York Hospital, Cornell Medical Center, Westchester Medical Center, New York, New York

Harry P. Koo MD

Associate Professor
Department of Surgery, Virginia Commonwealth University; Director of Pediatric Urology, Department of Surgery, Medical College of Virginia, Richmond, Virginia

James M. Kozlowski MD, FACS

Associate Professor of Urology, Surgery, and Tumor Cell Biology; Chief, Section of Urologic Oncology, Vice Chair
Department of Urology, Northwestern University Medical School, Chicago, Illinois

John N. Krieger MD

Professor
Department of Urology, University of Washington; Chief of Urology, VA Puget Sound Health Care System, Seattle, Washington

Jaime Landman MD

Endourology Fellow
Department of Surgery, Division of Urology, Washington University Medical Center, Barnes-Jewish Hospital, St. Louis, Missouri

Fredrick Leach MD, PhD

Principal Investigator and Senior Staff Urologist
Urologic Oncology Branch, National Cancer Institute, Bethesda, Maryland

Richard A. Leder MD

Associate Clinical Professor of Radiology, Division of Abdominal Imaging
Department of Radiology, Duke University Medical Center, Durham, North Carolina

W. Marston Linehan MD

Chief, Urologic Oncology Branch
National Cancer Institute, Bethesda, Maryland

Marguerite C. Lippert MD

Associate Professor
Department of Urology, University of Virginia Health Science Center, Charlottesville, Virginia

Larry I. Lipshultz MD

Professor
Scott Department of Urology; Chief, Division of Male Reproductive Medicine & Surgery, Baylor College of Medicine, Houston, Texas

Fray F. Marshall MD

Professor and Chairman

Department of Urology, Emory University, Atlanta, Georgia

Jack W. McAninch MD, MS

Professor of Urology
Department of Urology, University of California-San Francisco; Chief of Urology, Department of Urology, San Francisco General Hospital, San Francisco, California

David L. McCullough MD

Professor and Chairman
Department of Urology, Wake Forest University School of Medicine; Chief, Department of Urology, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina

W. Scott McDougal MD

Walter Kerr, Jr., Professor of Urology
Harvard Medical School; Chief of Urology, Department of Urology, Massachusetts General Hospital, Boston, Massachusetts

Elspeth M. McDougall MD, FRCSC

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

Edward J. McGuire MD

Professor
Department of Urology, The University of Michigan, Ann Arbor, Michigan

Kevin T. McVary MD, FACS

Associate Professor
Department of Urology, Northwestern University Medical School, Chicago, Illinois

Kiarash Michel MD

Clinical Attending
Department of Surgery, Division of Urology, Harbor–UCLA; Attending, Department of Surgery, Division of Urology, Cedars–Sinai Medical Center, Los Angeles, California

Douglas F. Milam MD

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

Michael E. Mitchell MD

Professor
Department of Urology, University of Washington; Chief, Division of Pediatric Urology, Children's Hospital and Regional Medical Center, Seattle, Washington

James E. Montie MD

Professor of Surgery
Department of Urology; Chairman, Department of Urology, University of Michigan Medical Center, Ann Arbor, Michigan

Khaled H. Mutabagani MD, PhD

Assistant Professor
Department of Physiology, King Abdul Aziz University College; Pediatric Surgeon, Department of Surgery, New Jeddah Clinic Hospital, Jeddah, Saudi Arabia

Charles E. Myers Jr. MD

Professor of Medicine and Urology
University of Virginia School of Medicine, Charlottesville, Virginia

Robert B. Nadler MD

Assistant Professor, Head
Section of Endourology, Laparoscopy, and Stone Disease, Department of Urology, Northwestern University Medical School; Department of Urology, Northwestern Memorial Hospital, Chicago, Illinois

Peter Nichols MD

Professor
Department of Pathology, University of Southern California School of Medicine; Director, Department of Pathology, University of Southern California/Norris Cancer Hospital, Los Angeles, California

Brian E. Nicholson MD

Instructor
Department of Urology, University of Virginia, Charlottesville, Virginia

J. Curtis Nickel MD, FRCSC

Professor
Department of Urology, Queen's University; Staff Urologist, Department of Urology, Kingston General Hospital, Kingston, Ontario, Canada

H. Norman Noe MD

Professor of Urology; Chief Pediatric Urology
University of Tennessee; Professor, Department of Urology, LeBonheur Children's Hospital, St. Jude Children's Hospital, Memphis, Tennessee

Robert O. Northway MD

Chief Resident
Department of Urology, Emory University, Atlanta, Georgia

Andrew C. Novick MD

Chairman
Urological Institute, The Cleveland Clinic Foundation, Cleveland, Ohio

Helen O'Connell MD, FRACS

Senior Academic Associate
Department of Surgery, University of Melbourne; Urologist, Department of Urology, Royal Melbourne Hospital, Melbourne, Victoria, Australia

Robert A. Older MD

Professor of Radiology and Urology
Department of Radiology, University of Virginia Health System, Charlottesville, Virginia

David K. Ornstein MD

Assistant Professor
Department of Surgery/Urology, University of North Carolina, Chapel Hill, North Carolina

Joseph Ortenberg MD

Professor
Departments of Urology and Pediatrics, Louisiana State University; Director of Urologic Education, Department of Surgery, Children's Hospital, New Orleans, Louisiana

Jayashree Parekh MD

Assistant Professor
Department of Radiology, University of Virginia Health System, Charlottesville, Virginia

J. Chadwick Plaire MD
Children's Urology Associates, Las Vegas, Nevada

Sepp Poisel MD

Associate Professor, Senior Physician
Department of Anatomy & Histology, Müllerstrasse, Innsbruck, Austria

Glenn M. Preminger MD

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

Derek Raghavan MD, PhD

Professor of Medicine and Urology
Department of Medical Oncology, University of Southern California, Keck School of Medicine; Chief, Division of Oncology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, California

Parvati Ramchandani MD

Professor
Department of Radiology, Division of Genito-Urinary Radiology, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania

Martin I. Resnick MD

Lester Persky Professor and Chairman
Department of Urology, Case Western Reserve University School of Medicine; Director, Department of Urology, University Hospitals of Cleveland, Cleveland, Ohio

Michael L. Ritchey MD
C.R. Bard, Inc., Edward J. McGuire Distinguished Chair in Urology; Professor of Surgery and Pediatrics; Director, Division of Urology, University of Texas–Houston Medical School, Houston, Texas

Chad W.M. Ritenour MD

Assistant Professor
Department of Urology, Emory University, Atlanta, Georgia

Ronald Ross MD

Professor
Department of Preventive Medicine, University of Southern California, Keck School of Medicine; Deputy Director, University of Southern California/ Norris Comprehensive Cancer Center, Los Angeles, California

Randall G. Rowland MD, PhD

Professor and Glenn Chair of Urology
Department of Surgery/Urology, University of Kentucky; Chief, Division of Surgery/Urology, University of Kentucky Medical Center, Lexington, Kentucky

Susan E. Rowling MD

Assistant Professor
Department of Radiology, University of Pennsylvania, Presbyterian Medical Center, University of Pennsylvania Health System, Philadelphia, Pennsylvania

Grannum R. Sant MD

C.M. Whitney Professor and Chairman
Department of Urology, Tufts University School of Medicine; Urologist-in-Chief, New England Medical Center, Boston, Massachusetts

Richard A. Santucci MD

Assistant Professor
Department of Urology, Wayne State University School of Medicine; Chief, Department of Urology, Detroit Receiving Hospital, Detroit, Michigan

Anthony J. Schaeffer MD

Professor and Chair
Department of Urology, Northwestern University Medical School; Northwestern Memorial Hospital, Chicago, Illinois

Hal C. Scherz MD

Assistant Clinical Professor
Department of Urology, Emory University; Chief Pediatric Urology, Georgia Urology, Children's Healthcare of Atlanta, Atlanta, Georgia

Francis X. Schneck MD

Clinical Assistant Professor
Department of Urology, University of Pittsburgh; Children's Hospital, Pittsburgh, Pennsylvania

J. Bayne Selby Jr. MD

Professor of Radiology
Department of Radiology, Medical University of South Carolina; Co-Director, Vascular/International Radiology, Medical University Hospital, Charleston, South Carolina

Donald G. Skinner MD

Professor and Chairman
Department of Urology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, California

Steven J. Skoog MD

Professor
Department of Surgery and Pediatrics, Oregon Health Sciences University; Director, Pediatric Urology, Doernbecher Children's Hospital, Portland, Oregon

Joseph A. Smith Jr. MD

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

Warren Snodgrass MD

Associate Professor
Department of Urology, Pediatric Section, University of Texas Southwestern Medical Center at Dallas; Physician, Department of Urology, Pediatric Section, Children's Medical Center, Dallas, Texas

Brent W. Snow MD

Professor of Surgery and Pediatrics (Pediatric Urology)
Division of Urology (Pediatric Urology), University of Utah Hospital/Primary Children's Medical Center, Salt Lake City, Utah

Howard M. Snyder III MD

Professor of Surgery in Urology
Department of Surgery, University of Pennsylvania School of Medicine; Associate Director, Pediatric Urology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

R. Ernest Sosa MD

Associate Professor of Urology
Weill Medical College; Associate Attending Physician, Department of Urology, New York–Presbyterian Hospital, New York, New York

J. Patrick Spirnak MD

Professor
Department of Urology, Case Western Reserve University; Director, Department of Urology, Metrohealth Medical Center, Cleveland, Ohio

William D. Steers MD

Jay Y. Gillenwater Professor and Chair
Department of Urology, University of Virginia, Charlottesville, Virginia

John P. Stein MD

Assistant Professor
Department of Urology, University of Southern California; Assistant Professor, Department of Urology, Norris Comprehensive Cancer Center, Los Angeles, California

William R. Strand MD

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

H. Strasser MD

Associate Professor
Department of Urology, University of Innsbruck, Innsbruck, Austria

Stevan B. Streem MD

Head
Section of Stone Disease and Endourology, Urological Institute, The Cleveland Clinic Foundation, Cleveland, Ohio

Gerald Sufrin MD

Professor and Chair
Department of Urology, University at Buffalo; Director, Department of Urology, Kaleida Health, Buffalo, New York

Charles D. Teates MD

Professor
Department of Radiology, University of Virginia Health System, Charlottesville, Virginia

Dan Theodorescu MD

Paul Mellon Chair in Urologic Oncology, Professor of Urology, Associate Professor of Molecular Physiology
University of Virginia, Charlottesville, Virginia

E. Darracott Vaughan Jr. MD

Professor of Urology
Department of Urology, Weill-Cornell University Medical Center; Chairman, Urologist-in-Chief, Department of Urology, New York-Presbyterian Hospital, New York, New York

Suzie N. Venn MS, FRCS

Senior Lecturer and Consultant
Institute of Urology, UCLH, London and St. Richard's Hospital, Chichester, United Kingdom

R. Dixon Walker MD

Professor
Department of Surgery and Pediatrics, University of Florida College of Medicine; Chief, Pediatric Urology, Shands Children's Hospital, Gainesville, Florida

McClellan M. Walther MD

Senior Investigator
National Institutes of Health, National Cancer Institute, Urologic Oncology Branch, Bethesda, Maryland

George D. Webster MB, FRCS

Professor of Urologic Surgery
Department of Surgery, Division of Urologic Surgery, Duke University Medical Center, Durham, North Carolina

Alan J. Wein MD

Professor and Chair
Division of Urology, University of Pennsylvania School of Medicine; Chief of Urology, University of Pennsylvania Health System, Philadelphia, Pennsylvania

Jeffrey P. Weiss MD

Clinical Adjunct Assistant Professor of Urology
Weill/Cornell University Medical College, New York, New York

Robert M. Weiss MD

Professor and Chief, Section of Urology
Department of Surgery, Yale University School of Medicine; Attending and Head of Urology, Department of Surgery, Yale–New Haven Hospital, New Haven, Connecticut

B. Dale Wilson MD
Department of Dermatology, Roswell Park Cancer Institute, Buffalo, New York

J. Stuart Wolf Jr. MD

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

Arthur W. Wyker Jr. MD

Clinical Professor of Urology
University of Virginia Health Sciences Center, Charlottesville, Virginia

Norman Zambrano MD

Instructor
Department of Urology, Catholic University of Chile, Santiago, Chile; Chief, Urology Service, Sotero Del Rio Hospital, Puente Alto, Santiago, Chile

Stephen A. Zderic MD

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

PREFACE

Adult and Pediatric Urology has been revised after only five years because of the rapid introduction of new information about urologic disease. The text, as in previous editions, has been written to serve as a practical reference for residents and practicing urologists. We have attempted to make the text readable and user-friendly and to provide a comprehensive description of the subject, rather than an encyclopedic dissertation. The authors have tried to assimilate all the important information about each subject and to evaluate it in order to reach the best conclusion or consensus. Practicing urologists and residents alike have commented favorably on the content and presentation of the material in the previous editions. We believe the new edition continues to present excellent coverage of the topics in a clear and concise manner.

The fourth edition consists of three volumes. The first two volumes cover adult urology. Most chapters have been completely rewritten. The coverage on prostatic diseases has been expanded; completely new chapters on anatomy, diagnostic imaging, surgical management of calculus disease, bladder cancer, diseases of the retroperitoneum, alternative therapies, office urology, AIDS, and spinal cord injury have been included. The third volume, under the very capable leadership of Michael Mitchell, covers pediatric urology. We have arranged the pediatric volume by pathophysiology and treatment modality to facilitate easy clinical referencing. The sections on hypospadias, exstrophy, laparoscopic surgery, and reconstruction techniques have been radically changed to include current techniques in state-of-the-art technologies.

With this new edition, we are pleased to present a companion CD-ROM that contains all of the text, figures, and tables found within the three volumes. In addition, we have used the power of electronic publishing to provide material that cannot be presented in print by including video clips of surgical procedures. These video clips concentrate on aspects of the procedures that cannot be conveyed adequately in still images. We hope the adage that a picture is worth a thousand words will be proven true and that these videos will provide a valuable resource for our readers. We also hope that the portable and searchable nature of the CD-ROM will further enhance the user-friendly nature of the fourth edition of *Adult and Pediatric Urology.*

No text is any better than its authors, editors, and publishers. Working with Jack Grayhack, Stuart Howards, and Michael Mitchell has been both pleasant and intellectually stimulating. Each of the editors has worked closely with his authors to ensure the best coverage possible for a wide array of subjects. The authors enthusiastically responded and produced scholarly, critical, and informative chapters that are easy to read. Anne Sydor, Brian Brown, and Jenny Kim of Lippincott Williams & Wilkins have been invaluable partners in this endeavor. I know of no other group who could have transformed so much manuscript into a completed textbook in such a compressed time frame. We believe the result to be an up-to-date, thorough, and eminently readable textbook of general urology.

For the editors

Jay Y. Gillenwater MD

Contents

SECTION I
ADULT UROLOGY

1

SURGICAL ANATOMY OF THE GENITOURINARY SYSTEM

Georg Bartsch

H. Strasser

Sepp Poisel

G. Bartsch and H. Strasser: Department of Urology, University of Innsbruck, Innsbruck, Austria.

S. Poisel: Department of Anatomy & Histology, Müllerstrasse, Innsbruck, Austria.

Contents

ABDOMINAL WALL

Part of "1 - SURGICAL ANATOMY OF THE GENITOURINARY SYSTEM "

Superficial Abdominal Muscles

Figure 1.1 shows an external view of the anterior abdominal wall.

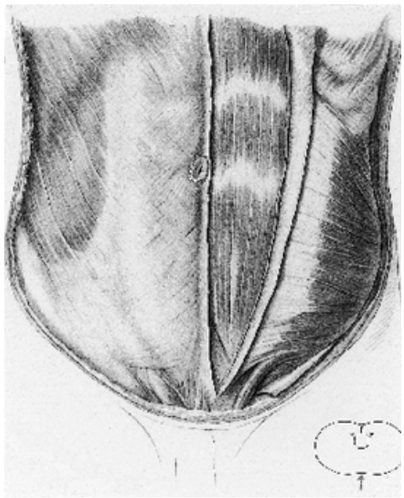

FIGURE 1.1. External view of the anterior abdominal wall. The anterior rectus sheath and external oblique muscle on the left side have been removed.

Lateral Group

External oblique muscle

Internal oblique muscle

Transversus abdominis

External Oblique Muscle

The external oblique muscle arises by eight slips from the external surfaces of the fifth through twelfth ribs. Its five upper slips interdigitate with the origins of serratus anterior, its three lower slips with the origins of latissimus dorsi. Its posterior fibers descend almost vertically to the iliac crest, and the adjacent anterior fibers pass obliquely forward and medially in their downward course.

About a fingerwidth from the lateral border of the rectus abdominis muscle, the external oblique fibers terminate in an aponeurosis. The aponeuroses of both external oblique muscles unite at the *linea alba,* where they attach to the pubic symphysis and the adjacent anterior surfaces of the superior pubic ramus.

The portion of the aponeurosis between the anterosuperior iliac spine and the pubic tubercle is thickened to form a tendinous band, the *inguinal ligament.* Just above and medial to the inguinal ligament is the *superficial inguinal ring,* bounded by the medial crus, lateral crus, and intercrural fibers. The latter are reinforcing fibers of the external oblique aponeurosis.

Internal Oblique Muscle

The internal oblique muscle originates from the deep layer of the lumbodorsal fascia, from the intermediate line of the iliac crest, from the anterorsuperior iliac spine, and from the lateral portion of the inguinal ligament. Its muscular fibers fan out broadly to their sites of insertion. The uppermost posterior fibers are inserted into the inferior borders of the

last three ribs. The intermediate fibers form an aponeurosis at the lateral border of the rectus abdominis muscle. This aponeurosis splits into an anterior and a posterior layer that pass around the rectus abdominis to form the rectus sheath before uniting with the contralateral aponeurotic fibers at the linea alba. The posterior rectus sheath terminates about three fingerwidths below the umbilicus at the *arcuate line.* The lower fibers of the internal oblique are continued onto the spermatic cord in males to form the *cremaster muscle.* In females, a few muscle fibers accompany the round ligament of the uterus within the inguinal canal.

Transversus Abdominis

The deepest of the three lateral abdominal muscles, the transversus abdominis, arises by six slips from the internal aspects of the seventh through twelfth costal cartilages, interdigitating with the slips of the costal part of the diaphragm.

Fibers also arise from the deep layer of the lumbodorsal fascia, the inner lip of the iliac crest, and the lateral part of the inguinal ligament. The transversus abdominis fibers pass in a horizontal direction and terminate in an aponeurosis along the laterally convex *semilunar line.* Above the arcuate line, this aponeurosis forms the posterior layer of the rectus sheath. Below the arcuate line, it unites with the anterior lamina of the internal oblique aponeurosis and helps form the anterior layer of the rectus sheath. Each transversus aponeurosis fuses with its counterpart at the linea alba.

Medial Group

Rectus abdominis

Pyramidalis

Rectus Abdominis

The rectus abdominis muscle arises by three slips from the external surfaces of the fifth through seventh costal cartilages, from the xiphoid process, and from ligaments in this region. The muscle tapers in its straight, descending course, especially in its lower one-fourth, and inserts by a short, strong tendon into the pubic crest. The fiber mass of the rectus abdominis is interrupted by three or more transverse tendinous bands, the *tendinous intersections,* which are intimately attached to the anterior rectus sheath.

Rectus Sheath.

The rectus sheath that envelops the rectus abdominis muscle is formed by the aponeuroses of the three lateral abdominal muscles. It is divided into an *anterior layer* (anterior rectus sheath) and a *posterior layer* (posterior rectus sheath). As noted, the aponeurosis of the internal oblique muscle splits into two parts that pass behind and in front of the rectus abdominis to reach the linea alba. Above the umbilicus, or more precisely above the arcuate line, the anterior wall of the sheath consists of the external oblique aponeurosis and, deep to it, the anterior layer of the internal oblique aponeurosis. Below the level of the arcuate line, the aponeuroses of all three abdominal muscles pass in front of the rectus abdominis muscle.

The posterior layer of the internal oblique aponeurosis is reinforced above the arcuate line by the aponeurosis of the transversus abdominis. Below the arcuate line, the posterior wall of the rectus sheath is formed entirely by the transversalis fascia.

Pyramidalis

The pyramidalis muscle arises broadly from the superior pubic ramus, anterior to the insertion of the rectus abdominis. It passes upward, gradually narrowing as it ascends, to insert on the linea alba. The pyramidalis is absent in approximately 20% of the population.

Lumbar Trigone and Variations

The lumbar trigone is a triangular interval bounded by the iliac crest, the posterior border of the external oblique muscle, and the anterior (lateral) border of the latissimus dorsi. The shape and size of the triangle are highly variable depending on the degree of overlap of its bordering muscles and their tendons of origin. If the musculotendinous plates overlap sufficiently, a lumbar trigone is not formed (Fig. 1.2A).

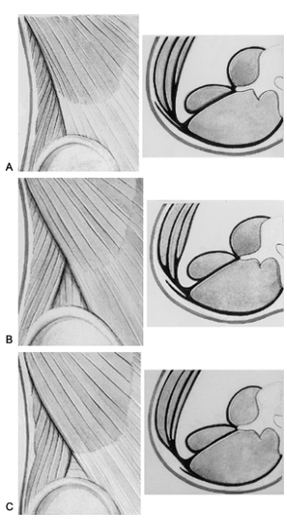

FIGURE 1.2. Variations of the lumbar trigone. **A:** Lumbodorsal fascia (superficial layer) overlies the external oblique muscle. **B:** Lumbodorsal fascia overlaps the internal oblique muscle. **C:** Lumbodorsal fascia forms a triangle (lumbar trigone) with the external oblique muscle.

If the muscles are less prominently developed, a lumbar triangle is present. The floor of the lumbar trigone may be

formed by the internal oblique, if this muscle is well developed (Fig. 1.2B), or by the deep layer of the lumbodorsal fascia (Fig. 1.2C). In the latter case, the lumbodorsal fascia is the only solid structural component of the posterior abdominal wall in the lumbar trigone.

Latissimus Dorsi

The *vertebral part* of the latissimus dorsi muscle arises from the spinous processes of the fifth through twelfth thoracic vertebrae and its *iliac part* from the lumbodorsal fascia and the posterior iliac crest. The *costal part* of the latissimus dorsi muscle arises from the external surfaces of the tenth through twelfth ribs, and a variable *scapular part* originates from the inferior angle of the scapula. The fibers of the latissimus dorsi pass laterally upward with varying degrees of obliquity to the humerus, where they insert into the crest of the lesser tubercle (Fig 1.3 and Fig. 1.4).

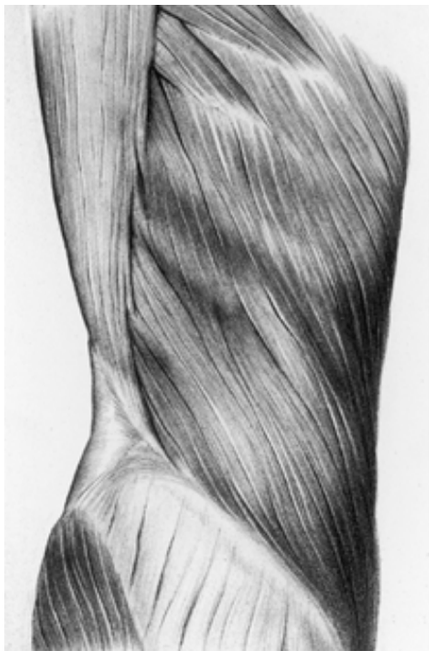

FIGURE 1.3. External view of the lateral abdominal wall.

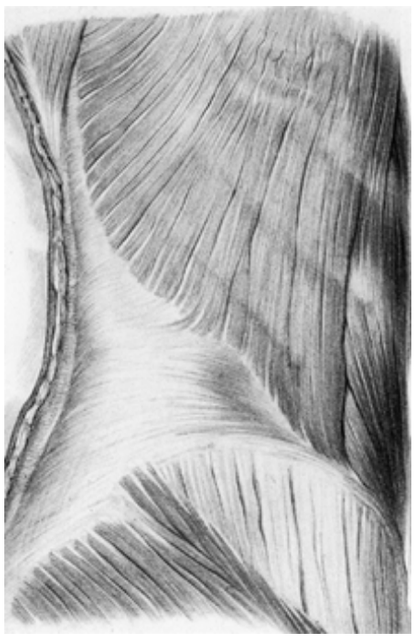

FIGURE 1.4. External view of the posterolateral abdominal wall, inferior portion.

Serratus Anterior

The serratus anterior muscle overlies the lateral chest wall and arises by nine and sometimes ten slips from the outer surfaces of the upper nine (or eight) ribs. It is inserted along the entire medial border of the scapula. Its tripartite insertion consists of a *superior part* to the superior angle of the scapula, an *intermediate part* to the medial scapular margin, and an *inferior part* to the inferior angle of the scapula.

Intercostal Muscles

The intercostal muscles partially occupy the intercostal spaces and are composed of an internal and an external layer.

The *external intercostal muscles* run forward from the costal tubercle to the margin of the rib cartilage. The external intercostals become membranous between the costal cartilages, each continuing forward to the septum as the *external intercostal membrane.* The external intercostal fibers run obliquely downward, passing laterally downward in

their posterior portion and medially downward in their anterior portion.

The *internal intercostal muscles* extend obliquely forward and upward from the costal angle to the sternum. The last two internal intercostal muscles are often fused with the internal oblique muscle, showing no apparent boundary. In the intercostal space between the costal angle and vertebral column, each internal intercostal muscle is replaced by an *internal intercostal membrane.*

Serratus Posterior Inferior

The serratus posterior inferior muscle arises from the superficial layer of the lumbodorsal fascia at the level of the lower two thoracic vertebrae and the upper two lumbar vertebrae (Fig. 1.5). It runs obliquely upward and laterally to attach by four slips to the inferior margins of the lower four ribs, somewhat lateral to their costal angles.

FIGURE 1.5. External view of the posterolateral abdominal wall, inferior portion. The latissimus dorsi has been removed to show the origins of the external oblique muscle.

Diaphragm

The diaphragm forms a musculotendinous partition between the abdominal and thoracic cavities (Fig. 1.6). Its central tendinous portion is termed the *central tendon,* and its muscular portion is divisible into a *sternal part,* a *costal part,* and a *lumbar part.*

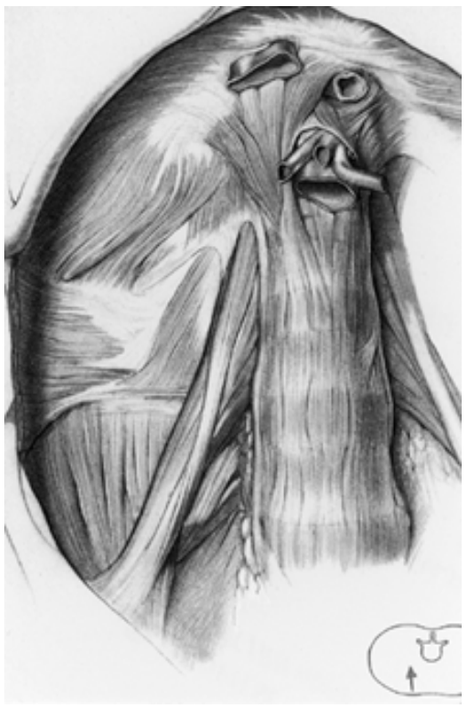

FIGURE 1.6. Internal view of the posterosuperior abdominal wall.

Lumbar Part

The lumbar part of the diaphragm arises by a *medial crus* and a *lateral crus.* A portion of the medial crus is sometimes split off to form an intermediate crus. The *right medial crus* arises from the anterior surfaces of the bodies of the first through fourth lumbar vertebrae; the *left medial crus* arises from the bodies of the first through third lumbar vertebrae. Both medial crura form the *aortic aperture* (aortic hiatus), which is bordered by the median arcuate ligament.

The *right medial crus* consists of three muscular bundles, the first arising from the lumbar vertebrae and merging directly with the central tendon. The second arises from the median arcuate ligament and forms the right border of the *esophageal aperture* (esophageal hiatus) of the diaphragm. The third muscular bundle, located posterior to the second, also originates from the median arcuate ligament and forms the left border of the esophageal aperture.

The *lateral crus* arises from the two tendinous arches of the medial and lateral arcuate ligaments. The medial arcuate ligament (medial lumbocostal arch or psoas arcade) extends from the lateral surface of the first (second) lumbar vertebral body to the first (second) costal process, passing over the origins of the psoas major muscle. The lateral arcuate ligament (lateral lumbocostal arch or quadratus arcade) extends from the costal process to the tip of the twelfth rib, passing over the quadratus lumborum muscle. The muscle fibers run steeply upward from both tendinous arches to the central tendon.

Costal Part

The costal part of the diaphragm arises from the inner surfaces of the cartilages of the lower six ribs, interdigitating with the transversus abdominis. The muscle fibers arch to their insertion at the anterolateral border of the central tendon.

Sternal Part

The sternal part, the smallest part, of the diaphragm arises by one or more small slips from the internal surface of the xiphoid process and from the posterior layer of the rectus sheath. The muscle fibers pass almost transversely to the anterior border of the central tendon.

Deep Abdominal Muscles

Psoas major

Quadratus lumborum

Psoas Major

The superficial part of the psoas major arises from the lateral surfaces of the twelfth thoracic vertebra and the first four lumbar vertebrae, and its deep part from the first through fifth costal processes. It unites with the fibers of the iliacus muscle and, enveloped by the iliac fascia, inserts into the lesser trochanter of the femur as the *iliopsoas muscle.*

The *psoas minor* is a variant present in fewer than 50% of individuals. It arises from the twelfth thoracic and first lumbar vertebrae and is attached to the iliac fascia and, via the fascia, to the iliopubic eminence.

Iliacus

The iliacus muscle arises from the iliac fossa and inserts conjointly with psoas major into the lesser trochanter of the femur. Their composite, the iliopsoas, passes through the *lacuna musculorum* (muscular compartment) beneath the inguinal ligament to reach the thigh.

Quadratus Lumborum

The quadratus lumborum is a flat muscle that lies adjacent to the vertebral column and stretches between the twelfth rib and iliac crest. It consists of two parts that cannot be completely separated from each other: a posterior part arising from the iliac crest and iliolumbar ligament and inserting into the costal processes of the first through third (or fourth) lumbar vertebrae and twelfth rib, and an anterior part passing from the costal processes of the lower three or four lumbar vertebrae to the last rib.

Pelvic Floor

The pelvic floor constitutes the posterior inferior boundary of the abdominal cavity (Fig. 1.7). It consists of the *pelvic diaphragm* and the *urogenital diaphragm.*

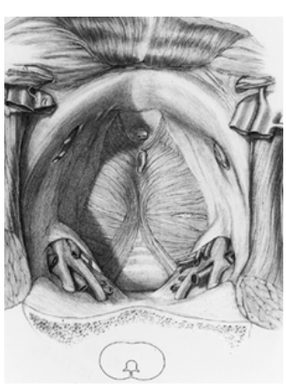

FIGURE 1.7. Internal view of the inferior abdominal wall (pelvic floor).

Pelvic Diaphragm

The pelvic diaphragm is composed of the *levator ani* and *coccygeus* muscles.

The *levator ani* muscle group consists of the puborectalis prerectal fibers, pubococcygeus, and iliococcygeus, which in some individuals are bounded superiorly by the sacrococcygeus and rectococcygeus muscles. The levator ani arises from the pubic bone lateral to the symphysis, from the tendinous arch of the levator ani (part of the obturator fascia), and from the ischial spine.

The most medial fibers of the puborectalis muscles form the *levator crura,* which bound the *levator hiatus* (genital hiatus). The prerectal fibers are attached to the perineum and separate the urogenital hiatus from the anal hiatus. The levator hiatus is traversed by the urethra in males and by the urethra and vagina in females. The rectum leaves the true pelvis behind the prerectal fibers. The pubococcygeus and iliococcygeus muscles are attached to the coccyx and anococcygeal ligament.

The *coccygeus* muscle passes from the ischial spine to the coccyx and completes the pelvic diaphragm posteriorly.

Striated Urethral Sphincter (Rhabdosphincter)

The rhabdosphincter and the transverse perineal ligament close the levator hiatus inferiorly. Contrary to standard descriptions, the muscle fibers of the rhabdosphincter are arranged in a loop-shaped fashion on the ventral and lateral aspects of the membranous urethra of the male and the caudal two-thirds of the female urethra. On gross anatomic and histologic examination, comparatively strong smooth muscular and connective tissue can be found dorsal to the membranous urethra (i.e., in the region of the perineal body). Both ends of the omega-shaped sphincter insert at the perineal body. The sphincter loop is continuous with muscle bundles that run along the anterior and lateral aspects of the prostate in the male and extend cranially to the bladder neck. Thus the rhabdosphincter of the urethra does not form a complete collar around the urethra. It should rather be described as a muscular coat ventral and lateral to the membranous urethra and the prostate of the male and the caudal two-thirds of the female urethra, the core of which is the omega-shaped loop around the urethra. Furthermore, the rhabdosphincter is separated from the ventral portions of the levator ani muscle by a sheet of connective tissue. Neither in anatomic dissections nor in serial histologic sections can any evidence of the classic muscular “urogenital diaphragm” be found. The transverse perineal ligament is traversed by the urethra and the rhabdosphincter.

RETROPERITONEAL SPACE

Part of "1 - SURGICAL ANATOMY OF THE GENITOURINARY SYSTEM "

Anatomy

Definition, Boundaries, and Contents

The *retroperitoneal space* is the space between the posterior parietal peritoneum and the posterior abdominal wall. It is bounded superiorly by the diaphragm, and it blends inferiorly with the connective-tissue stratum of the subperitoneal space.

The lateral boundaries of the retroperitoneal space are imprecisely defined. They are essentially formed by the close apposition of the posterior parietal peritoneum to the transversalis fascia on the inner aspect of the lateral abdominal muscles, the thin subserous connective-tissue layer forming a virtual boundary in that region.

The contents of the retroperitoneal space can be described as having either a primary or a secondary retroperitoneal location. Portions of the duodenum, pancreas, and ascending and descending colon reach the retroperitoneum secondarily. Primary retroperitoneal structures are the kidneys and renal pelves, ureters, adrenal glands, and large nerves and vessels (Fig. 1.8).

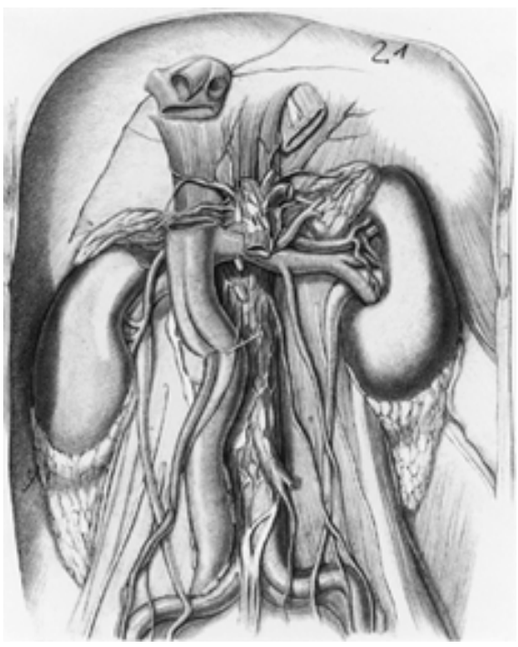

FIGURE 1.8. Topography of the organs, vessels, and nerves of the retroperitoneal space and posterior abdominal wall.

Kidneys

Position.

The kidneys are paired viscera that flank the vertebral column in the retroperitoneal space. Externally, the kidney presents a *medial border,* a *lateral border,* an *anterior surface,* a *posterior surface,* an *upper pole,* and a *lower pole.* The medial border presents a deep fissure, the *renal hilum,* which leads into the *renal sinus.* The upper pole of the kidney is more rounded than the lower pole because of its relation to the adrenal gland.

The terms of orientation for the kidney are somewhat imprecise because the organ is oriented at an angle to the cardinal planes. The anterior surface of the kidney is angled posterolaterally from the frontal plane, so the renal hilum normally is directed anteromedially. The long axes of both kidneys are convergent superiorly, so the upper poles of the kidneys are separated by a smaller distance (7 to 8 cm) than the lower poles (11 to 15 cm).

The level of the kidneys in relation to the vertebral column is subject to marked individual variations. Renal position also depends on individual body posture and the phases of respiration. Changes in renal position are more common and pronounced in children than in adults.

The right kidney in adults usually lies somewhat lower than the left kidney. The upper pole of the right kidney typically occupies a level between the body of the twelfth thoracic vertebra and the upper third of the first lumbar vertebra. The upper pole of the left kidney generally is higher than the right upper pole by half the height of a vertebral body. The lower pole of the right kidney usually is at the level of the third lumbar vertebra, and the lower pole of the left kidney occupies a correspondingly higher position (Fig. 1.9).

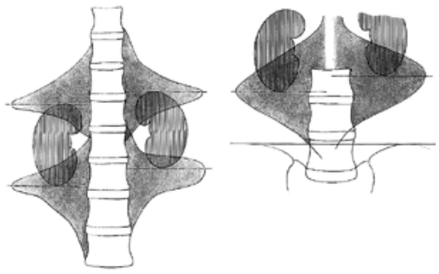

FIGURE 1.9. Range of variation in the levels of the renal poles. **A:** Position of the renal poles in relation to the lumbar spine. **B:** Position of the lower renal pole in relation to the iliac crest. The shaded areas indicate the range of variation.

The relation of the lower pole of the kidney to the highest point of the iliac crest is subject to the same individual variations. The right lower pole is approximately 3 cm above the iliac crest, on average, and the left lower pole is approximately 1 cm higher (Fig. 1.9).

Relations.

The kidneys are embedded in the perirenal fat capsule, which is separated from the outer, pararenal fat by Gerota's fascia. The relations of the anterior surface of the kidney are shown in Fig. 1.10 and Fig. 1.11 .

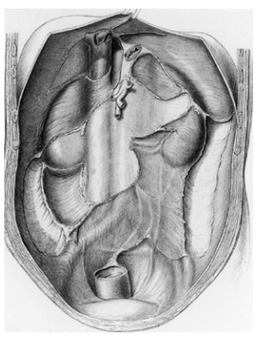

FIGURE 1.10. Relation of the kidneys to the parietal peritoneum and mesenteric roots.

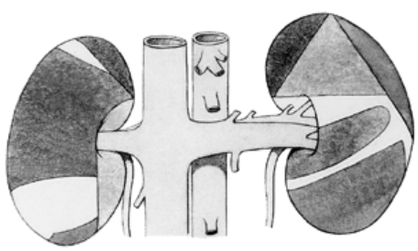

FIGURE 1.11. Contact areas of the kidneys, anterior aspect.

The posterior relations of the kidney are virtually identical on the right and left sides (Fig. 1.12). The cranial half of the posterior renal surface is in contact with the diaphragm. Their area of contact depends on the renal level and therefore is usually greater on the left side than on the right. The kidney apposes to the lateral crus of the lumbar part of the diaphragm. Between the lumbar and costal parts of the diaphragm is a variable amuscular interval, the lumbocostal trigone, which constitutes a site of least resistance. In this area, only the thin diaphragmatic fasciae separate the kidney and its fat capsule from the pleural cavity.

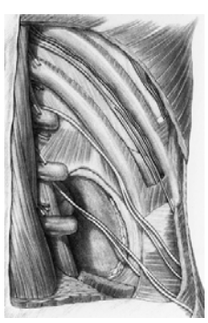

FIGURE 1.12. Posterior relations of the right kidney.

The caudal half of the posterior surface of the kidney is related to the quadratus lumborum muscle and the deep

lumbodorsal fascia. The subcostal, iliohypogastric, and ilioinguinal nerves descend obliquely in a medial-to-lateral direction between the kidney and posterior abdominal wall.

The posterior part of the medial border of the kidney lies on the psoas major muscle. With a normal renal position, the twelfth rib passes obliquely downward and laterally to cross the upper third of the posterior renal surface. Between the twelfth rib and kidney are the diaphragm and the costodiaphragmatic recess of the pleural cavity. Attention must be given to the inferior reflection of the pleura in retroperitoneal approaches to the kidney that include a rib resection.

Capsules.

Each kidney is enveloped by three capsules (Fig. 1.13): the fibrous capsule (capsule proper), the perirenal fat capsule, and Gerota's fascia (renal fascia, Gerota's capsule). The innermost *fibrous capsule* closely invests the renal parenchyma and is easily separated from the healthy kidney.

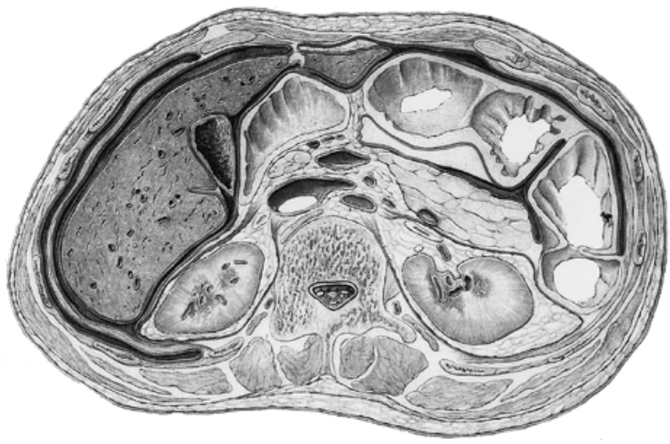

FIGURE 1.13. The transverse section through the abdomen at the level of the first lumbar vertebra (L1).

Surrounding the fibrous capsule is the *perirenal fat capsule,* which develops postnatally and is fully developed by puberty. The perirenal fat is connected to the inner fibrous capsule and the outer Gerota's fascia by loose connective tissue, which creates a mobile plane. The fat capsule is less well developed on the anterior surface of the kidney than posteriorly, and it envelops the kidney and adrenal gland. Composed of structural fat, the perirenal fat capsule has the primary function of keeping the kidney in place.

The outermost renal covering is *Gerota's fascia,* which forms a “sac” enclosing the kidney, adrenal gland, and perirenal fat capsule. Gerota's fascia is functionally and structurally distinct from the fascia that envelops the muscles and is more like the connective-tissue fascia that invests the organs in the true pelvis.

Gerota's fascia consists of two layers commonly termed the *prerenal (anterior)* and *retrorenal (posterior) fascia.* The fascial layers are fused approximately two fingerwidths lateral to the lateral renal border and above the adrenal gland. Gerota's fascia is also attached superiorly to the fascia of the diaphragm. The two layers of Gerota's fascia are separated below the kidney to allow passage of the ureter and blood

vessels. The prerenal and retrorenal layers fuse medially with the connective tissue surrounding the major blood vessels and nerves of the retroperitoneal space. The retrorenal fascia is firmly adherent to the muscular fascia of the posterior abdominal wall.

Lateral to the saclike Gerota's fascia is the *pararenal fat*, which differs from the perirenal fat capsule in that it is not composed of structural fat, so its volume is subject to marked individual and nutrition-dependent variations.

Renal Vessels

Arteries.

Normally, each kidney receives its blood supply from a single renal artery. Both renal arteries spring from the lateral aspect of the abdominal aorta, the right artery usually arising at a slightly lower level than the left. The origin of the renal arteries is usually situated below that of the superior mesenteric artery, between the inferior third of the first lumbar vertebra and the middle third of the second lumbar vertebra.

The right renal artery runs obliquely downward and laterally to the hilum of the kidney, passing behind the inferior vena cava. The accompanying renal vein is usually anterior to and above the artery, but in approximately 30% of cases, the artery is in front of the vein (Fig. 1.15). Anterior to the right renal hilum and vessels is the descending portion of the duodenum.

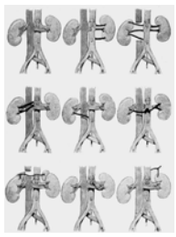

FIGURE 1.15. Typical patterns of aberrant and accessory renal arteries.

The left renal artery is shorter than the right and usually passes to the renal hilum above and partially behind the left renal vein. The hilum and renal vessels are covered anteriorly by the body of the pancreas and the splenic vessels.

The renal arteries divide at a variable distance from the hilum into two (57%) or three (43%) main branches (anterior, posterior, and inferior) that supply corresponding portions of the renal parenchyma. The branching of the renal arteries does not follow any consistent pattern in terms of right–left or gender distribution.

Variations in the number, course, and origin of the renal artery are common. In approximately 40% of cases, the kidney is found to have an atypical arterial supply. The presence of accessory or aberrant renal arteries is especially common. An “accessory” artery is a supernumerary artery that supplies the kidney as a separate vessel; “aberrant” arteries enter the renal parenchyma outside the hilum, generally at the upper or lower pole. Thus an accessory artery may or may not be aberrant. An aberrant artery may arise from the renal artery itself. Possible variations of the renal arteries are illustrated in Fig. 1.14, Fig. 1.15, Fig. 1.16 and Fig. 1.17 .

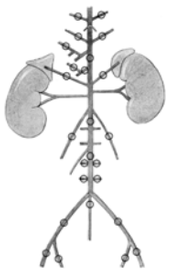

FIGURE 1.14. Schematic diagram of the abdominal aorta and kidneys. *Circles* indicate the potential origins of accessory (or aberrant) renal arteries.

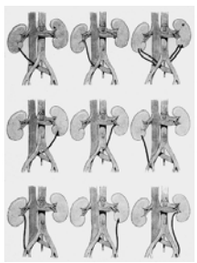

FIGURE 1.16. Typical patterns of aberrant and accessory renal arteries.

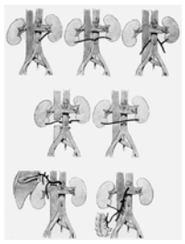

FIGURE 1.17. Typical patterns of aberrant and accessory renal arteries.

Veins.

The renal veins are interconnected by numerous anastomoses in the renal parenchyma and renal sinus, a pattern consistent with the general tendency for the venous system to form plexuses. The trunk of the renal vein is usually formed in the hilum by the convergence of two (53%) or three (34%) main tributaries that pass in front of the renal pelvis. A small tributary passing behind the renal pelvis occurs in approximately one-third of patients.

Outside the renal sinus, the veins usually are anterior to the renal arteries. The left renal vein commonly opens into the inferior vena cava at a higher level than the right renal vein. With a normally positioned inferior vena cava, the left renal vein is substantially longer (6 to 11 cm) than the right (2 to 4 cm). The right renal vein runs a straight, direct course from the hilum to the inferior vena cava; the left vein runs medially forward and passes in front of the aorta, just below the origin of the superior mesenteric artery, before entering the inferior vena cava. Phylogenetically, the left renal vein originates as part of the cardinal venous system and consequently receives the left suprarenal and testicular (or ovarian) veins.

Lymphatics

The intrarenal lymph vessels of the kidney accompany the arteries to the renal sinus and present in the hilum as

prevascular, retrovascular, and intervascular bundles. Regional lymph nodes encountered on the right side are the right lumbar (postcaval) lymph nodes and the intermediate nodes and rarely the preaortic nodes. The renal lymphatics on the left side drain into the left lumbar lymph nodes (lateral aortic and preaortic nodes) (Fig. 1.18).

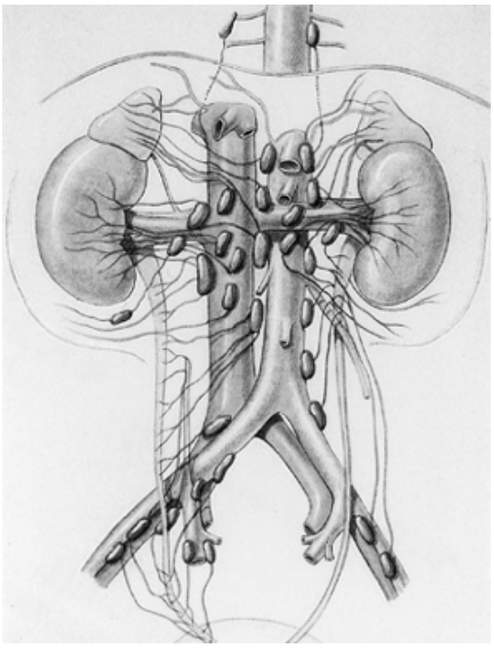

FIGURE 1.18. Lymph nodes and lymphatic vessels of the retroperitoneal space.

The lymph vessels draining the renal capsules pass to the lumbar lymph nodes separately from the lymph vessels of the renal parenchyma. A few lymph vessels from the renal capsule pass through the diaphragm and end in the intercostal nodes. Anastomoses have been described between the lymph vessels of the renal capsules and those of the liver, colon, cecum, and uterine tube.

Renal Nerve Supply

The kidneys derive their nerve supply from the renal plexus, which is formed by sympathetic and parasympathetic fibers from the celiac plexus and abdominal aortic plexus, as well as direct fibers from the sympathetic trunk (lumbar part). The renal plexus accompanies the renal arteries to the hilum. Autonomic nerve fibers can be identified along the arteries as far as the efferent vessels of the renal glomeruli.

Renal Pelvis

The *renal pelvis* is a hollow muscular organ that forms the initial segment of the excretory portion of the urinary tract. The tension of the muscular wall of the renal pelvis varies

with its momentary functional state, so the shape of the renal pelvis also varies.

The renal pelvis begins with 7 to 13 *minor calices* at the renal papillae. The minor calices generally unite to form two or three *major calices* that make up the true renal pelvis (dendritic type). In some cases, all of the minor calices may open directly into the renal pelvis, which then exhibits an ampulelike dilation (ampullary type of pelvis). Forms intermediate between these extremes are common. At the time of operation, the renal pelvis is easily accessible at the hilum through a posterior approach, except for the rare cases in which all of the pelvis is contained within the renal sinus. The only structures that cross the posterior aspect of the renal pelvis are the main posterior branch of the renal artery and the variable posterior branch of the renal vein.

The renal pelvis derives its arterial supply (Fig. 1.8) from one or more branches of the renal artery and is drained by the renal vein. Lymphatic drainage (Fig. 1.18) is to the lumbar lymph nodes. The nerves of the renal pelvis are derived from the renal plexus.

Ureter

The renal pelvis becomes continuous with the ureter below the hilum, with no distinct ureteropelvic boundary. Their junction is at the level of the second or third lumbar vertebra.

The ureter is considered to consist of an *abdominal (proximal) part* and a *pelvic distal part* whose junction occurs at the point where the ureter is crossed by the iliac vessels.

The *abdominal (proximal) part* of the ureter passes downward and slightly medially from the renal pelvis on the fascia of the psoas major, encased within a sheath of fibrofatty tissue. The lateral distance of the ureter from the costal processes of the lumbar vertebrae is variable. In infancy, the proximal part of the ureter is tortuous and may even exhibit proximal kinks that disappear by approximately 1 year of age.

The topographic relations of the ureters to anterior structures are different on the right and left sides because of the asymmetric development of the abdominal viscera. At its origin, the *right ureter* is overlapped by the descending part of the duodenum. In its descent, it is crossed anteriorly by the right colic artery and ileocolic artery, which pass below the secondary parietal peritoneum (originally the ascending mesocolon) to the cecum and ascending colon. The right ureter passes below the testicular or ovarian vessels in its retroperitoneal course. Just before entering the true pelvis, the right ureter is crossed by the root of the mesentery, giving it an indirect relation to the terminal segment of the ileum. A mobile cecum and a transversely oriented appendix also may relate anteriorly to the right ureter.

The initial part of the *left ureter* descends lateral and posterior to the superior duodenal fold, which conveys the inferior mesenteric vein to the splenic vein. As it descends further, the left ureter is crossed by the branches of the inferior mesenteric artery (left colic artery and sigmoid arteries), which lie below the secondary parietal peritoneum (originally the descending mesocolon). The left ureter, like the right, is crossed at varying levels by the testicular or ovarian vessels. Just before entering the true pelvis, the left ureter is crossed by the attachment of the sigmoid mesocolon and can be found at this level within the *intersigmoid recess.*

The right ureter is usually adherent to the peritoneum and must be separated from it during surgery. The left ureter has no firm attachments to the secondary parietal peritoneum, and only the portion in the intersigmoid recess is directly apposed to the peritoneum.

Vessels and Nerves of the Ureter.

The connective tissue surrounding the ureter (the adventitia) is permeated by an *arterial anastomotic network* (Fig. 1.8) composed basically of longitudinal vessels interconnected by transverse anastomoses. This periureteral arterial plexus is supplied by all arteries that have a close topographic relation to the ureter. The proximal part of the ureter is consistently supplied by one or two ureteral branches from the renal artery, from the testicular or ovarian artery, and occasionally by direct branches from the abdominal aorta. At the junction of the abdominal

and pelvic parts of the ureter, the plexus is supplied by branches of the iliac vessels (common iliac, external or internal iliac).

In surgical procedures on the kidney or renal pelvis, care must be taken not to injure the ureteral branches of the renal artery. These branches provide the essential blood supply to the proximal part of the ureter, and their caliber and connections with the periureteral plexus give them the capacity to supply the entire proximal part of the ureter.

Vascular plexuses in the muscular and submucous coats of the ureter receive blood from the adventitial plexus and contribute to the ureteral blood supply.

The *veins* draining the proximal part of the ureter essentially follow the course of the arteries. The venous drainage is directed toward the renal veins and the testicular or ovarian veins.

The *lymph vessels* draining the proximal part of the ureter (Fig. 1.18) start at networks of lymph capillaries in the muscular wall and adventitia. They pass from the proximal ureter to the lumbar lymph nodes, on the right side draining into the lateral caval and precaval nodes and on the left into the lateral aortic and preaortic nodes. Lymphatics draining the lower portion of the proximal ureter are distributed to the common iliac nodes. Connections generally are present between these two drainage pathways.

The abdominal part of the ureter derives its *nerve supply* from the renal plexus superiorly and from the abdominal aortic plexus inferiorly. The adventitia of the ureter contains a dense network of nerve fibers that receive branches from the plexus surrounding the testicular or ovarian artery.

Adrenal Gland

The paired adrenal glands (Fig. 1.8) are set on the upper pole and anteromedial surface of the corresponding kidney. They are surrounded by the perirenal fat capsule and Gerota's fascia. Because of the close relation of the adrenal gland to the kidney and the confining renal fascial sac, adrenal tumors can produce a distortion of the renal outline.

The right adrenal gland has the approximate shape of a pyramid whose base rests on the upper pole of the right kidney. The left adrenal gland is semilunar in shape and apposes to the upper part of the medial border of the left kidney. It usually extends to the renal hilum and is in contact with the renal vessels.

The posterior surface of the *right adrenal gland* is in contact with the diaphragm, and its inferior surface is related to the kidney. The anterosuperior surface of the gland is related to the bare area of the liver. Its anterior surface is behind the inferior vena cava medially, and the inferior part of its anterior surface is covered by parietal peritoneum.

The *left adrenal gland,* like the right, is only partially covered by peritoneum, which invests the upper half of its anterior surface. Thus part of the gland projects into the omental bursa and may relate topographically to the abdominal part of the esophagus. The anteroinferior surface of the left adrenal gland is in contact with the body of the pancreas and the splenic vessels. The lateral part of the posterior surface of the gland apposes to the kidney, and the medial part is in contact with the left crus of the diaphragm.

Vessels and Nerves of the Adrenal Gland.

Normally, at least three arteries contribute to the *arterial blood supply* of the adrenal gland (Fig. 1.8). These arteries are the superior, middle, and inferior suprarenal arteries, which arise from the inferior phrenic artery, abdominal aorta, and renal artery, respectively.

The superior suprarenal artery normally does not supply the gland as a single vessel (Fig. 1.8) but divides into 3 to 30 branches before entering the gland. Multiple superior suprarenal arteries also may occur. The middle suprarenal artery arises from the abdominal aorta at a variable level but always above the renal artery. The vessel may be absent or multiple (Fig. 1.8). The inferior suprarenal artery enters the undersurface of the adrenal gland by several branches that may arise separately from the renal artery or from accessory or aberrant vessels.

The *venous drainage* of the adrenal gland is generally handled by a single vessel, the suprarenal vein, which leaves the glandular tissue at the anterior surface of the adrenal gland. The right suprarenal vein takes a short, direct, transverse course to the inferior vena cava. The left suprarenal vein passes over the inferior part of the anterior surface of the gland and terminates at the left renal vein.

The *lymph vessels* (Fig. 1.18) from the adrenal cortex accompany the inferior phrenic and middle suprarenal arteries, and those from the adrenal medulla accompany the suprarenal vein. They terminate at the lumbar lymph nodes.

The *nerves* enter the posterior and medial aspects of the adrenal gland. The parasympathetic and sympathetic nerve fibers that form the *adrenal plexus* originate from the celiac plexus and the splanchnic nerves. Direct fibers from the sympathetic trunk can contribute to the formation of the adrenal plexus.

Major Vessels and Nerves of the Retroperitoneal Space

Abdominal Aorta.

The descending aorta enters the retroperitoneal space through the aortic aperture in the diaphragm (Fig. 1.8). The thoracic duct traverses the aperture behind the aorta, and the aorta is occasionally accompanied by a splanchnic nerve.

The aorta usually enters the abdominal cavity on the median plane but deviates toward the left side as it descends further, apposed to the upper four lumbar vertebrae and intervertebral discs. It ends at the level of the fourth lumbar vertebra by dividing into its terminal branches—the common iliac arteries and the median sacral artery.

The inferior vena cava ascends to the right and slightly in front of the aorta. The left lumbar veins course between the vertebral column and aorta in a space that also contains the postaortic lymph nodes. The abdominal aorta is covered anteriorly by the autonomic aortic plexus (celiac, superior

and inferior mesenteric) with corresponding ganglia and by the preaortic lymph nodes. Directly lateral to the aorta are the lateral aortic lymph nodes.

As the abdominal aorta descends, it passes behind the body of the pancreas, the left renal vein, and the horizontal (inferior) portion of the duodenum. Below the mesenteric root, the abdominal aorta is easily accessible to a transperitoneal surgical approach.

The branches of the abdominal aorta may be paired or unpaired, and the branches in both groups can be classified as visceral or parietal.

The unpaired visceral branches are as follows:

1. The celiac trunk, arising within the aortic aperture at the level of the twelfth thoracic vertebra
2. The superior mesenteric artery, arising at the level of the first lumbar vertebra
3. The inferior mesenteric artery, arising at the level of the third lumbar vertebra

The paired visceral branches are as follows:

1. The middle suprarenal arteries, arising at the level of the first lumbar vertebra
2. The renal arteries, usually arising at the same level from the aorta just below the suprarenal arteries
3. The testicular or ovarian arteries, arising at a variable level from the anterolateral aspect of the abdominal aorta and usually at different levels on the right and left sides

The unpaired parietal branch of the abdominal aorta is one of its terminal branches, the median sacral artery.

The paired parietal branches are as follows:

1. The inferior phrenic arteries, arising in the aortic aperture as the first branch of the abdominal aorta
2. Four pairs of lumbar arteries, arising from the back of the aorta at the levels of the first through fourth lumbar vertebral bodies

Inferior Vena Cava.

The inferior vena cava (Fig. 1.8) is formed by the union of the two common iliac veins approximately one fingerwidth below and to the right of the aortic bifurcation. The lower part of the inferior vena cava is overlapped anteriorly by the right common iliac artery and relates posteriorly to the body of the fifth lumbar vertebra.

The inferior vena cava ascends on the right side of the aorta and parallel to it until reaching the level of the lower pole of the right kidney, where it diverges slightly to the right from the abdominal aorta and travels in a groove on the posterior surface of the liver. The inferior vena cava enters the thoracic cavity through the vena cava foramen in the diaphragm (at the level of Th 10) and immediately opens into the right atrium of the heart. It is accompanied through the diaphragm by the right phrenicoabdominal branch of the phrenic nerve.

The anterior surface of the inferior vena cava is covered in its lower portion by peritoneum (primary parietal peritoneum) up to the level of the mesenteric root. As it ascends, the inferior vena cava loses its peritoneal covering (secondary retroperitoneal structure) and is apposed to the duodenum and pancreas (Fig. 1.10). Ascending further in the posterior wall of the epiploic foramen, the vena cava is again covered with peritoneum and is adherent to the bare area of the liver in the groove for the inferior vena cava.

The inferior vena cava has both parietal and visceral tributaries. The parietal tributaries are as follows:

1. The common iliac veins
2. The median sacral vein, which follows the course of the homonymous artery and may empty into the left common iliac vein
3. The lumbar veins, whose arrangement corresponds to that of the homonymous arteries
4. The inferior phrenic veins, which enter the inferior vena cava just before it pierces the diaphragm

The visceral tributaries are as follows:

1. The right testicular or ovarian vein, which opens into the inferior vena cava just below the termination of the right renal vein
2. The renal veins (discussed in connection with the kidney)
3. The right suprarenal vein
4. The hepatic veins, usually three in number, which generally enter the inferior vena cava in their course through the hepatic groove for the inferior vena cava

Variations of the inferior vena cava are common and usually result from developmental anomalies (Fig. 1.19). The retroperitoneal venous system develops from three paired, longitudinally oriented parallel channels: the caudal cardinal vein, supracardinal vein, and subcardinal vein, which are continuous caudally with the sacrocardinal vein. Further differentiation of the venous system is characterized by a progressive asymmetry in favor of the right side, with anastomoses between the right and left cardinal veins assuming key importance.

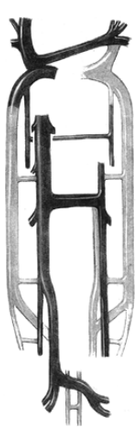

FIGURE 1.19. Development of the vena caval system. Vessels that do not persist are colored light gray.

The development of the vena caval system is shown in Fig. 1.19 . It can be seen that the caudal cardinal veins largely disappear, whereas the supracardinal veins persist in part as the azygos and hemiazygos veins. Simply stated, the subcardinal veins develop into the inferior vena cava on the right side and into the suprarenal and testicular or ovarian veins on the left side.

Embryonic development of the inferior vena cava may be disrupted, arrested, or misdirected at any stage by extrinsic or intrinsic factors that are not yet fully understood. Each primarily formed cardinal vein (except for the lower portion of the caudal cardinal vein) may persist wholly or in part during definitive development, giving rise to such variants as

a *double inferior vena cava* (2.2%) or *left inferior vena cava* (0.2%). All abnormal configurations of the inferior vena caval system are based on the persistence or anomalous involution of embryonic vascular channels.

Lymph Vessels.

The *lymph vessels* and regional lymph nodes of the retroperitoneal space are discussed earlier in this chapter in connection with specific organs. The *thoracic duct* and its tributaries are discussed here.

The thoracic duct begins at the upper end of the cisterna chyli in the retroperitoneal space. The cisterna receives the lumbar and intestinal lymphatic trunks and is situated in front of the first and second lumbar vertebral bodies, behind and to the right of the abdominal aorta. The normally positioned cisterna chyli is found between the aorta and inferior vena cava, just below the left renal vein. After a short intraabdominal course, the thoracic duct enters the thorax through the aortic aperture, passing behind the aorta, and ascends through the posterior mediastinum.

Nerves.

The large *nerve trunks* in the retroperitoneal space are derived mainly from the abdominal portion of the autonomic nervous system.

The anterior and posterior vagal nerve trunks enter the abdominal cavity through the esophageal aperture of the diaphragm. Only the posterior vagal trunk reaches the retroperitoneal space primarily, the bulk of its fibers passing between the left adrenal gland and the left medial crus of the diaphragm to the celiac ganglion.

Two nerves belonging to the sympathetic nervous system, the greater and lesser splanchnic, enter the retroperitoneal space through an aperture in the medial crus of the diaphragm. The greater splanchnic nerve runs between the medial crus of the diaphragm and the adrenal gland to the celiac ganglion. The fibers of the lesser splanchnic nerve terminate partly in the ganglion and may have direct connections with the renal plexus.

The two sympathetic trunks enter the retroperitoneal space after passing between the medial and lateral crura of the diaphragm. Both trunks lie on the psoas major muscles near their origin from the vertebral bodies. The left sympathetic trunk lies slightly behind and to the left of the abdominal aorta, and the right sympathetic trunk is posterior to the inferior vena cava. Connections between the right and left sympathetic trunks are generally present and course between the lumbar vertebral bodies and the aorta or inferior vena cava (Fig. 1.20).

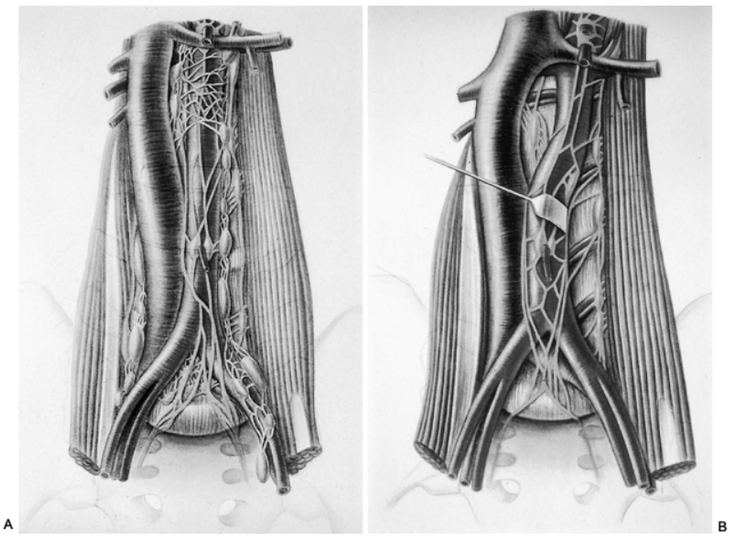

FIGURE 1.20. A: Right sympathetic trunk is situated dorsal to inferior vena caval vein, while left trunk is dorsal and lateral to abdominal aorta. **B:** L-3 ganglion is seen clearly on the left side because abdominal aorta is retracted medially.

The sympathetic trunks and their ganglia send branches (the lumbar splanchnic nerves) to the preaortic plexuses and their ganglia. The lumbar portion of the sympathetic trunk blends smoothly with the sacral portion at the arcuate line.

Application of Surgical Approaches

Supracostal Approach

The supracostal approach affords broad exposure of the retroperitoneal space (kidney, adrenal gland, proximal ureter) while avoiding the need for rib resection. Several anatomic circumstances make this approach possible: The eleventh and twelfth ribs terminate freely in abdominal muscle, both ribs articulate only with the corresponding vertebral body, and the twelfth rib is easily displaced downward following release of the muscles that insert on the twelfth rib or arise from it.

Exposure of the Lumbodorsal Fascia

After division of the subcutaneous fat, the thoracic fascia is divided, exposing the latissimus dorsi and external oblique muscles (Fig. 1.21).

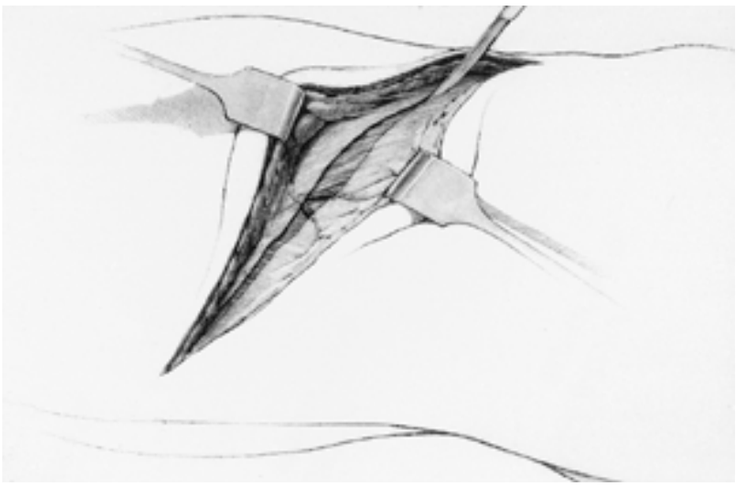

FIGURE 1.21. Exposure of the latissimus dorsi and external oblique muscles.

Incision of the Lumbodorsal Fascia

The lumbodorsal fascia is incised at the tip of the twelfth rib, exposing the pararenal fat between the lumbodorsal fascia and Gerota's fascia. The lumbodorsal fascia can be opened over the fat by bluntly dissecting forward (Fig. 1.22).

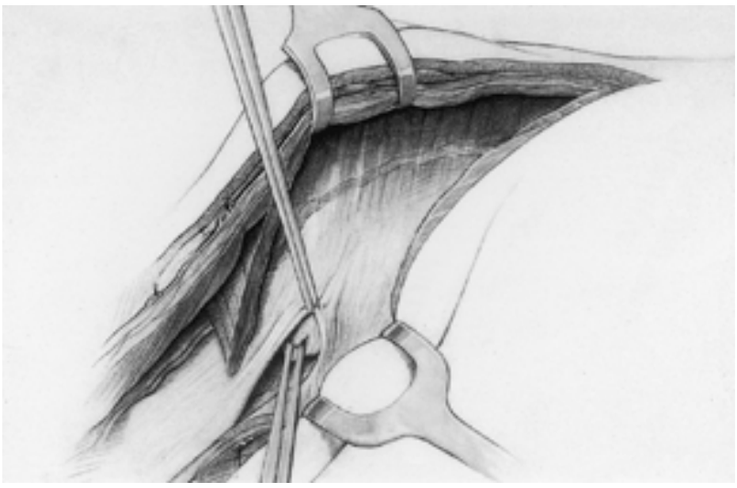

FIGURE 1.22. Incision of the lumbodorsal fascia.

As the twelfth rib is displaced downward and forward with a retractor, the lumbodorsal fascia is dissected from the inner periosteum of the rib (Fig. 1.23). This affords extrapleural entry to the thoracic cavity while sparing the intercostal nerves and vessels. The route of this approach is shown schematically in Fig. 1.24 .

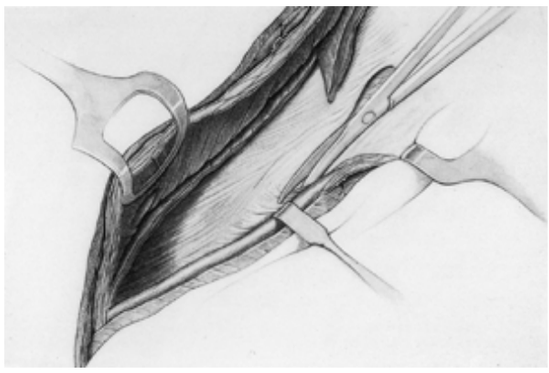

FIGURE 1.23. The thoracic cavity is opened extrapleurally, preserving the intercostal vessels and nerves.

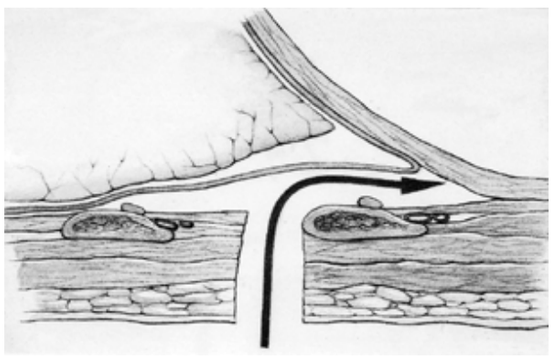

FIGURE 1.24. Schematic view of the dissection of the lumbodorsal fascia from the deep periosteum of the rib.

Dissection of the Lumbodorsal Fascia and Diaphragm from the Twelfth Rib

The lumbodorsal fascia and then the diaphragm are separated from the twelfth rib under vision, using the finger or a small sponge stick to guide the dissection. The incision at the twelfth rib can be carried over the quadratus lumborum muscle to the lateral arcuate ligament as part of the dissection, with the pleural cavity and lung remaining outside the operative field (Fig. 1.25).

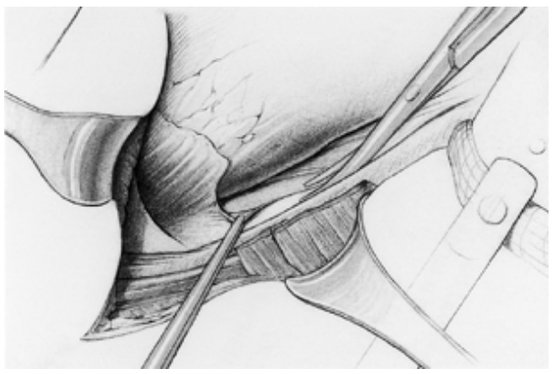

FIGURE 1.25. The pleural space and lung are outside the operative field. The quadratus lumborum muscle is visible below the lateral arcuate ligament.

Foley Muscle-splitting Approach

The Foley muscle-splitting approach gives access to the ureteropelvic junction and proximal ureter through a transfascial route.

Exposure of the Transversus Abdominis and Its Tendon of Origin

The latissimus dorsi and external oblique muscles are retracted, and a retractor is placed in the proximal part of the incision to expose the tendon of origin of the transversus abdominis and, anteriorly, the fibers of the internal oblique muscle (Fig. 1.26). The internal oblique is separated from the transversus abdominis along the line indicated and is

retracted forward with a second retractor. The tendon of origin of the transversus abdominis is incised in the direction of its fibers (Fig. 1.27).

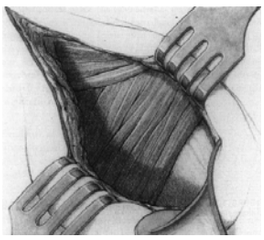

FIGURE 1.26. The internal oblique is separated from the transversus abdominis and its tendon of origin.

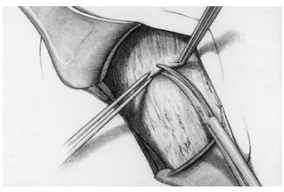

FIGURE 1.27. The transversus abdominis tendon of origin is incised, and the transversus muscle fibers are split.

Posterior Approach to the Adrenal Gland

The thoracic fascia is exposed. The latissimus dorsi and serratus anterior muscles are identified. Exposure is maintained with two retractors. The latissimus dorsi and serratus anterior are transected with a scalpel. The erector spinae muscle can be seen in the medial portion of the wound (Fig. 1.28).

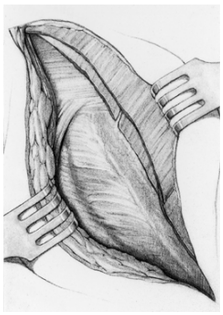

FIGURE 1.28. Exposure of the eleventh rib. The transected muscles are retracted.

The periosteum of the eleventh rib is divided with diathermy, and the rib is progressively isolated with a straight periosteal elevator and a curved stripper. The eleventh rib is resected as far medially as possible (Fig. 1.29).

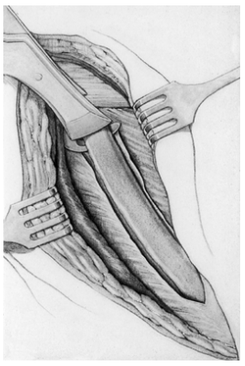

FIGURE 1.29. The eleventh rib is transected with rib shears.

Incision of the Rib Bed

The posterior rib bed is opened with a scissors, exposing the diaphragm. Care is taken to preserve the intercostal neurovascular bundle during incision of the rib bed.

With the aid of a wooden tissue protector or small sponge stick, the diaphragm is carefully divided with diathermy. The plane between the diaphragm and Gerota's fascia is carefully developed, and the diaphragm is incised anteriorly and posteriorly to establish entry into the retroperitoneal space. Gerota's fascia is identified (Fig. 1.30).

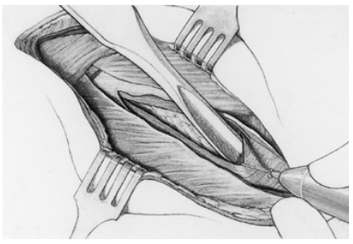

FIGURE 1.30. The diaphragm is divided with diathermy over a wooden tissue protector. Gerota's fascia is identified.

Thoracoabdominal Approach

The thoracoabdominal approach provides excellent exposure of the entire abdominal and retroperitoneal space. Because the intrathoracic portion of the inferior vena cava can also be exposed, this approach is useful for the removal of stage II and stage III tumor thrombi involving the vena

cava. A modification, the primary thoracoretroperitoneal approach, is useful for lymph node dissection in patients with testicular tumors.

Laparotomy and Thoracotomy

Starting at the anterior axillary line, the latissimus dorsi, serratus anterior, and external oblique muscles are transected with diathermy in line with the skin incision. The external and intercostal muscles are visible on the chest wall. Starting at the costal arch, the incision is first extended inferomedially, dividing the fibers of the rectus muscle in the epigastrium. The rectus abdominis is then bluntly freed laterally while sparing the nerves and vessels; this technique prevents denervation of the rectus musculature. The superior epigastric vessels are ligated. The rectus muscle is retracted laterally to expose the posterior layer of the rectus sheath. Small retractors maintain exposure in both the abdominal and thoracic portions of the field (Fig. 1.31).

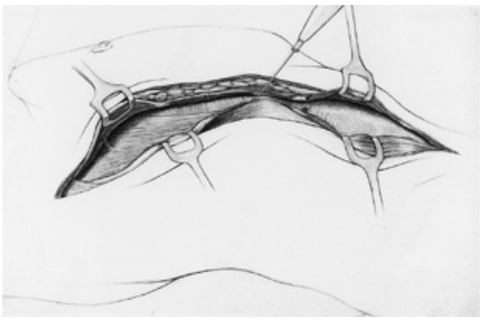

FIGURE 1.31. The serratus anterior and external oblique are transected, exposing the posterior rectus sheath.

In the abdominal part of the incision, the posterior rectus sheath is picked up with forceps on both sides along with the transversus abdominis fibers and peritoneum, and all three layers are transected to establish entry into the peritoneal cavity. The greater omentum can be identified. The abdominal cavity is opened to the level of the umbilicus (Fig. 1.32).

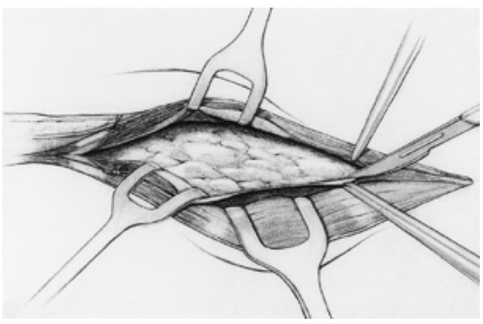

FIGURE 1.32. Entry into the abdominal cavity.

Division of the Costal Arch.

Before the costal arch is divided, the plane defined by the transversus abdominis and diaphragm is exposed. Once this plane has been identified, the costal arch is undermined at the osteochondral junction and divided. With this maneuver, the underlying intercostal arteries and veins can be dealt with under direct vision.

This dissection of the transversus abdominis and diaphragm is important in the primary thoracoretroperitoneal approach. In this modification, which avoids primary entry into the abdominal cavity, the approach is begun inferomedial to the costal arch and the peritoneum is retracted medially (Fig. 1.33).

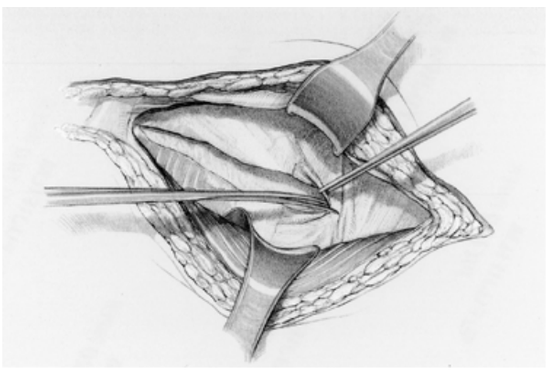

FIGURE 1.33. Primary thoracoretroperitoneal approach.

Division of the Diaphragm.

The transversus abdominis fibers are divided close to the costal arch, followed by incision of the diaphragm. The diaphragm is incised as far laterally as possible to preserve the phrenic nerve branches (Fig. 1.34).

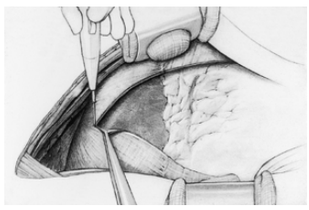

FIGURE 1.34. Division of the diaphragm.

Modification of the Thoracoabdominal Approach for a Stage II or III Tumor Thrombus in the Vena Cava.

After the abdominal cavity and chest have been opened, the incision in the mesocolon is carried along the colon and is continued along the mesentery to the duodenojejunal flexure. This line of incision permits a general mobilization of the large and small bowels, establishing access to a broad area of the retroperitoneal space. The left renal vein can be identified over the aorta and elevated to expose the superior mesenteric artery. The right renal artery is identified in the aortocaval space.

The peritoneum is dissected off the diaphragm. The right triangular ligament is incised at its attachment to the diaphragm so that the right lobe of the liver can be mobilized and deflected medially upward, exposing the hepatic veins. In this way, the entire retroperitoneal course of the vena cava can be visualized (Fig. 1.35) together with the right adrenal gland and suprarenal vein.

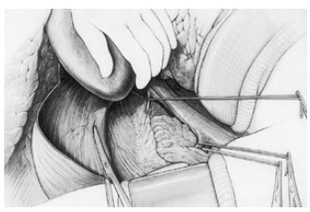

FIGURE 1.35. The right triangular ligament is sharply released from the diaphragm. The right adrenal gland and suprarenal vein are seen.

Use of the fifth interspace approach also permits exposure of the intrathoracic portion of the inferior vena cava. The parietal layer of the pericardium is incised above the diaphragm. After stay sutures are preplaced on both sides, the intrathoracic part of the vena cava can be freed and encircled with a tourniquet snare (Fig. 1.36).

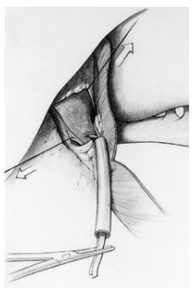

FIGURE 1.36. Exposure of the intrathoracic portion of the inferior vena cava.

Approach to the Retrocrural Lymph Nodes

Most positive suprahilar nodes are found in the retrocrural zone. The usual path of lymph flow from the retroperitoneum into the chest is periaortic and posterior (Fig 1.37 and Fig. 1.38). The lymphatic pathways traverse the diaphragm via the aortic hiatus. They first drain into the cisterna chyli and then into the posterior mediastinal nodes.

FIGURE 1.37. Path of lymph flow to the suprahilar region and the chest.

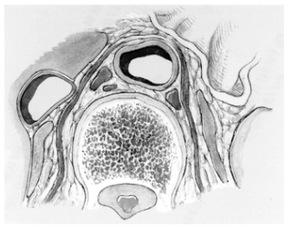

FIGURE 1.38. Transverse section. Location of retrocrural nodes in relation to the diaphragm and the aorta (schema).

The thoracic duct begins at the upper end of the cisterna chyli in the retroperitoneal space. The cisterna receives the lumbar and intestinal lymphatic trunks and is situated in front of the first and second lumbar vertebral bodies, behind and to the right of the abdominal aorta.

Dissection of the Lateral Crus, Exposure of the Inferior Phrenic Artery

The descending colon is retracted medially with the isolated left colic flexure. The left inferior phrenic artery and vein are

identified at the lateral crus, dissected, and ligated (Fig. 1.39). A middle suprarenal artery from the aorta is also ligated, and the adrenal gland is then freed from the lumbar part of the diaphragm and lateral crus and displaced inferolaterally (Fig. 1.40).

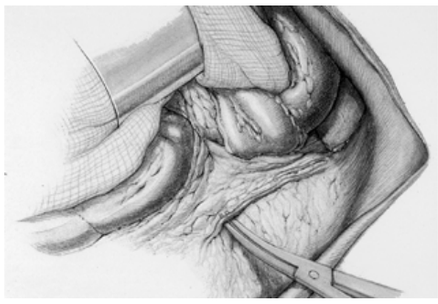

FIGURE 1.39. Exposure of the left inferior phrenic artery and vein.

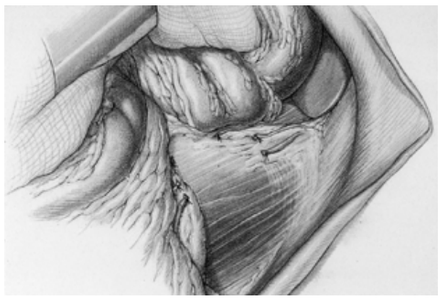

FIGURE 1.40. The left inferior phrenic artery and vein are ligated, and the lumbar part of the diaphragm is exposed.

Incision of the Aortic Aperture

After exposure of the abdominal aorta, the left renal artery is identified and dissected free. After ligation of the inferior phrenic artery, the aortic aperture is incised over the abdominal aorta, starting at the median arcuate ligament. If enlarged lymph nodes are found at the celiac trunk and superior mesenteric artery, both vessels must be dissected free (Fig. 1.41). The incision in the aortic aperture is carried to the esophageal hiatus. The inferior phrenic artery is again ligated close to the aorta (Fig. 1.42).

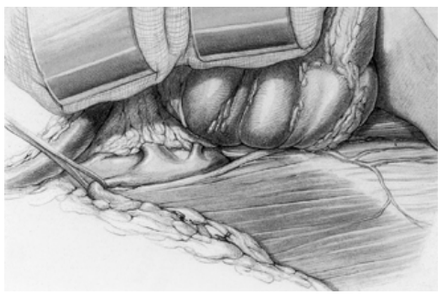

FIGURE 1.41. Dissection of the aorta and renal artery. The line of incision from the aortic hiatus to the esophagus is shown.

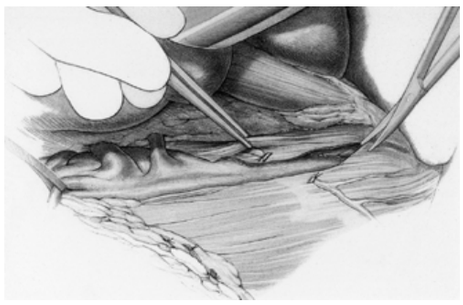

FIGURE 1.42. Incision over the abdominal aorta.

This approach provides exposure of the retroaortic space (Fig. 1.43). When the aorta is mobilized, attention must be given to the last two posterior intercostal arteries and first lumbar arteries at the lateral or posterior aspect of the vessel. These arteries may give origin to the great radicular artery (of Adamkiewicz), which contributes significantly to the blood supply of the spinal cord. Therefore segmental arteries must be preserved, especially on the left side of the body.

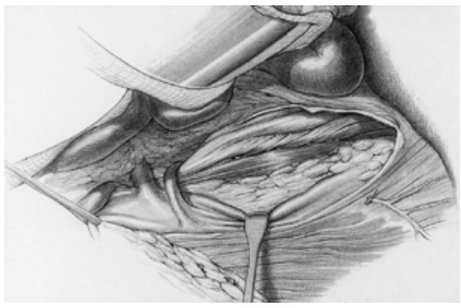

FIGURE 1.43. Exposure of the retroaortic and retrocrural spaces.

Anterior Subcostal Approach

Dissection of the Renal Vessels

For dissection of the renal vessels on the left side, the peritoneum is incised longitudinally between the aorta and inferior mesenteric vein, starting at the inferior duodenal fold (ligament of Treitz) (Fig. 1.44). This incision gives direct access to the vascular pedicle of the left kidney between the aorta and inferior mesenteric vein. The renal artery and vein can be dissected and snared (Fig. 1.45).

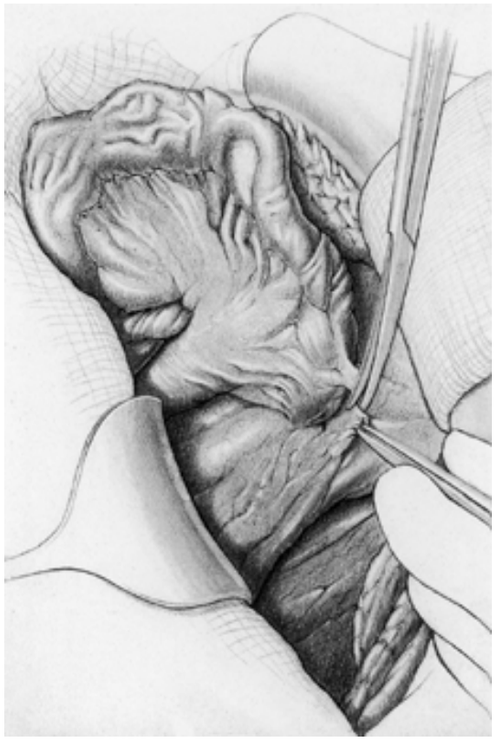

FIGURE 1.44. Incision of the inferior duodenal fold. The vascular pedicle of the kidney is approached between the aorta and inferior mesenteric vein.

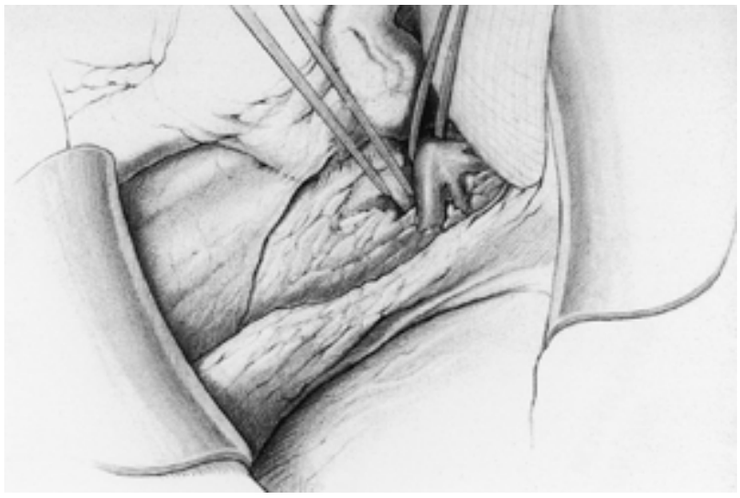

FIGURE 1.45. Exposure and isolation of the renal artery and vein.

Midline Transperitoneal Approach

Exposure of the Retroperitoneal Space

Starting at the inferior duodenojejunal fold, the retroperitoneal space is opened by incising distally along the root of the mesentery while the small bowel is packed away to the right side and the descending colon and left colic flexure are retracted to the left side (Fig. 1.46).

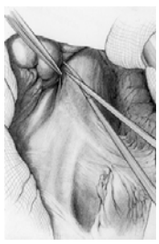

FIGURE 1.46. The retroperitoneal space is opened along the root of the mesentery, starting at the inferior duodenojejunal fold.

Next, the ascending part of the duodenum is dissected free along the line of the incision. For a suprahilar approach on the left side, the incision in the parietal peritoneum is extended farther upward and to the left so that the inferior mesenteric vein can be dissected and ligated (Fig. 1.47). This establishes broad access for the suprahilar lymph node dissection.

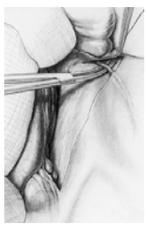

FIGURE 1.47. Left suprahilar approach. The inferior mesenteric vein is exposed and ligated.

The line of incision is now extended farther toward the right common iliac artery from the abdominal aorta so that the cecum can be dissected from the underlying retroperitoneal connective tissue (Fig. 1.48).

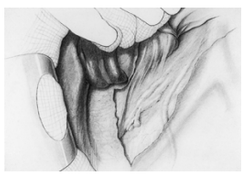

FIGURE 1.48. The incision is extended from the abdominal aorta over the right common iliac artery.

The incision is extended along the right paracolic sulcus and ended at the inferior border of the epiploic foramen (of Winslow) (Fig. 1.49). This provides access for dissecting the ascending colon and right colic flexure from Gerota's fascia.

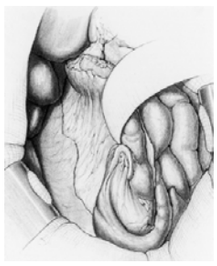

FIGURE 1.49. The incision in the right paracolic sulcus is extended to the inferior border of the epiploic foramen.

This extended incision (from the inferior duodenojejunal fold to the epiploic foramen) permits the entire small bowel, cecum, ascending colon, and right colic flexure to be mobilized (and if necessary exteriorized from the abdominal cavity). The abdominal aorta and inferior vena cava are visible below fibrous and fatty tissues, respectively, at the center of the retroperitoneal space (Fig. 1.50).

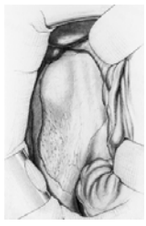

FIGURE 1.50. View of the incision from the ligament of Treitz to the inferior border of the epiploic foramen. The entire retroperitoneal space is visible.

Incision of the Retroperitoneal Fascia

The fibrous and fatty tissue overlying the center of the vena cava and abdominal aorta is now opened, and the lymph node dissection is carried out using a split-and-roll technique (Fig. 1.51).

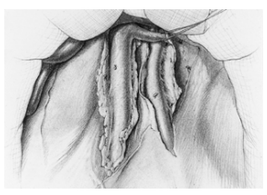

FIGURE 1.51. Split-and-roll technique of retroperitoneal lymph node dissection.

Nerve-sparing Retroperitoneal Lymph Node Dissection

Seminal emission and ejaculation are primarily under sympathetic control. The efferent fibers originating from T-12 to L-3 travel to the superior and on to the inferior hypogastric plexus (or pelvic plexus). The pelvic plexus also includes parasympathetic fibers originating from the pelvic nerves.

The sympathetic trunk consists of a series of spindle-shaped ganglia interconnected by short interganglionic rami to form a continuous chain of ganglia (Fig. 1.20). This trunk extends along the spinal column on either side from the base of the skull to the tip of the coccyx. It is connected to the spinal cord via the rami communicantes, which may behave in a number of different manners. Often, there are branches that course not only to the corresponding ganglia of the sympathetic trunk but also to the adjoining ganglia. In the lumbar region, where the rami communicantes are relatively long, their course is particularly variable. They pass beyond the tendinous origins of the psoas major, and a variable number of ganglia can be found at different levels at the anterolateral aspects of the vertebral bodies medial to the psoas major. The right sympathetic trunk is situated dorsal to the inferior vena cava, and the left trunk is located dorsal and lateral to the abdominal aorta. The transverse rami connect the two sympathetic trunks. Only rarely are the two trunks arranged symmetrically in the lumbar region. Furthermore, fusions of ganglia occasionally are encountered. The lumbar splanchnic nerves are the continuation of postganglionic fibers of the lumbar ganglia. They travel to the large paraaortic nervous plexus and eventually reach the superior hypogastric plexus, a continuation of the abdominal aortic plexus, located on either side of the abdominal aorta between the origins of the superior and inferior mesenteric arteries.

The superior hypogastric plexus is situated ventral to the aortic bifurcation and extends across the common iliac vein

in the direction of the promontory (Fig. 1.20). The right and left hypogastric nerves connect the superior hypogastric plexus with the inferior hypogastric plexus, which is on either side of the rectum in the lesser pelvis.

The afferent impulses triggering emission and ejaculation are conveyed via the pudendal nerve, whereas the efferent impulses inducing emission are transported to the target organs via the thoracolumbar sympathetic fibers (T-12 to L-3), the paravertebral ganglia, and the superior hypogastric plexus. The efferent impulses inducing ejaculation are conveyed via the parasympathetic fibers of the pelvic nerves (S-2 to S-3) and cause the bulbocavernous and ischiocavernous muscles to contract, which results in antegrade ejaculation.

The L-2 and L-3 ganglia are located close to each other; they may even fuse so that there is no interganglionic ramus. The lower margin of the L-3 ganglion is situated approximately one fingerwidth above the origin of the inferior mesenteric artery. If the abdominal aorta is displaced toward the median, the left L-3 ganglion is exposed medial to the psoas major on the lateral aspect of the L-3 vertebra. The right L-3 ganglion can be exposed by displacing the inferior vena cava toward the median (Fig. 1.20). The ganglion is located slightly ventral to the ventrolateral junction of the L-3 vertebral body. As mentioned, the two trunks are interconnected by the lumbar splanchnic nerves that arise from these ganglia.

Nerve-sparing Surgery

The aim of nerve-sparing surgery is to protect the sympathetic ganglia lying in the groove between the psoas muscle and the vertebral column. The sympathetic nerve fibers crossing over the distal aorta and its bifurcation must also be preserved (Fig. 1.52).

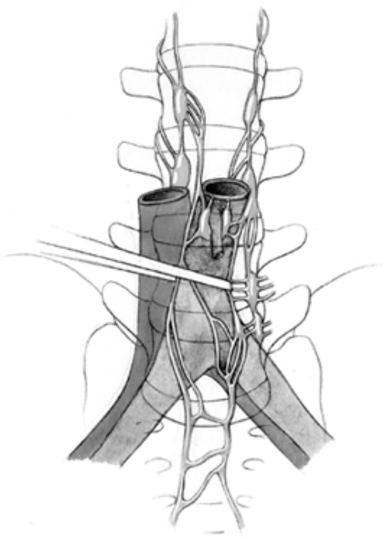

FIGURE 1.52. Nerve-sparing retroperitoneal dissection. Schematic drawing showing the sympathetic trunk, ganglia, and nerve fibers.

The sympathetic fibers can be identified with the help of magnifying lenses; the efferent fibers can be seen distally where they cross the common iliac artery. By reflecting the lymphatic tissue off the psoas muscle, the surgeon can identify the sympathetic trunk and trace the fibers distally from their origin at the sympathetic trunk. The sympathetic fibers are placed in vessel loops (Fig. 1.53). Subsequently, the lymphatic tissue is split over the aorta and rolled off.

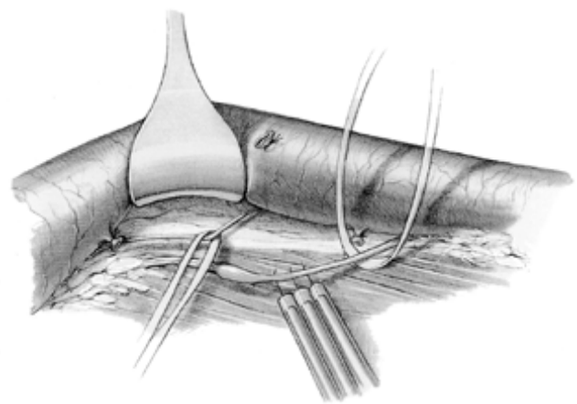

FIGURE 1.53. The nerve fibers to be spared are placed in vessel loops. Using an electric stimulator, ejaculation can be elicited intraoperatively.

The nerve-sparing technique can also be used in postchemotherapy surgery; however, in this type of elective surgery, patient selection is extremely important.

Suprahilar Node Dissection for High-stage Disease (Testicular Tumors)

Direct extension from an infrahilar tumor may project into the suprahilar zone; in this case, it is usually precrural and can be rolled down and away from the great vessels in the same way as tumors in the infrahilar region. Suprahilar disease can be managed by an anterior midline approach; the thoracoabdominal (thoracoretroperitoneal) approach should be used for tumors in the retrocrural zone.

In the anterior midline approach, the root of the small bowel mesentery is incised. The posterior attachments to the cecum and the mesocolon are dissected free using the plane of Toldt as an avascular field of dissection. After dissection of the duodenum and the head of the pancreas, the Kocher maneuver is performed.

On the right side, access to the suprahilar nodes is gained by an incision below the hepatoduodenal ligament, which is dissected free and placed in a vessel loop to expose the suprahilar portion of the vena cava (Fig. 1.54).

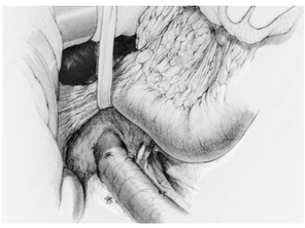

FIGURE 1.54. Exposure of the right suprahilar region; the hepatoduodenal ligament is placed in a vessel loop.

To gain access to the left suprahilar region, the left inferior mesenteric vein is ligated and divided, and the left colonic mesentery is incised and mobilized. The incision in the left mesocolon is made in an oblique manner, parallel to the inferior margin of the pancreas. After this maneuver, the lower vein of the pancreas can be fully mobilized and retracted from the anterior surface of Gerota's fascia (Fig. 1.55).

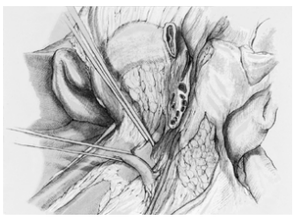

FIGURE 1.55. Anatomic approach to the suprahilar lymph node dissection, view from the right side.

The superior mesenteric artery is identified at the point where it crosses over the left renal vein (Fig. 1.55). Care must be taken to prevent excessive tension on this artery and to preclude injury to it by a retractor because it serves as a vascular pedicle for the small and large bowels. Therefore pads are placed on the pancreas and the pedicle of the superior mesenteric artery.

Dissection of the crura is started at the base of this pedicle and, on completion of the infrahilar node dissection, should be continued to the suprahilar region. The lymphatic connections between the infrahilar and suprahilar regions can be identified by elevating the renal vessels with malleable vein retractors.

PELVIS

Part of "1 - SURGICAL ANATOMY OF THE GENITOURINARY SYSTEM "

Anatomy

Pelvic Part of the Ureter

The pelvic (distal) part of the ureter makes up approximately half of its total length. It follows basically the same course in males and females, but its relations are gender specific (Fig 1.56 and Fig. 1.57). The entrance of the ureter into the true pelvis is located anterior or slightly medial to the sacroiliac joint. There the ureter is related to the iliac vessels, crossing either the common iliac vessels or the external and internal iliac vessels, depending on the position of these vessels and the level of their bifurcation. Because of the left-sided position of the abdominal aorta, the right ureter typically crosses the iliac vessels below their point of bifurcation; the left ureter generally crosses the common iliac vessels (Fig 1.56 and Fig. 1.57).

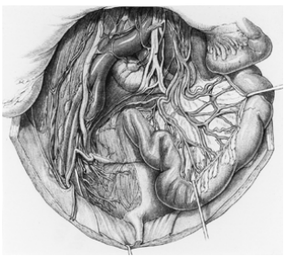

FIGURE 1.56. Pelvic dissection in a male. The peritoneum has been partially removed.

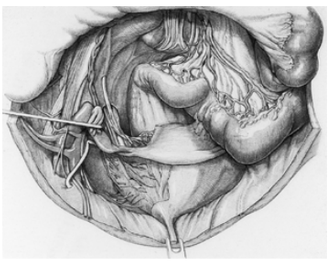

FIGURE 1.57. Pelvic dissection in a female. The peritoneum has been partially removed.

The first part of the pelvic portion of the ureter describes an anteriorly convex arch. It lies medial to the internal iliac artery and its branches, and it crosses the obturator nerve on the lateral pelvic wall just below the parietal peritoneum (Fig. 1.56). In the female, the ureter usually passes behind the ovary on the floor of the ovarian fossa (Fig. 1.57).

After crossing the pelvic vessels, the ureter diverges from the parietal peritoneum to enter the pararectal connective tissue (paraproctium). Just before or after this point, a sheet of connective tissue leaves the ureteral adventitia to establish a direct connection between the ureter and the rectal retinaculum.

After the ureter enters the pararectal connective tissue, its topographic relations display gender-specific differences.

In the male, the ureter passes through the pararectal connective tissue from behind forward, then turns slightly medially and closely approaches the tip of the seminal vesicle. There it crosses below the vas deferens. Surrounded by the veins of the vesical plexus, the ureter reaches and passes medially and obliquely through the bladder wall.

In the female, the ureter describes an inferiorly convex bend as it passes from the rectal retinaculum into the cardinal ligament (lateral cervical ligament). There it passes behind the uterine artery, which consistently gives off branches to the ureteral adventitia in this area. These branches travel in a thin sheet of connective tissue that is incorrectly termed the ventral *mesoureter* (Fig. 1.57).

Generally, the ureter runs approximately 1.5 to 2 cm lateral to the uterine cervix, although this distance can vary from 1 to 4 cm if the uterus occupies a paramedian position.

In its further course to the bladder, the female ureter is related to the fornix and anterior wall of the vagina. The left ureter generally is more extensively apposed to the front of the vagina than the right ureter, so it is more vulnerable to trauma in vaginal operations. In all discussions of ureteral relations, it should be kept in mind that a distended bladder or rectum can cause displacement and even tortuosity of the ureters.

Vessels and Nerves of the Pelvic Ureter

The *arteries* of the pelvic part of the ureter form a plexus in the ureteral adventitia that, in the initial part of the pelvic ureter, is supplied by ureteral branches of the iliac vessels. These may arise from the common iliac artery or from the internal or external iliac artery. Ureteral branches from the iliolumbar and superior gluteal arteries are less commonly observed.

As the ureter descends further, its adventitial arterial plexus receives blood from the superior vesical artery, the artery of the vas deferens or uterine artery, the vaginal artery, and the inferior vesical artery. Branches from the middle rectal artery also may reach the connective-tissue sheath of the ureter (Fig 1.56 and Fig. 1.57).

The *veins* of the pelvic part of the ureter reach the veins accompanying the arteries either directly or by way of the venous plexuses of the pelvis (vesical, prostatic, uterine, and vaginal plexuses).

The *lymph vessels* of the pelvic ureter drain into the regional lymph nodes on the pelvic wall: the external iliac, internal iliac, interiliac, and common iliac nodes.

The *nerves* of the pelvic ureter form dense networks in the adventitia, muscular wall, and mucosal layer of the ureter. They originate from the pelvic plexus, which in turn receives sympathetic fibers via the lumbar and sacral splanchnic nerves and the hypogastric plexus. Parasympathetic fibers reach the pelvic plexus via the pelvic splanchnic nerves from the sacral cord (Fig. 1.58).

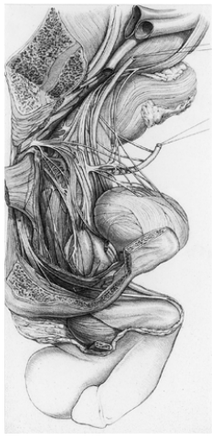

FIGURE 1.58. Nerves in a male pelvis, viewed from the right side: Portions of the coxa have been removed.

Relations of the Male Bladder to Adjacent Organs

The relations of the bladder to adjacent organs correlate closely with its relations to the pelvic connective tissue and peritoneum.

Peritoneal Covering of the Bladder

The bladder is attached to the peritoneum by loose connective tissue. This enables it to function as an expansile urinary reservoir that is mobile with respect to the peritoneum. Only a greatly distended bladder is fixed by its peritoneal covering (Fig. 1.59).

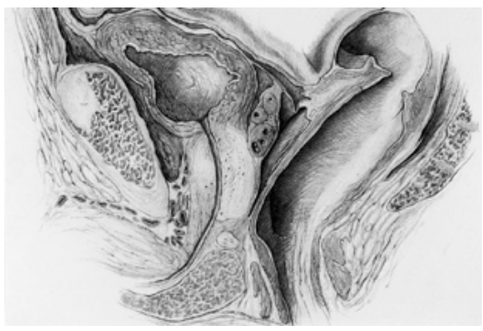

FIGURE 1.59. Midsagittal section through the pelvis.

The parietal peritoneum is continued from the anterior abdominal wall onto the bladder apex and covers the posterior surface of the bladder to the level of the tips of the seminal vesicles, sometimes extending to the level of the ureteral orifices. There the peritoneum is reflected onto the anterior wall of the rectum to form the rectovesical pouch, which is the lowest point of the peritoneal cavity. The entrance to the rectovesical pouch is bounded by the two sagittally oriented rectovesical folds. These peritoneal folds are backed with connective tissue that provides posterior support for the bladder base.

The peritoneum is recessed between the bladder and anterior abdominal wall to form the supravesical fossae

(Fig. 1.59). The right and left supravesical fossae are separated by the median umbilical fold. The supravesical fossa is bounded laterally by the medial umbilical fold. The peritoneal covering of the posterior bladder wall contains a reserve fold of peritoneum, the transverse vesical fold, which is progressively obliterated as the bladder distends.

Bladder and Pelvic Connective Tissue

The pelvic connective tissue consists of three main parts: the pelvic fascia (parietal and visceral), the neurovascular sheaths, and the loose connective tissue occupying the spaces of the pelvic viscera.

The *visceral pelvic fascia* is derived from the parietal pelvic fascia above the urogenital diaphragm at the site where the urethra pierces the diaphragm. The visceral fascia is reflected onto the prostate, and it invests the bladder as the vesical fascia.

The *neurovascular sheaths* are sheetlike condensations of intrapelvic connective tissue that invest and transmit nerves and blood vessels and that also perform retinacular functions. Portions distributed to the bladder and prostate assist in the fixation of the bladder base. The *puboprostatic ligament* (pubovesical ligament) extends from the symphysis and adjacent portions of the pubic bone to the prostate and continues onto the bladder neck. It binds the prostate and bladder to the anterior pelvic wall. The *paracystic connective tissue* (bladder retinaculum) passes to the bladder from the lateral pelvic wall. Between the paracystic connective tissue and *pararectal connective tissue* (rectal retinaculum) is the *rectovesical septum,* which represents the central portion of the lateral neurovascular sheath.

Loose connective tissue occupies the *spaces* between the condensations of the neurovascular sheaths and visceral fasciae. The *prevesical space* located between the anterior abdominal wall and bladder is bounded anteriorly by the transversalis fascia and posteriorly by the vesical fascia. The prevesical space is continuous inferiorly with the retropubic space. This space is bounded anteriorly by the posterior surface of the pubic symphysis, posteriorly by the prostatic fascia, and inferiorly by the urogenital diaphragm.

The rectovesical and retropubic spaces communicate laterally with the *paravesical space.* This mobile tissue plane is bounded posteriorly by the paracystic connective tissue, medially by the vesical fascia, and laterally and inferiorly by the parietal pelvic fascia.

Between the rectum and bladder is the *rectovesical space.* The rectovesical septum and the seminal vesicles subdivide this space into two separate compartments termed the *vesicogenital space* and the *rectogenital space* (Fig. 1.59,Fig. 1.60,Fig. 1.61 and Fig. 1.62).

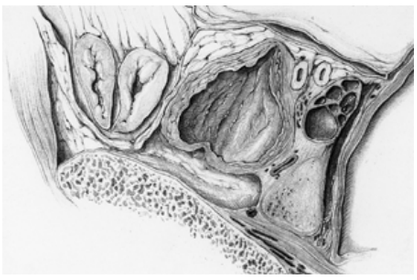

FIGURE 1.60. Paramedian section through the pelvis.

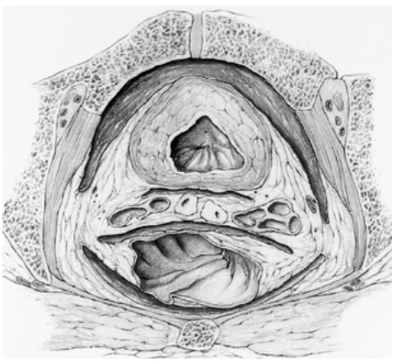

FIGURE 1.61. Transverse section through the pelvis at the level of the seminal vesicles.

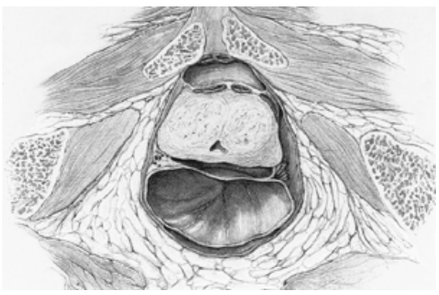

FIGURE 1.62. Transverse section through the pelvis at the level of the prostate.

Vessels and Nerves of the Bladder

The *arteries* of the bladder may arise directly from the internal iliac artery or from one of its visceral branches (Fig 1.56 and Fig. 1.58).

The superior vesical artery is almost always multiple. Usually, there are two superior vesical arteries, their number ranging from one to four. The superior vesical arteries generally arise from the patent, unobliterated portion of the umbilical artery but occasionally are derived from the obturator artery (4.5%). They supply the base and body of the bladder and generally anastomose with the inferior vesical artery.

The inferior vesical artery is usually a direct branch of the internal iliac but may arise from a nearby vessel such as the internal pudendal artery (25%) or inferior gluteal artery (4%). It supplies the bladder base in addition to the prostate and seminal vesicles.

The *veins* of the bladder commence as intramural plexuses. The larger vessels emerging from the bladder wall form the vesical plexus, which communicates with the venous plexus of the prostate. Both plexuses drain into the internal iliac vein.

The *lymph vessels* of the bladder communicate with one another in the paravesical space and may end directly at the external iliac and interiliac lymph nodes or may reach them by way of smaller nodes (anterior, lateral, and posterior vesical nodes). Connections with the internal iliac lymph nodes are occasionally observed.

The *nerves* supplying the bladder are derived from the pelvic plexuses (Fig. 1.59). The parasympathetic fibers (pelvic splanchnic nerves) of these plexuses originate from the second to fourth sacral segments and supply the detrusor muscle. The sympathetic fibers reach the vesical plexus from the first two lumbar segments by way of the hypogastric plexus.

Prostate

The prostate is enveloped by an external connective-tissue layer, the *prostatic capsule*, and by its visceral fascia, the *prostatic fascia.* The lateral portion of the prostatic fascia, the paraprostatic connective tissue, is well developed posteriorly to form Denonvilliers' fascia. Between the prostate and rectum is the *rectoprostatic space* (Fig 1.59 and Fig. 1.60).

The rectoprostatic space communicates superiorly with the *rectovesical space,* which is subdivided by the seminal vesicles and spermatic ducts into a *rectogenital space* and a *vesicogenital space* (Fig 1.61 and Fig. 1.62). The prostate is fixed to the symphysis anteriorly by the *puboprostatic ligaments,* and it is supported posteriorly by connective-tissue slips from the rectal retinaculum.

Relations of the Female Bladder to Adjacent Organs

The relations of the female bladder to the pelvic connective tissue are obviously gender specific. The parietal fascia of the pelvic floor is reflected onto the bladder at the bladder neck to form the vesical fascia.

The pubovesical ligaments in the female pelvis, derived from the intrapelvic neurovascular-retinacular sheaths, bind the bladder to the pubic symphysis.

The paracystic connective tissue passes from the lateral pelvic wall to the bladder. Tough connective-tissue fibers are distributed to this tissue from the cardinal ligament of the uterus.

The relation of the loose connective tissue to the female

bladder is the same anteriorly (prevesical space) and laterally (paravesical space) as in the male. Posteriorly, between the body of the bladder and the cervix, loose connective tissue occupies the *vesicouterine space.* The *vesicovaginal space* is located more caudally between the bladder base and the front of the vagina.

The relation of the female bladder to the pelvic connective tissue accounts in large part for its relations to adjacent organs.

The female urethra has two clinical subdivisions: a superior part and an inferior part. The superior part, comprising the cranial one-fourth of the urethra, can move relative to the vagina because of the loose connective tissue in the *urethrovaginal space.* The inferior part lacks a true space, and in that area, the vagina and urethra are fused together by their visceral fasciae. The anterosuperior portion of the female urethra is fixed by the lowermost fibers of the pubovesical ligaments, known also as the *pubourethral ligaments.*

Application of Surgical Approaches

Anterior Pelvic Exenteration in the Male: Approach to the Nerve-vessel-guiding Plates

Dissection of the Vesicoumbilical Plate

The urachus is isolated near the umbilicus and divided (Fig. 1.63). Entry into the peritoneal cavity at a more inferior level is established by dissecting the *vesicoumbilical plate* (medial umbilical fold, median umbilical fold, transversalis fascia, peritoneal fat, and peritoneum) downward *en bloc* to the lateral umbilical ligaments (Fig. 1.64).

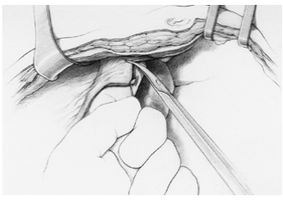

FIGURE 1.63. Dissection of the vesicoumbilical plate.

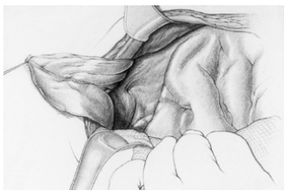

FIGURE 1.64. The freed vesicoumbilical plate is retracted inferiorly.

Dissection of the Lateral Bladder Pedicle (Lateral Bladder Retinaculum)

The right-handed surgeon places the fourth and fifth fingers of the left hand on the bladder and medial border of the lateral paracystic connective tissue with the third finger on the internal iliac artery. The index finger is swept medially behind the internal iliac artery into the depths of the pelvis. With this maneuver, the surgeon can displace the lateral retinaculum (lateral bladder pedicle) toward the bladder and the rectovesical septum (posterior bladder pedicle) toward the rectum. With the left index finger behind the lateral pedicle, the internal iliac artery is identified, followed by the anterior branches of the internal iliac artery, the lateral umbilical fold, the superior vesical artery, the inferior vesical artery, and the obturator artery. These vessels are individually isolated, identified, and ligated (Fig 1.65 and Fig. 1.66).

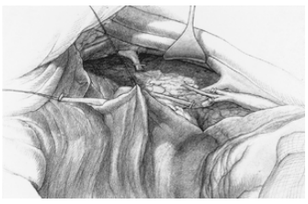

FIGURE 1.65. Dissection of the lateral bladder pedicle.

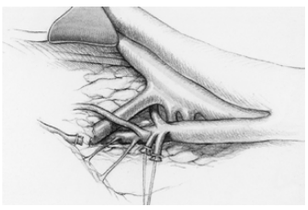

FIGURE 1.66. Close-up view of the dissection of the lateral bladder pedicle. The obturator artery, superior vesical artery, and inferior vesical artery are identified and clipped.

Variants of the Internal Iliac Artery

The branching pattern of the internal iliac artery is extremely variable. The most common variants of the parietal branches of the internal iliac artery are shown in Fig. 1.67 . The internal iliac artery usually divides at a variable level into an anterior and a posterior trunk. The origin of the obturator artery is largely independent of the primary bifurcation of the internal iliac artery.

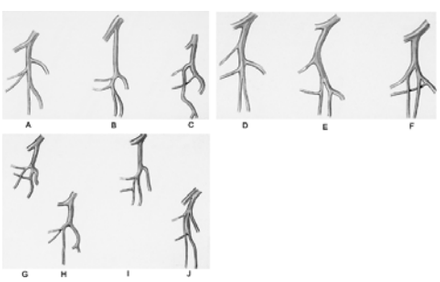

FIGURE 1.67. Variation in the branching pattern of the internal iliac artery. **A, D:** The superior gluteal artery leaves the pelvis through the suprapiriform foramen as the terminal branch of the posterior trunk of the internal iliac artery. The internal pudendal artery and inferior gluteal artery pass through the intrapiriform foramen as the terminal branches of the anterior trunk (49%). **B, C:** The anterior trunk does not divide unit it has passed through the intrapiriform foramen (10%). **E:** Both gluteal arteries and the internal pudendal artery arise by a common trunk (1.5%). **F, G:** The internal pudendal artery arises separately from the umbilical artery (0.5%). **G, H:** Both gluteal arteries form a common trunk that divides before (12%) or after (3.5%) leaving the true pelvis. **I, J:** The internal pudendal artery and the superior and inferior gluteal arteries arise separately in an irregular pattern (22.5%).

The *obturator artery* may arise from the anterior trunk of the internal iliac artery (Fig. 1.67A, Fig. 1.67B, and Fig. 1.67H ; 41.5%) or from the posterior trunk (Fig. 1.67C and Fig. 1.67F). It also may arise from a common trunk for the internal pudendal and inferior gluteal arteries (Fig. 1.67E and Fig. 1.67I). The obturator artery springs from the internal pudendal artery in approximately 4% of cases (Fig. 1.67G and Fig. 1.67J) and from the inferior gluteal artery in 5% (Fig. 1.67).

In 19% of cases, the obturator artery arises from the inferior epigastric artery and in 1% from the external iliac. The obturator artery is duplicated in approximately 5% of cases, one vessel arising from the external iliac artery and the other from the internal iliac artery or its branches.

The visceral branches of the internal iliac artery are also subject to considerable variation:

The *umbilical artery (patent section)* consistently gives rise to the superior vesical arteries and the artery of the vas deferens. Rarely, it gives off a middle rectal artery, the vaginal artery, or both.

The *inferior vesical artery* may arise directly from the internal iliac artery or one of its anterior branches. It generally anastomoses with the uterine artery (86%).

The *artery of the vas deferens* may be a direct branch of the internal iliac artery (rare) but usually arises from the umbilical artery. It is absent in 23% of cases and may give origin to a superior vesical artery.

The *middle rectal artery* is rarely absent and normally springs directly from the internal iliac. It also may arise from the vaginal artery or, very rarely, from the sacral arteries.

The *superior vesical arteries,* numbering from one to four, usually arise from the patent section of the umbilical artery but may branch from the uterine artery (9%), the artery of the vas deferens (9%), or the obturator artery (4.5%).

Anastomoses between the superior and inferior vesical arteries are generally present.

The *uterine artery* is usually a direct branch of the internal iliac but may arise conjointly with the vaginal or middle rectal artery. Duplication can occur. When necessary, the uterine artery can adequately assume the supply function of the vesical arteries.

Exposure of the Rectovesical Septum (Posterior Bladder Pedicle)

The neurovascular sheath transmits the arteries and veins of the seminal vesicles and prostate in addition to the pelvic splanchnic nerves. The space between the rectal fascia and Denonvilliers' fascia is developed. The posterior bladder pedicle is held between the second and third fingers as the second finger presses downward on the rectum, and the posterior pedicle is progressively ligated as far as the endopelvic parietal fascia. As traction is placed on the vas deferens and ureter to enlarge the space between the rectal fascia and Denonvilliers' fascia, individual portions of the posterior pedicle can be clipped or ligated under direct vision. The posterior pedicle is then progressively divided to the endopelvic parietal fascia (Fig. 1.68). The pelvic wall comes into view on the lateral side of these neurovascular bundles as they are progressively isolated and clipped or tied (Fig. 1.69).

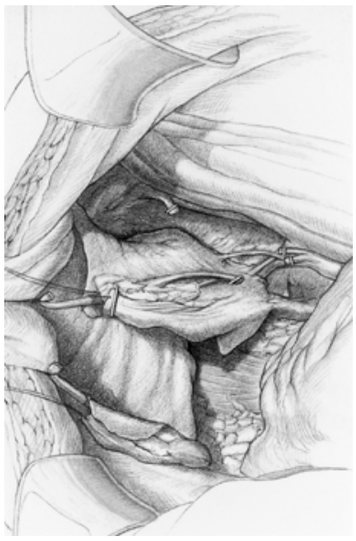

FIGURE 1.68. Exposure of the rectovesical septum (posterior bladder pedicle). The anterior branches of the internal iliac artery have been ligated, and the incision in the cul de sac has been completed. The right vas deferens and clipped ureter are retracted forward along with the freed lymph node package.

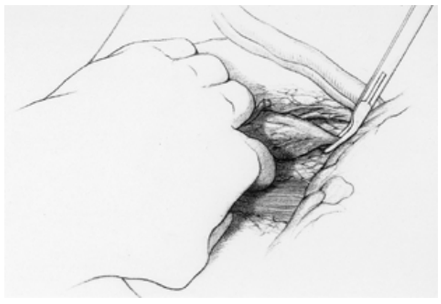

FIGURE 1.69. The posterior bladder pedicle is held between the second and third fingers while the second finger presses the rectum downward. The posterior pedicle is then progressively ligated.

Anterior Pelvic Exenteration in the Female

Exposure of the Posterior Bladder Pedicle

The peritoneum of the rectouterine pouch is incised from the pelvic wall aspect, and the specimen is retracted inferiorly by the vesicoumbilical plate and a uterine traction suture (Fig. 1.70). After division of the peritoneum over the rectum in the area of the rectouterine pouch, the posterior bladder pedicle, which includes the cardinal ligament in the female, is progressively ligated or clipped as far as the parietal pelvic fascia.

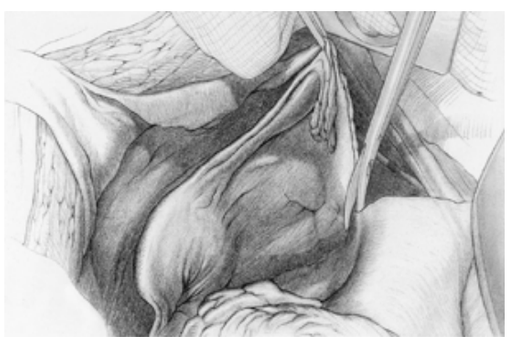

FIGURE 1.70. Line of incision in the peritoneum. Starting at the pelvic wall, the peritoneum is divided just over the rectum in the area of the rectouterine pouch.

Opening the Posterior Vaginal Wall

The posterior bladder pedicle is clipped or ligated approximately 3 to 4 cm past the cervix, and the posterior vaginal wall is opened (Fig. 1.71). Much as in an anterior exenteration in the male, the remaining posterior pedicle is encircled

(the second finger is in the vagina) and progressively ligated forward to the parietal pelvic fascia.

FIGURE 1.71. Exposure and division of the posterior bladder pedicle, which in the female includes the cardinal ligament. The posterior vaginal wall is opened 3 to 4 cm caudal to the cervix.

Continence Following Radical Prostatectomy and Orthotopic Reconstruction Following Female and Male Anterior Exenteration

Anatomy and Innervation of the Rhabdosphincter: Male

Macroscopic Anatomy.

The muscle fibers of the rhabdosphincter are arranged in a loop-shaped fashion on the ventral and lateral aspects of the membranous urethra (Fig. 1.72). On gross anatomic examination, comparatively strong smooth muscular and connective tissue can be noted dorsal to the membranous urethra (i.e., in the region of the perineal body). Both ends of the omega-shaped sphincter insert at the perineal body. The sphincter loop is continuous with muscle bundles that run along the anterior and lateral aspects of the prostate and extend cranially to the bladder neck. Thus, in the adult male, the rhabdosphincter of the urethra does not form a complete collar around the membranous urethra. It should rather be described as a muscular coat ventral and lateral to the membranous urethra and prostate, the core of which is the omega-shaped loop around the urethra. Furthermore, the rhabdosphincter is separated from the ventral portion of the levator ani muscle by a sheet of connective tissue.

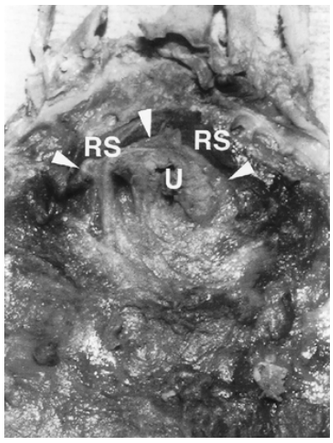

FIGURE 1.72. Anatomic specimen (adult rhabdosphincter, cranial view). RS, rhabdosphincter; U, urethra.

Histology.

The histologic findings in adult men confirm the data gained by gross anatomic examination (Fig. 1.73). The rhabdosphincter is a vertical muscular coat ventral and lateral to the prostate and membranous urethra extending from the bulb of the penis toward the region of the bladder neck. In all investigated specimens, striated muscle fibers corresponding to the deep transverse perineal muscle cannot be identified.

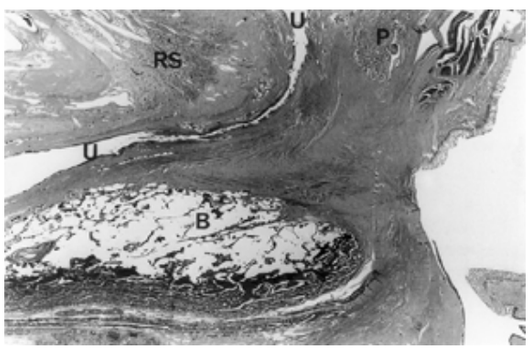

FIGURE 1.73. Histologic specimen (adult, sagittal section). B, bulb of penis; P, prostate; RS, rhabdosphincter; U, urethra.

Nerve Supply.

The pudendal nerve derives from the second, third, and fourth sacral spinal nerves. It takes a completely different course than the autonomic fibers of the pelvic plexus. The rhabdosphincter of the male urethra is supplied by fine branches of the pudendal nerve. These branches are given off lateral to the rhabdosphincter and

reach the muscle at its dorsolateral aspects; the mean distance from the membranous urethra to the point of entry of these fibers into the rhabdosphincter is 0.7 to 1.3 cm (Fig 1.74 and Fig. 1.75).

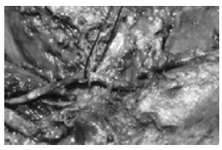

FIGURE 1.74. Anatomic specimen (adult, lateral view; the right hip bone has been completely removed).

FIGURE 1.75. Corresponding drawing to Fig. 1.74.

Anatomy and Innervation of the Rhabdosphincter: Female

On macroscopic examination, the sphincteric muscle is encountered on the ventral and lateral aspects of the urethra. Microscopically, this muscle corresponds to the omega-shaped rhabdosphincter in the male.

On histologic examination, in the cranial two-thirds of the urethra, three smooth muscle layers can be identified forming an outer and an inner longitudinal and a middle transverse layer. The inner longitudinal layer is delicate, thinning out toward the external meatus. The middle transverse layer is considerably thicker than the longitudinal layers (Fig. 1.76A, Fig. 1.76B and Fig. 1.76C). In serial transverse sections of the caudal urethra, there are abundant aspects, whereas dorsally there are mainly fibrous structures with only a few striated fibers. In transverse sections, the rhabdosphincter has an omega-like shape (Fig. 1.77).

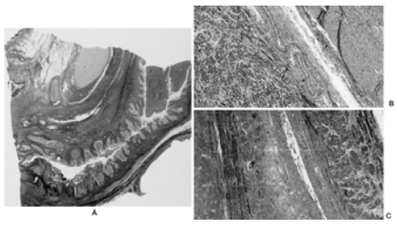

FIGURE 1.76. A: Median sagittal section of pelvic floor in fetal specimen. **B:** View of cranial two-thirds of female urethra: three layers of smooth muscle forming outer and inner longitudinal and middle transverse layers. **C:** In caudal third of the urethra, the rhabdosphincter is visible, with major portion in ventral and ventrolateral aspects of the urethra.

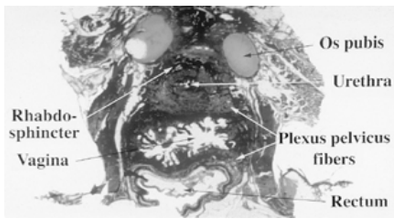

FIGURE 1.77. Transverse histologic section shows omega-shaped rhabdosphincter in caudal third of the urethra.

The autonomic fibers that supply the pelvic visceral organs emerge from the pelvic plexuses. They then course in a sagittal layer of connective tissue containing vessels and nerves (the vessel nerve plate) lateral to the rectum, in which they course to the ventral pelvic organs. The hypogastric and pelvic splanchnic nerves have been identified in this vessel nerve plate between the rectum and the pelvic wall. The cranial portion of the pelvic plexus is located close to the lateral margin of the rectouterine pouch; its ventral and caudal portions extend to the lateral aspect of the cervix (Fig. 1.78).

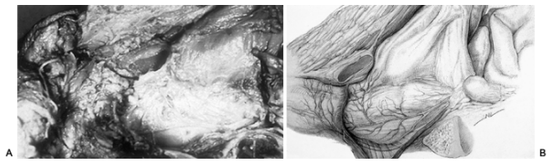

FIGURE 1.78. A: Lateral view of fetal specimen shows autonomic nerve supply to urethra relative to pelvic organs. **B:** Corresponding drawing to **A.**

The pudendal nerve courses alongside the internal pudendal vessels on the lateral aspects of the ischiorectal fossa inside the pudendal canal. The inferior rectal nerves, perineal nerves, and dorsal nerve of the clitoris branch off in the region of the pelvic floor. Arising from the terminal branch of the pudendal nerve, several thin branches run to the rhabdosphincter, which they enter on its lateral aspect (Fig. 1.79).

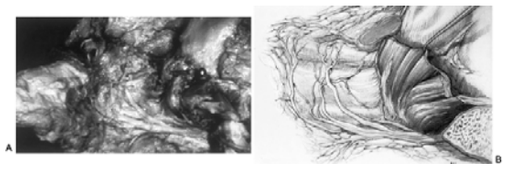

FIGURE 1.79. A: Several thin branches emerging from the pudendal nerve course to caudal third of urethra entering the rhabdosphincter at the lateral aspects. **B:** Corresponding drawing to **A.**

Radical Prostatectomy

Retropubic Versus Perineal Approach

The perineal approach, by preserving the paraprostatic tissue (lateral pelvic fascia), avoids injury to the dorsal vein complex. In a perineal prostatectomy, the prostate is removed within the paraprostatic tissue, whereas the retropubic prostatectomy removes the prostate together with all paraprostatic tissue. The retropubic approach involves incision of the paraprostatic tissue (lateral pelvic fascia) and division of the dorsal vein complex (arrow). Thus, in contrast to the perineal approach, the retropubic approach includes removal not just of Denonvilliers' fascia but also of the paraprostatic tissue (lateral pelvic fascia) (Fig. 1.80).

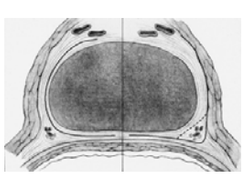

FIGURE 1.80. Approaches for perineal **(left)** and retropubic **(right)** prostatectomy. The significance of the paraprostatic tissue (lateral pelvic fascia) in each approach is shown (... = nerve-sparing approach for a retropubic radical prostatectomy).

Retropubic Radical Prostatectomy

Exposure and Division of the Striated Urethral Sphincter (Rhabdosphincter) and Membranous Urethra.

After division of the dorsal venous complex, the anterolateral aspects of the striated urethral sphincter (rhabdosphincter) can be identified. It forms an omega-shaped loop anterior and lateral to the membranous urethra, its two crura inserting into the central tendon of the perineum (Fig. 1.81). In anatomic dissections, after the prostate has been removed, the membranous urethra, the omega-shaped rhabdosphincter, and the central tendon can be seen on the inner aspect of the transverse perineal ligament. The deep dorsal penile vein, the dorsal penile artery, and the dorsal penile nerve course between the inner and outer fasciae of the transverse perineal ligament. The deep dorsal penile vein runs between the arcuate ligament and transverse

perineal ligament, and the dorsal penile artery and nerve run directly through the tissue of the transverse perineal ligament (Fig. 1.81).

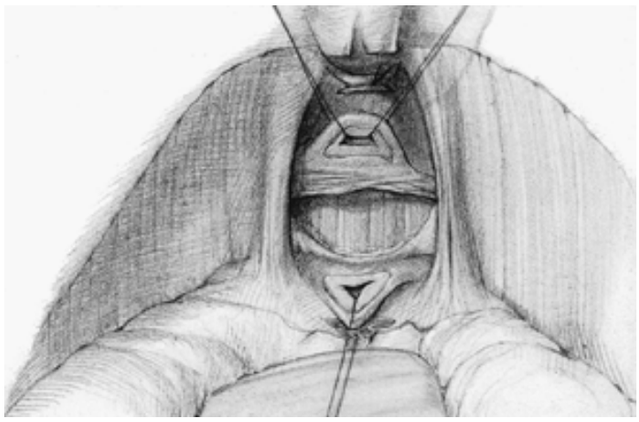

FIGURE 1.81. The rectourethral septum is incised, Denonvilliers' fascia is exposed, and the rectogenital space is entered. The rectal fascia is visible in the depths of the field.

Exposure of the Rectogenital Space.

The membranous urethra is divided on the line shown. The posterior prostatic fascia is divided at its attachment, the rectourethral septum (the apex of the wedge-shaped perineal body), and the rectogenital space is opened. The rectal fascia is identified at the posterior aspect of the rectogenital space.

Exposure of the Vesicogenital Space.

The prostate is now resected with the paraprostatic tissue between the rectogenital space and levator ani muscle. The seminal vesicles and the ampullae of the spermatic ducts are dissected from the bladder detrusor, following the course of the rectogenital space. The prostate is transected at the bladder neck and dissected out of the rectogenital space.

Modification: Nerve-sparing Radical Prostatectomy

In the modification of the nerve-sparing radical prostatectomy, the neurovascular bundle (base of the paraprostatic tissue) of the prostate is preserved. This bundle contains the cavernous nerves, fibers from the pelvic plexus to the membranous urethra, arterial branches to the prostate, the venous prostatic plexus, and prostatic lymph vessels (Fig. 1.82); to approach the neurovascular bundle, the paraprostatic tissue on the lateral surface of the prostate is incised and released. Located on the posterolateral aspect of the prostate, the neurovascular bundle is deeply embedded in the parietal layer of the fascia (paraprostatic tissue).

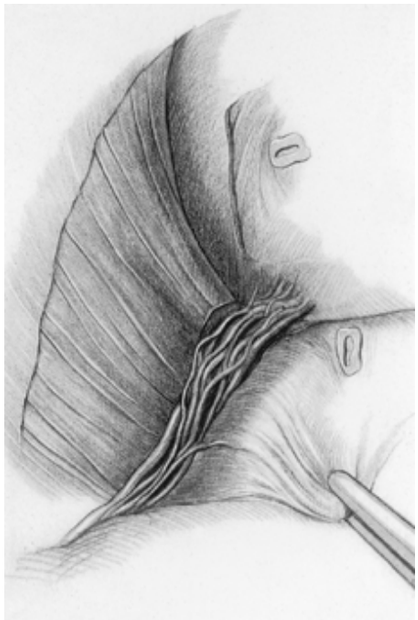

FIGURE 1.82. In this anatomic specimen, the left neurovascular bundle has been dissected out of the posterolateral portion of the paraprostatic tissue.

INGUINAL REGION

Anatomy

The inguinal canal obliquely traverses the abdominal wall in the medial portion of the inguinal region. The canal has a lateral-to-medial orientation, its lateral part being situated more deeply than its medial part. It has an average length of 4 to 5 cm in men and is about 5 mm longer in women.

The external (superficial) inguinal ring forms the external opening of the inguinal canal. Located in the external oblique aponeurosis, the ring is bounded by two thickenings in the aponeurosis termed the *medial* and *lateral crura* (Fig. 1.83). Both crura join at the superolateral aspect of the external ring and are sometimes reinforced in that area by transverse intercrural fibers. The development and location of these fibers are subject to marked individual variations, and the fibers can be dissected at the external inguinal ring in only 27% of the population.

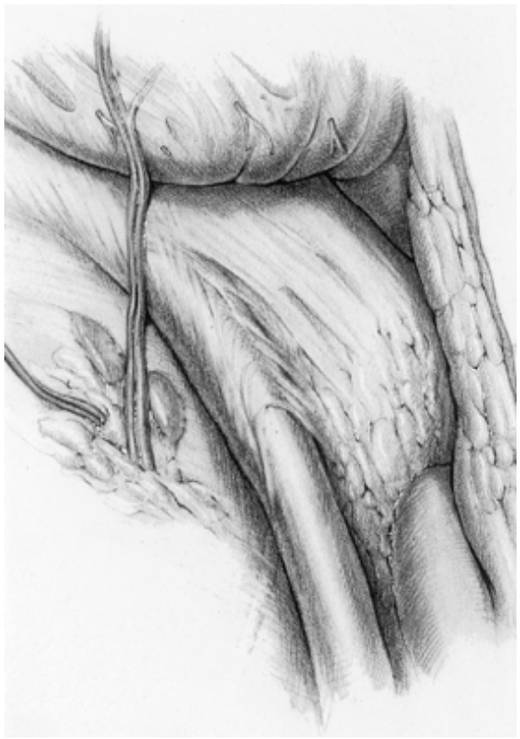

FIGURE 1.83. Inguinal region. Subcutaneous plane.

The external inguinal ring is exposed by incision of the external spermatic fascia. The ring is elliptical in shape and highly variable in size and length. In 80% of cases, the superolateral border of the external ring is located above the medial half of the inguinal ligament. In the remaining 20%, its boundary is more superolateral and, in extreme cases, may extend to the anterosuperior iliac spine.

The slitlike internal opening of the inguinal canal, the internal (deep) inguinal ring, represents an evagination of the transversalis fascia. It is covered internally by parietal peritoneum, so surgical exposure of the internal ring requires incision of the peritoneum.

The layers of the lateral abdominal wall contribute in varying degrees to the substance of the inguinal canal walls. The anterior wall is formed by the external oblique aponeurosis, which is continued onto the spermatic cord as the thin external spermatic fascia. The floor of the canal is formed by the inguinal ligament.

The caudal fibers of the transversus abdominis muscle form the roof of the inguinal canal. The internal oblique muscle does not contribute to formation of the canal roof. Its caudal fibers are continued onto the spermatic cord as the cremaster muscle. The cremaster, which forms the middle coat of the spermatic cord, varies greatly in development among different individuals, and the middle covering is considered to consist of both the spermatic fascia and the cremaster muscle. Normally, a definite plane of cleavage can be developed between the internal oblique and transversus abdominis muscles in the region of the inguinal canal.

The posterior wall of the inguinal canal is formed by the transversalis fascia. Medial to the internal ring this fascia is strengthened by the variable interfoveolar ligament (Hesselbach),

whose fibers are derived from the transversus aponeurosis. The posterior canal wall is further strengthened by the inguinal falx (Henle's ligament). These fibers also arise from the transversus aponeurosis and blend inferiorly with the inguinal ligament and lacunar ligament. Another term for the inguinal falx is the *conjoined tendon.*

The layered dissections in Fig. 1.83, Fig. 1.84, Fig. 1.85, Fig. 1.86 and Fig. 1.87 serve to clarify the arrangement of the individual abdominal tissue planes in the inguinal canal. The firm subcutaneous fatty layer in the inguinal region, permeated by fibrous strands and known also as *Camper's fascia,* is removed to expose the external oblique aponeurosis. This aponeurosis is continued onto the spermatic cord as the external spermatic fascia (Fig. 1.83). Incision of the outer coat of the spermatic cord exposes the middle layer, composed of the cremasteric fascia and the cremaster muscle, which is a continuation of the internal oblique muscle. The genital branch of the genitofemoral nerve can also be identified in this plane (Fig. 1.84). The external oblique aponeurosis can now be split further laterally and superiorly to expose the anterior terminal branch of the iliohypogastric nerve. The middle coat of the spermatic cord is divided to expose the internal spermatic fascia, which intimately invests the cord structures (Fig. 1.85). Division of the caudal fibers of the internal oblique muscle uncovers the portion of the transversus abdominis that forms the roof of the inguinal canal (Fig. 1.86). As the last step in the dissection, the internal coat of the spermatic cord is incised to expose the cord structures

themselves: the vas deferens, testicular artery, and pampiniform plexus (Fig. 1.87).

FIGURE 1.84. Spermatic cord after incision of the external spermatic fascia.

FIGURE 1.85. Spermatic cord after incision of the cremasteric fascia.

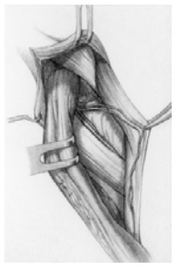

FIGURE 1.86. Spermatic cord after splitting of the internal oblique.

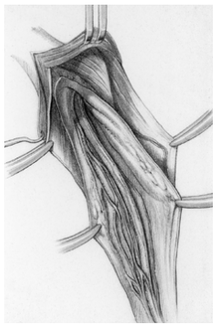

FIGURE 1.87. Spermatic cord after incision of the internal spermatic fascia.

Inguinal Approach

Exposure of the External Inguinal Ring

The subcutaneous fat and Camper's fascia are divided along with branches of the superficial epigastric vessels and the superficial circumflex iliac vessels. The external oblique aponeurosis is identified (Fig. 1.88).

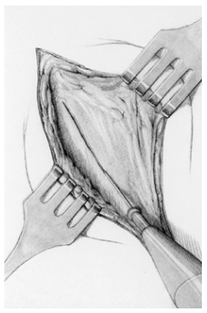

FIGURE 1.88. Exposure of the external inguinal ring.

Exposure of the Internal Inguinal Ring

The external oblique aponeurosis and the most anterior portion of the external spermatic fascia are divided, sparing the genital branch of the genitofemoral nerve on the cremaster muscle medially. The internal oblique muscle and cremasteric fascia are exposed (Fig. 1.89).

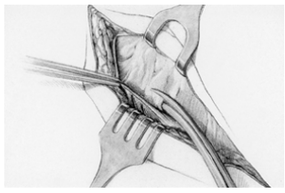

FIGURE 1.89. Division of the external oblique aponeurosis.

Further exposure of the inguinal canal is accomplished by incision of the cremasteric fascia and internal oblique muscle (Fig. 1.90). The iliohypogastric nerve and genitofemoral nerve are visible on the medial side.

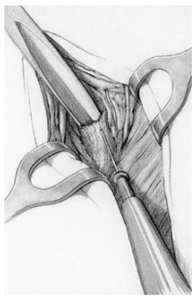

FIGURE 1.90. The cremasteric fascia and internal oblique are divided.

The internal oblique muscle is divided, exposing the transversus abdominis (Fig. 1.91). Following release of the cremaster muscle (whose fibers arise from the internal oblique), the spermatic cord with the surrounding internal spermatic fascia (derived from the transversalis fascia) is undermined and snared (Fig. 1.91). The internal fascia of the spermatic cord is dissected from the transversalis fascia to increase the length of the cord (Fig. 1.92). The external oblique aponeurosis and the incised internal oblique and transversus abdominis muscles are retracted upward in the proximal wound angle, allowing for further dissection of the spermatic cord, which is freed up into the internal inguinal ring (Fig 1.93 and Fig. 1.94). The inferior epigastric vessels can be seen medial to the inguinal ring.

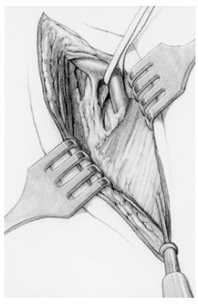

FIGURE 1.91. Mobilization of the spermatic cord and division of the transversus abdominis.

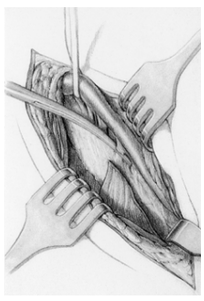

FIGURE 1.92. The spermatic cord is dissected from the transversalis fascia, and the internal ring is exposed.

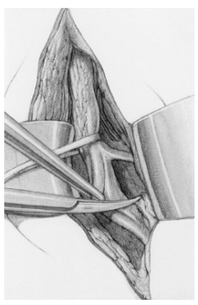

FIGURE 1.93. After incision of the internal spermatic fascia, the vas deferens and its artery are separated from the pampiniform plexus and testicular artery.

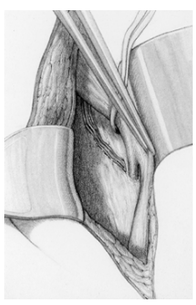

FIGURE 1.94. The inferior epigastric artery and the accompanying inferior epigastric veins are dissected free on the medial aspect of the spermatic cord.

EXTERNAL GENITALIA

Part of "1 - SURGICAL ANATOMY OF THE GENITOURINARY SYSTEM "

Dorsal Approach to the Penis

Exposure of the Dorsal Neurovascular Bundle

The superficial and deep penile fasciae are dissected and incised to the tunica albuginea along the lateral side of the penis (Fig. 1.95). A counterincision is made on the opposite side, and the neurovascular bundle (deep dorsal vein, artery, and nerve) is underrun and snared with a tape (Fig. 1.96).

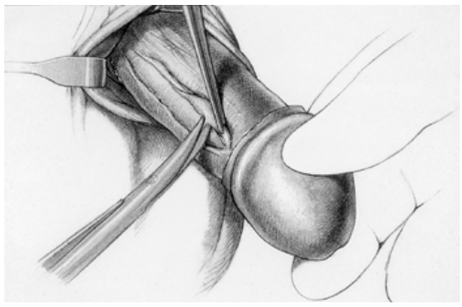

FIGURE 1.95. The superficial and deep fasciae of the penis are divided down to the tunica albuginea.

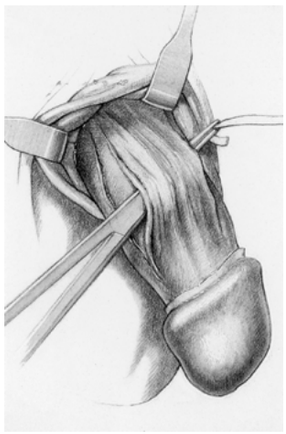

FIGURE 1.96. The neurovascular bundle is undermined and snared with a vascular tape.

The anatomic dissection in Fig. 1.97 shows the structures of the dorsal neurovascular bundle: the deep dorsal penile vein, the dorsal penile artery, and the dorsal nerve of the penis, located between the deep penile fascia and the tunica albuginea.

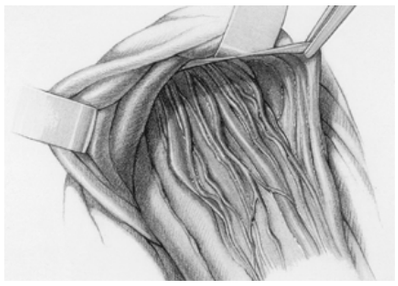

FIGURE 1.97. Anatomic dissection showing the structures of the neurovascular bundle: the deep dorsal penile vein, dorsal penile artery, and dorsal penile nerve.

The fascial planes of the penis are shown in schematic cross section in Fig. 1.98 .

FIGURE 1.98. Schematic cross section of the penis.

PERINEUM

Part of "1 - SURGICAL ANATOMY OF THE GENITOURINARY SYSTEM "

Anatomy of the Male Urethra and Pelvic Floor

The dissection shown in Fig. 1.99 demonstrates the relations of the corpus spongiosum to the pelvic floor. The corpus spongiosum is covered by the bulbospongiosus muscle and relates to the inferior aspect of the transverse perineal ligament, to which it is attached by loose connective tissue. The so-called “urogenital diaphragm” consists essentially of tough, transversely oriented connective-tissue fibers—the transverse perineal ligament. All pelvic muscles, as well as the levator ani of the pelvic diaphragm and the external anal sphincter, converge at the central tendon of the perineum. These structures are demonstrated more clearly by removal of the corpus spongiosum at the bulb of the penis along with the bulbospongiosus muscle (Fig. 1.100).

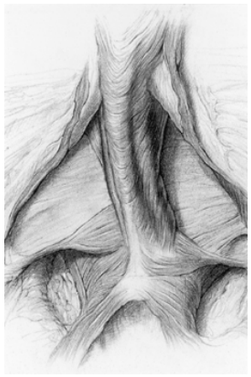

FIGURE 1.99. Anatomic dissection showing the pelvic floor structures from the inferior aspect.

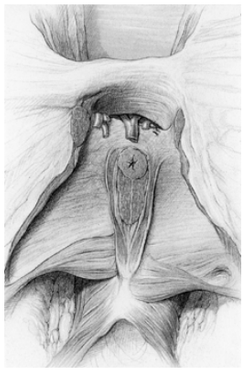

FIGURE 1.100. Transverse perineal ligament after removal of the corpus spongiosum (anatomic dissection).

In another dissection (Fig. 1.101), the pubic bone has been partially removed to demonstrate the neurovascular supply of the penis (dorsal penile artery and nerve, deep dorsal penile vein). Removal of the pubic symphysis and corpora cavernosa renders a view of the transverse perineal ligament (Fig. 1.102).

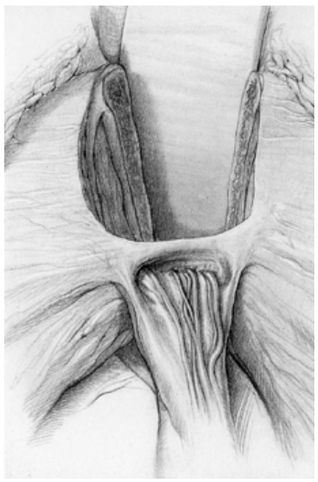

FIGURE 1.101. Dorsal neurovascular supply of the penis (anatomic dissection).

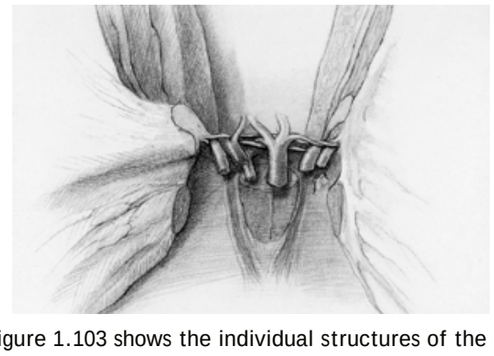

FIGURE 1.102. Appearance after resection of the corpora spongiosa and cavernosa (anatomic dissection).

Figure 1.103 shows the individual structures of the urogenital diaphragm in greater detail. Visible features include the pubic arcuate ligament, the transverse perineal ligament, and the external urethral sphincter, which forms a

“horseshoe” about the anterior and lateral aspects of the membranous urethra. The structures that pierce the transverse perineal ligament are also seen: the deep dorsal penile vein, the dorsal penile artery and nerve, and the membranous urethra. The bulb of the penis has been divided, leaving a remnant on the diaphragm.

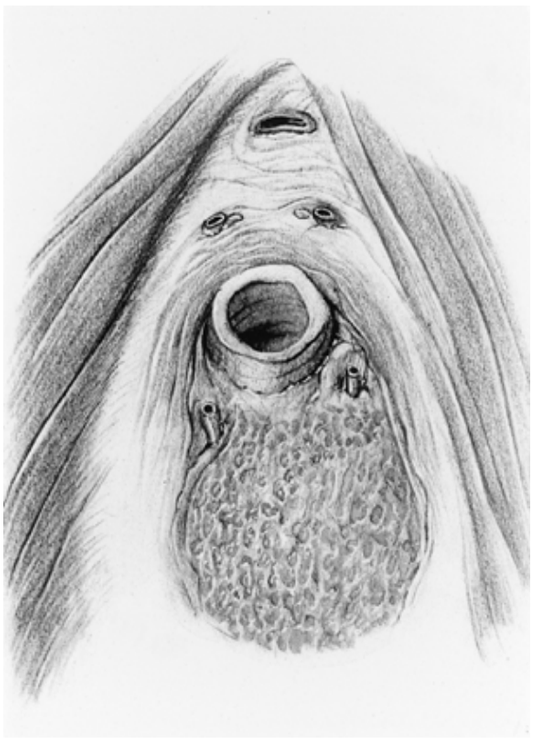

FIGURE 1.103. Close-up view of the transverse perineal ligament and rhabdosphincter (caudal view).

In Fig. 1.104, the anterior circumference of the membranous, urethra (from 9 to 3 o'clock) has been removed to demonstrate the lateral muscular portions of the striated

urethral sphincter (rhabdosphincter). The artery of the bulb of the penis (bulbar artery) runs lateral to the membranous urethra. The dorsal penile artery and nerve perforate the transverse perineal ligament. The deep dorsal penile vein lies between the public arcuate ligament and transverse perineal ligament.

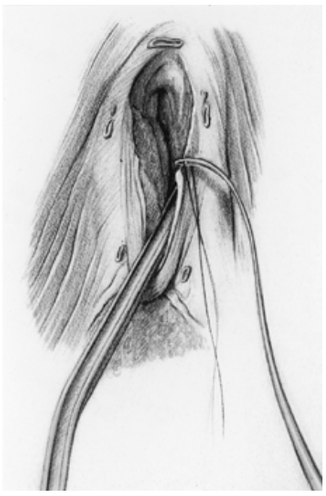

FIGURE 1.104. The urethral lumen is held open with a grooved probe. The lateral muscular portion of the rhabdosphincter can be seen.

Perineal Approach to the Posterior Urethra

Dorsal Approach Through the Perineal Body

The dorsal approach is made through the wedge-shaped perineal body, which extends from the central tendon to the rectourethral septum (Fig. 1.105). The dissected bulb of the penis is held upward by its posterior surface, and individual bulbospongiosus muscle fibers are severed. The dorsal aspect of the bulb is sharply separated from the inferior urogenital fascia and the transverse perineal ligament (Fig. 1.106).

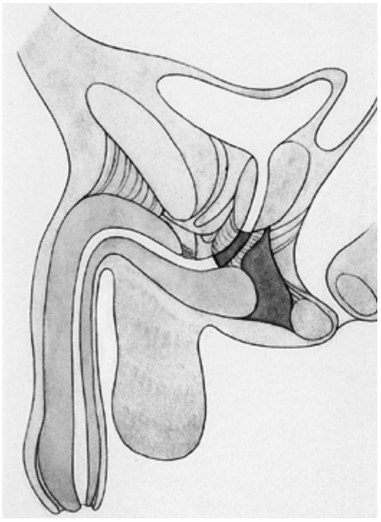

FIGURE 1.105. Schematic of the dorsal approach through the perineal body.

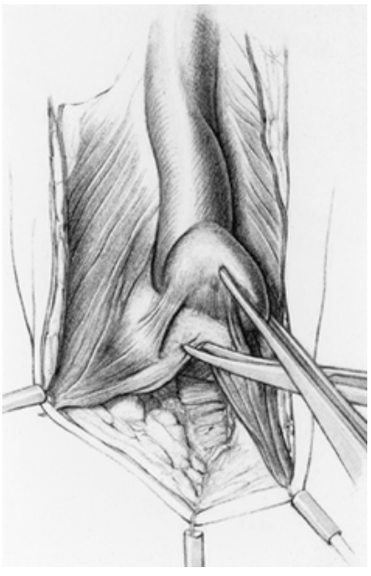

FIGURE 1.106. The bulbospongiosus muscle is removed. The tendinous origin of the bulbospongiosus is incised from front to back at the central tendon of the perineum.

Figure 1.107 illustrates the details of this approach. The corpus spongiosum is dissected free from the bulbospongiosus muscle, and the bulb is then dissected from the pelvic floor (transverse perineal ligament). The origins of the

bulbospongiosus at the central tendon are divided. The bulbar artery and vein also are divided at this stage.

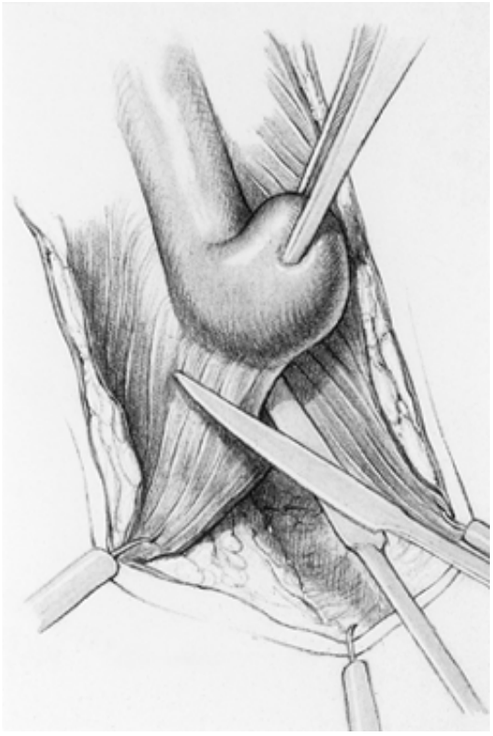

FIGURE 1.107. The bulbospongiosus fibers are detached from the dorsal aspect of the bulb.

Dissection of the Rectourethral Septum

Dissection of the rectourethral septum is used for the treatment of rectoprostatic fistulae or a very markedly displaced proximal prostatic urethral stump. The thick connective tissue at the apex of the perineal body is incised transversely.

Division of the rectourethral septum provides access for the dissection of Denonvilliers' fascia. The rectogenital septum is opened, and the posterior surface of the prostate is dissected free. A rectoprostatic fistula can be exposed by this perineal route.

2

STANDARD DIAGNOSTIC CONSIDERATIONS

Robert B. Nadler

Wade Bushman

Arthur W. Wyker Jr.

R.B. Nadler: Assistant Professor of Neurology, Head Section of Endourology, Laparoscopy, and Stone Disease, Northwestern University Medical School, Chicago, IL 60611.

W. Bushman: Assistant Professor of Urology, Northwestern University Medical School, Chicago, IL 60611.

A.W. Wyker, Jr.: Clinical Professor of Urology, University of Virginia Health Sciences Center, Charlottesville, VA 22908.

Contents

In evaluating a patient, the urologist relies primarily on a skillfully taken history supplemented by a careful physical examination and appropriate laboratory studies. More often than not, a careful and detailed history of the patient's chief complaints indicates the probable diagnosis even before a physical examination is made or any laboratory test is performed. Because a thorough understanding of urologic signs and symptoms is critical to proper evaluation, they are analyzed here in some detail. A special effort has been made to explain the mechanism of each sign or symptom and to discuss the differential diagnosis.

SIGNS AND SYMPTOMS

Part of "2 - STANDARD DIAGNOSTIC CONSIDERATIONS "

Frequency

Frequency is the most common urologic symptom. When it occurs at night, it is termed *nocturia;* it is particularly bothersome and often is the reason for medical consultation. To properly evaluate these symptoms, the urologist should appreciate the wide range of frequency and nocturia in the general population. Study of a normal adult population revealed an average diurnal frequency of four to five times for men and five to six times for women. Ninety percent voided between three and nine times per day, and nocturia was common one to two times in both sexes (6). *Significant urinary frequency* is generally defined as voiding at least every 2 hours and *significant nocturia* as more than two times; however, normalcy varies with each patient. Usually, it is a significant increase in an individual's urinary frequency or nocturia that precipitates medical attention.

Etiology and Mechanism

A change in urinary frequency may result either from a decrease in functional capacity of the bladder or from an increase in urine production. An excellent screening test is the determination of *urine output per voiding.* The voided volume will be low when the bladder capacity is reduced and normal or high with polyuria. This information should

be obtained as part of a 24-hour diary of fluid intake and voiding (Fig. 2.1).

VOIDING DIARY

INTAKE: All fluids and liquid based foods such as ice cream, jello, soup, etc.
OUTPUT: Amount of each urination
ACTIVITY: Note activity (working, relaxing at home, sleeping, etc.)

	DAY ONE			DAY TWO			DAY THREE		
TIME	INTAKE	OUTPUT	ACTIVITY	INTAKE	OUTPUT	ACTIVITY	INTAKE	OUTPUT	ACTIVITY
6AM									
7AM									
8AM									
9AM									
10AM									
11AM									
12N									
1PM									
2PM									
3PM									
4PM									
5PM									
6PM									
7PM									
8PM									
9PM									
10PM									
11PM									
12M									
1AM									
2AM									
3AM									
4AM									
5AM									

FIGURE 2.1. Sample of a 24-hour form for a diary of fluid intake and voiding.

A reduced functional bladder capacity may occur secondary to inflammation of the bladder, pressure on the bladder from extravesical lesions, infravesical obstruction, radiation damage, or neurologic disease. Normal bladder mucosa is pain and pressure sensitive, and when inflamed, its threshold is greatly decreased, so it takes fewer stimuli to initiate the desire to void. Acute bacterial cystitis is by far the most common cause of bladder inflammation. Other causes include cancer, stones, foreign bodies, drugs (e.g., cyclophosphamide), nonbacterial cystitis (viral, fungal, parasitic, interstitial), and inflammatory processes in the adjacent bowel or vagina. Extravesical lesions pressing on the bladder may cause frequency by mechanically interfering with normal bladder expansion or by causing an irritable focus in the

bladder wall. Common causes include pregnant uterus, fibroids, ovarian masses, and pelvic malignancies.

Infravesical obstruction provokes frequency by several mechanisms. Detrusor hypertrophy occurs along with changes in the neural regulation of bladder function such that the urge to void occurs at smaller than normal volumes. The result is an increase in urinary frequency. These patients typically note a decrease in the size and force of their urinary stream. With chronic obstruction, the bladder detrusor muscle may decompensate. Failure to empty the bladder, with elevated postvoid residual urine volumes, further diminishes the functional capacity of the bladder. Benign prostatic hyperplasia is the most common cause of infravesical obstruction. Other causes include carcinoma of the prostate, bladder neck obstruction, urethral stricture, and posterior urethral valves (in boys).

Neurologic disease causes urinary frequency by allowing uninhibited detrusor contractile activity during bladder filling. This may occur with disease affecting either the cerebral cortex (e.g., after a stroke) or spinal cord (e.g., spinal cord injury), as well as diseases affecting the central nervous system diffusely (e.g., multiple sclerosis). Urinary symptoms may be the presenting symptoms of an occult neurologic disease process, and a possible neurogenic cause should always be considered in the differential diagnosis of urinary frequency.

An increase in frequency, typically without any other urinary symptoms, will accompany increased urinary production. Causes of polyuria include ingestion of excess fluid, diabetes mellitus, chronic renal failure, and diabetes insipidus. In diabetes mellitus, the unreabsorbed glucose is an osmotic diuretic causing the polyuria. In chronic renal failure, there is impaired ability to concentrate the urine that causes *polyuria,* defined as a daily urine output in excess of 2,500 mL. Diabetes insipidus occurs with inadequate production or release of antidiuretic hormone (ADH) from the pituitary gland (central diabetes insipidus) or with inadequate fluid reabsorption by the kidneys despite normal ADH levels (nephrogenic diabetes insipidus) (36). The acquired concentrating defect in nephrogenic diabetes insipidus may occur with electrolyte disorders (hypokalemia and hypercalcemia), kidney disorders (pyelonephritis and obstructive nephropathy), drugs (e.g., lithium), and sickle cell disease and trait.

Emotional stress can cause urinary frequency. Characteristically, the patient experiences episodic frequency during stressful periods punctuated by periods of normalcy. Stress has been shown to induce a significant rise in intravesical pressure. Straub and associates (35) performed cystometrograms while interviewing normal subjects. Stressful topics evoked a significant rise in the intravesical pressure, usually accompanied by a desire to void. After reassurance and relaxation, the intravesical pressure returned to normal. Interestingly, discussion of emotion-laden material produced a bladder response only when it *disturbed the subject.* Some subjects seemed to enjoy venting their feelings, and they experienced no rise in their intravesical pressure.

Urgency

Urgency of urination is a sudden, strong desire to void. This symptom is usually attributed to an involuntary contraction of the detrusor muscle. Associated symptoms of urinary frequency are often attributable to lower-amplitude detrusor contractions occurring during bladder filling. When uninhibited detrusor activity occurs as a consequence of neurologic disease or injury, it is termed *detrusor hyperreflexia.* In the absence of neurologic disease, it is termed *detrusor instability.* It is a common feature of infravesical obstruction or inflammatory conditions of the bladder, but it is also commonly idiopathic in origin. Patients may prevent leakage and temporarily delay voiding by maintaining voluntary contraction of the external sphincter until the detrusor contraction has abated; however, urge incontinence is a regularly accompanying feature.

In patients with urgency, the urologist should look for evidence of irritative lesions of the lower urinary tract, intravesical obstruction, and neurologic disorders. Urinalysis is critical to look for pyuria and bacteriuria, which may indicate an infection, or hematuria, which might indicate a malignancy or stone. Similarly, an ultrasound or catheterized postvoid residual can rule out outflow incontinence and urgency in these patients.

Diminished Urine Flow

The determinants of urine flow during voiding are detrusor contraction strength, any contribution of abdominal straining, and infravesical resistance to urine flow. Although commonly referred to as *obstructive symptoms,* hesitancy, diminished or interrupted stream, need to strain, postvoid dribbling, and a sensation of incomplete emptying may occur with either impaired detrusor function or infravesical obstruction. There are many causes of detrusor hypocontractility. It may be idiopathic. It can also occur as a result of central nervous system disease (e.g., Parkinson's), peripheral neuropathy (e.g., diabetes mellitus), chronic overdistention, or longstanding infravesical obstruction. Infravesical obstruction, although uncommon in women, may occur with a large cystocele or tight urethral stricture. These are usually evident on physical examination. Among the causes of infravesical obstruction in men, bladder neck obstruction from benign prostatic hyperplasia is the most common. Although the constellation of irritative and obstructive voiding symptoms in men has generally been attributed to benign prostatic hyperplasia (BPH), a common diagnostic challenge is posed by men with obstructive symptoms in whom detrusor hypocontractility or infravesical obstruction may coexist. Measures used to assess the relative contribution of each factor include endoscopic evaluation of the

urethra and bladder neck for visual evidence of obstruction and urodynamic pressure-flow studies to measure detrusor pressure and urine flow during voiding.

The American Urological Association (AUA) symptom index (Fig. 2.2) is a widely used measure to quantify irritative and obstructive symptoms in men. This measure is not specific for obstruction, and because a number of studies have shown that BPH or bladder obstruction is often not the cause of bladder symptoms (3,8,29,37), obstructive and irritative voiding symptoms are now commonly described by the nonbiased term *lower urinary tract symptoms* (LUTS) (1).

INTERNATIONAL PROSTATE SYMPTOM SCORE (I-PSS)

Patient's Name

Date of Birth Date Completed

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
2. Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	
7. Nocturia Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	1	2	3	4	5	6	
Total I-PSS Score							

FIGURE 2.2. The AUA symptom index.

Urinary Retention

The patient with *acute* urinary retention typically experiences distress with an uncomfortably distended bladder and the inability to void more than small volumes of urine. Catheter drainage brings prompt symptomatic relief. Symptoms of patients with *chronic* retention usually include frequency, weak urine flow, and a sensation of incomplete emptying. Patients may experience the frequent leakage typical of overflow incontinence. The serum creatinine may be increased as a result of obstructive nephropathy. Generally, these patients experience little discomfort from their distended bladder, even though the residual urine volumes obtained by catheterization can be larger than those found in patients with acute urinary retention. Urinary retention, whether acute or chronic, can occur as a product of intravesical obstruction, impaired detrusor function, neurologic disease, or in rare cases, psychogenic causes. The role of the urologist is to provide bladder decompression and to identify the underlying condition or precipitating events that contribute to retention. Particular attention should be paid in cases of young men and women of all ages to rule out an occult neurogenic cause.

Urinary Incontinence

Urinary incontinence is the *involuntary* loss of urine. Blandy (4) described it as follows: “There is almost no symptom more degrading or miserable than incontinence of urine: it inevitably brings, at any stage after early childhood, shame, stink, soreness, and ostracism.”

Mechanism

The diagnostic approach to the incontinent patient emphasizes a careful history that notes the frequency and pattern of leakage, recognizes significant associated voiding symptoms, and identifies pertinent associated medical conditions. A careful physical examination and postvoid residual urine volume determination are essential.

Normal bladder function embraces two distinct activities: urine storage and urine evacuation. Incontinence may result from a problem with the urine storage phase because of an abnormal increase in bladder pressure during filling or because of a defective urinary sphincter mechanism. Alternatively, incontinence may result from a problem with the evacuation phase that prevents adequate emptying of the bladder. The classic forms of urge, stress, and overflow incontinence correspond neatly to this classification of incontinence mechanisms. Because most incontinent patients have one of these typical forms and a diagnosis usually can be made on the basis of history and physical examination alone, these types of incontinence are described in some detail. On evaluation, some patients are found to have atypical patterns of incontinence. These patients often have complex underlying mechanisms of voiding dysfunction and incontinence and may require more comprehensive urodynamic evaluation for accurate diagnosis.

Classification of Urinary Incontinence

Stress Incontinence

Women with stress incontinence have a characteristic history. They leak with coughing, sneezing, jogging, laughing, getting up from a chair, or engaging in other activities that cause a sudden rise in intraabdominal pressure. The normal mechanism to prevent leakage with straining depends on equal transmission of the increased pressure to the bladder and urethra. In women with the most common type of stress incontinence, a deficiency of pelvic support allows the urethra to herniate into the vagina (urethrocele). Less pressure is transmitted to the urethra than to the bladder, and the uncompensated rise in intraabdominal pressure results in leakage. The degree of leakage is proportional to the degree of straining. Characterized by leaking with minimal activities such as standing or walking, extremely severe stress incontinence is more likely the result of a deficiency in the intrinsic urethral sphincter mechanism rather than urethral hypermobility. Loss of the urethral sphincter function may occur with aging, from radiation therapy, from pelvic trauma, or from prior pelvic or antiincontinence surgery (5). The result is significant leakage with very small rises in intravesical pressure. Stress incontinence in the neurologically intact male without previous pelvic surgery is rare. Variable degrees of stress incontinence may be observed in men following prostatectomy; this incontinence is most often caused by deficient function of the intrinsic or extrinsic component of the distal urethral sphincter (30).

Overflow Incontinence

Overflow incontinence is distinguished by chronic failure of bladder emptying. This may occur with either intravesical obstruction or impaired detrusor function. Patients often have overt bladder decompensation with chronically high residual urine, often greater than 1,000 mL. The distended bladder is usually easily palpable and percussible in the lower abdomen. The intravesical pressure is consistently elevated, so slight increases in intraabdominal pressure may raise the intravesical pressure enough in women to overcome urethral resistance. Intermittent leakage may also occur because of uninhibited contractile activity in the stretched detrusor muscle. This is the mechanism of leakage in men with this form of urinary incontinence, most commonly seen with severe obstruction from BPH.

Urge Incontinence

Urge incontinence is an episodic form of urine leakage that occurs with involuntary contractions of the bladder detrusor muscle. The patient typically complains of a precipitous, unsuppressible urge to void. Patients may be able to forestall or minimize leakage for a brief period by contracting the external sphincter, but the typical patient experiences small- to large-volume leakage from what is essentially an involuntary voiding reflex. The most common cause is idiopathic detrusor instability. Specific causes also include inflammation adjacent to or in the bladder, longstanding intravesical obstruction, and varying forms of neurogenic bladder (detrusor hyperreflexia). Urge incontinence is particularly common in patients with a history of stroke and often occurs 3 to 6 months after the neurologic event. A careful history and 24-hour voiding diary usually reveal that episodes of leakage are most apt to occur with a full bladder, as a result of generous fluid intake, during periods of diuresis, or when regular toileting has been delayed. A cystometrogram may demonstrate uninhibited detrusor activity during filling. This can be useful in the cognitively impaired patient who cannot provide a useful history; however, the characteristic history provided by most patients makes this test superfluous.

Nocturnal Enuresis

Nocturnal enuresis is the repeated, involuntary loss of urine during sleep (17). If present since birth, it is termed *primary enuresis.* Bed-wetting spontaneously ceases with increasing age, being present in 15% of 5-year-old children, 5% of

10-year-old children, and 1% of 15-year-old children. If nocturnal enuresis follows a significant "dry" interval, it is termed *secondary enuresis.*

Etiology

Primary enuresis is caused by maturational lag of the central nervous system with delayed development of inhibitory control of the bladder. This delayed maturation theory is supported by the following findings in enuretics: (a) the high incidence of a spontaneous cure with time; (b) the presence of a bladder capacity smaller than that in normal children, with resultant increased frequency of voiding (Table 2.1 and Table 2.2); and (c) the documented hereditary aspect of enuresis. The evaluation of the child with uncomplicated primary nocturnal enuresis includes a physical examination, screening neurologic examination, urinalysis, and urine culture. If these are normal, reassurance and observation are indicated. In patients with a history of urinary infection or primary *diurnal* enuresis, evaluation should include an ultrasound of the bladder and kidneys to rule out obstruction.

TABLE 2.1. PHYSIOLOGIC MAXIMUM BLADDER CAPACITY

Age (yr)	Normal Children	Enuretic Children
4	296	180
5	301	238
6	359	279
7	394	217
8	428	272
9	457	281
10	473	353

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TABLE 2.2. FREQUENCY OF VOIDING IN 24 HOURS

Age (yr)	Normal Children	Enuretic Children
4	5.3	11.9
5	5.7	11.0
6	6.4	10.0
7	5.5	8.4
8	5.3	9.7
10	4.6	10.7

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Secondary enuresis often occurs in association with emotional stress in the child's life, and a diligent search should be made for contributing emotional factors. Examples are a disruption of the family by divorce or the birth of a sibling. Other causes for secondary enuresis include neurologic disease and obstruction. Therefore the evaluation of the child with secondary enuresis should include a careful physical examination, screening neurologic examination, radiographs of the lumbosacral spine to detect vertebral abnormalities, urinalysis and culture, and an ultrasound of the bladder and kidneys.

Hematuria

Hematuria is a dramatic indicator of disease in the urinary tract, yet it is often ignored by patients and physicians alike. The passage of blood-stained urine may be the first sign of serious disease in the urinary tract, and a single episode of hematuria warrants a thorough urologic investigation.

Classification

It is helpful clinically to classify hematuria in two ways: first by quantity and second by the time of its appearance during voiding. Quantitatively, it is called *microscopic hematuria* if demonstrable only under the microscope and *gross hematuria* if it is evident to the naked eye. Microscopic hematuria is more commonly nephrologic in origin, whereas gross hematuria is more commonly urologic in origin. Blood noted chiefly at the beginning of urination is called *initial hematuria,* and it indicates disease in the urethra. Similarly, blood noted only between voidings or as stains on underclothing or pajamas, while the voided urine is clear, indicates disease at the urethral meatus or in the anterior urethra. Blood noted chiefly at the end of urination is called *terminal hematuria,* and it indicates disease near the bladder neck or in the prostatic urethra. Uniformly bloody urine, *total hematuria,* occurs with disease in the bladder, ureters, or kidneys.

Significance

The significance of hematuria varies with the age of the patient (Table 2.3). Gross painless hematuria is often the first manifestation of a urinary tract tumor. The episodic nature of the bleeding and the absence of other symptoms should not lull either the patient or physician into a false sense of security. In one review of 1,000 patients with gross hematuria (19), tumors were found in 21.5%. Two-thirds of these were bladder tumors.

TABLE 2.3. THE MOST COMMON CAUSES OF HEMATURIA BY AGE AND SEX

0–20 yr
Acute glomerulonephritis
Acute urinary tract infection
Congenital urinary tract anomalies with obstruction
20–40 yr
Acute urinary tract infection
Stones
Bladder tumor
40–60 yr (men)
Bladder tumor
Stones
Acute urinary tract infection
40–60 yr (women)
Acute urinary tract infection
Stones
Bladder tumor
60 yr (men)
Benign prostatic hyperplasia
Bladder tumor
Acute urinary tract infection
60 yr (women)
Bladder tumor
Acute urinary tract infection

Microscopic hematuria may also signal the presence of a tumor. Although evaluation of 500 patients with asymptomatic microscopic hematuria revealed tumors in only 2.2% (15), a more recent study from the same institution evaluating 200 consecutive patients with asymptomatic microscopic hematuria found tumors in 12.5% (7). This figure reflects the newer diagnostic modalities available today, particularly urine cytology.

The other common urologic causes of hematuria are infection and stones. Less common causes include BPH, trauma, sickle cell disease or trait, tuberculosis, renal infarction, renal vein thrombosis, coagulation and platelet deficiencies, exercise-related causes (e.g., jogging), hypercalciuria, and vasculitis.

Diagnostic Approach

After a careful history and physical examination, the fundamental means of diagnosis are urinalysis, cytologic examination of the urine, intravenous urography, and cystoscopy. For gross hematuria, cystoscopy at the time of bleeding can be helpful in localizing the bleeding to the left or right upper urinary tract. After these fundamental studies have been completed, the diagnosis is apparent in approximately 75% of cases. For the remaining 25% with unexplained hematuria, further investigation can then be carried out with retrograde pyelography, ureteroscopy, and computed tomography (CT). Although hematuria cannot occur without a cause, in 5% to 10% of cases, no definite cause can be found (10).

Pain

Mechanism

The chief cause of pain in the urinary tract is distention from increased intraluminal pressure. The severity of the pain is not primarily related to the degree of distention but to the rapidity with which it develops. Gradual distention of the ureter, renal pelvis, or calyces may cause little or no pain. When intrapelvic pressures have been measured in patients with an acutely obstructing ureteral calculus, the higher the pressure, the more severe the pain. With longstanding obstruction, distention may be marked, but the pressure in the renal pelvis is normal or only minimally elevated and the patient experiences little or no pain. The concept that pain from obstruction is related to increased intraluminal pressure and distention is extremely useful clinically. Urologists are often asked to evaluate patients with pain in the back, flank, or abdomen. When an intravenous urogram at the time of a pain episode is normal with no dilation of the ureter, pelvis, or calyces and no delay of the nephrogram or excretory phase, one can state with confidence that pain is not caused by obstruction. Two other causes of renal pain are distention of the renal capsule and acute renal ischemia. Both produce steady, usually mild pain in the costovertebral angle region.

Type and Location

Pain caused by distention may be steady or intermittent. Intermittent pain, particularly when it is severe, is often termed *renal colic* and is most commonly caused by an obstructing stone in the lower ureter. With each peristaltic wave, more urine is pumped into the obstructed portion of the ureter, with a resultant increase in the hydrostatic intraluminal pressure and pain intensity.

Steady pain, most typical of distention of the renal capsule and acute renal ischemia, also occurs in up to 50% of patients with distention of the ureter, renal pelvis, or calyces. The constant level of pain with obstruction and distention is thought to reflect an absence of ureteral pressure waves.

The distribution of urinary tract pain has been carefully mapped out by distending the renal pelvis and various portions of the ureter with small balloon catheters (24). The location of renal and ureteral pain is shown in Fig. 2.3 .

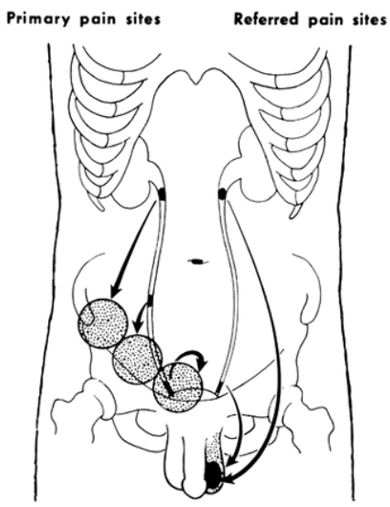


FIGURE 2.3. Sites of urologic pain. (Reprinted with permission from Wyker A, Gillenwater JY. *Method of urology.* Baltimore: Williams & Wilkins, 1975.)

Urinary tract pain does not occur in the central portion of the abdomen but is lateralized to the outer abdomen, flank, and costovertebral angle region. Ureteral pain follows a line along the lateral edge of the rectus muscle (Table 2.4).

Site of Balloon Distention	Site of Uretral Pain
Renal pelvis	Costovertebral angle
Upper ureter	Flank
Middle ureter	Middle inguinal canal
Lower ureter	Suprapubic area

TABLE 2.4. SITES OF URINARY TRACT PAIN

Pain Pathways and Referred Pain

Kidney and ureter pain impulses are carried in afferent fibers that accompany the sympathetic nerves and enter the spinal cord by means of the posterior spinal roots. Renal and ureteral pain can be abolished by sympathectomy of T-7 to L-3 or by sectioning posterior spinal roots T-11 and T-12 and L-1 and L-2.

Referred pain is pain projected to an area distant from the point of stimulation. It may occur in addition to or in the absence of true visceral pain. The exact mechanism of

referred pain is unknown, but the site of painful stimulus and the site of referred painful sensation usually share a common segmental innervation. Spinal cord segments T-11 and T-12 receive sensory fibers from both the upper ureter and testis, so distention of the upper ureter may cause referred pain to the ipsilateral testis. In similar manner, distention of the lower ureter may cause referred pain to the ipsilateral scrotum.

Pain in the Lower Urinary Tract

Bladder distention initially causes fullness and then pain in the suprapubic region and end of the penis associated with an intense desire to void (urgency). Normal bladder mucosa is sensitive to stimuli, and this sensitivity is greatly increased by inflammation. Suprapubic discomfort is typical. Stimulation of the trigone, ureteral orifices, or anterior urethra causes referred pain to the end of the penis. Pain from prostatic inflammation is usually described as perineal discomfort, which may radiate to the inguinal regions and lower back. Acute testicular pain such as that with trauma, torsion, or epididymo-orchitis often radiates to the groin.

Pain on Urination

Pain on urination is usually caused by inflammation of the lower urinary tract. Patients may localize their discomfort to the suprapubic area or to the end of the penis or urethra. Milder degrees of pain are often described as a burning sensation. The most common cause is bacterial infection. Other causes include nonbacterial cystitis, cancer, stone or foreign body in the bladder or urethra, and excess phosphates in the urine (phosphaturia).

It is important to determine when pain or burning is noted during urination. If it begins with the onset and stops abruptly at the end, the primary pathology is probably in the urethra. When the bladder is primarily involved, as in acute bacterial cystitis, patients experience some discomfort during urination, but often the most severe pain occurs after voiding has ceased.

Chronic Pelvic Pain

Chronic pelvic pain syndrome (CPPS) is a more accurate subclassification of prostatitis and prostatodynia developed in 1995. The National Institutes of Health (NIH) prostatitis classification system is based on the presence of acute and chronic bacterial prostatitis and the presence of white blood cells (WBCs) in the expressed prostatic secretions (EPS) (28). Patients typically have any combination of perineal, penile, testicular, or low back pain. The classification is based on the following culture and EPS data. *Type I* refers to patients with acute bacterial prostatitis, as documented by culture. *Type II* refers to patients with chronic bacterial prostatitis as documented by culture of the EPS. *Type IIIa* refers to patients with CPPS, more than 10 WBCs per high-power field (HPF) (400×) in their EPS, and negative cultures. *Type IIIb* refers to patients with CPPS, no inflammation in their EPS (fewer than 10 WBCs), and negative cultures. *Type IV* refers to patients with asymptomatic inflammatory prostatitis (patients without CPPS who are found incidentally to have more than 10 WBCs per HPF in their EPS). The cause of CPPS, especially type IIIa, remains elusive, although oxidative stress (32) and cytokines (2,16,26) may play an important role. Treatment at this time is most successful with biofeedback (9) and nonsteroidal antiinflammatory medications. The NIH Chronic Prostatitis Symptom Index (NIH-CPSI) is a nine-part questionnaire developed and validated to quantitate the pain of

urinary symptoms and effect that CPPS has on the quality of life in these patients (21). This questionnaire, similar to the AUA symptom index, is an important step for the practicing clinician to initially evaluate the patient and record the efficacy of the aforementioned treatments.

Sexual Dysfunction

Normal sexual function is difficult to define because of significant individual variation and the prevalence of age-related changes. However, most of these patients complain of diminished libido, erectile dysfunction, or both. Diminished libido may occur with acute and chronic illness or with psychologic or emotional stresses, and the existence of possible causative factors should be sought in the patient's history. The most common organic basis for diminished libido, a disturbance of the pituitary-gonadal hormonal axis, is evaluated by examining for evidence of hyperestrinism or hypogonadism (gynecomastia, decreased testicular volume) and obtaining a morning sample of serum testosterone. If the testosterone value is below the normal range, a free and total testosterone is repeated, along with measurements of follicle-stimulating hormone, luteinizing hormone, and prolactin. Hypergonadotropic hypogonadism (low testosterone, increased luteinizing hormone) is usually idiopathic, and pharmacologic testosterone supplement may yield a beneficial effect. Patients with hypogonadotropic hypogonadism (low testosterone, low luteinizing hormone) or with other evidence of pituitary endocrinopathy (elevated prolactin) merit a complete endocrine evaluation to rule out a hypothalamic or pituitary defect.

Erectile dysfunction, generally defined as failure to achieve and maintain an erection satisfactory for intercourse, is the most common complaint. The incidence increases with age, such that nearly 25% of men at age 65 are affected. There are many potential causes, and a careful history provides essential clues to the diagnosis. The manner of onset of erectile dysfunction, the degree of difficulty in attaining erection during masturbation versus with a sexual partner, a progression in the degree of dysfunction over time, and the presence or absence of nocturnal erections often distinguish an organic versus a psychogenic etiology. Typically, an organic etiology shows a gradual onset with progressive dysfunction over time, equal difficulty with a partner or during masturbation, and a loss of nocturnal erection. Psychogenic impotence more typically shows an abrupt or stuttering pattern of erectile dysfunction without a gradually progressive pattern, a situational pattern of erectile dysfunction, or maintenance of nocturnal erections.

Medical conditions contributing to erectile dysfunction include diabetes mellitus, neurologic disease, hypertension, hypercholesterolemia, peripheral vascular disease, a heavy smoking history, and some medications (e.g., antihypertensives). Psychologic factors that can contribute to erectile dysfunction include strained emotional relationships, performance anxiety, and unresolved inner conflicts associated with sexual behavior.

An occasional patient will report absence of emission. This may occur with autonomic denervation of the accessory sex organs as a complication of retroperitoneal surgery or longstanding diabetes mellitus, incompetency of the bladder neck following surgery, or diminished ejaculate volume from hypogonadism. The complaint of penile curvature and pain with erection (Peyronie's disease) is typically due to the presence of a fibrous plaque between the tunica albuginea and corpus cavernosum. It is usually palpable at the site of curvature reported by the patient.

Fever

To the urologist, as to most physicians, fever suggests the presence of infection. The most common cause is an acute urinary tract infection where significant temperature elevation is usually taken to indicate upper tract involvement. High spiking temperatures with shaking chills and systemic signs of sepsis should prompt radiographic imaging, usually with CT or ultrasound, to rule out upper tract obstruction. Infection with obstruction is a urologic emergency. Prompt drainage with a ureteral stent or percutaneous nephrostomy tube is essential to avert sepsis and allow effective antimicrobial treatment.

Occasionally, a patient will have an obstructing stone and a low-grade fever. A small amount of urinary extravasation from the renal pelvis, which can occur with acute ureteral obstruction, may produce a low-grade fever. In men lacking bacteriuria on urinalysis, high spiking fevers, and other signs of infection, empiric antibiotic coverage with close observation is reasonable. In women, the incidence of asymptomatic bacteriuria is more common and the possibility of infection above the point of obstruction considerably greater. The risks and benefits of prompt intervention to relieve obstruction versus antimicrobial coverage and observation must be considered on a case-by-case basis.

Acute bacterial prostatitis usually manifests as an acute febrile illness characterized by perineal discomfort, urinary frequency, hesitancy, diminished force of stream, and dysuria. Urinalysis usually reveals pyuria, and examination reveals a markedly tender, boggy prostate. Acute bacterial prostatitis or prostatic abscess may also occur in hospitalized patients with indwelling Foley catheters and should be considered as an occult source of fever and bacteremia. Physical examination is usually sufficient for diagnosis but may be aided by the use of transrectal ultrasound or CT to document a prostatic abscess. Prostate-specific antigen (PSA) determination often reveals significant elevation as a result of the acute or chronic inflammatory prostatic process (26).

Epididymitis with scrotal pain and swelling may be accompanied by fever. In men younger than 35 years of age, epididymitis can be caused by sexually transmitted diseases such as gonorrhea or *Chlamydia.* In older patients and in

patients with recent instrumentation, it is more likely due to urinary pathogens.

Renal Insufficiency

The urologist is often asked to evaluate patients with renal insufficiency for potentially reversible causes of renal dysfunction. Renal ultrasound is the best screening test for obstruction because it is neither nephrotoxic nor invasive and is very sensitive for detecting hydronephrosis associated with obstruction. When obstruction is the *sole* cause of renal insufficiency in a patient with two kidneys, it must be bilateral. Supravesical causes include conditions such as pelvic malignancy and retroperitoneal fibrosis causing bilateral ureteral obstruction, as well as obstructive processes (e.g., stone disease) affecting each unit independently. More commonly, bilateral hydronephrosis is seen with conditions affecting bladder function. These conditions include increased intravesical filling pressures from uninhibited detrusor contractions or diminished compliance, neurogenic bladder dysfunction, or severe outlet obstruction with failure to empty and elevated postvoid residual urine volumes. Therefore the screening evaluation for obstruction in the patient with renal insufficiency includes a postvoid residual determination by ultrasound or catheterization. Unilateral obstruction may contribute to renal insufficiency when only one kidney is present or when the normal compensatory response of the contralateral kidney is prevented by preexisting impairment of renal function. Clues to this possibility may be provided by a renal ultrasound showing a small (atrophic) contralateral kidney or one with echo-texture changes consistent with chronic intrinsic renal disease.

A renovascular cause of diminished renal function is another potentially reversible condition that the urologist may identify. It should be considered when there is no evidence of obstruction, no history or findings on urinalysis to support either acute or chronic intrinsic renal disease, or a history of conditions predisposing to vascular disease, such as hypertension, hypercholesterolemia, or diabetes mellitus, is present.

Medical History

Any urologic complaint must be framed in the context of the patient's medical history. In addition to inquiring about all previous genitourinary conditions or surgeries, the urologist must identify past or current disorders with potential effects on the genitourinary system (e.g., tuberculosis, diabetes mellitus). Each specific finding (e.g., microscopic hematuria) also prompts a search for pertinent conditions (e.g., sickle cell trait). The family history may be significant for genetic syndromes associated with urologic manifestations (autosomal-dominant polycystic kidney disease, Alport's syndrome, von Hippel–Lindau disease, tuberous sclerosis), as well as for diseases with known familial associations (stone disease, prostate cancer).

PHYSICAL EXAMINATION

Part of "2 - STANDARD DIAGNOSTIC CONSIDERATIONS "

Kidney

A kidney must be grossly enlarged or displaced to cause a perceptible bulge in the upper abdomen or flank. If a perinephric abscess is suspected, the patient should be in the knee–elbow position for an examination. The normal shallow depression below the lowermost rib may be obliterated by fullness and edema secondary to an underlying abscess.

Because of their location in the uppermost portion of the abdominal cavity, normal kidneys are usually not palpable. An exception is the newborn in whom both kidneys may be palpable during the first 48 hours of life because of the hypotonicity of all muscles. In approximately 10% of adults, usually thin women, the lower pole of the right kidney can be felt. Two maneuvers aid palpation: deep breathing and bimanual examination. The posterior hand lifts the soft tissue in the costovertebral angle, and the anterior hand presses deeply into the abdomen. The normal kidney is movable because it is fixed only by its vascular pedicle, and with deep inspiration, the descending diaphragm pushes the kidney down toward the examining fingers. The kidney is most easily felt between the fingers of both hands as a firm, smooth mass slipping upward as expiration starts. A renal mass is characteristically ballottable, unlike the liver and spleen, which usually can only be palpated with the anterior hand. Tenderness caused by inflammation in or around the kidney is best detected by exerting firm pressure in the costovertebral angle region.

In patients with hypertension, it is important to listen over the renal artery areas for the presence of a bruit. These murmurs are best heard anteriorly after complete exhalation.

Transillumination is occasionally helpful in newborns or small children with large, easily palpable abdominal masses. With the room as dark as possible, the mass should be manipulated against the abdominal wall with one hand while a high-intensity light (e.g., fiberoptic light cord) is firmly applied to the mass with the other hand. If the mass is cystic rather than solid, it will transilluminate, creating a reddish glow.

Ureter

In males, the ureter is not palpable by either abdominal or rectal examination, but in females, the lower ureter can be felt on vaginal examination. One or two fingers are gently pushed upward and outward, and at the limit of the fingertips, the ureter lies close to the bony pelvic wall and lateral to the ovary. From this point, the ureter can be followed to its junction with the bladder by carrying the fingers downward

and inward. If the ureter is normal, it is usually not identifiable because it is soft and nontender. If a stone is present, both the stone and ureter are usually palpable. The ureter can be felt as a tender tubular mass proximal to the stone.

Urinary Bladder

The normal empty or nearly empty bladder is neither palpable nor percussible because of its anatomic location in the pelvis. When it contains approximately 125 mL of urine, it rises out of the pelvis into the lower abdomen, projecting one fingerbreadth above the pubis. It rises progressively toward the umbilicus with further filling. If the bladder contains more than 500 mL of urine, it may be identifiable as a bulge in the middle lower abdomen. This swelling rising out of the pelvis is best appreciated by observing from the side, with the eyes more or less level with the lower abdomen. The distended bladder may be palpated as a firm, round, movable mass rising out of the pelvis into the lower abdomen. Whether or not a mass is palpable, the lower abdomen should be percussed from the umbilicus to the pubis. If the patient has a distended bladder, the normally resonant note is replaced by dullness. Percussion over a distended bladder may also cause the patient to experience a desire to void because of the sudden induced rise in intravesical pressure. An accurate measurement of bladder volume is obtained by catheter drainage or by bladder ultrasound.

To assess the extent of a bladder tumor, bimanual examination is performed when the patient is anesthetized and the bladder is empty. Intravesical masses are usually ballottable; fixation usually signifies gross perivesical extension.

Prostate and Seminal Vesicles

The prostate and seminal vesicles are palpated through the anterior rectal wall (Fig. 2.4). Rectal examination is best performed with the patient standing on the floor, knees slightly bent and elbows resting on the edge of the examining table. Bedridden patients are best examined in the lateral decubitus position, with their knees pulled up into their chest. The typical prostate is 4 cm wide, 2.5 to 3 cm high, and 4.5 cm long with a volume of 20 mL. Volume can be measured with the index finger, which is approximately 1.5 cm wide, or estimated based on the examiner's experience. Transrectal ultrasound with its accurate volume measurement allows the examiner a means to constantly evaluate his or her volume estimates. The normal gland is smooth, slightly movable, and nontender, and it has a rubbery consistency. Two distinct lobes can be felt separated by a median furrow with distinct lateral sulci. Indurated areas and nodules should be noted and a biopsy performed if appropriate. If the physician's finger is long enough, he or she may be able to feel the soft, tubular seminal vesicles above the prostate. Coming off the base of the prostate somewhat obliquely, they are most easily felt when they are distended or tender. EPS for microscopic examination can be obtained from most patients by deliberately massaging each prostate lobe in a lateral to medial direction.

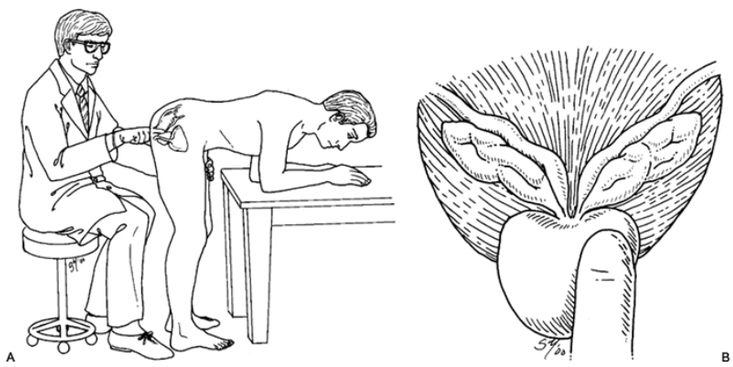


FIGURE 2.4. Palpation of the prostate and seminal vesicles. **A:** The prostate is best examined with the patient standing, knees slightly bent and elbows resting on the edge of the examining table. **B:** The examiner's index finger can be used to estimate the size of the prostate. (Reprinted with permission from Wyker A, Gillenwater JY. *Method of urology.* Baltimore: Williams & Wilkins, 1975.)

Scrotum and Testes

After the scrotal skin and perineum are inspected, the testes and epididymides should be palpated between the thumb and finger. The comma-shaped epididymis is closely attached to the posterolateral side of the testis. The physician can get his or her fingers into the groove between the epididymis and testis everywhere except superiorly, where the two structures are anatomically joined. In many men, a small ovoid lump, the rudimentary appendix testis, can be felt in or near the groove between the upper pole of the testis and the epididymis. The cord structures at the neck of the scrotum should be sifted through the physician's fingers. The solid cordlike vas is easily identified and followed to its junction with the tail of the epididymis. The other soft, stringy structures in the cord cannot be defined. To rule out the presence of the gravity-dependent varicocele, the cord must also be examined with the patient standing. If a varicocele is present, the intrascrotal varicosities secondary to valvular incompetence of the internal spermatic vein become distended in the upright position and feel like a bag of worms. Varicoceles tend to be left sided or bilateral due to the longer left gonadal vein attaching to the left renal vein. A solitary right-sided varicocele should alert the examiner to the risk of a retroperitoneal process.

Penis

If the patient is uncircumcised, the foreskin should be retracted to rule out phimosis with an obstructing, small aperture. To inspect the urethral meatus, the examiner must pinch the glans between the thumb and finger placed at the 6 and 12 o'clock positions. If the urethral meatus is not in the normal location, it can be found by following the midline raphe to its end on the undersurface of the penis. The shaft of the penis is palpated, looking particularly for the firm, fibrous plaques of Peyronie's disease. The floor of the urethra from the corona to the bulb should be palpated, looking for induration secondary to a stricture.

Pelvic Examination

Complete urologic examination of a woman includes a pelvic examination performed with the patient in lithotomy position. The vestibule and introitus are examined for evidence of mucosal atrophy, inflammation, or discharge. Any abnormal discharge is sampled for microscopic examination. The urethral meatus is examined and the urethra palpated for a mass or tenderness. Caruncle, a common benign finding in older women, is often seen as a purplish mass on the inferior aspect of the meatus. Calibration of the urethra is sometimes done to rule out urethral stenosis but is not a routine practice. Examination of the vaginal vault for cystocele, enterocele, or rectocele is performed in the course of a speculum examination of the cervix. Bimanual examination is carried out to identify any pelvic mass or tenderness.

URINALYSIS

Part of "2 - STANDARD DIAGNOSTIC CONSIDERATIONS "

A standard urinalysis consists of the following: determination of the physical characteristics of the urine, dipstick chemical tests, and microscopic examination of the urinary sediment. This key examination should not be delegated to uninterested laboratory personnel but should be performed by the physician. For reliable urinalyses, the urine must be collected properly and examined promptly.

Collection of the Urine Specimens

Of necessity, most urinalyses are performed on a random specimen freshly voided by the patient. However, the most information can be obtained if a first-morning specimen is examined. It is the best one for detecting formed elements in the urine and for determining whether urinary infection is present. The formed elements—red blood cells (RBCs), WBCs, and casts—are preserved in this characteristically acid and concentrated urine, whereas they may be lysed and disappear in dilute or alkaline urine. Bacterial colony counts are usually highest in this specimen because the bacteria have had more time to multiply during overnight incubation in the bladder.

For women, a voided sample is obtained by a clean-catch collection. The adequacy of the specimen for bacteriologic study depends on adequate cleansing with water of the periurethral areas to remove colonizing bacteria; avoiding bactericidal soap, which could produce a false-negative culture; and separation of the labia during collection. Only the midportion of the voided specimen should be collected. Urethral catheterization is performed when the patient is unable to perform the midstream collection properly because of handicap or body habitus, when microscopic examination of the voided specimen shows evidence of contamination by abundant squamous cells or mixed bacterial flora, or when previous culture of a voided specimen was positive for multiple organisms. The relatively minor drawbacks to urethral catheterization are the discomfort of the catheterization procedure itself and the potential for iatrogenic infection in up to 2% of patients from bacteria introduced into the bladder during the catheterization procedure.

For men, examination of the midstream urine (voided bladder 2) is the minimum urine examination, but the four-glass urine collection technique allows for the most thorough examination of the urine and prostate fluid. Stamey, Govan, and Palmer (33) originally described the four-glass urine collection technique as a method to distinguish urethral, bladder, and prostate infection in men. This technique was later modified by Meares and Stamey to include the EPS and is regarded as the gold standard for the evaluation

of the lower urinary tract in males (25). The technique provides samples for both microscopic analysis and bacterial culture, allowing for a quantitative assessment of the urine for leukocytes, erythrocytes, macrophages, and bacteria (27). General practice is for circumcised men to void into sterile containers, being careful not to touch their glans penis or hands to the inside of the container, which could introduce bacteria that typically colonize the skin. There is some debate among urologists whether cleansing the glans penis with an alcohol pad or bactericidal soap is necessary in circumcised men, but it is the authors' practice not to do so. However, uncircumcised men should retract the foreskin and clean the glans penis with an alcohol pad or bactericidal soap before providing a four-glass urine sample (27).

Voided Bladder 1

The voided bladder 1 (VB1) specimen should include the first 10 mL of urine. The VB1 represents the urethral cells and bacteria, which are washed out with the first 10 mL of urine. This specimen is important in the diagnosis of urethritis (27).

Voided Bladder 2

The voided bladder 2 (VB2) specimen represents the bladder urine. It should be collected from a midstream urine specimen by placing the sterile specimen container into the urine stream after voiding 100 to 200 mL (27).

Expressed Prostatic Secretions

The EPS should be collected into a sterile container while the examiner digitally massages the prostate. The uncircumcised patient should hold back his foreskin, and the examiner should be careful not to contaminate the sterile container by touching the patient's penis to it. Even with vigorous massage, the EPS may be unobtainable owing to anxiety and guarding on the part of the patient. Often, if the patient is left alone in a quiet room, he can relax his external sphincter and consequently “milk” his urethra manually and collect a drop or two of EPS for examination. The EPS should be examined at high power (400×) for leukocytes, erythrocytes, macrophages, RBCs, fat bodies, and bacteria (27).

Voided Bladder 3

The voided bladder 3 (VB3) specimen is another method to examine the EPS. It represents the first 10 mL of urine voided after massaging the prostate and includes any EPS that may be trapped in the prostatic urethra. It allows for the examination of the EPS when a drop of fluid is unobtainable by digital massage. No longer than 30 minutes should elapse after a prostatic massage to collect this specimen. The VB1, VB2, and VB3 specimens should be centrifuged for 5 minutes and the sediment examined at high power (400×) for leukocytes, macrophages, erythrocytes, bacteria, and fungal hyphae, with their numbers recorded. The VB1, VB2, EPS, and VB3 specimens should then be immediately plated and cultured or temporarily stored in a refrigerator at 4°C, until they can be cultured later that day (27).

For infants and small children, strap-on collection devices are used to collect specimens for routine analysis. However, these specimens are often unsatisfactory for culture, and specimens for culture are most often obtained by catheterization with a well-lubricated 5-Fr feeding tube. Suprapubic aspiration may be performed in small infants. Although this has the best reliability in terms of specimens for bacteriologic study, it is not practical for routine use.

Urine should be examined within 30 minutes of collection. If it is allowed to stand, bacterial growth may alkalize the urine with resultant destruction of RBCs, WBCs, and casts. If the urine cannot be examined promptly, it should be refrigerated.

Physical Characteristics of Urine

Color

The color of normal urine is determined by the concentration of urochrome, an endogenously formed yellow-brown pigment excreted at a uniform rate. Because the amount of pigment excreted each hour is the same, the color of the urine varies directly with the urine output. With high urine flow rates, the urine is pale, almost water colored, whereas with low urine flow rates it is a deep yellow color. The appearance of an abnormal urine color may occur from a number of causes. Certain urinary pigments may impart a pink-to-red color to the urine, mimicking hematuria. These include anthocyanins in beets and berries (beeturia), phenolphthalein (present in some laxatives), vegetable dyes (used for food coloring), heavy concentration of urates, phenazopyridine (Pyridium), and *Serratia marcescens* infection in infants (red diaper syndrome). Myoglobinuria occurring as a result of muscle breakdown is also a cause of nonhematuric tea-colored urine. Characteristically, the urinary sediment shows no RBCs, but the dipstick test is positive.

Pneumaturia

Pneumaturia is the passage of gas in the urine and generally is caused by a fistula between the intestinal tract and the urinary tract. Because gas is lighter than water, it always rises to the top of the bladder and consequently is passed at the end of urination (terminal pneumaturia). This fistula may occur at any level, from the stomach to the rectum of the intestinal tract and from the kidney to the urethra of the urinary tract, but the large majority involve the bladder and

the sigmoid colon or terminal ileum. The most common causes are diverticulitis of the sigmoid colon, carcinoma of the colon, and Crohn's disease.

Urinary tract infections caused by gas-forming bacteria and prior introduction of air into the bladder by means of insertion of a catheter or cystoscopy are occasional causes of pneumaturia.

Chyluria (Milky Urine)

Chyluria is the passage of lymph or chyle in the urine caused by the presence of an intrarenal, lymphatic-urinary fistula (11). The cause of this fistula is obstruction of the lymphatics superior to the kidney, usually the thoracic duct. With obstruction, there is increased back-pressure in the retroperitoneal and renal lymphatics, and eventually they rupture into a calyceal fornix. The most common cause of chyluria is filariasis resulting from *Wuchereria bancrofti.* The adult filarial worms invade the suprarenal lymphatics, causing obstruction and severe inflammation. Less common causes include posterior mediastinal and retroperitoneal tumors, tuberculosis, and trauma.

The passage of milky urine occurs intermittently, varying with the amount of fat ingested and sometimes with the patient's posture. Chylous urine contains fibrinogen, and fibrin clots may cause renal colic or urinary retention. The milky-colored appearance of the urine is usually diagnostic but may be confirmed by tests that confirm the presence of fat in the urine.

Clarity

Freshly voided urine is usually clear. Cloudiness of the urine is fairly common, however, and is usually caused by excessive amounts of crystals—amorphous phosphate in alkaline urine or amorphous urates in acid urine. This crystalluria is usually not clinically significant. The crystals can be dissolved, rendering the urine clear, by adding acid to dissolve the amorphous phosphates or by heating to dissolve the amorphous urates. Heavy pyuria, usually secondary to a bacterial infection, is a less common cause of cloudy urine.

Specific Gravity

The specific gravity of a solution is the measure of its density, an approximate measure of total solute concentration. The specific gravity of water is 1.000, plasma 1.010, and urine 1.003 to 1.040. Normally functioning kidneys conserve and excrete water as needed, accounting for the wide range of 1.003 to 1.040. Poorly functioning kidneys lose this ability, so urine specific gravity remains fixed at around plasma level (1.010).

Determination of the specific gravity of a random urine specimen is useful not only in assessing a patient's hydration status but also in interpreting the significance of dipstick chemical tests and urinary sediment findings. Substances such as WBCs, RBCs, and protein are generally excreted into the urine at a fairly constant rate. When the urine specific gravity is less than 1.007 as a result of a high urinary flow rate, the urine concentration of these elements may be significantly reduced. Also, in this hypotonic environment, RBCs are lysed, so patients with microhematuria may lack RBCs in the urinary sediment.

Chemical Tests

The standard urinalysis includes a dipstick assessment of nine different parameters. The pH, glucose, protein, ketone, bilirubin, and urobilinogen semiquantitative chemical tests provide the urologist with a powerful screening tool for metabolic abnormalities. The nitrite test serves as a screening for bacterial infection. Dipstick tests for blood and leukocyte esterase are commonly used in many settings as screens to determine the need for microscopic examination, but in the urologist's office, they are always used to complement the microscopic examination of the urinary sediment.

Urine pH varies between 5.0 and 8.0. It is usually more acidic in the early morning because of the excretion of a fixed acid load in the smaller volume of urine produced at night, and it is typically more alkaline after meals (alkaline tide). Specific medical conditions may be associated with characteristic changes in the range of urinary pH. Patients who form uric acid stones usually have a consistently acidic urine with a pH below 5.5. Patients with renal tubular acidosis type I (distal) are unable to acidify the urine below pH 5.5, even in the face of acid loading. This is in contrast to patients with type II renal tubular acidosis (proximal), who display the normal range of urinary pH (31). Alkaline urine above pH 8.0 is often associated with infection by urea-splitting organisms such as *Proteus.* Because leukocytes are lysed in very alkaline urine (above pH 8), it may sometimes be difficult to identify WBCs in the urinary sediment of patients with *Proteus* infection.

Detection of glucosuria by dipstick test indicates that the renal threshold for glucose reabsorption in the renal tubules (approximately 180 mg/dL) has been exceeded. This can occasionally be seen in normal patients, but most commonly, it is the result of hyperglycemia caused by diabetes mellitus. Although the semiquantitative dipstick test provides an approximate measure of the concentration of glucose in the urine, the clinician should realize that the degree of glucosuria is not necessarily an accurate indicator of the degree of hyperglycemia. Further medical evaluation and serum glucose determination are required. Elevated serum ketones, which may occur in diabetic ketoacidosis and in catabolic situations such as starvation, result in ketonuria detectable by the dipstick test.

The test for bilirubin will be positive when there are significant amounts of conjugated bilirubin filtered by the kidney and excreted in the urine. This is most commonly

seen in liver disease and biliary obstruction. Urobilinogen, absorbed via the enterohepatic circulation, is normally present in small amounts in the urine. Increased levels are seen with hemolysis, gastrointestinal hemorrhage, and hepatocellular disease. Diminished levels may result from antibiotic suppression of the gut bacterial flora, and urobilinogen may disappear with complete biliary obstruction.

The dipstick test is the most commonly used screening test for urinary protein, detecting protein concentrations as low as 10 mg/dL. Normal supernatant urine usually gives a negative test for protein because the daily protein excretion of normal individuals is usually less than 50 mg.

Proteinuria is defined as the excretion of more than 150 mg of protein in 24 hours. The dipstick has a pH-sensitive indicator dye that changes color with various concentrations of protein. Although more sensitive to negatively charged protein (albumin) than to positively charged protein (Bence Jones), it does give a positive test when the concentration of Bence Jones protein is greater than 50 mg/dL. When the dipstick is positive, the 24-hour protein excretion in the urine should be determined by analysis of a timed 24-hour collection.

There are four types of proteinuria: glomerular, tubular, overflow, and functional. Glomerular is the most common form of proteinuria, found in patients with significant glomerular damage. A defect in the glomerular filter permits increased filtration of normal plasma proteins, and because albumin has the highest concentration in the plasma, glomerular proteinuria is predominantly an albuminuria. Massive proteinuria with excretion of 4 g/day or more is characteristic of the nephrotic syndrome.

Proteinuria secondary to tubular or interstitial disorders of the kidney occurs when the proximal tubules are unable to reabsorb the normally filtered proteins. In tubular proteinuria, one usually finds increased amounts of low-molecular-weight proteins smaller than albumin in the urine, and the total protein excretion is usually 1 to 2 g/day.

Overflow proteinuria is caused by the presence in plasma of abnormal quantities of low-molecular-weight proteins that are filtered across the normal glomerular capillary wall and saturate the proximal tubular resorptive mechanism. Examples include Bence Jones proteinuria, myoglobinuria, and hemoglobinuria. This is the least common type of proteinuria.

When proteinuria occurs in the absence of any clear-cut renal or systemic disease, it is termed *functional* or *physiologic proteinuria.* The mechanisms responsible for this type of proteinuria are unknown but are probably hemodynamic. Functional proteinurias are characteristically intermittent and mild, with protein excretion rarely exceeding 1 g/day. Clinical states that may cause this type of proteinuria include fever, exercise, emotional stress, and renal venous hypertension (congestive heart failure). Orthostatic (postural) proteinuria is a special form of functional proteinuria seen in healthy young adults. These individuals excrete protein in their urine in the upright position but excrete little or none on recumbency.

Urinary Sediment

Examination of the urinary sediment is performed on a centrifuged sample of urine. All specimens should be mixed thoroughly before a sample is taken because formed elements fall to the bottom during storage. Approximately 15 mL is centrifuged for 3 to 5 minutes, the supernatant removed, the pellet resuspended in the residual fluid, and a drop placed under a cover slip for examination. Before the specimen is examined, the pH and specific gravity of the urine should be noted because of their potential to influence stability of the formed elements such as WBCs and RBCs in the specimen.

White Blood Cells

Pyuria is increased WBC excretion in the urine (20,22) and may be detected by a dipstick test for leukocyte esterase or by counting the number of WBCs in the centrifuged, unstained urinary sediment. A WBC excretion rate of 400,000 WBCs per hour may be considered the upper limit of normal. If this excretion rate of 400,000 WBCs per hour is divided by the average urine output per hour of 50 mL, the upper limit of WBC concentration in the urine would be 8,000 WBCs/mL. This translates to urinary sediment findings of 4 to 5 WBCs per HPF, and for clinical purposes, pyuria may be defined as more than 5 WBCs per HPF. This method of quantitating pyuria is imprecise. Factors that may alter the microscopic findings significantly include presence or absence of contamination of the urine specimen, urine production rate at the time the urine specimen was obtained, and the specifics of preparing and examining the urinary sediment.

Leukocyte esterase, an isoenzyme specific for leukocytes, is the basis for the leukocyte esterase test strip. Both false-positive and false-negative results may occur, and the dipstick test is best combined with microscopic examination of the urinary sediment. When leukocytes are not seen despite a positive dipstick test in the setting of alkaline urine (pH greater than 8.0), such as might occur with *Proteus* infection, alkaline lysis of the leukocytes should be suspected.

Pyuria is the body's response to the inflammation of the urinary tract, but it is not a particularly sensitive sign of infection. Although most patients with acute bacterial infection such as cystitis have pyuria, significant bacteriuria may be present without pyuria. A urine culture is the only reliable means to diagnose infection. Pyuria is also not a specific sign of infection. Although many physicians equate the two (pyuria and urinary infection), this is a dangerous concept that can lead to patients being inappropriately treated for long periods with antibiotics for presumed infection. Pyuria has numerous causes, including tumors, stones,

glomerulonephritis, foreign bodies, drugs (e.g., cyclophosphamide), fungal infection, and tuberculosis. When pyuria exists with a negative culture, a diligent search must be initiated to discover and treat the underlying cause.

Red Blood Cells

The average individual usually excretes approximately 30,000 RBCs per hour but may excrete up to 100,000 RBCs per hour. If the urine output is 50 mL/hour (1,200 mL/day), up to 2,000 RBCs/mL may be excreted, and this concentration of RBCs gives urine findings of 1 or fewer RBC per HPF. Greater than 1 RBC per HPF may be considered microscopic hematuria, but a commonly accepted benchmark for clinically significant hematuria is greater than 3 RBCs per HPF (23).

Osmotic Rupture of Red Blood Cells by Hypotonic Urine

The dipstick test for hematuria complements microscopic examination of the urinary sediment. RBCs are relatively resistant to alkaline lysis but are readily lysed in hypotonic urine. When the urine specific gravity is 1.007 or lower, the dipstick test will be positive even though no RBCs can be seen in the urinary sediment.

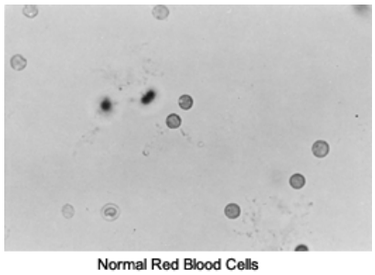
Urine containing 100,000 RBCs/mL with a urinary sediment finding of 30 RBCs per HPF was used as the standard in Table 2.5 .

Urine Specific Gravity	RBCs/HPF	Dipstick	% Lysis
1.001	0	++++	100
1.005	0	++++	100
1.007	0	++++	100
1.010	30	+	0
1.015	30	+	0
1.020	30	+	0
1.025	30	+	0
1.028	30	+	0

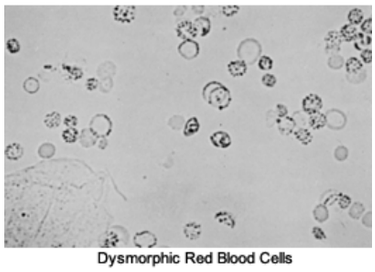
RBCs/HPF, red blood cells per high-power field.

TABLE 2.5. OSMOTIC RUPTURE OF RED BLOOD CELLS BY HYPOTONIC URINE

It is clinically important to know whether the RBCs present in the urinary sediment are glomerular or nonglomerular in origin because glomerular RBCs are diagnostic of glomerulonephritis. Two findings identify the glomeruli as the source of the RBCs: dysmorphic RBCs and RBC casts. Fairley and Birch (13) and Fassett and associates (14) used a phase microscope to study RBC morphology and reported that these dysmorphic RBCs were characteristic of glomerular bleeding. The marked RBC membrane distortions are thought to be caused by osmotic and physical changes during the passage of RBCs through the nephron. These findings have been confirmed by others. Stamey and Kindrachuk (34), in their excellent manual, showed many fine photographs contrasting dysmorphic RBCs of glomerular origin with RBCs of nonglomerular origin (Fig. 2.5). They also demonstrated that these dysmorphic RBCs could be identified under standard light microscopy, as well as phase-contrast microscopy.



Normal Red Blood Cells



Dysmorphic Red Blood Cells

FIGURE 2.5. Normal and dysmorphic red blood cells. (Reprinted with permission from Stamey TA, Kindrachuk RW. *Urinary sediment and urinalysis: a practical guide for the health science professional.* Philadelphia: WB Saunders, 1985.)

Casts

The basic foundation of all renal casts is a special protein, Tamm-Horsfall globulin, secreted by the tubular epithelial cells. A small number of these basic hyaline casts are excreted normally, so their presence in the urinary sediment is not clinically significant. If RBCs, WBCs, or sloughed tubular epithelial cells are present in the renal tubular lumina, they may become incorporated within the cast. If these casts are detected in the urinary sediment, the presence of renal disease should be suspected. Because Tamm-Horsfall protein is soluble at a pH of 7.1 or higher, *all* casts disappear in alkaline urine.

Bacteria

Nitrite is a product of bacterial metabolism in many species of Gram-negative bacteria, and its presence in the urine is a strong indicator of significant bacteriuria. The false-positive rate for the dipstick test is low, and it may reliably be used as the basis for empiric antibiotic therapy pending results of culture and sensitivity. The more significant false-negative rate of the dipstick test, even in the presence of bacteriuria, can be due to a number of factors, including the presence of non–nitrite-producing organisms or very dilute urine. Urine culture is the only reliable means to exclude bacteriuria.

On microscopic examination, an effort should be made to detect bacteria because more than ten bacteria per HPF usually signifies greater than 10^5 colony-forming units (cfu) per milliliter (18). The morphology of any observed bacteria should be noted. A polymicrobial appearance or the presence of filamentous bacilli characteristic of lactobacillus in a woman's voided specimen strongly suggests contamination by vaginal or periurethral flora. In patients to be treated for suspected urinary tract infection, the identification of rods, streptococci (enterococci), or cocci (staphylococci) in the urine may guide the selection of antibiotic therapy. The presence of fungal elements or trichomonads should likewise be noted.

Because the most common uropathogens are aerobic species (Gram-negative rods, enterococci, and staphylococci), the standard urine culture is a test for aerobic organisms. A positive culture result is generally considered to be greater than 10^5 cfu/mL on a voided specimen, but as few as 10^3 cfu/mL may represent significant bacteriuria if the specimen is obtained in sterile fashion (e.g., catheterization). Similarly, localizing quantitative cultures on split-voiding fractions may reveal low-level bacteriuria in one fraction (e.g., VB3) that is nonetheless significantly greater than the other fractions, thereby showing bacterial infestation in the source of that fraction (e.g., prostate). Less commonly, fungi or microbacteria may be the cause of urinary tract infection. Fungi may grow on routine culture media with prolonged incubation; however, if fungal infection is suspected, the fungal culture should be specifically requested. Sterile pyuria with or without microscopic hematuria is a cardinal feature of genitourinary tuberculosis. Diagnosis is made by submitting at least three morning urine specimens to be examined for acid-fast bacteria and cultured for acid-fast bacteria for up to 8 weeks.

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3

IMAGING

Contents

3A EXCRETORY UROGRAPHY

Robert A. Older

Part of "3 - IMAGING "

R.A. Older: Department of Radiology, University of Virginia Health System, Charlottesville, VA 22908.

Excretory urography remains a basic radiologic examination of the urinary tract and is the foundation for the evaluation of suspected urologic disease. Despite development of the newer diagnostic modalities, such as isotope scanning, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), excretory urography has maintained a prominent role in uroradiology. Some indications have been altered and will continue to change with the newer imaging modalities. Noncontrast spiral CT has become the study of choice for suspected ureteral stones (88). The initial evaluation of suspected urinary tract structural abnormalities, hematuria, pyuria, and renal calculus disease is performed with excretory urography. The examination is relatively inexpensive and simple to perform, with few contraindications.

When properly performed, excretory urography can provide valuable information about the renal parenchyma, pelvicalyceal system, ureters, and urinary bladder. Diagnostic results depend largely on the method by which excretory urography is performed. A closely monitored examination with specific radiographs determined by the needs of a patient provides the optimal examination. A study using only predetermined radiographs that are reviewed at a later time often provides inadequate diagnostic information. During urography, each radiograph should be evaluated immediately after it is obtained to determine which questions have been answered and which have not. Any necessary additional radiographs can then be obtained.

It is reasonable to have certain standard radiographs obtained in the immediate postinjection phase of a urogram. Further radiographs, however, should be determined on the basis of initial findings and not limited to a preset series.

CONTRAST MEDIA

Chemical Properties and Excretion

The first compounds introduced for clinical use in excretory urography during the early 1930s were diiodinated compounds that were hampered by low radiopacity and moderate toxicity. More often than not, retrograde pyelography was necessary to evaluate the urinary tract properly. The ability to achieve adequate opacification of the pelvicalyceal system and the renal parenchyma resulted from the introduction of the triiodinated benzoic acid derivatives in the early 1950s. Since then, several salts of triiodinated benzoic acid compound have been marketed for excretory urography with slight structural differences but similar physiologic and radiographic properties (Table 3A.1 and Fig. 3A.1).

Trade Name	Generic Name	Concentration (%)	Osmolality (mOsm/kg)	Iodine Content (mg/mL)
Renografin-60	Meglumine and sodium diatrizoate	60	1,420	288
Reno-M-60	Meglumine diatrizoate	60	1,500	282
Hypaque-50	Sodium diatrizoate	50	1,550	300
Hypaque-M-60	Meglumine diatrizoate	60	1,415	282
Conray-60	Meglumine iothalamate	60	1,400	282

TABLE 3A.1. COMMONLY USED IONIC CONTRAST MEDIA FOR EXCRETORY UROGRAPHY

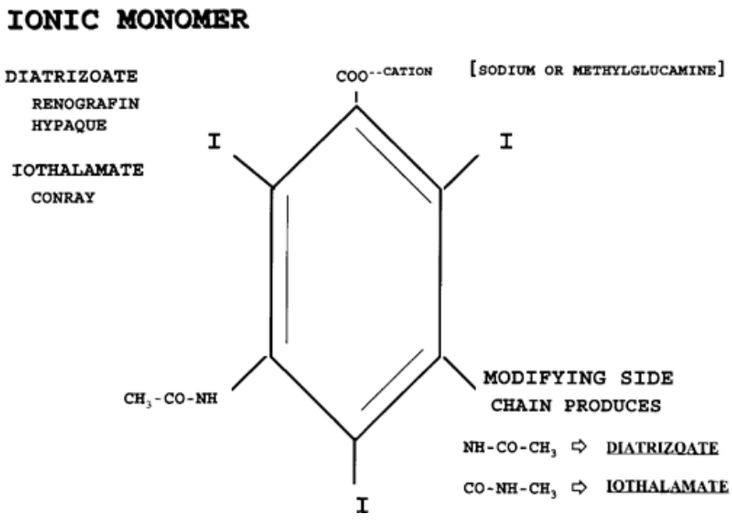

FIGURE 3A.1. Molecular structure of currently used ionic urographic contrast media. (From Older RA, Resnick MI, eds. *Basic radiologic techniques in diagnosis of genitourinary disease*, ed 2. New York: Thieme Medical Publishers, 1994, with permission.)

The ionic compounds are water-soluble salt solutions that are hypertonic with an osmolality 2.5 to 6.0 times that of plasma. The cations are either sodium or meglumine (methylglucamine). The large number of different ionic contrast media merely represents variations of concentration and cations for the anions diatrizoate or iothalamate. The name often denotes a specific iodine concentration along with the cation and anion used. For urography, only the 50% or 60% agents are routinely used.

Researchers have described objective differences in the pyelogram when comparing sodium and meglumine as the cation (9,21,75). In the laboratory, the sodium salt has produced higher urinary iodine concentrations, whereas meglumine has given better distention of the pelvicalyceal system because of a greater diuresis. Neither of the two cations produces any significant difference in the nephrogram (21,24,36). With the doses used in present-day excretory urography, the advantages and disadvantages are minimal. Good-quality urography can be achieved using either of the salts.

For urography, low-osmolar contrast and nonionic contrast are essentially the same. Ioxaglate, a low-osmolar, but ionic, dimer is used predominantly in angiography. Low-osmolar contrast media are now used in more than 60% of

all radiographic procedures. They contain the same iodine concentration as the conventional agents but are much less hypertonic (Table 3A.2). These new compounds have approximately half the osmolality of the conventional compounds. To reduce the osmolality of the contrast media, two basic approaches are used. Three of these compounds (iohexol, iopamidol, and ioversol) are nonionic formulations that consist of three iodine atoms attached to a fully substituted, uncharged benzene ring (Fig. 3A.2). Because no balancing cation is needed, osmolality is reduced to half that of the conventional agents at the same iodine content. The fourth agent (ioxaglate) is an ionic dimer that consists of two linked benzene rings, each with three iodine molecules, and a single negative charge balanced by a cation. Thus there are two particles to six iodine atoms, also halving the osmolality at an equal iodine concentration. This feature is a definite benefit in angiography, where ioxaglate is used primarily because the lower osmolality of ioxaglate causes less pain in intraarterial injections. The lower-osmolality compounds also cause fewer physiologic responses. The newer media produce less peripheral vasodilation and less effect on myocardial contractility and cardiac electrophysiology. These decreased effects may be caused by the lower osmolality or due to a lower chemotoxicity (10).

TABLE 3A.2. LOW-OSMOLALITY CONTRAST MEDIA

Trade Name	Generic Name	Concentration (%)	Osmolality (mOsm/kg)	Iodine Content (mg/mL)
Omnipaque 300	Iohexol	64.7	709	300
Omnipaque 350	Iohexol	75.5	862	350
Isovue 300	Iopamidol	61	616	300
Isovue 370	Iopamidol	76	796	370
Optiray 320	Ioversol	68	702	320
Hexabrix	Ioxaglate (sodium 19.6%, meglumine 39.3%)	58.9	600	320

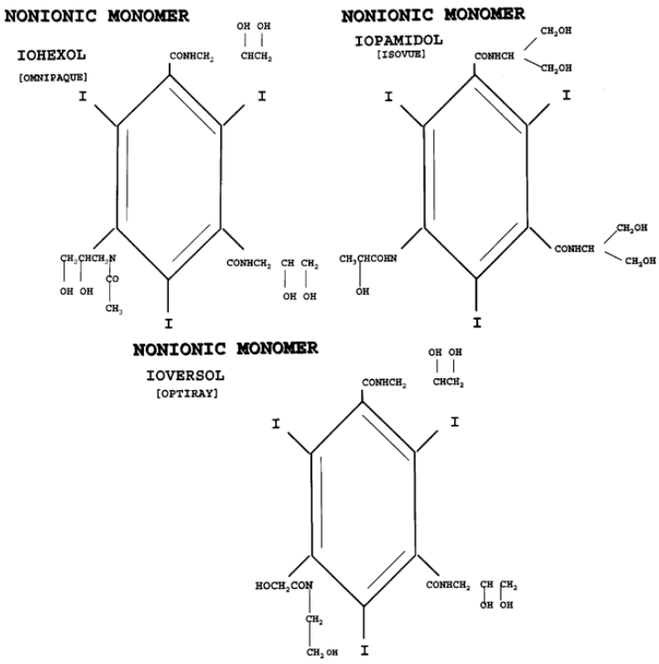

FIGURE 3A.2. Molecular structures of currently used nonionic urographic contrast. (From Older RA, Resnick MI, eds. *Basic radiologic techniques in diagnosis of genitourinary disease*, ed 2. New York: Thieme Medical Publishers, 1994, with permission.)

Clinical studies have demonstrated that the nonionic agents can produce a urogram equal to or better than ionic media (3,89). The lower osmolality and solute load allow the nonionic agents to produce a denser pyelogram with higher urinary iodine concentration (23,89). There is a potential for decreased distention of the collecting system because of reduced diuretic effect, but this has not been a significant problem. No significant difference in the nephrogram has been noted (23,89). Therefore using nonionic contrast does not decrease the diagnostic efficacy of urography.

Contrast material is almost entirely excreted by glomerular filtration with little or no tubular excretion. Approximately 0.5% to 2.0% is excreted by the liver and bowel. Most of this is excreted by the biliary system, although the small intestine, stomach, and salivary glands can excrete small amounts. *Vicarious excretion* is the term used when extrarenal excretion is apparent on the radiograph (8). Contrast medium may be seen in the gallbladder and colon 24 hours after injection in patients with decreased renal function, in whom extrarenal routes of excretion take on greater importance. Occasionally, this phenomenon is also seen in patients with normal renal function after they have received large doses of contrast medium (Fig. 3A.3) (70). The amount of contrast excretion by the kidney and collecting system with resultant radiopacity is related to plasma concentration and glomerular filtration rate (GFR) (17). Because GFR is fixed in the individual, only the plasma concentration can be manipulated. Increasing the amount of contrast material will increase the radiopacity of the urinary tract to a certain extent. At doses greater than 2 mL/kg, the radiopacity will not continue to increase significantly, but the risk of toxicity is increased. The method of injection will also alter the quality of the urogram. When a drip infusion is used, the plasma concentration plateau is slowly reached and falls off over a longer period. The drip infusion technique never achieves a plasma level as high as the bolus injection (Fig. 3A.4) (17) and is of no benefit, save convenience. The intensity of the nephrogram is related to the plasma concentration. Studies have shown that immediately after bolus injection, a peak plasma concentration is achieved, which then declines rapidly. The nephrogram will be maximal during this period of peak plasma concentration (32).

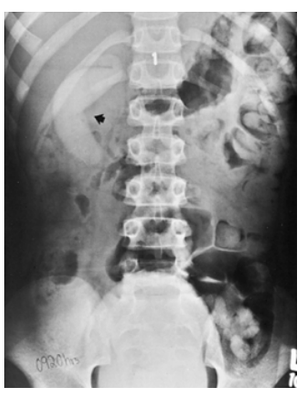

FIGURE 3A.3. Vicarious excretion of contrast material with opacification of the gallbladder *(arrowhead)*. X-ray film taken supine 24 hours after large dose of intravenous contrast material.

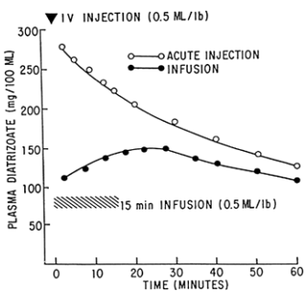

FIGURE 3A.4. Plasma diatrizoate concentration as a function of time and type of injection. IV, intravenous. (From Cattell WR. Excretory pathways for contrast media. *Invest Radiol* 1970;5:473, with permission.)

Following glomerular filtration, approximately 85% of the water resorption that concentrates the urine and increases radiopacity occurs in the proximal convoluted tubules. Additional resorption occurs in the distal convoluted tubules and collecting ducts, being regulated by antidiuretic hormone (ADH) and depending on the state of hydration. Because of this small contribution, the effectiveness of dehydration in increasing radiopacity is minimal, especially in light of the larger contrast doses used today. A comparison of patients with and without fluid restriction favored the fluid-restricted group in terms of radiographic scoring, but the difference was not statistically significant (22).

In most clinical situations, significant dehydration is not actually achieved. However, fluid restriction will limit fluid intake and the use of diuretic substances such as coffee, and it can avoid a state of excessive hydration with increased flow rate (43,64). We have found these urograms generally of better quality than those with no fluid restriction. Nephrotoxicity is the primary concern in fluid restricting a patient, and this should not be done in any patient with preexisting renal disease. Therefore, if it cannot be determined whether a patient has preexisting renal disease, fluid restriction should be avoided. In patients with normal renal function, overnight fluid restriction will probably improve the quality of the examination.

Physiologic Considerations

Following intravenous (IV) injection of ionic contrast material, there are several subjective effects, the intensity of which vary with the rate of injection and the individual. A sense of warmth and a “flushing” sensation are almost

universal and may be misinterpreted as a reaction. A metallic taste and circumoral tingling are commonly observed. Sensations of pelvic and perineal warmth are not unusual and may be distressing to some patients. These uncomfortable side effects are virtually eliminated with nonionic contrast media.

Several physiologic responses have been noted with intravascular injection of contrast media. There is usually a mild and transient decrease in the systemic blood pressure along with a transient decrease in the heart rate (90). Pulmonary arterial pressure has been found to be transiently increased by contrast medium (76). Renal blood flow is initially increased but is followed by a decrease in renal blood flow proportional to the dose administered (31). A depressant effect on the myocardium has been shown with decreased myocardial contractility that is thought to be secondary to calcium binding and a depressant effect on the sinoatrial (SA) and atrioventricular (AV) nodes (46,79). It has been suggested that subclinical bronchospasm occurs in most patients (80). These effects are all transient and seem inconsequential but may play a part in the untoward reactions seen in a small percentage of patients.

CONTRAST MEDIA REACTIONS

Incidence and Classification

Adverse reactions to intravascular contrast media are well known and are a source of concern, but fortunately, most cases are mild and insignificant. Several large series of patients have demonstrated an overall incidence of contrast reactions of all types ranging from 5% to 8% (85,86,97). However, major respiratory or cardiovascular reactions are reported to occur in fewer than 1% of patients. The reported frequency of fatal reactions ranges between 1 in 14,000 and 1 in 75,000 (4,42,84).

Contrast reactions are usually classified as mild, moderate, or severe. In most series, 95% or more of all reactions are classified as mild to moderate. A sense of heat and flushing, along with most cases of nausea and vomiting, should not be considered adverse reactions but rather common side effects of the contrast material. Mild reactions include mild urticaria and minimal respiratory symptoms. Moderate reactions include extensive urticaria, angioneurotic edema, and bronchospasm. Severe reactions include intense bronchospasm with laryngeal edema along with potentially lethal cardiovascular responses such as marked hypotension, pulmonary edema, and ventricular arrhythmias that can lead to cardiovascular collapse.

Etiology

Although adverse reactions to contrast media have been studied extensively over the years, their pathogenesis remains

somewhat obscure. Most evidence points toward a multifactorial concept in which several poorly understood responses to contrast media may lead to an adverse reaction.

Certain reactions such as urticaria, erythema, and bronchospasm appear to be allergic. They resemble an allergic reaction and respond as an allergic reaction to antihistamines and epinephrine. However, the allergy concept is controversial, with many researchers disputing its validity. Failure to find the classic immunoglobulin E (IgE)-type antibodies to contrast media in humans and the fact that individuals may react without prior exposure to contrast media do not support the allergy model (35,55,59). However, work by Brasch (11) supports the theory that contrast material may act as haptens and induce specific antihapten antibodies. Anticontrast media antibodies of both the immunoglobulin G (IgG) and IgE classes have been produced in rabbits. Contrast reactions in individuals without prior exposure are explained on the basis of antibody cross-reactivity, where the contrast media are similar to other antigens to which the individual has had prior exposure, such as other halogenated benzene rings found in food additives, pesticides, and other substances.

Some of the most severe reactions, however, do not resemble allergic reactions. Sudden major cardiovascular responses such as profound hypotension, pulmonary edema, ventricular arrhythmias, and myocardial infarction involve responses that are poorly understood. Hypertonicity and direct chemotoxicity of the contrast material have been suggested as etiologies (30,77). Enhanced vagal tone as the result of stimulation of the vasomotor center of the medulla and accentuation of contrast medium–induced myocardial toxicity has been suggested as the etiology in the sudden deaths of fluid-depleted dogs following IV injection of contrast material (47).

Lalli (52,53) has developed an interesting hypothesis based on the effect of contrast medium on the central nervous system (CNS) after crossing the blood–brain barrier. He believes that all reactions are ultimately neurogenic, centered on the hypothalamus and medulla. The combination of anxiety and contrast materials stimulating the hypothalamus can lead to a variety of neurogenic responses, such as hypotension, ventricular arrhythmias, and pulmonary edema. He thinks that anxiety plays a large role in contrast reactions and that examinations performed in a quiet, nonthreatening manner will reduce the number of adverse reactions.

A significant decrease in mild, moderate, and severe reactions has been demonstrated with nonionic contrast materials. The decrease is approximately a factor of 5 (45,73,98). Initially, there was controversy regarding the methodology of the comparative contrast studies, but the data have continued to indicate much greater safety for nonionic contrast materials (16), and safety is no longer a controversial issue.

Relationship to Previous Reactions and Hypersensitivity States

Studies have shown that individuals with known hypersensitivity states have contrast reactions on the order of twice those of the normal population, 10% to 12% versus 5%. Individuals who have had a previous contrast material reaction have a threefold increase; 15% to 16% of these individuals have a recurrent contrast reaction (85,97). The nature of the recurrent reaction is variable, with minor reactions being repeated more often than life-threatening reactions.

Value of Pretesting and Premedication

IV injection of a test dose of contrast medium has not been proved useful as a screen for potential contrast reactions. Yocum, Heller, and Abels (99) demonstrated some value in high-risk patients with pretesting, but it involved a sophisticated protocol using multiple serial dilutions of the contrast material. A standard 0.5- to 1.0-mL IV test injection is of little use and may precipitate life-threatening reactions (85).

Investigators have shown that the incidence of recurrent reactions can be reduced by half or greater of the expected incidence with prophylactic antihistamines and corticosteroids (38,48,99). Steroid premedication can reduce the risk of an adverse reaction for ionic contrast to a level close to that of nonionic contrast. However, steroid premedications are not effective unless given for at least 12 hours before the administration of contrast (56,58), and this has limited the feasibility of routine premedication in all patients (25). The combination of a steroid preparation with a nonionic agent further reduces the risk of an adverse reaction (57); this is our approach to patients with previous adverse reactions to contrast or those with a significant allergy history in general. For convenience, we use Decadron 4 mg orally every 6 hours for 24 hours before the examination. Although steroid preparations and nonionic contrast can reduce the risk of an adverse reaction, they do not completely eliminate the possibility, and the need for a contrast examination should be examined closely in this group of patients.

Treatment of Contrast Material Reactions

Contrast reactions usually occur immediately or within minutes following the injection. However, severe reactions can occur after 15 minutes or even later. All physicians, nurses, and technologists involved in urography should be well trained in the recognition of the early signs of a contrast reaction and in resuscitation. Prompt recognition of a reaction and immediate treatment can be lifesaving. In all excretory urograms, the IV needle or catheter used for delivering the contrast should be left in place for the duration of the examination in case a reaction develops and

IV access is needed. Blood pressure and electrocardiographic (ECG) monitoring equipment, as well as oxygen, should always be close at hand. In each room, there should be ready access to epinephrine, atropine, and diphenhydramine. In cases of cardiovascular collapse, a "crash cart" containing a defibrillator, an endotracheal set, and drugs useful during cardiac arrest should be nearby. Table 3A.3 summarizes therapeutic measures for contrast reactions with drug doses.

Urticaria
Mild: Observation.
Moderate: Diphenhydramine 25–50 mg PO/IM/IV (pediatric: 1–2 mg/kg IV/IM up to 50 mg).
Severe: Add cimetidine 300 mg, diluted to 20 mL, slow IV (pediatric: 5–10 mg/kg diluted to 20 mL, slow IV); *or* ranitidine 50 mg, diluted to 20 mL, slow IV (pediatric: use not established); *or* epinephrine IV, 1:10,000, 1.0 mL (0.1 mg) slowly over 2–5 min.

Bronchospasm (Isolated)
Oxygen: 6–10 L/min.
β_2-Agonist metered-dose inhaler (2–3 deep inhalations): Metaproterenol (Alupent), terbutaline (Brethaire), albuterol (Proventil).
Epinephrine: SC, 1:1,000, 0.1–0.2 mL (0.1–0.2 mg) (pediatric: 0.01 mg/kg up to maximum of 0.3 mg) (SC can be used if blood pressure normal); IV, 1:10,000, 1 mL (0.1 mg), slowly (e.g., over 3–5 min) (pediatric: 0.1 mL/kg IV up to 0.1 mg, may repeat every 5–15 min as needed).

Anaphylaxis-like Reaction (Generalized)
Oxygen: 6–10 L/min.
Suction, as needed.
Elevate patient's legs if hypotensive.
Intravenous fluids: Normal saline; Ringer's solution.
Epinephrine: IV, 1:10,000, 1 mL (0.1 mg), slowly (e.g., incrementally over 3–5 min), may repeat (pediatric: 0.1 mL/kg IV up to 0.1 mg, may repeat every 5–15 min as needed)
(*avoid* epinephrine in patients taking noncardioselective β-adrenergic blocking drugs); alternative drug therapy: isoproterenol 1:5,000 solution (0.2 mg/mL), 1 mL (diluted to 10 mL), titrate to effect at 1 mL/min (20 mg/min).
Antihistamines: H_1 blocker—diphenhydramine 50 mg, IV (*caution:* may exacerbate or cause hypotension); H_2 blocker—cimetidine 300 mg, diluted to 20 mL, slowly IV (pediatric: 5–10 mg/kg, diluted slowly); ranitidine 50 mg, diluted to 20 mL, slowly IV (pediatric: use not established).
β_2-Agonist metered-dose inhaler (2–3 inhalations): Metaproterenol (Alupent), terbutaline (Brethaire), albuterol (Proventil).
Corticosteroids: Methylprednisolone 100–1,000 mg IV, can be repeated.

Hypotension (Isolated)
Elevate patient's legs.
Oxygen: 6–10 L/min.
Intravenous fluids (primary therapy): Rapidly, 0.9% sodium chloride for injection (normal saline) or Ringer's solution.
If not responsive, consider vasopressor such as epinephrine 1:10,000 dilution 1 mL (0.1 mg) slowly over 2–5 min (93).

Vagal Reaction (Hypotension and Bradycardia)
Elevate patient's legs.
Oxygen: 6–10 L/min.
Intravenous fluids: Rapidly, 0.9% sodium chloride for injection (normal saline) or Ringer's solution.
Atropine: Adults 0.6–1.0 mg IV, repeat q3–5min to 2–3 mg total (pediatric: 0.02 mg/kg IV; maximum dose 0.6 mg; may repeat to maximum of 1 mg for infants and 2 mg for adolescents).

TABLE 3A.3. ACUTE REACTIONS TO CONTRAST MEDIA: TREATMENT

Mild reactions usually do not require treatment except for reassurance and comforting. One must cast a suspicious eye on all reactions, however, because they may progress to a more serious nature. If the urticaria is symptomatic, 25 to 50 mg of diphenhydramine given intramuscularly or intravenously is effective.

Progressive urticaria should be treated with diphenhydramine 0.25 to 50 mg intravenously or intramuscularly in adults. If urticaria is profound, one should consider cimetidine, ranitidine, or epinephrine (12,93). Bronchospasm alone can be treated with a β_2-agonist administered via metered-dose inhaler (13,14,93) or subcutaneous epinephrine (1:1,000) (20). Severe bronchospasm and evidence of laryngeal edema should be treated immediately with IV epinephrine because such a reaction may suddenly worsen and subcutaneous epinephrine at this point would be useless because of poor absorption. A dose of 1 mL of 1:10,000 epinephrine should be given intravenously (slowly, 2 to 5 minutes) (93). Epinephrine is short lived, and repeated doses may be necessary at 5- to 15-minute intervals.

Isolated hypotension may be treated initially with leg evaluation, oxygen, and fluids. If not responsive, IV epinephrine can be used (93). In hypotensive patients, it is extremely important to check the pulse rate. Bradycardia in a hypotensive patient indicates a vasovagal type of response, and treatment with 0.6 to 1 mg of IV atropine is usually extremely effective; 2 to 3 mg of atropine can be given over 10 to 20 minutes.

Severe cardiovascular reactions that involve hypotension, loss of consciousness, and airway obstruction require immediate therapy. In total cardiovascular collapse, additional IV lines and establishment of an adequate airway are mandatory when embarking on cardiopulmonary resuscitation. IV epinephrine is the treatment of choice for anaphylactoid reactions and should be given as soon as such a reaction is diagnosed. Prompt therapy can reverse an anaphylactoid reaction within minutes, whereas epinephrine given after full development of the reaction may not reverse it for hours. IV epinephrine is a potent medication, however, and is usually not needed for mild reactions. Rapid assessment of the patient as to the severity of a reaction is therefore essential.

Corticosteroids are of no value during the immediate reaction but may be helpful if the reaction takes a prolonged course. Methylprednisolone can be given (100 to 1,000 mg intravenously) (2).

Nephrotoxicity

Acute renal insufficiency following the use of intravascular contrast medium is a well-known potential complication that is fortunately uncommon in excretory urography. Acute renal insufficiency may be manifested by a transient rise in the serum creatinine or by acute oliguric renal failure. Some cases can be diagnosed during the urogram by development of an abnormally persisting, dense nephrographic pattern (Fig. 3A.5) (69,71). The true incidence of nephrotoxicity in excretory urography is not clear but is probably lower than 5% (66,94).

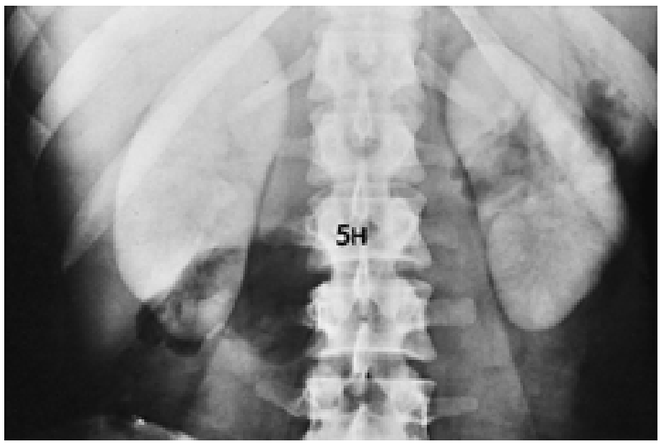

FIGURE 3A.5. Persistent dense nephrogram at 5 hours related to contrast-induced renal failure. (From Older RA, Resnick MI, eds. *Basic radiologic techniques in diagnosis of genitourinary disease,* ed 2. New York: Thieme Medical Publishers, 1994, with permission.)

Although renal toxicity is unlikely to occur from an IV injection of iodinated contrast material in a patient with normal renal function, patients with preexisting renal disease have consistently been shown to be at greater risk for contrast-induced nephropathy (7,37,60,94). VanZee and associates (94) found renal failure following urography to occur in only 0.6% of patients with normal renal function, but this increased to between 3.2% and 31% depending on the severity of preexisting renal disease. Minimal elevations of serum creatinine do not necessarily prohibit the use of iodinated contrast media when necessary for diagnosis, but preexisting renal disease does increase the risk of the examination, and this should be balanced against potential gain.

Studies have compared the nephrotoxicity of ionic and nonionic contrast media and have shown a decrease in nephrotoxicity with the low-osmolar contrast (41,60). A meta-analysis demonstrated significant benefit when low-osmolar contrast media are used in patients with prior renal impairment (7).

Acute renal insufficiency associated with contrast medium is generally self-limited. The serum creatinine usually peaks in 2 to 3 days and returns to the preexisting level within 1 to 3 weeks. Most patients completely recover, with few requiring dialysis.

The theories on the pathogenesis of contrast-induced renal failure include direct toxic effects of the contrast medium on the proximal tubular cells and ischemia resulting from damage to the renal microcirculation. Nephrotoxicity has been attributed to the hypertonicity of the contrast medium, resulting in a unique vacuolization of the cytoplasm of the proximal tubular epithelium termed *osmotic nephrosis* (67). Others think that acute tubular necrosis may result from ischemia due to vasoconstriction or sludging of the red blood cells in the renal microcirculation. Katzberg and associates (47) suggested that the hypertonicity of the contrast medium reduces the GFR by increasing the hydrostatic pressure in Bowman's capsule and the proximal tubules. In certain cases, precipitation of uric acid within the proximal tubules may lead to acute renal failure. Contrast material has a known uricosuric effect and may result in acute urate nephropathy in individuals with hyperuricemia.

A few cases of acute oliguric renal failure resulting in the death of patients with multiple myeloma have been reported following excretory urography. Because of these reports, some authorities considered multiple myeloma an absolute contraindication to excretory urography. However, excretory urography in patients with multiple myeloma is probably no different from that in patients with other forms of renal impairment (68,95). When necessary, excretory urography must be performed with caution, and dehydration should be avoided.

In high-risk patients who require a contrast examination, both dehydration and large contrast medium loads should be avoided. IV hydration performed overnight, as well as after the examination, may be helpful in preventing renal problems. Nonionic contrast media should be used in these patients. Sequential diagnostic studies that use intravascular contrast material should not be scheduled without allowing adequate intervals for observation and recovery (70).

Concurrent Use of Metformin (Glucophage) and Contrast Media

The concurrent use of metformin, an oral antihyperglycemic agent, and iodinated contrast media is of concern. A decrease in renal function could potentially decrease metformin excretion, which could subsequently lead to development of lactic acidosis. To prevent this potential complication, it is currently recommended that metformin be discontinued either before or at the time of a radiographic procedure in which iodinated contrast is to be used. The metformin should be withheld for 48 hours after the procedure and reinstated only after renal function has been reevaluated and shown to be normal (2).

Low-osmolality Contrast Media

Early experience with low-osmolar contrast demonstrated a decreased incidence of mild reactions and suggested a lower

incidence of moderate and severe contrast reactions. However, the early studies contained relatively small numbers of patients, making it difficult to arrive at a consensus on significant contrast reactions. Two studies involving large patient populations found a significantly decreased incidence of serious contrast reactions. In a Japanese study involving more than 300,000 patients, the incidence of all contrast reactions was four times less with the new agents. Even more striking, the incidence of severe reactions was six times less with the low-osmolality agents (45). This was corroborated by an Australian study involving more than 100,000 patients (73). Significantly increased safety of the low-osmolar agents is now accepted worldwide.

The disadvantage of the newer compounds is their higher cost compared with the conventional agents. This cost difference, which has been as high as 20:1, has decreased to approximately 4:1. (74). In European countries, there is almost universal use of nonionic media (92). In the United States, there is still controversy (27,87) regarding universal use of low-osmolar contrast media, but the significant cost reductions have made this a more feasible alternative.

TECHNIQUE

Several parameters must be considered to properly perform excretory urography. An adequate number of well-trained personnel should be employed to obtain good-quality radiographs, as well as to closely monitor the patient during the entire procedure. Emergency drug boxes and monitoring equipment should be available in every room where urography is performed. A physician should supervise all contrast administration and should remain close by in case complications arise. Regularly scheduled x-ray machine maintenance with established quality control guidelines for the technologists is essential.

Before the examination, the physician should have a completed x-ray request outlining the current problem and pertinent medical history (e.g., diabetes, nephrolithiasis, allergies). Laboratory values to assess renal function, blood urea nitrogen (BUN), and creatinine are important baselines, especially in debilitated or elderly individuals. Old films should be requested and reviewed.

For many years, bowel preparation was used to improve image quality of the urogram. Although helpful in some patients, these preparations often were not successful, and at the University of Virginia, we no longer use routine bowel preparation. A randomized prospective study found no difference in terms of overall quality between a prepared and an unprepared group of patients (34). Other studies have shown not only a lack of significant improvement of quality but also significant unpleasant side effects to these preparations (6). The need for bowel preparation has been reduced by the routine availability of tomography, which allows visualization of the kidneys despite considerable overlying bowel content (Fig. 3A.6).

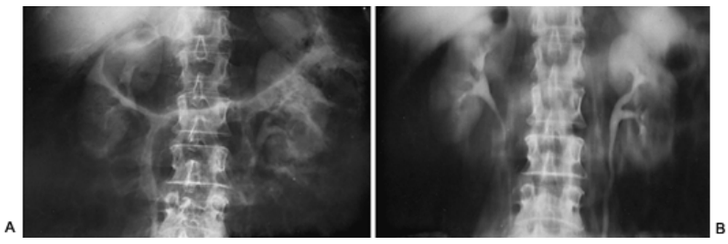

FIGURE 3A.6. A: Limited visualization due to overlying bowel content. **B:** Tomography dramatically improved visualization. (From Older RA, Resnick MI, eds. *Basic radiologic techniques in diagnosis of genitourinary disease,* ed 2. New York: Thieme Medical Publishers, 1994, with permission.)

Contrast Media: Dosage and Administration

An average dose of 0.5 to 1.0 mL of 60% contrast material per pound of patient's weight, with a maximum dose of 100 mL, is a generally accepted rule of thumb. Twenty grams of iodine was the dose recommended in the categorical genitourinary course at the 1978 Radiologic Society of North America (RSNA) Annual Meeting (63), and this dose has not changed significantly (64). This would be the equivalent of approximately 75 mL of contrast agent for a 150-pound patient. Dosage schedules for the newer nonionic contrast media were initially similar to the ionic agents because the concentrations were similar. However, cost considerations have necessitated that there be no waste when the very

expensive nonionic contrast is used, and many institutions have gone to a dose of 50 mL because most of the available nonionic media come in standard vials of 50 mL. A dose of 50 mL of iohexol was compared with a larger, weight-based dose and showed no significant diagnostic difference (33). Kennan, List, and Kengsakul (49) also evaluated lower dosages for nonionic contrast and found that with a 42% reduction in the amount of contrast, diagnostic images were still obtained. Currently, packaging of the nonionic media is more flexible, and a dose equivalent of 75 mL of a 60% solution could be used with no wasted contrast agent.

IV contrast is rapidly administered through a 19- or 21-gauge butterfly scalp vein needle or catheter-type needle, which is taped and left in place until the procedure is finished. Thus venous access is established throughout the examination in case of a reaction. The contrast medium should be administered as quickly as possible to demonstrate a good nephrogram phase. The antecubital fossa and dorsum of the hand are preferred sites for contrast injection, but central lines may be used as well. If venous access is unavailable, a foot vein may be cannulated. However, after the contrast material is given, the leg should be elevated and 100 mL of saline solution flushed through the line to decrease the possibility of thrombophlebitis. Ionic contrast medium is very irritating, and care should be taken to avoid extravasation into the subcutaneous tissues because skin slough can occur.

Radiographs: Technical Factors

Both the preliminary radiograph and the routine tomographic radiographs should be obtained using kilovolt peaks (KVPs) in the range of 60 to 70. The visibility of contrast media decreases with higher KVPs.

Many types of film–screen combinations are available; use depends on personal preference, as well as what is available at a particular institution. Radiation dose can be reduced by using a high-speed system, and high-quality urograms can be obtained with such a system. At the University of Virginia, we use high-speed film in combination with intensifying screens, which gives a speed of 600. This type of high-contrast film is well suited for stone detection.

Collimation to the area of interest is crucial to eliminate image degradation produced by scattered radiation. One of the most common errors in urography is failure to collimate properly, and technologists should be encouraged to collimate as close to the area of interest as possible.

Various radiographic views and maneuvers allow the physician the flexibility to tailor each examination to a patient's particular problem (54). The one mandatory film is "the scout," or *kidney, ureter, and bladder preliminary* (KUB). This view is a supine abdominal radiograph (14 inches by 17 inches) taken before contrast injection that includes the kidneys to the pubic symphysis (Fig. 3A.7). Two exposures may be necessary in large patients to cover the entire anatomy. A careful review of the film for technique and underlying abnormalities is required. The size, shape, and position of both renal outlines should be observed. Abnormal calcifications (e.g., renal and ureteral calculi, gallstones, aneurysm, fibroids) should be identified. Oblique views before contrast administration may be needed to prove that a calcification is indeed renal in origin (Fig. 3A.8 and Fig. 3A.9). Bony architecture should be scrutinized for pathology, such as metastasis (Fig. 3A.10). The bowel gas pattern should be evaluated for possible obstruction and abnormal gas collections (Fig. 3A.11 and Fig. 3A.12). The lung bases are often included on the film and may reveal occult pulmonary disease. Radiopaque substances, such as tablets, foreign bodies, and recently administered barium, will be demonstrated and may even preclude the examination.

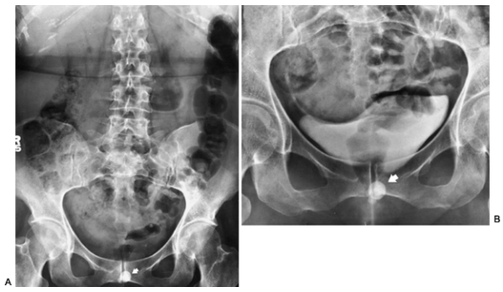

FIGURE 3A.7. A: The preliminary radiograph should include area from kidneys to pubic symphysis. Calcification overlying pubic symphysis *(arrow)* is a calculus within a urethral diverticulum. **B:** Coned-down bladder radiograph following contrast media injection demonstrating urethral diverticulum. The urethral calculus would have been missed if the radiograph before contrast injection did not include the pubic symphysis.

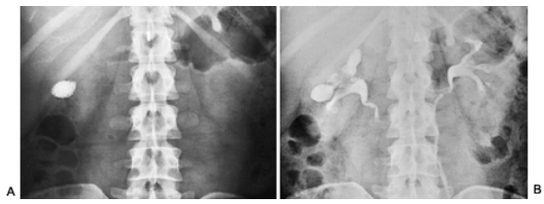

FIGURE 3A.8. Faceted stones **(A)** with a typical appearance for gallstones, but **(B)** shown to be within a calyceal diverticulum with excretory urography.

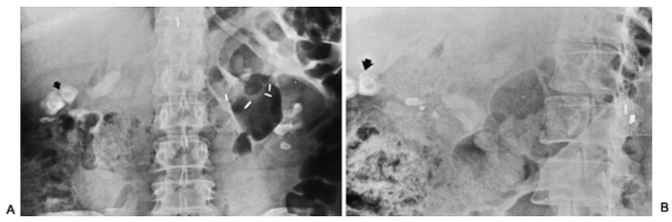

FIGURE 3A.9. A: Preliminary radiograph demonstrates calcific densities overlying both renal shadows. Two laminated calcific densities *(arrow)* overlying the right renal shadow are probably gallstones. **B:** Radiograph in the right posterior oblique projection confirms the presence of gallstones *(arrow)* in addition to renal calculi.

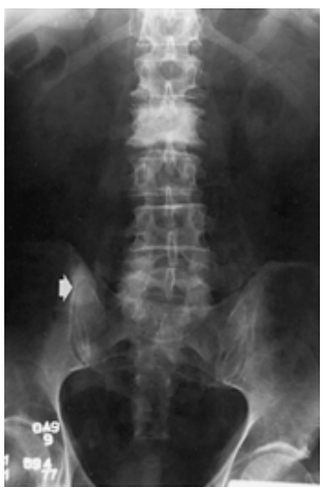

FIGURE 3A.10. Blastic metastases to pelvis *(arrow)* and spine (L-2).

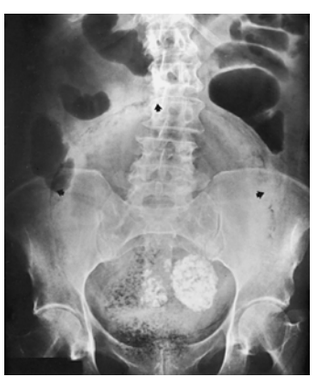

FIGURE 3A.11. Preliminary radiograph demonstrates significant distention of the bladder with air within the wall *(arrows)* in a patient with emphysematous cystitis. Large calcified uterine fibroids are noted within the pelvis.

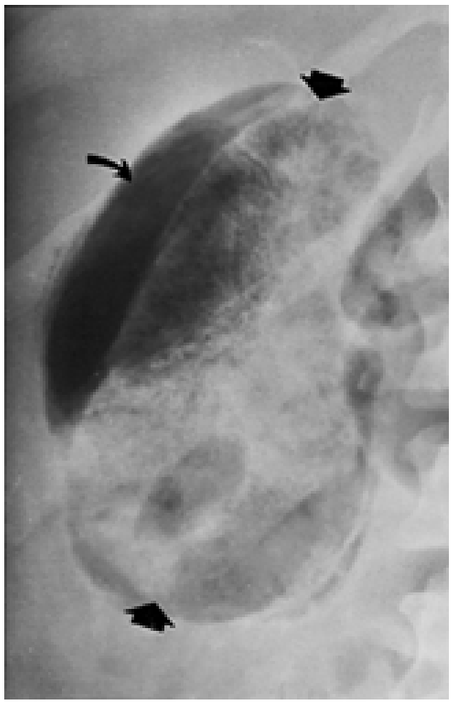

FIGURE 3A.12. Emphysematous pyelonephritis. Gas extends throughout the right kidney parenchyma *(black arrows)* and also to subcapsular space *(curved arrow).* (From Older RA, Resnick MI, eds. *Basic radiologic techniques in diagnosis of genitourinary disease,* ed 2. New York: Thieme Medical Publishers, 1994, with permission.)

The nephrogram phase is evaluated with a collimated film (11 inches by 14 inches) immediately after injection. The nephrogram phase demonstrates the densest opacification of the renal parenchyma and should be obtained within 1 minute after injection (Fig. 3A.13). The kidneys are compared and evaluated for size, shape, and position. In lieu of a 1-minute film, however, nephrotomography is often preferred. Three tomograms at 1-cm intervals in the supine position are taken at 30, 60, and 90 seconds after injection, providing excellent visualization of the renal contours (Fig. 3A.14). The nephrogram can be delayed (obstruction) (Fig. 3A.15), misplaced (pelvic, thoracic/kidney), irregular (mass) (Fig 3A.16), or prolonged (hypotension).

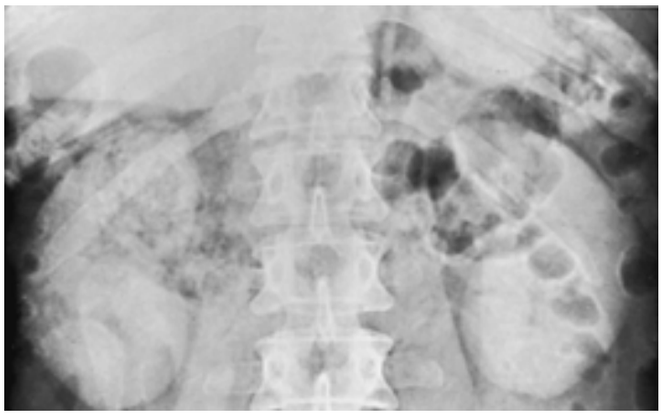

FIGURE 3A.13. The nephrogram phase demonstrates parenchymal opacification of both kidneys. Kidney size and contour abnormalities are best evaluated during the nephrogram phase.

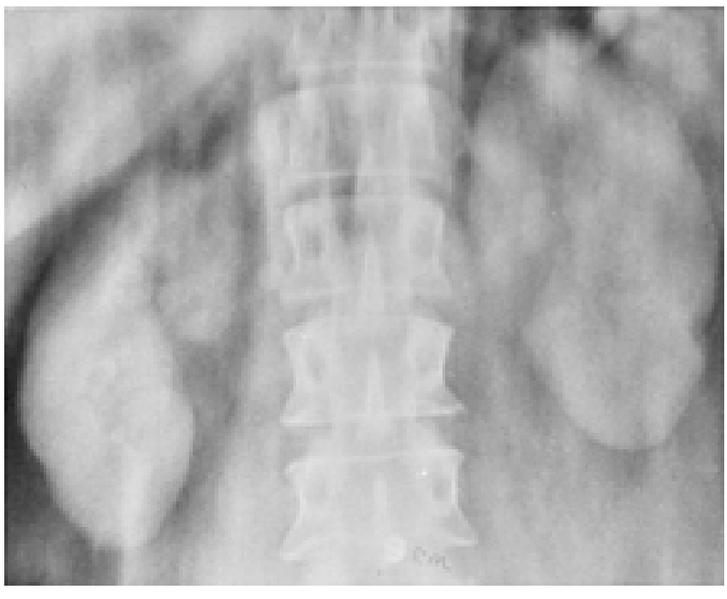

FIGURE 3A.14. Immediate postinjection tomogram clearly demonstrates the renal parenchyma bilaterally.

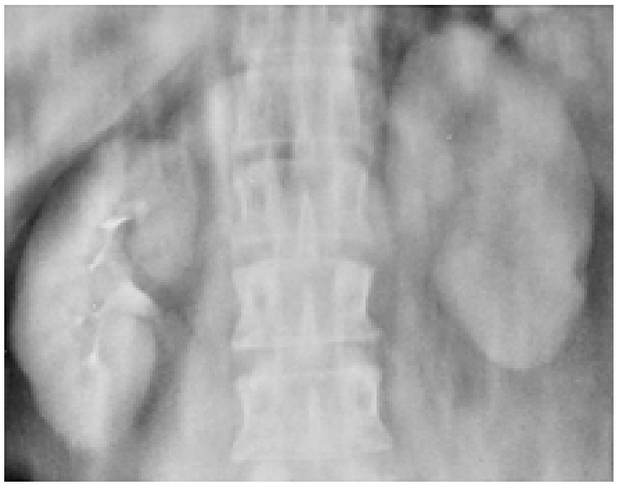

FIGURE 3A.15. Left-sided obstruction with delayed visualization of calyces. Same patient as Fig. 3A.14

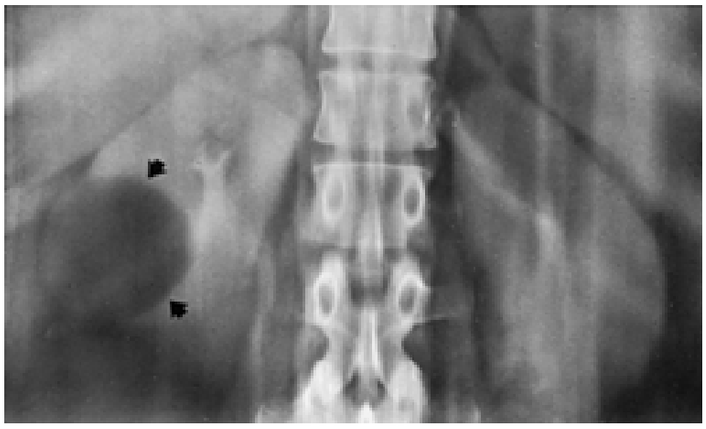

FIGURE 3A.16. Nephrotomography demonstrates a large, well-circumscribed mass in the lower pole of the right kidney *(arrows)* consistent with a renal cyst. Nephrotomograms provide excellent detail of renal contour abnormalities.

A 5-minute collimated film (11 inches by 14 inches) is obtained to demonstrate the pyelogram phase with opacification of both collecting systems and proximal ureters (Fig. 3A.17). Calyceal distortion, irregularity, or filling defect may signal underlying disease. Tomography can be used to better delineate the calyces, as can oblique views. Oblique views are also helpful in further evaluating filling defects and in clarifying pseudofilling defects such as might be related to overlapping calyces or crossing vessels. Posteriorly and anteriorly positioned masses may also be more apparent on oblique views because these present a different surface of the kidneys.

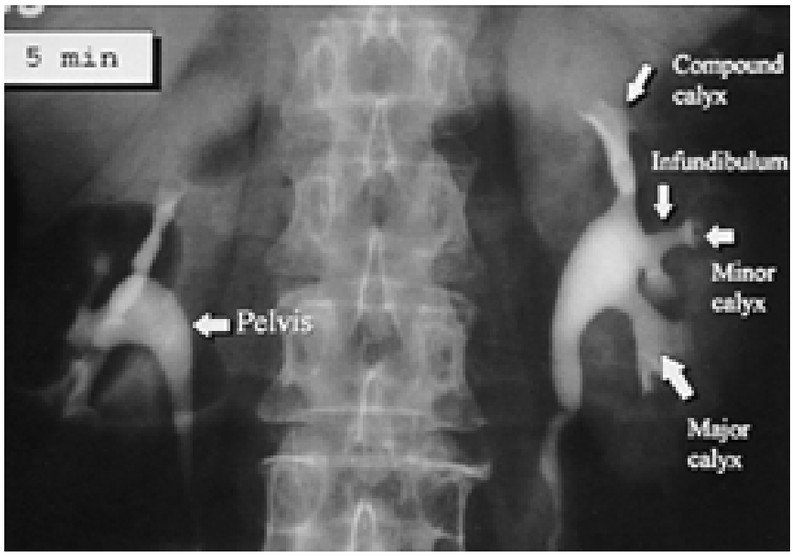

FIGURE 3A.17. Coned, 5-minute film of kidneys.

Relative obstruction of the ureters with an inflatable compression device placed across the lower abdomen after the nephrogram phase achieves optimal distention of the collecting systems and proximal ureters (Fig. 3A.18). Contraindications include suspected ureteral obstruction, abdominal aortic aneurysm, and recent abdominal or renal surgery. Another alternative is to place the patient in the Trendelenburg position after the 1-minute film to enable better filling of the collecting system. Both the compression device and Trendelenburg position are maintained until a 10-minute collimated kidney film is taken (14 inches by 11 inches). The patient is brought up into the reverse Trendelenburg position, or the compression device is released, and an immediate full (14 inches by 17 inches) film is taken in

hopes of catching the contrast medium flowing down both ureters to the bladder. The ureters and bladder are usually well demonstrated (Fig. 3A.19).

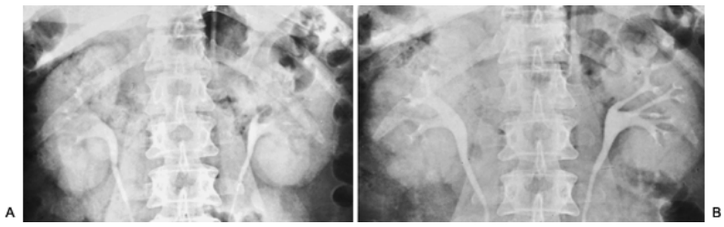

FIGURE 3A.18. A: Radiograph taken 5 minutes after contrast injection demonstrates the pyelogram phase with opacification of the collecting system and proximal ureters. **B:** Radiograph following the use of a compression device in the same patient. Note distention of collecting systems with improved visualization of the calyces and infundibula.

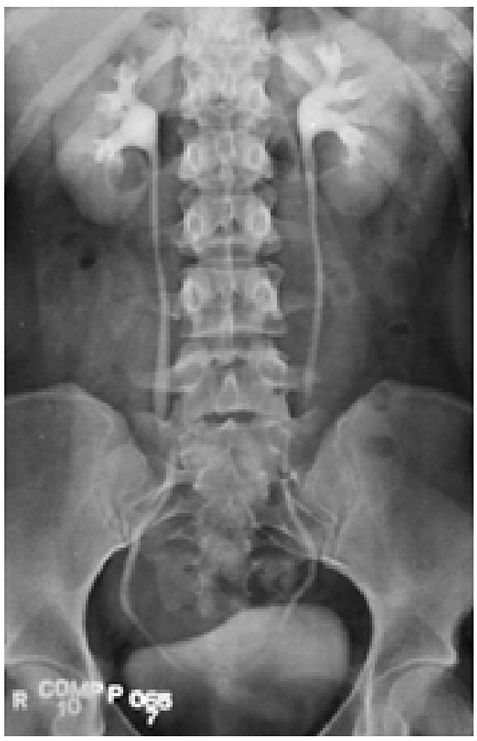

FIGURE 3A.19. Postcompression abdominal film demonstrating the ureters and bladder.

If necessary, the bladder can be evaluated with a collimated view (11 inches by 14 inches) for better anatomic detail (Fig. 3A.20). The lower ureteral segment and ureterovesical junction can be better delineated with oblique views either before or after voiding (Fig. 3A.21 and Fig. 3A.22). If there is inadequate definition or a suspicious finding in the distal ureters or bladder, a prone film (11 inches by 14 or 14 inches by 17 inches) will distend the anterior portions of the collecting system as they become dependent, that is, the middle and distal portions of the ureters. This is often helpful in localizing an obstruction (Fig. 3A.23). Lesions involving the anterior wall of the bladder are better visualized as well.

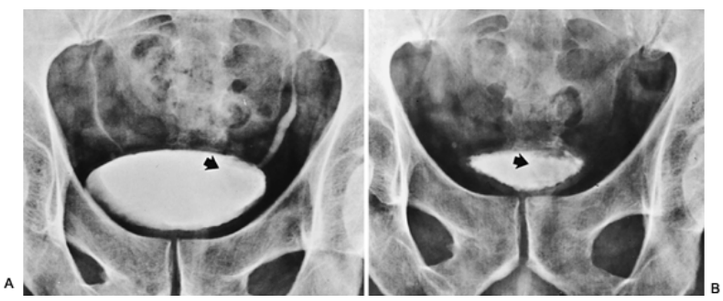

FIGURE 3A.20. A: The filled bladder suggests a filling defect near the left bladder wall *(arrow)*. **B:** The postvoid radiograph confirms the defect *(arrow)* proved to be bladder carcinoma.

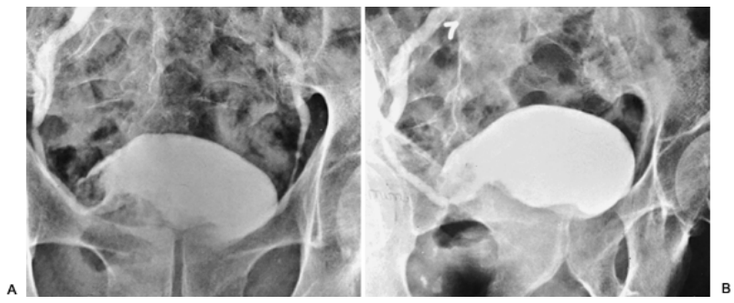

FIGURE 3A.21. A: Coned-down radiographs of the bladder suggest a mass involving the inferior aspect of the right wall of the bladder. **B:** Radiograph taken in the left posterior oblique projection confirms irregular mass near the insertion of the right ureter consistent with carcinoma.

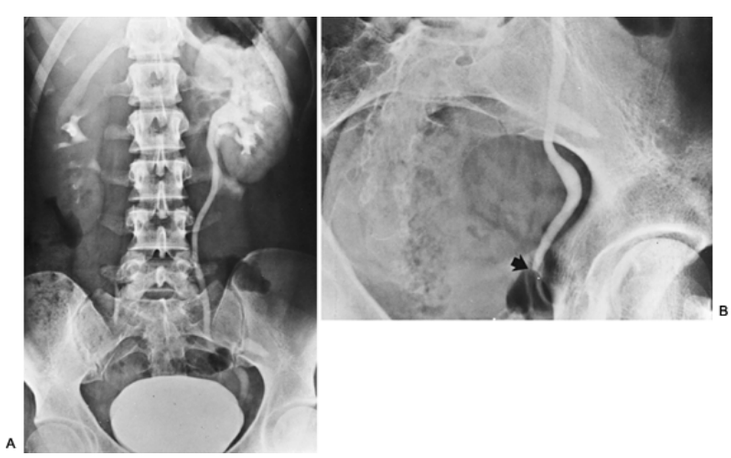

FIGURE 3A.22. A: Two-hour radiograph in a patient with left-sided renal colic. There is dilation of the left ureter down to the level of the bladder. The point of obstruction is not demonstrated. Note the peripelvic extravasation of contrast resulting from forniceal rupture. **B:** Postvoid radiograph in the left posterior oblique projection demonstrates the level of obstruction *(arrow)* due to a uric acid stone.

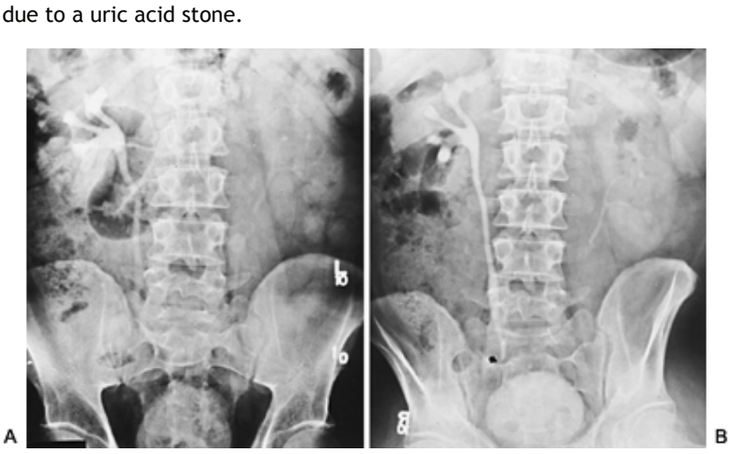

FIGURE 3A.23. A: Ten-minute radiograph in a patient with right renal colic. There is hydronephrosis and dilation of the ureter with poor definition of the level of the obstruction. **B:** Prone radiograph demonstrates excellent opacification of the ureter with identification of the level of the obstruction *(arrow)*.

Postvoid radiographs most often are used to assess bladder outlet obstruction resulting from prostatic hypertrophy in older adults. In the presence of a possible obstructive process involving the upper urinary tract, the postvoid radiograph can also be of benefit by demonstrating drainage. The combination of the patient's walking to the bathroom and emptying his or her bladder often aids significantly in evaluating the drainage of the upper tracts.

Fluoroscopy often provides additional information about urinary tract physiology. In combination with spot filming, fluoroscopy can reveal renal dynamics and relationships not seen with standard static radiographs.

TOMOGRAPHY

Tomography provides better visualization of the urinary tract by blurring out the surrounding structures. It is one of the most important refinements of the excretory urogram. Simple linear tomography is generally sufficient. We at Virginia use a short arc of 20 degrees, which will produce a tomographic cut of approximately 0.5 cm. Three such tomographic cuts are generally sufficient to visualize the kidneys.

The major contribution of tomography is in evaluating the renal parenchyma; therefore tomograms should be obtained immediately after the bolus injection of contrast when the nephrogram is most intense (Fig. 3A.14). This has been shown to increase detection of renal masses (39,72). Later in the urogram, during filling of the collecting structures, tomography can be used on a selective basis. It is most helpful when there is considerable overlying bowel content or poor concentration of the contrastmedium.

This will often salvage an otherwise nondiagnostic examination.

DIGITAL RADIOGRAPHY

Two types of digital radiography are available for use in urologic diagnosis. At present, digital radiography is not used extensively in the diagnosis of urologic disease, but with the potential for dose reduction and more efficient storage, its use will probably increase.

Digital luminescent radiography (Fig. 3A.24) does not use standard film but rather uses photo-stimulable plates with substances such as phosphorous and barium-fluoro-halide europium-doped crystals. This system has the advantage of significant dose reduction. Because the imaging plates used have a much wider linear dynamic range than conventional screen–film combinations, imaging can be performed at decreased radiation doses (29,65,100). Dose reductions up to 50% for urography (65) and as great as 90% in urethrocystography (100) have been achieved. In addition, repeat examinations are significantly reduced, if not eliminated, by this system. Studies that have compared the diagnostic capabilities of digital systems with standard radiographic systems have shown no significant decrease in image quality or diagnostic accuracy with the digital systems (28,29).

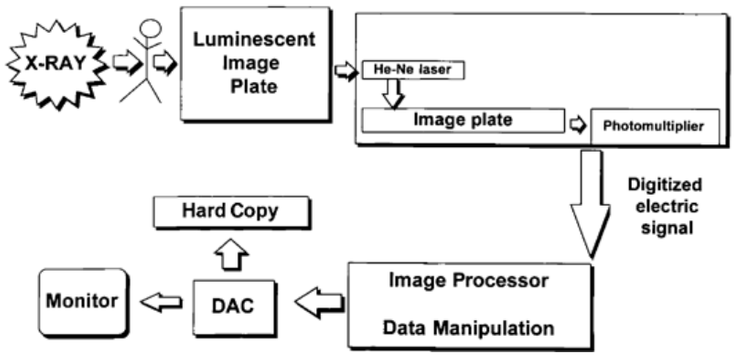

FIGURE 3A.24. Digital luminescent radiography. The luminescent plate is exposed and its energy state raised. Laser scanning releases radiation, which is converted to an electric signal and digitized. The digital image is processed and converted through a digital–analog converter to an analog image for the monitor or hard copy. (From Older RA, Resnick MI, eds. *Basic radiologic techniques in diagnosis of genitourinary disease,* ed 2. New York: Thieme Medical Publishers, 1994, with permission.)

The second type of digital system, digital fluororadiography, converts the fluoroscopic image to a digital image as shown in Figure 3A.25 . The optical image of the TV tube is converted by an analog–digital converter into a series of electrical signals, which are then converted into the digital image. The digital image is converted back to an analog image and can either be sent to the monitor for viewing or printed out as a hard copy. The images can be manipulated later by changing window settings, brightness, or edge enhancement as needed. In contrast to standard radiography, the image is immediately available for review, allowing more rapid decision making as to further films.

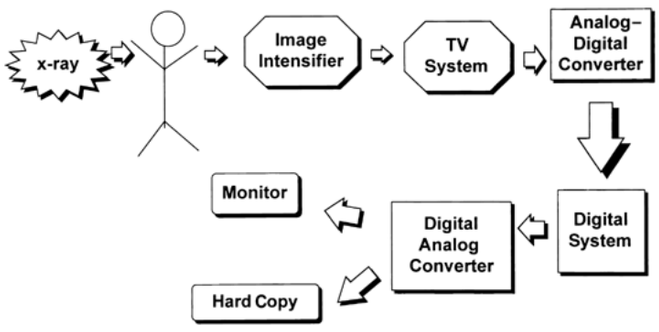

FIGURE 3A.25. Digital fluororadiography. (From Older RA, Resnick MI, eds. *Basic radiologic techniques in diagnosis of genitourinary disease,* ed 2. New York: Thieme Medical Publishers, 1994, with permission.)

THE PEDIATRIC PATIENT

Excretory urography in children requires special attention to several technical factors. First, establishment of rapport between the physician and the child and parents is crucial before obtaining radiographs. Explaining the procedure in a step-by-step fashion helps alleviate some of the anxiety regarding the examination. In the older age group, the clinician should direct the explanation primarily to the child.

Anesthesia or sedation is rarely indicated in excretory urography. In infants and preschool children, a “cradle” device is placed directly on the x-ray table for immobilization of the patient. Heat lamps, pediatric drug boxes, and resuscitative equipment should be available in each x-ray room.

Bowel preparation is not indicated in children. An adequate state of hydration is essential, especially in infants and younger children, to avoid dehydration from the diuresis caused by the excess solute load of the contrast medium. Abstinence from food for about 5 hours is sensible in most children to keep the stomach empty in case of emesis after contrast administration (19).

The contrast dosage in children is basically the same as for adults on a weight basis. Between 0.5 and 1.0 mL/lb (between 1 and 2 mL/kg) of patient's weight is a safe and effective amount of contrast medium to give a satisfactory

urogram. Nonionic contrast is indicated for infants and also recommended for young children. Venous access in young children may be difficult to obtain. The veins on the dorsum of the hand or foot are usually the most accessible for cannulation with a 25-, 23-, or 21-gauge butterfly needle. Other sites include the antecubital fossa and scalp veins in infants. Pneumothorax is a complication of external jugular vein injections, and the femoral vein should be avoided because of the reported risk of septic arthritis of the hip (19). Bolus injection technique is recommended, and the needle should remain in place until the study is terminated. Immediately after giving the bolus, a carbonated beverage or juice may be given to the patient. This allows distention of the gastric bubble for optimal visualization of the kidneys, as well as providing calories and fluid intake for the child.

The filming sequence in the pediatric age group is aimed at obtaining the most information from a minimum number of radiographic exposures. Collimation should be used when possible.

A preliminary film, which includes the kidneys to the pubic symphysis, should be scrutinized carefully for underlying skeletal anomalies such as sacral agenesis and spinal dysraphism. A search for abdominal masses, an abnormal bowel gas pattern, and any calcifications should also be conducted.

In most cases, the entire pediatric excretory urogram can be completed with two postcontrast films. The nephrogram phase is demonstrated with a 1-minute collimated view of the kidneys. A large 10-minute film usually demonstrates both collecting systems, ureters, and the bladder. A postvoid bladder film is usually not obtained in children. However, additional views may be indicated for a particular clinical history or to clarify further abnormalities seen while performing the urogram.

Tomography is not used routinely for children but, if available, can often resolve a diagnostic problem, especially in a child with considerable overlying bowel content. There is a reluctance to use tomography in children because of radiation concerns. One or two tomograms actually may decrease the number of radiographs needed in a difficult diagnostic case and could possibly obviate the need for a follow-up imaging study, such as CT, which might involve even greater radiation.

INDICATIONS FOR EXCRETORY UROGRAPHY

The following list includes current indications for excretory urography. Some of these, such as obstruction, also use other technology; others, such as trauma, are controversial.

- Stone disease
- Preoperative extracorporeal shock wave lithotripsy (ESWL)
- Acute abdominal pain or colic
- Suspected obstruction
- Blunt trauma thought to involve only the urinary tract
- Hematuria, especially if abnormality of the collecting structures is suspected
- Complicated or unusual infection, including tuberculosis
- Postoperative evaluation of urologic procedures
- Preoperative evaluation for endourologic procedures
- Suspected transitional cell carcinoma
- Questionable abnormality on isotope or ultrasound studies

These indications represent a combination of those indications that have persisted for many years, as well as relatively new indications, such as preoperative ESWL. Many previously accepted indications for urography are no longer considered justified. The evaluation of hypertension is one

of these (51,78). Uncomplicated urinary tract infections, preoperative studies for various types of surgery (91), and enuresis are no longer studied routinely (51,78). Trauma has become a somewhat controversial indication with differing opinions regarding the value of urography.

Indications for urography have also been reduced by increasing availability of alternative methods of diagnostic imaging. A broad knowledge of the other imaging modalities is necessary to determine the proper examination. Urography is still widely used for obstruction, but ultrasound has become the primary screening study for this entity, and improvements in the diuretic renogram also erode the territory of urography. However, urography has the advantage of providing a unique combination of anatomy and function and for this reason continues to be used in suspected obstruction.

Urography and ultrasound are complementary examinations; this is particularly true in stone disease. There are those who have advocated replacement of the urogram by a combination of ultrasound and an abdominal film (40). However, a determination in each case as to which study would be most helpful is what should be done. Ureterovesical junction stones are detectable by a skilled ultrasonographer, but stones more proximal in the ureter are often difficult to find and can be demonstrated more easily by urography. Urography is generally more available, and interpretive experience also favors urography (18). To detect small ureteral stones, a sonographer with considerable experience and patience is needed.

Renal calculi can be evaluated by either technique. Some stones are more apparent with an abdominal radiograph or tomography, whereas others are better seen with ultrasound. Stone dimensions and degree of fragmentation following ESWL are better demonstrated with radiographs, but small stones, nonopaque stones, and small amounts of fragmented stone debris are often better demonstrated with ultrasound.

Noncontrast spiral CT has gained wide acceptance as the initial evaluation of renal colic and suspected ureteral stones. This has further reduced the use of intravenous pyelography (IVP), especially as an emergency procedure (88).

CT or ultrasound is used to study abdominal masses and retroperitoneal disease, which are no longer studied with urography. Similarly, urography is no longer used for evaluation of adrenal disease, but CT, MRI, or isotope techniques are used. Urography is still used as a primary study for hematuria. The urogram provides not only parenchymal information but also visualization of the collecting structures. Although sensitivity of excretory urography for detection of mass lesion is significantly less than CT (96), urography is excellent for lesions, such as transitional cell carcinoma, papillary necrosis, and other abnormalities of the collecting structures that might produce hematuria.

Patients in whom excretory urography may no longer be the study of choice are those with an above-average risk of complication. This may be an allergic reaction, abnormal cardiovascular response, or nephrotoxicity related to the contrast medium.

Urography can be performed in patients with a history of allergies to contrast media; however, if the reaction was severe, other modalities, such as ultrasound, CT without contrast, or radioisotope scanning, would probably be a better choice. Patients with significant heart disease have been shown to have a higher incidence of arrhythmias during bolus injection for urography; in these patients, other modalities should be considered. Urography is no longer used for evaluation of renal failure. Diagnostic ultrasound has improved to the extent that it can accurately determine whether obstruction is present, often the question being asked in a patient with renal failure (26,40,81,82). In addition, the potential toxicity of iodinated contrast media is now well established. Patients with mild renal failure are at significant risk for contrast-induced renal toxicity (1,5,7,15,50,60,69,70 and 71,83,94). Contrast-induced renal failure is a major cause of renal failure in the hospital population (44).

The indications for excretory urography in children have undergone changes in the past few years and are very limited. Ultrasonography and CT have virtually replaced the excretory urogram in the evaluation of abdominal and renal masses, hydronephrosis, and abdominal pain and as a screen for associated renal anomalies in children with other congenital anomalies (61). Ultrasonography is evolving into the initial screening procedure for pediatric urologic disease because of excellent detail in children and lack of radiation exposure.

Excretory urography is sometimes used in evaluating urinary tract infection in children in whom reflux has been demonstrated on voiding cystourethrography. The excretory urogram provides better definition of cortical scarring associated with vesicoureteral reflux (62), but ultrasound is often sufficient for this purpose. Excretory urography is also indicated in calculus disease, in nonmedical hematuria, and in children who have recently undergone urologic surgery.

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3B CYSTOGRAPHY AND URETHROGRAPHY

Richard A. Leder

Part of "3 - IMAGING "

R.A. Leder: Division of Abdominal Imaging, Department of Radiology, Duke University Medical School, Durham, NC 27710.

INTRODUCTION

Cystography and urethrography are imaging studies performed of the bladder and/or urethra before, during, and after the administration of contrast material. The goal of cystography and/or urethrography is to detect abnormalities of the lower urinary tract. Abnormalities of the bony pelvis, or pelvic soft tissues that may affect the bladder or urethra, may also be detected. This should be accomplished using the minimum radiation necessary to provide sufficient anatomic detail for the diagnosis of normal or abnormal urinary findings.

These examinations are performed under the direct supervision of physicians who have received documented formal training in the performance, interpretation, and reporting of uroradiologic studies. The supervising physician must be familiar with multiple disease processes of the lower genitourinary tract and understand the cystographic and urethrographic manifestations of these diseases. Furthermore, the physician performing these studies must be knowledgeable of alternative imaging techniques that may be required, such as ancillary studies either after a cystogram or urethrogram or as a replacement for these techniques. In particular cases, the lower tract evaluation may be accomplished with ultrasonography, computed tomography, nuclear medicine, or magnetic resonance imaging (MRI).

The physicians and technologists performing these studies should have an understanding of and experience in proper film technique; film sequencing; and the volume, concentration, and method of administering contrast material. Cystography and/or urethrography should be performed after an appropriate history and preprocedure screening are performed. Risk factors must be assessed before these examinations are performed. Some patients may require a steroid premedication regimen. The signs and symptoms of an adverse reaction from the administration of contrast material must be well known to the physicians and support staff caring for patients undergoing these examinations. Understanding of and proficiency in the recognition and treatment of adverse contrast reactions are required. Medication and resuscitative equipment must be immediately available to treat adverse contrast reactions.

Imaging findings and interpretations should be reported in a timely fashion in compliance with the American College of Radiology standards on communications. Urgent or acute findings should be communicated promptly to the ordering physician (1).

CONTRAST MATERIAL

Contrast for urethrography must be sufficiently viscus and dense for proper visualization of the urethra. The meglumine salts of diatrizoate or iothalamate are most useful for this examination. Sixty percent (weight/volume) solutions are typically used in retrograde urethrography to provide maximal opacification of the urethra. Meglumine salts of diatrizoate and/or iothalamate are also the most widely used contrast agents for cystography. Solutions containing 15% (weight/volume) contrast media are optimal for cystography. Solutions that contain greater than 15% contrast media may result in very dense opacification of the bladder, and subtle abnormalities may not be detected. Higher

concentrations of contrast media may be irritating to the bladder mucosa. Systemic reactions following retrograde urethrography are extremely rare. Although uncommon, systemic reactions to contrast media may occur during cystography (5). Patients who have had adverse reactions to intravenous contrast material may be studied using either nonionic low-osmolar contrast or potentially both a steroid premedication and nonionic contrast (25).

The initial interview of patients undergoing either cystography or urethrography must include an allergy history, particularly a history of allergic reactions to contrast material. If the patient is thought to be at sufficient risk for a allergic reaction, nonionic contrast can be used. For cystography, dilute Isovue-300 (iopamidol 61% Bracco Diagnostics Inc. Princeton, New Jersey) is used. For urethrography, nondilute Isovue 300 can be used for the injection of contrast into the urethra.

URETHROGRAPHY

Normal Anatomy

The male urethra extends from the bladder neck to the external meatus, extending through the prostate gland and urogenital diaphragm. The urogenital diaphragm attaches anteriorly and laterally to the inferior rami of the public arch and the ischia. Posteriorly, the triangle is attached to the perineum and is continuous with the anal fascia. Near its apex, the diaphragm is perforated by the urethra approximately 1 cm below the symphysis pubis. This diaphragm divides the urethra into two portions: the anterior portion below the urogenital diaphragm and the posterior urethra above.

The anterior urethra extends from the inferior aspect of the urogenital diaphragm to the external meatus. The anterior urethra is divided into two parts by the penoscrotal junction inferiorly and the suspensory ligament superiorly. The penile urethra lies anterior to the penoscrotal junction. Distally, the penile urethra is dilated to form the fossa navicularis. Proximal to the penoscrotal junction lies the bulbous urethra. The bulbous urethra dilates slightly in its most inferior aspect and proximally terminates in a symmetric cone shape (Fig. 3B.1). The glands of Littre lie along the anterior urethra (Fig. 3B.2). Cowper's glands empty into the dilated portion of the bulbous urethra. The corpus spongiosum surrounds the anterior urethra.

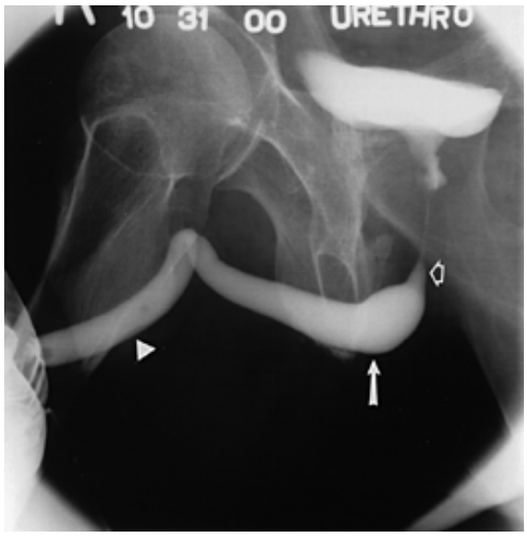

FIGURE 3B.1. Normal retrograde urethrogram, prior transurethral resection of the prostate (TURP). Contrast injected into the penile urethra shows excellent filling of the penile *(arrowhead)* and bulbar urethra *(arrow)*. The cone of the bulbous urethra is well depicted *(open arrow)*. The prostatic urethra is dilated in this patient status post TURP. A small air bubble is seen in the penile urethra.

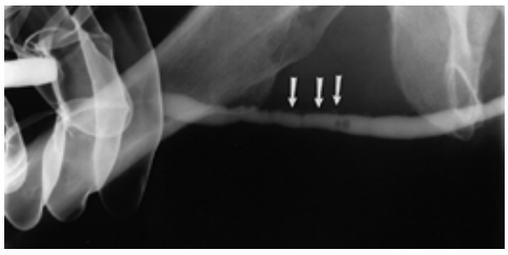

FIGURE 3B.2. Glands of Littre. Contrast has been injected into an Intracath placed in the penile meatus. Small contrast outpouchings are seen in the anterior urethra *(arrows)*. These are the glands of Littre. Air bubbles are incidentally noted in the penile urethra.

The posterior urethra extends from the bladder neck to the urogenital diaphragm. The posterior urethra is composed of two parts: the membranous urethra and the prostatic urethra. The membranous urethra lies within the urogenital diaphragm and is 1 to 1.5 cm in length and 5 to 7 mm in caliber. The prostatic urethra extends through the prostate gland to the bladder neck. Anatomic features that may be noted when examining the posterior urethra include the verumontanum. This is a mound of smooth muscle on the posterior wall of the prostatic urethra. The superior aspect of the verumontanum lies above the middle of the prostatic urethra. The verumontanum extends inferiorly into the distal third of the prostatic urethra, tapering distal to form the urethral crest. There are three small orifices in the verumontanum. The superior opening is the prostatic utricle. Below and to the side of the prostatic utricle are the orifices of the ejaculatory ducts. On the side of the verumontanum is the prostatic sinus into which the prostatic ducts drain.

To understand urethrography, one must appreciate the presence of the urinary sphincters. The internal sphincter, which is composed of smooth muscle, surrounds the proximal portion of the prostatic urethra at the bladder neck. The intrinsic sphincter is also composed of smooth muscle and lies below the verumontanum. The external sphincter is composed of striated muscle and lies at the level of the membranous urethra. The internal sphincter of the bladder neck maintains passive continence. This internal sphincter is a circular band of smooth muscle, which is sympathetically controlled; it relaxes when bladder contraction occurs. Damage may occur in cases of traumatic pelvic injury or postsurgical obliteration, as can occur after a transurethral prostatic resection (TURP). The intrinsic sphincter consists of a 5-mm band of circular smooth muscle encircling the membranous urethra and extending proximally to surround the distal prostatic urethra. If damage occurs to the internal sphincter, passive continence may be maintained by the intrinsic sphincter. The intrinsic sphincter serves to empty the posterior urethra back into the bladder at the end of micturition. The external sphincter surrounds both the intrinsic sphincter and the membranous urethra. This sphincter is voluntarily controlled and is composed of striated muscle. Active continence is maintained by the external sphincter (22,23).

Technique

Although the technique of retrograde urethrography varies, the aim is to achieve consistent visualization of the urethra after the installation of contrast. Films must be exposed during the retrograde injection of contrast to adequately visualize the posterior urethra. The milking action of the intrinsic sphincter rarely allows opacification of the posterior urethra if contrast is not actively flowing through this portion of the urethra.

The initial film before a urethrogram is a coned film of the pelvis taken in a right posterior oblique position. The supervising physician reviews this film for abnormalities related to the pelvis, pelvic soft tissues, or bony structures. The patient is interviewed regarding possible heart murmurs, valve replacement, or the presence of a joint replacement. If any of these conditions exist, these patients are started on prophylactic antibiotics before the placement of a catheter and the injection of contrast. A 60-mL syringe is then filled with Reno-30 (diatrizoate meglumine 30%, Bracco Diagnostic Inc., Princeton, New Jersey). One standard technique requires the placement of a Foley catheter approximately 1 inch into the penis. A small amount of saline is injected into the balloon of a Foley catheter, with the dilated balloon fixed in the fossa navicularis. Films are obtained during the retrograde injection of contrast material. Typically, a 14- or 16-Fr Foley catheter is used for this study. Contrast material should be preinjected through the Foley catheter to purge air from the lumen. Patients are placed in a 45-degree right posterior oblique position so that the shaft of the penis is draped over the soft tissues of the thigh. After an initial volume is injected, resistance may be encountered due to spasm of the external sphincter. If there is spasm of the external sphincter, there will often be leakage of contrast from the meatus. In an attempt to overcome spasm of the external sphincter, patients are asked to attempt to void. Simultaneous to this action, contrast is injected in the hopes of filling the posterior urethra. Gentle pressure on the plunger of the syringe typically overcomes this resistance. There will be a noticeable decrease in effort when contrast begins to flow into the posterior urethra and bladder. This examination does not require fluoroscopic imaging (34).

Currently, we inject contrast into a syringe connected to a 19-by-$^{7}/_{8}$ butterfly needle apparatus from which the needle has been removed. This tubing is placed into the urethral meatus. Traction is placed on the penis, and manual compression is made close to the glans penis. Using this technique and appropriate penile traction, the hands of the individual injecting contrast will be outside the collimated beam. Alternatively, radiation-reduction gloves can be worn. The postinjection film is evaluated for adequate filling of all urethral segments. If necessary, additional images can be performed after repeat injection(s).

Other techniques are available for the performance of urethrography, including the use of a Brodney clamp (Fig. 3B.3) (11). This apparatus is no longer available at our institution. Nonetheless, practitioners have aimed to improve the diagnostic quality of retrograde urethrography using alternative techniques, including the use of an external compression “device.” One such technique includes the placement of a 20-Fr Foley catheter with a 30-mL balloon placed under the penis. A bandage, 3 to 4 cm wide and approximately 60 cm long, is cut from the edge of a sterile disposable polythene drape; this is then wound around

the penis and the catheter. The balloon of the external Foley catheter is inflated with air to produce firm pressure on the urethra. This technique aims to achieve external compression and serve as a penile clamp for retrograde urethrography (15).

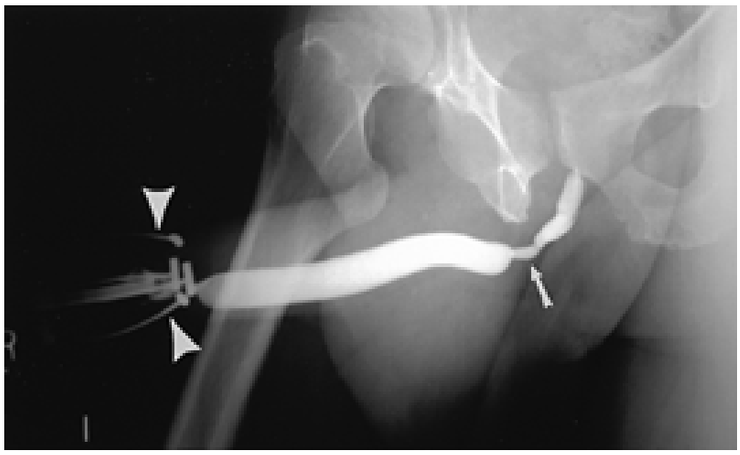

FIGURE 3B.3. Brodney clamp. A Brodney clamp *(arrowheads)* is seen positioned over the glans of the penis. Contrast has been injected in a retrograde fashion, and a bulbar urethral stricture *(arrow)* is demonstrated.

Other imaging techniques include pericatheter retrograde urethrography. This can be accomplished by placing an Intra-Cath alongside an indwelling Foley catheter, permitting the injection of contrast adjacent to an indwelling Foley catheter. Compression distally should prevent spillage of contrast. The use of a pericatheter device can also serve the same purpose. A pericatheter device either 1 or 0.5 cm wide may be advanced along an indwelling catheter, through the meatus, and into the urethra until the injection arm of the device reaches the penile meatus. The standard device is 7 cm long; a smaller version is 4 cm long (18). The use of a disposable retrograde urethrogram catheter (“golf tee” catheter) made of soft blended plastic polymer has also been described. This catheter is 9 cm in overall length and has a 14-Fr outer diameter. The proximal end is flared and fits over a Toomey (standard catheter tip) syringe. The catheter is advanced to the level of the proximal flare, effectively occluding the penile meatus. Gentle pressure is applied around the base of the glans penis to prevent leakage of contrast. Mild traction is applied to stretch the urethra (24).

Although not our standard practice, a technique of double-contrast urethrography has also been described. Contrast coating of a urethral lesion has been described using 10 mL of iodized oil (Lipiodol) emulsion into the urethra, followed by 20 mL of air (43). A “choke” voiding urethrogram may be obtained by leaving a catheter in place and allowing the patient to void against pressure. This can be performed after the bladder is filled for a cystogram or after an intravenous urogram is performed. Meatal compression voiding urethrography (MCVU) using a Zipser clamp is described as a simple and accurate alternative to retrograde and noncompression voiding urethrography. Bladder filling with contrast either via a urethral catheter or as a result of an excretory urogram is first accomplished. The patient places the Zipser clamp behind the corona of his penis and signals the technologist when he begins to void. A radiograph is exposed, and the patient is told to stop voiding. If adequate urethral visualization is accomplished in full distention, the examination is concluded (8,13).

A recently described technique for retrograde urethrography includes the use of an appropriate-sized Bommelaer vacuum uterine cannula. This cannula is applied to the penile glans by increasing the negative pressure of the vacuum to a maximum of 25 mm Hg. After correct coupling of the cannula to the glans, contrast material is injected and spot films obtained. This technique permits better visualization of the distal tip of the anterior urethra, an area typically obscured by the presence of a Foley catheter. Patients experience less discomfort with this procedure compared with the Foley technique because the inflation of the balloon in the fossa navicularis is avoided. Opacification of the posterior urethra was reported to occur at a similar rate to that seen when using a Foley balloon method (3,27).

Urethrography of the Male Urethra

Radiographic landmarks seen during the performance of retrograde urethrography include the cone shape of the proximal bulbous urethra, the verumontanum within the prostatic urethra, and the bladder neck. Between the tip of the cone of the bulbous urethra and the inferior aspect of the verumontanum lies the membranous urethra. The penile urethra extends from the external meatus to the penoscrotal junction. The bulbous urethra lies between the inferior aspect of the urogenital diaphragm, where it exhibits a symmetric cone shape; it extends to the penoscrotal junction. The verumontanum is visualized as a smooth oblong-filling defect in the posterior wall of the prostatic urethra. Occasionally, a Cowper's duct or utricle may fill with contrast. Cowper's ducts are seen as faint lines of contrast adjacent of the proximal portion of the bulbous urethra. Cowper's ducts are posterior and lateral to the membranous urethra and extend from Cowper's glands to enter the cavernous portion of the bulbous urethra (41). The opacified

utricle appears as a small tear drop–shaped cavity protruding posteriorly from region of the verumontanum. The glands of Littre appear as small linear collections of contrast material parallel to the superior margin of the anterior urethra. This is often associated with chronic infection or urethral stricture disease. Strictures may also account for opacification of Cowper's ducts and glands (Fig. 3B.4).

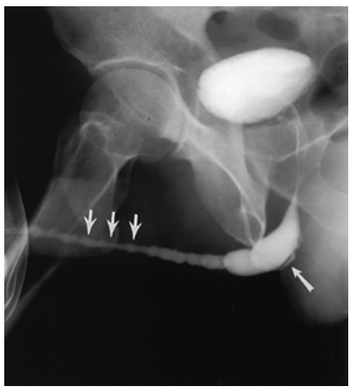

FIGURE 3B.4. Glands of Littre/Cowper's duct. There is a diffuse beaded appearance of the anterior urethra consistent with a long anterior urethral stricture. The bulbous urethra is dilated. A small amount of contrast is seen in Cowper's duct *(single arrow)*. Small contrast collections on the ventral surface of the urethra are consistent with the glands of Littre *(multiple arrows)*.

Rupture of the urethra during retrograde urethrography, although rare, can produce opacification of the corpus spongiosum, the paired corpora cavernosa, and the draining veins of the penis. Rupture may be secondary to a tight external sphincter or stricture, both processes causing increased intraurethral pressure during the injection of contrast material and an iatrogenic urethral tear. Corporal filling and venous filling may also be produced by trauma (whether caused by a Foley catheter or Brodney clap), previous urethral instrumentation, or external trauma (2) (Fig. 3B.5).

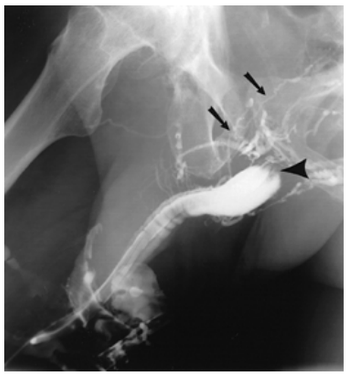

FIGURE 3B.5. Urethral extravasation. Contrast has been injected along side an indwelling Foley catheter. There is gross extravasation of contrast in the region of the membranous urethra *(arrowhead)*. Filling is seen of the periurethral soft tissues, with widespread filling of pelvic veins *(arrows)*.

Urethrography of the Female Urethra

The female urethra is approximately 4 cm long and extends from the internal to the external urethral orifice. It courses in an oblique and downward fashion and is slightly curved. The urethral meatus is anterior to the vaginal opening; contrast material does not usually enter the vagina during voiding.

Standard voiding cystourethrography in females includes preliminary films of the pelvis to establish a baseline reference. The bladder is then partially filled, and supine views can be obtained to evaluate for potential reflux. After the bladder is completely filled, patients are placed in a standing position. Lateral, anteroposterior, and oblique fluoroscopic images can be obtained during the voiding and postvoid stages. These procedures can be videotaped. Films are scrutinized for the presence of a urethral diverticulum, evidence of urethral prolapse or hypermobility, and stress incontinence (29).

Double-balloon urethrography is described as a more sensitive diagnostic test for diagnosing a female urethral diverticulum (12). This technique requires the placement of a Bardex Davis model catheter (Bard Urological Division). The catheter is inserted into the bladder, and the balloon is inflated to 30 mL and pulled back until it is seated in the trigone. A sliding balloon is then pushed against the external meatus and inflated to 20 mL to produce a seal. Contrast is injected into the central lumen of the catheter. If leakage is seen into the bladder around the proximal balloon, the pressure and/or position of the balloon must be adjusted to reestablish the seal. In a recently reported study, double-balloon urethrography had a greater sensitivity (100%) than voiding cystourethrography (44%) relative to a confirmed surgical diagnosis (16) (Fig. 3B.6). Other authors have suggested that although the voiding cystourethrogram is not as sensitive as the double-balloon technique, it can still be used as a screening test. If the results of voiding cystourethrography are inconclusive and clinical suspicion persists, a double-balloon examination or MRI can be performed (28,33,40). Transrectal sonography has also been described in the diagnosis of urethral diverticula in women (39).

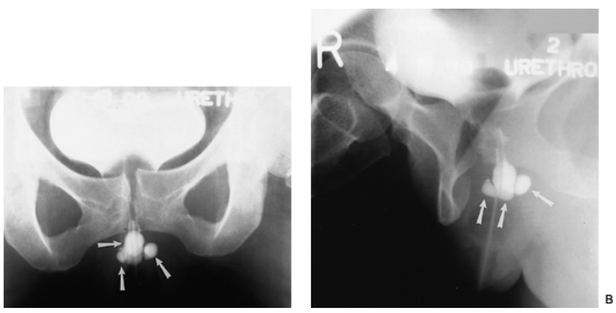

FIGURE 3B.6. A, B: Multiple urethral diverticula. Double-balloon retrograde urethrography reveals multiple diverticular outpouchings *(arrows)*. This patient previously had a normal voiding cystourethrogram.

A variation in the double-balloon technique has been described. Dilute contrast may be used to inflate the intravesical and external balloons of the double-balloon catheter. The proximal balloon is inflated with 25% concentration contrast medium (Renografin 60, Conray 60, or Hypaque 50 diluted with saline) and then drawn snugly down to the internal urethral meatus. The external balloon is inflated with 50% contrast medium. Nondilute contrast medium is injected into the main lumen of the catheter. This is performed on the radiologic examination table, which facilitates fluoroscopic and spot films and provides suitable positioning of the patient during the injection of contrast material. The variation in concentration of contrast between the proximal and distal balloons and the full-strength contrast in the diverticulum permit more precise delineation of the relationship of the diverticulum to the bladder base, the internal sphincter, and the external urinary meatus (19).

An alternative examination in the investigation of potential female urethral diverticula simply requires obtaining a postvoid film after cystography. Comparison between a preliminary coned film of the pelvis and the postvoid film

may show accumulation of contrast in an expected periurethral location (Fig. 3B.7). This is an easy technique to use and does not require a double-balloon catheter.

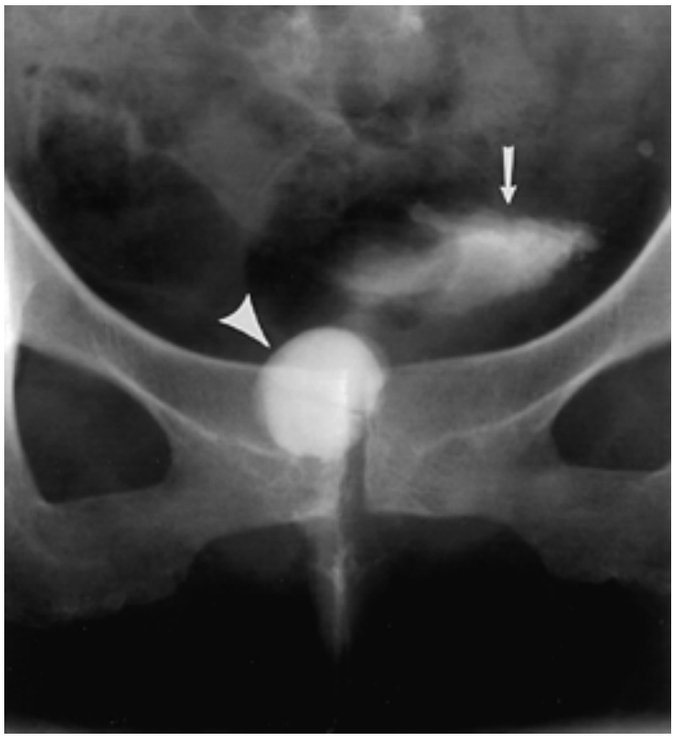

FIGURE 3B.7. Female urethral diverticulum. A rounded contrast collection is seen overlying the right public symphysis *(arrowhead)*. This is separate from the small residual contrast in the bladder *(arrow)*. Filling of this urethral diverticulum is demonstrated on the postvoid film from a cystogram.

Also described is the use of an Allis clamp to grasp the vaginal mucosa while a rubber olive-tip Brodney device is applied snugly to the urethral meatus. This maneuver is stated to result in elongation of the urethra, preventing compression and accordion-like shortening of the urethra (38). In our experience, patients who are suspected of having diverticular disease are best imaged with either a double-balloon technique or MRI.

Urethrography: Findings

Lesions that can be diagnosed on urethrography include traumatic injuries, congenital anomalies, obstructions, strictures, acquired diverticula, and neoplastic lesions. Congenital anomalies include hypospadias, posterior and anterior urethral valves, and urethral duplications. These anomalies, when severe, are usually treated surgically during childhood. Congenital duplication of the urethra is rare. Most duplications are incomplete and asymptomatic, requiring no treatment. A less common but clinically important entity is a complete patent duplication. These patients are symptomatic, with a double stream being the most common symptom. In all cases, the ventral channel proves to be the more normal urethral channel. These lesions have been classified into type I (blind and complete urethral duplication), type

IIA (complete patent duplication with two meatus), type IIA1 (two noncommunicating urethras arising independently from the bladder), type IIA2 (a second channel arising from the first and coursing independently to a second meatus), type IIB [complete patent urethral duplication with one meatus (two urethras arising from the bladder or posterior urethra reuniting to form a common distal channel)], and type III (urethral duplication as a component of partial or complete caudal duplication) (32). Cysts of Cowper's duct may be congenital in children but are typically acquired in adults secondary to urethral infection. A localized collection at the floor of the bulbous urethra is the typical appearance (9,35).

The presence of a double-density sign points to the diagnosis of a male urethral diverticulum. The double-density sign in the bulbous urethra is confirmed as a posterior urethral diverticulum after obtaining an oblique view accounting for the creation of this double density (31) (Fig. 3B.8).

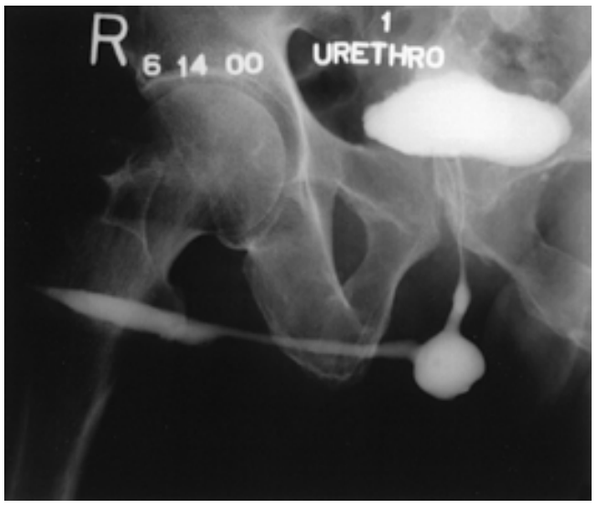

FIGURE 3B.8. Urethral diverticulum. Contrast is seen filling a bulbar urethral diverticulum. The distal bulbar urethra and proximal penile urethra are diffusely strictured.

Congenital saccular anterior urethral diverticula are uncommon. Congenital diverticula are termed *saccular* or *diffuse* on the basis of their anatomic configuration. A localized protrusion from the lumen into the ventral wall of the anterior urethra is a saccular-type diverticula. A generalized dilation of the entire anterior urethra, also termed *megalourethra* or *urethral ectasia,* is characterized as a diffuse type. Saccular-type diverticula may produce anterior urethral obstruction via a valvelike mechanism. The radiographic appearance of a saccular diverticulum is characteristic. Contrast will fill an oval outpouching on the ventral aspect of the anterior urethra. The diverticulum involves the midportion of the penile urethra but can involve the bulbous urethra as well. There is a broad communication between the urethral lumen and the diverticulum. Primary differential considerations when detecting this entity are anterior urethral valves and a dilated Cowper's gland duct (17). Female urethral congenital anomalies are extremely rare. An ectopic ureter may insert into the female urethra and fill during voiding. An ectopic ureter may masquerade as a urethral diverticulum (6).

Urethral stricture disease is common as a result of infection, instrumentation, or trauma. Gonorrheal infection may lead to fibrous scar formation. Inflammatory strictures are found most commonly in the bulbar urethra. The glands of Littre are more abundant in this portion of the urethra and presumably harbor infectious bacteria. Urethritis may also be secondary to conditions such as tuberculosis and schistosomiasis, causing abscesses in the periurethral tissues and perineal fistula formation. The “watering-can” perineum describes the presence of urethral cutaneous fistulae in patients with longstanding strictures (36). Often, these strictures are the result of postgonococcal disease.

Acquired female urethral diverticula occur posterior to the midurethra, although rarely they may occur anteriorly. These originate from infected periurethral glands, which may form an abscess that ultimately ruptures into the urethra. Filling defects within a urethral diverticulum may be secondary to debris, the presence of calculus disease, or rarely, a tumor (10).

Primary carcinomas of the urethra are uncommon but are seen more commonly in women than in men. Most tumors are squamous cell carcinomas; a smaller percentage are transitional cell carcinomas or adenocarcinomas. In men, carcinomas are often associated with an anterior urethral stricture (42).

A well-known artifact in urethrography is the pseudostricture of the urethra. This is caused by pressure on the under surface of the penis by a collecting vessel. This should not be mistaken for a stricture. A short proximal stricture can appear to be long on a voiding study if flow through the narrowed area is not forceful enough to distend the urethra. A smooth uniform narrowing of the entire anterior urethra distal to the penoscrotal junction causes this characteristic pseudostricture. If doubt remains, a retrograde examination or repeat voiding urethrography should be performed (20).

CYSTOGRAPHY

Technique

The first film exposed during the performance of a cystogram is a scout kidney, ureter, bladder (KUB). This is typically exposed using 65 kV and 900 mA at 60 ms. This plain film is evaluated for the presence of abnormal calcifications; abnormal gas collections; and any potential abnormalities related to the kidneys, ureters, or pelvis. Before a Foley catheter is placed, patients are interviewed regarding their history of cardiac valvular disease and the presence of

any joint replacement. Patients who have either a heart murmur (mitral or aortic prolapse/regurgitation), a prosthetic heart value, or an orthopedic joint replacement are placed on prophylactic antibiotics before the placement of the Foley catheter for the cystogram.

Typically, a 14-Fr, 16-inch Dover Rob-Nel catheter (Sherwood Medical, St. Louis, Missouri) is placed into the bladder. A bottle of Cystografin (diatrizoate meglumine 18%, Bracco Diagnostics Inc., Princeton, New Jersey) is infused into the Rob-Nel catheter. Contrast is infused until the patient complains of fullness. At this point, a supine KUB is exposed in addition to a left posterior oblique film. The supervising physician checks these films. The catheter is then removed, and a voiding film is obtained in a right posterior oblique. If the patient is unable to void for this film, an oblique film is exposed with the patient straining. The supervising physician reviews this film. Subsequent to this, the patient is allowed to void completely and a postvoid film is obtained in a frontal supine position. When cystography is performed, every effort should be made to administer as much contrast as the patient can comfortably retain. In the posttrauma setting, this is particularly important to avoid missing bladder extravasation. Ideally, 300 to 500 mL of contrast is administered.

Normal Anatomy

The bladder is oval shaped, with its greatest dimension in the vertical or horizontal position (especially in women). The bladder wall appears smooth when there is full distention and the bladder is normal (Fig. 3B.9). Continence is maintained at the level of the bladder neck. Filling of the posterior urethra may occur in patients who have had a prostatectomy or in patients who have an incompetent internal sphincter. A small amount of air may be seen within the bladder when air is introduced during instrumentation. The bladder base is flat in a supine position and cone shaped when the patient is erect. Voiding occurs when the smooth muscles of the bladder detrusor contract. There are three layers of muscle in the bladder: outer and inner longitudinal muscle and middle circular muscle. Pelvic floor musculature will relax during micturition, and the bladder will descend and change its appearance.

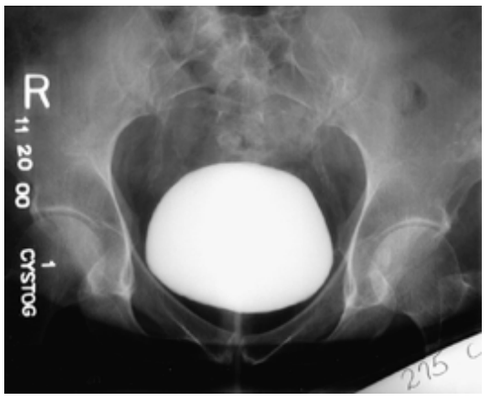

FIGURE 3B.9. Normal cystogram. Contrast (275 mL) fills this normal bladder as part of a pretransplant evaluation. There is no reflux. Calcification is seen in the iliac arteries bilaterally.

Films are evaluated for the presence of reflux, diverticula, possible mural lesions, and extravasation. If voiding films are desired, these are typically obtained with the patient in an upright position. A receptacle, which is radiolucent, is given to the patient. Filming is performed in an oblique position (Fig. 3B.10). As described previously, this technique can be modified by having the patient void against resistance. This can be accomplished by pinching the distal aspect of the penis or by using a penile clamp such as a Zipser clamp.

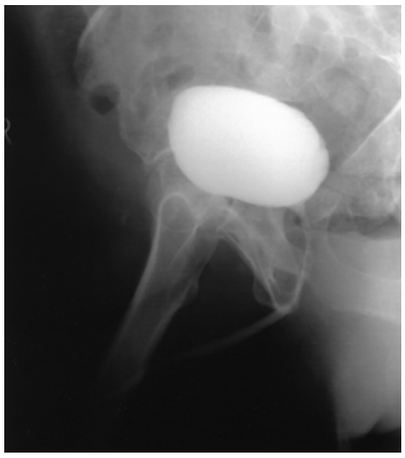

FIGURE 3B.10. Voiding film, normal voiding cystourethrogram. Contrast fills a normal-appearing bladder. There is no evidence of reflux. Filling is seen of a normal-appearing urethra.

Indications

Cystoscopy remains the gold standard for the urologic evaluation of the bladder; radiographic investigation is performed in a number of settings, including the evaluation

of possible vesicoureteral reflux, evaluation of bladder diverticular disease, investigation of a potential bladder injury in a trauma patient, and common in our practice, documenting the bladder appearance in patients before a renal transplant.

The vast majority of cystograms are performed in the posttrauma setting; cystography may also be performed in postsurgical patients who have had radical retropubic prostatectomies. Reconstructive techniques of the vesicourethral anastomosis after radical retropubic prostatectomy involve placement of a urethral catheter for stenting the anastomosis and drainage of the bladder. Traditionally, this catheterization period is approximately 2 to 3 weeks. Cystographic evaluation in these postoperative patients permits evaluation of postoperative extravasation, allowing extension of the catheterization period. An abnormal appearance of the bladder contour in cystography suggests the presence of an intrapelvic fluid collection such as a hematoma or lymphocele. Ultrasound or computed tomography (CT) may be performed to diagnose these fluid collections as well as guide potential drainage (4,21).

Posttrauma cystograms should include standard frontal, oblique, and occasionally lateral views. In severely immobile patients, oblique views are often omitted. Postdrainage films in these patients assume added importance. Small amounts of extravasation should be readily identified on the postdrainage film (37). Recently, more attention has been paid to the diagnosis of bladder injury using CT because most posttrauma patients will have CT scans to exclude intraabdominal injuries. These studies should be evaluated closely for the presence of a bladder injury. CT cystography in the detection of bladder rupture has a reported overall sensitivity and specificity of 95% and 100%, respectively (7). Other authors have addressed the radiographic and clinical predictors of bladder rupture and compared CT cystography with conventional cystography in the evaluation of bladder injuries. These results show that CT cystography is clearly an accurate method for evaluating bladder injuries (14,26,30).

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3C COMPUTED TOMOGRAPHY

Parvati Ramchandani

Susan E. Rowling

Part of "3 - IMAGING "

P. Ramchandani and S.E. Rowling: Department of Radiology, University of Pennsylvania Medical Center, Philadelphia, PA 19104.

FUNDAMENTALS OF COMPUTED TOMOGRAPHY IMAGING

Computed tomography (CT) plays a crucial role in the diagnosis, management, and follow-up of many urologic disorders. A detailed discussion of the physical principles involved in the production of a CT image is beyond the scope of this chapter. However, a basic understanding of the physics of CT and its recent technologic advances is helpful to the ordering clinician to ensure appropriate patient referral and optimal scanning protocols.

CT is similar to conventional radiographic tomography in that a single slice or section of a patient is imaged. However, an important difference is that the x-ray beam passes only through the area of interest and not through adjacent structures, thus eliminating degradation of the image by superimposition of structures outside the slice. The entire urinary tract is directly shown in cross section, so overlying gas or bony structures do not obscure the areas of interest, as can occur with intravenous urography (IVU) or ultrasonography. Compared with magnetic resonance imaging (MRI), CT has better spatial resolution, is more widely available, usually has shorter scanning time, and is of lower cost. However, when an apparent renal mass is indeterminate in imaging features on CT, the greater contrast sensitivity of MRI may allow better detection of intratumoral enhancement. CT and MRI may therefore be complementary for such lesions. Anatomic regions such as the retroperitoneal structures, which are only indirectly imaged by conventional means, are directly visualized by cross-sectional techniques such as CT.

The creation of an image by CT relies on the inherently different attenuation characteristics of the various tissues in the body. CT has much higher contrast sensitivity than conventional radiographs and thus allows the differentiation of tissues with much smaller density differences than is possible with plain radiographs. Thus calculi that are nonopaque on abdominal films (e.g., uric acid stones) are seen as dense structures on CT scans.

Basically, a CT image is a two-dimensional representation of the distribution of different x-ray attenuation coefficients, or densities, of the various tissues within a narrow cross section of the subject's anatomy. The x-ray tube circles around the patient, emitting narrowly collimated x-ray beams from multiple different angular projections that pass through the subject and are sensed on the opposite side by a series of x-ray detectors. By reconstruction, an image is produced that is comprised of quantified grayscale values,

known as *pixels,* that assign density values to individual points within the section. Each pixel value is directly related to the linear attenuation coefficient of the corresponding volume element of the slice, called a *voxel*. The density measurements are then standardized using the Hounsfield scale, named after Sir Godfrey Hounsfield, the inventor of the first clinically viable CT scanner (4,12,34). This scale assigns water a CT number, or Hounsfield Unit (HU), of zero and assigns all other tissue values ranging from -1,000 to approximately +2,000, depending on their attentions relative to water. Using this scale, air is -1,000 HU, fat is approximately -50 to -100 HU, fluid is 0 to +20 HU, soft tissue is between +40 and +60 HU, and cortical bone is between +1,000 and +2,000 HU. CT numbers may vary slightly between manufacturers and are a function of scanner kV (4,12).

The attenuation value of a specific tissue is measured by placing a cursor over the region of interest (ROI) on the workstation and instructing the computer to give the average CT number for that region. The number actually represents the average attenuation of the voxels within the cursor. Therefore measurements are most accurate if the ROI cursor is smaller than the structure being measured, if the cursor is placed well within its boundaries, and if the structure fills the entire slice width of the voxel. Measurements are subject to partial-volume artifact if the structure being measured is smaller than the slice width (4). For example, if the slice thickness is 10 mm and the ROI cursor is placed over a 5-mm renal cyst within the slice, the attenuation measurement will be erroneously high, representing the average of the cyst fluid and the adjacent 5 mm of renal parenchyma. Partial-volume artifact also occurs if an object extends only partially into a CT slice or if two different structures extend into the same slice; it is also exacerbated by patient motion and differences in respiration between slices, leading to respiratory misregistration. Partial-volume artifact is diminished when shorter scan times, thin-section collimation, and single breath-hold scanning techniques are used (4).

Following reconstruction, a CT image is processed to make certain anatomy or pathology more conspicuous by changing the window level and window width. The dynamic range of CT scanners is 4,096 different grayscale values. However, because a maximum of 256 gray levels can be displayed in a typical image, a small subset of the entire grayscale range must be chosen to optimize contrast within specific tissue types (12). The window level controls the image brightness. A midgray level in the center of the display range is selected. The window width defines the range of densities, from black to white, around the midgray level that will be displayed in the image. For example, the typical window level for soft tissue imaging within the abdomen and pelvis is 50 HU with a window width of 200 HU. Therefore only tissues with CT numbers of -50 to +150 HU will be displayed. Those with numbers less than -50 HU will be black, and those values greater than +150 will be white (12). Selecting a narrower window width will enhance contrast, as well as noise, but may be helpful in identifying subtle mass lesions, particularly those in the liver. In contrast, imaging the lung parenchyma requires a lower window level of approximately -700 HU and a wider width of 2,000 HU to enable display of a larger range of densities, including air-filled lung and soft tissue (12). A CT scan of the abdomen and pelvis is routinely reviewed in soft tissue, liver, bone, and lung windows. A liver window or similar narrow window is often helpful in improving lesion conspicuity within the kidneys, particularly when there is intense contrast enhancement of the renal parenchyma.

CT scanning geometry has evolved from first- to fourth-generation scanners. Rapid scan times and optimal spatial resolution require a large number of x-ray detectors, an integral feature of third- and fourth-generation scanners. First-generation scanners had a single x-ray tube and detector. Most modern scanners use third-generation geometry, in which the x-ray tube and a large number of detectors (referred to as a *detector array*) are rigidly fixed opposite one another and rotate together around the patient as the detector samples the fan of divergent rays. In fourth-generation scanners, the detector array forms a complete 360-degree outer ring that samples x-ray beams from the inner x-ray tube and generator as they rotate around the patient. The major advantage of the later-generation models is a faster scan time of 1 second or less and improved spatial resolution (4,12).

Helical computed tomography (HCT), or spiral CT imaging, became commercially available in the early 1990s (4,36,37). In conventional CT scanning, the x-ray tube focal spot lies within a single plane, the table and patient are stationary as data are collected from each slice of anatomy, and the table is moved incrementally between each slice acquisition until the entire area of interest is imaged. During HCT, the table and patient are not stationary during image acquisition, but rather move at a predetermined constant speed while the x-ray tube, and usually the detector array, rotate 360 degrees around the patient. Therefore the x-ray tube focal spot forms a continuous helix around the patient, rather than multiple contiguous circular planes, enabling rapid acquisition of a volumetric data set. Whereas conventional CT images are typically reconstructed from the entire 360-degree angular view set, HCT images are reconstructed from half (180 degrees) of the available view set (4). Because the acquired views do not lie in a plane, the view set is not comprised of actual projections of the slice, but rather is interpolated from the adjacent volumetric data to create the image slice. For this reason, HCT is subject to increased volume averaging artifact. However, the benefits of diminished motion and respiratory misregistration outweigh the mild increase in partial-volume averaging. One of the greatest advantages of HCT is

the ability to improve z-axis resolution by retrospectively selecting a narrower collimation using overlapping reconstruction. This feature is important when attempting to characterize small lesions based on attenuation measurements (4,26).

The development of HCT has enabled imaging of large anatomic regions in a single breath hold, which helps eliminate problems of respiratory misregistration between adjacent slices and helps improve lesion characterization. HCT also enables imaging during the optimal phase, or multiple phases, of enhancement following bolus injection of iodinated intravenous contrast media. In addition, identical image levels are more consistently achieved before and after intravenous contrast media for assessment of lesion enhancement characteristics (26). The risk of imaging during suboptimal phases of contrast enhancement, common in conventional CT imaging, is much reduced with HCT. The three-dimensional data set acquired during HCT imaging has also been critical in the development of three-dimensional CT reconstruction and CT angiography (CTA) (66). The more recent development of multidetector-row HCT (MDCT), also known as *multislice HCT*, and subsecond gantry rotation times, has further revolutionized CT imaging. Much more rapid scan times, improved longitudinal resolution, greater longitudinal coverage, and diminished radiation doses and intravenous contrast load are now possible (66).

COMPUTED TOMOGRAPHY OF THE KIDNEYS

Technique

Complete evaluation of the kidneys requires precontrast and postcontrast imaging. Thus, in patients with a suspected or known renal mass, or those with hematuria, both precontrast and postcontrast scanning should be performed. However, for some indications, such as evaluation of a patient with suspected acute renal colic, unenhanced (noncontrast) scanning alone is generally sufficient to answer the clinical question. Although many renal abnormalities may be detectable on postcontrast images, definitive evaluation of renal masses requires assessment of enhancement in the mass, for which thin-section images through the kidneys both before and after the administration of intravenous contrast media are necessary. It is imperative to use identical scanning parameters before and after contrast administration to ensure that attenuation measurements are obtained from exactly the same location within a lesion and that any change in attenuation can be attributed to lesion enhancement.

The dose of intravenous contrast depends on patient size but generally is between 100 and 150 mL (20 to 50 g of iodine). Oral contrast is given to all patients except those being evaluated for acute renal colic.

The kidneys can be imaged in three distinct phases after contrast administration: the corticomedullary phase (CMP), the nephrographic phase (NP), and the excretory phase (EP) (Fig. 3C.1). The CMP occurs between 25 and 80 seconds after initiation of the contrast bolus, when much of the contrast remains in the renal cortical capillaries, proximal tubules, and peritubal spaces (8,41,86). Because the medullary pyramids are lower in attenuation compared with the cortex, there is an increased chance of either missing a central low-attenuation mass or mistaking a normal pyramid for a mass (Fig. 3C.2 and Fig. 3C.3). More rarely, the enhancing renal cortex may obscure an intensely enhancing vascular cortical neoplasm (86). The NP occurs between 85 and 130 seconds after the initiation of contrast administration as contrast filters through the glomeruli, loops of Henle, and collecting ducts, creating homogeneous parenchymal enhancement. EP images are obtained 3 to 5 minutes after intravenous contrast administration. At this point, the renal parenchyma remains homogeneous but is diminished in attenuation compared with the NP (86). EP images are typically recommended if a urothelial tumor is suspected because contrast in the collecting system increases the conspicuity of a low-attenuation mass. They are also often helpful in distinguishing central renal cell carcinomas (RCCs) from transitional cell tumors located within a calyx or renal pelvis (81). Delayed images obtained after 15 minutes may be helpful in characterizing incidentally identified renal masses when preliminary unenhanced images were not obtained. It has been shown that the attenuation of renal neoplasms diminishes with time as the contrast "washes-out," whereas the density of high-attenuation cysts does not change with time (54,86).

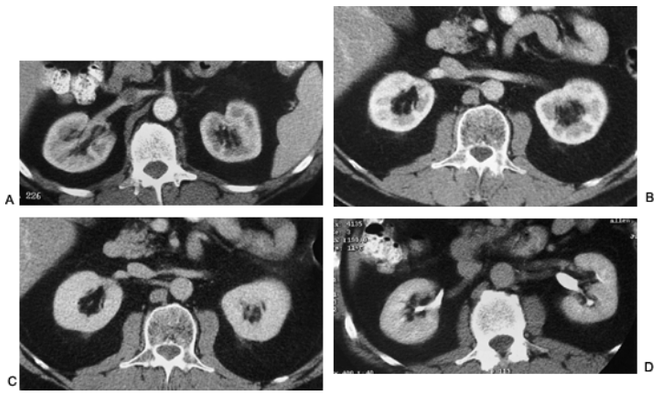

FIGURE 3C.1. Phases of renal contrast enhancement. In corticomedullary phase **(A, B),** the renal cortex and medulla are very distinct. Note flow artifact in cava on **A** and course of renal vessels. In nephrographic and excretory phases **(C, D),** the parenchymal enhancement is homogeneous, making it easier to detect renal masses.

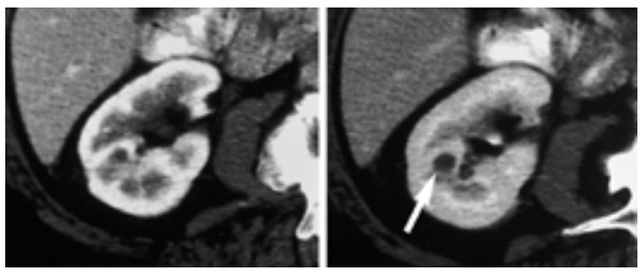

FIGURE 3C.2. Renal cyst obscured on corticomedullary phase (CMP) of enhancement. Image on right in nephrographic phase (NP) demonstrates a small cyst *(arrow)*, which is a much more subtle finding on the CMP image on the left.

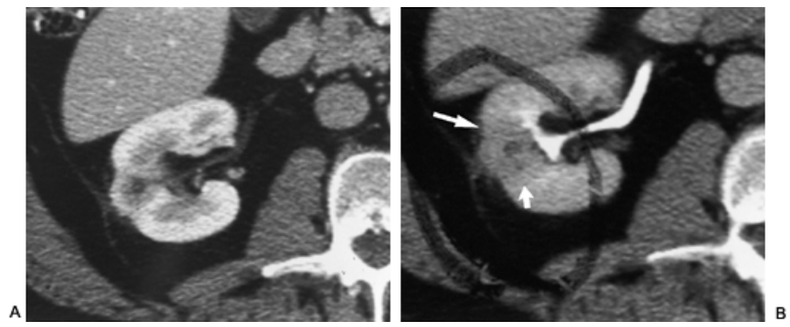

FIGURE 3C.3. Small renal cell carcinoma, poorly seen on corticomedullary phase (CMP) imaging. On CMP image **A,** there is an irregular bulge in the renal contour. The different enhancement of this lesion is much more obvious *(arrows)* on the excretory phase imaging **(B).** (Artifact on image circling area of interest).

Recognition of these phases of normal renal enhancement and the effect on renal mass detection, conspicuity, and characterization is very important. Masses may be difficult to recognize and characterize if imaging is performed during the CMP alone (Fig. 3C.2 and Fig. 3C.3). Of all renal lesions detected in the NP, only 67% to 72% are also detected in the CMP of imaging (8,18,78). In one study (18), the addition of NP imaging to CMP imaging resulted in a 4.4-fold increase in detection of medullary lesions, and a 1.2-fold increase in the detection of cortical lesions. False-positive results are also more common in the CMP of imaging (5,18,78). However, renal venous involvement is best seen during the CMP of enhancement (45).

Current scanning protocols for renal mass characterization are performed as follows. During HCT, unenhanced (precontrast) images are obtained through the kidneys at 5-mm increments. Intravenous contrast is then administered using a mechanical power injector at a rate of 2 or 3 mL per second. Following initiation of the contrast bolus, contiguous 5-mm scans are obtained through the kidneys. CMP images are acquired after a delay of 30 to 40 seconds, and NP images acquired after a delay of 100 seconds. If indicated, EP images are acquired 3 to 5 minutes after

contrast bolus (18,45,78,86,88). It has been shown that the timing of the NP is variable and depends on multiple factors, such as the patient's cardiac output and renal function and the dose and rate of injection of the contrast media. Therefore it may be helpful to use a bolus-tracking device such as Smart-Prep (GE Medical Systems, Milwaukee, Wisconsin), which triggers the onset of HCT at the completion of the CMP (7) and ensures true NP imaging. As stated, postcontrast series should use scanning parameters identical to those used during the initial unenhanced series. If the entire abdomen is to be imaged, it is possible to scan the remainder of the abdomen and pelvis between the CMP and NP images (86).

Vascular-phase imaging, or CTA, is recommended in patients who are undergoing preoperative planning for nephron-sparing surgery, repair of ureteropelvic junction obstruction, or donor nephrectomy (32). Specific techniques for CTA are considered in Chapter 3F . With the advent of MDCT, it is now possible to perform high-quality CTA of the renal arteries and aorta and high-resolution imaging of the kidneys for lesion detection in a single examination. In the past, renal lesions were often suboptimally evaluated during the CMP of enhancement obtained during CTA.

Anatomic Considerations

The perinephric fat outlines the surface of the kidney; the renal capsule cannot be distinguished from the renal parenchyma. The fat in the renal sinus is of low attenuation and outlines the collecting system and the blood vessels, which course anteromedially. The perirenal fascia and the septa extending from the kidney to the anterior or posterior renal fascia are visible as linear soft tissue densities (48). The anterior renal fascia is usually seen on the left, less commonly

on the right, and it separates the structures in the anterior pararenal space, such as the pancreas, retroperitoneal duodenum, and the ascending and descending colon, from the kidneys. The posterior renal fascia is commonly seen posterior to both kidneys.

The right adrenal gland is superior to the upper pole of the kidney, just dorsal to the inferior vena cava (IVC). The left adrenal gland is more anteriorly and medially located, with the splenic vein just anterior to it as a consistent landmark (30).

The renal parenchyma is of homogeneous soft tissue density on noncontrast images with attenuation values of 30 to 60 HU. The renal pelvis and proximal infundibula may be seen as water-density structures, particularly if the renal pelvis is extrarenal. The calyces are not identifiable without contrast excretion. After intravenous contrast administration, the renal vessels and cortex enhance brightly. In the first 60 seconds after contrast administration (the CMP), there is sharp distinction between the cortex and the medulla (Fig. 3C.1A and Fig. 3C.1B), but the medulla also soon enhances brightly (the NP) (Fig. 3C.1C). On delayed images, dense urine is seen in the collecting system in patients with normal renal function (Fig. 3C.1D). The ureter courses anteroinferiorly over the psoas muscle.

The renal veins lie ventral to the arteries, with the longer left renal vein (Fig. 3C.1B) coursing between the aorta and the superior mesenteric artery to the IVC (which may be oval or slitlike at this level). The right renal vein is shorter and, with a more oblique course into the cava, and may not always be well imaged on CT scans. The right renal artery crosses behind the cava to enter the kidney (Fig. 3C.1B) while the left courses directly to the kidney (Fig. 3C.1C and Fig. 3C.1D).

Normal Variants and Congenital Anomalies

Pseudotumors, named variously as the column of Bertin, dromedary hump, or hilar lip, may occur in the kidneys due to variations in the pattern of lobar fusion and may simulate renal masses on IVU and sonography. Compensatory hypertrophy due to focal scarring can also simulate a mass. All pseudotumors are isointense to the renal parenchyma on precontrast and postcontrast imaging and are readily distinguished from true renal masses.

Anomalies such as retroaortic renal vein; retrocaval ureter (Fig. 3C.5); circumaortic renal vein; and persistent, duplicated, or left-sided IVC can be recognized on CT, as can renal agenesis (Fig. 3C.6), malpositioned or ectopic kidneys,

and fusion anomalies such as horseshoe kidneys or cross-fused ectopy. With renal agenesis, it is imperative to look for genital anomalies as well (Fig. 3C.6). CT is very accurate at distinguishing true renal agenesis from atrophic, nonfunctioning kidneys. Ectopic ureteral insertions, whether associated with duplication anomalies or not, can also be demonstrated.

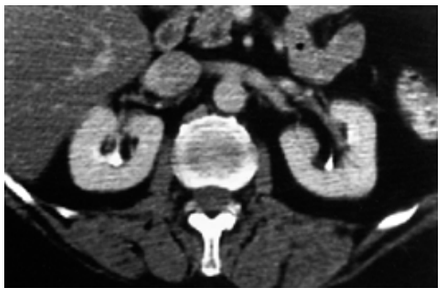

FIGURE 3C.4. Course of renal vessels. Note that the right renal artery courses behind the cava. The renal sinus fat surrounds the vessels.

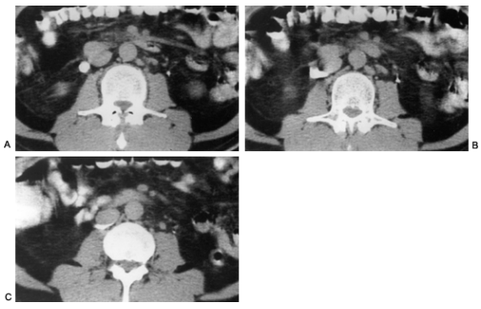

FIGURE 3C.5. Retrocaval course of mildly dilated right ureter is well seen. **A–C** tracks slices from superior to inferior.

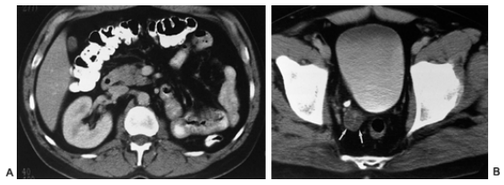

FIGURE 3C.6. A 30-year-old man with left renal agenesis and absent left seminal vesicle. There appears to be cystic change in the right seminal vesicle also *(arrows)*.

Renal Masses

Renal Cell Carcinoma

The burgeoning use of CT in modern-day clinical practice is making the incidental discovery of RCCs an increasingly familiar scenario. Such masses may be detected during a CT scan being performed for symptoms referable to organ systems other than the urinary tract or for the workup of vague signs and symptoms. In a Japanese survey (3), incidentally discovered renal cell cancers increased from 20 in 1980 to 338 in 1988. Increasingly, more RCCs are detected at a smaller size (less than 3 cm in diameter) (1,19); in one study, 25% of incidentally discovered cancers were found to be smaller than 3 cm as compared with only 5% in the pre-CT era (71) (Fig. 3C.7). Contrast-enhanced CT is more sensitive than either sonography or IVU in detecting renal masses smaller than 3 cm (94% versus 79% and 67%, respectively) (1,84).

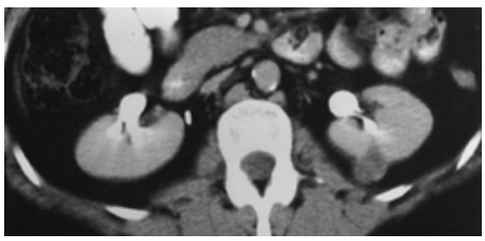

FIGURE 3C.7. Small left renal cell carcinoma discovered incidentally in a 42-year-old woman being evaluated for right abdominal pain. The mass is exophytic and enhances less than the normal renal parenchyma, expected findings with renal carcinoma.

CT is the recommended investigative modality when a renal mass is indeterminate in its characteristics on sonography, if a patient has a malignancy that metastasizes to the kidneys, or if there is a palpable flank mass. It is also the imaging modality of choice for evaluating a suspected renal mass and for staging a known neoplasm.

Imaging Features of Renal Cell Carcinoma

1. Distortion or bulge of the renal contour can occur. Because RCCs arise from the cortex, 95% of these lesions are exophytic (87) (Fig. 3C.8).

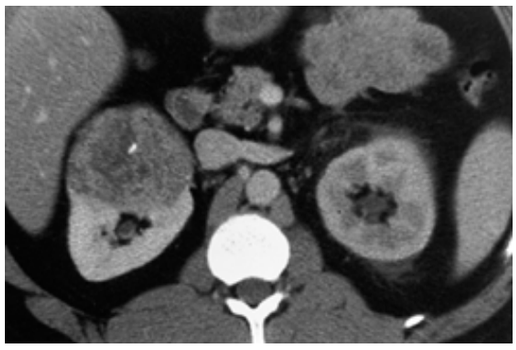

FIGURE 3C.8. Exophytic right renal cell carcinoma with a focus of calcification. On this contrast-enhanced scan, the mass is enhancing heterogeneously.

2. On unenhanced images, small lesions are homogeneous and isodense to the kidneys. Large masses vary from being nearly isodense to the kidneys (Fig. 3C.9) and slightly heterogeneous to being hypodense with necrotic areas (Fig. 3C.10A) or hyperdense due to hemorrhage (85). Calcification is seen in approximately 30% of cases when the tumors are larger than 3 cm (Fig. 3C.8, Fig. 3C.9, and 3C.10); smaller lesions are calcified about 3 % of the time (85,87).

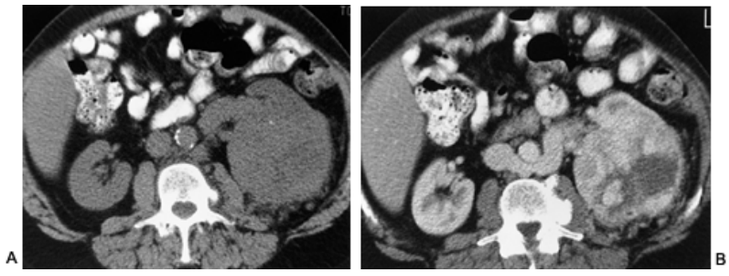

FIGURE 3C.9. Large left renal cell carcinoma. **A:** Unenhanced image demonstrates a small amount of calcification in the mass. **B:** Following contrast enhancement, there is irregular enhancement and a shaggy border to the mass, more likely due to perinephric collateral vessels than to perinephric extension. Note that the left renal vein is retroaortic.

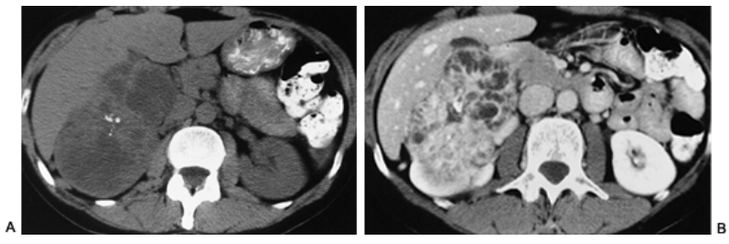

FIGURE 3C.10. Large, necrotic renal cell carcinoma. **A:** Unenhanced image shows calcification and low-attenuation areas in the mass, representing areas of cystic necrosis. **B:** There is avid, heterogeneous enhancement after contrast administration. The areas of cystic necrosis do not enhance.

3. After contrast administration, all RCCs enhance, but less so than the normal renal parenchyma. Most small tumors tend to have homogeneous enhancement, whereas larger tumors may show heterogeneity in enhancement (Fig. 3C.9B and Fig. 3C.10B), particularly if there is central necrosis. Papillary RCCs tend to demonstrate central cystic or necrotic degeneration and calcification, and they enhance less than the non-papillary cell types.

Staging of Renal Cell Carcinoma

The classification schemes for staging RCC are not reiterated here.

Stage I disease (confined within renal capsule) is difficult to distinguish from stage II disease (extension into perinephric fat but contained within Gerota's fascia) by CT scanning. Thickening of the renal fascia and the bridging septa (Fig. 3C.9) is more often the result of vascular engorgement and enlargement and edema in the perinephric region than the result of tumor extension (35). This shortcoming of CT is not usually a clinically significant issue because both stage I and II tumors are surgically respectable.

CT has a sensitivity of greater than 95% for the detection of regional lymph node metastases to the renal hilum or retroperitoneum (stage III disease) (Fig. 3C.11). Nodes larger than 1 cm in short axis diameter are considered to be enlarged by CT criteria. Lymphadenopathy can be caused by metastatic disease or reactive hyperplasia; these conditions

are indistinguishable on CT imaging (76). Cystic necrosis may be seen in the nodes that are often hypervascular (Fig. 3C.11).

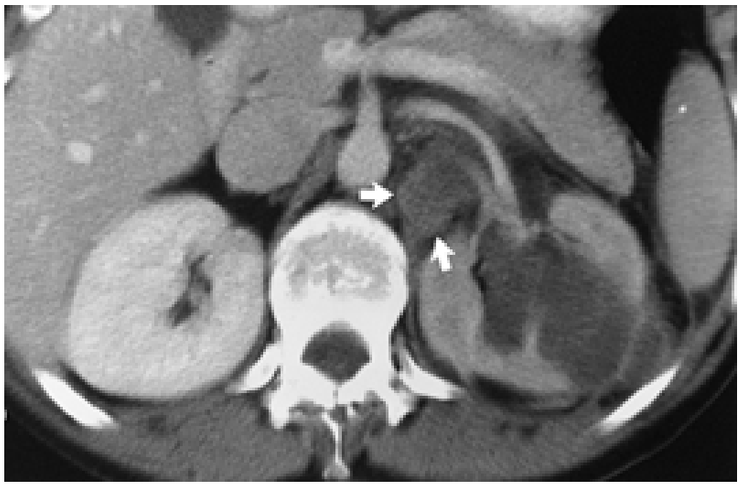

FIGURE 3C.11. Lymph node metastasis with left renal cell carcinoma. Contrast-enhanced scan shows nonenhancing areas of cystic necrosis with a large paraaortic node, which also appears to be necrotic *(arrows)*. There were multiple other enlarged nodes on other cuts (not shown). The renal vein is compressed by the nodal enlargement, which is likely the cause of the decreased nephrogram in the left kidney.

Tumor extension into the renal vein or IVC is well evaluated with contrast-enhanced CT (Fig. 3C.12), with reported sensitivity and specificity rates in the range of 80% and 96% (35,38). A good bolus of contrast within the vascular structures facilitates evaluation of the venous structures—the tumor thrombus is seen as a filling defect in the brightly enhanced blood within the vessel. It is important not to misdiagnose streaming artifact in the IVC (from unopacified blood returning from the lower extremities or the renal veins) as tumor thrombus (Fig. 3C.1A). Enlargement of the renal vein may suggest the presence of tumor thrombus but can also be related merely to increased flow from a hypervascular neoplasm. Tumor thrombus is easier to detect in the left renal vein than in the right renal vein.

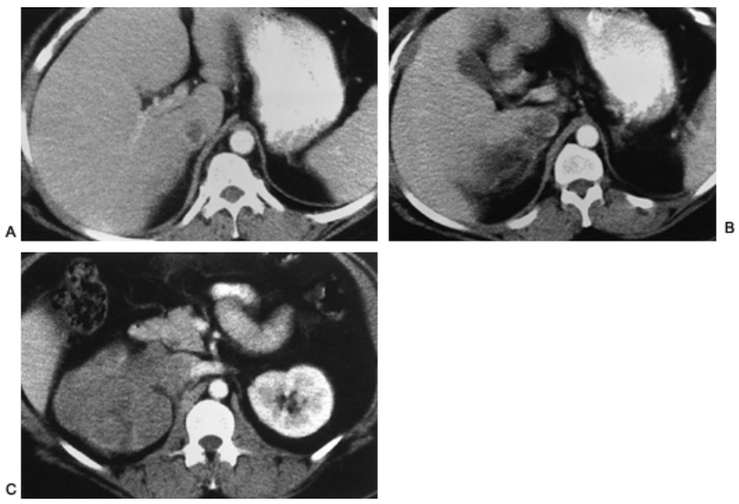

FIGURE 3C.12. Renal cell carcinoma with caval extension. There is a filling defect in the intrahepatic cava **(A),** subhepatic cava **(B),** and the right renal mass is seen extending into the renal vein and the inferior vena cava (C).

Adrenal involvement, whether due to direct extension in large tumors or to contralateral hematogenous metastasis, is well evaluated with CT (29).

Direct tumor spread to contiguous organs is detectable on CT as loss of the expected tissue planes between the kidneys and the adjacent organs such as the liver, spleen, psoas muscle, or pancreas. However, imaging in the axial plane alone (as with routine CT scanning) has the disadvantage that volume averaging of oblique tissue interfaces makes it difficult to determine whether a renal lesion merely abuts an adjacent organ such as the liver or actually invades it (Fig. 3C.10B). In such cases, MRI is often useful for further evaluation because imaging can be performed in the appropriate plane to answer the question.

CT or MRI scanning of the abdomen combined with CT scanning of the chest is the current recommendation for assessment of distant metastatic disease in patients with RCC

Chest CT is highly sensitive for detecting metastatic disease, but its low specificity is a drawback because abnormalities related to granulomatous disease may be indistinguishable from metastatic disease (55). Radionuclide bone scanning is not recommended as a routine procedure and is indicated in patients with symptoms worrisome for metastatic disease. Because 5% of RCCs are bilateral, careful attention must be paid to the contralateral kidney in every case.

Accuracy of CT in Diagnosis of RCC

Contrast-enhanced CT scanning has an overall accuracy in the 95% range for the diagnosis of RCC, with the diagnosis of small renal masses proving the most difficult. False-positive diagnosis of RCC can be as high as 17% (67), even with contemporaneous imaging techniques. When a renal mass is indeterminate in nature on CT imaging, MRI can sometimes be helpful in demonstrating enhancement within the lesion, therefore better characterizing it. Alternatively, follow-up scans may demonstrate growth of the lesion. RCCs grow at a mean rate of 0.5 cm per year, a rate much faster than seen with benign lesions (6).

Postoperative Findings

Recurrence in the operative bed, liver, remaining kidney, adrenal glands, and the retroperitoneum can be assessed on follow-up CT examinations. The migration of normal structures into the operative bed, such as bowel, may simulate a recurrent tumor. Baseline scans are therefore of value in serial follow-up, particularly in patients who have undergone nephron-sparing surgery, so that the postoperative alterations in the appearance of the kidney are not misdiagnosed

as tumor recurrence (39). Wedge-shaped or concave defects may be seen at the site of resection, and there may also be fat pads placed at the resection site.

Urothelial Tumors

Urothelial tumors are the second most common primary malignancies of the kidney, with transitional cell carcinoma (TCC) accounting for the vast majority (approximately 85% to 90%). Squamous cell carcinomas (SCCs) are the next most common, accounting for 6% to 7% of primary renal pelvic tumors. Other rarer urothelial tumors are not considered here.

CT Imaging Features of Urothelial Neoplasms (14,57,81,82)

Although most cases of TCC are diagnosed on IVU or retrograde pyelography, an occasional case may be picked up serendipitously on CT.

1. An intraluminal soft tissue mass in the pyelocalyceal system or ureter, which is isodense on precontrast images (31 to 48 HU), may be seen (57). TCC enhances less than the adjacent parenchyma after contrast administration (attenuation values of 43 to 82 HU) (Fig. 3C.13). In the EP, the mass may be outlined by the excreted contrast (Fig. 3C.14). With contemporaneous imaging techniques, TCC lesions larger than 1 cm can be visualized (81).

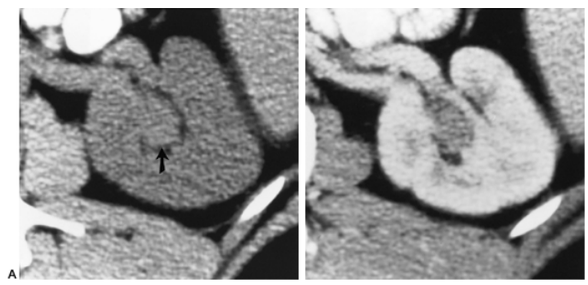

FIGURE 3C.13. Transitional cell carcinoma in the left renal pelvis. There is a soft tissue mass in the left renal sinus *(arrow)* on the unenhanced image **(A),** which enhances slightly after contrast **(B).** The sinus fat does not appear to be invaded.

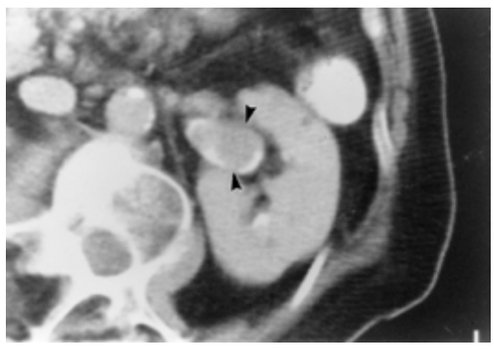

FIGURE 3C.14. Transitional cell carcinoma in the left renal pelvis is seen as a filling defect *(arrowheads)*.

2. Stippled calcification may be seen on the surface of the mass.
3. Rather than a well-defined mass, there may be concentric or eccentric thickening of the wall of the renal pelvis or ureter. Early flat or plaquelike lesions that would not be identifiable on IVU can often be detected on CT.
4. There may be hydronephrosis proximal to the lesion in the collecting system. An obstructive lesion will cause alterations in the nephrogram, which may be delayed, dense, striated, or persistent (Fig. 3C.15).

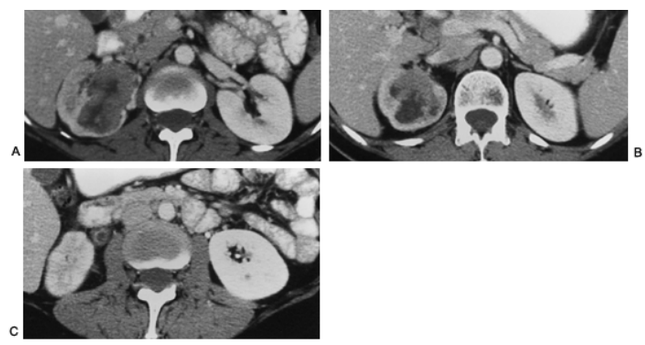

FIGURE 3C.15. Transitional cell carcinoma of the right renal pelvis, which is partially obstructing. Contrast-enhanced images demonstrate a mass in the right renal pelvis and lower pole collecting system **(A, B).** Because of the obstruction, the right nephrogram is delayed compared with the left kidney (C).

5. The reniform shape of the kidney is maintained even with large TCCs that infiltrate the renal sinus and the renal parenchyma.
6. Venous involvement (renal vein or the IVC), lymph node involvement, or distant metastases may be seen with stage IV tumors.

Utility of CT in Patient with TCC

CT is highly accurate in distinguishing stage III and IV disease from stage I and II disease because parenchymal invasion, tumor extension through the wall of the renal pelvis or ureter, lymphadenopathy, and other metastatic spread are well demonstrated. CT imaging can therefore be crucial in staging such patients if conservative management is being contemplated. Furthermore, in patients with high-grade obstruction in whom IVU is nondiagnostic, the level of obstruction can be demonstrated on CT and the obstructing ureteral lesion easily distinguished from obstruction due to a stone or other periureteral pathology (42).

The distinction between stage I disease (limited to mucosa) and stage II disease (invasion of muscle) is not possible with CT.

CT is extremely useful in the characterization of a radiolucent filling defect seen on urography and in distinguishing radiolucent calculus from a urothelial tumor or blood clots (57). On nonenhanced CT, all renal calculi have densities greater than 200 HU (as compared with mean density of 39 HU for TCC lesions), whereas blood clots are often denser than normal parenchyma (50 to 90 HU). Following administration of a bolus of contrast, TCC lesions show slight enhancement, but blood clots do not enhance.

Squamous Cell Carcinomas

SCCs are aggressive and tend to present late in their course, usually as an infiltrating renal mass rather than as an intraluminal or mucosal lesion. The kidney is usually enlarged and not functioning. Staghorn renal calculi are often associated, and in fact, calculi have been reported in 4 of 5 patients with renal SCC on CT. There may be infiltration of adjacent organs at presentation (56).

Angiomyolipoma

Angiomyolipomas (AMLs) are benign renal neoplasms that contain varying proportions of mature adipose tissue, smooth muscle, and blood vessels; one or two of these elements may predominate. The radiographic appearance can therefore range the spectrum from being nearly completely fatty to nearly all soft tissue (10,50,83). The detection of regions of fat within a lesion is confirmatory of the diagnosis of an AML; the density measurements in the fatty areas range from -10 to -50 HU. Calcification is usually not present, and if hemorrhage has occurred, it too will be evident (Fig. 3C.16, Fig. 3C.17, and Fig. 3C.18).

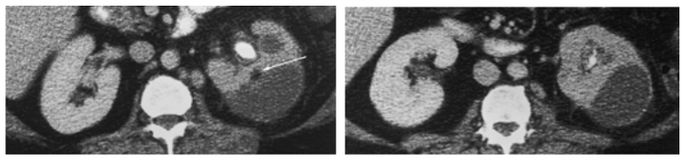

FIGURE 3C.16. Tiny angiomyolipoma *(arrow)* in the left kidney, which has caused a subcapsular hematoma. Note the compression of the renal contour. Patient also has a calculus in the renal pelvis.

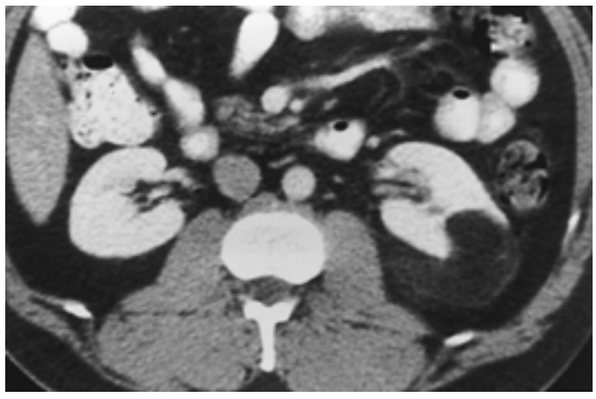

FIGURE 3C.17. Angiomyolipoma in the left kidney with a predominantly fatty composition. Note that the density of the lesion is similar to the retroperitoneal fat. Soft tissue strands are also seen within the mass, representing the other components.

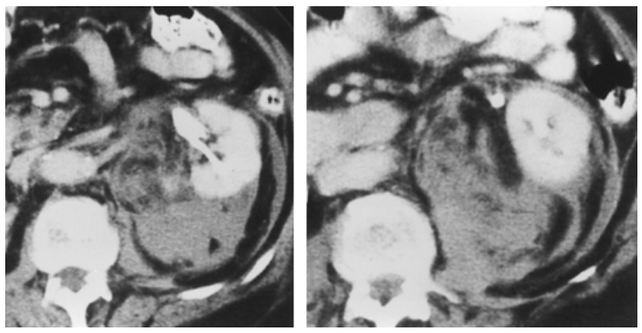

FIGURE 3C.18. Angiomyolipoma that has bled. Note the high-density blood that has accumulated in the perinephric space. Fat within the angiomyolipoma (AML) is also visible as dark patches. The kidney is displaced by the hemorrhage.

Most AMLs are asymptomatic and found incidentally on imaging. Lesions larger than 4 to 5 cm, being more prone to hemorrhage, may become clinically apparent because of hematuria or symptoms associated with perinephric or retroperitoneal hemorrhage. There may also be mass effect caused by displacement of adjacent organs. AMLs can increase in size over time, particularly lesions that are larger than 4 cm; thus follow-up is warranted for such lesions (74).

Typically, AML is a unilateral lesion in a middle-aged woman. Numerous bilateral AMLs should raise the suspicion

of tuberous sclerosis (TS) because 80% of patients with TS have AMLs; 30% also have renal cysts. Sporadic occurrence of bilateral AMLs in patients without TS can also occur.

Fat within a renal mass is indicative of an AML. However, there are reports of RCCs that may appear to have fat within them because the tumor has engulfed renal sinus fat or undergone osteoid metaplasia with resultant fat and marrow deposition within the tumor (31).

Other Renal Tumors

Oncocytoma is an uncommon solid renal neoplasm with a distinctive histologic appearance. The CT features of this lesion are largely indistinguishable from those of an RCC (22).

Renal sarcomas are similar in radiographic appearance to RCCs. Leiomyosarcomas are the most common primary renal sarcoma, and they can arise from the renal capsule or the walls of renal veins or the IVC.

Lymphomatous involvement of the kidney is usually due to hematogenous or direct spread from an extrarenal source. Primary renal lymphoma is very rare because there is no lymphomatous tissue within the kidney. Non-Hodgkin's disease involves the kidneys far more frequently than Hodgkin's disease (92% versus 8%). The CT appearance is variable (65). There may be multiple discrete masses (31% cases), a solitary mass (23%), or tumor infiltration in the perirenal space (40%) (Fig. 3C.19).

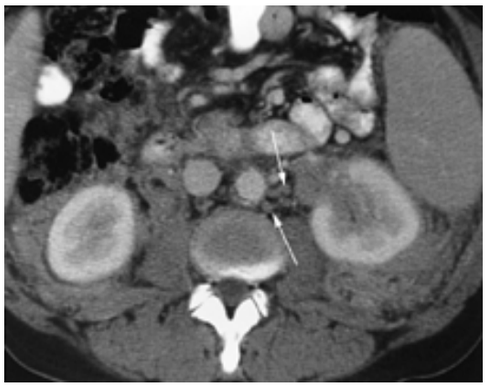

FIGURE 3C.19. Lymphoma presenting as a rind of soft tissue in the perinephric region bilaterally. There are also several small retroperitoneal lymph nodes *(arrows).*

Renal metastases are seen in association with metastatic disease elsewhere in a patient with a known primary malignancy. They are usually multiple and bilateral and are smaller than a 1 cm (33). An individual lesion may be indistinguishable from RCC, and percutaneous biopsy may be necessary to establish the diagnosis, if required.

Renal medullary carcinoma is a highly aggressive tumor that arises in the medulla near the renal papilla and then invades the parenchyma. It has been described in young patients, commonly but not exclusively African Americans, with sickle cell trait or hemoglobin SC disease. The central infiltrative pattern of tumor growth and extensive necrosis in a young patient should suggest the diagnosis. Mean survival from first symptoms to death is about 15 weeks (21).

Renal Cystic Masses

Simple Renal Cysts

Simple renal cysts are ubiquitous lesions that increase in number and size with age (20). Cysts should be of homogeneous water density (less than 20 HU) with thin or imperceptible walls, have a sharp interface with the renal parenchyma, and demonstrate no enhancement after contrast administration (Fig. 3C.20). No follow-up is necessary for lesions that meet these criteria.

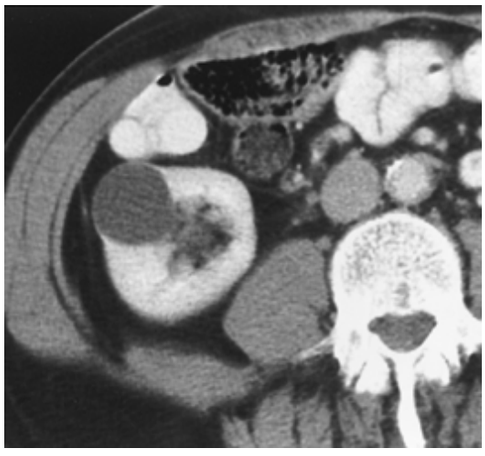

FIGURE 3C.20. Simple renal cyst. The walls are thin, and there is no enhancement within the lesion.

Complicated Cysts

Cysts that are complicated by hemorrhage or infection will have an alteration in their imaging characteristics and may be confused with cystic renal neoplasms such as cystic RCCs or Wilms' tumor. The Bosniak classification system for renal cysts was devised to help categorize complicated renal cysts and predict the risk of malignancy (11). A *type I* lesion meets all of the aforementioned criteria for a simple cyst. A *type II* cyst (Fig. 3C.21, Fig. 3C.22, and Fig. 3C.23) is minimally complicated and demonstrates thin septations or minimal calcification on septa or the walls or is of high density (40 to 90 HU before contrast administration). These lesions have minimal risk for malignancy. *Type III* lesions may have one or more features suggestive of malignancy but no definite sign of malignancy. Such lesions exhibit thick or nodular walls or septations, thick or irregular calcification, and heterogeneous density but no enhancement of the walls or the septa in the lesion. Approximately 50% of these lesions will prove to be malignant, and surgical treatment or close follow-up is required for these lesions. *Type IV* lesions demonstrate unquestionable enhancement of a component of the lesion and are considered cystic tumors (Fig. 3C.24 and Fig. 3C.25).

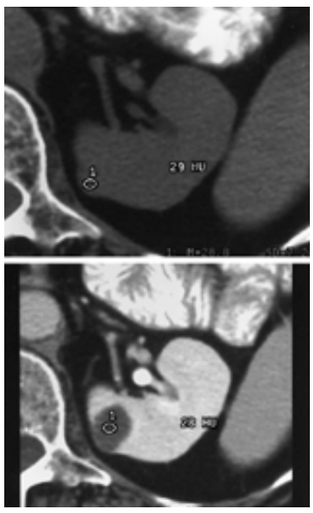

FIGURE 3C.21. High-density cyst. Bosniak II lesion. The lesion is of higher density (29 HU) than expected for a simple cyst (0 to 20 HU). However, there is no enhancement after contrast administration. The increased density is related to the presence of hemorrhage or proteinaceous material within the lesion.

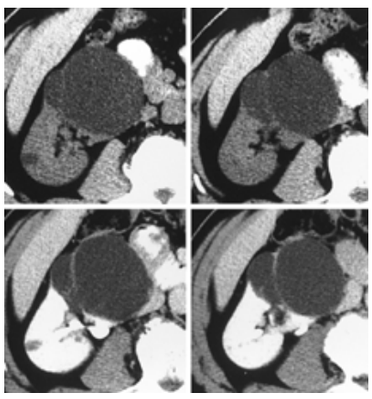

FIGURE 3C.22. Septated cyst. Bosniak II lesion. Nonenhaced images *(top row)* and enhanced images *(bottom row)* demonstrate thin septations within the cystic lesion.

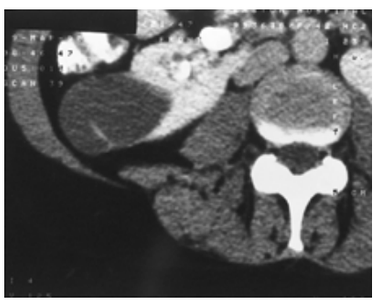

FIGURE 3C.23. Bosniak II cyst. Short thin septation in right renal cyst.

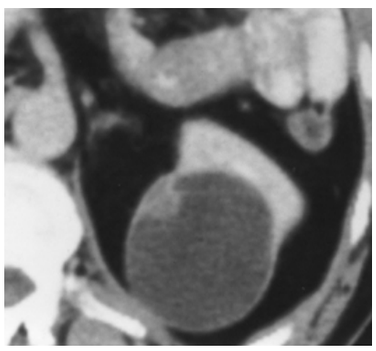

FIGURE 3C.24. Cystic renal cell carcinoma. Bosniak IV lesion. There is an enhancing nodule within the lesion that is predominantly cystic.

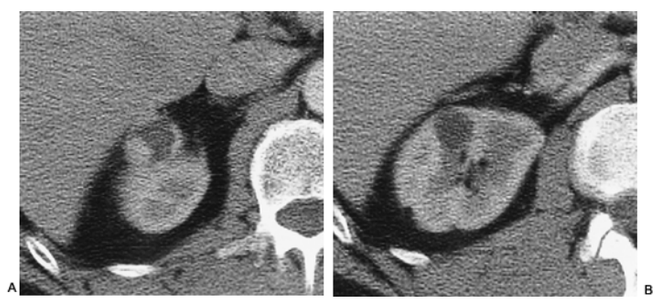

FIGURE 3C.25. Cystic renal cell carcinoma. Small right renal lesion has a thick irregular wall superiorly **(A)** and a relatively cystic appearance in its inferior aspect **(B).** However, nodular thickening in any portion of the lesion makes it a category IV lesion.

Multilocular Cystic Nephroma

A localized cystic disease of unknown etiology with no known hereditary pattern of inheritance, multilocular cystic nephroma (MCN) is a benign neoplasm. Multiple epithelial-lined cysts are separated by fibrous septa of varying thicknesses; a minority of lesions may have microscopic foci of nephroblastoma or sarcoma in the septa. The septations often enhance on contrast-enhanced CT, making it difficult to reliably exclude cystic RCC or Wilms' tumor, even when MCN is strongly suspected by imaging. Surgery is therefore indicated for these lesions (15).

Parapelvic Cysts

Parapelvic cysts occur in the renal sinus and may simulate hydronephrosis on noncontrast scans. Images in the EP of the CT scan will demonstrate mass effect on the collecting system.

Cystic Renal Diseases

Autosomal-dominant polycystic kidney disease (ADPKD) causes cyst formation in the kidneys, liver, pancreas, and spleen (Fig. 3C.26). The kidneys are often greatly enlarged, and multiple cysts of varying sizes are seen throughout the parenchyma. Cysts may show hemorrhage (and therefore be hyperdense) and calcification in the walls. Calculi are also common (51).

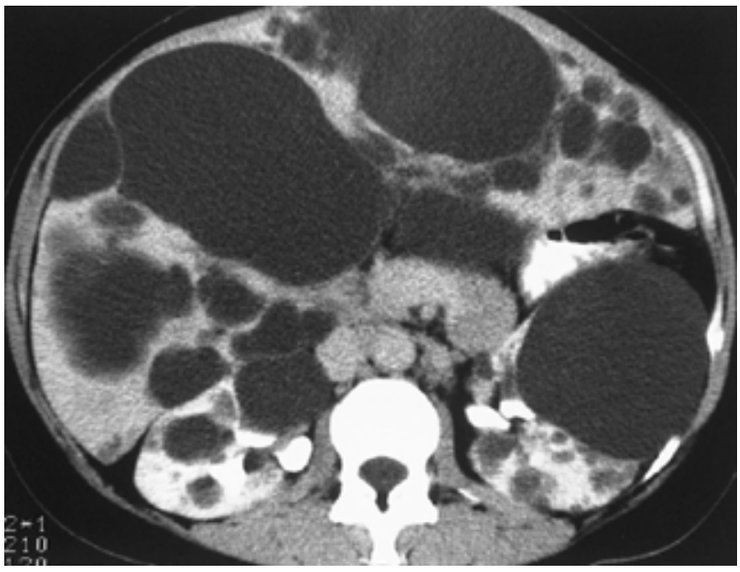

FIGURE 3C.26. Autosomal-dominant polycystic kidney disease. Innumerable large cysts in the kidneys and liver are pathognomonic of the disease.

Multiple bilateral simple renal cysts in an individual patient may be difficult to differentiate from ADPKD. The absence of a family history, normal renal function, lack of cysts in other organs (e.g., the liver), and normal renal size favor the diagnosis of multiple simple cysts.

Acquired Cystic Kidney Disease

Patients with chronic renal failure, particularly those receiving chronic dialysis, can develop numerous cysts in the kidneys; 90% of patients may demonstrate renal cysts after 5 to 10 years of dialysis therapy (52). There is also an increased incidence of RCC, which is three to six times greater than the annual incidence of renal carcinoma in the general population (62). Early in the course, the kidneys are small in size but increase in volume with time. The appearance may be indistinguishable from ADPKD, but no cysts occur in organs other than the kidneys.

Syndromes Associated with Renal Cysts

Many syndromes are associated with renal cysts; such diseases are also referred to as *pluricystic kidney disease* (64) and are not discussed here.

Two syndromes in which renal cysts occur in association with neoplasms are of particular importance to urologists. *TS* is associated with AMLs in 40% to 80% of patients, and renal cysts are seen in approximately 15% of patients. There may also be a slight increased incidence of RCC (9,16).

von Hippel-Lindau disease is an autosomal-dominant hereditary disease associated with renal cysts and cancers, pancreatic cysts, pheochromocytomas, and retinal and central

nervous system hemangioblastomas (17). Approximately 60% of patients will have renal cysts, and 29% of patients develop clear cell renal carcinomas. As many as 600 microscopic tumorlets may be present in the parenchyma of each kidney.

Renal Inflammatory Processes

In patients with clinically suspected *acute pyelonephritis,* CT is used not for its diagnosis, but rather to detect complications when the clinical response to appropriate therapy is not satisfactory. CT is the best imaging method to delineate the extent of the renal inflammatory process and also evaluate for extrarenal extension of the disease (72,73).

The CT findings in acute pyelonephritis (40) are as follows: (a) The most common finding is the presence of one or more round or wedge-shaped areas of decreased attenuation, seen only on contrast-enhanced scans. These areas enhance less than the normal parenchyma (Fig. 3C.27). Delayed scans may show increased density in these same areas due to eventual filling of tubules that are obstructed by the surrounding edema (Fig. 3C.28 and Fig. 3C.29). This is likely the CT equivalent of a focal, delayed obstructive nephrogram. These zones of acute pyelonephritis have straight borders rather than rounded contours and extend from the renal collecting system to the capsule. (b) Striated bands of alternating low and high density may be seen within the wedge-shaped areas (striated nephrogram), representing slow flow of contrast-opacified urine through tubules that are obstructed by adjacent bands of interstitial edema. (c) Thickening of the renal fasciae and perinephric septa may occur as a result of edema. (d) Global or focal enlargement of the kidney may be seen. (e) Severe infections may lead to focal or global scarring and atrophy, detected on follow-up scans.

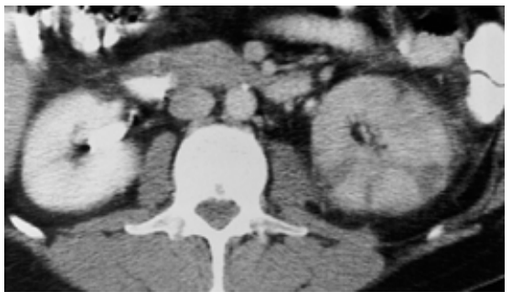

FIGURE 3C.27. Acute pyelonephritis of left kidney. Contrast-enhanced computed tomography scan. Note perinephric fascial thickening due to edema and wedge-shaped defects in the parenchyma that extend from the collecting system to the capsule. The nephrogram is delayed overall compared with the right kidney.

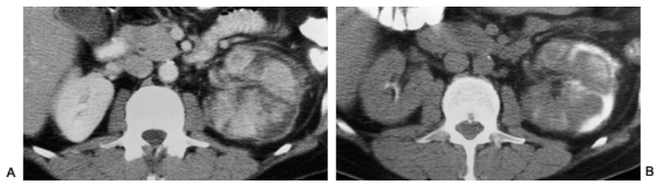

FIGURE 3C.28. Acute pyelonephritis. Contrast-enhanced scans. **A:** Early images demonstrate wedge-shaped filling defects in the parenchyma. **B:** Delayed images demonstrate a striated nephrogram with persistent opacification of some regions, likely obstructed tubules.

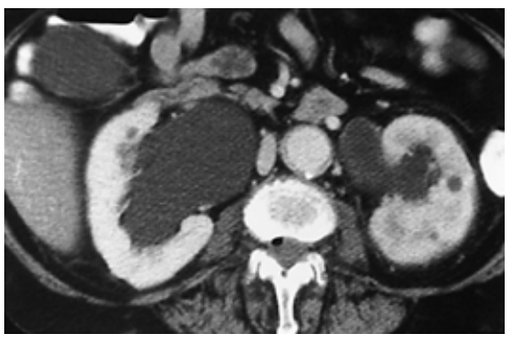

FIGURE 3C.29. Acute pyelonephritis of the left kidney in a patient with bilateral hydronephrosis due to bladder outlet obstruction. Note the patchy and irregular nephrogram in the left kidney. This appearance cannot be separated radiographically from changes due to acute obstruction. There is also a small cyst in the left kidney.

Emphysematous pyelonephritis (EPN) is a severe gas-forming infection in which gas is seen within the renal parenchyma itself. Identification of this entity requires aggressive treatment. Emphysematous pyelitis, on the other hand, is a gas-forming infection limited to the collecting system; it does not portend the same grave prognosis as does EPN.

The most common abnormality in *renal abscess* is an area of low attenuation on noncontrast images, which represents the liquefied center of the abscess cavity. Following contrast administration, a thick and irregular rind of enhancement

is seen surrounding the abscess cavity (Fig. 3C.30). The remainder of the kidney may range from being normal in appearance to showing signs of acute pyelonephritis (72).

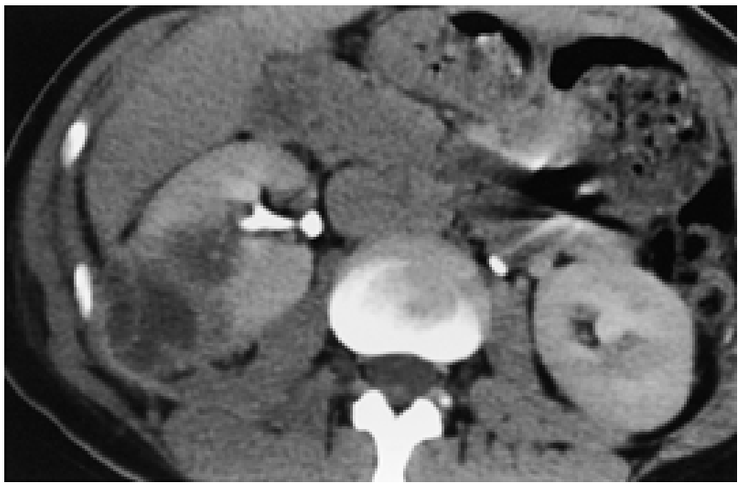

FIGURE 3C.30. Renal abscess. Irregular abscess cavities in the right kidney. Patient has right renal calculi (not shown). Note the asymmetric right perinephric fascial thickening.

Xanthogranulomatous pyelonephritis is an uncommon chronic infection associated with calculi and obstruction. The kidney is enlarged, and calculi, often staghorn, are present. The kidney is usually nonfunctioning. Perinephric extension is seen in 14% of patients, and fistulae may also occur (77).

Renal Trauma

CT is very accurate in the categorization of renal injuries, and it is the imaging modality of choice when significant renal injuries are suspected (25,61). Both oral and intravenous contrast should be used in such patients; delayed imaging is often required to detect contrast extravasation (Fig. 3C.31), which indicates laceration of the collecting system.

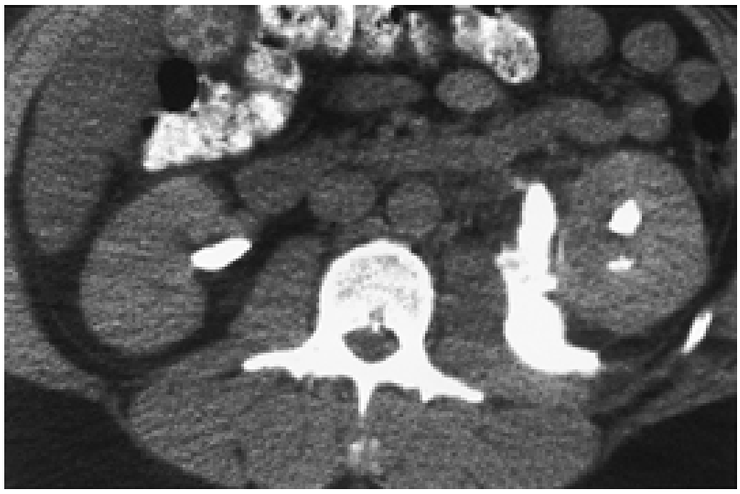

FIGURE 3C.31. Contrast extravasation in a patient who sustained blunt trauma. Delayed images demonstrate contrast tracking along the left perinephric space. The patient had extravasation from the collecting system in the left kidney (not shown).

The grading system of renal injuries by the American Association for the Surgery of Trauma (AAST) cannot be addressed here. However, there is a close relationship between the grading system and CT abnormalities seen in this setting.

Renal contusion (grade I lesion) causes decreased enhancement of a focal area; it may be slightly hyperdense on nonenhanced scans because of hemorrhage. Grade II and III lesions are cortical lacerations that do not extend into the collecting system and are seen as defects in the parenchyma (Fig. 3C.32). Deep corticomedullary lacerations (grade IV injuries) extend into the collecting system and result in extravasation of contrast from the collecting system. Renal fractures, a shattered kidney (grade V injuries) (Fig. 3C.33), and renal vascular injury are also well depicted by CT.

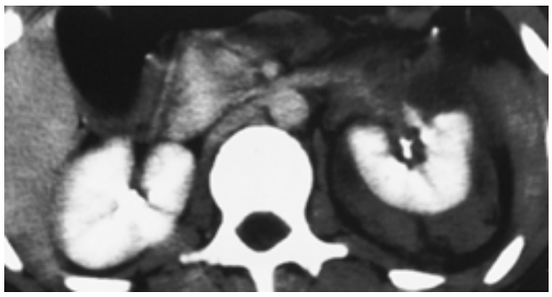

FIGURE 3C.32. Renal laceration. Note laceration in the right kidney. Both kidneys are functioning well. There is a perinephric hematoma on the left side (appears dark due to the contrast setting on the scan).

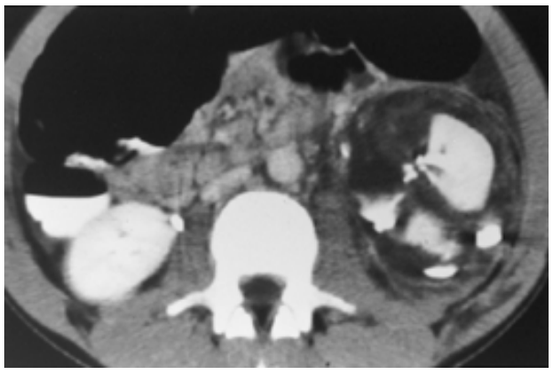

FIGURE 3C.33. Renal fractures and left perinephric hematoma. Delayed images also demonstrated contrast extravasation (not shown).

Subcapsular hematomas are typically lenticular in shape and compress the adjacent kidney, whereas perinephric hematomas may displace the kidney. These may accompany any of the injuries described previously.

COMPUTED TOMOGRAPHY IN CALCULUS DISEASE OF THE URINARY TRACT

CT is more sensitive than abdominal radiography or nephrotomography in detecting calculi and calcifications (58,59). Spiral CT was more accurate than radiography and nephrotomography in both detecting and measuring renal calculi in a phantom *in vitro* (58). In another series (59), no residual stones were missed on noncontrast CT after percutaneous nephrostolithotomy, whereas plain film radiography detected only 46% of residual calculi.

Stones within the collecting system are obscured by excreted contrast within the collecting system; therefore, as with IVU, it is imperative that scans be obtained before the administration of contrast for accurate detection of calculi. All kidney stones are homogeneously dense on CT, except for the rare pure matrix stone and calculi that occur in patients infected with HIV who are being treated with protease inhibitors (13). Stones of different compositions have considerable overlap in their CT attenuation values, making prediction of the chemical type problematic by CT densitometry. Nonopaque/poorly opaque calculi such as uric acid and cystine stones have CT numbers in the range of 300 to 500 HU, whereas calcium stones are in the range of 500 to -1,000 HU.

When a filling defect is seen on an IVU or retrograde pyelogram, CT is valuable in differentiating nonopaque stones from blood clots or neoplasms because calculi are of so much higher density. CT is also useful in the preprocedural evaluation of patients with stones and congenital anomalies of the kidney or the bony structures, which make percutaneous procedure technically more complex.

HCT has proved to be particularly advantageous in the evaluation of the patient with acute renal colic and suspected ureteral calculi; it is replacing excretory urography for this indication (26,68,70). The advantages of CT are manifold: (a) No prescan preparation is necessary, unlike for an IVU; (b) the entire urinary tract from the kidney to the bladder can be imaged in a single breath hold, in less than a minute; (c) the location and size of a stone in the ureter can be accurately delineated; (d) no intravenous contrast material administration is necessary; (e) more anatomic information about the kidney and ureter can be obtained than from ultrasound; and (f) other intraabdominal processes that may be mistaken clinically for renal colic can be diagnosed (e.g., appendicitis, diverticulitis, bleeding aortic aneurysm, adnexal masses).

CT imaging for the evaluation of acute renal colic is performed without the administration of intravenous or oral contrast media because both may obscure a stone. However, this protocol should be altered and oral contrast media administered if there is any suspicion of bowel pathology. Intravenous contrast may become necessary if it is unclear

whether a calcification lies within or adjacent to the ureter. Oral and intravenous contrast are also occasionally helpful in confirming that acute ureteral obstruction is the cause of flank pain and in excluding other causes of flank pain. In as many as one-third of patients evaluated by CT for acute flank pain, significant abnormalities outside the urinary tract may be detected (47,69).

Ureteral calculi causing acute renal colic demonstrate the following findings: (a) stone within the ureter and (b) hydroureteronephrosis and asymmetric perinephric stranding (Fig. 3C.34). These two signs together have a positive predictive value of 97%, and the absence of these signs has a negative predictive value of 93%. Overall, for the detection of ureteral calculi in the setting of acute flank pain, HCT has accuracy and positive and negative predictive values of 98% (69,70). The main difficulty in identifying ureteral calculi is the confusion created by phleboliths (Fig. 3C.35). Stones that are larger than 6 mm, located in the proximal third of the ureter, or not associated with perinephric stranding are less likely to pass spontaneously (27,80) (Fig. 3C.36).

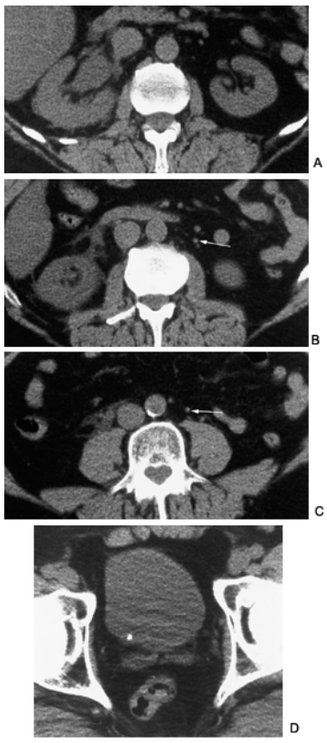

FIGURE 3C.34. Right renal colic due to a calculus at the right ureterovesical (U-V) junction. Note stranding in the perinephric **(A)** and periureteral **(B, C)** regions, right hydroureteronephrosis and stone at right U-V junction **(D).** Left ureter, long arrow (B, C).

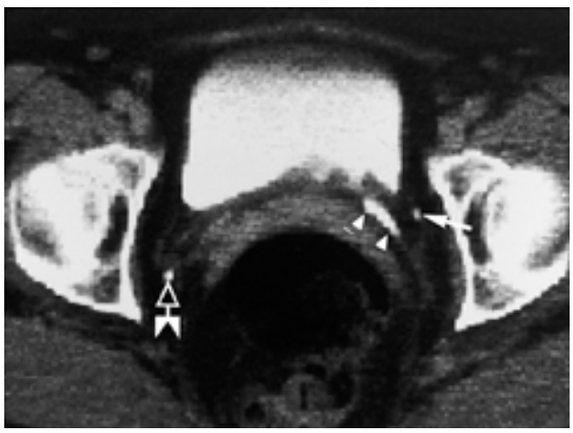

FIGURE 3C.35. Contrast-enhanced scan demonstrates the opacified left ureter *(arrowheads)* and an adjacent phlebolith *(long arrow)*. Broken arrow, right ureter.

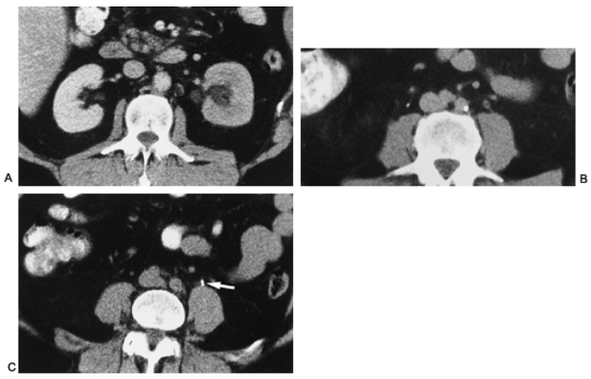

FIGURE 3C.36. A–C: Left ureteral obstruction. There is left ureteral dilation due to a left ureteral calculus *(arrow)*. Note the delayed nephrogram in the left kidney due to the obstruction. No perinephric stranding is seen, a sign associated with decreased likelihood of spontaneous stone passage.

COMPUTED TOMOGRAPHY OF THE ADRENALS

The normal adrenal glands and most masses can be identified on nonenhanced scans (Fig. 3C.37). Intravenous contrast administration is often helpful in characterizing adrenal masses, and the routine use of oral contrast prevents unopacified bowel loops from being mistaken for adrenal masses. Other structures that may be confused as being adrenal masses are vascular structures such as dilated or tortuous splenic arteries, splenic veins, or a dilated inferior phrenic vein.

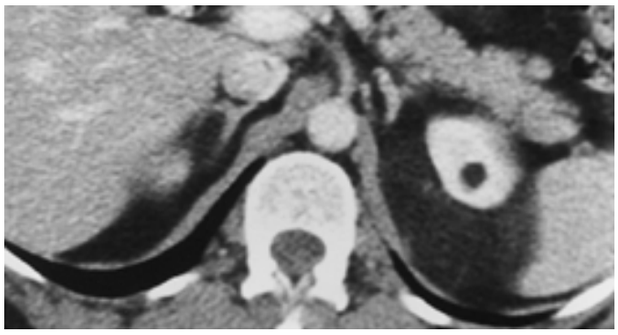

FIGURE 3C.37. Normal right and left adrenal glands. Upper pole of right kidney is immediately posterior to the right adrenal. There is a small cyst in the upper pole of the left kidney.

Adenomas

Both nonhyperfunctioning (nonfunctional) and hyperfunctioning adenomas are morphologically similar in appearance (Fig. 3C.38). Therefore imaging findings have to be correlated with clinical findings and biochemical evidence. CT has approximately 85% sensitivity in detecting adrenal adenomas; tumors that are missed are usually smaller than 1 cm. A focal bulge or enlargement of the gland is indicative of the presence of a mass. Adenomas are rounded, homogeneous, soft tissue masses with well-defined margins, and they have densities that range from 0 to 20 HU on nonenhanced scans. If there is abundant fat within the lesion, the density measurements will be close to that of water (0 HU). On enhanced scans, adenomas have a density between 30 and 37 HU at 30 to 60 minutes after contrast injection (46,79), whereas nonadenomas measure greater than 41 HU.

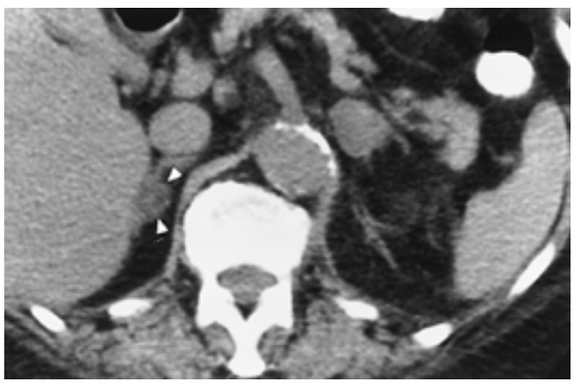

FIGURE 3C.38. Adenoma arising from the inferior aspect of the lateral limb of the right adrenal gland *(arrowheads)*.

Adrenal Hyperplasia

In adrenal hyperplasia, there is symmetric enlargement of the adrenal glands but retention of the normal shape. However, there is overlap in the CT appearance of normal and hyperplastic glands in that many patients with clinical evidence of hyperplasia may have normal-appearing adrenal glands. Bilateral enlargement is indicative of hyperplasia.

Adrenal Carcinomas

Adrenal carcinomas tend to be large, undergo central necrosis, and invade adjacent organs. If the mass is very large, the organ of origin may be difficult to determine, particularly if the adjacent organs are invaded and the normal adrenal gland is obliterated by the tumor. An adrenal carcinoma may be difficult to distinguish from a renal adenocarcinoma on CT. Calcification is seen in one-third of cases (28); venous extension, liver metastases, and lymphadenopathy may also be seen.

Incidental Adrenal Mass

Most incidentally discovered adrenal masses are benign. However, an adrenal mass in a patient with a known primary mass raises the question of adrenal metastases. If the mass is of low density, as described earlier, it is most likely is a benign adenoma. In one series, mean attenuation values were 2.2 HU for adenomas and 29.8 HU for metastases (49). If the threshold for nonenhanced CT density is set at 10 HU, the sensitivity-to-specificity ratio for diagnosis of an adenoma is 74%:96%. If the adenoma is lipid poor, the density will be higher and it may be difficult to distinguish it from a metastasis by CT. MRI may be warranted in such a case for further characterization.

Pheochromocytoma

Pheochromocytomas are hypervascular neoplasms with a tendency for hemorrhagic necrosis, even when benign. Heterogeneous enhancement of the mass is seen with contrast, an appearance that may be indistinguishable from that of an adrenal carcinoma. Thus correlation with biochemical tests is crucial for the diagnosis. Approximately 90% of pheochromocytomas arise from the adrenal glands, whereas 10% are extraadrenal.

If the patient has known hypertensive episodes, adequate pharmacologic adrenergic blockade should be in place before contrast administration so that a hypertensive crisis is not precipitated (intravenous injection of contrast can raise plasma catecholamine levels) (23,63).

Myelolipoma

Myelolipoma is a benign, nonfunctioning neoplasm of the adrenal gland containing variable amounts of fat and myeloid elements. Calcification may also be seen in the lesion (Fig. 3C.39). Large lesions may hemorrhage, although this is uncommon. The presence of foci of fat within an adrenal lesion is diagnostic of a myelolipoma (43).

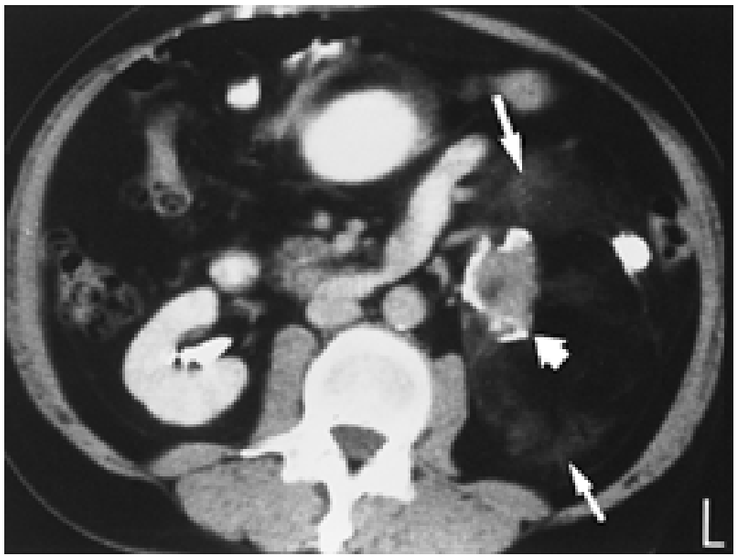

FIGURE 3C.39. Large left adrenal myelolipoma. The entire adrenal gland is replaced with low-density fatty tissue *(long arrows)*. Note the large calcification within the lesion *(short arrow)*.

Retroperitoneum

Lymphadenopathy

With CT, size alone is used to diagnose abnormalities in lymph nodes because intranodal architecture is not depicted on CT. Retroperitoneal and pelvic lymph nodes that are greater than 10 mm in short axis diameter are considered abnormal, although multiple smaller (6 to 8 mm) nodes are also cause for suspicion. Massively enlarged retrocaval and retroaortic nodes can displace these vascular structures.

CT is the preferred imaging method for staging patients with testicular neoplasms (Fig. 3C.40). Residual retroperitoneal masses that remain visible on CT scans after treatment can represent posttreatment fibrosis or teratoma, but they cannot be reliably differentiated from residual viable tumor (75).

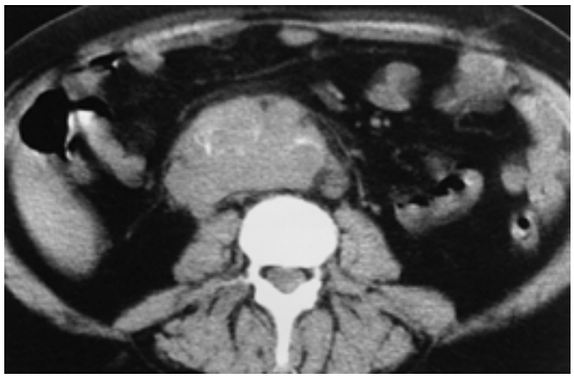

FIGURE 3C.40. Retroperitoneal lymphadenopathy in a patient with testicular cancer. There is a small amount of calcification in the nodes, likely the result of therapy. The vascular structures are not identifiable on this unenhanced scan.

Primary Retroperitoneal Tumors

Retroperitoneal tumors are well depicted on CT, and their effect on the urinary tract is also elegantly demonstrated. Most solid retroperitoneal tumors are of soft tissue attenuation and cannot be distinguished on CT.

Retroperitoneal Fibrosis

Fibrous tissue proliferation around the aorta and the IVC is the hallmark of retroperitoneal fibrosis (RPF). A soft tissue density that obscures the contours of the IVC and the aorta is seen (Fig. 3C.41). The process may extend into the pelvis, and there may be vascular or ureteral encasement. On noncontrast CT, the density of the soft tissue is similar to that of muscle. Following contrast administration, variable enhancement is seen. Malignant forms of RPF cannot be distinguished from the benign ones (2).

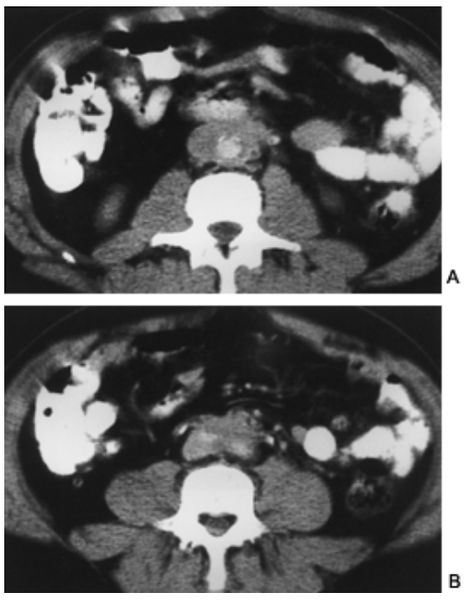

FIGURE 3C.41. Retroperitoneal fibrosis. **A:** There is soft tissue encasement of the aorta and the cava, obscuring the tissue planes that lie between them. **B:** The process extends caudally to encase the common iliac vessels also.

COMPUTED TOMOGRAPHY OF THE PELVIS

The entire abdomen and pelvis is imaged so rapidly with current scanners that on the initial scans through the pelvis, the urinary bladder is often not opacified with contrast excreted by the kidneys. Delayed images through the pelvis are required if assessment of the bladder wall is necessary, as in patients with bladder cancer. Pelvic lymph nodes larger than 1 cm in short axis diameter are considered abnormally enlarged. Normal-sized nodes may be difficult to differentiate from adjacent vessels and nerves without intravenous contrast.

Urinary Bladder

Tumors

CT scanning cannot reliably assess the presence or depth of muscle invasion of bladder tumors. However, gross invasion of perivesical structures can be ascertained, as can lymphadenopathy.

Bladder tumors are seen as sessile or pedunculated masses that project into the lumen or as focal or diffuse wall thickening (Fig. 3C.42). Perivesical extension causes blurring of the soft tissue planes; in more advanced cases, a soft tissue mass projecting into the adjacent tissues will be seen (Fig. 3C.43). The overall accuracy for detecting perivesical extension is 65% to 85%, and the accuracy for detecting lymph node involvement is 70% to 90% (44).

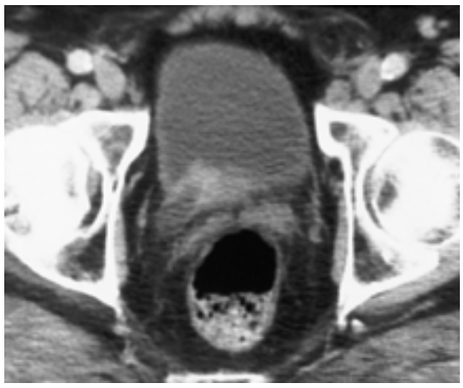

FIGURE 3C.42. Bladder cancer at the right ureteral orifice. There is ureteral dilation, which may be partially mechanical. No definite perivesical extension is seen.

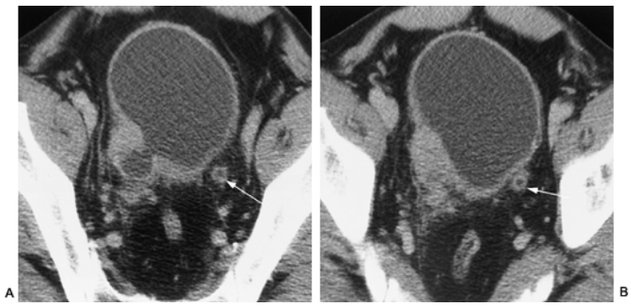

FIGURE 3C.43. Bladder cancer involving a right posterior bladder diverticulum. Note the soft tissue mass within the diverticulum **(A)** and perivesical extension of the mass **(B).** The left distal ureter is thickened *(arrow)* **(A, B),** raising the possibility of tumor involvement.

Trauma

Because CT is often the initial study performed in patients with blunt abdominal or pelvic trauma, CT cystography is a convenient way to assess for bladder injury. It is important to adequately distend the bladder actively and not rely on passive filling of the bladder with excreted contrast (Fig. 3C.44). With these caveats in mind, the sensitivity of CT cystography is comparable to that of conventional cystography for diagnosing bladder injuries (53).

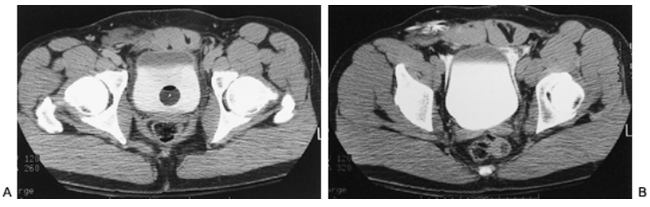

FIGURE 3C.44. Extraperitoneal bladder rupture. Patient in a motor vehicle accident. **A:** Images with passive bladder filling demonstrate no extravesical contrast. **B:** When bladder is filled till there is a detrusor contraction, contrast extravasation from urinary bladder becomes obvious.

Prostate

The main utility of CT in patients with prostate cancer is in the detection of lymphadenopathy (Fig. 3C.45). The sensitivity for the detection of intraprostatic tumor, transcapsular extension, and seminal vesicle involvement is low (24,60).

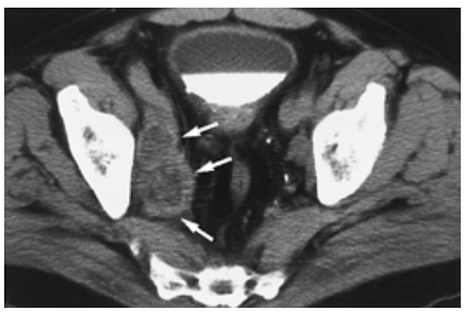

FIGURE 3C.45. Large, necrotic obturator lymph nodes *(arrows)* in a patient with prostate cancer.

In postoperative patients being evaluated for local recurrence, artifact emanating from metal clips can obscure the surgical bed.

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3D ULTRASOUND

J. Patrick Spirnak

Martin I. Resnick

Part of "3 - IMAGING "

J.P. Spirnak and M.I. Resnick: Department of Urology, Case Western Reserve University, Cleveland, OH 44106.

The development of ultrasound instrumentation effective in the evaluation and treatment of many medical conditions dates back to the 1940s, when Firestone first described a technique using ultrasonic waves to detect flaws in metal castings (71). During World War II, the principles of ultrasound were used to develop sonar (sound navigation ranging), a tracking technique useful in identifying submerged enemy submarines. The first medical use of ultrasound was reported by an Austrian psychiatrist, Karl Dussik (29), who attempted to locate brain tumors with the use of two opposing ultrasound transducers. In the early 1950s, Howry and Bliss (46) used discarded naval equipment and studied and recorded the echo patterns obtained from a variety of soft tissue structures. They initially used water immersion techniques, and it was not until the early 1960s that they began experimenting with handheld scanners applied directly to the body surface. Since the early 1970s, with the development of real-time capability, grayscale imaging, high-frequency transducers, color-flow Doppler, and power Doppler, ultrasound has gained an important role in the clinical evaluation of many urologic abnormalities. The emerging use of ultrasound contrast agents promises to enhance and expand many of these applications.

BASIC PRINCIPLES OF ULTRASOUND

Ultrasound consists of sound waves of frequencies beyond the audible range of the human ear [greater than 20,000 Hz (cycles per second)]. For medical purposes, diagnostic ultrasound

equipment uses sound waves between 2 million and 10 million MHz. Sound travels in a wave form that is dependent on the medium in which it travels and has a multitude of variables, including density, pressure, temperature, and particle motion (54). Sound waves are described in terms of frequency, period, amplitude intensity (determined by the source), propagation speed (determined by the medium), and wavelength (determined by the source and medium) (Fig. 3D.1).

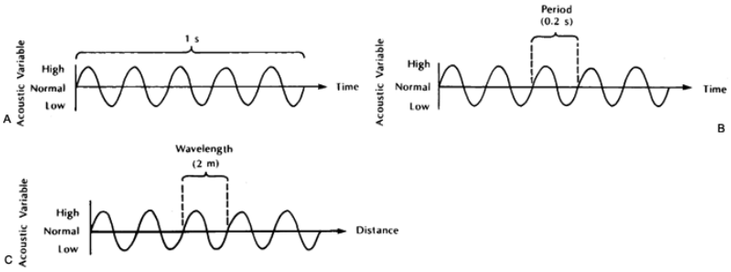


FIGURE 3D.1. A: Frequency. The number of complete variations (cycles) that an acoustic variable goes through in 1 second. In this diagram, five cycles occur in 1 second. One hertz is 1 cps. One megahertz is 1 million cps. **B:** Period. The time for one complete cycle. The period in this diagram is 0.2 seconds. **C:** Wavelength. The distance over which one cycle occurs. In this diagram each cycle is 2 m. (Adapted with permission from Kremkau FW. *Diagnostic ultrasound principles, instruments and exercises,* ed 3. Philadelphia: Saunders, 1989.)

The source of the ultrasound beam is a transducer consisting of a piezoelectric transmitter and receiver (Fig. 3D.2A). The piezoelectric crystal generates a wave at a frequency that is dependent on the strength of the current applied to it and the size of the crystal. Sound waves are produced by the deformation of the crystal associated with electrical excitation. Short impulses, approximately 10 ms each, of alternating current are applied to the crystal, and the ultrasound beam thus generated is focused by the transducer into a beam several millimeters in width. The thickness of the crystal determines the frequency of the generated sound waves. The sound waves are focused with an acoustic lens that produces a narrow beam only a few millimeters in diameter with good lateral resolution.

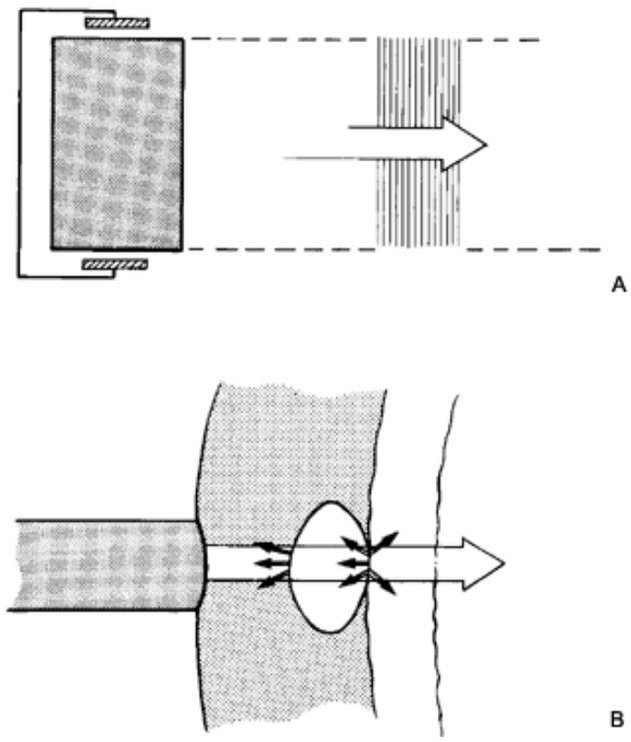


FIGURE 3D.2. A: High-frequency sound waves are transmitted after excitation of a piezoelectric crystal. **B:** Transmitter sound waves are reflected at tissue interfaces where there is a change in acoustic impedance. Reflected sound waves obey laws of optics—the angle of incidence is equal to the angle of reflection.

The body and its contents are the molecular medium that propagates the generated sound waves. In the presence of a homogeneous fluid medium (e.g., renal cyst, full urinary bladder), the sound waves are propagated in an uninterrupted manner. No sound waves are reflected back to the transducer, and therefore this area appears without echoes *(anechoic).* If the sound waves encounter a different density of tissue, a portion is reflected back to the source and that area is imaged. If the area or structure has a greater number of reflected waves than surrounding regions, it is termed *hyperechoic,* and if the echoes are less, the region appears *hypoechoic* (Fig. 3D.2B). The reflecting boundary is called an acoustic interface, and it exists because of the differing acoustic impedances between the two media. *Acoustic impedance* is the product of a medium density and the speed of sound in the medium. The greater the difference in acoustic impedance between the two media, the greater the amount of sound reflected back from the interface. Typically less than 1% of incident energy is reflected.

Whether the sound waves are reflected also depends on the relative size of the interface and the frequency of the generated wavelength. Sound waves of higher frequencies are generally reflected by smaller surface interfaces but have less depth of penetration, thereby giving better spatial resolution

at the expense of decreased sound wave penetration. The use of lower-frequency sound waves sacrifices spatial resolution but makes it possible to image deeper structures. Appropriate transducer selection is critical for the success of the evaluation, and it is generally best to select the highest frequency that permits adequate tissue penetration and visualization of the desired structures. For example, higher-frequency transducers (7 MHz) are used for transrectal prostate imaging and lower-frequency ones (3.5 MHz) are used to view the kidneys.

During the course of the examination, the ultrasound transducer functions not only as a source of the sound waves but also as a receiver of the sound waves that have been reflected from the different tissue interfaces (Fig. 3D.3). The sound waves' energy is converted in the transducer by the piezoelectric crystal to electrical energy, which is then processed and displayed as a dot on a cathode ray tube (oscilloscope). The sound waves reflected back to the transducer are highly dependent on the angle of the reflector (Fig. 3D.4 and fig. 3D.5). Amplitude, or A-mode, records reflect echoes as spikes arising from a horizontal baseline and represent one of the earliest displays used in medical ultrasound (Fig. 3D.6). The main application of this mode is to measure the distances from the margins of a mass to the skin surface or to determine the internal architecture of the mass, but with the development of two-dimensional and real-time imaging this mode is rarely used. The brightness modulated display, or B-mode, is a two-dimensional image obtained while the transducer is moved along a given arc; the resultant display is of a cross-sectional image of the examined area. With the development of scan converters and real-time imaging, images are now displayed in varying shades of gray (grayscale imaging). Gray-scale imaging offers a significant improvement in the quality of images compared with those obtained with early B scanners. Use of Doppler, in particular color-flow and power Doppler, has allowed measurement of flow and detection of flow in vascular structures.

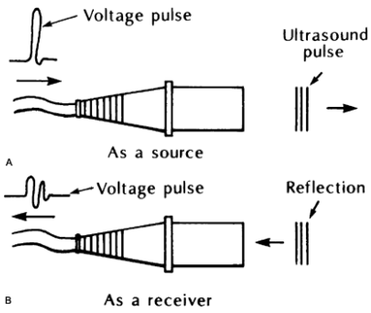


FIGURE 3D.3. Transducer operating in pulsed mode. **A:** Electrical pulses are converted to ultrasound pulses. **B:** Neural ultrasound pulses are converted to electrical pulses. (Adapted with permission from Kremkau FW. *Diagnostic ultrasound principles, instruments and exercise*, ed 3. Philadelphia: Saunders, 1989.)

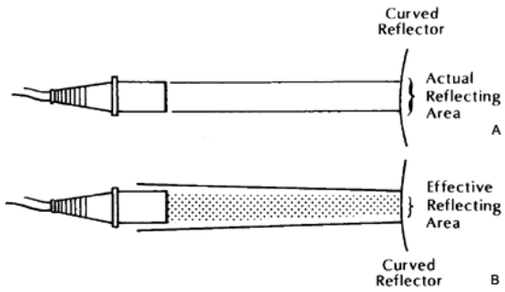


FIGURE 3D.4. Curved reflector. **A:** Propagated sound waves. **B:** Reflected sound waves received by transducer in shaded areas. (Adapted with permission from Kremkau FW. *Diagnostic ultrasound principles, instruments and exercise*, ed 3. Philadelphia: Saunders, 1989.)

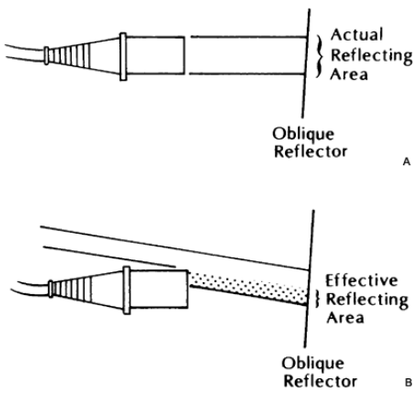


FIGURE 3D.5. Oblique reflector. **A:** Propagated sound waves. **B:** Reflected sound waves reached by transducer in shaded area. The remaining sound waves miss the transducer. (Adapted with permission from Kremkau FW. *Diagnostic ultrasound principles, instruments and exercise*, ed 3. Philadelphia: Saunders, 1989.)

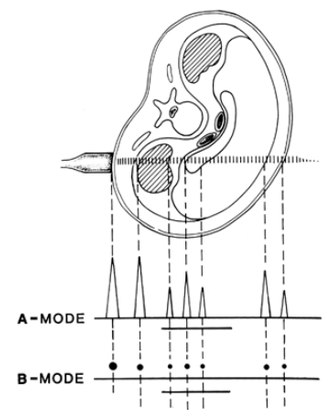


FIGURE 3D.6. Amplitude mode (A-mode) delineates reflected echoes as spikes arising from a horizontal baseline. The echo amplitude is plotted against distance between transducer and reflecting tissue interface. Brightness modulated display (B-mode) is a composite two-dimensional image obtained while transducer is moved along a given arc. Echoes are shown as multiple dots or points on the oscilloscope screen, the brightness of which is dependent on the intensity of the echo.

The transducer and its mechanism of action (mechanical sector and radial; array-linear, curved, and phased) are other important components of the instrumentation. In both forms of imaging, the sound waves sweep repeatedly through the tissue and structures to be imaged. Mechanical scanners use a variety of principles and can be composed of rotating transducers or groups of transducers, oscillating

transducers, and the combination of oscillating transducers and reflectors (Fig. 3D.7). In most instances, the oscillating or rotating component is surrounded by a cup of liquid that is incorporated within the transducer assembly. Various ingenious techniques have been devised (54). Array transducers operate by the application of voltage pulses to single elements or groups of elements in succession (Fig. 3D.8). In the linear-array scanner, many small elements are aligned side by side much like the teeth of a comb, and the plane of the structure to be imaged is determined by the orientation of the scanner. In most instances, the scanner provides a real-time image. Phased-array and curved-array systems operate by applying voltages to all elements in the assembly. By allowing small time differences that can be controlled electronically, the pulsed sound waves can be shaped and steered in an infinite number of directions (Fig. 3D.9).

With the linear-array system, real-time images are obtained. By orienting the transducer differently, a variety of scanned planes can be realized. Much work will continue to enhance the quality and resolution of the image received.

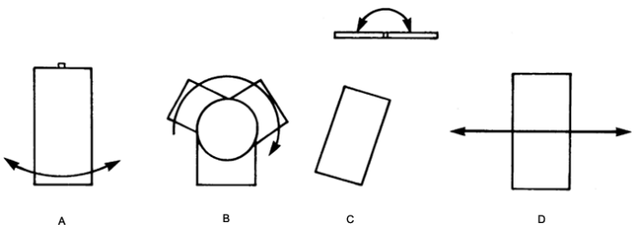
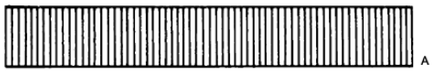


FIGURE 3D.7. Mechanical real-time transducers. **A:** Oscillating. **B:** Rotating. **C:** Oscillating. **D:** Linearly translating. (Adapted with permission from Kremkau FW. *Diagnostic ultrasound principles, instruments and exercise*, ed 3. Philadelphia: Saunders, 1989.)



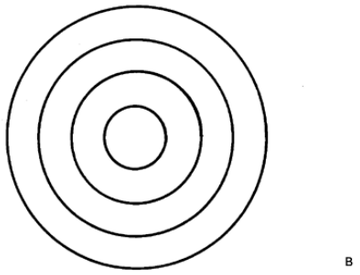


FIGURE 3D.8. Frontal view. **A:** Linear-array transducer with 64 elements. **B:** Annular array with four elements. (Adapted with permission from Kremkau FW. *Diagnostic principles, instruments and exercise*, ed 3. Philadelphia: Saunders, 1989.)

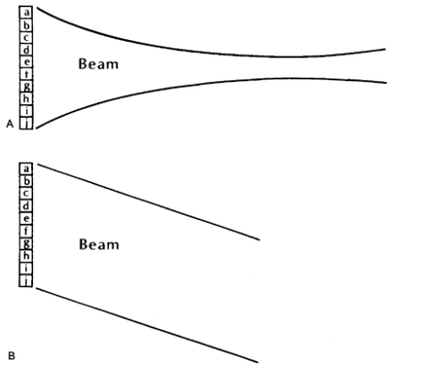


FIGURE 3D.9. Linear phased-array scanner. **A:** Beam focusing is accomplished by applying voltage pulse to the upper and lower elements earlier than the middle elements. **B:** Beam steering is accomplished by applying voltage pulses to the upper elements earlier than the lower elements. (Adapted with permission from Kremkau FW. *Diagnostic ultrasound principles, instruments and exercise*, ed 3. Philadelphia: Saunders, 1989.)

Doppler instrumentation is based on the principle of a change in reflected frequency caused by reflector motion. Differences between incident and reflected frequencies are related to the speed of the reflector or media boundary—the greater the speed, the greater the difference. *Doppler shift* refers to the difference between the incident frequency and the reflected frequency, and the Doppler equation provides a quantitative relationship between the flow speed and frequency change. The development of color-flow techniques and power Doppler has permitted assessment of the direction of blood flow in arteries and veins, which has been useful in evaluation of a variety of benign and malignant urologic disorders.

Doppler instruments provide either continuous or pulsed voltages to the transducer. Continuous-wave instruments detect flow that occurs anywhere along the transmitted beam, but recently, pulsed-wave instruments have been introduced that provide information at a specific depth. Echoes can be received from different depths, depending on the receiver length and location, which can be controlled by the operator. Combination instruments are now available with the development of real-time cross-sectional ultrasound imaging in association with pulsed Doppler instrumentation (Fig. 3D.10). These instruments have allowed for the measurement of blood flow within specific blood vessels with the advent of color-flow technique and have been used in the assessment of blood flow within the kidney, testes, and penis. Power Doppler has greater sensitivity than conventional color Doppler, and it is particularly of value for assessing small vessels with low flow velocity (38). Echo-contrast development consisting of microbubble technology continues and offers much potential in clinical practice (15,107).

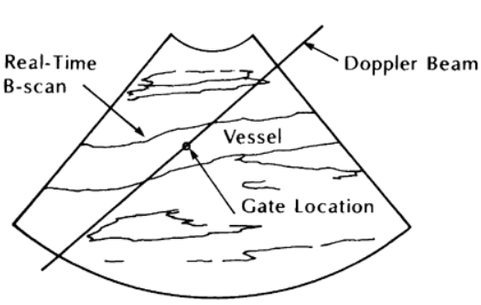


FIGURE 3D.10. Combination of real-time imaging and pulsed Doppler instrument. Blood flow measurement can be obtained within specific blood vessels. (Adapted with permission from Kremkau FW. *Diagnostic ultrasound principles, instruments and exercise*, ed 3. Philadelphia: Saunders, 1989.)

The images available for interpretation with most diagnostic ultrasound instruments are grayscale views; stop-action views can be obtained from a real-time examination. Real-time ultrasonography offers the advantage of dynamic imaging similar to that obtained with fluoroscopy. The obtained images are representations of a spectrum of echoes arising from the surface and substance of the given structure in two dimensions. With current scanners, a complete cross section of a structure is formed one line at a time. After one line is drawn, the transducer is moved slightly and pulsed again to draw another line. Typically 10,000 lines per second are drawn, enabling a complete image of the structure to be obtained. A permanent record of the scan can be recorded on Polaroid film, radiographic film, videotape, computer floppy disks, laser disks, and thermal paper.

Newer, less expensive equipment is making ultrasound examination of the urinary tract practical in the office setting. In addition, the equipment can be used for vascular flow studies, which is useful in the evaluation of men with erectile dysfunction and for assessing blood flow to a testicle when torsion of the spermatic cord is suspected. It can also be used in conjunction with urodynamic studies to image the bladder, bladder neck, and proximal urethra. Ultrasound examinations performed at the time of an office visit can speed diagnosis and treatment and reduce the cost of patient care.

RENAL ULTRASOUND

When ultrasound images of the kidneys are obtained, patients can be scanned in the supine, decubitus, or prone positions and images are obtained in the transverse and longitudinal planes (Fig. 3D.11). In the past, the kidneys were usually examined with the patient in the prone position; however, the frequent location of the upper poles beneath the rib cage often led to incomplete or unsatisfactory studies. Currently, the right kidney is best examined with the patient in the supine position, using the liver as an acoustic window. The best images of the left kidney are usually obtained with the patient in the right lateral decubitus position, with the spleen as an acoustic window. When indicated, different views can also be obtained in the oblique plane by moving the transducer through different arcs relative to the longitudinal and transverse planes.

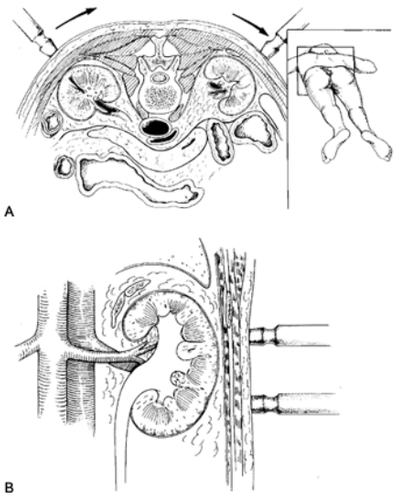


FIGURE 3D.11. Image planes of a transverse renal scan **(A)** and a longitudinal renal scan (B).

Renal Anatomy

The adult kidneys are paired, retroperitoneal structures lying between the twelfth thoracic and second lumbar vertebrae. Each kidney is approximately 10 cm long, 5 cm wide, and 2 to 5 cm thick. The right kidney is typically lower than the left. Ultrasonography continues to be an excellent modality to determine renal size. The upper pole of the right kidney is in contact with the adrenal superomedially and the duodenum anteromedially, and the posterior aspect of the right lobe of the liver overlies its anterior surface. Overlying the lower pole of the right kidney is the hepatic flexure of the colon and loops of small bowel. The anterior surface of the left kidney is in contact with the spleen, left adrenal, stomach, pancreas, descending colon, and small bowel. Posteriorly, the kidneys are in contact with the twelfth rib, diaphragm, transversus abdominis muscle, quadratus lumborum muscle, and psoas major muscle.

Each kidney is surrounded by a closely adherent, dense, fibrous capsule, which is surrounded by perinephric fat and enclosed in Gerota's fascia. On ultrasound examination, the renal outline is determined by the acoustic interface formed by the renal capsule and surrounding fat. Transverse scans show the kidney to be round or bean-shaped, whereas longitudinal images reveal an elliptic configuration (Fig. 3D.12). The renal parenchyma is relatively homogeneous, with the cortex appearing more echogenic than the medulla. Located in the center of the longitudinal renal scan is a dense echo complex consisting primarily of peripelvic fat, renal vessels, lymphatic vessels, and normal collecting system. The renal medullary pyramids appear somewhat less echogenic (more sonolucent) than the renal cortex and are often identified abutting on the dense sinus fat. The arcuate arteries separate the cortex from the renal medulla and, when visualized, allow for an accurate assessment of the renal cortical thickness. The renal vascular pedicle often can be identified with real-time scanning techniques. Doppler instrumentation has permitted assessment of blood flow in the main renal artery, and its branches have been used to evaluate patients with suspected renal vascular lesions and to assess for renal viability in the presence of severe hydronephrosis (13,65). Color-flow and power Doppler studies have provided detailed images of both the extrarenal and renal vasculature and are being increasingly used in patient evaluations (38,79,81).

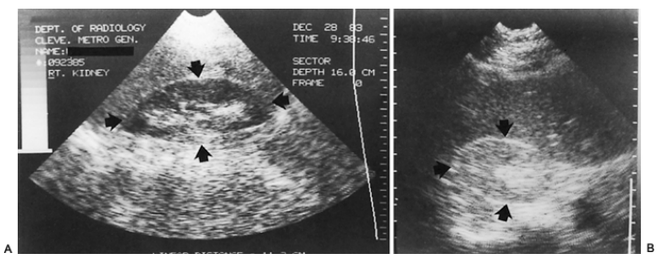


FIGURE 3D.12. Longitudinal **(A)** and transverse **(B)** scans of normal kidney. Note sharp demarcation of renal capsule *(arrows);* pelvic-calyceal system noted centrally as echogenic area.

Indications for Renal Ultrasound

Renal Mass

The question of a renal mass is usually raised by an abnormality found on excretory urography. In the adult, simple renal cysts are the most commonly diagnosed renal mass lesion. They are rarely seen in children. They occur with increasing frequency beyond age 30 years, and in an autopsy series, approximately 50% of all patients older than 50 years had at least one renal cyst (53). Ultrasound can identify cystic masses as small as a few millimeters in diameter. Solid mass lesions 1 to 2 cm wide also are routinely identified. The ability to identify a renal mass lesion depends on the depth of the lesion beneath the skin and the patient's body habitus.

Ultrasound has been extremely valuable in differentiating a simple renal cyst from other renal masses and is therefore the first study obtained in the evaluation of a suspected renal mass. On ultrasound, a renal cyst is typically spherical or slightly ovoid, demonstrates no internal echoes, has a clearly identifiable thin wall separate from the surrounding renal parenchyma, and allows enhancement of ultrasound transmission beyond the cyst (Fig. 3D.13). When these criteria are strictly adhered to, diagnostic accuracy rates approaching 100% have been reported (93). If a renal mass meets all of these criteria and the patient is asymptomatic, no further evaluation is required. If, however, the patient is symptomatic (pain or hematuria), cyst aspiration under ultrasound guidance can be performed to confirm the diagnosis. Aspirated fluid is routinely sent for cytologic study, lactate dehydrogenase, culture, and cholesterol determinations. While cyst puncture is performed, contrast material and air may be injected into the cyst to better define the cyst's margins and contours of the wall. Typically, computed tomography (CT) with and without injection of intravenous contrast agent is useful in assessing these symptomatic patients, thus avoiding the need for cyst aspirations. CT can also be used to help delineate a complex mass initially imaged with ultrasound, but occasionally, these studies are unable to exclude the presence of a renal malignancy, and often renal biopsy or surgical exploration is required to establish the correct diagnosis.

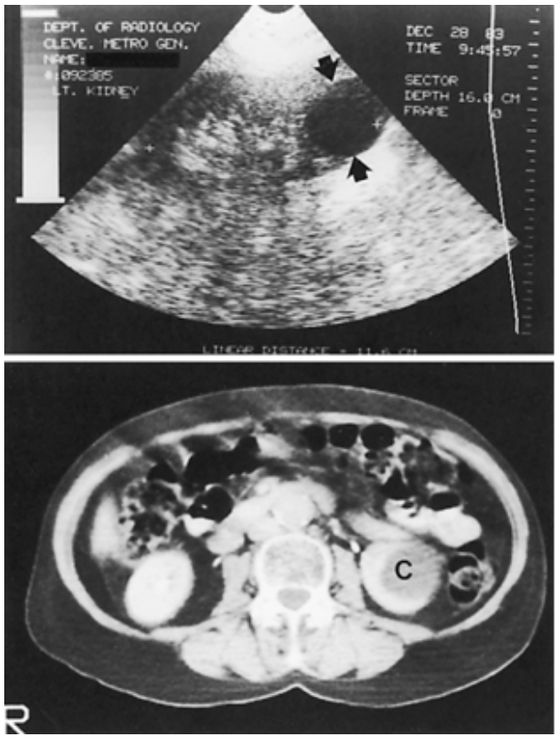


FIGURE 3D.13. A: Longitudinal renal scan showing characteristic findings of a simple renal cyst *(arrows)*. **B:** Cyst *(C)* demonstrated on computed tomography scan.

The finding on ultrasound of a solid or indeterminate (complex) renal mass raises the possibility of the presence of a renal malignancy and dictates that additional evaluation be performed. Ultrasound characteristics of a solid renal mass include the presence of internal echoes, poor delineation

of the posterior wall, and the lack of enhancement on through transmission (Fig. 3D.14).

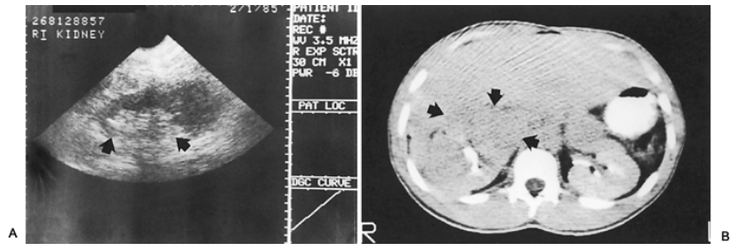


FIGURE 3D.14. Longitudinal renal ultrasound **(A)** and computed tomography scan **(B)** demonstrating findings of a hypernephroma *(arrows)*.

The ultrasonic diagnosis of solid lesions is not as accurate as that of cystic lesions, and a false-negative rate has been reported to be as high as 14% (110). Therefore the diagnosis of a solid lesion requires further evaluation and possibly exploration. Color-flow and power Doppler studies have been used to differentiate solid renal masses (e.g., renal cell carcinoma versus renal lymphoma), and they have also been used to detect intravascular extension of invasive renal malignancies (37,55).

Angiomyolipoma, a benign tumor, seems to be the only solid renal mass with typical ultrasonographic features that allow presumptive diagnosis and safe differentiation from other solid mass lesions (62). If the lesion contains a high concentration of fat, it will be extremely echogenic, even more so than a solid renal mass. Hyperechogenicity coupled with the CT findings of fat lucency allows the diagnosis to be made with certainty (92) (Fig. 3D.15). Computer-aided tissue echo quantification has permitted the differentiation of small hyperechoic renal cell carcinomas from angiomyolipoma (111).

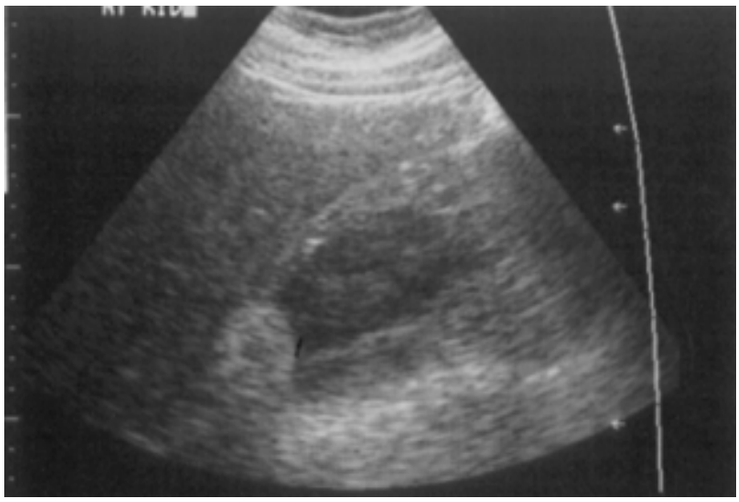


FIGURE 3D.15. Sagittal ultrasound of the right kidney shows a hyperechoic lesion at the superior aspect of the kidney. Computed tomography examination demonstrated fat within the tumor, indicative of an angiomyolipoma. (Permission granted by Urologic Multimedia, Inc.)

In the presence of a complex cystic lesion, the most likely diagnosis is necrotic tumor, hematoma, or abscess. The clinical course coupled with the findings on angiography or CT allows an accurate, certain diagnosis. When the diagnosis remains obscure, aspiration biopsy or exploration is often required.

A relatively new application is the use of ultrasound intraoperatively to monitor the cryoablation of small renal masses (126). Ultrasound has also been reported to be of value in the evaluation of the patient with acute renal trauma by determining the presence of urinary extravasation, perirenal hematoma, and renal fracture.

Collecting System Masses

Renal ultrasound has been extremely helpful in evaluating a noncalcified mass of the collecting system detected on excretory urography. A noncalcified or poorly calcified renal calculus (uric acid) demonstrates classic ultrasound findings. Typically, these calculi demonstrate increased echogenicity with acoustic shadowing (Fig. 3D.16). Other common soft tissue masses of the collecting system include tumors primarily of transitional cell origin, blood clots, and sloughed renal papilla (Fig. 3D.17). These abnormalities, although usually easily distinguishable from a nonopaque stone, often require urologic studies (e.g., ureteroscopy, biopsy) to arrive at the correct diagnosis. Intraluminal ultrasonography has

allowed assessment of the ureter and collecting system, which has been of value when other imaging studies have failed (118).

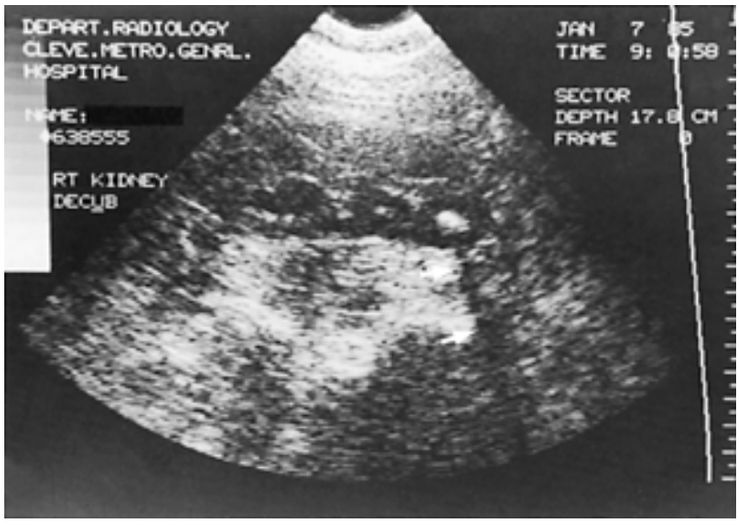


FIGURE 3D.16. Longitudinal scan demonstrating stone in the lower pole calyx. Stone is highly echogenic. Note area of acoustic shadowing *(arrows)*.

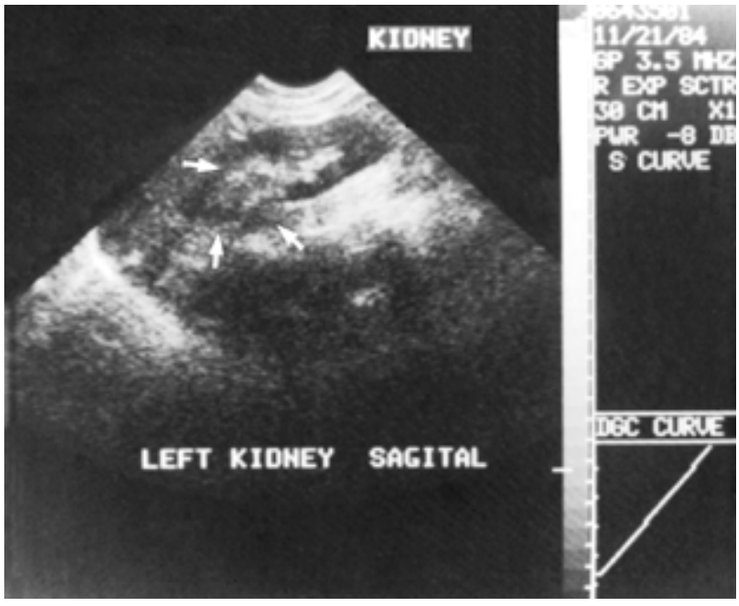


FIGURE 3D.17. Longitudinal renal scan demonstrating upper pole mass *(arrows)*. Surgical exploration revealed transitional cell carcinoma.

Renal Failure and Hydronephrosis

Although accounting for only 5% of all cases of renal failure, ureteral obstruction is potentially reversible and is usually accompanied by hydronephrosis. As a screening study to rule out obstruction as the cause of renal failure, ultrasound has a sensitivity approaching 100% (49,116). Patients with renal failure resulting from parenchymal disease characteristically have small kidneys with diffuse increases in echogenicity. Doppler studies also have been useful in monitoring the renal vasculature in both critically ill patients and those with renovascular disease (40,91). Color-flow studies with measurement of resistive index (RI) have been used to assess parenchymal viability in an attempt to differentiate those kidneys that are worth repairing from those with minimal chance of recovery that should be removed (13).

Studies also have indicated that minimum hydronephrosis can be substantial when there is a clinical question of the presence of renal obstruction (51). The renal sinus that normally appears as a region of intense echogenicity because of many dense interfaces becomes interspaced with hypoechoic regions with the development of hydronephrosis. These hypoechoic regions represent the dilated calyces and infundibula (Fig. 3D.18). As the dilation of the collecting system becomes more pronounced, this central echogenic region may be unidentifiable altogether (Fig. 3D.19). This finding aids in the diagnosis of longstanding hydronephrosis and parenchymal thinning. The dilated intrarenal collecting system can be imaged with longitudinal scans to reveal a dilated renal pelvis and, at times, upper ureter (Fig. 3D.20).

Lesions that may be misinterpreted as hydronephrosis include congenital megacalycosis, calyceal diverticulum, pelvic cysts, and a prominent extrarenal pelvis. False-positive studies can also be secondary to instances of high urinary output.

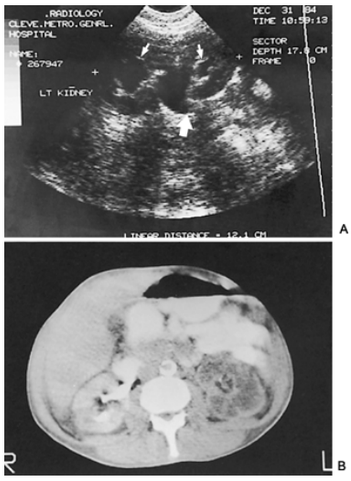


FIGURE 3D.18. A: Longitudinal scan demonstrating hydronephrosis secondary to ureteropelvic junction obstruction *(large arrow)*. Note dilated calyces *(small arrows)*. **B:** Computed tomography scan of same patient showing hydronephrotic kidney.

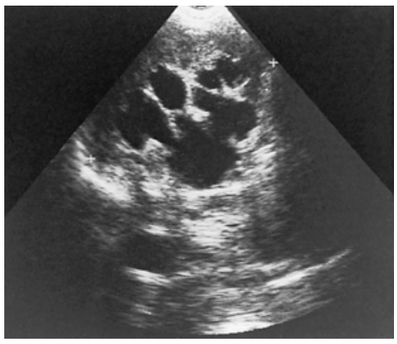


FIGURE 3D.19. Longitudinal scan demonstrating severe hydronephrosis with thinning of the renal parenchyma.

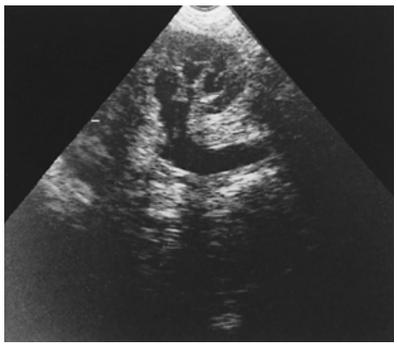


FIGURE 3D.20. Longitudinal scan demonstrating dilation of renal pelvis and upper ureter.

The assessment of the presence or absence of hydronephrosis has many implications in urologic practice. Although important in the evaluation of patients with impaired renal function, its assessment has application in evaluations made before and after treatment of many patients. Ultrasonography has been useful in the follow-up of patients after extracorporeal shock wave lithotripsy for the detection of hydronephrosis. Although abdominal radiographs are helpful in determining the presence of residual stone fragments, particularly in the ureter, ultrasound is a valuable adjunct in evaluating for the presence of hydronephrosis.

In addition, the technique is useful in follow-up of patients who have ureteral stones that are being observed and allowed to pass. The development or resolution of hydronephrosis can be easily assessed with this technique. False-negative studies can occur when urinary output is low or in instances when collecting system dilation is prevented by the presence of severe perineal and ureteral disease (e.g., inflammation, tumor).

Experience has indicated that Doppler studies are also useful in the evaluation of patients with acute renal obstruction. Changes in flow patterns and resistive indices are proving to be of increasing value to the clinician evaluating these patients (90,91,104). Other useful applications of ultrasonography relate to the postoperative follow-up of patients. Individuals undergoing urinary diversion or other surgical procedures on the urinary tract (e.g., pyeloplasty, ureteroneocystostomy) can be evaluated during the postoperative period to also assess for the development of resolution of preexisting hydronephrosis. Finally, the routine follow-up of patients with a variety of urologic disorders is improved with ultrasound assessment. Those with neurogenic bladders (e.g., spinal cord injury, myelomeningocele) can be assessed with this technique, as can those with malignancies (e.g., prostate carcinoma) and long-term postoperative patients (urinary diversion). Further evaluation and treatment can then be undertaken if hydronephrosis is detected.

RENAL TRANSPLANTATION

Because of its superficial position in the pelvis, the transplanted kidney is particularly well suited for ultrasound evaluation, which has also proved to be useful in evaluating posttransplant diminishing urine output. The short-term changes in renal volume associated with refection can usually be differentiated from an obstructive cause. It is also possible to detect the presence of perirenal hematomas, lymphoceles, and urinomas that may occur in the transplant patient.

Power Doppler and color-flow studies have been used to detect the presence of acute rejection. These studies have been helpful not only in the detection of acute rejection but also for the differentiation of acute rejection from the various other causes of renal failure (e.g., obstruction) (90,95,100,102,120).

PERIRENAL EVALUATION

Ultrasonography is useful in the evaluation of the perirenal space. Perirenal fluid collections may represent hematoma

or urinoma, which usually are associated with an antecedent history of trauma or prior renal surgery (Fig. 3D.21). Urinomas tend to be cystic, whereas hematomas may be solid, cystic, or a combination of both, depending on the stage of clot breakdown. Ultrasound offers an accurate, noninvasive, radiation-free means of following the presence and course of perinephric hematomas resulting from blunt trauma.

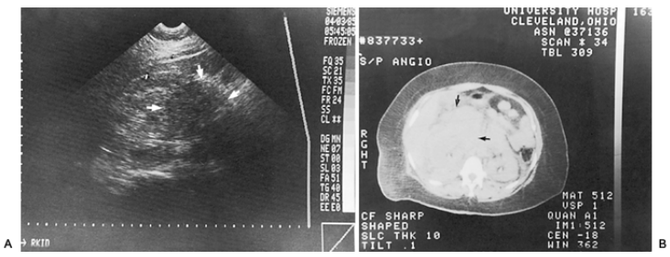


FIGURE 3D.21. A: Large perirenal hematoma after blunt abdominal trauma *(arrows)*. **B:** Computed tomography scan of same patient.

The presence of a perinephric abscess is usually suggested by a febrile course unresponsive to the usual antibiotic regimen. Sonographically, the perinephric collection appears as a complex mass with the internal architecture dependent on the amount and type of pus and the presence or absence of gas within the abscess (Fig. 3D.22). Ultra-sound can be used to assist in percutaneous drainage of these collections, which in many instances has supplanted the need for open surgical procedures.

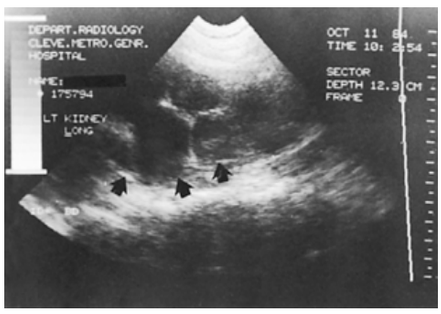


FIGURE 3D.22. Transverse scan showing complex perirenal mass, proved to be multiloculated perinephric abscess. Note multiple loculations *(arrows)*.

SCREENING PROCEDURES

Renal ultrasonography has a role in the evaluation of suspected adult polycystic renal disease. The sonographic appearance is that of enlarged kidneys with randomly distributed cysts (Fig. 3D.23). Early cystic renal changes are ultrasonically visualized before any other signs or symptoms are apparent in affected individuals.

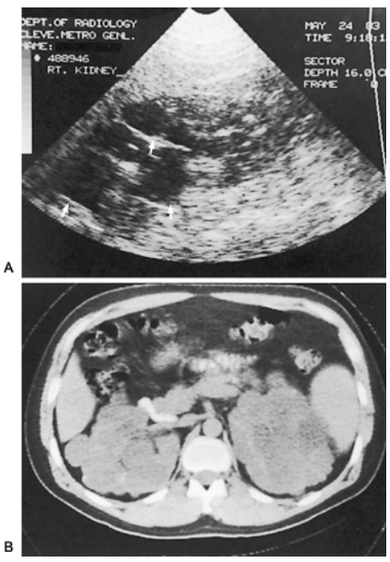


FIGURE 3D.23. A: Transverse scan showing multiple cysts *(arrows)* in an enlarged kidney. Changes typical of adult polycystic kidney disease. **B:** Computed tomography scan of same patient.

FETAL RENAL ULTRASOUND

Obstetric ultrasonography is often performed during the course of pregnancy and is useful in the evaluation of fetal size, gestational age, fetal lie, and placental position. Recent advances in ultrasound technology have improved the visualization of fetal anatomy and have led to increased identification of unsuspected congenital anomalies. Between 15 and 17 weeks of gestation, it is possible to identify the fetal kidneys by ultrasound approximately 50% of the time (58). By 20 weeks of gestation, it is unusual not to be able to identify the kidneys accurately. It is therefore currently possible to diagnose accurately the presence of in utero hydronephrosis; however, in most instances, it is impossible to differentiate its many etiologies: posterior urethral valves, primary megaureter (Fig. 3D.24), ureteropelvic junction obstruction, multicystic kidney (Fig. 3D.25), duplication anomalies with or without ureteroceles (Fig. 3D.26), vesicoureteral reflux, or prune-belly syndrome (22,28,50,127). The diagnosis of fetal hydronephrosis best serves to alert the

primary physician to the need for additional urologic evaluation in the early neonatal period. When indicated, appropriate surgical intervention may be expeditiously performed.

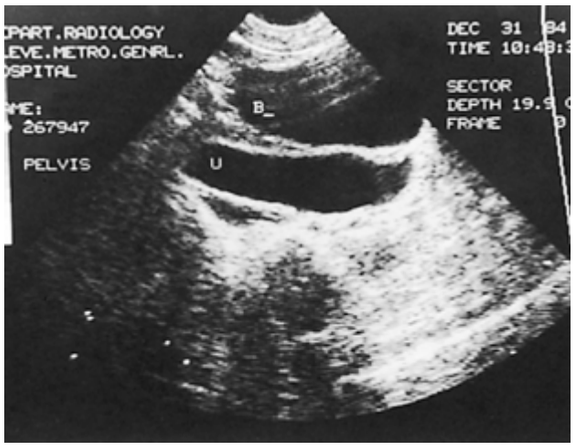


FIGURE 3D.24. Longitudinal pelvic scan showing dilated megaureter. B, bladder; U, ureter.

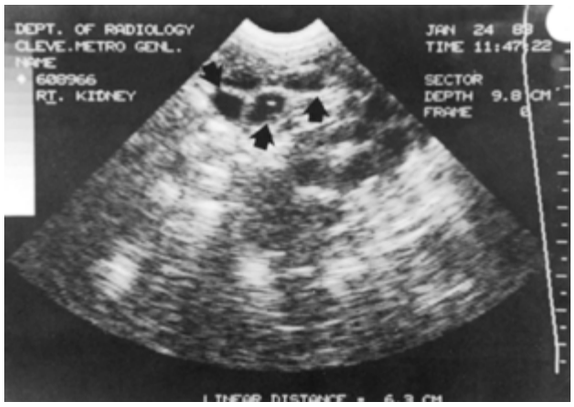


FIGURE 3D.25. Ultrasonic changes of multicystic kidney. Note multiple cysts *(arrows)*.

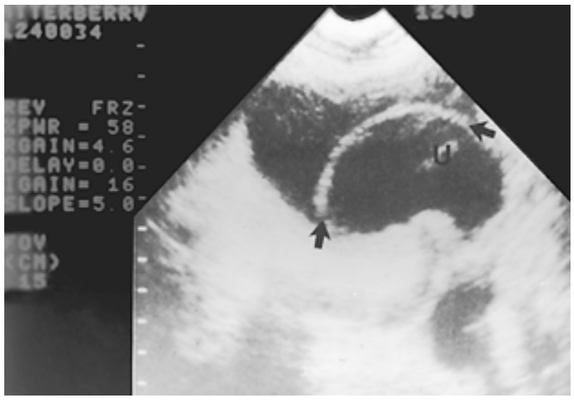


FIGURE 3D.26. Longitudinal scan of bladder demonstrating presence of ureterocele *(U)*. Note thin wall of ureterocele *(arrows)*.

RETROPERITONEAL SCANNING

The retroperitoneal space is a difficult area to examine with conventional radiographic methods, but it is well suited for sonographic studies. It is possible to identify lymph node enlargement, primary retroperitoneal tumors, and aortic aneurysms with a considerable degree of accuracy (Fig. 3D.27). Ultrasound may be helpful in determining the cause of ureteral deviation in patients with obstruction detected on excretory urography. In patients with retroperitoneal nodal metastases (e.g., testicular tumor), ultrasound

remains an excellent way to follow up the response to chemotherapeutic regimens without the risk of repeated radiation exposure. More commonly, CT studies are used to assess the retroperitoneum and in most instances are the primary studies used. When indicated, ultrasound-guided biopsies can be performed of suspicious structures. Ultrasound examination of the retroperitoneum also has been used to identify and locate accurately the undescended testicle. The study is helpful in identifying the inguinal testis, but it is less accurate in localizing the intraabdominal testis.

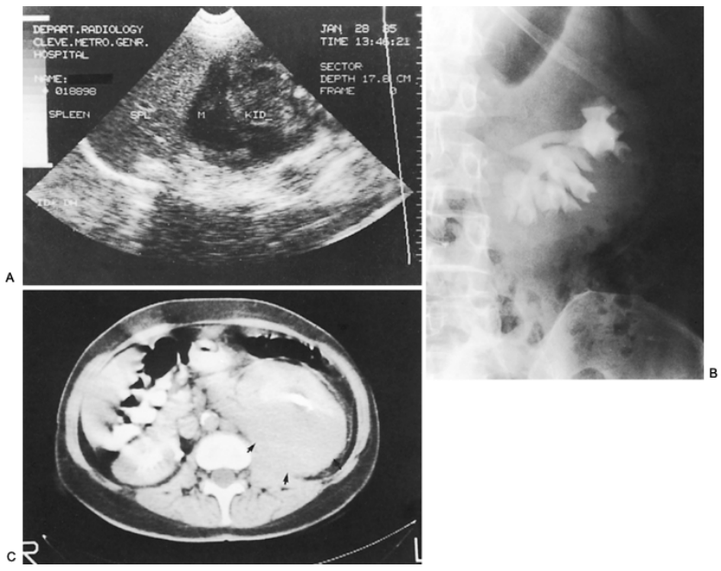


FIGURE 3D.27. A: Longitudinal scan of retroperitoneum demonstrating left perirenal mass. KID, kidney; M, mass; SPL, spleen. Surgical exploration revealed lymphoma. Intravenous urogram **(B)** and computed tomography **(C)** from same patient.

ULTRASONOGRAPHY OF THE ADRENAL GLAND

Because of their small size and protected location beneath the rib cage, it is often difficult to study the normal adrenal glands sonographically (9). Similarly, the evaluation of adrenal masses smaller than 3 cm is probably best performed with other radiographic techniques (e.g., CT, magnetic resonance imaging). Radionuclide and serum studies may also prove invaluable.

SCROTAL ULTRASONOGRAPHY

The superficial location and the maneuverability of the intrascrotal contents make the anatomic area well suited for sonographic evaluation. The primary use for scrotal ultrasound is in differentiating intratesticular lesions (tumors) from abnormalities arising from the paratesticular tissues. With the currently available high-frequency “small-parts” transducers, grayscale real-time techniques, and color-flow and power Doppler availability, a complete scrotal examination can be performed in minutes while providing excellent tissue resolution. The procedure is usually performed by first immobilizing the testicle with the free hand and then

placing the transducer directly in contact with the scrotal skin. Mineral oil or acoustic gel is routinely used as a coupling agent to help reduce artifact (27).

Normal Ultrasonic Scrotal Anatomy

Sonographically, the scrotal wall appears as a hyperechoic strip 3 to 4 mm thick. Between the scrotal wall and the testicle is an anechoic area, usually no more than a few millimeters in width, which represents a small amount of fluid normally present between the visceral and parietal layers of the tunica vaginalis. The normal testicle measures about 4 by 3 by 3 cm and is characterized by a homogeneous, fine granular echo pattern (Fig. 3D.28). The tunica albuginea appears as a thin hyperechoic layer surrounding the testicle. Posteriorly, the tunica albuginea reflects into the testicle to form the mediastinum testis, a structure that usually is seen only with the newer small-parts transducers. The epididymis runs along the posterolateral aspect of the testicle. The head, or globus major, is seen above the superior pole of the testicle and, when normal, appears to be either hyperechoic or of the same echogenicity as the testicle. The body and tail of the epididymis sonographically appear as a coarser echo pattern than the testicle. The vas deferens, when visualized, appears as a circular hyperechoic area on transverse scans. Doppler and color-flow studies allow for assessing testicular perfusion, thus detecting vascular abnormalities associated with the spermatic cord. These studies have also been of value in the evaluation of patients with testicular trauma and intratesticular masses.

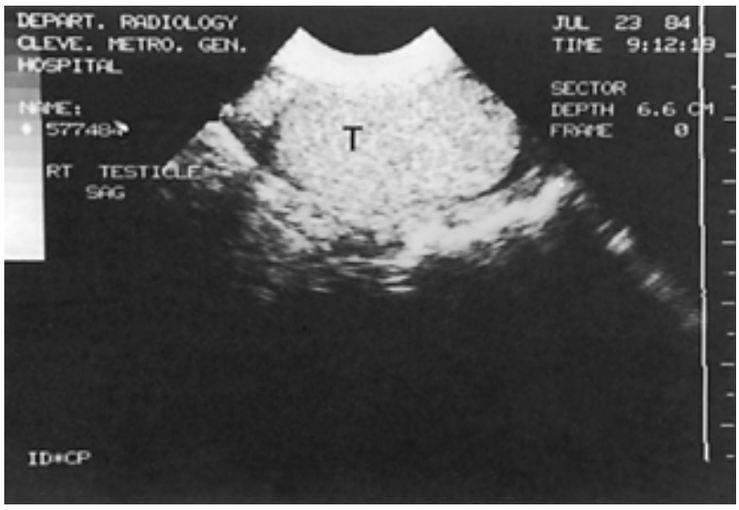


FIGURE 3D.28. Scrotal ultrasound showing sonographic appearance of normal testicle *(T)*.

Applications of Scrotal Ultrasound

Patients with scrotal swelling and pain represent a diagnostic challenge and require prompt evaluation. Scrotal ultrasound has been helpful in differentiating the presence of inflammatory lesions (orchitis or epididymitis) from spermatic cord torsion, traumatic testicular disruption, and testicular or paratesticular tumors. Sonographically, epididymitis appears as a hypoechoic enlargement (inflammatory edema), usually involving the globus major. A reactive hydrocele may also be present (Fig. 3D.29). In the presence of epididymo-orchitis, the testicle adjacent to the involved epididymis may demonstrate areas. Individuals with presumed epididymo-orchitis who fail to respond to antibiotic therapy may demonstrate a testicular or scrotal abscess on ultrasound examination. When acute scrotal swelling occurs as a result of trauma, ultrasound has been helpful in differentiating testicular rupture from a normal testicle surrounded by hematoma (Fig. 3D.30). Acutely, the ischemic testicle is enlarged, with decreased echogenicity compared with the normal testicle. Color-flow studies can assess testicular perfusion and are invaluable in evaluating children with an acutely painful testicle (8,14,86,114). When properly

performed, these studies are as reliable as radionuclide imaging and approach an accuracy of 98%.

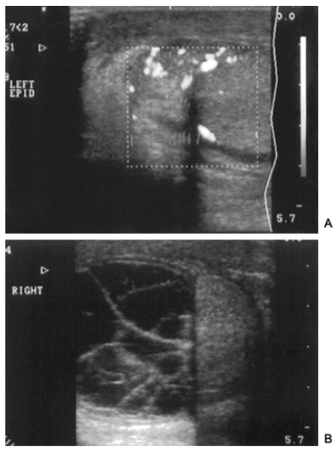


FIGURE 3D.29. A: Scrotal examination using power Doppler shows marked hyperemia involving a swollen left epididymis. These are typical features with acute epididymitis. **B:** Ultrasound of a different patient demonstrates a reactive hydrocele related to acute epididymitis. This shows a weblike pattern with multiple thick septations. (Permission granted by Urologic Multimedia, Inc.)

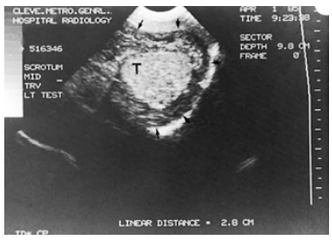


FIGURE 3D.30. Scrotal ultrasound demonstrating large hematoma *(arrows)* surrounding normal testicle *(T)*.

A *hydrocele* is a fluid collection that occurs between the visceral and parietal layers of the tunica vaginalis, making accurate testicular examination difficult to perform on physical examination. Scrotal ultrasound has been helpful in identifying hydroceles secondary to a malignant process. In the presence of a hydrocele, the quality of the testicular sonogram may be improved because of the fluid, which acts as a biologic water bath. Typically, a simple hydrocele appears as an anechoic area surrounding the testes anterolaterally (Fig. 3D.31). The presence of a hypoechoic inhomogeneous mass in the testicle is suggestive of a malignancy and warrants surgical exploration (Fig. 3D.32). Unlike embryonal cell carcinoma, seminoma sonographically has a more homogeneous pattern (Fig. 3D.33). Nonseminomatous testicular tumors often demonstrate increased flow on Doppler studies. Individuals with repeated bouts of epididymal infection may also have scrotal pain and swelling. Ultrasonically, a diagnosis of chronic epididymitis is suggested by an enlarged hyperechoic epididymis (Fig. 3D.34).

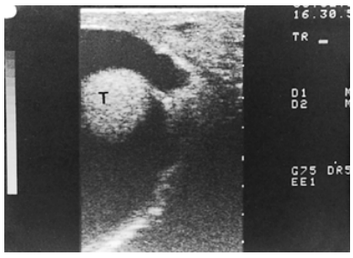


FIGURE 3D.31. Scrotal ultrasound demonstrating characteristic findings of normal testicle *(T)* surrounded by large hydrocele.

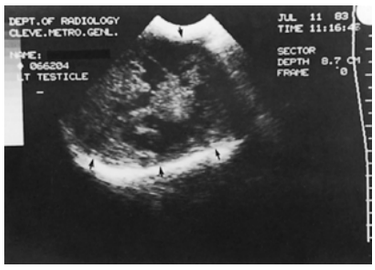


FIGURE 3D.32. Scrotal ultrasound demonstrating large inhomogeneous testicular mass *(arrows)*. Pathologic examination revealed embryonal cell carcinoma.

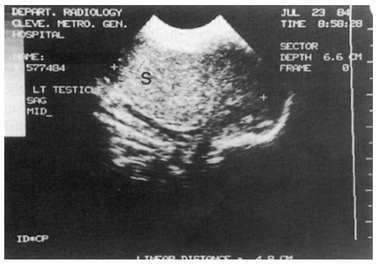


FIGURE 3D.33. Homogeneous testicular mass *(S)* pathologically proved seminoma.

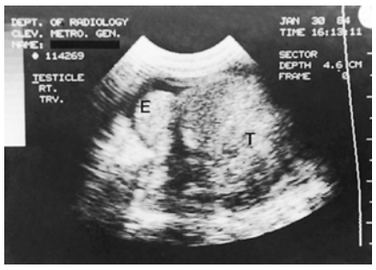


FIGURE 3D.34. Scrotal ultrasound demonstrating changes typical of chronic epididymitis. Note enlarged hyperechoic epididymis *(E)* and normal testicle *(T)*.

Scrotal ultrasound, particularly when combined with Doppler studies, has been helpful in identifying the subfertile male patient with a nonpalpable or subclinical varicocele (30,88). The clinical significance of the subclinical or nonpalpable varicocele continues to be debated. Testicular microlithiasis is usually bilateral and has been found to be associated with testicular malignancies and infertility (2,77). The disorder is usually identified incidentally and, when found without clinical evidence of malignancy, is followed with periodic ultrasound examinations. Ultrasound studies have also been used to assess postpubertal testicles having undergone prepubertal orchidopexy (121) and in following the remaining testes after unilateral orchiectomy for testicular

germ cell tumors (63). Ultrasonography has also been used to assess not only the location of undescended testes, but their histologic characteristics as well (6).

TRANSRECTAL ULTRASONOGRAPHY OF THE PROSTATE

Since its inception in the 1960s, abdominal and scrotal ultrasound has gained an important role in the evaluation of many urologic disorders. However, because of the relatively inaccessible pelvic location of the prostate, ultrasonic evaluation of this structure with conventional techniques has not been as widely accepted. In the late 1950s, Wild and Reid were the first to develop and test a transrectal ultrasonic probe (43). Although their initial experience with the transrectal approach resulted in visualizing only the rectal wall, the possible usefulness of this technique as a means to evaluate the lower urinary tract and particularly the prostate was clearly demonstrated. In 1964, Takahashi and Ouchi (115) used a transrectal probe equipped with a radial scanning device and obtained poor-quality tomographic pictures of the prostate, which had no clinical value. It was not until 1967 that Watanabe and associates (122,123) obtained the first clinically useful transrectal ultrasonic tomograms of the prostate. Since then, additional advances in instrumentation and technique have allowed for more reliable ultrasonic visualization of this pelvic organ. Today, the use of transrectal ultrasonography is helpful in the assessment of both benign and malignant disorders of the prostate and has been particularly valuable in biopsy and assessment of treatment of patients with carcinoma of the prostate.

Instrumentation

The transducer and its mechanism of action (mechanical sector and radial, array-linear, and phase) are important components of the current instrumentation used in this technology. Most transducers used for imaging the prostate vary in frequency from 6.0 to 7.5 MHz. This allows for excellent visualization of the posterior prostate, but because of the limited penetration of high-frequency sound, visualization of the anterior prostate is limited, especially when associated with significant enlargement. There is increasing interest in the role of color-flow Doppler studies; however, the utility of these studies continues to be debated (12,47,68,82,105). Different types of transducers are available, but most are typically biplanar and use radial or sector transducers. This allows imaging of the prostate in the transverse and sagittal planes. The transducer of the radial scanner rotates 360 degrees and propagates sound waves perpendicular to the long axis of the transrectal probe. Within the human body and with respect to the prostate gland, the sound waves are directed perpendicular to the long axis of the body and prostate. The direction is called *transaxial* or *axial,* and it is similar to the transverse plane of a CT image. Linear-array and mechanical sector scanners have eliminated the need for the rectal balloon, and the probe is placed in direct contact with the rectal wall. A decided advantage of these instruments is that transrectal prostate core biopsies and aspirations can be performed under ultrasonic guidance. In the phased-array scanner, many small transducers are aligned side by side, and when the scanner is oriented parallel to the long axis of the body, the sonographic images obtained are in the longitudinal or sagittal plane. Mechanical sector and phased-array scanners can provide images in either plane, and new biplanar probes incorporate both types of transducers in one unit.

Transverse images yield more information about the lateral margins and symmetry of the prostate, whereas longitudinal images delineate the apex and base of the gland more clearly. The longitudinal orientation appears to be more ideal for ultrasound guidance of prostate biopsy, even though the technique was first demonstrated with a radial scanner. Use of axial and longitudinal projections provides increased sensitivity in the examination of the prostate, and probes with both capabilities have been developed and will likely continue to be the standard.

Technique of Examination and Prostatic Biopsy

Technically, transrectal ultrasonography is minimally invasive and easy to perform. The entire examination takes 15 to 20 minutes and can be performed in the office on an outpatient basis without the need for anesthetics. Before beginning the examination, the clinician should perform a rectal examination to exclude the presence of anal or rectal abnormalities that may contraindicate transrectal probe insertion. In addition, a careful digital examination of the prostate should be undertaken. The examination may be performed with the patient in the lithotomy, lateral decubitus, knee-chest, or sitting position. Before performing the

study a cleansing enema can be administered, but this is not necessarily done routinely. The transrectal probe is then inserted approximately 8 to 9 cm above the anal verge, and serial sonograms are obtained. It is important to perform the study systematically. When transverse images are obtained, sonograms are typically obtained at increments of 5 mm beginning at the bladder and seminal vesicles and progressing toward the apex. When a longitudinal scanner is used, images are obtained at increments of 5 degrees right and left of center. All images should be appropriately marked and hard copies obtained so that they may be referred to at a later date. Permanent records can be obtained with Polaroid film, multiple format cameras, thermal printers, videotape, laser disks, and computer floppy disks.

Applications

Over the past 10 years, significant advances have been made in the technology and methodology associated with transrectal ultrasonographically guided biopsies of the prostate. Although initial reports used the transperineal route (43), more recent experience has been with transrectal approaches (60). In addition, data are being obtained on the relative merits of both core and aspiration techniques (60). Spring-loaded devices also have been used in association with ultrasound-guided systematic or sextant core biopsies, and they have resulted in sampling of the prostate with a reduction in the pain associated with the procedure (117). Technologic improvements in ultrasound instrumentation have resulted in the development of transducers that permit viewing of the prostate in a variety of planes, which also has increased the accuracy of biopsy techniques (32,60).

Transperineal biopsies have generally been performed with the aid of radial or linear-array scanners (Fig. 3D.35 and fig. 3D.36), but since the development of transrectal techniques, these procedures are performed rarely. The biopsy is performed under sterile conditions, and the perineum is cleansed and draped in the standard manner. Biopsies can be performed with the patient in either the lithotomy or lateral decubitus position, depending on the examiner's preference. When the radial scanner is used, often a grid with multiple holes is placed against the perineum and the site of needle entry corresponds to the grid that appears on the viewing screen (97). When an area of interest is imaged, the biopsy needle is inserted in the appropriate site on the

grid and the movement of the needle is monitored on the viewing screen. One of the disadvantages of this system is that the needle cannot be tracked or followed continuously during the entire biopsy. If care is not exercised, tissue may be obtained that is cephalad or caudad to the particular area to be sampled. This disadvantage can be overcome with the use of a linear-array transducer. It is of interest that the techniques developed for biopsy have recently been used for interstitial radiation of the prostate. The approach allows for accurate seed implantation, which is a treatment modality for carcinoma of the prostate that is being used with increasing frequency.

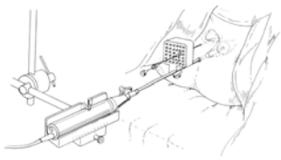


FIGURE 3D.35. Diagram demonstrating transperineal biopsy with radial transducer.

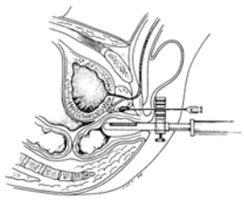


FIGURE 3D.36. Diagram demonstrating transperineal biopsy with linear-array transducer.

Transrectal biopsies are performed most commonly with a biplanar probe (Fig. 3D.37). Before performing the transrectal biopsy, many clinicians prefer to administer broad-spectrum oral antibiotics 1 hour before the procedure and to give the patient a cleansing enema. As with the transperineal biopsy, the procedure can be performed with the patient in either the lateral decubitus or the lithotomy position, based on the examiner's preference. Some clinicians use the knee-chest position because they believe the drainage of blood from the gland and associated collapse of prostatic and periprostatic veins improves the ultrasound image. Most of the newer instruments have markers that appear on the viewing screen when the transducer is in the biopsy mode, and these correspond to the path of the needle. Aligning the area from which a biopsy specimen is to be taken with these markers ensures that reliable biopsies can be obtained (Fig. 3D.38). Devices also have been developed for obtaining either aspiration or core biopsy. Although higher than with the perineal biopsy, the risk of sepsis remains low (less than 1%).

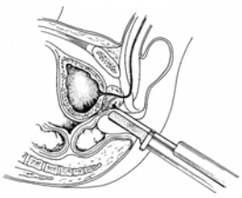


FIGURE 3D.37. Diagram demonstrating transrectal biopsy with end-fire multiplane probe.

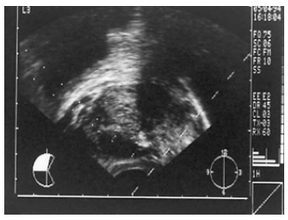


FIGURE 3D.38. Sagittal scan with markers indicating path of biopsy needle.

The normal prostate is viewed as a symmetric triangular ellipsoid structure that is delineated circumferentially by the continuous prostatic capsule (Fig. 3D.39). The capsule or margin is usually well defined, highly echogenic, continuous, and free of distortion. The anteroposterior diameter appears shorter than the transverse diameter because the posterior portion of the prostate becomes concave as a result of compression by the probe during the examination. The internal sonographic structure of the prostate is composed of multiple fine diffuse homogeneous echoes that probably represent acoustic interfaces created by numerous glands that are present. The posterior peripheral zone can usually be delineated from the more anterior, fibromuscular stroma and the central and transition zones.

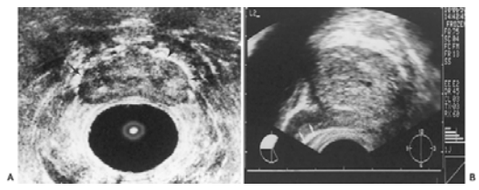


FIGURE 3D.39. A: Transverse image of normal prostate. **B:** Sagittal image of normal prostate. Note relationship of seminal vesicles *(arrows)* to prostate. Urinary bladder is to the left.

Benign prostatic hyperplasia is limited to the transition zone and appears as diffuse enlargement, with the greatest increase in size occurring in the anteroposterior diameter. The prostate margin remains well defined but thicker than is found in the normal gland. The hyperplastic portion of the gland consists of multiple fine homogeneous echoes believed to represent small adenomas located in fibrous tissue between glandular elements and multiple microcysts created by dilated prostatic ducts containing secretions, corpora amylacea, and microcalculi (Fig. 3D.40). Often, the transition zone that gives rise to benign prostatic hyperplasia can be differentiated from the more echogenic peripheral zone from which 70% of carcinomas arise. It is often difficult to distinguish the transition zone from the central zone in the presence of significant hyperplasia. Prostatic calculi, often present at the interface of the peripheral and transition zones, commonly can be identified by their marked echogenicity in association with typical "shadowing" (Fig. 3D.41).

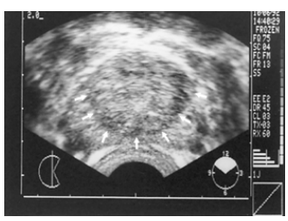


FIGURE 3D.40. Transverse image demonstrating typical appearance of benign prostatic hyperplasia. *Arrows* indicate transition zone border.

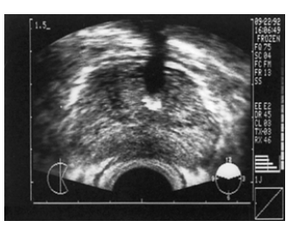


FIGURE 3D.41. Transverse image demonstrating hyperechogenicity and shadowing associated with prostatic calculi.

Unlike the usual homogeneous sonographic appearance of the normal hyperplastic prostate, the ultrasonic characteristics of carcinoma of the prostate are varied. Early studies with B-mode and initial gray-scale imaging reported that prostate cancers appeared as echo-dense or hyperechoic areas (52). With improvement in instrumentation and the

use of higher-frequency transducers, the appearance of tumors changed. Some investigators began to demonstrate that prostatic malignancies, particularly when they are small and localized, appear as hypoechoic areas located in the peripheral zone (Fig. 3D.42), but others demonstrated that tumors can be hyperechoic, hypoechoic, isoechoic, or of mixed echogenicity (24,59,98). There does not appear to be a reliable correlation between histologic grade and ultrasonic pattern other than the fact that small tumors that tend to be well differentiated often appear hypoechoic and larger, and high-grade tumors tend to have a mixed pattern. Isoechoic tumors tend to have a mixed pattern. Isoechoic tumors tend to be better differentiated. Newer, high-resolution equipment visualizes a prostate tumor as an echopenic focus before it obtains a more echogenic appearance. A desmoplastic reaction and associated calcification

are often associated with tumor growth and invasion. These changes may contribute to the mixed pattern observed with advanced tumors (99).

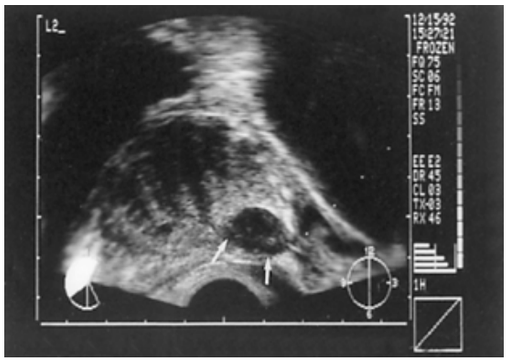


FIGURE 3D.42. Transverse image demonstrating appearance of peripheral zone hypoechoic carcinoma *(arrows)*.

Unfortunately, many structures and benign processes within the prostate can have ultrasonic characteristics similar to the hypoechoic appearance of small prostate malignancies, including small nodules of hyperplasia, cysts, infarcts, inflammatory processes, cystic atrophy, blood vessels, and muscle tissue. Many carcinomas are isoechoic and cannot be imaged with this technique. In addition, anterior tumors often cannot be distinguished reliably from the normally hypoechogenic appearance of this region of the gland.

Improvements in technology have resulted in the development of newer devices that may improve the ability of ultrasonography to detect and stage prostate malignancies. Color Doppler, power Doppler, ultrasound contrast agents, and three-dimensional studies have all been used, but unfortunately, none has been able to locally determine the extent of disease once the diagnosis of carcinoma has been established (26,33,68,82,105).

Clinical Applications

Although transrectal prostatic ultrasonography has had its greatest use in the assessment of patients with carcinoma of the prostate, other applications include the evaluation of patients with both acute and chronic prostatitis and men with infertility (48). Experiences indicate that the technique is useful in the assessment and the detection of seminal vesicle abnormalities that may be associated with infertility, and ductal obstruction also has been confirmed with this technique.

Sekine and associates (108) have developed a transrectal electronic linear-array scanner that allows one to obtain longitudinal sonograms of the lower urinary tract. With real-time imaging, dynamic studies obtained while the patient is voiding may provide valuable diagnostic information on voiding dysfunction (87,109).

Staging

Transrectal ultrasonography has been useful in the evaluation of patients already diagnosed as having carcinoma of the prostate. The technique is valuable in assessing prostatic size and in detecting unrecognized invasive disease. Early reports show that the stage of prostatic carcinomas, as determined by transrectal ultrasonography, corresponded with the stage diagnosed pathologically on radical prostatectomy specimens (Fig. 3D.43). Pontes and associates (94) demonstrated a sensitivity of 89% and 100% for preoperative ultrasonic detection of capsular and seminal vesicle involvement, respectively. The specificity of detecting capsular penetration and seminal vesicle involvement was only 50% and 28%, respectively, because of the inability of the study to detect microscopic disease. Fujino and Scardino (34) reported the ability of ultrasound to detect invasive disease in 8 of 18 patients who had no extension of the disease by rectal examination. Lee and colleagues (61) introduced the concept of obtaining biopsy specimens from areas with a high probability of invasion, such as the apex and point at which the seminal vesicles enter the central zone. Areas of microscopic invasion that were not evident on digital rectal or routine ultrasound examination have been detected. More recent experience has indicated that ultrasound staging is limited, and its value in clinical decision making remains questionable (4,66,101,112). Others have attempted to characterize specific components of the tumor to assist in ultrasound staging, but the value of this methodology is limited (119).

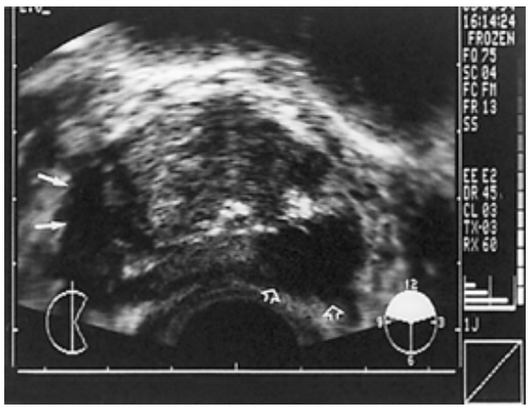


FIGURE 3D.43. Transverse image demonstrating distortion of border of prostate *(arrows)* associated with invasive carcinoma. Note hyperechogenicity of tumor.

Measurement of Prostate Gland Size

Transrectal ultrasonography is useful in documenting prostate gland volume, and it is accurate within 5% in determining true prostatic weight (39). This ability allows ultrasound to provide information regarding the response of the tumor to therapy. These determinations are based largely on total gland volume and not tumor volume. Prostate ultrasonography has documented reduction in prostate size after administration of endocrine therapy when used as treatment for patients with disseminated cancer. Within 3 to 6 months after either orchiectomy or estrogen therapy, a sonographically detectable 20% to 30% decrease in prostate volume occurs (17,96). Changes with estrogen therapy are slightly slower to occur than those with surgical castration.

Further usefulness of ultrasound has been demonstrated in the evaluation of prostate cancer patients treated with radiotherapy and chemotherapy. Studies have indicated that

the maximum reduction in the size of the prostate occurs usually by 9 months after radiotherapy and 3 months after chemotherapy (34). As a response to therapy, in addition to decrease in size, the prostate resumed a more symmetric shape, the margin reformed and thickened, the degree of extracapsular extension diminished, and the seminal vesicles became normal in appearance. These techniques also have been used to measure prostatic size to document response to endocrine agents (e.g., 5α-reductase inhibitors) in the treatment of benign prostatic hyperplasia. A similar reduction in prostate size has been recognized.

Ultrasound-guided Biopsy, Interstitial Radiation Therapy, and Cryotherapy

As noted, transrectal prostatic ultrasonography is useful as an aid in the placement of the biopsy needle within a specific suspicious area of the prostate. Transrectal ultrasonically guided biopsies are widely used (Fig. 3D.44), and new aspiration and core biopsy needles with spring-load guns continue to be developed. Problems exist because not all tumors can be visualized ultrasonically, and more studies are required to correlate the area of the ultrasound biopsy with the physical findings. Hodge and colleagues (42) used ultrasound-guided biopsy to ensure accurate placement of the biopsy needle in the peripheral zone of the prostate. Multiple “systematic” biopsies are performed, and with this approach, more than 50% of patients with palpable abnormalities (e.g., firm areas, nodules) have been diagnosed as having carcinoma. It has also been recognized that the larger the prostate, the lower the yield in establishing a diagnosis of carcinoma (64). Ultrasound-guided biopsies have a role in the evaluation of patients with or suspected of having prostate cancer [e.g., abnormal digital rectal examination, elevated or change in prostate-specific antigen (PSA)]. Repeat ultrasound-guided biopsies after a negative digitally directed biopsy are thought to be worthwhile in patients with suspicious palpable abnormalities. In patients with nonpalpable but suspected prostate malignancy (e.g., elevated PSA), ultrasound-directed biopsy of sonographically suspicious areas or when performed in a sextant manner has been shown to assist in establishing the diagnosis of prostate cancer. Experience indicates that the diagnosis of cancer can be increased by obtaining a greater number of cores (e.g., more than six) and by performing biopsies on more lateral aspects of the prostate to enhance sampling of the peripheral zone. In addition, the technique has a role in the evaluation of patients treated with definitive radiation therapy who have no palpable abnormalities, but suspicion of recurrence based on change in serum PSA.

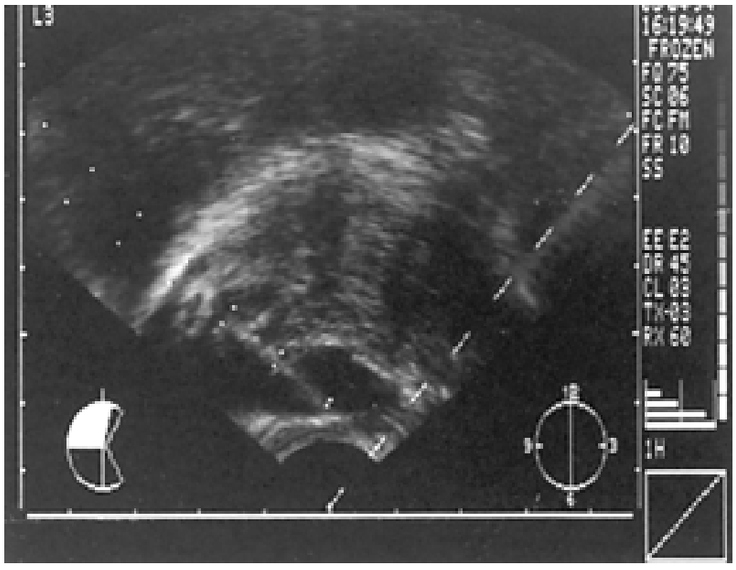


FIGURE 3D.44. Sagittal image with biopsy guide with visualization of hyperechoic needle demonstrating the use of ultrasound guidance to assist in a biopsy.

As noted earlier, ultrasound can also be used to direct radioactive seed implantation into the prostate when using this treatment modality (44). Permanent implantation of radioactive seeds offers some advantages over external beam radiation, and the implantation technique is less time-consuming for the patient and staff than a full course of external beam therapy. In addition, a higher concentration of seeds can be placed in and around the area of malignancy. The disadvantage of this technique is that extracapsular tumors with ill-defined margins may not be irradiated adequately and that regional lymphatic vessels are not treated appropriately. These problems may be overcome by combining interstitial therapy with external beam or endocrine therapy. Studies are in progress to assess these alternatives. Ultrasound has also been used to monitor the “ice ball” during cryoablation for treating prostatic malignancies. The monitoring not only ensures adequate treatment of the malignancy but also helps protect the rectum from injury.

Its important to recognize that ultrasound is unable to visualize a significant number of tumors located within both the peripheral and transition zones. In addition, the presence of these tumors may only be suggested by the finding of an elevated PSA with a prostate that may be free of palpable abnormalities. Ultrasound may be useful in assisting in biopsy, but ultrasound should not be used as a discriminator as to who should or should not be biopsied. This decision should be made on the basis of clinical indications (i.e., abnormal digital rectal examination or elevated serum PSA).

ULTRASONOGRAPHY OF THE URINARY BLADDER

The urinary bladder is an extraperitoneal musculomembranous sac that functions primarily as a urinary storage reservoir. In children younger than 6 years of age, the bladder is predominantly an intraabdominal organ lying beneath the anterior abdominal wall. In adults, it is a pelvic organ lying, when empty, beneath the symphysis pubis. When distended,

the bladder assumes a globular shape and is easily studied with the transabdominal approach. Recently, transrectal and transurethral approaches have been used to study and define subtle bladder abnormalities.

Transabdominal Scanning

Transabdominal ultrasound imaging of the bladder is usually performed with the patient in the supine position and the bladder distended. Although it is not necessary to have a Foley catheter in place, its presence is helpful in identifying the bladder neck (Fig. 3D.45). Usually, a 3.5-MHz transducer is used to obtain transverse and longitudinal images.

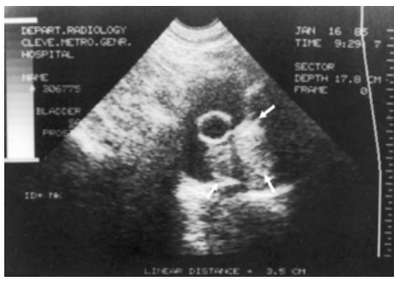


FIGURE 3D.45. Longitudinal abdominal scan showing urinary bladder and enlarged prostate *(arrows)*. Note Foley catheter balloon at the bladder neck.

Transrectal Scanning

Transrectal ultrasonic imaging of the bladder is performed with the same equipment and technique as previously described (Fig. 3D.46).

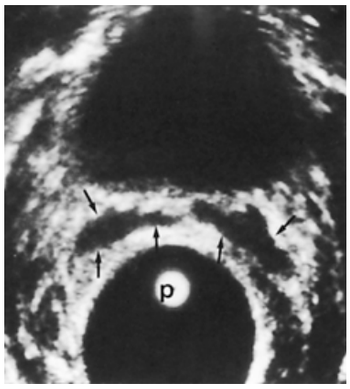


FIGURE 3D.46. Transrectal scan of normal bladder and seminal vesicles *(arrows)*. Rectal probe *(p)* is in place.

Transurethral Scanning

Although both transabdominal and transrectal approaches have been helpful in evaluating bladder abnormalities, subtle changes in the bladder wall (e.g., muscular invasion by tumors) are often not discernible. Experience by Gammelgaard and Holm and others suggests that the bladder may be best studied with the transurethral approach (80).

The scanner for transurethral ultrasonography consists of a motor that rotates a long rod, which is connected at the opposite end to an interchangeable transducer. The scanner fits within a standard resectoscope sheath and is interchangeable with the usual optical system. Two 5.5-MHz transducers are available. One emits the ultrasonic beam at 90 degrees to the instrument, whereas the other emits the beams at 135 degrees to the probe in retrograde fashion and is useful in studying the bladder neck region. With these two transducers, complete visualization of the entire bladder is possible. Probes with multiple and variable angulations are also available. During routing cystoscopy, when further evaluation of a detected bladder lesion is desired, the telescope is removed from the sheath and is replaced with the sterilized scanner. Dynamic scans using the transducers are obtained. The entire bladder wall can be rapidly scanned in a matter of minutes.

Normal Bladder

Ultrasonically, the normal bladder appears as a globular structure, the shape of which varies depending on the patient's position and degree of distention. The bladder wall is hyperechoic and appears as a symmetric, smooth surface. When distended, the fluid-filled bladder is anechoic (Fig. 3D.47).

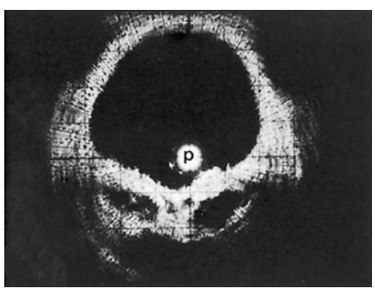


FIGURE 3D.47. Transurethral scan of normal urinary bladder. Note seminal vesicles posterior to the bladder. p, transurethral probe.

Clinical Application

Bladder tumors are a common urologic problem, the treatment of which depends on an accurate assessment of the grade of the primary tumor. With currently available staging modalities, errors may occur in nearly 50% of cases (10). Large, exophytic tumors appear ultrasonically as echogenic masses projecting into the lumen of the echo-free bladder (Fig. 3D.48). These areas are fixed to the wall; unlike blood clots or stones, they do not move as the patient changes position. Ureteroceles, although fixed to the bladder wall, are easily recognized by their thin echogenic wall surrounding a relatively anechoic center. Bladder stones readily move about with changes in intravesical

volume and patient position, and like renal stones, they appear as dense hyperechoic areas associated with sonic shadowing.

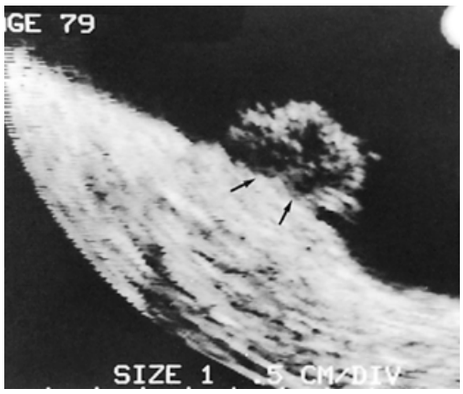


FIGURE 3D.48. Transurethral bladder scan demonstrating large, exophytic bladder.

Superficial bladder tumors or minimally infiltrative tumors (stage T_1 or T_2) do not cause distortion or fixation of the bladder wall, and they demonstrate a well-defined base (Fig. 3D.49 and fig. 3D.50). Multiple scans obtained during bladder filling demonstrate free movement of the bladder wall.

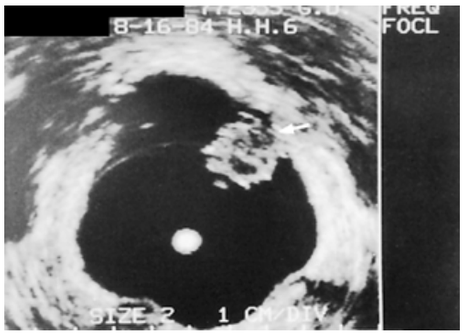


FIGURE 3D.49. Transurethral bladder scan demonstrating superficial bladder tumor. Note lack of bladder wall invasion *(arrow)*.

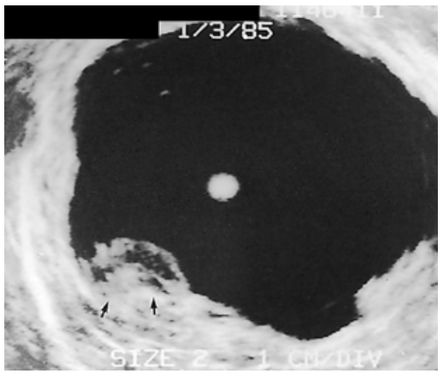


FIGURE 3D.50. Transurethral bladder scan demonstrating minimally invasive tumor *(arrows)*.

Infiltrative tumors tend to be broad based, and the bladder wall may be fixed and distorted. Stage T_3 tumors that have completely extended through the bladder wall are visualized as an extravesical mass (Fig. 3D.51).

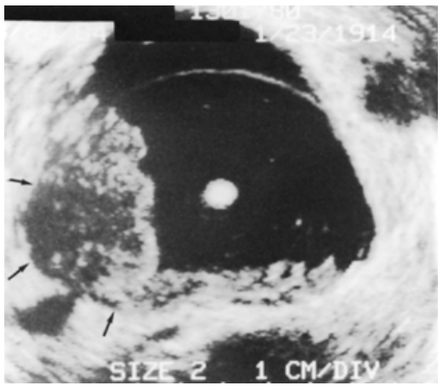


FIGURE 3D.51. Transurethral bladder scan demonstrating tumor invasion beyond bladder wall *(arrows)*.

Probably the most common use of bladder ultrasonography has been in the estimation of residual urine in patients with voiding disorders. The study is helpful in estimating total bladder capacity and postvoid residual urine when urethral instrumentation is not desired or is contraindicated (16,79,103). The most commonly used formula is that of a prostate ellipse:

Volume = 0.5 × Diameter_1 × Diameter_2 × Diameter_3

where $diameter_1$ is width, $diameter_2$ is height, and $diameter_3$ is length.

When these measurements are used, the correlation between catheterized and estimated residual volume has been

reported to be as high as 98%. A three-dimensional device was recently described for this purpose (70).

Other applications include assessment of patients for vesicoureteral reflux (23,36,124) and increasingly assessment of abnormalities in bladder structure and function. Although limited, perineal and transvaginal ultrasonography has been reported to be of assistance in identifying the presence of vesicovaginal fistula (1,125). The technique of “video urodynamics” has been used with Doppler sonography (84,85), and urethral abnormalities have also been identified in assessing patients with stress urinary incontinence and other urethral disorders (7,31,56,57). It is likely that with continued technologic improvements these studies will be expanded because of their availability and cost-to-benefit ratio.

PENILE ULTRASONOGRAPHY

Ultrasonography of the penis has been used primarily in three clinical areas: assessment of Peyronie's disease, evaluation of urethral strictures, and assessment of impotence. This latter category is discussed in detail in the chapter related to the assessment of men with erectile dysfunction.

Peyronie's disease is an uncommon problem that is related to the excessive deposition of collagen and associated calcium in the tunica albuginea of the corpus cavernosum. Patients usually have pain and deformity of the penis associated with erection, and on physical examination a palpable area of “plaque” is often evident. Ultrasound has been used to visualize the area of fibrosis, and shadowing often can be noted secondary to the areas of calcification. Correlation has also been noted with xeroradiography (3,21). The ultrasound studies may have a role in the diagnosis of the condition but possibly may have a more important one in documenting progression or regression of the areas of abnormality.

Another interesting application of penile ultrasonography relates to the assessment of the distal male urethra. Experience has indicated that this technology is useful in the assessment of patients for urethral strictures, and excellent correlative data have been obtained with standard radiographic urethrography. An advantage of this technique is that the periurethral tissue can be seen clearly, and it is believed that this method of imaging may allow for a more informative decision regarding the most appropriate treatment of urethral stricture (19,20,35,76). Other interesting applications relate to imaging of urethral calculi (113).

Doppler ultrasound studies are widely used in the assessment of men with erectile dysfunction. Both inflow and outflow abnormalities can be readily identified. The penile arteries can be readily identified with current technology and changes in flow identified following intracorporeal injection with vasoactive agent. Recent experience also indicates these studies may be of value in determining the role of oral agents in treating patients with erectile dysfunction (20,25,41,73,78,83,106).

INTRAOPERATIVE ULTRASONOGRAPHY

Intraoperative real-time renal scanning displays a cross section of renal tissue and, using multiple images, allows accurate, three-dimensional stone localization. Most intraoperatively used portable ultrasound units use a frequency of 7 to 10 MHz and are modifications of the small ophthalmic ultrasound probe. The study is of value when performing open stone surgery. After adequately mobilizing the kidney, it is scanned in multiple planes until the stone is identified by its characteristic dense echo pattern and the presence of acoustic shadowing (Fig. 3D.52). Fine-needle probes are then passed to the stone and a nephrotomy made directly over the stone. With this technique, an experienced ultrasonographer can identify stones 2 mm or more in diameter.

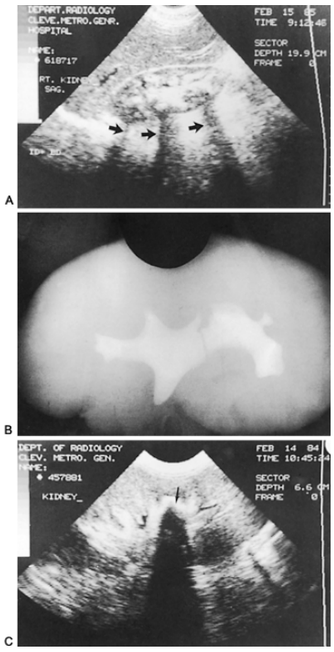


FIGURE 3D.52. A: Preoperative renal scan of large staghorn calculus. Note multiple areas of acoustic shadowing *(arrows)*. **B:** Intraoperative radiograph before nephrotomy. **C:** Intraoperative ultrasound localizing small retained stone fragment *(arrow)*.

Ultrasound probably has greater application at time of partial nephrectomy when removing small renal malignancies. Assimos and associates (5) reported the role of intraoperative ultrasonography in assisting in partial nephrectomy in patients with small renal tumors. The study is helpful in delineating the location and extent of these lesions. An additional application used intraoperative ultrasound to assess tumor involvement of the renal vein in patients with adrenal malignancy (67). More recently, ultrasonography has been used in association with laparoscopic cryoablation of renal malignancies. Ultrasound can monitor the formation of the “ice ball,” thus ensuring adequate treatment (126).

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3E MAGNETIC RESONANCE IMAGING

Peter L. Choyke

Part of "3 - IMAGING "

P.L. Choyke: Department of Radiology, Uniformed Services University of Health Sciences, National Institute of Health, Bethesda, MD 20892.

Magnetic resonance imaging (MRI) is an important method of imaging the urinary tract. Not only has image quality and speed improved, but there are now many new applications for MRI in urology. With the advent of surface coils, contrast agents, and faster pulse sequences, the scope of information that can be derived from MRI has greatly expanded. This chapter reviews the basic principles underlying MRI, describes advances in magnetic resonance (MR) technology, and summarizes the current role of MRI in the genitourinary tract.

BASIC PRINCIPLES

More than half of the human body is composed of water, and each molecule of water contains two hydrogen protons. Hydrogen protons are ubiquitous and can be found not only in water but also attached to the aliphatic chains of fatty acids. Regardless of their chemical environment, each hydrogen proton, when it is placed in a magnetic field, will align either with or against the direction of the applied magnetic field. A slight preponderance of the protons will align in the same direction as the field because this is a lower-energy state. This small excess of protons aligned with the field as opposed to against the field is responsible for the MR signal.

Not only do the protons align with (or against) the externally applied magnetic field, but they also precess or rotate around the axis of the main magnetic field. This precession occurs at a precise frequency that is dependent on the strength of the externally applied magnetic field and is known as the *resonant,* or *Larmor, frequency.*

If a radio frequency (RF) pulse, tuned precisely to the resonant frequency, is applied to protons, they will absorb this energy and begin to deviate from alignment with the external magnetic field. Commonly, these RF pulses are left on long enough to deviate the protons 90 or 180 degrees with respect to the main magnetic axis, although any angle can be obtained. When the RF pulse is completed, however, the protons will quickly relax to their resting state; that is, they realign with the magnetic field. This relaxation process has two components. First, the axis of each proton returns to alignment with the main magnetic field. This process is termed *T_1 relaxation.* Also, protons dephase with respect to each other; that is, they start aligned, or "in phase," with each other but end up randomly distributed. An analogy has been drawn with runners who begin a race at the same starting line but later may be spread around the track depending on their speed and endurance. Similarly, protons are initially aligned during exposure to an RF pulse but will separate from each other with time. This process is termed *T_2 relaxation.* T_1 and T_2 relaxation occur simultaneously, and neither process can be isolated from the other. Thus a T_1-weighted scan means that most of the effects are due to T_1 relaxation but T_2 relaxation also influences the image. Similarly, T_2-weighted images are influenced by T_1 differences among tissues.

Each tissue has its own properties with regard to T_1 and T_2. These are summarized in Table 3E.1 . Fat, for instance, has the most rapid T_1 (relaxes quickly to equilibrium), whereas urine has a very long T_1 (relaxes slowly to equilibrium). On T_1-weighted images, fat is bright and urine is dark. The T_2 of urine is longer than that of fat, so on

T_2-weighted images, urine is brighter than surrounding pelvic fat.

Tissue	T_1*	T_2
Fat	High	Less high
Muscle	Low	Low
Liver	Medium	Medium
Adrenal	Medium	Medium
Cyst	Low	High
Pheochromocytoma	Medium	Very high
Kidney		
Cortex	Medium	High
Medulla	Medium (less than cortex)	High
Cyst	Low	High
Hemorrhagic cyst	High	High
Tumor	Medium	Higher (variable)
Urine	Low	High
Bladder wall	Low	Low
Prostate		
Transition zone (TZ)	Medium	Low
Peripheral zone (PZ)	Medium (higher than TZ)	High
Tumor	Medium	Lower than PZ
Seminal vesicles	Low	High
Cortical bone	Low	Low
Marrow	Very high	High
Metastases	Medium	Low
Blood		
Fast flow	Low	Low
Slow flow	Medium to high	High
Tumor thrombus	Medium	Medium
Lymph nodes	Medium	Medium

*Low, black; medium, gray; high, white.

TABLE 3E.1. SIGNAL INTENSITIES in T_1- and T_2-WEIGHTED IMAGES

T_1 and T_2 weighting is achieved by varying the timing of the pulse sequences applied to the resting protons. In a typical T_1-weighted image, a 90-degree RF pulse (a pulse that deviates protons 90 degrees) is followed by a 180-degree RF pulse. This second pulse is used to refocus the dephased protons. This is analogous to interrupting the race described previously and having the runners turn around and run back to the starting line. The slower runners have a head start over the faster runners, so all the runners reach the starting line at approximately the same time. For protons, this signal, or "echo," can be measured at the time the protons become rephased (i.e., arrive at the "finish line"). The 90- and 180-degree sequence is repeated at short intervals until enough sequences have been acquired to form an image. By keeping the repetition time (TR) or time between repeated sequences to a minimum and also by minimizing the echo time between the 90- and 180-degree RF pulses (TE/2), T_1 weighting is achieved. Conversely, by lengthening the TR and TE, T_2 weighting is achieved. Typical values for a T_1-weighted spin echo scan are TR = 500 ms and TE = 15 ms, and typical values for a T_2-weighted spin echo scan are TR = 2000 ms and TE = 100 ms, although these numbers vary depending on manufacturer and model and the particular imaging requirements.

Other factors besides T_1 and T_2 influence an image. Flowing blood can cause an increased or decreased signal in vessels, depending on the imaging technique. Iron and other metals can induce strong local magnetic field gradients that degrade the image due to "susceptibility effects." The proton concentration and physical state can also affect the signal: cortical bone and calcifications in the urinary tract have few free protons and thus yield very low signal intensities on all pulse sequences.

Paramagnetic contrast agents can be also used to modify the T_1 relaxation process in tissues. Gadolinium ion is *paramagnetic;* that is, it becomes "magnetic" when placed in a magnetic field. Gadolinium shortens the T_1 value of protons that come nearby, thus leading to enhancement of blood and vascular tissues. Because unchelated gadolinium ion is highly toxic, it must be tightly chelated to a harmless carrier that speeds its removal from the body by glomerular filtration. Gadolinium chelate enhancement on MRI is analogous to iodinated contrast media enhancement on computed tomography (CT); tumors are enhanced but less so than renal parenchyma, and the collecting system and bladder become opacified while cystic ischemic or necrotic areas are not enhanced. Paradoxically, at very high concentrations of gadolinium, there is a darkening of signal as a result of shortening of T_2.

The magnet that supplies the external magnetic field in which the patient lies can be a permanent magnet, a resistive electromagnet, or a superconducting electromagnet. The advantages of the permanent magnet are that it does not require a large power source and it can have a more open architecture than other types of magnets. This is desirable for claustrophobic patients, pediatric patients, or interventional procedures requiring MR guidance. Resistive electromagnets are relatively energy inefficient, requiring large amounts of electric current. The advantage of the supercooled magnet is that it can generate a much higher magnetic field because the coil windings become superconducting at liquid helium temperatures. Higher field strength means higher signal for a given period of scanning, and this allows for faster imaging or higher-resolution images (or both). Field strength is measured in units of Tesla (T) (1 Tesla = 10,000 gauss). For reference, the earth's magnetic field varies from 0.5 to 2 gauss. Magnetic field strengths for MRI units currently on the market vary from 0.02 to 3 T.

There have been several recent technical improvements in MRI. One innovation is called *fast spin-echo* or *turbo spin-echo imaging*. This technique produces T_2-weighted scans in much less time than conventional T_2-weighted scans. This time reduction results in fewer artifacts resulting

from motion. Fast spin-echo acquires groups of phase encodings during each excitation, greatly improving the efficiency of scanning.

Another innovation is the suppression of the fat signal in MRI. Fat is ubiquitous in the abdomen and pelvis. Because the protons in fat are in a different molecular milieu than the protons of water, they have a slightly different resonant frequency. With the application of an RF pulse that selectively suppresses the signal from fat but not water, the image is "fat suppressed." By removing the fat from an image, the dynamic range of the image (gray scale) is changed, and the scan becomes more sensitive to slight increases in signal intensity due to enhancement. Instead of fat representing the brightest signal, the contrast-enhancing structure becomes the brightest signal and is easier to see. Fat-suppressed scans show greater enhancement for a given dose of gadolinium chelate and thus are more sensitive for detecting disease.

Another type of fat suppression is known as *chemical shift imaging*. Because protons in fat and water resonate at different frequencies, there are times when the protons in fat and water are in phase and times when they are completely opposed to each other. It is possible to time the imaging to "catch" the protons when they are either in phase or out of phase with each other. If one compares fat–water in-phase and fat–water out-of-phase images and detects a loss of signal for the latter, one can infer that the tissue in question contains some lipid. This is particularly useful in detecting adrenal adenomas, angiomyolipomas, and dermoids, as is described later. Because in-phase and out-of-phase images must be obtained with different pulse sequences, it is often helpful to normalize the signal intensity of the adrenal adenoma to another organ, such as the liver, muscle, or the spleen.

One of the main criticisms of MRI has been that it is too slow and thus motion artifacts degrade the image. It is now possible to obtain MR images during a single breath hold by using a type of scan known as *gradient echo imaging*. Instead of applying a second 180-degree RF pulse after the initial 90-degree RF pulse, magnetic gradients are used to refocus the MR signal. It is now routinely possible to obtain MR images at a rate of 50 to 100 ms per image. This is useful for following a contrast bolus within a renal lesion or in assessing contrast enhancement within a bladder lesion. Even faster imaging may become routinely available with echo planar imaging, or "snapshot" MRI.

Another development in MRI technology is magnetic resonance angiography (MRA). MRA can be used to image the abdominal vasculature, including the aorta and renal arteries and veins. An intravenous bolus of gadolinium chelate is administered and a three-dimensional (3D) acquisition is obtained through the abdomen during a single breath hold (10 to 20 seconds). These images can be reconstructed as projection images much like a conventional angiogram.

Surface coils have enabled high-resolution images to be obtained from targeted areas. The advantage of surface coils is that the signal is unattenuated by distance. Meanwhile, because the signal is collected only from the area of interest and not from the rest of the body, which often acts as an antenna for extraneous RF, signal to noise is further improved. This enhances the signal-to-noise ratio, which in turn can be used to obtain higher-resolution or faster images. Surface coils can be thought of as magnifying lenses for MRI. Endorectal surface coils for prostate imaging are one example of surface coils, but other noncavitary types of surface coils are commonly used for pelvic and renal imaging. Phased-array surface coils are combinations of coils that take advantage of the gain in signal-to-noise ratio afforded by multiple surface coils but allow a wider field of view to be scanned.

It is important to be aware of contraindications to MRI. Patients with pacemakers, implanted infusion pumps, cochlear implants, or any other implanted electronic devices should not be scanned with the device in place because it may be ruined or cause aberrant function. Patients with cerebral aneurysm surgical clips should generally not undergo MRI because these clips can become magnetic and torque. Newer aneurysm clips are MR compatible. Most other surgical clips, heart valves (with the exception of early Starr-Edwards valves), and orthopedic pins and screws are made of nonmagnetic stainless steel and are not contraindications for MRI. Patients with shrapnel imbedded in their bodies may experience movement of the fragment or pain during MRI. A metal worker who has chips of metal lodged in the eye may develop intraocular hemorrhage and blindness and should be evaluated with orbital radiographs before MRI if there is any question of an ocular metallic foreign body. In general, consultation with a radiologist is recommended if there is any doubt about the safety of a device. Claustrophobia is a relative contraindication for MRI but usually can be ameliorated by mild, oral anxiolytics. Because young children (younger than 5 years) usually cannot hold still long enough for an MRI, they must be sedated if adequate studies are to be obtained. There are no contraindications to gadolinium chelate administration except for severe renal dysfunction (creatinine clearance less than 20 mL per minute), in which case dialysis is recommended after use of the contrast. Gadolinium chelates have been used as a substitute for iodinated contrast in conventional x-ray angiography in patients with poor renal function, but there are reports of nephrotoxicity using this direct intraarterial method.

Limitations of MRI include the inability to detect calcification, susceptibility to flow and other motion artifact, and lack of a good oral contrast agent with which to differentiate normal bowel from pathology.

The cost of MRI not only has made it less attractive but also has made it a high-profile target for regulators. With increasing competition in the medical marketplace, MRI has become less expensive. This is achieved by efficiencies in throughput and overhead. Manufacturers are also offering

smaller, less expensive MRI units. As a result, one of the barriers to the use of MRI, its cost, is becoming less of an issue.

ROLE OF MAGNETIC RESONANCE IMAGING IN THE GENITOURINARY TRACT

Kidney

When it was introduced, MRI was not generally considered helpful in the management of most renal masses compared with CT and ultrasound because of severe motion artifacts and nonspecificity (14). However, U.S. Food and Drug Administration (FDA) approval of contrast agents with gadolinium has made MRI more clinically applicable (16). MRI with gadolinium chelate enhancement is directly analogous to CT with iodinated contrast. However, because CT is less expensive and more available, it is still the preferred technique for evaluating parenchymal abnormalities of the kidney. MRI can be substituted for CT when there is a severe iodinated contrast allergy or renal dysfunction (39,91) (Fig. 3E.1, Fig. 3E.2, and Fig. 3E.3). The original gadolinium chelate introduced in 1988 was gadopentetate dimeglumine (GD-DTPA) (Magnevist, Berlex Laboratories); since

1993, two other compounds, gadoteridol (Gd-D03A) (ProHance, Squibb) and gadodiamide (Gd-DTPA-BMA) (Omniscan, Winthrop), have become available in the United States. All of these contrast agents are thought to have the same enhancement properties and offer a very high safety profile. Allergic reactions requiring treatment occur in less than 1% of the population. Gadolinium chelates do not cross-react with iodinated contrast agents, and they are not thought to have the same nephrotoxic potential as iodinated contrast agents, although allergies to both agents can be seen (32). Any patient with a strong history of multiple allergies should be considered at increased risk of reacting to a gadolinium chelate.

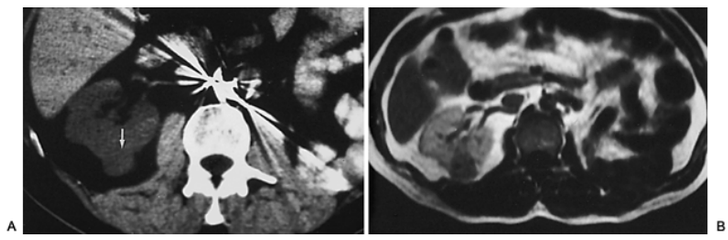

FIGURE 3E.1. A 47-year-old patient with prior nephrectomy for renal cell carcinoma and a severe contrast allergy. **A:** Noncontrast computed tomography (CT) scan 2 years after nephrectomy demonstrated a nonspecific bulge in the posterior kidney *(arrow)*. Because intravenous iodinated contrast media could not be given, a magnetic resonance imaging (MRI) scan was performed with gadolinium. **B:** An enhancing mass corresponding to the lesion seen on CT that proved to be a recurrent renal cell carcinoma.

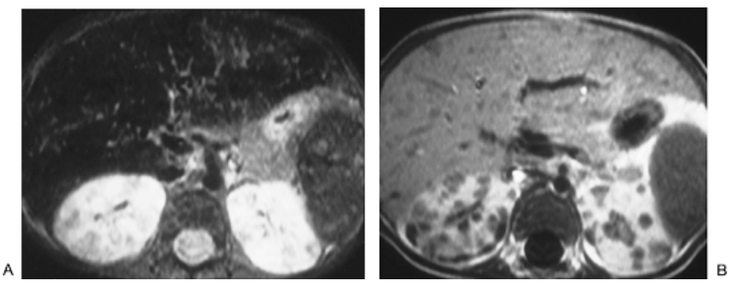

FIGURE 3E.2. Use of gadolinium-enhanced MRI in the presence of renal failure. This patient had been treated for acute myelogenous leukemia and developed fevers. Renal function was significantly diminished (serum creatinine = 2.9 mg/dL). **A:** Noncontrast T_2-weighted scan demonstrates nonspecific heterogeneous signal within the renal parenchyma. **B:** Postgadolinium-enhanced MRI demonstrates multiple distinct filling defects in the kidney and liver. These proved to be fungal *(Candida)* abscesses.

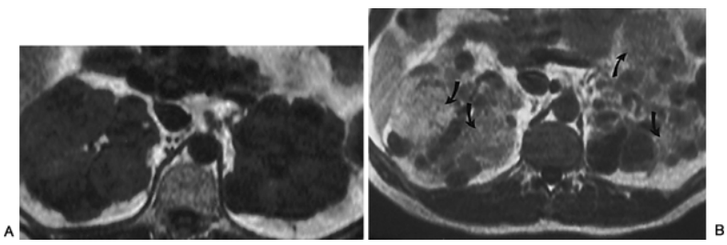

FIGURE 3E.3. Use of gadolinium-enhanced magnetic resonance imaging (MRI) scan for detecting renal masses in renal failure. This 38-year-old patient was thought to have autosomal-dominant polycystic kidney disease. When a family member was discovered to have symptoms of von Hippel Lindau disease, he was reevaluated. Because of his renal failure, gadolinium-enhanced MRI was performed. **A:** Precontrast T_1-weighted image demonstrates enlarged kidneys with a typical appearance of autosomal dominant polycystic kidney disease. **B:** Contrast-enhanced MRI, however, demonstrates multiple areas of enhancement consistent with renal cell carcinomas *(arrows)*. This was confirmed surgically by bilateral nephrectomy and subsequent transplant.

Gadolinium chelates have been proposed as alternatives to iodinated contrast or conventional angiograms in patients with renal dysfunction. Because gadolinium is a heavy metal, it attenuates x-rays sufficiently to be a potential substitute for iodinated contrast. However, this approach should be viewed with caution because renal failure may occur after intraarterial gadolinium chelate administration.

Occasionally, contrast-enhanced CT and ultrasound results are indeterminate or contradictory regarding the type of renal lesion present. A common example is the hemorrhagic cyst, which may be hyperdense on CT and thus difficult to evaluate for enhancement, whereas the ultrasound may demonstrate echogenic debris within the lesion (Fig. 3E.4). MR has better sensitivity for enhancement

within some masses than does CT and can detect small mural neoplasm (Fig. 3E.5). In such cases, contrast-enhanced MRI may be useful as a "tie breaker" study to help guide proper management. The multiplanar capabilities of MRI may also be useful in certain instances when CT and ultrasound may be limited by patient size (Fig. 3E.6).

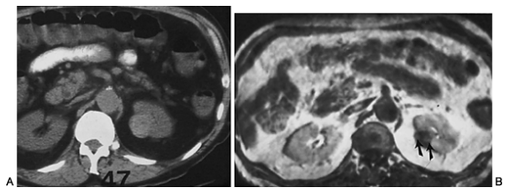

FIGURE 3E.4. Magnetic resonance in the evaluation of indeterminate renal masses. **A:** This hemorrhagic cystic lesion in the left kidney measured 47 HU on computed tomography. Postcontrast scan showed no enhancement. **B:** Postcontrast gadolinium study demonstrates two small nodules of enhancement in the wall *(arrows)* of the lesion, which were foci of low-grade renal carcinoma.

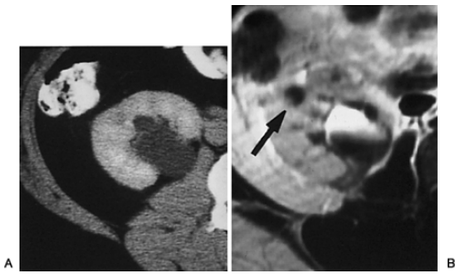

FIGURE 3E.5. The value of magnetic resonance imaging (MRI) in indeterminate renal masses. **A:** Contrast-enhanced computed tomography (CT) scan shows an inhomogeneous renal parenchyma but no definite focal masses. **B:** Postcontrast T_1-weighted image demonstrates a cystic mass in the right kidney with a small mural nodule *(arrow)*, as well as several additional smaller lesions in the parenchyma. The patient had a ureteropelvic junction stenosis, accounting for the dilated renal pelvis. The fluid level in the renal pelvis on the MRI is due to the more concentrated gadolinium layering below the less concentrated (bright), more dilute urine.

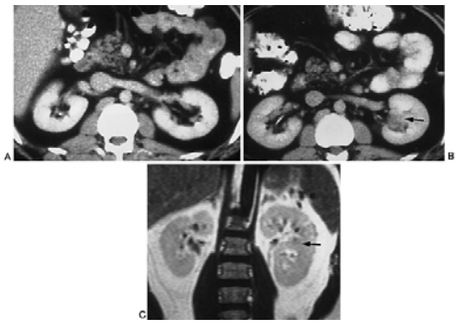

FIGURE 3E.6. Value of the multiplanar capabilities of magnetic resonance imaging (MRI) for renal imaging. **A:** Baseline computed tomography (CT) scan showed normal kidneys. **B:** A follow-up CT scan with intravenous contrast showed what appeared to be a mass in the renal pelvis *(arrow)*. This could not be confirmed with ultrasound. **C:** Coronal MRI of the kidneys with gadolinium enhancement demonstrates a septa of Bertin *(arrow)*, which most likely accounts for findings on this CT scan. No renal mass is identified with MRI.

When an MRI of the kidney is performed for renal masses, a torso-phased array coil should be used to boost signal. It is important that thin-section (5 to 7 mm) T_1-weighted MRI be performed before and after contrast media. This allows the direct measurement of lesion enhancement. The same parameters must be used before and after contrast to enable comparison of signal intensity. Unlike CT density measurements, MR signal intensity units are arbitrary and thus "rules" have not been generated regarding abnormal enhancement. If possible, fat-suppressed T_1-weighted images should be used because of the augmented sensitivity to contrast enhancement with this technique (72,79,80). However, conventional T_1 weighting should not be discarded because fat-saturated scans can hide vascular neoplasms (Fig. 3E.7). Cysts will not enhance and will remain very low in signal intensity, whereas solid lesions, such as renal cancers, will increase in signal intensity after contrast medium administration. Careful attention to the wall of the cyst may reveal a small mural cancer (Fig. 3E.7 and Fig. 3E.8). T_2-weighted MRI should also be performed to detect cysts, which will be very high in signal intensity, but tumors will also tend to be high in signal intensity except for rare cases of tumor or hemorrhage (Fig. 3E.9). MRI cannot differentiate benign oncocytomas and malignant renal cell carcinomas (23). Some authors advocate that serial scanning be performed during breath holding and contrast enhancement to demonstrate the enhancement pattern (22,49), but this is generally not necessary.

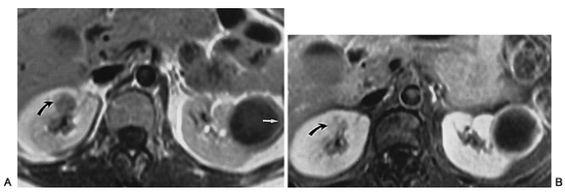

FIGURE 3E.7. The advantage of fat-suppressed T_1-weighted images for detecting enhancement in renal masses. **A:** Conventional contrast-enhanced T_1-weighted image demonstrates a thickened wall of a cystic left kidney *(white arrow)*, but definite enhancement is not seen. A right-sided mass *(curved arrow)* is readily seen in the right kidney. **B:** Fat-suppressed T_1-weighted image after intravenous contrast demonstrates markedly enhanced wall of the cystic mass, which proved to be a renal cell carcinoma. The contralateral solid mass *(curved arrow)* is harder to identify on the fat-suppressed image.

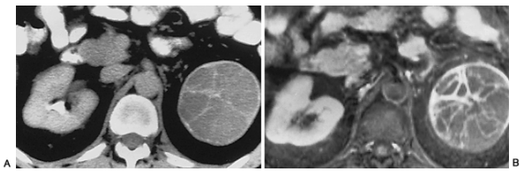

FIGURE 3E.8. The value of fat-suppressed T_1-weighted enhanced magnetic resonance imaging (MRI) for detecting mural enhancement. **A:** Contrast-enhanced computed tomography (CT) scan demonstrates a large cystic mass in the left kidney. It is not evident how much enhancement there is in the wall of the mass. **B:** Fat-suppressed T_1-weighted image after gadolinium enhancement demonstrates markedly enhanced irregular walls of the cystic mass, suggesting a malignancy. This lesion proved to be a cystic renal cell carcinoma.

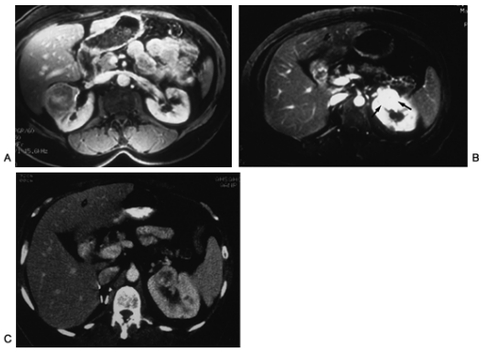

FIGURE 3E.9. Gadolinium-enhanced magnetic resonance imaging (MRI) contrasting a hypovascular and a hypervascular tumor. **A:** Hypovascular solid renal mass is easily seen on this fat-suppressed gadolinium-enhanced MRI. **B:** Hypervascular mass *(arrows)* in another patient is more difficult to see on this dynamic enhanced fat-suppressed MRI. **C:** The computed tomography (CT) scan of the lesion in **B** readily depicts the lesion. Lesions tend to enhance more on MRI than on CT.

Another application of renal MRI is in staging renal cancers for venous invasion. Enhanced CT can be equivocal with respect to caval thrombus due to streaming of contrast media in the inferior vena cava (IVC) during a bolus of iodinated contrast media. MRI can be used to detect thrombi within the renal veins and IVC when the CT is equivocal (56). MRI has proven to have a 90% to 100% positive predictive value for tumor thrombus in the IVC (Fig. 3E.10, Fig. 3E.11, and Fig. 3E.12) (1,27,29,37,61,78). MRI often cannot differentiate stage I from stage II renal cancers, although this is not a clinical problem. Extrinsic compression of the IVC due to bulky adenopathy may make assessment of thrombus difficult (36). Depending on the imaging technique, either the normal-flowing blood can have a low signal intensity with the tumor thrombus intermediate in signal or the normal-flowing blood can be high in signal intensity with tumor thrombus appearing as a low-signal defect (Fig. 3E.10). Scans should be obtained in all three planes to ensure that the IVC is fully evaluated; flow artifacts can cause false-positive results if only one plane is used. MRI can be used for nonneoplastic causes of renal vein thrombosis, such as with glomerulonephritis or lupus nephritis. MRI is also useful in identifying potential adjacent organ invasion, including the liver, pancreas, and

spleen. The bones should always be evaluated on the sagittal image because MRI may be more sensitive than bone scan for detecting early bone metastases in the spine (40).

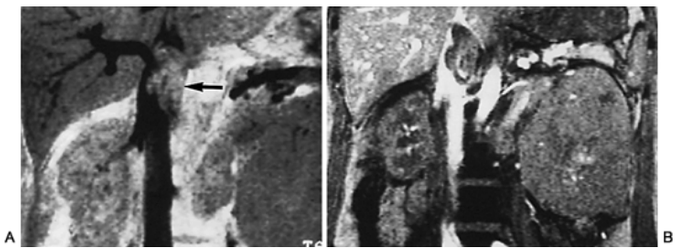

FIGURE 3E.10. Two techniques for identifying tumor thrombus within the inferior vena cava. **A:** There is a large left-sided renal mass. A tumor thrombus *(arrow)* is identified within the inferior vena cava. Because of the spin-echo technique used, the flowing blood appears dark and the tumor thrombus is relatively higher in signal intensity. **B:** When a gradient-echo technique is used, the flowing blood becomes bright in signal intensity, whereas the tumor thrombus is dark. Either technique can be used for detecting a thrombus within the inferior vena cava.

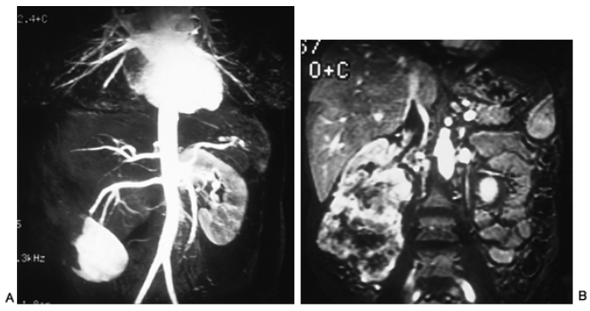

FIGURE 3E.11. New methods of staging renal cancers with magnetic resonance imaging (MRI). **A:** Magnetic resonance angiogram (MRA) of a patient with a large right renal cancer demonstrates the elongation of the right renal artery and extrarenal branching of this vessel. **B:** Delayed MRA from another case demonstrates filling defect in the inferior vena cava arising from the right renal cancer. The absence of enhancement within the thrombus distally (bland thrombus) contrasts with the more proximal portion of the thrombus that shows enhancement.

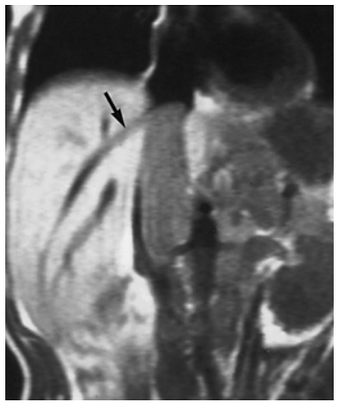

FIGURE 3E.12. Inferior vena caval thrombus caused by large left-sided renal cell carcinoma. T_1 coronal magnetic resonance imaging demonstrates a large thrombus within the inferior vena cava with extension of the thrombus into the right hepatic vein *(arrow)*.

MRI is useful in detecting fat within angiomyolipomas (AMLs). CT demonstrates fat within an AML, which is diagnostic, but occasionally the fat may be obscured by previous hemorrhage or may not be visible. T_1-weighted images obtained before and after fat suppression will confirm that the mass is an angiomyolipoma if it contains fat, but neither CT nor MRI can differentiate a nonfatty AML from a renal cancer.

Renal lymphoma is often a multifocal process and can result in renal insufficiency (39). Noncontrast CT and ultrasound can be insufficient to identify renal lymphoma; however, MRI with gadolinium chelate enhancement will readily demonstrate the multiple masses within the renal parenchyma typical of renal lymphoma (Fig. 3E.2). In fact, this technique is readily applied to any patient with a parenchymal defect caused by renal infection, hemorrhage, or infarct (44) (Fig. 3E.13).

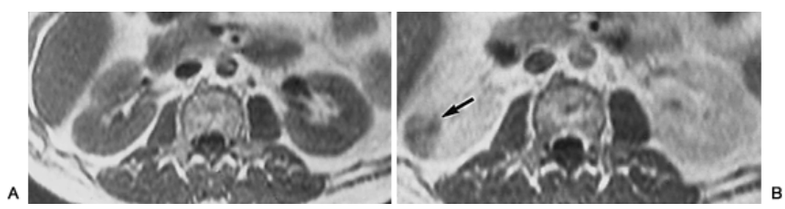

FIGURE 3E.13. Role of magnetic resonance imaging (MRI) in detecting renal infection in an immunocompromised patient. This patient was immunocompromised as a result of aplastic anemia. Previous exposure to nephrotoxic antibiotics had impaired his renal function. **A:** Precontrast T_1-weighted image shows no detectable abnormality. **B:** Postcontrast T_1-weighted image demonstrates a focal defect in the periphery of the right kidney *(arrow)*. Subsequent percutaneous biopsy demonstrated cryptococcus.

The evaluation of renal arteries by MRA is an important application of MRI. Sensitivity for renal artery stenosis varies from 90% to 100% overall to 90% for proximal renal artery and 82% for branch renal artery stenosis. Several studies have shown MRA to be a highly accurate method of detecting main renal artery stenosis (6,25,28,59). Although this technique is sensitive, it may overestimate the degree of stenosis because of flow-related artifacts (Fig. 3E.14). Because renal MRA is noninvasive, it is the preferred method of diagnosing renal artery stenosis and is more reliable than Doppler ultrasound. It is now possible to measure renal arterial velocity directly from an MR angiogram using phase-contrast MRA (6,52,76).

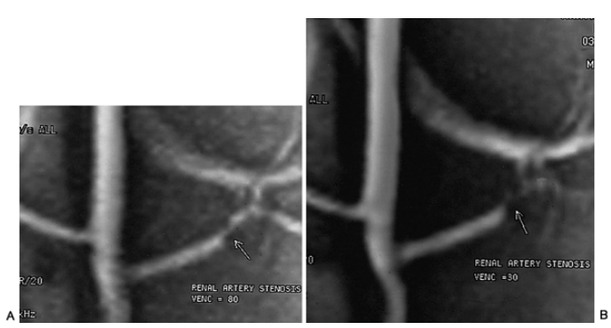

FIGURE 3E.14. Renal artery stenosis *(arrows)* detected with magnetic resonance angiography (MRA). **A:** This stenosis is demonstrated by MRA using appropriate parameters (VENC-80). **B:** Using other parameters (VENC-30), the stenosis appears more severe than it actually is.

One particularly useful application of MRA is in the renal transplant recipient, in whom renal arterial anastomotic stenosis is common (54,63). MRA is particularly well suited for these patients because surface coils can be used, which increase the available signal, thus permitting high-resolution images. Moreover, the use of iodinated contrast media is often contraindicated in patients with poorly functioning renal transplants. MRI can provide information about the integrity of the renal transplant parenchyma, obstruction of the ureter, and perinephric collections (31,33). Gadolinium chelate–enhanced imaging is useful in this setting to document renal infarctions and focal lesions such as tumors and infections. MRA can also be used to evaluate potential living related donors

for vascular or parenchymal abnormalities before transplantation (3,64).

Adrenal

CT is the best method of evaluating the adrenals based on its sensitivity and availability (49). Often, however, CT findings are nonspecific, and MRI can then be used to characterize the features of an adrenal mass to determine if it is malignant (26). MRI of the adrenal gland may be particularly useful in confirming the presence of pheochromocytomas and in differentiating adrenal adenomas from metastatic disease.

Pheochromocytomas are often cystic and contain large amounts of free water. This is easily recognized as a high-signal-intensity mass on T_2-weighted images (55,95) (Fig. 3E.15). Naturally, not all pheochromocytomas are very high in signal intensity; hemorrhage within the tumor can cause lower signal intensity on T_2-weighted images (51). Nevertheless, the high-signal appearance of most pheochromocytomas and paragangliomas makes MRI useful for quickly identifying adrenal and ectopic sites of pheochromocytoma. Metaiodobenzyl guanidine (MIBG) studies are often more difficult to obtain and interpret. Other sites of paragangliomas, such as the organ of Zuckerkandl, the retroperitoneum, the bladder, the carotid bulb, and the jugular foramen, are also well suited to the multiplanar capabilities of MRI. Thus most pheochromocytomas, regardless of location, can be identified by MRI. Many other pathologic processes can have high signal intensity on T_2-weighted MRI,

including metastases and cysts; however, these can usually be distinguished by the clinical setting (Fig. 3E.16). If bilateral or ectopic pheochromocytomas are discovered, a hereditary cause such as multiple endocrine neoplasia (MEN) II, MEN III (MEN IIb), von Hippel Lindau, or neurofibromatosis must be considered (66) (Fig. 3E.17). Neumann and co-workers (66) have shown that hereditary forms of pheochromocytoma occur more frequently than previously thought among patients with apparently sporadic pheochromocytomas. MRI can be helpful when retroperitoneal surgical clips obscure evaluation on CT (Fig. 3E.18).

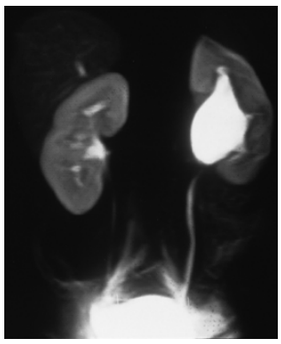

FIGURE 3E.15. A magnetic resonance urogram demonstrating a left ureteropelvic junction narrowing and hydronephrosis. This image was acquired using a fast T_2-weighted breath-hold scan.

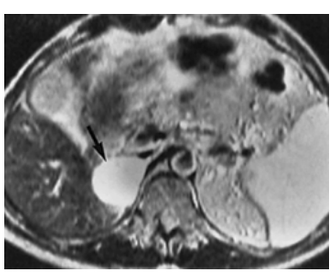

FIGURE 3E.16. High-signal-intensity adrenal mass not representing a pheochromocytoma. This T_2-weighted image demonstrates a very-high-signal-intensity lesion in the right adrenal gland. There is no clinical or chemical evidence of a pheochromocytoma. This patient had melanoma with metastases to the right adrenal gland.

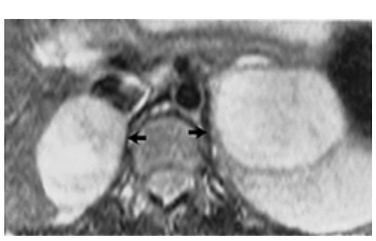

FIGURE 3E.17. Bilateral pheochromocytomas in a patient with MEN IIb syndrome. This young woman experienced hypertensive crisis during childbirth. Subsequent workup revealed bilateral pheochromocytomas *(arrows)* on T_2-weighted magnetic resonance imaging. Bilateral pheochromocytomas are usually associated with hereditary forms of pheochromocytoma.

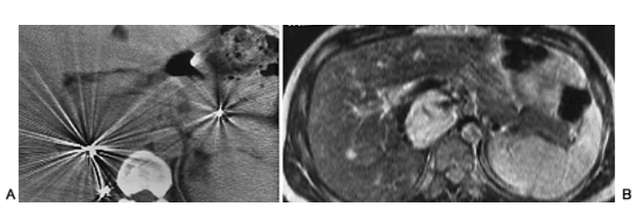

FIGURE 3E.18. The advantage of magnetic resonance imaging (MRI) in detecting retroperitoneal lesions when multiple surgical clips are present. This patient had resection of adrenal carcinoma several years before. **A:** Multiple clips obscure the retroperitoneum on this precontrast computed tomography (CT) scan. **B:** T_2-weighted image demonstrates a recurrence adjacent to the inferior vena cava. The MRI is less influenced by surgical clip artifact than is the CT.

Adrenal adenomas and adrenal metastases are common findings on CT, yet it is difficult to separate one from the other on the basis of CT alone. One important parameter is lesion size. Lesions smaller than 2 cm are more likely to be benign, but size alone is not sufficient to predict behavior (57). The adrenal adenoma contains intracellular lipid because it is composed of cortical tissue, which produces and stores steroid-based hormones. Thus low-density (less than 10 Hounsfield units [HU]) measurements on CT within a small (less than 2 cm) mass are virtually diagnostic of an adenoma (49,50,94). Very-low-density measurements (less than -10 HU) suggest a myelolipoma. However, many adenomas are greater than 15 HU in density. Metastatic lesions to the adrenals usually do not contain lipid but are generally high in extracellular water due to the leakiness of neoplastic vessels. The differences in histology and physiology can be exploited with several different strategies, each of which focuses on signal intensity differences between the tightly packed lipid-containing cells of adenomas and the loosely packed cells with a relatively large amount of extracellular water of metastases. The original attempts to differentiate these two entities with MRI included the ratio of signal intensity of the mass to that of the liver or fat on T_2-weighted images (12,70). Adenomas tend to have a low adrenal mass-to-liver signal ratio, whereas metastases tend to have a higher ratio. However, considerable overlap exists using these techniques (9,94). Another technique is to use dynamic enhanced MRI during rapid contrast media infusion (48). Metastases enhance at a much faster rate and attain higher-signal-intensity changes than adenomas. Although this technique appeared to be successful in one study, dynamic enhancement has not been widely applied (48,85).

Mitchell and associates (60) showed that reliable differentiation of adrenal adenomas and metastases could be achieved using chemical shift MRI. In this technique, fat- and water-bound protons are imaged with in-phase and out-of-phase scans. If the signal intensity of the adrenal mass decreases on the out-of-phase image relative to the in-phase image, the lesion contains lipid and therefore represents an adenoma (Fig. 3E.19). Lesions that show either no change or an increase in signal within the mass on the out-of-phase image do not contain lipid and therefore are more likely to be malignant. Initially, this technique was reportedly almost 100% accurate (60,93); however, subsequent data have shown some overlap between adenomas and metastases (15,47,70,85). Nevertheless, the chemical shift technique appears to be the most successful strategy for separating adenomas and metastases by MRI (82). Lesions deemed to be adenomas by MRI deserve follow-up until this technique is more established. Advocates of MRI argue that MRI is at least as effective as percutaneous adrenal biopsy and does not carry with it the 2% to 10% complication rate of adrenal biopsy (11,81,82,92). Of course, additional functional assessment for a chemically active adenoma is useful in identifying benign but functional lesions that should be removed (18).

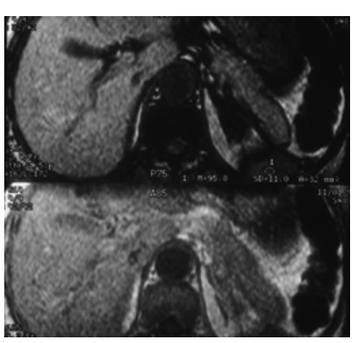

FIGURE 3E.19. Chemical shift magnetic resonance imaging to determine that an adrenal mass is benign. *Top image* is an out-of-phase T_1-weighted scan that demonstrates a low-signal left adrenal mass. *Bottom image* shows an increase in signal in the same lesion when scanned with an in-phase T_1-weighted scan. The decrease in signal within the left adrenal mass is highly suggestive of a benign process such as an adrenal adenoma or hyperplasia.

Ureter and Bladder

MRI of the ureter is now possible, although it does not yet have the resolution of plain film radiography. In MR

urography, strongly T_2-weighted scans are obtained through the ureters in the coronal plane (4). Alternatively, T_1-weighted scans are obtained after low-dose administration of gadolinium chelates with a small dose of furosemide (Lasix) to enlarge the ureter (67). Stenoses, obstructions, and filling defects caused by stones or tumors can be seen with these techniques. They are especially useful in pediatric and pregnant patients, in whom exposure to ionizing radiation is undesirable (7). MR urography provides a noninvasive method of surveying the ureters for causes of hematuria.

A routine role for MRI in bladder disease has not been established. MRI is clearly not as good as cystoscopy for diagnosing bladder tumors or evaluating hematuria. MRI has been used to document tumors within diverticula, to characterize suspected intravesical pheochromocytomas, and to aid in the identification of urachal tumors.

MRI has been suggested as a method for staging bladder cancer invasion of the bladder wall (10). Assessment of tumor invasion is currently limited by sampling error and accuracy, especially in the assessment of extravesical extension. It has only recently become pragmatic even to consider bladder cancer staging by MRI because the spherical nature of the bladder means that there are an infinite number of planes perpendicular to the bladder wall. To obtain truly perpendicular sections at all points in the bladder requires 3D imaging, which has now become feasible (5). One of the major improvements in bladder MRI was the use of pelvic phased-array coils, which boost the available signal significantly. With a 3D data set, the bladder wall can be “sectioned” in any plane perpendicular to the bladder wall at the tumor site (Fig. 3E.20). Thus the depth of muscle invasion becomes possible to measure. Fat-suppression techniques have also proven useful in identifying invasion of the perivesical fat.

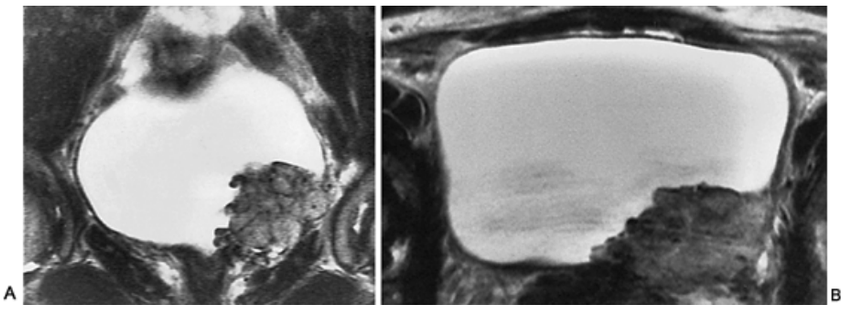

FIGURE 3E.20. Transmural invasion of bladder tumor using phased-array surface coils. **A:** A coronal T_1-weighted magnetic resonance imaging (MRI) demonstrates a papillary mass within the base of the bladder with extension outside the bladder wall. **B:** Axial T_1-weighted MRI demonstrates the extent of the mass through the wall in another plane.

Several different methods of assessing the bladder wall for tumor invasion have been suggested. Highly T_2-weighted images of the bladder wall demonstrate a trilayer appearance to the bladder wall corresponding to the mucosa, submucosa-lamina propria, and muscularis layers. The degree of disruption of these bands can be used to indicate the depth of tumor invasion and is accurate in 73% of patients (5). The other method of assessing bladder wall invasion is with dynamic enhanced MRI, which is performed after a bolus injection of a gadolinium chelate contrast agent. Normally, after contrast administration, an enhancing

trilayer appearance is seen corresponding to the three layers seen with T_2 weighting. The layers are disrupted to varying degrees by the invading tumor (5,62,83,86,89). This technique has achieved greater than 90% accuracy in some centers (5) (Fig. 3E.21).

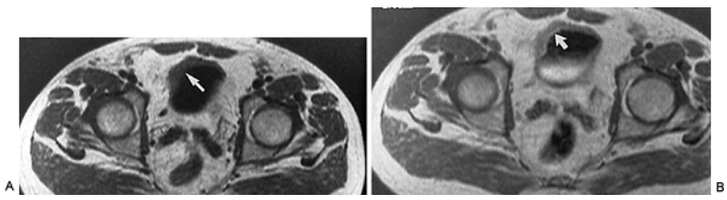

FIGURE 3E.21. The use of gadolinium enhancement to detect bladder wall tumors. **A:** Precontrast T_1-weighted magnetic resonance imaging scan demonstrates a thick rind of bladder tumor against the anterior lateral wall *(arrow)*. **B:** Postcontrast enhancement demonstrates enhancement of the tumor with small projections into the perivesical fat. The mucosal surface of the tumor is enhanced to a greater extent than the transmural component of the tumor.

The major limitation of MRI for local staging is that microscopic disease cannot be detected. The clinical importance of this is uncertain, but it lessens the accuracy of MRI staging. Also, tumors at the bladder outlet can be difficult to evaluate because the anatomy of the layers of the bladder wall is somewhat different at this site. Nevertheless, overall, extravesical extension is detected with a sensitivity of approximately 93% (65,86). Endorectal surface coils and phased-array surface coils placed on the low pelvis have been used to improve the signal-to-noise ratio and hence the resolution of the images. Conventional body coil MRI is used to detect lymphadenopathy; however, MRI is no more accurate than CT for assessing adenopathy because both modalities depend on changes in size as the criterion for positivity. As is well known from CT, nodes may be enlarged by hyperplastic changes, and small nodes may be infiltrated with tumor.

A recent development in MRI has been the dynamic assessment of pelvic floor relaxation. In this study, a rapid T_2-weighted image is obtained sagittally through the bladder base, uterus, and rectum at rest and then again during a straining maneuver (97). Cystoceles, uterine prolapse, rectal prolapse, and enteroceles are surprisingly well seen without having to resort to cystoproctolography, which is an uncomfortable and embarrassing procedure (53,96). The MR procedure is equally applied in men and in women, although it is usually a greater clinical issue in women because it is associated with incontinence (17,30,58).

Prostate

MRI of the prostate offers the possibility of accurate local staging of prostate cancers. With sufficient resolution, it is possible to visualize the neurovascular bundle and prostatic capsule with reliability. Results with whole body coil imaging, however, were disappointing, and it became clear that endorectal coils were needed for accurate staging (43,71). With the advent of endorectal surface coils, prostate MRI became a feasible method of staging local spread of prostate cancer. The endorectal coil allows a significant gain in signal-to-noise ratio, which permits high-resolution images. Thus fine detail of the prostatic surface and internal anatomy can be obtained (Fig. 3E.22, Fig. 3E.23, and Fig. 3E.24). Initial reports demonstrated a very high sensitivity for extracapsular disease versus localized disease (75); however, a subsequent multiinstitutional trial has had difficulty reproducing these results (69,90). As more experience has been gained it has become clear that MRI is useful in specific instances in which the risk of extracapsular disease is high based on prostate-specific antigen (PSA) and tumor grade (46).

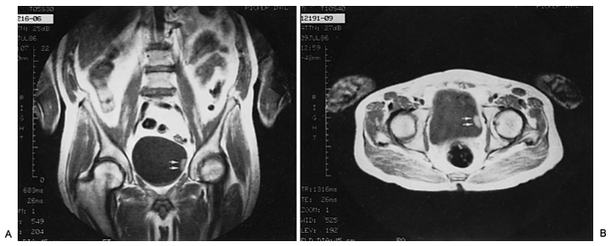

FIGURE 3E.22. Superficial bladder cancer on T_1-weighted magnetic resonance imaging. The small tumor *(double arrows)* is seen in the coronal **(A)** and axial **(B)** planes. Note that the bladder wall is undisturbed and there is no evidence of transmural invasion. No adenopathy is present. The natural contrast between the tumor and the urine in the bladder allows the tumor to be delineated.

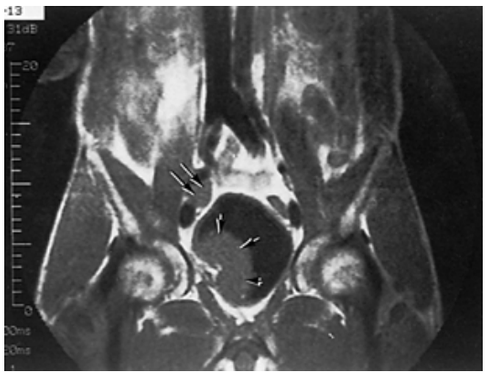

FIGURE 3E.23. Coronal T_1-weighted magnetic resonance imaging scan of large muscle invasive bladder cancer *(short arrows)* and tumorous pelvic lymph node *(long arrows)*.

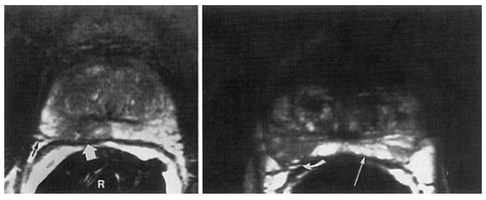

FIGURE 3E.24. Endorectal coil magnetic resonance imaging scan showing stage B prostate cancer. A transverse section demonstrates the thick Denonvilliers' fascia *(white arrows)*. The tumor, which is low in signal intensity, can be seen in the background of the high-signal-intensity peripheral zone. The neurovascular bundle *(black arrow)* is spared. R, rectum. (Courtesy of Dr. Ronald M. Summers, NIH.)

To be successful, prostate MRI must be performed with an endorectal surface coil, which is inflated in the rectum with 60 to 100 mL of air and with a phased-array pelvic coil placed anteriorly on the pelvis (42). Glucagon (1 mg intramuscularly) is administered to reduce bowel motion. T_2-weighted images must be obtained with the highest resolution (3 to 4 mm thick with the smallest possible field of view). Field of view must be limited, and a large matrix size must be used. Axial and oblique coronal views through the prostate long axis should be obtained. Contrast enhancement, especially when applied dynamically, is useful in some instances (84,88).

T_2-weighted axial endorectal coil images and oblique coronal T_2-weighted images allow the apex to be evaluated more fully. Scanning should be extended through the seminal vesicles on both planes. T_1-weighted body coil images should be obtained through the pelvis to detect lymphadenopathy. As with bladder cancer, the criterion for lymph node involvement on MRI is increased size, which has well-known limitations.

The normal T_2-weighted image of the prostate demonstrates a high-signal peripheral zone with a central hypointense region corresponding to the central gland (central and transitional zones). The urethra is often high in signal intensity because of the presence of small amounts of urine and glandular tissue in the prostatic urethra. The central gland is surrounded by a hyperintense peripheral zone, which is the site of most prostate cancers. The posterior median raphe in the peripheral zone is often hypointense. Surrounding the peripheral zone on all but the posterior wall is the high-signal periprostatic venous plexus (Santorini's plexus), which serves as a marker for the margin of the prostate. The neurovascular bundles are seen at approximately the 5 and 7 o'clock positions on the axial views. Denonvilliers' fascia is seen as a thick low-signal band between the prostate and rectum (Fig. 3E.24). The seminal vesicles appear as multiple locules of high signal intensity above the prostate. The vas deferens are thick-walled structures medial to thin-walled seminal vesicles.

Prostate cancers appear as areas of relative hypointensity compared with the peripheral zone (68) (Fig. 3E.25). Of course, this appearance is not universal. Several hyperintense prostate cancers (mucinous adenocarcinoma) have been reported; moreover, hypointense lesions can represent biopsy artifact, hyperplasia, infarction, and other nonneoplastic disorders. To avoid a potentially misleading biopsy artifact, MRI should not be performed within 3 weeks of a biopsy.

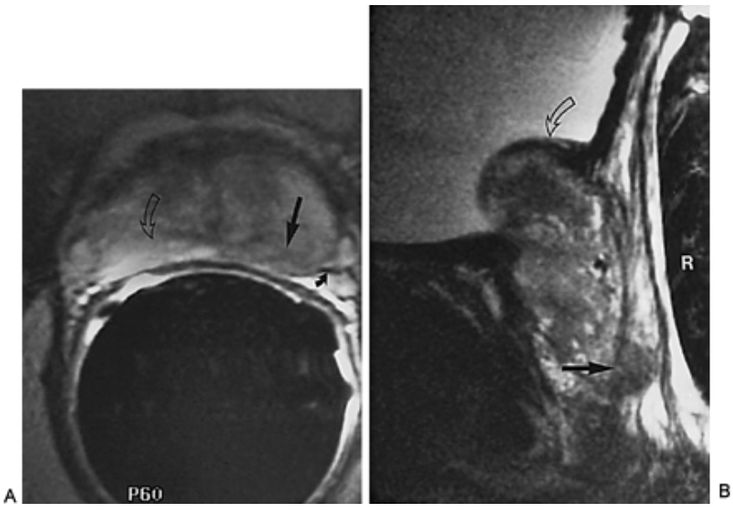

FIGURE 3E.25. Endorectal coil magnetic resonance imaging scan showing T_3 prostate cancer. **A:** The transverse image demonstrates the hypointense tumor *(black arrow)* involving the left prostatic hemisphere. The tumor abuts and involves the neurovascular bundle. *Curved arrow* demonstrates normal peripheral zone. **B:** Sagittal view demonstrates the bulging of the capsule *(straight arrow)* from the tumor. Prostatic hyperplastic nodules are seen within the bladder base *(curved arrow)*.

The seminal vesicles, normally high in signal intensity, become focally hypointense when involved with tumor on T_2-weighted images. However, this can be mimicked by epithelial hyperplasia of the glandular lining of the seminal vesicle or by atrophy. Thus hypointense seminal vesicles are suspicious but not absolutely diagnostic of extracapsular extension. Contrast-enhanced MRI may show areas of tumor, which should enhance while benign entities remain low in signal intensity (84).

The reported accuracy of endorectal coil imaging varies from 51% to 82% depending on patient mix and experience (69,90). Overall, the staging accuracy is approximately 68% to 70% in most studies (13,69). Most staging errors with MRI occur from understaging, which will not deny patients potentially curative surgery. False-positive studies are unusual but are more problematic because they would deny potentially curative surgery. Another issue is that intraobserver disagreement occurs with some frequency using endorectal coil MRI, and proper training is essential before these studies begin to yield clinically useful data (35,73). However, with improvements in MRI technique it is expected that image interpretation will become more uniform and reliable. For instance, accuracy can be greatly improved by using a computer-based algorithm that considers both MR and clinical features of the patient. MR has also been proposed as a method of guiding placement of brachytherapy seeds (19). MR spectroscopy (MRS) has recently been proposed as a diagnostic technique. There is a growing recognition that extracapsular disease per se is not necessarily a contraindication to radical prostatectomy (46,74). Better methods of determining inherent biologic aggressiveness of tumors are being sought. One method, MRS, is based on the metabolic signature of cancers relative to the rest of the prostate. Using ^1H spectroscopy, the normal prostate is unusually rich in citrate and choline. Cancers are lower in citrate, resulting in abnormal choline-to-citrate ratios. Data indicate that the magnitude of substrate ratios such as choline to citrate reflects the biologic

aggressiveness independent of other factors such as PSA and Gleason score.

Testicle

MRI does not currently have a routine role in the evaluation of testicular disease. This is because of the combined success of physical examination and testicular sonography for diagnosing the most testicular diseases. There is experimental evidence that MRI may be useful in the evaluation of testicular torsion and neoplasia. However, it is unlikely that MRI will be a mainstream test for these indications.

The testicles are normally very bright on T_2-weighted images. Testicular MRI must be performed with surface coils to achieve high-resolution images. Tumors are even more hyperintense but often are heterogeneous in signal intensity. Cysts and dilated rete testis will be uniformly hyperintense on T_2-weighted images. Therefore MR is useful when the differential consideration of a testicular ultrasound is dilated rete testis versus a neoplasm. Testicular tumors enhance significantly with intravenous contrast media, but the appearance on MRI is nonspecific regarding histology (21). MRI may be valuable in local staging of the scrotum because small disruptions of the tunica albuginea may be missed on ultrasound and physical examination. However, MRI does not contribute sufficient information to be justified routinely.

Dynamic enhanced testicular MRI has been used to evaluate testicular ischemia in animals. Enhancement is very delayed or absent on the torqued side, and time activity curves analogous to the radionuclide scan can be obtained (20). Delayed washout of the contrast medium may be related to venous compression. Better anatomic detail is possible with MRI than with sonography, and the torqued spermatic cord can be directly visualized. Advantages of MRI are that it does not require radiation, it can provide a semiquantitative assessment of perfusion, and it may provide more information about the viability of the testicle than either nuclear medicine or color-flow Doppler studies. Disadvantages include its cost, limited availability on an emergency basis, and requirement for intravenous contrast.

Penis

The anatomy of the penis is readily depicted on MRI (38). On T_1-weighted images, the corpora are relatively low in signal. The corpora are high in signal intensity on T_2-weighted imaging. The urethra is not seen unless a Foley catheter is in place (Fig. 3E.26). Absence of a high signal within the corpora can be seen in thrombosis associated with priapism (45,77) (Fig. 3E.27). The plaques of Peyronie's disease can also be detected with MRI and can be used to guide and monitor treatment (34,87). Fractures of the

penis, in the setting of pelvic crush injuries, can be evaluated for surgical repair using MRI (2,8,24).

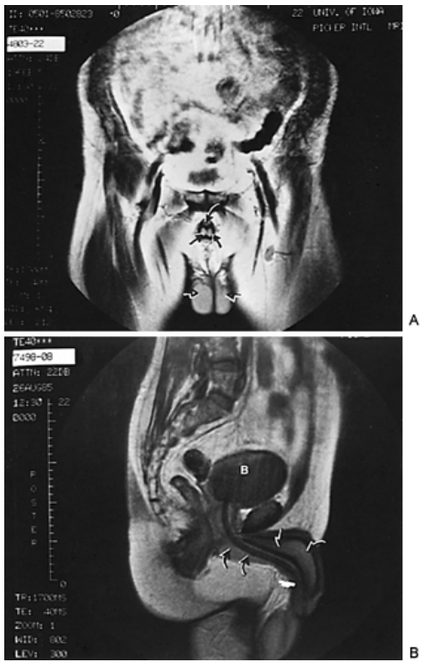

FIGURE 3E.26. A: Coronal T_1-weighted magnetic resonance imaging (MRI) scan of normal pelvis showing corpus spongiosum *(curved arrow),* corpora cavernosa *(straight arrows),* and testicles *(open arrows).* **B:** Sagittal T_1-weighted MRI of normal pelvis showing corpus cavernosum *(straight arrow)* and bulbocavernosus muscle *(curved arrows).* There is a catheter in the bladder (B).

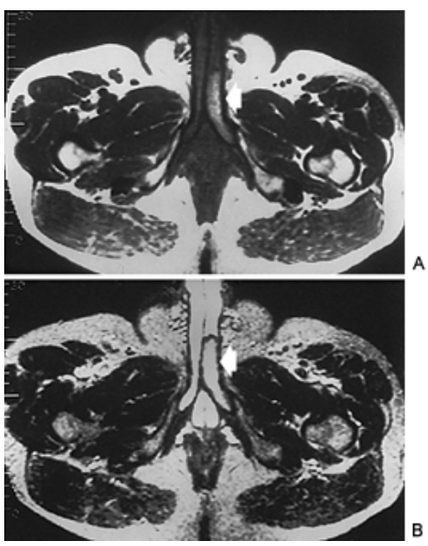

FIGURE 3E.27. Partial penile thrombus with priapism. **A:** T_1-weighted image demonstrates a high-signal-intensity thrombus *(arrow)* within the left corpora cavernosa. **B:** T_2-weighted image demonstrates a high-signal-intensity rim. (Reprinted with permission from Kimball DA, Yuh WTC, Farmer RM. MR diagnosis of penile thrombus. *J Comput Tomogr* 1988;12:604.)

Investigators have evaluated the potential of dynamic enhanced MRI for determining the cause of erectile dysfunction (41). They have found delayed enhancement of corpora in patients with arterial insufficiency. Valvular disease results in a rapid washinn and washout of contrast media (41). The future of penile MRI for erectile dysfunction will depend on the success of procedures to correct erectile dysfunction.

MAGNETIC RESONANCE IMAGING IN THE FUTURE

There are several exciting trends in MRI. MR technology continues to improve in total imaging time, spatial resolution, and flexibility. Recently, determination of the functional status of organs has become possible with dynamic enhancement or changes in perfusion. Focus is now directed at the brain because it is the most straightforward organ to assess, but functional studies may soon be directed at other organs, including the kidneys and testicles. This may affect the assessment of renal function and primary testicular infertility. MRS may also prove to be a useful diagnostic tool.

Open-bore magnets that decrease patient anxiety but also allow for invasive procedures under MRI are widespread. These may permit biopsy or even operative procedures to be performed with real-time MR guidance. The quality of open-bore magnets has greatly improved, although the flexibility of such units remains limited.

New contrast agents are being developed to improve the tissue specificity of MRI. Such agents may be able to

distinguish malignant and benign nodes noninvasively. Ultrasmall iron dextran particles already have shown promise in this area in animals. Tissue-specific antibody imaging may also be possible. The goal of this research is to improve the tissue specificity of MRI and allow noninvasive “MR biopsies” to be reliably performed, and this continues to be an active area of research.

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3F VASCULAR IMAGING

J. Bayne Selby Jr.

Part of "3 - IMAGING "

J.B. Selby, Jr.: Department of Radiology, Medical University of South Carolina; Vascular/International Radiology, Medical University Hospital, Charleston, SC 29425.

The dramatic advances that have occurred in radiologic imaging techniques over the last 20 years make it difficult for editors of textbooks to decide what is worthy of inclusion and what should be discarded. The solution in this chapter was to give different imaging modalities used for urologic investigations their own section. This works fine until one addresses imaging of urology conditions that have a predominantly vascular basis. The current state of imaging in regard to vascular disease can at times require the use of any or all of the different modalities. Angiography, still the gold standard for visualization of vascular issues, is being rapidly supplemented by computed tomographic angiography (CTA), magnetic resonance angiography (MRA), color Doppler ultrasound, and nuclear medicine. With the current emphasis on cost containment, efficient workups, and clinical pathways, trying to determine when and where to use each of these modalities can be perplexing. This chapter attempts to define the strengths and weaknesses of each imaging technique by approaching the subject from a clinical question standpoint. Technical descriptions of the different modalities, except for angiography, are covered in other chapters.

TECHNIQUE OF ANGIOGRAPHY

The basics of angiography have not changed since Seldinger (22) described his technique for percutaneous puncture of the common femoral artery in 1953. However, the tools have undergone significant improvements, with a resultant increase in success rates and decrease in complications. Although angiography is still an invasive procedure compared with ultrasound or computed tomography (CT), this fact alone should not prevent a patient from having an angiogram if indicated. Most series quote the incidence of serious complications from angiography in the range of 0.5% to 2.5% (14,23,24); however, these studies were all done before 1980, when catheters were larger and stiffer, fluoroscopic visualization was inferior to that available today, and digital subtraction angiography had not been developed. In addition, nonionic contrast was not available at that time. No large series of complications from angiography have been published recently, but it is reasonable to assume that the basic procedure is safer than it was 25 years ago.

The most important aspect of preprocedure evaluation of the patient is assessment of renal function. The amount of contrast material used for a study is usually not an issue in otherwise healthy individuals, but diabetic patients and patients with impaired renal function are more susceptible to acute renal failure (4,5,10,17). A baseline creatinine level

should always be obtained and any recent trends noted. The risk of acute renal failure is greater in someone with a creatinine of 2.5 mg/dL that has been rising over the last week than in a patient who has been stable at that level. There is no clear consensus on whether bleeding parameters should be checked, although the majority still check prothrombin time, partial thromboplastin time, and platelets. Anyone with a history of bleeding tendencies should have appropriate laboratory studies. Most angiographers require an international normalized ratio of less than 1.5 before proceeding with angiography.

In the past, most patients were admitted to the hospital the night before a procedure. This is no longer true unless the patient happens to already be an inpatient. Therefore particular attention must be paid to adequate hydration before the study (7). Outpatient angiography is now common. Outpatients usually arrive early in the morning, are evaluated, receive an intravenous catheter and groin preparation, and are then taken to the angiography suite.

The procedure is usually performed using conscious sedation such as midazolam and fentanyl, as well as local anesthesia at the arterial puncture site. Sterile preparation and drape is observed. Access is obtained through either common femoral artery. If the femoral arteries are unavailable for any reason, angiography can be performed from an axillary artery approach. Translumbar aortography is no longer performed. Nonionic contrast material is nearly always used in angiography. The risk of contrast reaction is much less. There is currently debate over whether nonionic contrast carries a lower risk of nephrotoxicity. This is covered in more detail in other chapters. Carbon dioxide and gadolinium are sometimes used as contrast agents in patients with severely compromised renal function (2,12,26). Procedures are most often performed using a 5-Fr catheter. For many interventions, microcatheters, which can be placed through a 5-Fr catheter, are used.

After the procedure is completed, the catheter is removed from the groin and pressure is held for approximately 15 minutes. Historically, patients had to lie flat with their legs straight for 6 hours after the procedure, but many sites now allow patients to ambulate earlier. Also, a number of percutaneous closure devices have recently become available. These devices act by using either a suture or a collagen plug to obtain immediate hemostasis. As more experience is gained with these devices, the recovery period will continue to shorten.

As mentioned earlier, many imaging techniques can be used to aid in the diagnosis and treatment of vascular-related problems. The remainder of this chapter provides guidance on the appropriate use of various imaging modalities in a number of common clinical problems. This is not meant to be a thorough discussion of each entity because these are covered in later chapters.

RENOVASCULAR HYPERTENSION

It is fair to say that this is one area where the treatment of the disease has progressed more rapidly than the diagnosis. Angioplasty and metal stents have significantly simplified the treatment of renovascular hypertension over the last 15 years (Fig. 3F.1), but our ability to accurately detect the presence of the disease has changed little. It is also fair to say that there is more variability from institution to institution in the diagnostic techniques used than in any other of the clinical situations discussed here.

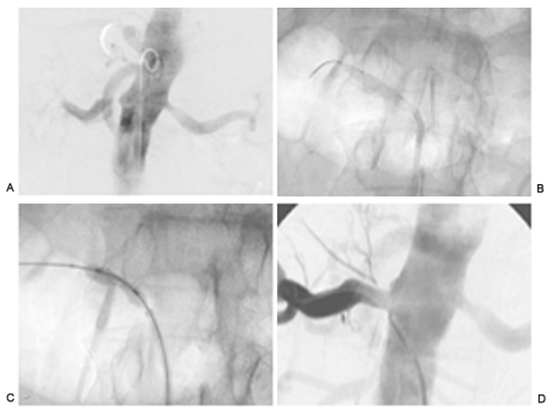

FIGURE 3F.1. Patient with difficult to control hypertension on four medications. Creatinine elevated at 1.7 mg/dL. **A:** Digital subtraction angiography demonstrates a 99% stenosis in the right renal artery and a less severe stenosis on the left. **B:** A balloon-on-a-wire low-profile system is used to dilate the lesion. **C:** Because of a residual 40% stenosis, a balloon-expandable stent is placed. **D:** Stent in place and no residual stenosis.

All the imaging techniques are aimed at identifying a renal artery stenosis. This must then be correlated with other clinical data to determine the likelihood that the stenosis is related to the hypertension. Venography with renal vein sampling for renin is the one exception. Lateralization of elevated renin to one kidney is presumptive evidence of renovascular hypertension. Angiography can be done at the same time to determine the presence or absence of a stenosis. Unfortunately, it takes a number of days to get the renin assay results back, so if this approach is taken, angioplasty/stent placement must be postponed until the results are available. In practice, renal vein sampling for renin is not usually performed at most institutions except in questionable cases or when it is unclear how to proceed. One example is the case in which no arterial stenosis is found but peripheral renins are clearly elevated. Renal vein sampling may indicate which kidney is the culprit. Another example is the case in which a stenosis is found but does not appear significant. Obtaining renal vein renins can then be used to determine whether to bring the patient back for treatment of the questionable stenosis.

As far as imaging of a stenosis is concerned, angiography is still the gold standard; however, CTA (18) and MRA (8) have both made dramatic improvements over the last 10 years. The success of these two modalities is highly dependent on the experience and interest of the radiologists at a given institution. At medical centers with little experience in either CTA or MRA, their reliability is variable. Many centers have begun using these as a standard screening examination, and in experienced hands, the accuracy exceeds 85%. More important, the negative predictive value can be greater than 95% (18). Angiography is still performed at the time of treatment, but using CTA or MRA can greatly reduce the number of negative angiograms. CTA and MRA have the advantage of being noninvasive, but they both require intravenous contrast material. Gadolinium is now used for almost all MRA, and CTA requires rapid intravenous contrast injection. Computerized three-dimensional (3D) reconstruction techniques show promise of replacing standard two-dimensional imaging in the near future. This allows examination of the artery in 360 degrees and increases the sensitivity of the examination.

Nuclear medicine renal scans, with or without captopril, can be useful in cases of unilateral stenosis (6). Interpretation becomes more difficult if both sides show symmetric function. At institutions where CTA and MRA have not been pursued, renal scans remain the primary screening tool for renal artery stenosis.

The use of ultrasound in the evaluation of arterial stenoses has become common. In fact, many vascular surgeons perform carotid endarterectomy based on ultrasound findings alone in some cases. Unfortunately, the renal arteries lie deep within the body, making ultrasound examination difficult and, in some cases, impossible. Although there have been technologic improvements in ultrasound transducers, this method remains the most operator dependent of all imaging methods. Some operators have obtained a high success rate using this as a screening examination, but they are in the minority.

In summary, many options are now available for imaging renal artery stenoses, but only angiography maintains a high accuracy rate from institution to institution. The best approach is to discuss this issue with the radiologists at a given medical center and ask them which technique they prefer for screening. In cases with a strong clinical impression of renovascular hypertension, it may be quickest and most cost-effective to proceed directly to angiography.

RENAL TUMOR DIAGNOSIS

Imaging of tumors is covered in other sections, but there is a vascular-related topic worth mentioning: determination of renal vein and inferior vena cava (IVC) invasion by tumor.

Invasion of the IVC by renal cell carcinoma was a diagnosis made by venography up until the advent of ultrasound. Now CT and magnetic resonance imaging (MRI) also have that capability. Interestingly, this is one

area where angiography (venography) may not represent the gold standard. CT and MR are both capable of detecting a thrombus in the IVC. Both modalities have pitfalls, as does venography, primarily related to flow phenomena (21). Ultrasound, on the other hand, is limited only if the IVC cannot be well visualized. Ultrasound also has the advantages of requiring no contrast and being the least expensive. Comparisons of the different modalities consistently show that ultrasound should be the first choice. Venography can be reserved for those cases in which the IVC is not well seen. Although ultrasound is the best examination, if a CT or MRI has already been obtained and the question of caval invasion is answered in an unequivocal manner, there is no need to pursue additional studies.

RENAL TUMOR EMBOLIZATION

There are usually no specific arterial questions that must be answered when working up renal tumors, and CT and MRI have done away with the old technique of intraarterial epinephrine in the diagnosis of small lesions. However, percutaneous arterial embolization should be kept in mind for very large tumors or when there are other reasons to make extra efforts to decrease blood loss, such as when operating on a patient who will not accept blood transfusions. In these instances, preoperative embolization can be helpful (Fig. 3F.2). Angiography is performed in the standard manner, and the number of renal arteries is defined. Transcatheter embolization is then performed with alcohol (13), Gelfoam, or another embolic material. Embolization of renal cell carcinomas is one of the older applications of this technique, and therefore much experience has been gained. The procedure should be straightforward for any fellowship-trained interventional radiologist. The patient should proceed to surgery within the next 48 hours because parasitization of vessels by the tumor occurs rapidly.

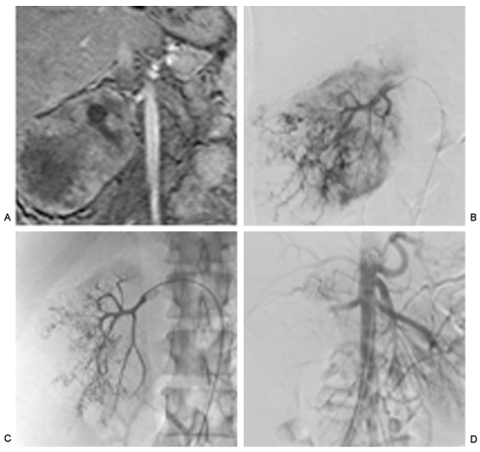

FIGURE 3F.2. This patient is a 56-year-old man with right flank mass and hematuria. **A:** Magnetic resonance imaging scan demonstrates renal cell carcinoma fed by enlarged renal artery. **B:** Digital subtraction angiography confirms single renal artery. **C:** Absolute alcohol is used to embolize tumor preoperatively. Occlusion balloon is in place to prevent reflux. **D:** Follow-up angiogram shows no flow through renal artery.

OCCULT HEMATURIA

Occasionally, a patient with hematuria undergoes the standard battery of tests and no cause can be found. In this context, if bleeding is seen coming out of a ureter during cystoscopy, angiography should be the next step. An arteriovenous malformation becomes a possibility, and the other imaging modalities will not reliably demonstrate these lesions. Angiography, on the other hand, will not only make the diagnosis, but embolization can be undertaken (3), often at the same sitting.

Modern angiographic catheters and embolic materials make this procedure very simple. A standard renal arteriogram is done in multiple projections. If an arteriovenous malformation or arteriovenous fistula is found, embolization can be undertaken at the same sitting. If a 5-Fr catheter can easily be advanced selectively into the branch vessel that is the culprit, embolization can be performed with no additional maneuvers. If not, microcatheters can be used that almost always allow catheterization of third-, fourth-, or even fifth-order branches (Fig. 3F.3). Coils are used for embolization with Gelfoam occasionally needed as an adjunct. This is clearly the best modality for making the diagnosis, and the fact that a minimally invasive treatment is available at the same time is a plus.

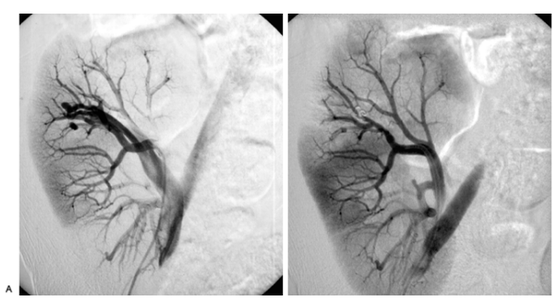

FIGURE 3F.3. Renal transplant patient with persistent hematuria following biopsy. **A:** Renal artery injection shows small pseudoaneurysm and early draining vein emptying into iliac vein. **B:** Following placement of two microcoils, fistula is occluded with minimal loss of parenchyma.

LIVING RENAL DONOR WORKUP

In recent years, CTA has become the procedure of choice (25). CT is less invasive than angiography, gives functional information not available on MRA, and is probably less expensive. In comparison with ultrasound and MRA, CT has been shown to be superior in depicting accessory renal arteries (9,19) (Fig. 3F.4). Standard CT examinations for this indication require three parts. An initial noncontrast scan should be obtained to exclude any calcifications in the kidneys. This is followed by a true CTA examination. Our protocol uses 3-mm-thick slices 1 mm apart from the celiac axis to the bifurcation. We inject 3.8 mL of 150 mL of Omnipaque 350 per second, with a 12-second delay. A delayed scan is then performed to evaluate the kidney and ureters.

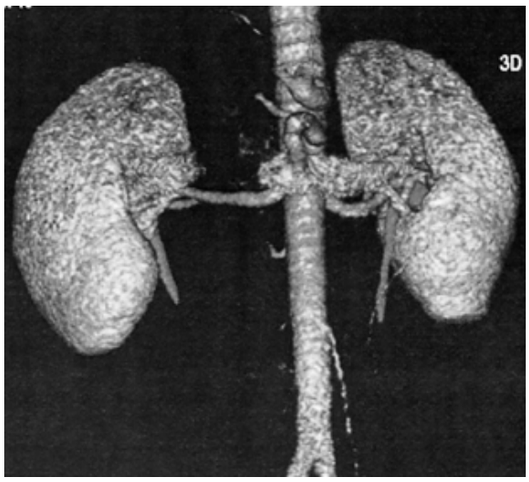

FIGURE 3F.4. Living renal donor computed tomography angiogram shows single arteries to each kidney and left renal vein passing anterior to the aorta. Different color schemes can be used depending on the preference of the viewing physicians. See also Color Figure 3F.4.

The standard axial images are reviewed along with 3D reconstructions. The fact that 3D images can be rotated 360 degrees (Fig. 3F.5) can be a major advantage in determining the number and location of renal arteries. Using a posterior view can be helpful in visualizing the left renal artery where it lies behind the vein. When both sets of images are used, it is only in rare cases that angiography is still needed. An additional advantage to the 3D reconstructions at our institution is that the surgeons prefer those images to take to the operating room.

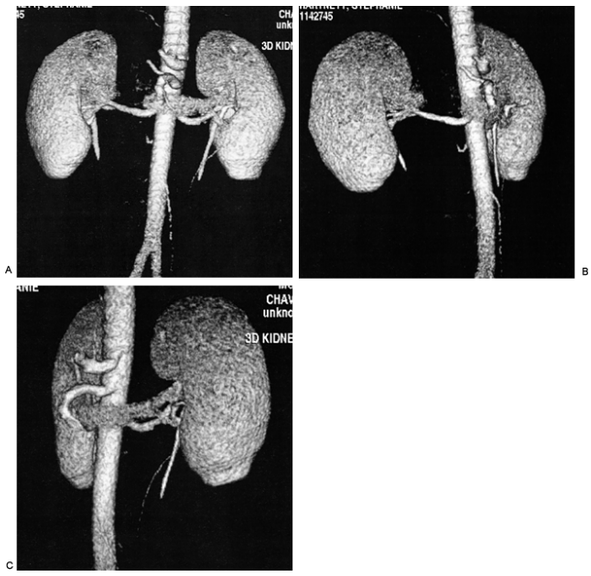

FIGURE 3F.5. Living renal donor. Image can be viewed in 360 degrees to better evaluate each artery and other structures. **A:** Anteroposterior view showing single arteries to each kidney. **B:** Right oblique showing no stenosis in the right renal artery. **C:** Left oblique showing left renal vein passing anterior to aorta.

MRA with gadolinium has become a good method of visualizing the renal arteries at institutions with experience in this technique; however, it does not have the advantages of CT in picking up calcifications or in demonstrating function by contrast material in the collecting system.

URETEROPELVIC JUNCTION OBSTRUCTION

Preoperative assessment for treatment of ureteropelvic junction obstruction includes defining the location and number of crossing vessels. Until recently, this has been one of the few situations in which there has been no substitute for angiography. CTA is now proving to be of value for this condition (20). Adding 3D reconstructions has the potential to give minimally invasive surgeons even more information.

Because this is a relatively new application of CT, it may be helpful to do a comparison with angiography until sufficient experience is gained to be sure the findings of CTA are reliable.

TRAUMA

Angiography remains the gold standard for trauma to the kidney where vascular injury is suspect. CT is the best overall screening tool, but doing a true CT angiogram in this situation is difficult and unreliable. If either occlusion of the renal artery is suspected or if the patient is actively bleeding from the kidney, emergency angiography should be undertaken immediately.

Occlusion of the renal artery or avulsion of the renal pedicle, once diagnosed by angiogram, should be taken immediately to the operating room. There is no minimally invasive technique at this time that can be used to treat this condition.

Bleeding from the kidney can be treated with transcatheter embolization. Angiography will demonstrate the bleeding site, and then a standard embolization technique, such as that mentioned in the occult hematuria section, can be used. This is one instance in which the embolization technique is not only less invasive but is probably easier to

perform than trying to control bleeding from a branch vessel surgically.

TRANSPLANT KIDNEYS

The fact that a transplanted kidney is in a different location has important ramifications for vascular imaging. Because of the superficial location, ultrasound is very accurate in determining the presence or absence of a stenosis. The main difficulty lies in separating the transplant artery from the internal iliac artery and its branches. If ultrasound finds high velocities suggestive of renal artery stenosis, angiography can be undertaken for confirmation and to treat with angioplasty or stent placement. Nuclear medicine studies can be undertaken to evaluate renal blood flow and excretion, but they are not as helpful in renal artery stenosis because there is no “other” kidney for comparison.

Ultrasound can also be useful in evaluating any other vascular abnormalities that might occur. Because these

kidneys often undergo biopsy, there is the potential for pseudoaneurysm or arteriovenous fistula formation. Ultrasound can often detect either one of these conditions. Angiography again is reserved for confirmation and treatment. Three-dimensional CT has recently been suggested to be of value in the vascular evaluation of transplant kidneys (11). Although this work is relatively recent, with the current explosion in fast CT techniques, it can be expected that the application of CT in the transplant setting will increase.

There is an additional attribute of transplant kidneys that makes a difference in angiography. Because angiography is often undertaken in the setting of a rising creatinine, it is helpful to limit iodinated contrast material or even exclude it completely. Carbon dioxide can be used as a very good contrast material, particularly with latest-generation digital equipment. Transplant kidneys are particularly well suited to this because the kidney lies anterior to the feeding vessel. Carbon dioxide contrast, being lighter than blood, will tend to fill anterior structures better. Unfortunately, because of the same reasoning, native kidneys do not visualize as well with carbon dioxide contrast material. Special maneuvers such as turning the patient onto his or her side must be performed. Some institutions have also begun using gadolinium, a non–iodine-based contrast material, to evaluate the kidneys.

IMPOTENCE AND PRIAPISM

Impotence is increasingly being recognized as a more common problem than previously believed. With this recognition has come greater emphasis on diagnostic arterial studies. Ultrasound with Doppler (16) can be helpful, but angiography remains the most sophisticated study (1). Internal pudendal arteriography can be performed from a femoral artery puncture. Intraarterial vasodilators and pharmacologic erection are necessary for a complete evaluation. Although the techniques are straightforward, this is not a procedure routinely used at all medical centers. Therefore the experience of any individual should be considered before requesting these studies.

Priapism is a rare but exceptionally painful condition. Imaging studies are not usually required, but Doppler ultrasound is being increasingly used when necessary. When the veins do not appear to be the problem, investigation of the arterial system with angiography can be helpful. Catheterization of the hypogastric arteries is required. Microcatheters can then be used to selectively catheterize the internal pudendal arteries. If high-flow priapism is thought to exist and other treatment methods have failed, embolization has been successful (27).

MRA and CTA, although becoming increasingly used in place of angiography, have not yet been shown to be of benefit in either of these two conditions.

VARICOCELE

Varicocele is another condition that rarely needs any imaging technique; however, venography may be used to evaluate the venous drainage in cases in which there is a recurrent varicocele or where embolotherapy is requested. CTA and MRA with 3D reconstructions can both show enlarged gonadal veins, but because embolotherapy is undertaken at the same time as venography, there is usually no reason to obtain cross-sectional imaging studies. Venography is usually performed from a femoral vein approach with catheterization of the left renal vein. The gonadal vein is then catheterized, and contrast material is injected with the table tilted in reverse Trendelenburg position. The main vein and any collateral channels are identified, and embolization can be performed. This procedure is particularly helpful in patients with anatomic variants of venous drainage (15).

A wide variety of embolic materials have now been used for this indication. Initially, detachable balloons were most common, but sclerotherapy agents and injection of boiling contrast material have subsequently been used. The introduction of microcatheters with the resultant decrease in spasm of the veins has led to increased use of metal coils. In Europe, sclerotherapeutic agents are used more commonly (15).

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3G NUCLIDE STUDIES

Barbara Y. Croft

Judith M. Joyce

Jayashree Parekh

Charles D. Teates

Part of "3 - IMAGING "

B.Y. Croft: Biomedical Imaging Program, National Cancer Institute, Bethesda, MD 20852.

J.M. Joyce: Western Pennsylvania Hospital, Pittsburgh, PA 15224.

J. Parekh and C.D. Teates: Department of Radiology, University of Virginia, Charlottesville, VA 22908.

Radioactive tracers have been used for more than 30 years to measure renal function and to image the urinary tract. Because of the kidneys' rich vascularity, unique function, and high metabolic rate, a number of radiopharmaceuticals have been used to study this organ system. The anatomic placement of the urinary tract is favorable for external counting and imaging, except that the bladder is anterior and the kidneys are posterior. Nuclear medicine has made unique and valuable contributions to the study of the genitourinary tract, but it cannot compete with other modalities such as radiography and sonography for high-resolution anatomic imaging. On the other hand, none of the other imaging modalities has the ability of nuclear medicine for functional imaging or quantitation.

This chapter outlines the pharmaceuticals used in genitourinary evaluation, radiation dose from nuclear procedures in relation to radiographic procedures, instrumentation, and clinical applications. Nuclear medicine procedures applicable to patients with genitourinary disease that are not specific to the genitourinary system are not discussed in any detail. Included among the latter techniques are procedures for imaging infection (gallium citrate Ga-67 scans and indium In-111 oxine-labeled or technetium-99m [^{99m}Tc] HMPAO-labeled white blood cell [WBC] scans), bone imaging (e.g., ^{99m}Tc methylene diphosphonate), lung scanning (^{99m}Tc macroaggregated albumin and xenon-127 gas or xenon-133 gas), and cardiovascular studies (thallium-201 images of myocardial perfusion or ^{99m}Tc-tagged red blood cells [RBCs] for evaluation of cardiac function). These and other nuclear procedures are beyond the scope and intent of this chapter.

RENAL RADIOPHARMACY

Pharmaceuticals

Chemical Structures

The chemical structures for the various compounds in use in nuclear medicine renal work range from the simple to the

complex. The compounds themselves vary in their pharmacology from the general to the specific.

Xenon-127 and xenon-133 are the simplest compounds in use; they are also nonspecific. Xenon is a monatomic gas, belonging to the noble, or “inert,” gas group. It is sparingly soluble in water or isotonic saline and quite soluble in fat. Xenon-127 has the better half-life for storage, the better energy for imaging, and confers the smaller radiation dose, but xenon-133 has been the more available and cheaper isotope.

The radioactive nuclide most used in nuclear medicine is ^{99m}Tc, which has a 6-hour half-life and a 140-keV gamma ray energy. It is ideal for examinations taking less than 1 day using the Anger camera, the most common nuclear medical imaging instrument today. The radionuclide is obtained in the pertechnetate form, TcO_4^-, from a “generator.” A new generator is delivered to most laboratories weekly. There is a supply of sterile, pyrogen-free ^{99m}Tc in most nuclear medicine laboratories at all times. The pertechnetate form may itself be used in studying renal blood flow and cystograms. Other technetium radiopharmaceuticals are compounded from purchased kits and available pertechnetate.

Most of the compounds in use have been chosen because of specific interaction with the kidneys. For example, ethylenediamine tetraacetic acid (EDTA) is a chelating compound with the ability to bond a positive metal ion; the nitrogens provide electrons for the covalent bonds, as do the oxygens of the acetic acids. The compound in routine use in nuclear medicine is diethylenetriamine pentaacetic acid (DTPA). It bonds its three nitrogens and five acidic oxygens to positively charged metal ions. EDTA and DTPA are shown schematically in Fig. 3G.1 . The method for naming these compounds has been to assume that biomedical people could not remember the chemical names and that the initials were not sonorous enough, so parts of the chemical names or initials have been turned into the simpler names *edetate* and *pentetate*.

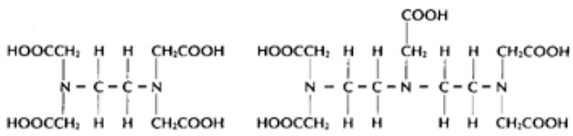

FIGURE 3G.1. Chemical structures of *(left)* ethylenediamine tetraacetic acid (EDTA) and *(right)* diethylene triamine pentaacetic acid (DTPA).

Commercial kits are available for compounding ^{99m}Tc DTPA, ^{99m}Tc glucoheptonate (GH) (Fig. 3G.2), and ^{99m}Tc meso-2,3-dimercaptosuccinic acid (DMSA) (Fig. 3G.3). All three kits contain stannous chloride as a reducing agent, so Tc^{4+} will be the positive ion species chelated by the organic compound. The package inserts should be consulted for special instructions in using the radiopharmaceuticals.

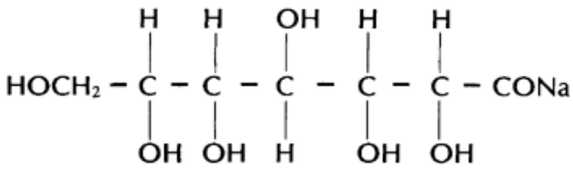

FIGURE 3G.2. Chemical structure of sodium glucoheptonate (GH).

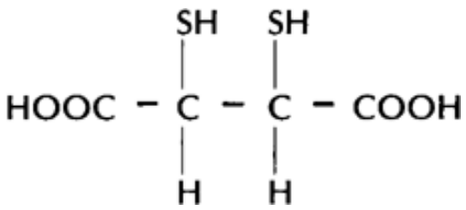

FIGURE 3G.3. Chemical structure of dimercaptosuccinic acid (DMSA).

More recently, ^{99m}Tc mercaptoacetyltriglycine (MAG_3) (Fig. 3G.4) has been introduced for renal tubular function studies (51). It has the advantages of ^{99m}Tc and kit formulation using stannous ion. It has been approved by the U.S. Food and Drug Administration (FDA) for renal imaging and for studying renal function.

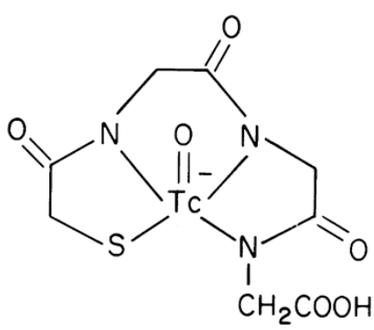

FIGURE 3G.4. Chemical structure of ^{99m}Tc MAG_3.

The chromium isotope, ^{51}Cr, has been chelated to EDTA for renal work. The half-life of ^{51}Cr is 27.8 days, and although the chemical characteristics of ^{51}Cr EDTA are favorable (5), the yield of radioactive decay products available for counting is low. Therefore ^{51}Cr EDTA is used for examinations requiring blood sampling but not those requiring imaging.

The iodine isotopes, ^{123}I and ^{131}I, have been attached to the ortho position of hippuric acid to create compounds for renal tubular function studies. The structure is given in Fig. 3G.5 . Because ^{123}I has a 13.2-hour half-life, ^{123}I hippurate (Hippuran) must be made on site with recently purchased ^{123}I or must be purchased for the studies for that day. The ^{131}I hippurate, with an 8-day half-life, may be kept on hand at all times if demand for its use is sufficient.

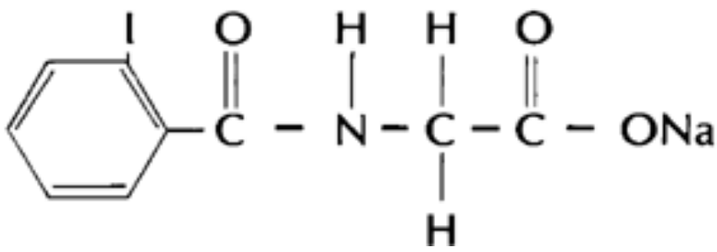

FIGURE 3G.5. Chemical structure of sodium *o*-iodohippurate (OIH).

BIOLOGIC BEHAVIOR

Xenon is more soluble in fat than in blood. If the patient is caused to rebreathe from a closed system containing radioactive xenon mixed with air or oxygen, the patient becomes more and more radioactive, with fat accumulating the major part of the activity. If the patient is then caused to breathe air alone, the washout of the xenon from the tissues can be observed with nuclear medical instruments. The rate of washout correlates with the blood flow to the organ or area. This technique has been used in many organs in the body.

The specific behavior of ^{99m}Tc DTPA and ^{51}Cr EDTA is considered later in this chapter in the discussion of glomerular filtration rate (GFR). A variable amount (10% or less) of injected ^{99m}Tc DTPA is bound to protein.

^{99m}Tc GH is injected intravenously (IV). The material is found in the plasma, and blood clearance is rapid (1,4), similar to DTPA. The GH clears by both tubular secretion and glomerular filtration. Approximately 70% of the material is excreted in the urine of normal subjects. Approximately 6% of the dose is retained in each kidney, largely in the cortex, permitting imaging of the cortex 3 to 4 hours after injection. A normal variation is clearance by the liver into the gallbladder and intestines.

^{99m}Tc DMSA is slowly injected IV. It is distributed in the plasma, loosely bound to plasma proteins. The activity clears from the plasma with a half-time of 60 minutes and concentrates in the renal cortex. Approximately 16% of the activity is excreted within 2 hours, increasing to 25% by 6 hours. At 2 hours, 15% is concentrated in each kidney; this increases to 20% by 6 hours (1). Imaging is best performed 3 hours or more after injection.

Iodinated hippurate has been used extensively in the examination of renal function; there is a voluminous literature on the use of this compound. The biologic behavior of iodinated hippurate is discussed in the section on effective renal plasma flow. Most of the hippurate is actively secreted by renal tubules. In a normal person, 70% of the compound is excreted in the urine in 30 minutes.

^{99m}Tc MAG_3, also known as *mertiatide*, is another renal tubular agent; it is confined to the plasma, having less RBC binding than sodium iodohippurate (OIH) (35). The plasma protein binding of MAG_3 is approximately twice as great as that of OIH. MAG_3 has a plasma clearance of approximately half that of OIH, probably as a result of decreased glomerular filtration and lower tubular secretion.

Dosimetry

Both nuclear studies and radiographic procedures result in patient exposure to ionizing radiation. The major difference between the two procedures is that radioactive pharmaceuticals produce patient exposure from internal sources, whereas that from a radiographic diagnostic procedure results from external irradiation. Exposure from radiographic procedures can be accurately determined if the unit is accurately calibrated and the exposure factors are known. In nuclear procedures, the patient dosage is determined by the biologic handling of the pharmaceutical, the physical behavior of the radionuclide, and patient dosage. Alterations in patient physiology, as for example in renal failure, affect the absorbed dose of radiation markedly if the radiopharmaceutical behavior is altered by the disease process. In recent years, patient exposure has been reduced in both areas by improvements in radiopharmaceuticals, nuclear instrumentation, radiographic and fluoroscopic equipment, and film and screen sensitivity. The patient exposures listed in Table 3G.1 and Table 3G.2 are considered average exposures and may not be accurate for a given patient or a particular institution. There are inaccuracies in published radiation dose calculations for a number of these materials (55). Personnel exposures should be low with both types of procedures if appropriate protective measures such as syringe shields and equipment shielding are used. The procedure potentially resulting in the highest exposure is fluoroscopy because a typical fluoroscope exposes the patient and personnel to as much as 10 rad per minute.

TABLE 3G.1. TYPICAL ABSORBED DOSES (RAD) FROM COMMON RADIONUCLIDE STUDIES

Agent	Usual Dosage (mCi)	Kidney	Bladder Wall	Gonads	Whole Body
^{99m}Tc DTPA					
Adult[a]	15.0	1.35	1.73[b]	0.16[b]	0.09
10-year-old	9.75	0.68	7.8[b]	—	0.29
^{99m}Tc glucoheptonate					
Adult[d]	15.0	2.55	4.2[b]	0.2[b]	0.15
10-year-old[e]	9.75	1.95	7.8[b]	0.2[b]	0.07
^{99m}Tc DMSA					
Adult[e]	5.0	3.8	1.4[b]	0.1[b]	0.08
10-year-old[e]	3.25	2.3	0.98[b]	0.07[b]	0.07
^{99m}Tc MAG_3					
Adult[f]	5.0	0.07	2.4[b]	0.08[b]	0.03
10-year-old	3.25	0.08	1.2[b]	0.06[b]	0.02
^{131}I hippurate					
Adult[g]	0.2	0.03	1.1[b]	0.02[b]	0.006[h]
10-year-old[e]	0.13	0.01	1.0[b]	0.003[b]	0.008
^{123}I hippurate[i] (p,5n)					
Adult[f]	1.0	0.03	1.0[b]	0.03[b]	0.02
10-year-old[j]	0.65	0.01	0.05[b]	0.003[b]	0.009
^{99m}Tc cystography[c]	1.0	—	0.07	0.002	

[a]Package insert, Cinitichem, Inc., Tuxedo, NY, 1988.
[b]Bladder and gonad doses determined by frequency of voiding.
[c]Koenigsberg and colleagues (30).
[d]Package insert, E.I. du Pont de Nemours & Co., Billerica, Md, 1987.
[e]Esser and colleagues (14).
[f]Stabin (47).
[g]Package insert, Squibb Diagnostics, Princeton, NJ, 1989.
[h]Unblocked thyroid dose as high as 8.7 rad.
[i]Dimitriou and colleagues (11).
[j]Croft calculation, based on ^{131}I hippurate values.

TABLE 3G.2. ADULT DOSES FROM RADIOGRAPHIC PROCEDURES

Procedure	Dose
Intravenous urograms	
(No. of films/examinations)	(5.31)
Mean exposure/examination	3.133 R
Mean marrow dose/examination	0.103 rad
Mean male gonadal dose/examination	0.207 rad
Mean female gonadal dose/examination	0.588 rad
Mean dose to total body/examination	0.278 rad
Fluoroscopy	
Exposure/min	2–10 rad

Reprinted with permission from Gorson RO, Lassen M, Rosenstein M. Patient dosimetry in diagnostic radiology. In: Waggener RG, Kereiakes JG, Shalek RJ, eds. *CRC handbook of medical physics,* vol 2. Boca Raton, Fla: CRC Press, 1984:474, 487, 488.

Certain terms must be defined to understand exposure to ionizing radiation. The patient dose of a radiopharmaceutical is measured by the number of atoms disintegrating per second. The term most commonly used in nuclear medicine is *millicurie (mCi),* defined as 3.7×10^7 disintegrations per second. A *microcurie (μCi)* is 3.7×10^4 disintegrations per second.
The Système Internationale (SI) units are coming into more common use; the SI unit for radioactive decay is the becquerel (Bq), which is 1 disintegration per second. Because many disintegrations occur per second, reference is often made to megabecquerels (MBq), 10^6 disintegrations

per second, and to gigabecquerels (GBq), 10^9 disintegrations per second. Therefore 1 mCi is equal to 37 MBq, 37×10^6 Bq. Obviously, a radionuclide with a long half-life in the patient will usually expose the patient to more ionizing radiation than another radiopharmaceutical with a shorter effective half-life. The effective half-life is influenced both by the physical decay rate of the nuclide and by the biologic turnover of the pharmaceutical.

Two terms are commonly used as measures of x-ray and patient exposure. The *roentgen* (R) is a measure of ionization of air by x-rays or gamma rays. There is no physical difference between an x-ray and a gamma ray. An x-ray originates from atomic electrons, and a gamma ray originates in the nucleus of an atom. One R results in 2.082×10^9 ion pairs in 1 mL of air at standard atmospheric pressure. The term *roentgen* is usually used to express the output of an x-ray machine. The amount of energy absorbed by a patient's tissue is expressed in rad. The *rad* is defined as 100 ergs absorbed per gram of tissue. In most tissues, exposure to 1 R results in approximately 1 rad of absorbed energy. The two terms are used somewhat interchangeably, but it should be remembered that the roentgen is a measure of exposure, whereas the rad is a measure of energy absorbed by tissue.

The SI unit for exposure to ionizing radiation is the coulomb per kilogram, and for absorbed radiation is the gray (Gy), with 100 rad equal to 1 Gy. Table 3G.3 gives the conversion factors to SI units.

	Customary Units	SI Units
Radioactive materials	1 curie (Ci) 2.7×10^{-11} Ci	3.7×10^{10} becquerels (Bq) 1 Bq
Absorbed dose	1 rad 100 rad	0.01 gray (Gy) 1 Gy

TABLE 3G.3. CONVERSION FACTORS TO SI UNITS

Table 3G.1 lists typical absorbed doses in patients receiving the five most common radionuclide studies of the urinary tract. The bladder receives the highest exposure

from most of these pharmaceuticals, but this dose can be reduced considerably by frequently emptying the bladder. Free iodine, present to some extent in ^{131}I hippurate, will result in exposure to the thyroid. The dose of the thyroid can be reduced by more than 90% by giving Lugol's solution, saturated solution of potassium iodide, or other blocking agents before the study.

The doses listed from radiographic procedures in Table 3G.2 are based on a survey performed by the Bureau of Radiologic Health between 1964 and 1970. The patient exposures can be reduced somewhat from the values listed by using better collimation of the x-ray beam, by using improved films and screens, and by reducing the number of films or fluoroscopic exposures.

INSTRUMENTATION

Two types of instruments are most often used to detect ionizing radiation in clinical applications. The oldest and simplest technique uses a gas detector. In this type of instrument, a charge is placed across electrodes in a chamber containing some type of gas. Gamma rays or x-rays cause the gas to ionize, thereby resulting in current flow across the electrodes. The amount of voltage between the electrodes determines the amount of current flow, the sensitivity of the detector, and the useful range of radiation that the instrument can accurately measure. The walls of the chambers can be altered to allow detection of very poorly penetrating radiation or highly penetrating radiation.

Two types of gas detectors are commonly used in nuclear medicine laboratories. A Geiger-Müller (GM) survey meter is usually used for detecting contamination in the nuclear medicine laboratory. This gas detector operates with a relatively high voltage, making the detector sensitive for small amounts of radiation. A typical range of usefulness is between 0 and 50 millirads per hour (1 rad = 1,000 mrad). The ionization chamber is usually attached to a rate meter and an electronic package by an electrical cord that allows survey of work areas. The probe is relatively nondirectional. The standard survey meter is intended for detection of x-rays and gamma rays and is not very suitable for low-energy beta ray detection.

The second type of gas detector usually found in the laboratory is a dose calibrator. At one time, most of the radiopharmaceuticals administered in nuclear medicine laboratories had relatively long half-lives and were purchased as needed from a pharmaceutical supplier in precalibrated doses. Patient doses were withdrawn from a precalibrated vial, and activity was calculated based on the known activity per cubic centimeter. As discussed previously, many of the radiopharmaceuticals carry the radioactive label ^{99m}Tc.

Technetium is eluted daily from a shielded ion exchange column containing molybdenum-99. The elution is unpredictable, and therefore the patient dose must be accurately measured in the laboratory. Highly accurate dose calibrators currently available allow the measurement of bulk quantities of individual patient doses of radiopharmaceuticals. The dose calibrators use a gas-filled ionization detector. Physically, the detector is a well chamber that allows the vial or syringe to be inserted for high-efficiency counting. These instruments are capable of accurately measuring over a wide range of activity, typically from approximately 1 μCi to more than 2,000 mCi. One millicurie equals 1,000 μCi. The dose calibrators are designed to give a digital readout of activity and are usually accurate to within 5%. The dose calibrators must be checked daily against known standard amounts of activity. These chambers operate with a relatively low voltage to allow measurements of high radiation intensities, and they are not accurate for measuring low-energy x-rays, low-energy gamma rays, or beta rays.

The other major category of detectors of ionizing radiation uses solid crystals. In most laboratories, the detector is sodium iodide, doped with an impurity such as thallium. Sodium iodide is hygroscopic, and therefore the crystal is completely enclosed in a barrier impervious to water, such as aluminum or glass. Ionizing radiation is absorbed by the crystal, converting the energy to visible light. Thus the sodium iodide crystal is called a scintillation crystal or scintillation detector. The light produced by each ionizing event is quite small and is detected by a nearby photomultiplier (PM) tube, which has a photocathode that converts light energy into a small electronic pulse. The electronic pulse is amplified more than 1 million times within the PM tube, making it large enough to be amplified and processed in standard electronic circuits. Thus an ionizing event in the crystal produces light that is converted into an electronic pulse. The magnitude of the pulse is related to the amount of energy contained in the ionizing event. The pulse can be analyzed to determine the energy of the x-ray or gamma ray that hit the crystal. Pulses can be integrated over a variable time to give counts per second or counts per minute. The count rate can be displayed on a meter or a digital printout, or it can be stored in a computer.

A single crystal detector is usually mounted in some type of lead or other heavy-metal shielding so that the crystal is sensitive to x-rays or gamma rays from a localized region (Fig. 3G.6). Typically, a single crystal–single PM tube system is used for measuring count rate from the thyroid for thyroid uptake determination or monitoring the count rate in the kidneys during a renogram. Under these circumstances, the probe and its collimator are positioned so that

the crystal monitors the count rate in the organ and nearby tissues being surveyed. The successful use of this detector assumes that the organ can be accurately localized from anatomic landmarks.

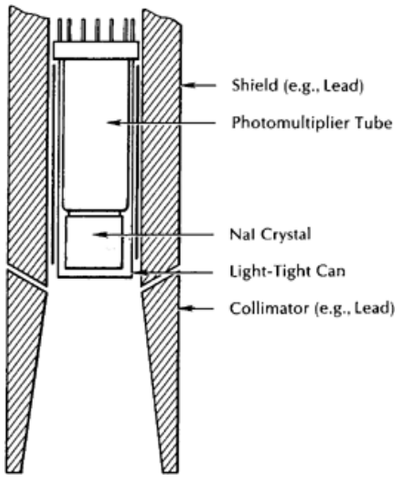

FIGURE 3G.6. Typical probe detector system. The sodium iodide (NaI) crystal and photomultiplier (PM) tube are shielded by lead to restrict the field of view to the desired anatomic region. The crystal is enclosed in a polished can to increase the reflection of light to the PM tube and protect the crystal from degradation by moisture.

A sodium iodide scintillation detector can be manufactured in the form of a "well counter." This is used for counting in vitro samples. In effect, the sample is inserted into a hole in the protected crystal so that high counting efficiency is achieved. As with the scintillation probe, the activity can be counted over time to determine sample activity.

The imaging device used in most departments is the Anger camera. The camera contains a single crystal, measuring up to 50 cm in diameter, that is round, square, or rectangular in shape and 0.25 to 0.375 inches thick. Behind the crystal, there is a matrix of PM tubes, typically numbering anywhere from 37 to 91, which look at the intensity of light from each scintillation in the crystal (Fig. 3G.7). The light striking the multiple PM tubes is analyzed so that the location of the scintillation is determined, as well as the total energy from the x-ray or gamma ray. The front of the crystal is protected by a collimator. The multiple holes in the collimator determine the origin of the photons that hit the crystal. Ordinarily, most Anger cameras are used with a parallel-hole collimator that sees a field of view 25 to 50 cm in size depending on the size and shape of the system. The thickness of lead septa between holes is selected for the appropriate energy of the photons being imaged, that is, low energy (up to 160 keV) and medium energy (160 to 360 keV). The hole diameter and collimator thickness are selected for desired resolution and counting efficiency.

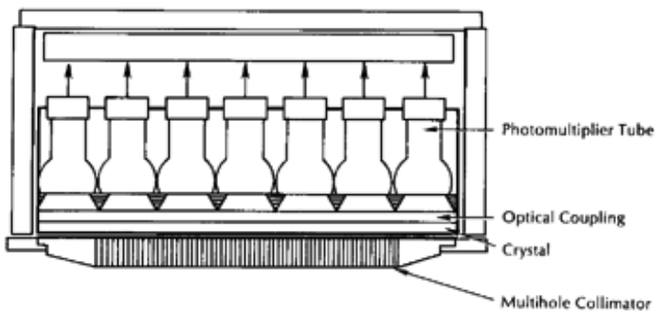

FIGURE 3G.7. Diagram of a cross section through a 37 photomultiplier (PM) tube gamma camera. The PM tubes are arranged in a hexagonal array, with three rings of tubes surrounding a central tube. Gamma rays or x-rays pass through the collimator and interact with the crystal, producing light. The location of the scintillation and the total energy absorbed are determined from the signal output by the PM tubes. The amplified signal is analyzed for energy levels and sent to the cathode ray tube or computer for recording.

The camera electronics include an energy discriminator (spectrometer) to be sure that only the appropriate energy is accepted. The crystal detects stray cosmic rays, scattered x-rays, and so forth, as well as the desirable photons emitted by the nuclide being imaged. The image quality will suffer unless the unwanted radiation is excluded by energy discrimination.

The final image that is viewed depends on where the signal is sent once it leaves the PM tubes and analyzers. It may enter a cathode ray tube (CRT) that puts a series of dots on the screen. By using time-lapse photography of the CRT, an image is generated on Polaroid film or transparency film. The same signals may be sent to a computer for storage and later manipulation.

Computers have been used in nuclear medicine for years to digitize and store the information from the scintillation probe or Anger camera for later manipulation. Over the years, the storage capacity and sophistication of programs have improved greatly. When using a computer to store and manipulate data, it is essential that the information be stored in an adequate format. If images are integrated for 1 minute each, for instance, the data cannot be later analyzed at 1-second intervals. Therefore the appropriate prescription for the storage must be determined before initiating the study. Most commercial computers now have several software programs that allow histogram displays of activity versus time. These curves can be stripped or analyzed to allow washin and washout rate determinations, fractionation of individual renal function, and analysis of blood clearance rates to determine GFR and effective renal plasma flow. In addition, computer manipulation is essential to enhance images from an Anger camera and perform specialized procedures such as single photon emission computed

tomography (SPECT). SPECT creates tomographic images in much the same way as computed tomography (CT) scanning, by combining images from multiple positions as the camera rotates about the patient.

PROCEDURES

The following sections describe the range of procedures available in nuclear medicine to assist the renal diagnostician. For easy reference, the examinations, radiopharmaceuticals, and typical doses of radioactivity are outlined in Table 3G.4 .

Examination	Agent	Dose of Activity
Renal blood flow imaging	^{99m}Tc compound	15 mCi
Effective renal plasma flow		
Imaging	^{131}I hippurate	200 μCi
Blood sampling only	^{131}I hippurate	30 μCi
Imaging	^{123}I hippurate	1.0 mCi
Imaging	^{99m}Tc MAG_3	10 mCi
Blood sampling only	^{99m}TC MAG_3	300 μCi
Glomerular filtration rate		
Imaging	^{99m}Tc DTPA	15 mCi
Blood sampling only	^{99m}Tc DTPA	300 μCi
Blood sampling only	^{125}I iothalamate	100 μCi
Blood sampling only	^{51}Cr EDTA	100 μCi
Renal cortical imaging	^{99m}Tc DMSA	5 mCi
Cystography	^{99m}Tc pertechnetate	1 mCi
Testicular imaging	^{99m}Tc pertechnetate	15 mCi

TABLE 3G.4. RADIOPHARMACEUTICALS AND ACTIVITY DOSAGE FOR GENITOURINARY EXAMINATIONS

Renal Imaging

Renal images are typically performed with Anger cameras. The arrival of activity can be recorded in the form of renal vascular studies. This information can also be analyzed by computer to compare the washin rates for the two kidneys. Most of the technetium pharmaceuticals can be used for the vascular sequence, provided adequate amounts of activity (15 to 20 mCi) are injected, but the later static views show varying features depending on the pharmaceutical used. The vascular sequence is typically recorded on film and by the computer at one frame per 2 seconds, but the framing rate can be tailored to the patient's age and the injected dose. In general, faster sequences are desired for children. The limiting factor on the renal vascular sequences is generally the low information density due to a small number of counts per image, so higher imaging rates may actually cause deterioration of the images. Because of its ability to add frames together, the computer is often a more satisfactory method than film for recording and displaying this information.

The static images of the kidneys are collected immediately after the vascular sequence and up to several hours later. Static images may contain as many as 1 million counts and require up to several minutes' accumulation time. ^{99m}Tc DTPA is filtered and concentrated in the tubules and is then excreted through the collecting system. Activity in the calyces, renal pelvis, and ureters decreases after 5 to 10 minutes, and delayed views beyond 30 minutes have little value unless the patient has obstruction.

The ^{99m}Tc MAG_3 imaging sequence is very similar to DTPA; it is best used in a dynamic fashion for vascular imaging and the renogram referred to later.

^{99m}Tc GH and DMSA show progressive accumulation in the kidneys over several hours; delayed views will show better images of the renal cortex after the background and collecting system activity have decreased. Patient hydration will influence the washout rates from the kidneys just as with a renogram. This effect is used in the “furosemide (Lasix) renogram,” discussed under Hydronephrosis and Hydroureter later in this chapter.

Renograms

Initially, renograms were performed using multiple, single-crystal probes positioned over the patient's back. The probes were positioned by external anatomic landmarks, but this often did not locate the kidneys in the field of view of the probes. Later, workers positioned the probes by injecting a small amount of renal tracer (e.g., ^{203}Hg chlormerodrin) and finding the maximum count rate before injection of ^{131}I hippurate. More recently, most renograms have been performed with Anger cameras, even though the sensitivity of a camera is somewhat less than that of a probe. The versatility of data recorded from a camera more than offsets the disadvantage of the higher pharmaceutical dose required. A renogram may be performed using external probes with as little as 30 μCi of ^{131}I hippurate. Renograms performed on Anger cameras typically use 200 μCi of the same agent. With the camera, the accumulated information is usually stored by a computer for later analysis of individual kidney count rates and generation of renogram curves. The camera-generated data are acquired by the computer at intervals of 10 to 15 seconds for as long as 30 minutes to 1 hour.

The term *renogram* simply indicates that an activity versus time graph is being generated from the kidney activity. Classically, the renogram study was performed with ^{131}I hippurate, but other agents such as ^{99m}Tc DTPA or MAG_3 may be used. The shape of the renal curve is obviously affected by the pharmaceutical used. The shape is also affected by patient preparation and positioning. For instance, the classic renogram is performed with the patient

mildly dehydrated and seated in front of the Anger camera. Drainage from the upper collecting system is more consistent in the upright position, but unfortunately, there is more tendency for the patient to move. Patients who cannot maintain this position comfortably and consistently may be imaged in the supine position. Follow-up patient studies should always be performed in the same position, if possible.

Hydration state affects the timing and shape of the renogram curves. Phase I (Fig. 3G.8), lasting approximately 30 seconds, represents the arrival of the IV-injected pharmaceutical in the blood pool of the kidney and adjacent tissues. There will be a phase I increase in count rate regardless of the status of the kidney because there is blood pool activity in all tissues. The activity during this phase is poorly related to renal blood flow. Phase II typically lasts 4 to 6 minutes and terminates when activity in the kidney reaches a maximum. As the kidney extracts the radiopharmaceutical from blood, the count rate gradually rises. Because the blood levels fall rapidly during the first few minutes, activity in the urine is maximum initially and gradually falls with time. When this most active urine leaves the region of interest being analyzed, the count rate will start to fall. Thus the rate of increase in count rate during phase II is directly related to the renal blood flow and renal function. The rate of increase of activity is not affected by hydration, but the duration of phase II is inversely related to the urine formation rate.

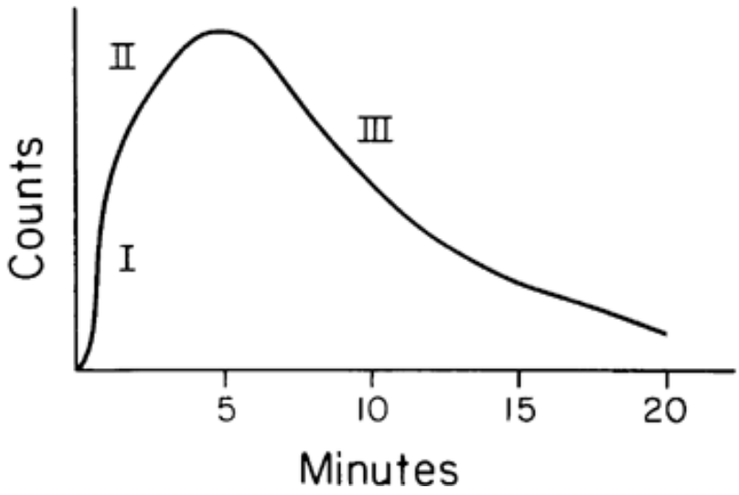

FIGURE 3G.8. Renogram curve showing count rate versus time. The shape is affected by the radiopharmaceutical injected intravenously. The idealized curve shown is typical of that following hippurate injection in a moderately hydrated patient, recording activity with a gamma camera and computer. Phase I is vascular content in kidney and background. As the kidney extracts the tracer, activity rises in phase II. When the collecting system starts emptying through the ureter, activity falls in phase III.

Phase III starts at the peak of renal activity and illustrates a gradual fall in count rate as the most concentrated activity is washed from the collecting system. The time that is required for the count rate to fall to half of the peak value is called the half-time for washout, and this time is affected by urine formation rate. Numerous other aspects of the shape and timing of the renogram curve have been analyzed, but none is specific for disease process. However, if hydration state and positioning are consistent, changes in the slope of phase II, the time to peak, and the half-time for washout do reflect changes in renal status.

Mathematical Model: Two-Component Model

To be able to quantitate the results of functional studies, a model is developed to describe the organ function. A connection is made between the numbers that are available from the noninvasive examination and the properties that it is desired to measure. In the case of the kidneys, the quantities to be measured include renal plasma flow, GFR, and individual kidney function. Whether renal plasma flow or GFR is measured depends on the pharmaceutical used in the measurement.

The estimation of renal blood flow and function can be computed by the Fick principle, which when applied to the kidney gives the following formula:

Clearance = $U_V/(A - V)$

where *U* is the concentration of the test substance in the urine, *V* is the volume of urine, *A* is the concentration of the substance in the renal artery, and *V* is the concentration of the substance in the renal vein. If the substance is completely removed by the kidney, the renal vein concentration can be assumed to be zero; the arterial concentration may be assumed to be equal to the peripheral venous concentration. Thus the formula is simplified as follows:

Clearance = U_V/A

To perform a clearance measurement using Fick's principle, blood is sampled and a total urine collection is made during continuous IV infusion of the agent for three 20-minute periods. The assumption is made that the body reaches a steady state in which the input of the measured substance is the same as the output. One can further assume that measurements of the quantity of the substance in the infusion and the peripheral venous concentration are sufficient. If the separate function of each kidney is desired, catheters must be placed in each ureter.

It was discovered by Sapirstein and co-workers (42) that a single injection of the test substance could be substituted for continuous infusion with no compromise in the total functional information.

In a renal function examination using a radiopharmaceutical, the numbers that are available are the relative concentration in the kidneys as attenuated by tissue and the amount of activity per unit volume in the blood during the examination. The relative concentration in the urine in the bladder during the examination may be compared with the absolute concentration in voided urine at the end

of the examination, especially in transplant patients whose kidney and bladder are close enough together for imaging at the same time. Note that unless complex techniques are resorted to, only samples removed from the patient can be quantitated in an absolute way.

It has been observed that the radioactivity per unit volume of plasma of radiopharmaceuticals injected for renal examination decreases according to a biexponential curve as a function of time. This means that the curve of plasma activity as a function of time shown in Fig. 3G.9 can be decomposed into two straight lines (on a semilogarithmic scale as shown in Fig. 3G.10). Each of these lines is described by its intercept with the activity axis, which is its concentration at time equals zero, and its half-time, or the amount that disappears per unit time. Thus one curve yields four numbers.

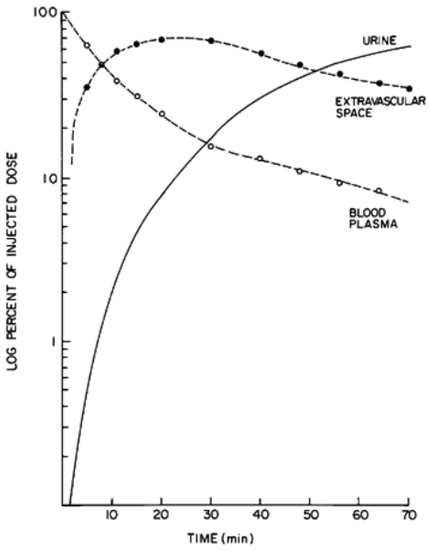

FIGURE 3G.9. The semilog graph of percent of injected dose versus time illustrates the amount of sodium *o*-iodohippurate in the blood, urine, and extravascular space.

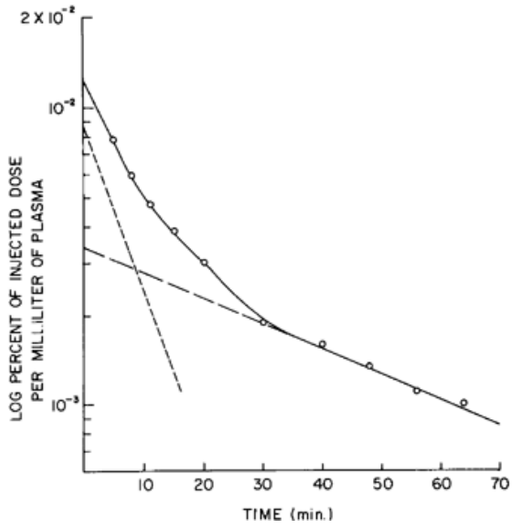

FIGURE 3G.10. The semilog graph of percent of injected dose per milliliter of plasma versus time shows a biexponential functionality. The two exponential parts are shown.

If, in turn, we consider a model of renal function (Fig. 3G.11), it is possible to write differential equations describing the loss of material from one compartment and the gain of an equal amount by another, following the arrows of the model and using the language and symbolism of reaction-rate chemistry. The model pictured is called an *open two-compartment mammillary model* (33). Such differential equations can be solved to yield mathematical functions that describe the concentration in each compartment as a function of time. For this model, the function that describes the concentration in the vascular compartment as a function of time is a biexponential curve. Thus the kinetic variables in the model can be related to the numbers generated from patient plasma sampling. The renal clearance is a function of all four numbers, which come from both parts of the curve:

$$\text{Clearance} = \ln(2)(A_1 \times t_1 + A_2 \times t_2)$$

where A_1 and A_2 are the fractions of the injected dose per milliliter for each of the two parts of the curve at time zero, and t_1 and t_2 are the half-times for the two parts of the curve.

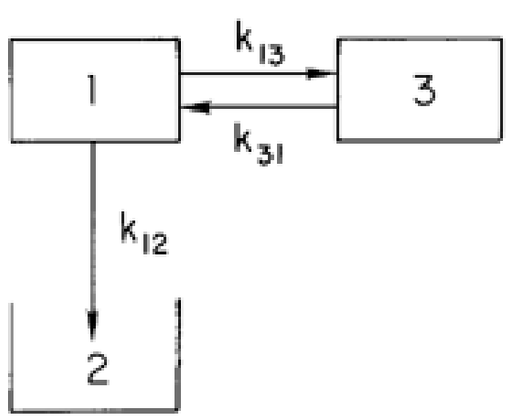

FIGURE 3G.11. The open two-compartment mammillary model. Compartment *1* is the plasma, compartment *3* is the extravascular space, and compartment *2* is the urine. There is kinetic equilibrium between compartments *1* and *3*, and there is no return from compartment *2*. *k* indicates the rate constant for transfer from compartment i to compartment j.

The measurements of the plasma disappearance curve may be made in several different ways. One method is to

take plasma samples over a time suitable for defining the two parts of the curve; ten samples are sufficient to permit curve-fitting and the discrimination of poor samples. Some laboratories have simplified this method to taking one blood sample at a particular time with the subsequent calculation of renal clearance by a relationship connecting the clearance to the single-sample activity and several constants. A second method involves the measurement of a major blood pool in the body, such as the cranium or the heart, with a probe detector, combined with a blood sample that is compared with a standard to permit calibration of the plasma disappearance curve.

Clearly, using eight to ten blood samples to define the biexponential curve is the more accurate method, although simplification of the test procedure is necessary in some instances. In such a case, a method that accurately defines the longer half-life part of the curve should be sufficient to eliminate the difficulties of a single sample. In this case, the clearance equation becomes as follows:

$$\text{Clearance} = \ln(2)(A \times t)$$

where A is the fraction of the injected dose per milliliter of plasma at time zero, and t is the half-time of the line.

It should be pointed out that the simplified methods may not allow the accurate comparison of one patient to an absolute scale but may permit the progress of that patient's disease to be observed with changes in the renal function value because a particular patient's measurement is reproducible.

Constant Infusion Methods

Constant infusion methods, in which there is an IV infusion of saline containing the radioactive material, seem simple and appealing. Once a steady state is reached, measurements of urine and blood concentrations and interval urine volumes are all that is required to perform a clearance measurement.

The apparent simplicity is not real. The patient must be given a priming dose of the material to ensure that the blood and extravascular space will come to equilibrium during the constant infusion period, and the patient must be well hydrated to be able to urinate on command at given intervals. Urinary retention, normally up to 100 mL, is greater than this in certain diseases, and highly variable. Bladder retention can be estimated with external detectors, but this complicates the examination.

Computer Processing for Fractionation

The fractionation of renal clearance into values for the individual kidneys is accomplished by reference to the images acquired by the Anger camera at 15-second intervals after injection of the tracer dose. Regions of interest are drawn around the kidneys; background-corrected activity versus time curves are generated. From this point, two different methods can be used to complete the calculation.

In the slope method, the slopes of the curves for the two kidneys between 60 and 150 seconds after injection are calculated using least-square methods. The two slope values are added together, and the fractional contribution of each kidney's slope to the total is calculated. This is the fractional contribution that each kidney makes to the clearance.

In the integrated count method, the counts for each kidney between 60 and 150 seconds after injection are found, after background correction; this is a relative measure of the activity multiplied by time in each kidney. The two integrated counts are added, and the fractional contribution of each kidney to the total is calculated. Once again, this is the fractional contribution that the kidney makes to the clearance.

Both of these methods give similar results for kidneys that function well. The results for poorly functioning kidneys are open to more uncertainty for several reasons: The selection of the background region becomes more critical; the difference between kidneys and background is small and shows great variability; and the statistical uncertainties of radioactive detection are more serious for lower counts, so all the calculations have greater uncertainty.

When percentages are used for comparisons, they must always add up to 100%. This means that if one kidney remains the same after some elapsed time but the other improves in clearance, the one that remains the same will appear to have lost function on a percentage basis. It is thus incumbent on the observer to look at both the percentages and the absolute clearance values.

Glomerular Filtration Rate

The glomeruli produce an ultrafiltrate of the plasma by means of a physical process, which is nonselective for substances of low molecular weight. The volume of this ultrafiltrate, expressed in milliliters per minute, is defined as the GFR. The formation of the filtrate is regulated by the hydrostatic pressure gradient, osmotic pressure, the filtration surface, and membrane porosity.

To measure GFR, the agent must have the following characteristics (45):

1. Be nontoxic, physiologically inert, and chemically stable
2. Be easily and accurately measured in blood and urine
3. Be fully filterable through the glomerular membrane
4. Not combine with plasma proteins
5. Not be resorbed, synthesized, destroyed, or excreted by tubules
6. Have a constant clearance with high or low urinary flow, and greater or lesser concentrations of the agent in the plasma

7. Have a clearance equal to that of other tracers already proved adequate for GFR measurement, such as inulin
8. Be eliminated exclusively by the kidneys

The standard for comparison for GFR measurements is inulin clearance in a protocol that includes continuous IV infusion and three 20-minute complete urine collections and three blood samples drawn during the urine sampling periods. The protocol is not practical for clinical use.

The use of radioactively labeled compounds has simplified GFR measurement by simplifying the measurement of the agent. Of the radioactively labeled materials, ^{99m}Tc DTPA comes closest to fulfilling the criteria for GFR measurement. It can also be used in combination with an imaging examination to visualize renal and ureteral anatomy and to quantitate the fraction of the GFR attributable to each kidney (fractionation). Inulin, labeled with the beta-minus emitter carbon-14, can also be used with the standard continuous infusion method or in a plasma sampling mode, as can sodium iothalamate and other radiographic contrast agents, labeled with ^{125}I or ^{131}I. DTPA and EDTA have also been used. The ready availability of ^{99m}Tc DTPA makes its use simpler than any of the other materials mentioned here.

The measuring process is described earlier in this chapter. Ten plasma samples obtained during 1.5 to 2 hours of blood sampling after a single IV injection should be sufficient to define the two parts of the biexponential curve. The single-sample technique uses a function of the form where *A, B,* and *C* are constants, and *S* is the fraction of the injected dose per milliliter of plasma in the 3-hour sample (7).

The radionuclide technique described by Gates (18) is an alternative method of measuring the GFR. The calculation is based on the renal uptake on Anger camera images during the 2- to 3-minute interval following tracer (^{99m}Tc DTPA) arrival in the kidneys. The GFR is computed by using the following formula:

GFR = A(L + R) – B

where *L* and *R* represent the depth-corrected percentages of renal uptake for the left and right kidneys and *A* and *B* are constants. The formula was derived from linear regression analysis comparing the renal uptake of ^{99m}Tc DTPA with 24-hour creatinine clearance in 51 adult studies.

The advantage of this method is that it allows rapid determination of split renal function, as well as total GFR, without blood samples. The accuracy of this method, however, has been called into question. Ginjaume and co-workers (19) compared four methods of measuring GFR and found that the effective volume technique using one blood sample taken at 2 hours was the best compromise between accuracy and convenience and that the Gates method presented practical problems due to uncertainty in background subtraction and kidney-depth approximation.

The mean value of GFR in the normal adult is approximately 130 mL per minute in men and 120 mL per minute in women, with an uncertainty of 10%. The GFR of the newborn is between 20% and 40% of the adult value and increases progressively until, at age 1 year, it becomes equal to adult values in relation to the standard surface area.

Effective Renal Plasma Flow

If the renal tubules can be assumed to remove a substance totally from the blood during perfusion, a study of the concentration of that substance could yield values of renal blood flow. Most of the substances used in such a measurement are concentrated in the plasma, so the measurement is of renal plasma flow (RPF).

The ideal substance for estimating RPF should have the following characteristics:

1. Be nontoxic, physiologically inert, and chemically stable
2. Be easily and accurately measured in blood and urine
3. Be fully secreted by renal tubules
4. Be readily dissociated from any plasma protein complex in its transit through the kidney
5. Not be resorbed, synthesized, or destroyed by tubules
6. Have a saturable clearance so that high concentrations have lesser clearance values
7. Have nearly total renal extraction
8. Be eliminated exclusively by the kidneys

Both because only a portion of renal blood flow is presented to renal secretory tissue as opposed to the small fraction that normally perfuses the nonsecretory tissue (perirenal fat, pelvis, and capsule) and because no substance perfusing the kidney will be totally extracted, the calculated clearance will be less than the total renal plasma flow, so it is termed *effective renal plasma flow* (ERPF). Extraction efficiency of the tubules may be decreased in disease, as may renal blood flow.

Para-aminohippurate (PAH) was found to meet the aforementioned criteria best. Sodium iodohippurate (OIH) was found to be similar in behavior to PAH; in addition, it can be labeled with radioactive isotopes of iodine, such as ^{131}I, ^{123}I, and ^{125}I, making detection of the material simpler than in the previously used chemical methods. ^{131}I and ^{123}I have the added advantage of ready imaging with the Anger camera.

Because ^{131}I OIH disappears from the blood according to a biexponential function, the open two-compartment mammillary system is appropriate for analysis. Again, the examination protocol may be combined with imaging so that the images and fractional ERPF for each kidney are obtained along with the total ERPF value. The protocol may be based on serial blood sampling between 5 and 70 minutes after IV injection of ^{131}I OIH, to define the biexponential curve, or a less accurate single-sampling method can be used. Tauxe and co-workers (49) performed

an elaborate analysis, which suggested that it was feasible to use a single blood sample, at 44 minutes after injection, and a polynomial to calculate the ERPF:

ERPF = A + B/S + C/S

where *A, B,* and *C* are constants, and *S* is the fraction of the injected dose per milliliter of plasma.

Normal ERPF values lie above 600 mL per minute, with a 10% uncertainty. Approximately 50% of the function should be attributable to each kidney. Filtration fraction is the comparison of GFR and ERPF measurements. The normal value is approximately 0.2. Tauxe (48) documents ERPF values in normal patients and patients with unilateral nephrectomy.

Renal plasma flow can also be measured with ^{99m}Tc MAG_3 (40,41). As the agent becomes widely available and more controlled studies are performed, the ERPF ratio between MAG_3 and OIH will be better known. From the University of Alabama research, the 44-minute MAG_3 concentration is 0.563 times the OIH value (41).

Nuclear Cystography

Although cystograms may be performed after the bladder has filled following an IV injection of a radiopharmaceutical, the study is more accurate in detecting ureteral reflux if the tracer is placed directly in the urinary bladder. From $^3/_{10}$ to 1 mCi of ^{99m}Tc pertechnetate is mixed with 250 to 500 mL of sterile saline in an IV bottle. The IV bottle should not be more than 3 feet above the bladder. After the tubing is attached to the catheter, the bladder is slowly filled and the time and volume are recorded. At the same time, sequential images are recorded by the camera and computer. The patient is then instructed to void with the catheter in place; if voiding is impossible, the catheter is withdrawn.

The recording sequence varies somewhat among laboratories, but in general, frames are recorded on film and in the computer at 15- to 30-second intervals. Posterior projections are used. Images or computer curves may reveal reflux up the ureters. The severity of reflux is usually gauged by the volume of infused fluid required to produce significant reflux. Increasing volumes instilled before reflux occurs implies improvement.

Scrotal Imaging

Nuclear imaging to evaluate scrotal pathology has been used since 1973 with excellent accuracy reported. Its primary role is the differentiation of testicular torsion from epididymitis in patients with an “acute” scrotum. The standard radionuclide used is ^{99m}Tc pertechnetate.

In our procedure, the patient is given an oral dose of potassium perchlorate 30 minutes before radionuclide dose to block thyroid uptake. Potassium iodide can also be used. Positioning includes taping the penis to the abdominal wall and supporting the testicle on a tape sling to rest the testicle on a slightly higher plane than the thigh. A large-field-of-view camera is positioned anteriorly, and no shielding is used.

A bolus of 20 mCi of ^{99m}Tc pertechnetate is injected IV. A flow sequence of 3 seconds per frame at 70-mm image size is used, and then static images with a LEAP collimator are obtained immediately and at 5 and 10 minutes for 500,000 counts per view. The analysis is described in the following section.

CLINICAL APPLICATIONS

Acute Renal Failure

Acute renal failure may be caused by anatomic or physiologic abnormalities. Anatomic causes of renal failure include occlusion of renal arteries and veins and obstruction of the urinary tract at any level. Physiologic causes of acute renal failure include blood volume depletion (“prerenal”) and acute tubular necrosis (ATN). The first step in evaluation of acute renal failure is sonography to evaluate the status of the collecting system (3). Contrast studies are not recommended because of their potential adverse effect on renal function. If the sonogram shows no evidence of dilation of the collecting system, the next step is dynamic renal scintigraphy.

We recommend ^{99m}Tc DTPA or ^{99m}Tc MAG_3. The technetium compounds provide better anatomic detail than either ^{123}I hippurate or ^{131}I hippurate. An important part of this examination is the visual evaluation of renal blood flow. The flow portion of dynamic imaging is the essential part in the evaluation of renal arterial blood flow. Analysis is based on observing the symmetry and the intensity of kidney visualization. The peak of activity in the kidney should be no more than 3 seconds after the peak of activity in the aorta. The intensity of activity in a normal-sized kidney should equal or exceed the early activity in the spleen (16).

Unilateral delay or decrease in kidney visualization on the flow study signifies a vascular abnormality. The possible vascular abnormalities include renal artery occlusion secondary to embolism, thrombosis, or dissection of an aortic aneurysm; renal artery laceration secondary to trauma; renal artery stenosis; and renal vein thrombosis. Unilateral delay can also be caused by severe unilateral ureteral obstruction or damage from infection or other disease. The sonographic findings are helpful in this differential.

Bilateral delay or decrease in renal perfusion is less specific. This pattern could be due to bilateral vascular compromise, severe prerenal circulatory failure, severe renal causes of failure (including ATN), and severe bilateral ureteral obstruction (Fig. 3G.12). Obstruction is again excluded by the sonographic findings.

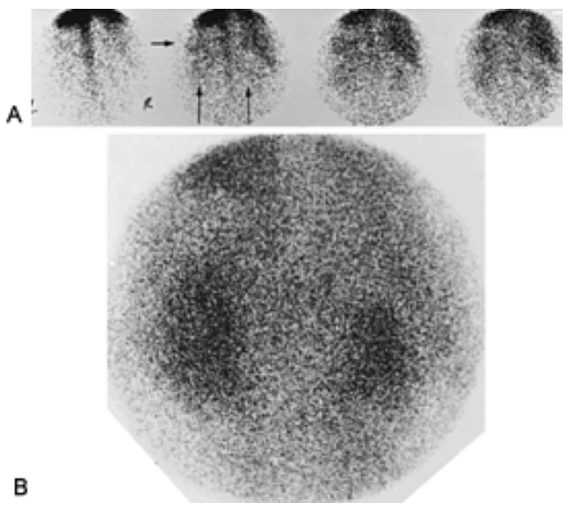

FIGURE 3G.12. Woman, 64 years old, with acute tubular necrosis following partial resection of her small bowel. **A:** ^{99m}Tc DTPA vascular sequence shows symmetrically poor renal blood flow. *Vertical arrows,* kidneys; *horizontal arrow,* spleen. **B:** Static image at 20 minutes demonstrates moderate bilateral uptake. No bladder activity was demonstrated.

The static images are analyzed for renal size and position along with symmetry, uniformity, and promptness of uptake

bilaterally. In normal kidneys, the immediate postdynamic images demonstrate symmetric, homogeneous activity in the renal cortices. Within 5 minutes, background activity lessens and the collecting systems are well visualized.

Renal size and position can suggest the cause, as well as prognosis, of the disease process. Bilaterally, normal-sized kidneys suggest recent onset and potential reversibility. Small kidneys indicate chronic disease, congenital or acquired, and irreversibility. Large kidneys can be seen in polycystic disease, an infiltrating disease such as amyloidosis, or renal vein thrombosis (44).

Evaluation of symmetry and uniformity of uptake on the static views compared with the flow study can also suggest underlying causes. Asymmetry of uptake with a corresponding flow abnormality correlates with a vascular problem. Lack of uniformity of uptake is caused by localized parenchymal disease. Wedges or segments of decreased activity that correlate with vascular distributions imply vascular abnormalities. Mass lesions may also cause nonuniformity and are discussed later in this chapter.

Promptness of uptake is also an important indicator. Delay in uptake in the kidneys suggests poor renal function secondary to parenchymal compromise. Causes include prerenal circulatory failure; renal disease, such as ATN; and postrenal obstruction. When severe enough, this compromise can decrease the flow as described previously.

In the severely oliguric or anuric patient, renal function may be so severely compromised that ^{99m}Tc DTPA or ^{99m}Tc GH scans are inadequate. In that case, ^{131}I hippurate is recommended because renal concentration can occur with as little as 3% of normal function (38). ^{99m}Tc MAG_3 provides results that are comparable to those with hippurate in patients with impaired renal function (50).

Chronic Renal Failure

In evaluating the azotemic patient, excretory urography becomes inadequate when the plasma creatinine level exceeds 5 mg per 100 mL. Large bolus doses of organic iodides may improve visualization radiographically but adversely affect already compromised renal function. ^{99m}Tc MAG_3 is the recommended agent for evaluation of chronic renal failure. Technetium compounds are chosen because flow studies can be performed. Additional experience with ^{99m}Tc MAG_3 shows that this compound is preferred to hippurate or DTPA. As in acute renal failure, the size, position, promptness, symmetry, and uniformity of renal uptake of the kidneys are important in guiding investigation and narrowing the diagnostic possibilities (46).

Masses and Pseudomasses

In evaluating a renal mass, the purpose of noninvasive tests is to narrow the diagnostic possibilities and avoid intervention if the mass is benign. The current resolution of scintigraphy is not as good as that of radiography. Lesions as small as 1 cm have been detected on phantoms, but a larger lesion centrally placed in the kidney may not be detected by scintigram. On the other hand, peripheral lesions or those obscured by fat or bowel gas may be better visualized. Therefore radiologic and radionuclide techniques are complementary in evaluation of renal masses.

Ultrasound is generally the recommended first procedure for initial characterization of a renal mass. If lobulation is noted, a normal variant, or “pseudomass,” of the kidney may be present, such as a hypertrophied column of Bertin, splenic impression, dromedary hump, or fetal lobulation. The next step is nuclear imaging with ^{99m}Tc DMSA, used because of its concentration in the parenchyma. If the lobulation is secondary to a pseudomass, the static images will demonstrate normally functioning parenchyma. In some cases, the pseudomass may actually be more intense because of the increased thickness of the parenchyma (37).

If lobulation is not seen sonographically and the mass is atypically cystic, complex, or solid, CT or angiography is recommended. In determining whether a mass is vascular or nonvascular, radionuclide vascular flow studies are 80% to 85% accurate, a rate lower than the other two modalities.

Whether the mass is neoplasm, infarction, abscess, cyst, or localized pyelonephritis, the renal study will be abnormal due to replacement of normal parenchyma that concentrates radionuclide. A typical cyst or infarct will demonstrate no activity on blood flow or on early and delayed images. A

typical renal carcinoma will demonstrate activity on blood flow and early images but a photon-deficient area on delayed images (Fig. 3G.13). An abscess or localized pyelonephritis may be similar to a cyst or tumor, depending on the size and amount of hyperemia.

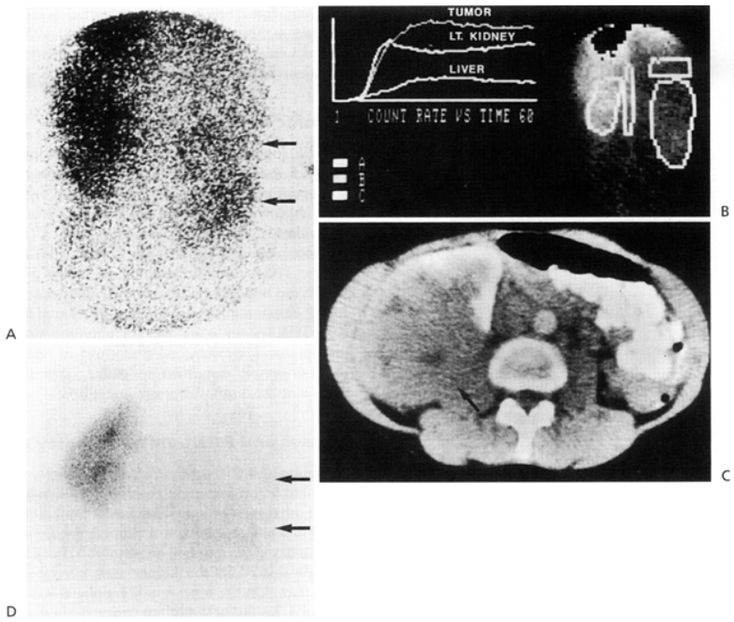

FIGURE 3G.13. Woman, 38 years old, with right hypernephroma. ^{99m}Tc glucoheptonate study showed initial delay of flow to right kidney (0 to 30 seconds). **A:** View at 40 seconds shows definite vascularity of tumor *(arrows)*. **B:** Histogram of blood flow to abdominal organs demonstrates initial delay in blood flow to tumor, then increased activity compared with left kidney. Normal delay in flow to liver is seen, corresponding to portal venous supply. **C:** Static views at 5 minutes show minimal function of right kidney, particularly in the upper pole. **D:** Computed tomography scan shows large right renal mass *(arrows)* with crescentic area of functioning renal tissue present along anteromedial aspect. Bowel loops in the left abdomen are opacified with oral contrast agent.

Hydronephrosis and Hydroureter

One of the most important applications of renal scintigraphy is in the evaluation of urinary tract obstruction. Renal imaging can help in the diagnosis, determination of timing for surgical intervention, and evaluation of therapy. It is also valuable in assessing renal function, which cannot be evaluated reliably by intravenous pyelography (IVP). In the setting of acute obstruction, any renal function implies salvageability, whereas in chronic obstruction, poor function suggests permanent damage.

When the ultrasound examination shows urinary tract dilation, the next question is whether obstruction is present. Conventional urography and radionuclide scanning are unreliable in differentiating obstructive from nonobstructive hydronephrosis.

Perfusion studies introduced by Whitaker (54) obtaining pressure–flow relationships have provided a more functional approach. The procedure requires placing a catheter into the renal pelvis to obtain pressure readings. This is an invasive procedure that can involve a significant radiation dose when done fluoroscopically.

Using parenteral diuretics allows radionuclide renography to be modified to obtain similar information by noninvasive methods. Published reports indicate a high degree of accuracy in distinguishing the dilated obstructed system from the nonobstructed (53).

The success of diuretic renography is directly dependent on strictly following the procedure. First, the patient must be well hydrated either by oral or IV methods. The patient needs to void just before injection or have a Foley catheter inserted for constant drainage. We prefer ^{99m}Tc DTPA because of its excellent visualization of the collecting system and inject 15 mCi (or the appropriate pediatric dose). MAG_3 is used in newborns or where renal function is poor. Images are taken every 5 minutes and continuously on computer until the *entire* collecting system is filled with radionuclide. (If this takes longer than 1 hour, the study decreases in reliability.) The patient then voids and is injected with furosemide, 1 mg/kg, up to 40 mg IV. Images are taken every 5 minutes for the next 30 minutes.

Computer analysis of the renal collecting system activity is performed, resulting in computer curves of the counts. Three curve patterns are possible. A definite decrease in counts with time after furosemide administration represents a nonobstructive pattern (Fig. 3G.14), whereas a definite increase is obstructive (Fig. 3G.15). A plateau signifies an indeterminate pattern, which could be secondary to poor renal function and poor response to furosemide, or a very large atonic hydronephrotic sac. Providing the renal function is good, $T_{1/2}$ (half-time for washout) of less than 10 minutes is normal; greater than 20 minutes indicates obstruction; and 10 to 20 minutes is indeterminate. These numbers are not absolute, and the volume of the affected collecting system is related to the half-time of washout. A distended bladder can also delay the washout, and catheterization of the bladder is often necessary. Efforts have been made to develop consistent methods for performing diuretic renograms for better consistency among institutions (9).

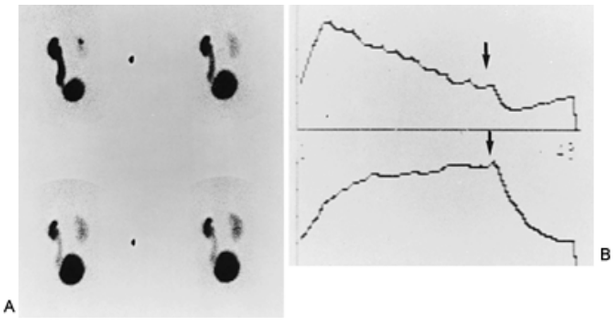

FIGURE 3G.14. Boy, 2 years old, following left ureteral reimplantation. ^{99m}Tc DTPA study. **A:** Posterior images demonstrate left hydronephrosis and hydroureter and a normal right kidney. The top left image was taken 30 minutes after radionuclide injection, at time of furosemide administration. Subsequent images were taken at 5-minute intervals showing radionuclide excretion. **B:** The right kidney *(top curve)* has excreted most of the radionuclide before furosemide administration. The *bottom curve* shows decreasing counts in the left kidney only after furosemide *(arrow)* signifying no evidence of obstruction.

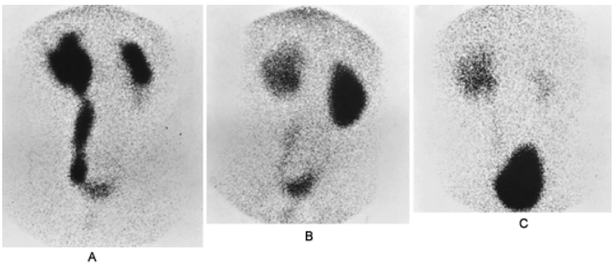

FIGURE 3G.15. Boy, 5 years old, with dilated, nonobstructed collecting system on the left and a dilated, obstructed collecting system on the right. Furosemide ^{99m}Tc DTPA study. **A:** Posterior image taken at 30 minutes after radionuclide injection, at time of furosemide administration. **B:** Twenty minutes after furosemide administration, the nonobstructed left system has emptied and the obstructed right side has accumulated more. **C:** Postoperative image at 25 minutes after furosemide administration shows resolution of obstructed right system.

Vesicoureteral Reflux

Reflux nephropathy is a recognized problem in the pediatric population, and it is evaluated in the workup of urinary tract infection. It is also recognized in some adults as a cause of hypertension, proteinuria, and renal failure. The traditional study is a voiding cystourethrogram, which can deliver a radiation dose of several hundred millirads to several rads. The retrograde radionuclide cystogram gives a fraction of this radiation dose depending on several factors, including the amount of material instilled and the time the solution remains in the bladder before voiding (8).

The traditional voiding cystourethrogram can categorize reflux into grades of severity by visualizing the morphology of the urinary tracts. The radionuclide grading is determined by the volume in the bladder when reflux occurs and the amount of reflux. The anatomy of the collecting system, as well as the base of the bladder and urethra, cannot be assessed (Fig. 3G.16). However, the residual volume after voiding can be accurately determined.

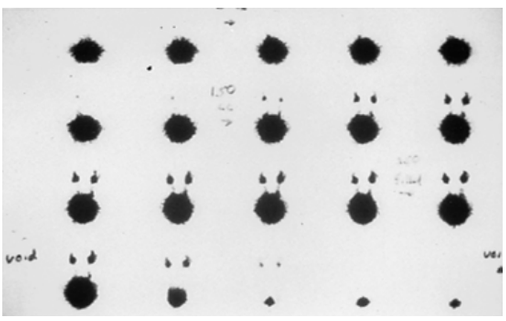

FIGURE 3G.16. Retrograde ^{99m}Tc pertechnetate voiding cystoureterogram demonstrates activity in both ureters and kidneys. The left side refluxes first as the bladder fills, indicating worse reflux. After voiding, activity cleared from the upper tracts.

The quantity of reflux that is significant in a single study

is not yet defined. Serial studies can be of value for comparison to determine whether improvement has occurred. Accurate records of the volumes of solution instilled resulting in reflux are important, as is quantitation of reflux by visual and computer analysis. An increased volume instilled before reflux implies improvement (32). More recently, grading of reflux by radionuclide cystography has been correlated with the criteria for grading established by the International Reflux Study Committee (56). Despite the emphasis in the international study on calyceal detail (26), the correlation is stated to be 80% to 100%.

Studies have now shown that kidney infection, associated with reflux, often causes sufficient damage to result in scarring, proteinuria, or hypertension. Sonography and contrast urograms are relatively insensitive for detection of initial damage (13,43). Renal scans and SPECT with ^{99m}Tc DMSA significantly increase the detection rate and are the recommended screening procedures (Fig. 3G.17).

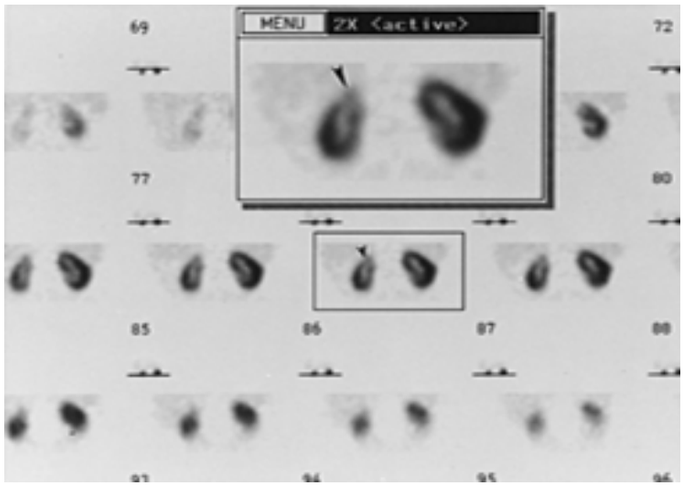

FIGURE 3G.17. Boy, 8 years old, with chronic renal insufficiency and recurrent urinary tract infections. ^{99m}Tc DMSA coronal SPECT images show the right kidney to be smaller than the left kidney with a significant scar in the upper pole *(arrowheads)*. The selected image is magnified. This size defect is often difficult to demonstrate on planar views.

Renovascular Abnormalities

Renal artery stenosis not only plays a role in hypertension but also is a potentially treatable cause of renal failure. In most patients, renal damage has already occurred. Damage can cause abnormalities on the renal images that resemble other diseases, making the results nonspecific. However, this test can still be valuable in following patients with documented renal artery stenosis.

As with renal artery embolism, dynamic radioisotope scanning with technetium compounds is preferred (Fig. 3G.18). On the initial flow images, decreased perfusion of the affected kidney is noted along with reduced concentration followed by a prolonged parenchymal transit time. The sensitivity is 60% to 85%. Serial studies can guide in timing for intervention and evaluation of open surgical or angioplastic treatment.

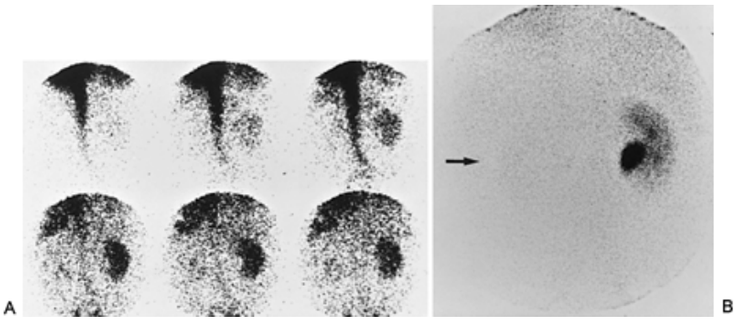

FIGURE 3G.18. Man, 65 years old, with sudden onset of left flank pain and hematuria. **A:** ^{99m}Tc glucoheptonate flow study shows good flow to the right kidney and minimal flow to the left. **B:** Delayed view demonstrates minimal left renal uptake *(arrow);* the right kidney appears normal. The combination of significantly decreased flow to the entire left kidney and delayed uptake is compatible with left renal artery embolus.

Some centers prefer hippurate scanning to evaluate unilateral renovascular disease. Emphasis is on observing differences in the time interval between injection and peak activity (transit time) and on the symmetry of the downslope of the third phase on the renogram curve. The affected kidney will show a prolonged transit time and a slower decline in the excretory phase. A difference of 20% or more in these parameters is generally considered the criterion for positive diagnosis. Accuracy from 87% to 96% has been claimed (34). Analysis of ERPF and fractionation of renal function allow measurement of individual renal flow (Fig. 3G.19).

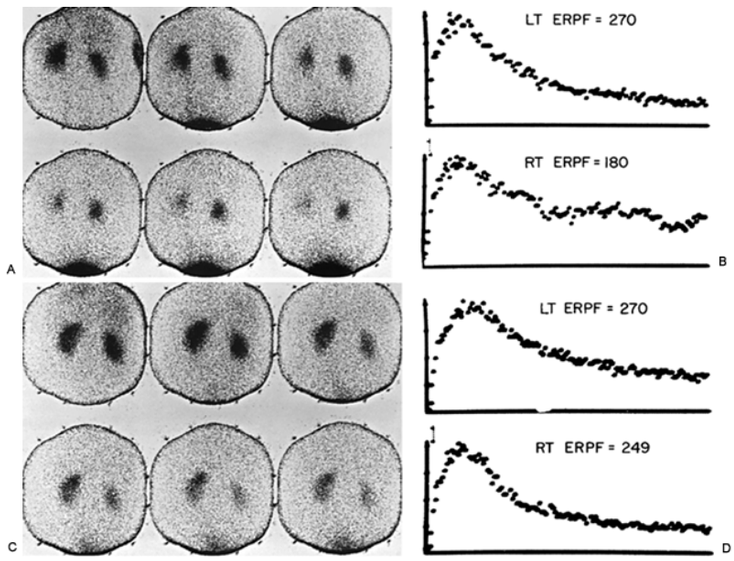

FIGURE 3G.19. Angioplasty of renal artery. **A, B:** Preangioplasty for right renal artery stenosis. ^{131}I hippurate scan shows delayed clearance of the right kidney on the static views and the renogram curve. The effective renal plasma flow (ERPF) was diminished on the right (180 mL per minute) compared with the left. **C, D:** Postangioplasty there was improvement in clearance of the right kidney and the ERPF on the right increased to 249 mL per minute.

Recent studies have shown that the specific effects of angiotensin-converting enzyme inhibitors (captopril) on renal function add both sensitivity and specificity to the radiorenogram. Various authors have advocated using ^{99m}Tc DTPA, ^{99m}Tc MAG_3, or ^{131}I hippurate. Although success has been obtained with all three tracers, the theoretical reasons for using an enzyme inhibitor would seem to favor the use of DTPA. In part, the lack of optimal sensitivity of radiorenograms is due to the intrarenal compensation for a decrease in renal perfusion pressure distal to a stenotic renal artery. It has been demonstrated that the release of renin and subsequent formation of angiotensin II cause a

selective vasoconstriction in the efferent renal arterioles, thus maintaining glomerular filtration pressure. Only when the renal artery stenosis becomes more severe is this compensation inadequate to maintain renal function. Recent studies have shown that comparing renal excretion of ^{99m}Tc DTPA, ^{99m}Tc MAG_3, or ^{131}I hippurate before and after oral administration of 25 to 50 mg of captopril improves the sensitivity of the renogram from 60% to more than 90% (Fig. 3G.20). In addition, there is increased specificity because a lack of response indicates that the compensation mechanism is inoperative (17). Although blockage of the converting enzyme affects the renograms performed with hippurate, MAG_3, and DTPA, the use of the latter agent would seem to be preferred because it is excreted by only glomerular filtration, the physiologic process most affected when compensatory efferent arteriolar vasoconstriction is blocked. However, studies have shown excellent results with MAG_3 (12,15,36).

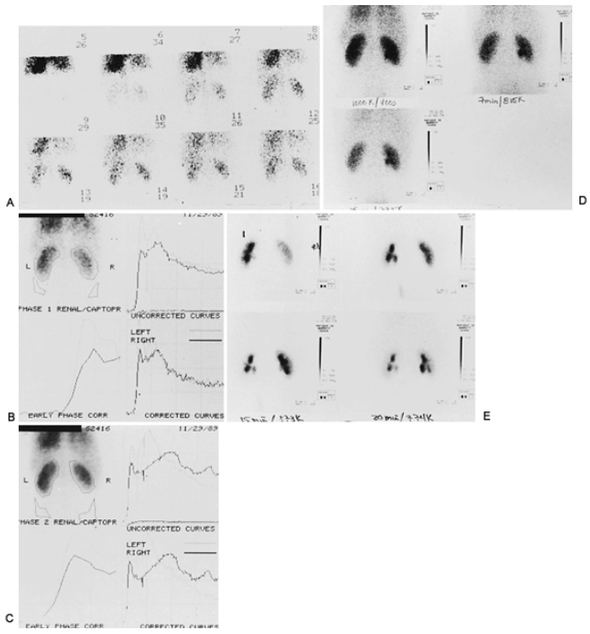

FIGURE 3G.20. Boy, 17 years old, with recent-onset hypertension. Angiographic studies later confirmed 90% stenosis of right renal artery. The vascular sequence **(A)** showed flow reduced somewhat on the right (57% left, 43% right). Baseline ^{99m}Tc DTPA images showed 60% of glomerular filtration rate on the left and 40% on the right. The images suggest slower emptying of the calyces and pelvis on the right **(B).** Renogram curves show the right curve (dark) smaller than the left (light) on both uncorrected and background-corrected graphs **(C).** However, the reduced flow and function could be caused by a small kidney, not necessarily renal artery stenosis. The repeat DTPA study after 25 mg captopril orally **(D, E)** shows further decrease in function on the right (36%) with delayed washout of activity. This adverse response to the converting enzyme is highly suggestive that arterial stenosis with renin release is a causative factor in the hypertension.

Renal vein thrombosis is an uncommon entity that can be imaged with radionuclides. Technetium compounds are preferable because flow studies and detailed static views can be obtained. Typically, in renal vein thrombosis, the involved kidney is enlarged, with decreased flow and poor, delayed uptake (Fig. 3G.21).

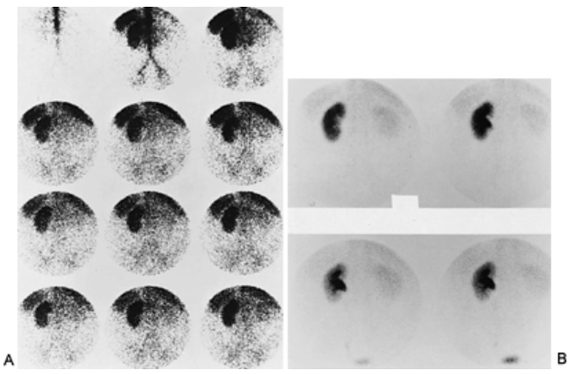

FIGURE 3G.21. Man, 27 years old, developed hematuria after retroperitoneal resection for testicular cancer. ^{99m} Tc glucoheptonate study. **A:** Renal flow study shows poor flow to right kidney. **B:** Static images at 5-minute intervals postinjection show poor right renal uptake. The combination of asymmetric poor flow along with poor function implies renal vein thrombosis. However, usually the involved kidney is also enlarged.

Transplant Evaluation

Radionuclide imaging is a routine part of the assessment of renal function following renal transplant. Our technique involves injection of the patient with ^{99m}Tc MAG_3. Routine images are taken in the anterior position as previously described because of the kidney's position. Computer analysis produces the renogram curves. We look at the total transplant counts, shape of the renogram curve, bladder-to-kidney count ratio at 30 minutes, and static views. Total transplant counts are helpful to compare in serial studies; we have no absolute value for determination of function based on one individual scan. Estimation of renal function with the Gates technique is more quantitative (18).

The bladder-to-kidney ratio is determined by drawing regions of interest around the kidney and the bladder and obtaining total counts at a specific time (23). The normal ratio at 30 minutes is 3:1 to 5:1 with hippurate, but it can be up to 10:1 or more with MAG_3. For this parameter to be useful, the Foley catheter must be clamped, which cannot usually be done until after the first week. Also, native kidneys may still have some function and falsely imply good transplant function.

In the early postoperative period (up to 4 weeks), serial radionuclide scanning and sonography are helpful in following renal function and determining the cause of oliguria or anuria. Total absence of flow and function, along with a photopenic area on the static images, can be caused by renal artery or vein thrombosis, hyperacute rejection, or severe urinary obstruction. Obstruction can usually be diagnosed by ultrasound; however, nonobstructed dilation of the collecting system can occasionally occur after transplantation. Diuretic renography may be helpful in differentiating obstruction from nonobstruction if adequate function is present.

Diminished early radionuclide uptake with progressively increasing activity in later views and poor excretion can be seen with ATN, acute rejection, and urinary obstruction. This pattern implies preserved blood flow but decreased concentrating and excreting capability. A kidney with ATN typically can extract hippurate or MAG_3 from the blood but has difficulty transporting it into the tubular lumen ("tubular block"). Cadaver transplants virtually always show an element of ATN in the early postoperative period. Postoperative ATN will resolve without therapy, after 1 day to several weeks.

As the kidney improves after ATN, the total excreted counts will increase and the bladder-to-kidney ratio will improve (Fig. 3G.22). The shape of the curve may not change initially but contains more counts; after further improvement, the curve will start peaking in the first 10 minutes. Any reversal of this sequence or failure of improvement implies rejection. However, other processes, such as infection or renal artery stenosis, also cause a deterioration in renal function. Considerable confusion has been added to this evaluation in recent years because of the toxicity of the immunosuppressive agent cyclosporine. Unfortunately, by usual techniques it is not possible to differentiate between cyclosporine toxicity and rejection. After 6 months, a renogram is of little value unless serial studies are maintained; serial laboratory values (creatinine and blood urea nitrogen [BUN]) are more pertinent and economical.

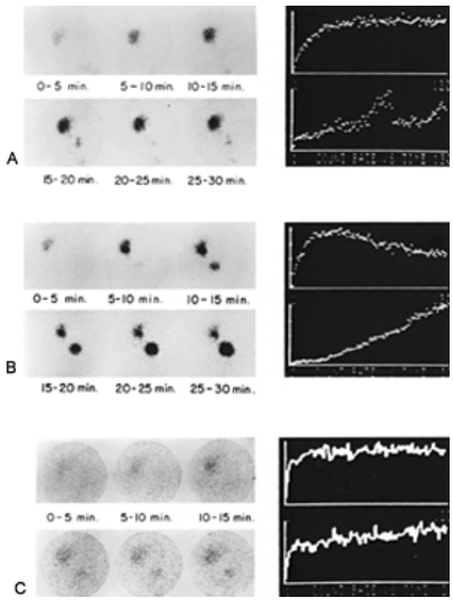

FIGURE 3G.22. Man, 54 years old, with end-stage renal disease who received a cadaver transplant kidney in the right iliac fossa. A series of renograms was performed using 200 µCi of ^{131}I hippurate. **A:** Baseline study 24 hours after transplantation. Sequential camera images *(left)* show progressive accumulation of activity in kidney with transport to urinary bladder. The renogram curves *(right)* reflect progressive kidney accumulation, the plateau occurring after approximately 10 minutes as the tracer emptied into the urinary bladder. The lower curve, from the urinary bladder, shows intermittent emptying because the Foley catheter was not clamped. **B:** The transplant function gradually improved as the acute tubular necrosis cleared. On this study performed 6 weeks after transplantation, the renogram curve *(above)* shows a peak at approximately 8 minutes with a gradual fall in count rate during phase III. Tracer gradually accumulated in the bladder, with a bladder-to-kidney ratio of 2.8:1 at 30 minutes. **C:** Repeat study at 3 months after transplantation. Serum creatinine levels were increased with significant deterioration in renal function. Note the very flat renogram curve *(above)* and minimal accumulation of activity in the urinary bladder. Not only has the bladder-to-kidney ratio deteriorated to 0.6:1, but the total excreted activity in the kidney and bladder fell to approximately 25% of prior values. The patient underwent therapy for rejection with a subsequent improvement in renal function.

Leaks may develop at the ureterovesical anastomosis, at the cystotomy site, or from a renal biopsy site (Fig. 3G.23). These can be well demonstrated by collection of the radionuclide outside of the urinary tract. Hematomas or lymphoceles (Fig. 3G.24) appear as photondeficient areas around the kidney or between the kidney and bladder.

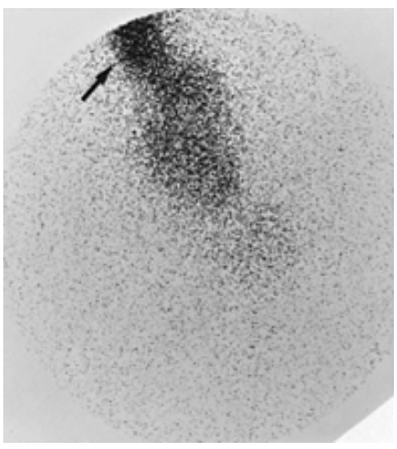

FIGURE 3G.23. Man, 24 years old, 3 weeks after a cadaver transplant. ^{131}I hippurate study shows extravasation of radionuclide at the superior margin of the transplant *(arrow)* representing a urinary anastomotic leak.

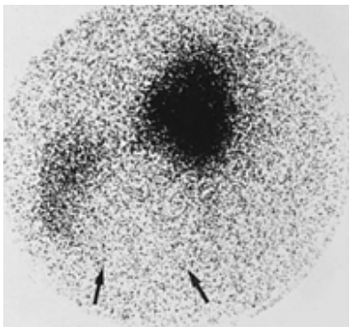

FIGURE 3G.24. Man, 42 years old, developed nephrotic syndrome after transplant. ^{131}I hippurate study shows large photopenic area *(arrows)* compressing the left lateral aspect of the bladder, which proved to be a lymphocele obstructing urinary excretion.

Some centers use technetium compounds to evaluate renal transplants, including evaluation of renal blood flow dynamically. In the normally perfused transplant, activity on the flow or dynamic images should do the following:

1. Appear in the graft within 6 seconds of its appearance in the adjacent iliac artery
2. Obtain maximum activity per unit area equal to or greater than that in the adjacent artery
3. Clearly fall after the peak

Renal blood flow is usually preserved in ATN but deteriorates in rejection. The evaluation of the static views is similar to that of the hippurate images. We have found the MAG_3 renogram to be better than that from hippurate or DTPA alone.

Other agents used include ^{99m}Tc sulfur colloid, gallium citrate Ga-67, and labeled platelets. Although such studies may be useful, they are not routine and are beyond the scope of this chapter.

Congenital Anomalies

Congenital anomalies such as horseshoe kidney (Fig. 3G.25), crossed fused ectopia, and ectopic kidneys are easily demonstrated by radionuclide scanning. ^{99m}Tc DTPA and MAG_3 are the agents of choice.

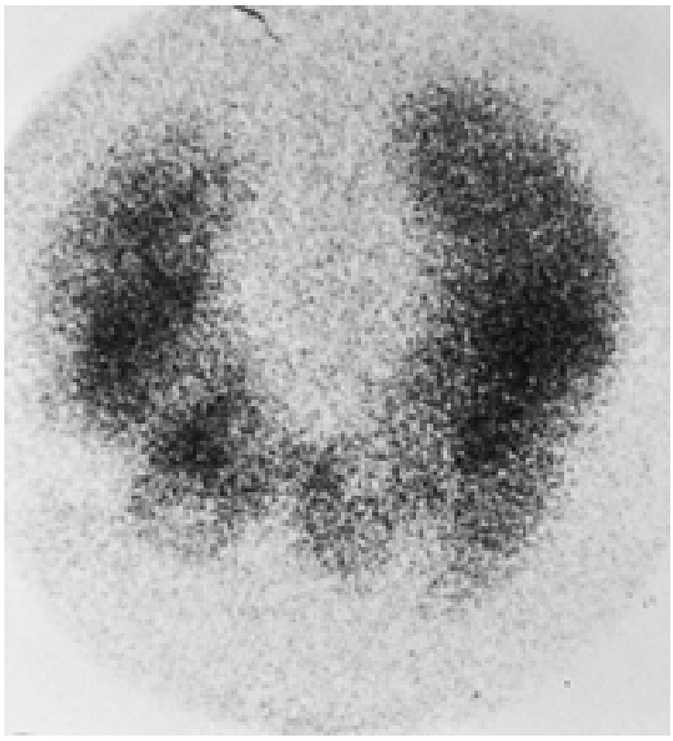

FIGURE 3G.25. Boy, 8 years old, with recurrent urinary tract infections. ^{99m}Tc iron hydroxide DTPA study demonstrates a horseshoe kidney. This anterior view shows the bridging tissue better than a posterior view.

A renal mass in the infant or child should first be evaluated by ultrasound. A solid mass should then be studied by CT. A cystic mass can be either a multicystic dysplastic kidney or hydronephrosis, which can sometimes be difficult to differentiate sonographically. A MAG_3 scan is the next recommended study. Nonvisualization of the corresponding kidney on early and delayed views confirms dysplasia (Fig. 3G.26). However, delayed films may show some activity secondary to a small amount of residual functioning tissue, which is usually irregularly located in a photopenic mass. A more uniform cortical rim sign with gradual filling of the central collecting system is typical of hydronephrosis. The time of appearance of these features during the scanning period depends on the severity of obstruction.

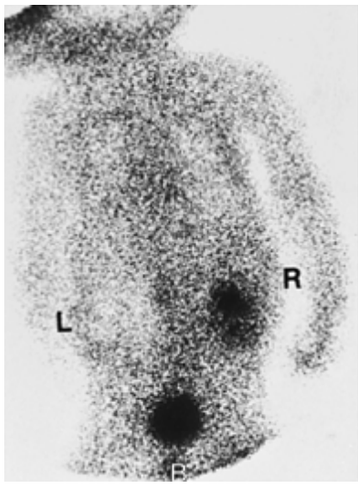

FIGURE 3G.26. Boy, 3 days old, with cystic left kidney on ultrasound. ^{99m}Tc glucoheptonate study demonstrates a normal right kidney and a photon-deficient area in the region of the left kidney that remained photopenic, compatible with a multicystic kidney. Bladder activity *(B)* was evident on this delayed static image.

TRAUMA

The excretory urogram and CT are the traditional modes of initial evaluation of the kidneys in the trauma setting. Many reports have shown the sensitivity of radionuclide image for detection of extent of damage and the evaluation of renal function. However, we advocate CT scanning for initial evaluation because other organs and the retroperitoneum can be evaluated simultaneously. Nuclear imaging can be valuable in following renal function after trauma.

The agent of choice is ^{99m}Tc MAG_3 or DTPA, because blood flow to the kidneys can be rapidly evaluated. If there is no immediate blood flow to either kidney on the flow study or initial static images, immediate angiography or surgical exploration may be necessary. Extravasation and obstruction can also be detected by scanning.

Scrotal Imaging

Scrotal imaging provides an accurate means of distinguishing between the most common causes of “acute” scrotum: epididymitis and testicular torsion. Less common causes include hydroceles and testicular tumors.

In classic acute epididymitis, hyperemia occurs in the head, body, and tail of the epididymis. The radionuclide angiogram shows significantly increased perfusion through the spermatic cord vessels. On the static views, increased tracer activity usually extends laterally, corresponding to the location of the epididymis (Fig. 3G.27).

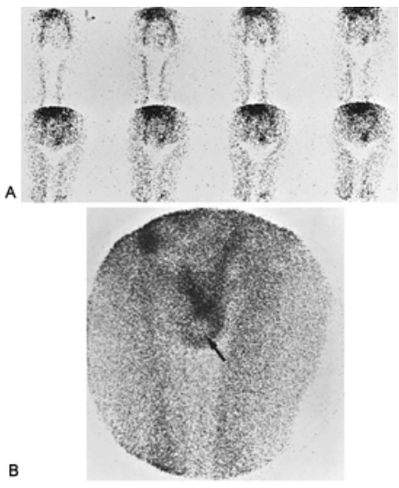

FIGURE 3G.27. Boy, 11 years old, with left testicular swelling. **A:** ^{99m}Tc pertechnetate flow study shows increased blood flow to the left epididymis. **B:** Increased activity along the lateral aspect of the left scrotum on the static views is present, compatible with epididymitis. The right scrotum *(arrow)* contained a hydrocele, causing the photopenic appearance. The differentiation between a photopenic and ischemic testicle and a hydrocele is easy after physical examination and transillumination.

If the inflammatory process spreads to the testis, it is termed *epididymo-orchitis*. The radionuclide activity then extends also medially to involve the testis. Extensive scrotal swelling or rotation of the scrotum in positioning may produce medial activity in the absence of testicular involvement.

If the inflammation is confined to a small area of the epididymis, focal hyperemia occurs only in the infected

part, and the radionuclide angiogram may often show “normal,” barely perceptible activity. Later images may show a focal “spot” of increased activity.

Torsion of the spermatic cord has been described as displaying four radionuclide patterns (25). The first is seen if spontaneous detorsion occurs within 4 hours after torsion, which usually results in a normal scan. Occasionally, mild hyperemia is present throughout the entire hemiscrotum.

In early testicular torsion of less than 7 hours' duration, the testicle is often viable. The radionuclide angiogram shows no increase of perfusion through the vessels or to the scrotum. The scrotal scans demonstrate a cold area in the location of the testicle. In this second pattern, minimal, if any, activity is seen in the dartos, making the cold area often difficult to see.

Midphase testicular torsion occurs approximately 7 to 24 hours after torsion, when the testicle may still be viable. A reactive edema and erythema are present, resulting in increased activity in the scrotal region. This results in a halo of activity around the cold testicle (Fig. 3G.28), the third pattern.

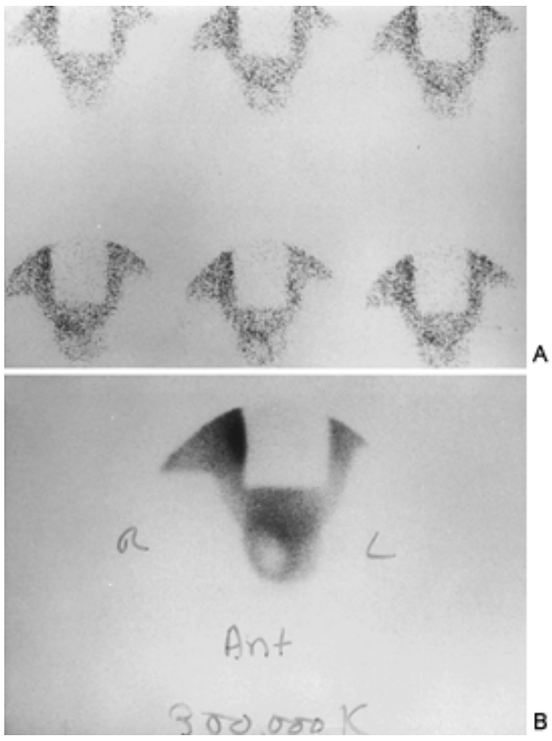

FIGURE 3G.28. Midphase testicular torsion. **A:** Flow study shows no hypervascularity but a developing focal area of increased uptake along the superior aspect of the right testis on later views. **B:** Delayed view shows photopenic area of right testis with surrounding increased uptake along all borders. Because the shield obscured the spermatic vessels, we no longer advocate its use.

The final pattern of “missed testicular torsion” occurs usually more than 24 hours after torsion. The testicle may still be viable if the twist is less than 360 degrees. The radionuclide angiogram will often show dartos perfusion. An intense halo of activity with a cold center is present and occasionally increased activity in the region of the spermatic cord. A testicular abscess can have a similar pattern. This symmetric halo should not be confused with the asymmetric curvilinear activity in epididymitis.

A hydrocele is a collection of fluid between the layers of the tunica vaginalis. It may be primary or secondary to epididymitis, testicular torsion, tumor, trauma, or posthernia repair. On the radionuclide angiogram, the perfusion is normal or a reflection of the underlying cause. The scrotal scan demonstrates a lucency around the central nidus of testicular tissue.

Radionuclide scanning of testicular tumors is usually performed to exclude other causes of the pain and swelling. The radionuclide angiogram may show normal or moderately

increased perfusion. If increased, the scrotal perfusion is diffuse rather than linear or halolike. A cool area may represent a focal area of central necrosis or relative tissue avascularity (25).

EVALUATION OF PROSTATE CANCER

Adenocarcinoma of the prostate is the most commonly diagnosed malignancy in men. As in the case of all malignancies, appropriate therapeutic intervention requires accurate staging. Clinical examination, serum prostate-specific antigen (PSA) level, Gleason score, and imaging modalities such as bone scintigraphy, CT, and magnetic resonance imaging (MRI) are used for staging prostate carcinoma. However, the sensitivity of CT and MRI is poor in detecting lymph node metastases (52). A monoclonal antibody (Capromab pendetide) that reacts with prostate-specific membrane antigen (PSMA) has been commercially available for imaging prostate carcinoma for several years. PSMA is a glycoprotein produced by both the benign and malignant epithelial cells of the prostate gland. Capromab pendetide is a murine immunoglobulin (IgG_1) that is radiolabeled with indium-111 and reacts with more than 95% of prostate carcinomas (21). It is available for injection in a kit form (10). In-111 chloride is used for radiolabeling. After IV injection, Capromab pendetide is slowly cleared from the bloodstream. It is eliminated via the kidneys and by the gastrointestinal tract.

The incidence of adverse events following the antibody infusion is low (4%). The incidence of human antimurine antibody (HAMA) titers greater than 8 ng/mL after a single IV injection is reported to be 8%. The FDA has approved it for single injection. The incidence of HAMA levels greater than 8 ng/mL after repeated injections is reported to be 19%, but the incidence of adverse reactions is only 5%, with altered biodistribution present in 7% (21,31).

Anterior and posterior imaging of the chest, abdomen, and pelvis is performed at 72 to 96 hours. On a normal scintiscan, activity is seen in the liver, kidneys, bone marrow, urinary bladder, and bowel. Occasionally, significant bowel activity can cause interference with image interpretation, and a laxative 24 hours before imaging is routinely used. Sometimes, additional delayed imaging at 96 to 120 hours is necessary. Planar imaging is followed by SPECT imaging of the pelvis and abdomen (Fig. 3G.29). We recommend simultaneous blood pool imaging with ^{99m}Tc-labeled RBCs at 72 to 96 hours to provide an outline of the blood vessels and improve the specificity (29). Image coregistration with pelvic CT using blood vessels as anatomic landmarks is technically feasible and improves specificity (20). Some authors use a subtraction analysis software that subtracts the ^{99m}Tc-RBC data set from the In-111 data set to allow easier identification of the metastatic sites (39).

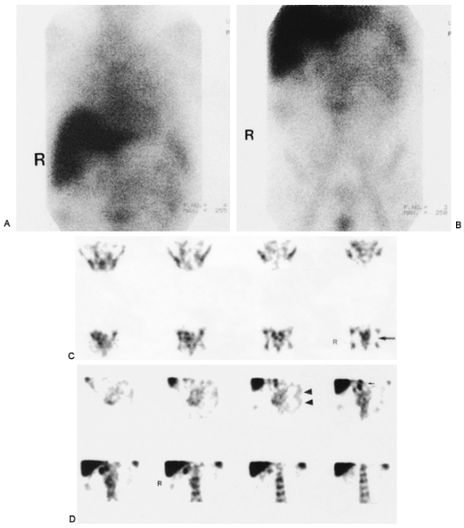

FIGURE 3G.29. Man, 65 years old, with newly diagnosed prostate cancer. **A:** Anterior planar image of the chest and abdomen was obtained 96 hours after the injection of In-111 Capromab pendetide. Uptake is seen in the blood pool of the heart, liver, and bowel. **B:** Anterior planar image of the abdomen and pelvis shows uptake in the iliac vessels, bowel, and bone marrow. **C:** Transverse SPECT images of the pelvis show uptake in the prostate *(arrow),* consistent with carcinoma. **D:** Coronal SPECT images of the abdomen (day 5) show uptake in the bowel *(arrowheads),* as well as focal uptake in the midline suggestive of periaortic lymph nodes.

Altered biodistribution manifested by intense liver, bone marrow, and urinary bladder uptake is sometimes seen. The etiology for this phenomenon is unknown, but it decreases the sensitivity of the test. Accumulation of the antibody is seen in areas of inflammation such as arthritis, fractures, surgical incision sites, and reactive lymph nodes. Accumulation in Paget's disease of the bone and necrotic tumors has also been reported (21).

Since the availability of this antibody, many clinical studies have been performed. It is useful in patients with new diagnosis of prostate carcinoma who are at high risk for metastatic disease and in patients with elevated PSA after radical prostatectomy.

Hinkle and colleagues (24), in a multicenter trial, studied 51 patients with prostate carcinoma at high risk for metastases with the antibody scan. All of the patients underwent prostatectomy and open pelvic lymphadenectomy. They reported the sensitivity and specificity for detecting extraprostatic disease as 75% and 86%, respectively. The accuracy and positive predictive value was 81% and 79%, respectively. A study by Burgers and co-workers (6) also compared the imaging findings on the antibody scan with CT or MRI and surgery. They reported an accuracy of 92% for detecting prostate cancer and 81% for extraprostatic lesions with the antibody imaging compared with an accuracy of 53% and 48% with other imaging modalities such as CT or MRI. They also reported “skip metastases” in two patients at the level of aortic bifurcation. These patients had negative pelvic lymph nodes at surgery (6). Although these statistics are better than CT or MRI, the results vary considerably. Babaian and colleagues (2) reported a sensitivity and specificity of 44% and 86%, respectively, in a study of 19 patients undergoing pelvic lymph node dissection. However, all of these studies were reported before the use of ^{99m}Tc-RBC blood pool imaging.

In 181 patients with recurrent prostate cancer after radical prostatectomy and rising PSA, antibody imaging was performed to evaluate local recurrence and distant metastases (27). All patients had prostatic fossa biopsied. Immunoscintigraphy showed disease in 60% of patients, with localization more frequently to the prostatic fossa (34%). Extraprostatic localization was seen in 42%. Abdominal lymph nodes showed localization in 23% and pelvic lymph nodes in 22% of the patients. Only 50% of the patients with positive scans in the prostatic fossa had the finding confirmed by biopsy. The overall sensitivity was 49%, specificity 71%, positive predictive value 50%, and negative predictive value 70%. The investigators concluded that single biopsy of the prostatic fossa is insensitive because of the sampling error involved. The accuracy for detecting distant metastases was not evaluated by this study because the extraprostatic sites of antibody localization were not confirmed by other conventional imaging modalities or biopsies in this study (27).

Thirty-two patients with failed radical prostatectomy were evaluated with the antibody scan (28). After pelvic radiotherapy, these patients were followed for 13 months. Seventy percent of patients with antibody localization only to the prostate bed had a durable complete response; 22% had a positive extraprostatic and extrapelvic localization (28).

Haseman and colleagues (22) imaged 14 patients with elevated PSA with Capromab pendetide imaging and F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging. All patients had biopsies of the prostatic fossa. In the limited number of patients studied, antibody scan was superior to PET imaging in the detection of both local recurrence and lymph node metastases (22). However, more studies are needed to confirm this finding.

Antibody imaging with Capromab pendetide is used for patients with a new diagnosis of prostate cancer and high risk of metastatic disease and in patients with failed radical prostatectomy. Capromab pendetide imaging is challenging, and experience, along with dual isotope imaging with ^{99m}Tc-RBC labeling, is of great help.

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4
URINARY TRACT INFECTIONS

Anthony J. Schaeffer
A.J. Schaeffer: Department of Urology, Northwestern University Medical School, Chicago, IL 60611.

Contents

Urinary tract infections are common, affect men and women of all ages, and vary dramatically in their presentation and sequelae. Although the urinary tract is normally free of bacterial growth, bacteria that generally ascend from the rectal reservoir may cause urinary tract infections. When bacterial virulence increases or host defense mechanisms decrease, bacterial inoculation, colonization, and infection of the urinary tract occur. Clinical manifestations can vary from asymptomatic bacterial colonization of the bladder to irritative voiding symptoms associated with bacterial infection, upper tract infections associated with fever and chills, and bacteremia associated with severe morbidity, including

sepsis and death. The clinical challenges are (a) to identify patients at risk; (b) to prevent or minimize infections by reducing factors that increase the risk of infection; (c) to accurately and efficiently diagnose infections; and (d) to provide prompt, effective, and safe therapy in a cost-effective manner. This chapter defines various types of infection and reviews the epidemiology and bacterial and host factors instrumental in urinary tract infections. The clinical manifestations and diagnostic techniques used to identify the site and severity of infection are then discussed. Pertinent antimicrobial agents and their use are reviewed. Common clinical scenarios are discussed, beginning with the clinical and laboratory findings, the differential diagnoses, and sequential management steps necessary to achieve satisfactory results.

DEFINITIONS

Part of "4 - URINARY TRACT INFECTIONS "

Urinary tract infection is an inflammatory response of the urothelium to bacterial invasion. *Bacteriuria* is a commonly used term that means bacteria in the urine. It has been assumed to be a valid indicator of either bacterial colonization or bacterial infection of the urinary tract. Although this is usually true, studies in animals (153,232) and humans (75) have indicated that bacteria may colonize the urothelium without causing bacteriuria. *Pyuria,* the presence of white blood cells (WBCs) in the urine, is generally indicative of infection and a significant inflammatory response of the urothelium to the bacterium. Bacteriuria in the absence of pyuria is generally indicative of bacterial colonization without infection of the urinary tract. Alternatively, bacteriuria may represent bacterial contamination of an abacteriuric specimen during collection. The possibility of contamination increases as the reliability of the collection technique decreases from suprapubic aspiration, to catheterization, to voided specimens. The term *significant bacteriuria* has a clinical connotation and is used to describe the number of bacteria in a suprapubically aspirated, catheterized, or voided specimen that exceeds the number usually caused by bacterial contamination from the skin, the urethra, or the prepuce or introitus, respectively. Hence, it represents a urinary tract infection.

Infections are often defined by their presumed site of origin. *Cystitis* describes a clinical syndrome associated with dysuria, frequency, urgency, and occasionally suprapubic pain. These symptoms, although generally indicative of cystitis, may also be associated with infection of the urethra or vagina or noninfectious conditions such as interstitial cystitis, bladder carcinoma, or calculi. Conversely, patients may be asymptomatic and have infection of the bladder and possibly the upper urinary tract.

The term *bacterial nephritis* should be reserved for interstitial renal inflammation primarily caused by the immediate or late effects of bacterial infection in the renal parenchyma. *Pyelonephritis* refers to bacterial nephritis involving the renal parenchyma and collecting system. *Acute pyelonephritis* refers to a clinical symptom complex or pathologic lesion characterized by fever, chills, and flank pain, or tenderness that is always associated with urinary tract infection. It may, however, have no morphologic or functional components detectable by routine clinical modalities. *Chronic pyelonephritis* describes a shrunken, scarred kidney that can only be diagnosed when there is postinfectious morphologic, radiologic, or functional evidence of renal disease. However, it need not be associated with urinary tract infection at the time of study.

Acute prostatitis is a febrile urinary tract infection associated with prostate tenderness and swelling and irritative voiding symptoms. *Chronic bacterial prostatitis* is a subtle condition characterized by recurrent relapsing urinary tract infections caused by persistence of the pathogen in the prostatic secretory system between courses of antimicrobial therapy. *Nonbacterial prostatitis* refers to an inflamed prostate without bacterial infection.

Urinary tract infections may also be described in terms of the anatomic or functional status of the urinary tract and the health of the host. Infections occurring in a functionally and anatomically normal urinary tract and a healthy host are considered *uncomplicated* infections. A *complicated* infection is associated with factors that increase the chance for acquiring bacteria and decrease the efficacy of therapy (Table 4.1). The urinary tract is functionally or anatomically abnormal, the host is compromised, or the bacteria have increased virulence. Renal diseases that reduce the concentrating ability of the kidney or neurologic conditions that alter bladder-emptying capabilities are commonly encountered functional abnormalities. Examples of common anatomic abnormalities include obstruction associated with calculi or enlargement of the prostate or congenital or acquired sites of residual urine, such as calyceal or bladder diverticula.

- Functional or anatomic abnormality of urinary tract
- Male gender
- Pregnancy
- Elderly
- Diabetes
- Immunosuppression
- Childhood urinary tract infection
- Recent antimicrobial use
- Indwelling urinary catheter
- Urinary tract instrumentation
- Hospital-acquired infection
- Symptoms for greater than 7 days at presentation

TABLE 4.1. FACTORS THAT SUGGEST COMPLICATED URINARY TRACT INFECTION

Infections may be defined by their relationship to other urinary tract infections. A *first* or *isolated infection* is one that occurs in an individual who has never had a urinary tract infection or has one remote from a previous urinary tract

infection. An *unresolved infection* is one that has not responded to antimicrobial therapy. A *recurrent infection* is one that occurs after documented, successful resolution of an antecedent infection. If the infection is a new event associated with reintroduction of bacteria into the urinary tract from outside, the term *reinfection* is appropriate. If the recurrent infection is due to bacteria reemerging from a focus within the urinary tract, the term *bacterial persistence* or *bacterial relapse* is used. These definitions require careful clinical and bacteriologic assessment and are important because they influence the type and extent of the patient's evaluation and therapy.

The presumed source of bacteria that causes the infection can be used to further define infections. *Domiciliary infections,* or *outpatient-acquired infections,* occur in individuals who are not institutionalized at the time they incur the infection. *Nosocomial infections,* or *health care–associated infections,* occur in individuals who are hospitalized or institutionalized and, often, in those who are catheterized (i.e., catheter-associated nosocomial urinary tract infections). Domiciliary infections are usually caused by common fecal bacteria (i.e., Enterobacteriaceae) and are generally susceptible to most antimicrobial therapy, whereas nosocomial infections are frequently caused by *Pseudomonas* and other more antimicrobial-resistant strains.

EPIDEMIOLOGY

Part of "4 - URINARY TRACT INFECTIONS "

Urinary tract infections are among the most common infectious diseases acquired by humans, affecting more than 7 million people annually in the United States and accounting for substantial morbidity (140). Urinary tract infections affect approximately 30% of women between the ages of 20 and 40, a prevalence 30 times more than in men, and at least half of all women will experience one or more infections during their lifetime (140,190). However, with increasing age, the ratio of women to men with bacteriuria progressively decreases. At least 20% of women and 10% of men older than 65 years of age have bacteriuria (23). Many adults previously had urinary tract infections as children (104). Once a patient has an infection, he or she is likely to develop subsequent infections. Longitudinal studies in young women with symptomatic recurrent infections have shown an overall attack rate of 0.2 infections per month (182). Infections tended to occur in clusters that were followed by remission-free intervals that averaged approximately 1 year. However, most remissions were followed by recurrent urinary tract infection, thus underscoring the importance of genetic factors in the pathogenesis of recurrent urinary tract infections in women.

Risk factors can be compounded. The prevalence of bacteriuria increases with institutionalization or hospitalization and concurrent disease. In a study of women and men older than 68 years of age, Boscia and Kaye (23) found that 24% of functionally impaired nursing home residents had bacteriuria compared with 12% of healthy domiciliary subjects (24). It is well established that in the presence of obstruction, infection stones, or diabetes mellitus, urinary tract infections in adults can lead to progressive renal damage (96). In the absence of these complicating factors, it is difficult to implicate infection in the pathogenesis of severe renal disease in adults.

PATHOGENESIS

Part of "4 - URINARY TRACT INFECTIONS "

Successful invasion of the urinary tract is determined in part by the virulence characteristics of the bacteria, the inoculum size, and the inadequacy of host defense mechanisms. These factors also play a role in determining the ultimate level of colonization and damage to the urinary tract.

Routes of Infection

Ascending Route

Most bacteria enter the urinary tract from the fecal reservoir via ascent through the urethra into the bladder. This route is enhanced in individuals with significant soilage of the perineum with feces, women using spermicidal agents (142), and patients with intermittent or indwelling catheters.

The weight of clinical and experimental evidence strongly suggests that most episodes of pyelonephritis are caused by retrograde ascent of bacteria from the bladder through the ureter to the renal pelvis and parenchyma. Although cystitis is often restricted to the bladder, in approximately 50% of instances, there is further extension of the infection into the upper urinary tract (32). Although reflux of urine is probably not required for ascending infections, edema associated with cystitis may cause sufficient changes in the ureterovesical junction to permit reflux. Once the bacteria are introduced into the ureter, they may ascend to the kidney unaided. However, this ascent would be greatly increased by any process that interferes with the normal ureteral peristaltic function. Gram-negative bacteria and their endotoxins, as well as pregnancy and ureteral obstruction, have a significant antiperistaltic effect.

Bacteria that reach the renal pelvis can enter the renal parenchyma by means of the collecting ducts at the papillary tips and then ascend upward within the collecting tubules. This process is hastened and exacerbated by increased intrapelvic pressure from ureteral obstruction or vesicoureteral reflux, particularly when it is associated with intrarenal reflux.

Hematogenous Route

Infection of the kidney by the hematogenous route is uncommon in normal individuals. However, the kidney is

occasionally secondarily infected in patients with *Staphylococcus aureus* bacteremia from oral sites or with *Candida fungemia.* Experimental data indicate that infection is enhanced when the kidney is obstructed (322).

Lymphatic Route

Direct extension of bacteria from the adjacent organs via lymphatics may occur in unusual circumstances, such as a severe bowel infection or retroperitoneal abscesses. There is little evidence that lymphatic routes play a significant role in the vast majority of urinary tract infections.

Urinary Pathogens

Most urinary tract infections are caused by facultative anaerobes usually originating in the bowel flora. Uropathogens such as *Staphylococcus epidermidis* and *Candida albicans* originate in the flora of the vagina or perineal skin.

Escherichia coli is by far the most common cause of urinary tract infections, accounting for 85% of community-acquired and 50% of hospital-acquired infections. Other Gram-negative Enterobacteriaceae, including *Proteus* and *Klebsiella,* and Gram-positive *Enterococcus faecalis* and *Staphylococcus saprophyticus* are responsible for the remainder of most community-acquired infections. Nosocomial infections are caused by *E. coli, Klebsiella, Enterobacter, Citrobacter, Serratia, Pseudomonas aeruginosa, Providencia, Enterococcus faecalis,* and *S. epidermidis* (175). Less common organisms such as *Gardnerella vaginalis, Mycoplasma* species, and *Ureaplasma urealyticum* may infect patients with intermittent or indwelling catheters (81,167).

The prevalence of infecting organisms is influenced by the patient's age. For example, *S. saprophyticus* is now recognized as causing approximately 10% of symptomatic lower urinary tract infections in young, sexually active females (192), whereas it rarely causes infection in males and elderly individuals. A seasonal variation with a late summer to fall peak has been reported (148).

Virulence characteristics play a role in both selecting the organism that will invade the urinary tract and determining its level of infection within the urinary tract. It is generally believed that uropathogenic strains, such as *E. coli,* are selected from fecal flora not by chance but rather by the presence of virulence factors that enable them to adhere to and colonize the perineum and urethra and migrate to the urinary tract where they establish an inflammatory response in the urothelium (298,399). Subsequently, other virulence factors that play a role in the persistence and expansion of infection include resistance to serum bactericidal activity (21), hemolysin (150), and aerobactin (164). Half of all second urinary tract infections are caused by the same strain that causes the first and has identical virulence factors (94).

Bacterial Adherence in the Pathogenesis of Urinary Tract Infections

It is well established that bacterial adherence to epithelial cells is an essential early step in the initiation of urinary tract infections. This interaction is influenced by the adhesive characteristics of the bacteria, the receptive characteristics of the epithelial surface, and the fluid bathing both surfaces. Bacterial adherence is a specific interaction that plays a role in selecting the organism, the host, and the site of infection. Portions of this section on bacterial adherence have been published (298).

Bacterial Adhesins

The bacterial cell structures that seem to be most important in binding the bacteria to epithelial cells are long filamentous protein appendages called pili, or fimbriae (Fig. 4.1). Bacteria may produce a number of antigenically and functionally different pili on the same cell; others produce a single type; and in some, no pili are seen (179). A typical piliated cell may contain 100 to 400 pili. These supramolecular structures are usually 5 to 10 nm in diameter, up to 2 μm long, and appear to be composed primarily of subunits known as pilin, which have molecular weights of 17 to 27 kDa, depending on the type of pili (179). *Pili* are defined functionally by their ability to mediate hemagglutination (HA) of specific types of erythrocytes. The most well-described pili are type 1 and P pili. Type 1 pili are commonly expressed on both nonpathogenic and pathogenic *E. coli* and appear to facilitate bacterial colonization of the vaginal mucosa and bladder. These pili mediate HA of guinea pig erythrocytes (67). The reaction is inhibited by the addition of mannose; thus type 1 pili are termed *mannose-sensitive HA* (MSHA) (275,357). P pili have receptors that adhere to α-D-Galp-(1-4)ß-D-Galp belonging to the globoseries of glycolipids (168,196), which are found on P blood group antigens and in uroepithelium (356). Adherence

of P-piliated strains to human red blood cells is not inhibited by mannose; hence, P pili are termed *mannose-resistant HA* (MRHA) (169,275,357).

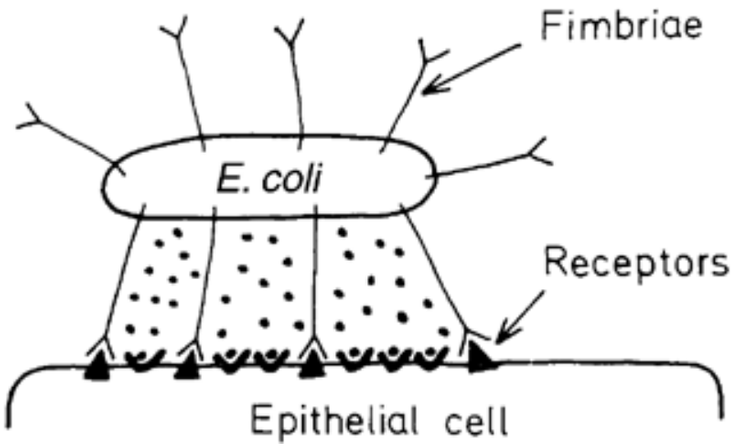

FIGURE 4.1. Bacterial adherence. Adhesins on pili mediate attachment to specific epithelial cell receptors. (Reprinted with permission from Schaeffer AJ. The role of bacterial adherence in urinary tract infection. *AUA Update Series* 1989;8:18.)

Bacterial pili are subject to rapid phase variation *in vitro* and *in vivo* wherein bacteria revert between states of expression and nonexpression of pili. For example, some bacteria grown in a broth medium express pili, whereas the same strain grown on the same medium in a solid state will cease production of pili. Occurrence of phase variation may contribute to the pathogenesis of infections (72,154).

Evidence for the role of type 1 and P pili in urinary tract infection has been established by *in vitro* and *in vivo* studies. Svanborg Eden and associates (355) were the first to report a correlation between bacterial adherence *in vitro* and severity of urinary tract infections. They showed that *E. coli* strains from girls with acute pyelonephritis had high adhesive ability, whereas strains from girls with asymptomatic bacteriuria or normal feces had low bacterial adherence. Between 70% and 80% of the pyelonephrogenic strains had adhesive capacity, but only 10% of the fecal isolates adhered. This association is not observed in individuals with abnormal urinary tracts. Lomberg and colleagues (200), for example, showed that in girls, recurrent pyelonephritis with gross reflux (in which most of the scarring historically occurs) was minimally associated with P-piliated *E. coli* strains.

Type 1 pili consist of a helical rod composed of repeating Fim A subunits joined to a 3-nm wide distal tip structure containing the adhesin Fim H (165). Binding of the Fim H adhesin to mannosylated host receptors present on the urothelium is critical to the ability of *E. coli* to colonize the bladder and cause cystitis (52,190,360). Animal studies showed that *E. coli* expressing type 1 pili, but not those not expressing pili, can cause urinary tract infections (159). Furthermore, anti-type 1 pili antibodies and competitive inhibitors protected animals from experimental urinary tract infections (7,153).

An animal model of ascending urinary tract infections and studies of isolates from different sites in patients with urinary tract infection provide evidence that phase variation can occur during *E. coli* urinary tract infection *in vivo.* Type 1 piliated *E. coli* that were capable of phase variation were introduced into the mouse bladder in the piliated phase, and the bacteria recovered from the bladder and urine 24 or more hours after inoculation were tested for piliation. All of the animals had bladder colonization, and 78% of the bacteria recovered showed type 1 piliation. The bacteriologic state of the urine often differed from that of the bladder. The urine was sterile in 59% of the animals with bladder colonization, and the bacteria recovered from the urine were often nonpiliated. Phase variation also occurred over time. When bladder and kidney cultures were examined 1, 3, and 5 days after intravesical inoculation of piliated bacteria, organisms recovered from the bladder remained piliated, whereas organisms recovered from the kidney and urine showed significantly less piliation (297a) (Fig. 4.2).

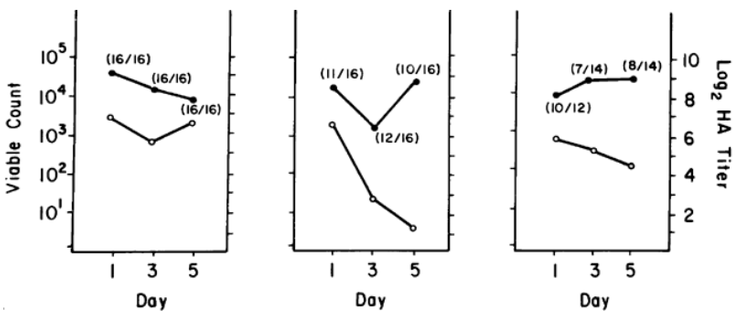

FIGURE 4.2. Time study after intravesical inoculation with strain I-149 that compared the mean viable-bacteria count *(open circle)* and HA titer *(closed circle)* for bladders **(A),** kidneys **(B),** and urine specimens **(C)** from the same animals. Each point is the mean of all the animals tested. The numbers in parentheses show the proportion of animals inoculated that gave positive cultures. The HA titers were tested after 18 hours of growth on agar. The HA titer of bacteria recovered from the kidney decreased significantly by day 5 (P <.001). (Reprinted with permission from Schaeffer AJ, Amundsen SK, Schmidt LN. Adherence of *E. coli* to human urinary tract epithelial cells. *Infect Immun* 1979;24:753.)

Studies in humans using indirect immunofluorescence of fresh urine bacteria have confirmed *in vivo* expression and

phase variation of pili. Kisielius and associates (178) analyzed the urine of adults with lower urinary tract infection and detected type 1 pili in 31 of 41 specimens and P pili in 6 of 18 specimens. The piliation status of the bacterial population in the urine was heterogeneous, varying from predominantly piliated to a mixture of piliated and nonpiliated cells (Fig. 4.3). Strains isolated from different sites in the urogenital tract showed variation in the state of piliation. These results demonstrate that *E. coli* type 1 and P pili are expressed and subject to phase variation *in vivo* during acute urinary tract infections.

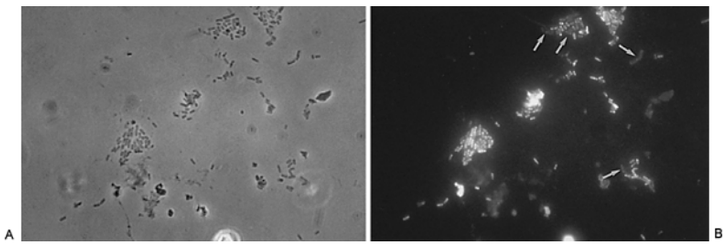

FIGURE 4.3. Phase-contrast micrograph **(A)** and immunofluorescence **(B)** stained with antiserum to type 1 pili of strain I-149 and with fluorescein-5-isothiocyanate (FITC)-conjugated second antibody of nonadherent *E. coli* in the urine of a patient with acute urinary tract infection showing a mixture of piliated and nonpiliated *(arrows)* cells. (Reprinted with permission from Kisielius PV, Schwan WR, Amundsen SK, et al. *In vivo* expression and phase variation of type-1 and P pili by *Escherichia coli* in the urine of adults with acute urinary tract infections. *Infect Immun* 1989;57:1656.)

This process of phase variation has obvious biologic and clinical implications. For example, the presence of type 1 pili may be advantageous to the bacteria for initially adhering to and colonizing the bladder mucosa. Subsequently, type 1 pili may be unnecessary for strains in suspension in urine, and in fact detrimental because they enhance apoptosis, phagocytosis, and killing by neutrophils (232,318). In the kidney, P pili may then take over as the primary mediator of bacterial attachment via their binding to the glycolipid receptors (348).

Epithelial Cell Receptivity

The significance of epithelial cell receptivity in the pathogenesis of ascending urinary tract infection has been studied initially by examining adherence of *E. coli* to vaginal epithelial cells and uroepithelial cells collected from voided urine specimens. Fowler and Stamey (92) established that certain indigenous microorganisms (e.g., lactobacilli, *S. epidermidis*) avidly attached themselves to washed epithelial cells in large numbers. When vaginal epithelial cells were collected from patients susceptible to reinfection and compared with such cells obtained from controls resistant to urinary tract infection, the *E. coli* strains that cause cystitis adhered much more avidly to the epithelial cells from the susceptible women. These studies established increased adherence of pathogenic bacteria to vaginal epithelial cells as the first demonstrable biologic difference that could be shown in women susceptible to urinary tract infection.

Subsequently, Schaeffer and colleagues (298) confirmed these vaginal differences in women, but in addition, they observed that the increased adherence was also characteristic of buccal epithelial cells. As can be seen in Fig. 4.4, there is a striking similarity in the ability of both cell types to bind the same *E. coli* strain. In addition, there was a significant relationship between vaginal cell and buccal cell receptivity. Seventy-seven different *E. coli* strains were tested for their ability to bind to vaginal and buccal epithelial cells. A direct nonlinear relationship between buccal and vaginal adherence in controls and patients was confirmed for urinary, vaginal, and anal isolates. Thus high vaginal cell receptivity was associated with high buccal cell receptivity.

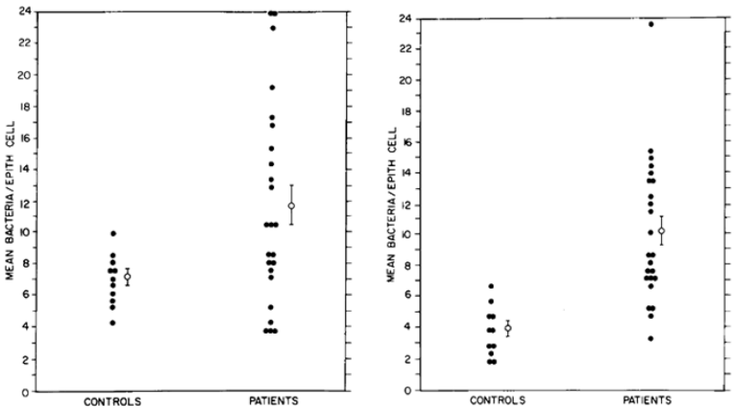

FIGURE 4.4. *In vitro* adherence of *E. coli* to vaginal **(A)** and buccal **(B)** cells from healthy controls and patients with recurrent urinary tract infections. Values represent an average of 14 **(A)** and 11 **(B)** determinations in each individual. The *open circles* and *bars* represent the means plus standard error. (Reprinted with permission from Schaeffer AJ et al. Association of *in vitro Escherichia coli* adherence to vaginal and buccal epithelial cells with susceptibility of women to recurrent urinary-tract infections. *N Engl J Med* 1981;304:1062.)

These observations emphasize that the increase in receptor sites for *E. coli* on epithelial cells from women with recurrent urinary tract infections is not limited to the vagina and thus suggest that a genotypic trait for epithelial cell receptivity may be a major susceptibility factor in urinary tract infections. This concept was extended by examining the human leukocyte antigens (HLAs), which are the major histocompatibility complex in humans and have been associated statistically with many diseases (299). The A3 antigen was identified in 12 (34%) of the patients, a frequency significantly higher than the 8% frequency observed in healthy controls. Thus HLA-A3 may be associated with increased risk of recurrent urinary tract infections.

Bladder urothelial cells deposit on their apical surfaces a quasi-crystalline array of hexagonal complexes made up of four integral membrane glycoproteins known as *uroplakins* (132,353). *In vitro* binding assays have shown that two of the uroplakins, UPIa and UPIb, bind *E. coli* expressing type 1 pili (397). Blood group antigens, carbohydrate structures bound to membrane lipids or proteins, also constitute an important part of the uroepithelial cell membrane. The presence or absence of blood group determinants on the surface of uroepithelial cells may influence an individual's susceptibility to a urinary tract infection. Sheinfeld and associates (313) determined the blood group phenotypes in women with recurrent urinary tract infection and compared them to age-matched women controls. Women with Lewis Le(a-b-) and Le(a+b-) phenotypes had a significantly higher incidence of recurrent urinary tract infections than women with Le(a-b+) phenotypes. There was no significant difference in the distribution of ABO or P blood group phenotypes. The Lewis antigen controls fucosylation. The protective effect in women with the Le(a-b+) phenotype may be due to fucosylated structures at the vaginal cell surface or in the overlying mucus, which decreases availability of putative receptors for *E. coli* (238). In addition, Stapleton and co-workers (349) have shown that unique *E. coli*–binding glycerides are found in vaginal epithelial cells from nonsecretors but not from secretors. These studies individually and collectively support the concept that there is an increased epithelial receptivity for *E. coli* on the introital, urethral, and buccal mucosa that is characteristic of women susceptible to recurrent urinary tract infections and may be a genotypic trait.

Variation in Receptivity

A small variation in both vaginal cell and buccal cell receptivity may be observed from day to day in healthy controls. Adherence ranges from 1 to 17 bacteria per cell and appears to be both cyclic and repetitive. When adherence was correlated with the days of a woman's menstrual cycle, higher values were noted in the early phase, diminishing shortly after the time of expected ovulation (day 14) (Fig. 4.5). The number of bacteria per epithelial cell often correlated with the value obtained on the same day of the menstrual cycle 1 or 2 months previously. Premenopausal women are particularly susceptible to attachment of uropathogenic *E. coli* and nonpathogenic lactobacilli at certain times during the menstrual cycle and to *E. coli* during the early stages of pregnancy. The importance of such hormones

as estrogens in the pathogenesis of urinary tract infection is therefore a matter of great interest, especially because the clinical urologist may see women who have recurrent cystitis at regular intervals, possibly in response to these hormonal changes.

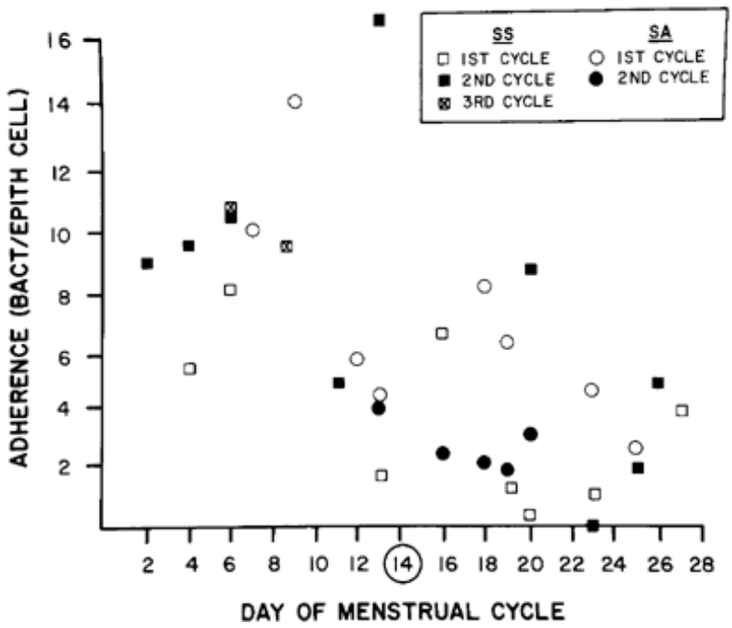

FIGURE 4.5. Relationship between the adherence of *E. coli* and the day of the menstrual cycle on which uroepithelial cells were obtained from two women with no history of urinary tract infections. Adherence was measured on the same day that the cells were collected. (Reprinted with permission from Schaeffer AJ, Amundsen SK, Schmidt LN. Adherence of *E. coli* to human urinary tract epithelial cells. *Infect Immun* 1979;24:753.)

Reid and Sobel (275) found that uropathogens attached in larger numbers to uroepithelial cells from women older than 65 years of age than to cells from premenopausal women 18 to 40 years of age. Raz and Stamm (274) noted that susceptibility to recurrent urinary tract infection was increased by the lowered estrogen levels found in the postmenopausal women and that estrogen replacement decreased uropathogenic bacterial colonization and the incidence of urinary tract infection.

The possibility that vaginal mucus might influence bacterial receptivity was investigated by Schaeffer and colleagues (302). Type 1 piliated *E. coli* bound to all of the vaginal fluid specimens (372). The binding capacity of vaginal fluid from women colonized with *E. coli in vivo* was greater than that from noncolonized women (293). The importance of vaginal fluid in bacteria–epithelial cell interactions was investigated in an *in vitro* model that measured the effect of vaginal fluid on the binding of bacteria to an epithelial cell line (100). Vaginal fluid from colonized women enhanced binding of bacteria to epithelial cells. Conversely, vaginal fluid from noncolonized women inhibited adherence. Thus the vaginal fluid appears to influence adherence to cells and presumably vaginal mucosal colonization. Subsequent studies demonstrated that secretory immunoglobulin A (IgA) is the primary glycoprotein responsible for vaginal fluid receptivity (272).

Natural Defenses of the Urinary Tract

Periurethral and Urethral Region

The normal flora of the vaginal introitus, the periurethral area, and the urethra usually contain microorganisms such as lactobacilli, coagulase-negative staphylococci, corynebacteria, and streptococci that form a barrier against uropathogenic colonization (79,211,263). Changes in the vaginal environment related to estrogen and pH may alter the ability of these bacteria to colonize. More commonly, however, acute changes in colonization have been associated with use of antimicrobial agents and spermicidal agents that alter the normal flora and increase the receptivity of the epithelium for uropathogens. The importance of vaginal colonization with uropathogens is supported by the classic longitudinal observations of Stamey and associates (337) on women who were prone to recurrent urinary tract infections. Episodes of bacteriuria were often preceded by uropathogenic colonization of the vaginal introitus and periurethral areas with bacteria from the fecal flora that subsequently infected the bladder. Between episodes of bacteriuria, women with recurrent urinary tract infections showed a higher prevalence and a greater density of perineal colonization with urinary pathogens than did healthy control subjects (300,330). Other studies have shown reduced titers of cervical IgA (339) and low vaginal pH (336) associated with increased susceptibility to urinary tract infections.

Little is known about the factors that predispose patients to urethral colonization with uropathogens. The proximity of the urethral meatus to the vulvar and perianal areas

suggests that contamination occurs frequently. The nature of urethral defense mechanisms other than flow of urine is largely unknown. Bacterial multiplication in the normal urethra may be inhibited by the indigenous flora (42). Although colonization of the periurethral and urethral regions is prerequisite to most infections, the ability of the organisms to overcome the normal defense mechanisms of the urine and the bladder is clearly pivotal.

Urine

In general, fastidious organisms that normally colonize the urethra will not multiply in urine and rarely cause urinary tract infections (40). In contrast, urine will usually support the growth of nonfastidious bacteria (8). Urine from normal individuals may be inhibitory, especially when the inoculum is small (173). The most inhibitory factors are the osmolality, urea concentration, organic acid concentration, and pH. Bacterial growth is inhibited by either very dilute urine or a high osmolality when associated with a low pH. Much of the antibacterial activity of urine is related to a high urea and organic acid content (324). From a clinical perspective, however, these conditions do not appear to significantly distinguish between patients who are susceptible or resistant to infection.

The presence of glucose in the urine may increase infections. This is consistent with the increased frequency and severity of infection in diabetes (8). Urine obtained from pregnant women exhibits a more suitable pH for growth of *E. coli* in all stages of gestation (9). Uromodulin (Tamm-Horsfall protein), a kidney-derived mannosylated protein that is present in an extraordinarily high concentration in the urine (greater than 100 mg/mL), may play a defensive role by saturating all the mannose-binding sites of the type 1 pili, thus potentially blocking bacterial binding to the uroplakin receptors of the urothelium (68,188).

Bladder

Bacteria presumably make their way into the bladder fairly often. Whether small inocula of bacteria persist, multiply, and infect the host depends in part on the ability of the bladder to empty (58). Additional factors responsible for defense include antiadherence mechanisms and antibacterial properties of the bladder mucosa. Alterations in any or all of these defense mechanisms presumably enhance the ability of bacteria to colonize and infect. The mucopolysaccharides that coat the surface of the uroepithelial cells may modulate receptivity and prevent bacterial attachment. However, damage to the bladder mucus may allow bacteria to gain access to the urothelium.

One consequence of bacterial colonization of the bladder is the exfoliation and excretion of infected and damaged superficial cells. Mulvey and colleagues (232) demonstrated that this process is mediated by type 1 piliated bacteria that induce programmed cell death. However, some bacteria can resist this innate host defense mechanism by invading into deeper tissue. The possibility that these factors may be modified to reduce susceptibility to infection has been explored primarily through immunization in animal and human systems. For example, in a monkey model, vaccination with P fimbria has been shown to reduce adherence of P-fimbriated *E. coli* to uroepithelial cells and prevent acute pyelonephritis (280). Similarly, vaccination of mice with Fim H adhesin prevents cystitis in mice (191). Vaccination in women may reduce colonization of the vaginal introitus and subsequent ascending bacteria (369).

Kidney

The renal medulla and renal papilla have been identified as highly susceptible to infection because of high osmolality, low pH, low blood flow, and a high concentration of ammonia, which is thought to inactivate complement (17). Hyperosmolality of the renal medulla also favors the conversion of bacteria to a cell-wall–deficient state that is resistant to cell-wall–active antimicrobials and may lead to persistent infection despite therapy (118). The cortex, on the other hand, is much more resistant to infection. No natural barrier or defense mechanism against bacterial adherence has been identified in the kidney. Tamm-Horsfall protein may bind bacteria and prevent or diminish adherence and colonization, but its role requires further study.

During pyelonephritis and cystitis, an acute inflammatory response occurs. This response is aimed at limiting bacterial spread and persistence within the kidney. However, the infiltrating phagocytic cells drawn to the infection may also contribute to local tissue damage and result in renal scarring (281).

Immune Mechanisms

The urinary tract is part of the secretory immune system. Most of the human and experimental animal studies have focused on the immune response to bacterial infections of the upper tract and colonization of the vaginal introitus. Kidney infections are accompanied by both serum and local kidney immunoglobulin synthesis and the appearance of type-specific antibodies in the urine. Antibodies in serum against the O antigen and, to a lesser extent, the K antigen of the infecting *E. coli* strain have been found (289). Serum antibodies directed at type 1 and P pili have also been identified after acute pyelonephritis (65,277). In pyelonephritis, IgG and SIgA also appear in the urine and may become evident before antibodies are detected in the serum. These antibodies are synthesized locally within the kidney and may enhance bacterial opsonization and ingestion of the invading microorganisms by local phagocytic cells. These

antibodies may have further protective function. Svanborg Eden and Svennerholm (354) showed that IgG and SIgA derived from the urine of patients with acute pyelonephritis reduced *in vitro* adherence of the same strain of *E. coli* to uroepithelial cells. Similarly, immunization with *E. coli* P pili resulted in immunoglobulin production in experimental animals that prevented ascending pyelonephritis by reducing the adhesive capacity of the invading autologous uropathogenic *E. coli* (249,280).

The role of urinary immunoglobulins in preventing infection of the bladder is less clear. IgA-producing lymphocytes have been demonstrated in the submucosa of infected rat bladders (133). Infection of the lower urinary tract is usually associated with a reduced or undetectable serologic response, reflecting the superficial nature of this type of cystitis. However, Uehling and Wolf (368) showed that bladder immunization of rats with bacterial antigens decreases *in vivo* adherence of *E. coli* to bladder mucosa and that bladder immunization with killed bacteria may also protect rats against pyelonephritis (367). The protective function of urinary immunoglobulins was also emphasized by the observations of Riedasch and associates (278) that lower urinary levels of SIgA were associated with an increased risk of urinary tract infection in humans.

Uehling and colleagues (369) have also demonstrated that vaginal immunization with mixtures of *E. coli* may prevent or reduce uropathogenic colonization of the introitus and reduce subsequent urinary tract infections. This line of research may lead to the development of vaccines to reduce the incidence of recurrent infection.

Evidence supports a protective role of cell-mediated immunity in urinary infections. Profound depression of or even absent T-cell function has not been associated with increased frequency of urinary tract infection or altered course of infection. The innate immune system response to an infection in the bladder or kidneys is primarily of local inflammation, which is followed by an adaptive response characterized in part by an antibody response to the infecting bacteria. Neutrophils from the urinary tract appear to be essential for bacterial clearance, and their recruitment plays a pivotal role in resistance to urinary tract infections (122). In mice, a urinary tract infection will spontaneously resolve in most cases; however, in mice with specific genetic backgrounds, a urinary tract infection can persist. This suggests that the presence or absence of specific host genes may determine how effectively a urinary tract infection will be resolved (145). The role of immune deficiencies in human susceptibility to urinary tract infections warrants investigation.

Alterations in Host Defense Mechanisms

Obstruction

Obstruction to urine flow at all anatomic levels is a key factor in increasing host susceptibility to urinary tract infection. Obstruction inhibits the normal flow of urine, and the resulting stasis compromises bladder and renal defense mechanisms. Stasis also contributes to the growth of bacteria in the urine and their ability to adhere to the urothelial cells. In the animal model of experimental hematogenous pyelonephritis, the kidney is relatively resistant to infection unless a ureter is ligated. Under these circumstances, only the obstructed kidney becomes infected (119). Clinical observations support the role of obstruction in pathogenesis of urinary tract infection and in increasing severity of infection. Mild episodes of cystitis or pyelonephritis can become life-threatening when obstruction to urine flow becomes present. Although obstruction clearly increases the severity of infection, it need not be a predisposing factor. For example, men with large residual urine may remain uninfected for years. However, if they are catheterized, even small inocula may lead to severe infections that are difficult to eradicate.

Vesicoureteral Reflux

Hodson and Edwards (136) first described the association of vesicoureteral reflux, urinary tract infection, and renal clubbing and scarring. Children with gross reflux and urinary tract infections usually develop progressive renal damage manifested by renal scarring, proteinuria, and renal failure. Those with a lesser degree of reflux usually improve or completely recover spontaneously or after treatment of the urinary tract infection. In adults, the presence of reflux does not appear to decrease renal function unless there is stasis and concurrent urinary tract infections.

Underlying Disease

There is a high incidence of renal scarring in patients with underlying conditions that cause chronic interstitial nephritis, virtually all of which produce primary renal papillary damage. These conditions include diabetes mellitus, sickle cell disorders, adult nephrocalcinosis, hyperphosphatemia, hypokalemia, analgesic abuse, sulfonamide nephropathy, gout, heavy-metal poisoning, and aging (97). An increased incidence of clinical overt urinary tract infections appears to occur in women with diabetes mellitus, but there is no substantial increase among diabetic men (90,250,371). Autopsy studies have shown the incidence of pyelonephritis to be fourfold to fivefold higher in diabetic than in nondiabetic individuals (279). However, such studies may be misleading because it is difficult to distinguish renal parenchymal changes resulting from pyelonephritis from the interstitial inflammatory changes of diabetic nephropathy.

Although most urinary tract infections in diabetic patients are asymptomatic, diabetes appears to predispose the patient to more severe infections. One study using antibody-coated bacteria techniques to localize the site of infection showed the upper urinary tract to be involved

in nearly 80% of diabetic patients with urinary tract infections (90). This evidence of increasing immunologic response in diabetic patients who acquire bacteriuria suggests renal parenchymal involvement and a potential increase in morbidity. Once established, upper urinary tract infections are often complicated by emphysematous pyelonephritis, papillary necrosis, perinephric abscess, or metastatic infection (384).

Other conditions that may increase the susceptibility of the kidney to infection include hypertension and vascular obstruction (97). Association of renal infection with several other renal diseases, including glomerulonephritis, atherosclerosis, and tubular necrosis, which are not associated with papillary necrosis, does not lead to pyelonephritis and scarring.

Pregnancy

The prevalence of bacteriuria in pregnant women varies from 4% to 7%, and the incidence of acute clinical pyelonephritis ranges from 25% to 35% in untreated bacteriuric women (331). This is probably the result of dilation of the ureters and pelvis of the kidney secondary to pregnancy-related hormonal alterations. It is not surprising that untreated bacteriuria in the first trimester is accompanied by a substantial incidence of acute pyelonephritis, because Fairley and associates (82) documented that half of these women have upper tract bacteriuria. Untreated bacteriuria involving these dilated upper tracts would be expected to produce a significant number of abnormalities that should be radiologically apparent. Kincaid-Smith and Bullen (177) performed a culture on 4,000 women at their first antenatal visit. Of 240 bacteriuric women, 148 returned for intravenous urography 6 weeks after delivery. Approximately 40% of these patients had radiologic abnormalities consistent with pyelonephritis or analgesic nephritis. Brumfitt and colleagues (28) showed that the incidence of radiologic abnormalities in bacteriuria of pregnancy was proportional to the difficulty in clearing the infection. Patients who responded promptly to a single course of therapy had a 23% incidence of radiologic abnormalities, but those who remained bacteriuric despite repeated therapeutic efforts had a 65% incidence of radiologic changes. Thus prolonged bacteriuria and pyelonephritis of pregnancy appear to be associated with significant radiologic abnormalities. However, there is little evidence to suggest that bacteriuria of pregnancy or acute pyelonephritis of pregnancy causes these renal radiologic abnormalities.

CLINICAL MANIFESTATIONS

Part of "4 - URINARY TRACT INFECTIONS "

Symptoms and Signs

Pyelonephritis is classically associated with fever, chills, and flank pain. Nausea and vomiting are commonly present. Cystitis is usually associated with dysuria, frequency, urgency, suprapubic pain, and hematuria. Lower tract symptoms are commonly present and usually predate the appearance of upper tract symptoms by several days. Renal or perirenal abscess may cause indolent fever and flank mass and tenderness. In the elderly, the symptoms may be much more subtle (e.g., epigastric or abdominal discomfort), or the patient may be asymptomatic (282). Patients with indwelling catheters often have asymptomatic bacteriuria, but fever associated with bacteremia may occur rapidly and become life-threatening.

Diagnosis

Presumptive diagnosis of urinary tract infection is made by direct or indirect analysis of the urine and is confirmed by urine culture. Assessment of the urine provides clinical information about the status of the urinary tract. The urine and the urinary tract are normally free of bacteria and inflammation. False-negative urinalysis and culture can occur in the presence of urinary tract infection, particularly early in an infection when the numbers of bacteria and WBCs are low or diluted by increased fluid intake and subsequent diuresis. Occasionally, the urine may be free of bacteria and WBCs despite bacterial colonization and inflammation of the uroepithelium (75,153). False-positive urinalysis and culture are caused by contamination of the urine specimen with bacteria and WBCs during collection. This is most likely to occur in voided specimens but can also occur during urethral catheterization. Suprapubic aspiration of bladder urine is least likely to cause contamination of the specimen; therefore it provides the most accurate assessment of the status of bladder urine.

Urine Collection

In circumcised men, voided specimens require no preparation. For men who are not circumcised, the foreskin should be retracted and the glans penis washed with soap and then rinsed with water before specimen collection. The first 10 mL of urine (representative of the urethra) and a midstream specimen (representative of the bladder) should be obtained. Prostatic fluid is obtained by performing digital prostatic massage and collecting the expressed prostatic fluid on a glass slide. In addition, collection of the first 10 mL of voided urine after massage will reflect the prostatic fluid added to the urethral specimen. Catheterization of a male patient for urine culture is not indicated unless the patient cannot urinate.

In women, contamination of a midstream urine specimen with introital bacteria and WBCs is common, particularly when the woman has difficulty spreading and maintaining separation of the labia. Therefore the female should be instructed to spread the labia, wash and cleanse the periurethral area with a moist gauze, and then collect a

midstream urine specimen. Cleansing with antiseptics is not recommended because they may contaminate the voided specimen and provide a false-negative urine culture. If the voided specimen shows evidence of contamination as indicated by vaginal epithelial cells and lactobacilli on urinalysis, catheterization should be performed and a midcatheterized specimen collected. Suprapubic aspiration is highly accurate, but because it carries some morbidity, there is limited clinical usefulness except for a patient who cannot urinate on command, such as patients with spinal cord injuries.

Urinalysis

Urinalysis provides rapid identification of bacteria and white cells and presumptive diagnosis of urinary tract infection. Usually, the sediment from an approximately 5- to 10-mL specimen obtained by centrifugation for 5 minutes at 2,000 rpm is analyzed. Microscopic bacteriuria is found in more than 90% of infections with counts of 10^5 colony-forming units (CFU) per milliliter of urine or greater and is a highly specific finding (161,340). However, bacteria are usually not detectable microscopically with lower colony count infections (10^2 to 10^4/mL). Significant pyuria can be determined simply and reliably with a microscope by accurately examining the centrifuged sediment or by using a hemocytometer to count the number of WBCs in the unspun urine. Approximately 1 to 2 WBCs per high-power field (HPF) in sediment from a centrifuged specimen represents about 10 WBCs/mm^3 in an unspun specimen. More than 2 WBCs per HPF in a centrifuged specimen or 10 WBCs/mm^3 of urine correlates well with the presence of bacteriuria and is rarely seen in nonbacteriuric patients (344). In clinical studies, determination of pyuria in voided urine specimens has a reported sensitivity of 80% to 95% and a specificity of 50% to 76% for urinary tract infection (depending on the definition of infection, the patient population, and the method used to evaluate for pyuria) (308,340,386,393).

Microscopic hematuria is found in 40% to 60% of cases of acute cystitis and is uncommon in other dysuric syndromes (343,386). Thus microscopic bacteriuria and hematuria lack sensitivity but are highly specific for urinary tract infections.

Urine Culture

Confirmation of urinary tract infection requires documentation of bacteria by culture. Urine should be cultured immediately or refrigerated at 40°C. Direct surface plating is the traditional quantitative culture technique used by most microbiology laboratories. A known amount of urine is streaked on split agar plates. Half of the plate contains a nonselective medium, such as blood agar, for growth of any bacteria, and the other half contains a selective medium, such as MacConkey, which is specific for Gram-negative bacteria. Each bacterial rod or cluster of cocci will form a single colony after overnight growth in an incubator. Dip-slide culture is a simpler, less expensive, and somewhat less accurate technique. An agar-coated slide is dipped in the urine and replaced into its sterile container. An approximate colony count is determined after overnight incubation at room temperature by comparing the appearance of the slide with a series of pictures provided by the manufacturer.

The definition of significant bacteriuria as greater than 10^5 CFU/mL was originally published by Kass and Finland (171) to differentiate infected from contaminated urine in voided specimens from women with asymptomatic bacteriuria. Most bacteria, when allowed to incubate for several hours, will reach colony counts to this level. However, this cutoff has limitations because about one-third of women with acute symptomatic cystitis caused by *E. coli, S. saprophyticus,* and *Proteus* have colony counts in midstream urine specimens between 10^2 and 10^4 CFU/mL (329,345). Thus, in dysuric women, the appropriate threshold value for defining significant bacteriuria is 100 CFU/mL or greater (345).

In a clinical setting, false-positive urine cultures are problematic. Women susceptible to infections often carry large numbers of pathogenic bacteria on the perineum that could contaminate a voided urine specimen. Contaminated cultures often show more than one organism and include indigenous bacteria such as lactobacilli. Diagnostic accuracy of voided specimens in women can be optimized by detailed history, proper collection techniques, and carefully performed urinalysis.

Midstream urine specimens in men or catheterized specimens in women are less likely to be contaminated, and hence counts of 10^2 CFU/mL are usually diagnostic of significant bacteriuria. Any uropathogen identified in a urine specimen obtained by suprapubic aspiration should be considered significant.

Rapid Screen Methods

Biochemical and enzymatic tests have been devised to detect bacteriuria and pyuria (261). The Griess test detects the presence of nitrite in urine that is formed when bacteria reduce the nitrate normally present in urine. Tests for detecting pyuria by determining leukocyte esterase activity have also been developed (46). In a study comparing traditional urine culture with these indirect tests, the combination of nitrite and leukocyte esterase tests (either test positive) had a sensitivity of 71% and a specificity of 83% when compared with 10^3 CFU/mL or greater of urine cultures (262). However, several investigators (155,258) noted substantial variability in the sensitivity and specificity results, which could be markedly influenced by the types of patients and infections chosen to evaluate the tests. This concept of spectrum bias was illustrated by a study that reported

differences in the sensitivity of reagent strip testing, ranging from 56% to 92%, by changing only the groups of patients included in the analysis. Although false-positives are relatively uncommon, the borderline sensitivity of these tests, especially among patients with less characteristic symptoms of urinary tract infections, does not allow these inexpensive tests to replace careful microscopic urinalysis in symptomatic patients (311). Their main role is in screening asymptomatic patients (261).

IMAGING

Part of "4 - URINARY TRACT INFECTIONS "

Imaging studies are not required in most cases of urinary tract infections because clinical and laboratory findings alone are sufficient for correct diagnosis and adequate management of most patients. However, febrile infections, infection in an otherwise healthy male, signs or symptoms of urinary tract obstruction, failure to respond to appropriate therapy, and a pattern of recurrent infections suggesting bacterial persistence within the urinary tract warrant imaging for identification of underlying abnormalities that require modification of medical management or percutaneous or surgical intervention.

Excretory urography has traditionally provided excellent anatomic assessment of the urinary tract and remains the best examination for detection of lesions of the collecting system and ureter. Ultrasonography and computed tomography (CT) scans have gained considerable acceptance. Ultrasonography serves as a rapid, noninvasive means of evaluating the renal collecting system, parenchyma, and surrounding retroperitoneum for evidence of infection, and it is particularly useful for identifying hydronephrosis, calculi, and abscess. A single radiograph for calculi should accompany ultrasonography. Ultrasonography examination is also useful for diagnosing postvoid residual urine. CT clearly is the modality of choice for identifying inflammatory processes that involve the renal, perirenal, and pararenal spaces and radiolucent calculi. Magnetic resonance imaging may provide some advantages in delineating the extent of inflammation.

Although gallium-67 scanning has been reported to be useful in the diagnosis of pyelonephritis and renal abscess, it is uncommonly required and may be positive in noninfectious entities. Indium-111–labeled WBC studies have limited efficacy in establishing the presence of an inflammatory focus, particularly when the patient's clinical presentation does not suggest an infectious process.

ANTIMICROBIAL THERAPY

Part of "4 - URINARY TRACT INFECTIONS "

Therapy for urinary tract infections must ultimately eliminate bacterial growth in the urinary tract. This can occur within hours if the proper antimicrobial agent is used. Efficacy of the antimicrobial therapy is critically dependent on the antimicrobial levels in the urine and the duration that this level remains above the minimum inhibitory concentration of the infecting organism (141). Hence, resolution of infection is closely associated with the susceptibility of the bacteria to the concentration of the antimicrobial agent achieved in the urine (215,333,338). Inhibitory concentrations in urine are achieved after oral administration of all commonly used antimicrobial agents, except for the macrolides (erythromycin). The concentration of the antimicrobial agent achieved in blood is not important in treatment of uncomplicated urinary tract infections. Blood levels are critical in patients with bacteremia and febrile urinary infections consistent with parenchymal involvement of the kidney and prostate.

In patients with renal insufficiency, dosage modifications are necessary for agents that are cleared primarily by the kidneys and cannot be cleared by another mechanism. In renal failure, the kidneys may not be able to concentrate an antimicrobial agent in the urine; hence, difficulty in eradicating bacteria may occur. Urinary tract obstruction may also reduce concentration of antimicrobials within the urine.

The antimicrobial selection and the duration of therapy must consider the spectrum of activity of the drug against the known pathogen or the most probable pathogens based on the presumed source of acquisition of infection, whether the infection is judged to be uncomplicated or complicated, potential adverse effects, and cost. An often underemphasized but important characteristic is the drug's impact on the fecal and vaginal flora and the hospital bacterial environment. Bacterial susceptibility will vary dramatically in patients exposed to antimicrobials and in individuals in inpatient and outpatient settings. It is imperative that each clinician keep abreast of changes that affect antimicrobial use patterns.

Bacterial Resistance

In the last several years, the frequency and spectrum of antimicrobial-resistant urinary tract infections have increased in both the hospital and community. The increasing frequency of drug resistance has been attributed to combinations of microbial characteristics, bacterial selection pressure due to antimicrobial use, and societal and technologic changes that enhance the transmission of drug resistance (50). Bacterial resistance may occur because of natural (inherited) chromosomal-based resistance or by acquired chromosomal- or extrachromosomal (plasmid)-mediated resistance due to exposure of an organism to antimicrobials. Inherited resistance exists in a bacterial species because of the absence of the proper mechanism on which the antimicrobial agent can act. For example, *Proteus* and *Pseudomonas* species are always resistant to nitrofurantoin. Chromosomal-mediated resistance can be acquired by

urinary bacteria during therapy for urinary tract infections. Before antimicrobial therapy, relatively resistant mutants of a bacterial strain may be present in the urine at very low concentrations. The remainder of the bacteria, which are susceptible to the administered antimicrobial agent, will be eradicated by therapy, but within 24 to 48 hours, a repeat urine culture will show high bacterial counts of the resistant mutant. In essence, the antimicrobial therapy has selected out the resistant mutant. This phenomenon is most likely to occur when the antimicrobial level in the urine is close to or below the minimum inhibitory concentration of the drug. Underdosing and noncompliance, as well as diuresis induced by increased fluid intake, can contribute to this process.

Resistance may also be acquired and transferable via extrachromosomal plasmids, which contain the genetic material for the resistance. This so-called R-factor resistance occurs in the fecal flora and is much more common than selection of preexisting mutants in the urinary tract. All antimicrobial classes are capable of causing plasmid-mediated resistance with the exception of the fluoroquinolones and nitrofurantoin. Hence, patients previously exposed to ß-lactams, aminoglycoside, sulfonamide, trimethoprim (TMP), and tetracycline will often have R-factor resistance to both the antimicrobial to which the bacteria were exposed and also to other antimicrobials. In addition, the plasmids carrying the resistant genetic material are transferable both within species and across genuses. Thus, for example, a patient receiving tetracycline may harbor several fecal strains that are resistant to tetracycline, ampicillin, sulfonamides, and TMP. Because the fecal flora is the major reservoir for bacteria that ultimately colonize the urinary tract, infections that occur after antimicrobial therapy and that can cause plasmid-mediated resistance are commonly caused by organisms with multidrug resistance.

Antimicrobial resistance is also influenced by the duration and amount of antimicrobial used. For example, documented increased use of fluoroquinolones in the hospital setting has been directly associated with increased resistance of bacteria (particularly *Pseudomonas*) to the fluoroquinolones. Resistance tends to increase the longer the antimicrobial is used. Conversely, reduction in duration of therapy and in the amount of the drug use can lead to reemergence of more susceptible strains.

Most studies reporting antimicrobial resistance have been based on surveys of laboratory isolates, generally without correlation with clinical or epidemiologic factors (e.g., the presence and nature of symptoms, age, sex, and whether the infection was complicated). Gupta and colleagues (117) determined the prevalence of and trends in antimicrobial resistance among uropathogens isolated from a large, well-defined population of women with acute uncomplicated cystitis. Over a 5-year period, the prevalence of resistance to trimethoprim/sulfamethoxazole, ampicillin, and cephalothin increased significantly, whereas resistance to nitrofurantoin and ciprofloxacin remained uncommon. However, fluoroquinolone resistance of *E. coli* has increased from less than 1% to 7% in hospitalized patients. Previous use of fluoroquinolones and the presence of underlying urologic diseases were the strongest determinants for urinary tract infections caused by resistant strains (76).

Antimicrobial Formulary

Trimethoprim/sulfamethoxazole

The combination of trimethoprim/sulfamethoxazole (TMP-SMX) has been the most widely used antimicrobial for the treatment of acute urinary tract infections. TMP alone is as effective as the combination for most uncomplicated infections and may be associated with fewer side effects (163); however, the addition of SMX contributes to efficacy in the treatment of upper tract infection via a synergistic bactericidal effect and may diminish the emergence of resistance (31). TMP alone or in combination with SMX was effective against most common uropathogens, with the notable exception of *Enterococcus* and *Pseudomonas* species. TMP and TMP-SMX are inexpensive and have minimal adverse effects on the fecal flora. Disadvantages are relatively common adverse effects, consisting primarily of skin rashes and gastrointestinal complaints (49).

Nitrofurantoin

Nitrofurantoin is effective against common uropathogens, but it is not effective against *Pseudomonas* and *Proteus* species (157). It is rapidly excreted from the urine but does not obtain therapeutic levels in most body tissues, including the gastrointestinal tract. Therefore it is not useful for upper tract and complicated infections (387). It has minimal effects on the resident fecal and vaginal flora and has been used effectively in prophylactic regimens for more than 30 years. Acquired bacterial resistance to this drug is exceedingly low.

Cephalosporins

All three generations of cephalosporins have been used for the treatment of acute urinary tract infections (387). In general, as a group, activity is high against Enterobacteriaceae and poor against enterococci. First-generation cephalosporins have greater activity against Gram-positive organisms, whereas second-generation cephalosporins have activity against anaerobes. Third-generation cephalosporins are more reliably active against community-acquired and nosocomial Gram-negative organisms than other ß-lactam antibiotics. Their cost should limit their use to complicated infections and situations where parenteral therapy is required and resistance to standard antibiotics is likely. Cephalosporins produce less resistance among fecal bacteria

than the aminopenicillins, but the incidence of *Candida* vaginitis is nearly the same (157).

Aminopenicillins

Ampicillin and amoxicillin have been used often in the past for the treatment of urinary tract infections, but the emergence of resistance in up to 30% of common urinary isolates has lessened the usefulness of these drugs (141). The effects of these agents on the normal fecal and vaginal flora can predispose patients to reinfection with resistant strains and often lead to *Candida* vaginitis (157). The addition of the ß-lactamase inhibitor clavulanate to amoxicillin greatly improves activity against ß-lactamase–producing bacteria resistant to amoxicillin alone. However, its high cost and frequent gastrointestinal side effects limit its usefulness. The extended-spectrum penicillin derivatives (e.g., piperacillin, mezlocillin, azlocillin) retain ampicillin's activity against enterococci and offer activity against many ampicillin-resistant Gram-negative bacilli. This makes them attractive agents for use in patients with nosocomially acquired urinary tract infections and as the initial parenteral treatment of acute uncomplicated pyelonephritis acquired outside of the hospital, although less expensive agents are equally effective.

Aminoglycosides

When combined with TMP-SMX or ampicillin, aminoglycosides are the first drugs of choice for febrile urinary tract infections. Their nephrotoxicity and autotoxicity are well recognized; hence, careful monitoring of patients for renal and auditory impairment associated with infection is indicated. Once-daily aminoglycoside regimens have been instituted to maximize bacterial killing by optimizing the peak concentration-to-minimum inhibitory concentration ratio and reduce potential for toxicity (239). Administering an aminoglycoside as a single daily dose can take advantage not only of its concentration-dependent killing ability but also of two other important characteristics: time-dependent toxicity and a more prolonged postantibiotic effect (103,401). The regimen consists of a fixed 7-mg/kg dose of either gentamicin or tobramycin. Subsequent interval adjustments are made by using a single concentration in serum and a nomogram designed for monitoring of once-daily aminoglycoside therapy (Fig. 4.6). This regimen is clinically effective, reduces the incidence of nephrotoxicity, and provides a cost-effective method for administering aminoglycosides by reducing ancillary service times and serum aminoglycoside determinations.

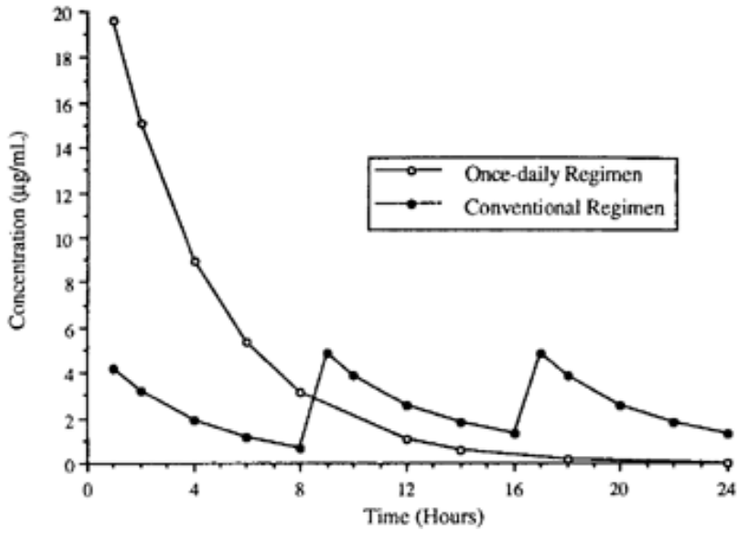

FIGURE 4.6. Simulated concentration-versus-time profile of once-daily (7 mg/kg every 24 hours) and conventional (1.5 mg/kg every 8 hours) regimens for patients with normal renal function.

Aztreonam

Aztreonam has a similar spectrum of activity as the aminoglycosides, and as with all ß-lactams, it is not nephrotoxic. However, its spectrum of activity is less broad than the third-generation cephalosporins. It should be used primarily in patients who have penicillin allergies.

Fluoroquinolones

Fluoroquinolones share a common predecessor in nalidixic acid and inhibit DNA gyrase, a bacterial enzyme integral to replication. The fluoroquinolones have a broad spectrum of activity that makes them ideal for the empiric treatment of urinary tract infections. They are highly effective against Enterobacteriaceae, as well as *Pseudomonas aeruginosa.* Activity is also high against *S. aureus* and *S. saprophyticus,* but in general, antistreptococcal coverage is marginal. Most anaerobic bacteria are resistant to these drugs; therefore the normal vaginal and fecal flora are not altered (396). Bacterial resistance initially appeared to be uncommon, but it is being reported at an increasing rate because of indiscriminate use of these agents (374,396).

These drugs are not nephrotoxic, but renal insufficiency prolongs the serum half-life, requiring adjusted dosing in patients with creatinine clearances of less than 30 mL per minute. Adverse reactions are uncommon; gastrointestinal disturbances are more common. Hypersensitivity, skin reactions, mild central and peripheral nervous system reactions, and even acute renal failure have been reported (138). Administration of the fluoroquinolones to immature animals has caused damage to the developing cartilage; therefore they are currently contraindicated in children, adolescents, and pregnant or nursing women (47). There are important drug interactions associated with the fluoroquinolones. Antacids containing magnesium or aluminum interfere with absorption of fluoroquinolones (63). Certain fluoroquinolones (enoxacin and ciprofloxacin) elevate plasma levels of theophylline and prolong its half-life (396).

For most uncomplicated urinary tract infections, the fluoroquinolones have been only slightly more effective than TMP-SMX. However, as resistance to TMP-SMX increases, the fluoroquinolones have distinct advantages in empiric treatment of patients recently exposed to antimicrobials and in the outpatient treatment of complicated urinary tract infections (61,117). They may be considered as first-line agents in areas where a significant level of resistance (greater than 20%) exists (in common bacteria) to agents such as ampicillin and TMP-SMX.

BLADDER INFECTIONS

Part of "4 - URINARY TRACT INFECTIONS "

Uncomplicated Cystitis

Most cases of uncomplicated cystitis occur in women. Approximately 25% to 30% of women 20 to 40 years of age have a history of urinary tract infections (190). Although it is much less common, young men may also experience acute cystitis without underlying structural or functional abnormalities of the urinary tract (185). Risk factors include sexual intercourse and use of spermicides (93,139). Sexual transmission of uropathogens has been suggested by demonstrating identical *E. coli* in the fecal and urinary flora of sex partners.

The presenting symptoms of cystitis are variable but usually include dysuria, frequency or urgency, and suprapubic pain. Because acute cystitis, by definition, is a superficial infection of bladder mucosa, fever, chills, and other signs of dissemination are not present. Some patients may experience suprapubic tenderness, but most have no diagnostic physical findings. In women, physical examination should include the possibility of vaginitis, herpes, and urethral pathology, such as a diverticulum.

E. coli is the causative organism in approximately 75% to 80% of cases of acute cystitis in young women (192). *S. saprophyticus,* a commensal organism of the skin, is the second most common cause of acute cystitis in young women, accounting for 10% to 20% of these infections (166). Other organisms less commonly involved include *Klebsiella* and *Proteus* species and *Enterococcus.* In men, *E. coli* and other Enterobacteriaceae are the most commonly identified organisms.

Laboratory Diagnosis

The presumptive laboratory diagnosis of acute cystitis is based on microscopic urinalysis, which indicates microscopic bacteriuria, pyuria, and hematuria. Indirect dipstick tests for bacteria (nitrite) or pyuria (leukocyte esterase) may also be informative but are less sensitive than microscopic examination of the urine. Urine culture remains the definitive test, and in symptomatic patients, the presence of 10^2 CFU/mL or more of urine usually indicates infection (345).

Routine urine cultures are often not necessary. It is generally more cost-effective to manage many patients who have symptoms and urinalysis findings characteristic of uncomplicated cystitis without an initial urine culture because treatment decisions are usually made and therapy is often completed before culture results are known (181). This position was supported by a cost-effectiveness study (38) in which it was estimated that the routine use of pretherapy urine cultures for lower urinary tract infection increases costs by 40% but decreases the overall duration of symptoms by only 10%.

Thus, in patients with symptoms and signs suggesting acute cystitis and in whom no complicating factors are present, a urinalysis that is positive for pyuria, hematuria, or bacteriuria, or a combination, should provide sufficient documentation of urinary tract infection and a urine culture may be omitted. A urine culture should be obtained for patients in whom symptoms and urine examination findings leave the diagnosis of cystitis in doubt, however. Pretherapy cultures and susceptibility tests are also essential in the management of patients with recent antimicrobial therapy or urinary tract infection. In these situations, various pathogens may be present and antimicrobial therapy is less predictable and must be tailored to the individual organism (341).

Differential Diagnosis

Cystitis must be differentiated from other inflammatory infectious conditions in which dysuria may be the most prominent symptom, including vaginitis, urethral infections caused by sexually transmitted pathogens, and miscellaneous noninflammatory causes of urethral discomfort (180). Characteristic features of the history, physical examination, and voided urine or other specimens allow patients with dysuria to be assigned to one of these diagnostic categories. Vaginitis is characterized by irritative voiding associated with vaginal irritation and is subacute in onset. A history of vaginal discharge or odor and multiple or new sexual partners is common. Frequency, urgency, hematuria, and suprapubic pain are not present. Physical examination reveals a vaginal discharge, and examination of vaginal fluid demonstrates inflammatory cells. Differential diagnosis includes herpes simplex virus, gonorrhea, *Chlamydia,* trichomoniasis, yeast, and bacterial vaginosis. Urethritis causes dysuria that is usually subacute in onset and is associated with a history of discharge and new or multiple sexual partners. Frequency and urgency of urination may be present but are less pronounced than in patients with cystitis, and fever and chills are absent. Urethral discharge with inflammatory cells or initial pyuria in the male is characteristic. The common causes of urethritis include gonorrhea, *Chlamydia,* herpes simplex virus, and trichomoniasis. Appropriate cultures and immunologic tests are indicated. Urethral injury associated with sexual intercourse, chemical

irritants, or allergy may also cause dysuria. A history of trauma or exposure to irritants and a lack of discharge or pyuria are characteristic.

Management

Antimicrobial Selection

Oral antimicrobial agents for treatment of acute uncomplicated cystitis are listed in Table 4.2 . TMP and TMP-SMX are effective and inexpensive agents for empiric therapy. They are recommended in areas where the prevalence of resistance to these drugs among *E. coli* strains causing cystitis is less than 20% (377). When used alone, TMP is as efficacious as TMP-SMX and is associated with fewer side effects, presumably because of the absence of the sulfa component (123). Nitrofurantoin has maintained an excellent level of activity over three decades and is well tolerated, but it is more expensive than TMP-SMX. It is not associated with plasmid-mediated resistance, however, so it is an excellent choice for patients with recent exposure to most other antimicrobials. The high *in vitro* resistance to ampicillin and sulfonamide and the high cost of amoxicillin/clavulanate and the cephalosporins limit their usefulness. The fluoroquinolones offer excellent activity, and they are well tolerated. Their use for uncomplicated cystitis should be limited to patients with allergy to less costly drugs, to patients with previous exposure to antibiotics causing bacterial resistance, and to areas where the prevalence of resistance to TMP or TMP-SMX is 20% or greater (377).

Drug	Dosage	Cost Per Day[a]
TMP-SMX	1 double-strength tablet b.i.d. (160/800 mg)	$0.28
Trimethoprim	100 mg b.i.d.	$0.38
Sulfasoxazole	1 g, followed by 500 mg q.i.d.	$0.32
Ciprofloxacin	500 mg b.i.d.	$8.30
Enoxacin	400 mg b.i.d.	$6.84
Levofloxacin	500 mg q.i.d	$8.58
Nitrofurantoin	100 mg q.i.d.	$3.24
Amoxicillin	250 mg t.i.d.	$0.68
Cephalexin	500 mg q.i.d.	$4.52

[a]Prices in dollars reflect the average wholesale price to the pharmacist as of February 2000. When products were available from multiple sources, the least expensive generic supply prices were used. The price to the patient is dependent on the pharmacist's professional fee structure.

TABLE 4.2. ORAL ANTIMICROBIAL AGENTS FOR UNCOMPLICATED CYSTITIS

Duration of Therapy

The traditional approach of 7 to 14 days of therapy for acute uncomplicated cystitis overtreats most patients, is more costly, and is associated with more side effects than shorter-term therapy (312). As an alternative, investigators initially proposed single-dose therapy wherein patients were given 1 to 2 days of conventional therapy in one dose. Although single-dose therapy was nearly as effective as 7-day therapy in healthy women with cystitis (85,266), resolution of symptoms was sometimes slower. Furthermore, it proved less effective in the presence of recent urinary tract infections, with the use of spermicides, and when more than 10^5 CFU/mL of urine was present (85).

Three-day therapy now appears to be the preferred regimen in uncomplicated cystitis in women (244,377). In an excellent review of more than 300 separate clinical trials of single-dose, 3-day or 7-day treatment with TMP, TMP-SMX, fluoroquinolones, and ß-lactam antimicrobial therapies, it was concluded that, irrespective of the antimicrobial used, single-dose therapy is not as effective as 3-day therapy. Three-day therapy is as effective as a 7- to 10-day course of treatment (377). Three-day therapy with TMP-SMX, TMP, amoxicillin, or cloxacillin has been associated with cure rates similar to longer courses of therapy and an incidence of adverse effects as low as that seen with single-dose therapy and lower than seen with longer courses of therapy (3,44,189,218). Seven-day therapy often causes more adverse effects and therefore is recommended only for women with symptoms of 1 week or more, men, and individuals with possible complicating factors. Other options include nitrofurantoin, perhaps as 7-day therapy, and fosfomycin single-dose therapy; each of these requires further study. ß-Lactams as a group are less effective in treatment of cystitis than TMP, TMP-SMX, and the fluoroquinolones.

Cost of Therapy

The cost of treating a urinary tract infection involves not only the initial evaluation and cost of the drug but what occurs subsequently. The most important prediction of high cost-effectiveness is high efficacy against the most common urinary pathogen—*E. coli*. The lower the effectiveness against this bacterium, the greater the number of revisits, cases of progression to pyelonephritis, and follow-up costs. Antimicrobial cost is a poor prediction of cost-effectiveness as illustrated by the finding that the most expensive and least

expensive drugs, the fluoroquinolones and TMP-SMX, are approximately equally cost-effective (283). Both of these drugs are more cost-effective than nitrofurantoin and amoxicillin.

UNRESOLVED URINARY TRACT INFECTIONS

Part of "4 - URINARY TRACT INFECTIONS "

Unresolved infection indicates that initial therapy has been inadequate in eliminating bacterial growth in the urinary tract. If the symptoms of urinary tract infection do not resolve by the end of treatment or if symptoms recur shortly after therapy, urinalysis and urine culture with susceptibility testing should be obtained. If the patient's symptoms are significant, empiric therapy with a fluoroquinolone is appropriate pending results of the culture and susceptibility testing.

The causes of unresolved bacteriuria during antimicrobial therapy are shown in Table 4.3 . Most commonly, the bacteria are resistant to the antimicrobial agent selected to treat the infection. Typically, the patient has received the antimicrobial therapy in the recent past and developed fecal colonization with resistant bacteria. ß-Lactams, tetracycline, and sulfonamides are notorious for causing plasmid-mediated R factors that simultaneously carry resistance to multiple antimicrobial agents. The second most common cause is development of resistance in a previously susceptible population of bacteria during the course of treatment of urinary tract infections. This problem occurs in approximately 5% of the patients receiving antimicrobial therapy. It is easy to recognize clinically because culture on therapy shows that the previous susceptible population has been replaced by resistant bacteria of the same species. It can be shown that resistant organisms were actually present before contact with the initial antimicrobial agent, but they were present in such low numbers that it was impossible to detect by *in vitro* susceptibility studies before therapy. When the antimicrobial concentration in the urine is insufficient to kill all the bacteria present, the more resistant forms will emerge. This characteristically is seen in patients who are underdosed or who are poorly compliant and hence have inadequate dose regimens. The third cause is the presence of an unsuspected, second pathogen that was present initially and is resistant to the antimicrobial therapy chosen. Treatment of the dominant organism unmasks the presence of the second strain. The fourth cause is rapid reintroduction of a new resistant species while the patient is undergoing initial therapy. Rapid reinfection that mimics unresolved bacteriuria should alert the clinician to the possibility of an enterovesical fistula. If the culture obtained on therapy shows that the initial species is still present and susceptible to the antimicrobial chosen to treat the infection, the unresolved infection must be caused by either inability to deliver an adequate concentration of antimicrobial agents into the urinary tract or an excessive number of bacteria that “override” the antimicrobial activity. In patients with azotemia, a determination of urinary antimicrobial concentrations usually shows that the level of the drug is below the minimal inhibitory concentration of the infecting organism.

1. Bacteria resistance to the initial drug selected for treatment[a]
2. Development of resistance from initially susceptible bacteria
3. Bacteriuria caused by two different bacterial species with mutually exclusive susceptibilities
4. Rapid reinfection from a new, resistant species during initial therapy for the original susceptible organism
5. Azotemia
6. Staghorn calculi in which the "critical mass" of the susceptible bacteria is too great for antimicrobial inhibition
7. Papillary necrosis from analgesic abuse

[a]The first four causes are characterized by identification of bacteria resistant to the antimicrobial agent the patient is receiving.
Modified with permission from Stamey TA. *Pathogenesis and treatment of urinary tract infections.* Baltimore: Williams & Wilkins, 1989.

TABLE 4.3. CAUSES OF UNRESOLVED BACTERIURIA IN DESCENDING ORDER OF IMPORTANCE

In patients with papillary necrosis, severe defects in the medullary concentrating ability dilutes the antimicrobial agent. A large mass of bacteria within the urinary tract is most commonly associated with a giant staghorn calculus. Even though adequate urinary levels of bactericidal drugs are present, the concentration is inadequate to sterilize the urine. This occurs because even susceptible bacteria cannot be inhibited once they reach a certain critical density, particularly if attached to a foreign body.

RECURRENT URINARY TRACT INFECTIONS

Part of "4 - URINARY TRACT INFECTIONS "

Recurrent urinary tract infections are caused by either reemergence of bacteria from a site within the urinary tract *(bacterial persistence)* or new infections from bacteria outside the urinary tract *(reinfection).* Clinical identification of these two types of recurrence is based on the pattern of recurrent infections. Bacterial persistence must be caused by the same organism in each instance, and infections that occur at close intervals are characteristic. Conversely, reinfections usually occur at varying and sometimes long intervals and often are caused by different species. The distinction between bacterial persistence and reinfection is important in management because patients with bacterial persistence can usually be cured of the recurrent infections by identification and surgical removal or correction of the focus of infection. Conversely, women with reinfection usually do not have an alterable urologic abnormality and usually require long-term medical management. Reinfections in men are uncommon and may be associated with an underlying abnormality,

such as urethral stricture; therefore, at a minimum, endoscopic evaluation is indicated.

Bacterial Persistence

Although patients with bacterial persistence are relatively uncommon, their identification is important because they represent the only surgically curable cause of recurrent urinary tract infections. A systematic radiologic and endoscopic evaluation of the urinary tract is mandatory. Excretory urography and cystoscopy provide the initial screening. Urea-splitting organisms, such as *P. mirabilis,* cause infection stones that are relatively radiolucent. If such a stone is suspected, plain film tomograms and, if necessary, computed tomographic scans without contrast should be obtained (114). Retrograde urography may be required in selected patients to delineate abnormalities, such as diverticulum or nonrefluxing ureteral stump.

The infection that ultimately leads to an infection stone commonly begins inconspicuously as inadequately treated cystitis. Underlying urinary tract abnormalities are not a prerequisite for this type of infection. However, patients with indwelling catheters, urinary diversions, or other urinary tract abnormalities are particularly susceptible to these infections. Medical management with continued suppressive antimicrobial therapy and acidification temporarily relieves symptoms and retards deterioration of renal function in some patients. Complete removal of the calculus is generally required for bacteriologic cure and to prevent renal damage due to obstruction (319). Percutaneous nephrolithotomy and extracorporeal shock wave lithotripsy (ESWL) are now the preferred treatment for most renal and upper ureteral calculi. Follow-up radiographs are essential to ensure that all the stone fragments are removed, and cultures must demonstrate that the urease-splitting bacteria are eradicated. Most of the other congenital or acquired abnormalities listed in Table 4.4 require surgical removal for eradication of the source of bacterial persistence. Chronic bacterial prostatitis is treated initially with long-term antimicrobial therapy and, in select cases, by radical transurethral resection (222).

1. Infection renal stone
2. Chronic bacterial prostatitis
3. Infected pericalyceal diverticulum
4. Infected nonrefluxing ureteral stump following nephrectomy
5. Atrophic, infected kidney
6. Medullary sponge kidney
7. Infected urachal cyst
8. Infected necrotic papilla from papillary necrosis

[a]Although patients with bacterial persistence are relatively uncommon, these circumstances are important because they represent the only surgically curable causes of recurrent urinary tract infections.
Modified with permission from Stamey TA. *Pathogenesis and treatment of urinary tract infections.* Baltimore: Williams & Wilkins, 1980.

TABLE 4.4. CAUSES OF BACTERIAL PERSISTENCE OF URINARY TRACT INFECTIONS[a]

In patients in whom the focus of infection cannot be eradicated, long-term, low-dose antimicrobial suppression is necessary to prevent symptoms of infection. The antimicrobial drugs used for low-dose prophylaxis will also be effective for bacterial suppression if the persistent strain is susceptible. These include nitrofurantoin, TMP-SMX, cephalexin, and the fluoroquinolones.

Reinfections

Patients with recurrent infections caused by different species or occurring at long intervals almost invariably have reinfections. These reinfections most often occur in women and girls and are associated with ascending colonization from the fecal flora. Reinfections in men are often associated with a urinary tract abnormality. The possibility of a vesicoenteric or vesicovaginal fistula should be considered when the patient has any history of pneumaturia, fecaluria, diverticulitis, obstipation, previous pelvic surgery, or radiation therapy. Evaluation of the patient with presumed reinfections must be individualized.

Failure to recognize and correct abnormalities that reduce formation, transmission, and elimination of urine by the urinary tract increases the incidence of reinfection in susceptible patients and reduces the effectiveness of antimicrobial therapy. Abnormalities should be corrected and urinary tract function restored by medical, pharmacologic, or surgical management. A thorough urologic evaluation is essential in all men and in women with evidence of upper tract infections (fevers, chills, flank pain, hemorrhagic cystitis, or other risk factors, such as history of unexplained hematuria, obstructive symptoms, neurogenic bladder dysfunction, renal calculi, fistula, analgesic abuse, or severe disease such as diabetes mellitus). In women, diaphragm-spermicide use has been associated with an increased risk of urinary tract infection and vaginal colonization with *E. coli* (143). Spermicides containing the active ingredient nonoxynol-9 may provide a selective advantage in colonizing the vagina, perhaps by a reduction in vaginal lactobacilli and through enhancement of adherence of *E. coli* to epithelial cells (116,144). Thus spermicidals should be discontinued in women with recurrent urinary tract infection, and other forms of contraception should be used. In postmenopausal women, the risk of infection is reduced by estrogen replacement (274).

Excretory urography will demonstrate the anatomy of the urinary tract and provide reasonable assessment of its functional status. In healthy women, upper tract abnormalities associated with reinfections are very rare; therefore routine excretory urography is not indicated. Cystoscopy should be performed in men or women who have frequent

reinfections and symptoms suggestive of obstruction, bladder dysfunction, and fistula. Dilation of a stenotic urethra to a normal caliber would appear appropriate. There is little evidence, however, that repeated urethral dilation is indicated in the routine management of most women.

Antimicrobial management in women who have had two or more symptomatic urinary tract infections over a 6-month period or three or more episodes within a 12-month period involves one of three regimens: low-dose continuous prophylaxis, self-start intermittent therapy, or postintercourse prophylaxis.

Low-dose Continuous Prophylaxis

Low-dose continuous prophylaxis is indicated when the urine culture shows no growth (usually when a patient has completed antimicrobial therapy). Nightly therapy is then begun with one of the following drugs: (a) nitrofurantoin 50 to 100 mg half-strength (HS) (332), (b) TMP-SMX, 40 to 200 mg (346), (c) TMP 50 mg (346), or (d) Keflex 250 mg (213). Patients will have less than one urinary tract infection per year while taking these regimens. Every-other-night therapy is also effective and is probably practiced by most patients. When breakthrough infections occur, they are not necessarily accompanied by symptoms; therefore we advocate monitoring for infections every 1 to 3 months, even in asymptomatic patients. Breakthrough infections usually respond to full-dose therapy with the drug used for prophylaxis. However, cultures and susceptibility tests may indicate that another drug is indicated. After the infection is cured, prophylaxis may be reinstituted. Low-dose prophylaxis is usually discontinued after about 6 months, and the patient is monitored for reinfection. Approximately 30% of women will have spontaneous remissions that last up to 6 months (183). Unfortunately, many of the remissions are followed by reinfections, and low-dose prophylaxis must be reinstituted. At this point, many patients prefer an alternative form of management.

Self-start Intermittent Therapy

With self-start intermittent therapy, the patient is given a dip-slide device to culture the urine and is instructed to perform a urine culture when symptoms of urinary tract infection occur (294). The patient is also provided a 3-day course of empiric, full-dose antimicrobial therapy to be started immediately after performing the culture. It is important that the antimicrobial agent selected for self-start therapy have a broad spectrum of activity and achieve high urine levels to minimize development of resistant mutants. In addition, there should be minimal or no side effects on the fecal flora. Fluoroquinolones are ideal for self-start therapy because they have a spectrum of activity broader than any of the other oral agents and are superior to many parenteral antimicrobials, including aminoglycosides. Nitrofurantoin and TMP-SMX are acceptable alternatives, although they are somewhat less effective. Antimicrobial agents such as tetracycline, ampicillin, SMX, and cephalexin in full doses should be avoided because they can give rise to resistant bacteria (395).

The culture is brought to the office as soon as possible. If the culture is positive and the patient is asymptomatic, a culture is performed 7 to 10 days after therapy to determine efficacy. In most cases, the therapy is limited to two inexpensive dip-slide cultures and a short course of antimicrobial therapy. If the patient has symptoms that do not respond to initial antimicrobial therapy, a repeat culture and susceptibility testing of the initial culture specimen are performed and therapy adjusted accordingly. If symptoms of infection are not associated with positive cultures, urologic evaluation should be performed to rule out other causes of irritative bladder symptoms, including carcinoma in situ, interstitial cystitis, and neurogenic bladder dysfunction. Our experience with this technique has been very favorable, and we find that it is particularly attractive to patients who have less frequent infections and are willing to play an active role in their diagnosis and management.

Postintercourse Prophylaxis

Antimicrobial management through postintercourse prophylaxis is based on research establishing that sexual intercourse can be an important risk factor for acute cystitis in women (241). Diaphragm users have a significantly greater risk of urinary tract infection than do women who use other contraceptive methods (86). Postintercourse therapy with antimicrobials, such as nitrofurantoin, cephalexin, TMP-SMX, or a fluoroquinolone taken as a single dose, will effectively reduce the incidence of reinfection (224,265).

RENAL INFECTION (BACTERIAL NEPHRITIS)

Part of "4 - URINARY TRACT INFECTIONS "

Although renal infection is less prevalent than bladder infection, it often is a more difficult problem for the patient and his or her physician because of its often varied and morbid presentation and course, the difficulty in establishing a firm microbiologic and pathologic diagnosis, and its potential for significantly impairing renal function. Although the classic symptoms of acute onset of fever, chills, and flank pain are usually indicative of renal infection, some patients with these symptoms do not have renal infection. Conversely, significant renal infection may be associated with an insidious onset of nonspecific local or systemic symptoms, or it may be entirely asymptomatic. Therefore a high clinical index of suspicion and appropriate radiologic and laboratory studies are required to establish the diagnosis of renal infection.

Unfortunately, the relationship between laboratory findings and the presence of renal infection often is poor.

Bacteriuria and pyuria, the hallmarks of urinary tract infection, are not predictive of renal infection. Conversely, patients with significant renal infection may have sterile urine if the ureter draining the kidney is obstructed or the infection is outside of the collecting system.

The pathologic and radiologic criteria for diagnosing renal infection may also be misleading. Interstitial renal inflammation, once thought to be caused predominantly by bacterial infection, is now recognized as a nonspecific histopathologic change associated with a variety of immunologic, congenital, or chemical lesions that usually develop in the absence of bacterial infection. Infectious granulomatous diseases of the kidney often have either radiologic or pathologic characteristics that mimic renal cystic disease, neoplasia, or other renal inflammatory disease.

The effect of renal infection on renal function is varied. Acute or chronic pyelonephritis may transiently or permanently alter renal function, but nonobstructive pyelonephritis is no longer recognized as a major cause of renal failure. However, pyelonephritis, when associated with urinary tract obstruction or granulomatous renal infection, may lead rapidly to significant inflammatory complications, renal failure, or even death.

If urinary tract infection is associated with fever, chills, and flank pain, the infection is judged to be more severe and usually involves the kidneys. Bacterial nephritis, whether isolated or recurrent, may cause acute or chronic renal parenchymal damage and act as the source for recurrent episodes of renal or lower urinary tract infection (13,95).

Interstitial renal inflammation is a nonspecific cellular response of the renal interstitium that may or may not be complicated by fibrosis and varying degrees of tubular or glomerular damage. It generally has been believed that bacterial infection of the kidney, such as pyelonephritis, was the most common cause of interstitial renal inflammation and subsequent development of serious renal disease. More recently, however, the nonspecific nature of the histopathologic changes of interstitial renal inflammation has been appreciated. As a result of urologic evaluations of patients with chronic preexisting interstitial renal inflammation, it is now recognized that interstitial renal inflammation is associated with immunologic reactions, congenital lesions, or papillary damage in the absence of bacterial infection and that bacterial infection is often a secondary event. Thus histologic evidence alone is too often assumed indicative of bacterial nephritis and is not sufficient to establish whether interstitial changes in the kidney are either primary or secondary to bacterial infection or of noninfectious causes.

Pathology

The opportunity for pathologic confirmation of acute bacterial nephritis is rare. The kidney may be edematous. Focal acute suppurative bacterial nephritis caused by hematogenous dissemination of bacteria to the renal cortex is characterized by multiple focal areas of suppuration on the surface of the kidney (Fig. 4.7). Histologic examination of the renal cortex shows focal suppurative destruction of glomeruli and tubules. Adjacent cortical structures and the medulla are not involved in the inflammatory reaction. Acute ascending pyelonephritis is characterized by linear bands of inflammation extending from the medulla to the renal capsule (Fig. 4.8). Histologic examination usually reveals a focal wedge-shaped area of acute interstitial inflammation with the apex of the wedge in the renal medulla. Polymorphonuclear leukocytes or a predominantly lymphocytic and plasma cell response are seen. Bacteria also may be present.

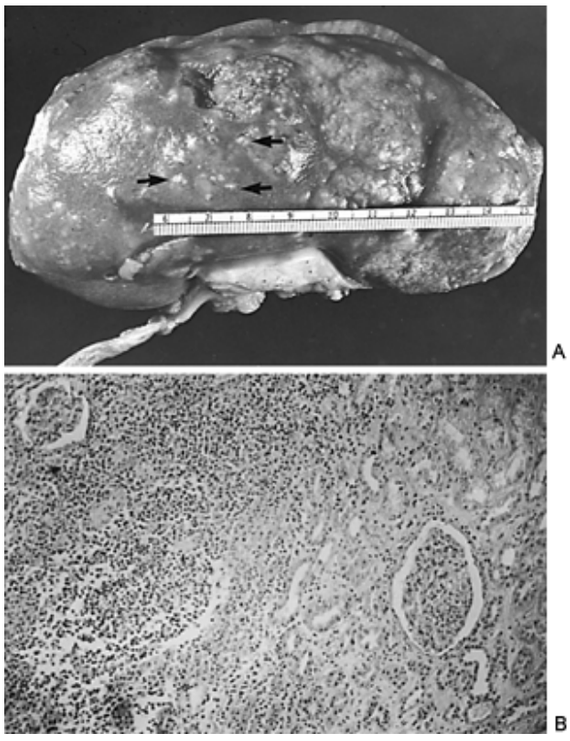

FIGURE 4.7. Acute focal suppurative bacterial nephritis. **A:** Surface of kidney. *Arrows* indicate focal areas of suppuration. **B:** Renal cortex showing focal suppuration destruction of glomeruli and tubules.

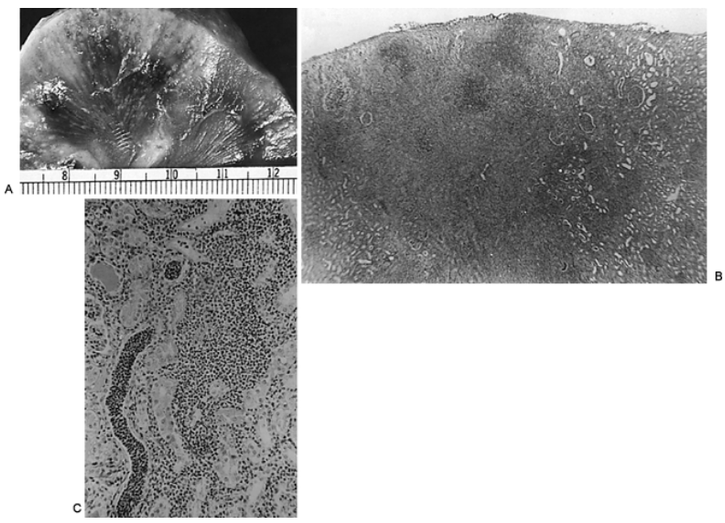

FIGURE 4.8. Acute ascending pyelonephritis. **A:** Cortical structures, tubules, and collecting ducts diffusely infiltrated with inflammatory cells. **B:** Section of the renal cortex showing wedge-shaped destruction of renocortical structures as a result of ascending infiltration with inflammatory cells. **C:** Thickened and inflamed tissue surrounding the collecting ducts in the medulla. A polymorphonuclear cast of segmented neutrophils is clearly visible.

The changes that appear to be most specific for chronic pyelonephritis are evident on careful gross examination of the kidney and consist of a cortical scar associated with retraction of the corresponding renal papilla (97,131,135,137). The kidney shows evidence of patchy involvement with numerous chronic inflammatory foci mainly confined to the cortex but also involving the medulla (Fig. 4.9). The scars may be separated by intervening zones of normal parenchyma, causing a grossly irregular renal outline. The microscopic appearance, as with most chronic

interstitial disease, includes the presence of lymphocytes and plasma cells. Although glomeruli within scars may be surrounded by a cuff of fibrosis or be partially or completely hyalinized, glomeruli outside these severely scarred zones are relatively normal. Vascular involvement is variable, but in patients with hypertension, nephrosclerosis may be found. Papillary abnormalities include deformity, sclerosis, and sometimes necrosis. Studies in animals have clearly indicated the critical role of the papilla in the initiation of pyelonephritis (98). However, these changes are not necessarily specific for bacterial infection and may occur in the absence of infection as a result of other disorders such as analgesic abuse, diabetes, and sickle cell disease.

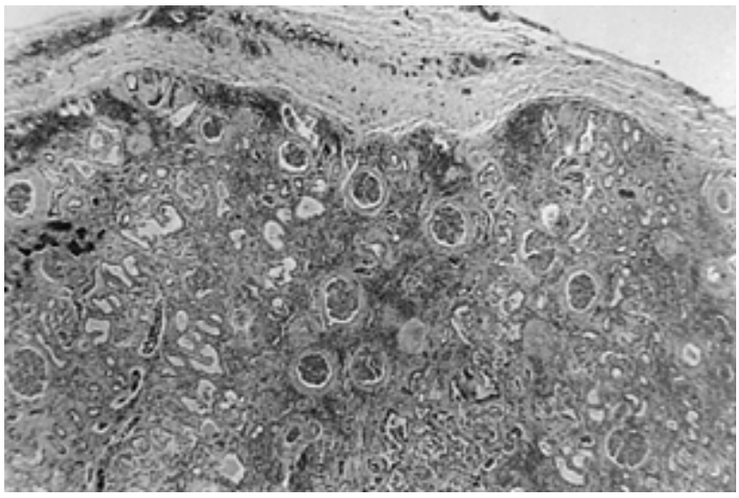

FIGURE 4.9. Chronic pyelonephritis. The renal cortex shows thickened fibrous capsule and focal retracted scar on surface of kidney. Focal destruction of tubules in center of picture is accompanied by periglomerular fibrosis and scarring.

The classic pathologic description of chronic pyelonephritis has traditionally been that of Weiss and Parker (382); however, their autopsy studies included late stages of the disease, which are often complicated by hypertension and vascular changes and are best referred to as *end-stage kidneys.* They repeatedly emphasized that patients with this form of renal disease did not always have clinical evidence of bacterial infections of the urinary tract sufficient to explain the severe loss of renal tissue. Stamey and Pfau (334) presented a case of pure symptomatic pyelonephritis, incurable with drug therapy and uncomplicated by vascular hypertension. The microscopic sections together with Heptinstall's comments represent an unusual opportunity to study the pathologic characteristics of this disease in its purest form.

Acute Pyelonephritis

Clinical Findings

The onset of acute pyelonephritis is usually abrupt. The classic clinical features are chills, fever (100°F or greater), and costovertebral angle or flank pain accompanied by symptoms of cystitis.

Although some authors regard loin pain and fever in combination with significant bacteriuria as diagnostic of acute pyelonephritis, it is clear from localization studies using ureteral catheterization (335) or the bladder wash-out technique (83) that clinical symptoms correlate poorly with the site of infection (77,80,321,333). In a large study of 201 women and 12 male patients with recurrent urinary tract infection, Busch and Huland (32) showed that fever and flank pain are no more diagnostic of pyelonephritis than they are of cystitis. Of patients with flank pain, fever, or both, more than 50% had lower tract bacteriuria. Patients with bladder symptoms or no symptoms frequently had upper tract bacteriuria. Approximately 75% of patients give a history of previous lower urinary tract infections.

On physical examination, there often is tenderness to deep palpation in the costovertebral angle. Variations of this clinical presentation have been recognized. Acute pyelonephritis may also simulate gastrointestinal tract abnormalities with abdominal pain, nausea, vomiting, and diarrhea. Asymptomatic progression of acute pyelonephritis to chronic pyelonephritis, particularly in compromised hosts, may occur in the absence of overt symptoms.

Laboratory Findings

The patient may have leukocytosis with predominance of neutrophils. Urinalysis usually reveals numerous WBCs, often in clumps, and bacteria. Leukocytes exhibiting brownian motion in the cytoplasm (glitter cells) may be present if the urine is hypotonic, but they are not in themselves diagnostic of pyelonephritis. The presence of large amounts of granular or leukocyte casts in the urinary sediment is suggestive of acute pyelonephritis. A specific type of urinary cast characterized by the presence of bacteria in its matrix has been demonstrated in the urine of patients who have had acute pyelonephritis (Fig. 4.10) (199). Bacteria in the casts were not easily distinguished by simple bright-field microscopy without special staining of the sediment. Staining the sediment with a basic dye such as dilute toluidine blue or KOVA (I.C.L. Scientific, Fountain Valley, California) stain demonstrated the bacteria in casts without difficulty. Urine cultures are invariably positive. Most often, the causative microorganism is *E. coli.* However, more resistant species, such as *Proteus, Klebsiella, Pseudomonas,* or *Serratia,* should be suspected in patients who have recurrent urinary tract infections, are hospitalized, or have indwelling catheters, as well as in those who required recent urinary tract instrumentation. Except for *Enterococcus faecalis* and *S. epidermidis,* Gram-positive bacteria rarely cause pyelonephritis. Blood cultures should be obtained in patients with severe toxicity because bacteremia and sepsis are common.

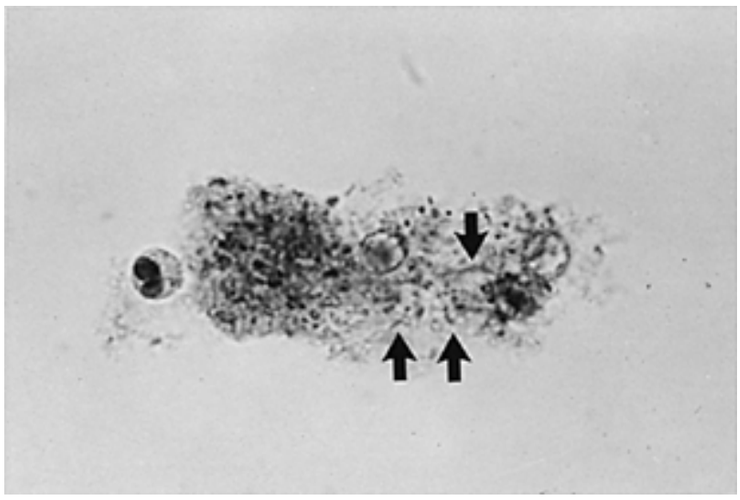

FIGURE 4.10. Bright-field micrograph of a mixed bacterial leukocyte cast from patient with acute pyelonephritis. Only the bacteria and the nucleus of a leukocyte stain strongly. *Arrows* show some bacteria. Many more are clearly demonstrated by through-focusing (toluidine blue O stain, magnification ×640). (Reprinted with permission from Lindner LE, Jones RN, Haber MH. A specific urinary cast in acute pyelonephritis. *Am J Clin Pathol* 1980;73:810.)

Differential Diagnosis

Acute appendicitis, diverticulitis, and pancreatitis can cause a similar degree of pain, but the location of the pain often is different. Results of the urine examination are usually normal. Herpes zoster can cause superficial pain in the region of the kidney but is not associated with symptoms of urinary tract infection; the diagnosis will be apparent when shingles appear.

Initial Management

Hospitalization, initially with complete bed rest, intravenous fluids, and antipyretics, is required for patients with significant toxicity. Patients with less severe disease may be managed as outpatients. Bladder outlet obstruction and associated urinary retention should be relieved by an indwelling urethral or suprapubic catheter. Upper tract obstruction, if suspected, should be ruled out by ultrasonography or intravenous urogram. An obstructed kidney has difficulty concentrating and excreting antimicrobial agents. In addition, obstruction in effect creates a potential abscess, pyonephrosis, which can rapidly destroy the renal parenchyma and endanger the patient's life. Any substantial obstruction must be relieved expediently by the safest and simplest means.

Until the results of the culture and susceptibilities are available, broad-spectrum antimicrobial therapy should be instituted. A Gram stain of the urine sediment is helpful to guide the selection of the initial empiric antimicrobial

therapy. Outpatient, single-drug oral therapy with a fluoroquinolone is more effective than TMP-SMX for patients with domiciliary infections (359). Many physicians administer a single parenteral dose of an antimicrobial (ceftriaxone, gentamicin, or a fluoroquinolone) before initiating oral therapy (158,267). If a Gram-positive organism is suspected, amoxicillin or amoxicillin ***/*** clavulanic acid is recommended (377). If a patient is sufficiently ill to require hospitalization (high fever, high WBC count, vomiting, dehydration, or evidence of sepsis) or fails to improve during the initial outpatient treatment period, the patient should be admitted and treated with intravenous antimicrobials. A parenteral fluoroquinolone, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside is recommended (377). If Gram-positive cocci are causative, ampicillin/sulbactam with or without an aminoglycoside is recommended.

Subsequent Management

Even though the urine usually becomes sterile within a few hours of starting antimicrobial therapy, patients with acute pyelonephritis may continue to have fever, chills, and flank pain for several more days (18). Ambulatory patients should be treated with a fluoroquinolone for 7 days (359). Alterations in antimicrobial therapy may be made depending on the patient's clinical response and the results of the culture and susceptibility tests. Susceptibility tests should also be used to replace potentially toxic drugs, such as aminoglycosides, with less toxic drugs, such as the fluoroquinolones, aztreonam, and cephalosporins. For women with uncomplicated pyelonephritis, 7-day fluoroquinolone therapy is associated with greater bacteriologic and clinical cure rates than 14-day TMP-SMX therapy (359). In hospitalized patients with bacteremia, parenteral therapy should be continued for 7 days. If results of the blood cultures are negative, parenteral therapy can be discontinued after several days. In either case, an appropriate oral antimicrobial drug (fluoroquinolone; TMP, TMP-SMX, or amoxicillin or amoxicillin/clavulanic acid for Gram-positive organisms) should be continued in full dosage for an additional 10 to 14 days.

Excretory urography is usually performed after institution of adequate therapy and resolution of the patient's symptoms; therefore it is not surprising that most patients with pyelonephritis have a normal excretory urogram (317,385). However, if obtained during acute pyelonephritis, the most common radiologic abnormality is renal enlargement, which occurs from generalized renal edema as a consequence of the inflammatory process (Fig. 4.11A). An overall length of 15 cm or a length 1.5 cm greater than the unaffected side has been established as criteria for the diagnosis of renal enlargement in acute pyelonephritis (56,317,385). The inflammatory response may also cause cortical vasoconstriction, which is presumably responsible for the diminished nephrogram and delayed appearance of the pyelogram, as well as compression of the collecting structures, so that the calyces have an attenuated or spidery appearance. In addition to these abnormalities, calyceal and ureteral dilation have occasionally been reported (124). This finding has been commonly attributed to a decrease in ureteral peristalsis caused by bacterial endotoxin. Although ureteral dilation may occur with infection, this diagnosis should not be made until obstruction, either past or present, has been excluded.

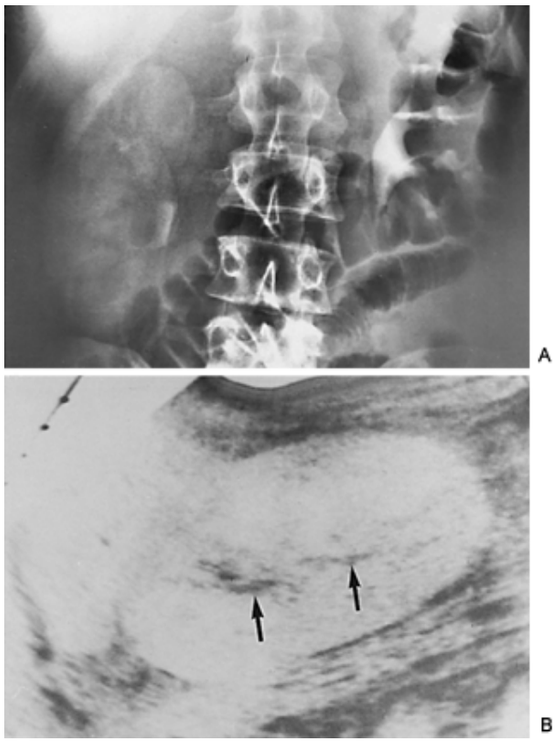

FIGURE 4.11. Acute pyelonephritis. **A:** Excretory urogram. Ten-minute film demonstrates enlarged right kidney with minimum function. Findings are consistent with edema. **B:** Ultrasound of the right kidney demonstrates renal enlargement, hypoechoic parenchyma, and compressed central collecting complex *(arrows).*

Ultrasound (Fig. 4.11B) and CT show renal enlargement, hypoechoic or attenuated parenchyma, and a compressed collecting system. In patients with fever greater than 72 hours, these studies are most helpful for ruling out obstruction and identifying complicated renal and perirenal infections (327).

Unfavorable Response to Therapy

When the response to therapy is slow or the urine continues to show infection, an immediate reevaluation is mandatory.

Urine and blood cultures must be repeated and appropriate alterations in antimicrobial therapy made on the basis of susceptibility testing. Radiologic investigation is indicated to attempt to identify unsuspected obstructive uropathy, urolithiasis, or underlying anatomic abnormalities that may have predisposed the patient to infection, prevented a rapid therapeutic response, or caused complications of the infectious process, such as renal or perinephric abscess. Radionuclide imaging may be useful to demonstrate functional changes associated with acute pyelonephritis (decrease in renal blood flow, delay in peak function, and delay in excretion of the radionuclide) (87) and cortical defects associated with vesicoureteral reflux.

Follow-up

Repeat urine cultures should be performed on the fifth to seventh day of therapy and 10 to 14 days and 4 to 6 weeks after discontinuing antimicrobial therapy to ensure that the urinary tract remains free of infections. For the few patients who have recurrent infections that presumably represent "relapse," re-treatment for 6 weeks has been recommended (162).

Depending on the clinical presentation and response and initial urologic evaluation, some patients may require additional evaluation (e.g., voiding cystourethrogram, cystoscopy, bacterial localization studies) and correction of an underlying abnormality of the urinary tract.

Acute Focal or Multifocal Bacterial Nephritis

Acute focal or multifocal bacterial nephritis is an uncommon, severe form of acute renal infection in which a heavy leukocyte infiltrate is confined to a single renal lobe (focal) or multiple lobes (multifocal).

Clinical Findings

The clinical presentation of patients with acute bacterial nephritis is similar to that of patients with acute pyelonephritis but usually is more severe. About half of the patients are diabetic, and sepsis is common. Generally, leukocytosis and urinary tract infection resulting from Gram-negative organisms are found; more than 50% of the patients are bacteremic (385).

Radiologic Findings

The diagnosis must be made by radiologic examination. The urographic findings are those of a mass, most commonly poorly marginated and suggestive of renal abscess or tumor (Fig. 4.12A). The mass has slightly less nephrographic density than the surrounding normal renal parenchyma.

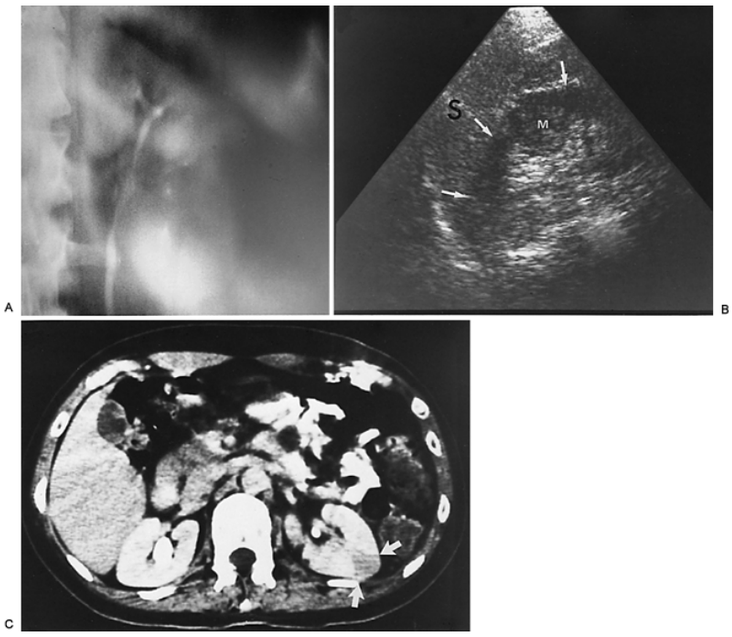

FIGURE 4.12. Acute focal bacterial nephritis. **A:** Excretory urogram. Five-minute tomogram demonstrates normally functioning upper and lower poles and a poorly marginated midrenal mass with poor function and absent collecting system visualization. **B:** Ultrasound; longitudinal view of the left kidney demonstrates spleen *(S)* and left kidney *(arrows).* Note irregular midpole mass *(M)* of slightly higher echo texture than surrounding normal renal parenchyma. **C:** Contrast-enhanced computed tomography scan demonstrates a wedge-shaped area of low density *(arrows)* in the middle portion of the left kidney. The findings resolved after antibiotic therapy.

Ultrasonography and CT aid in establishing the diagnosis. On ultrasonography, the lesion is typically poorly marginated and relatively sonolucent with occasional low-amplitude echoes that disrupt the cortical medullary junction (56) (Fig. 4.12B). Contrast enhancement is necessary with CT studies because the lesion is difficult to visualize on the unenhanced study (Fig. 4.12C). Wedge-shaped areas of decreased enhancement are seen. No definite wall is evident, and frank liquefaction is absent. Conversely, abscesses tend to have liquid centers, are usually round, and are present both before and after contrast enhancement. More chronic abscesses may also show a ring-shaped area of increased enhancement surrounding the lesion (56). Gallium scanning reveals uptake that is in the region of and larger than the previously demonstrated mass (284). In patients with multifocal disease, the findings are similar, but multiple lobes are involved.

Management

Acute bacterial nephritis probably represents a relatively early phase of frank abscess formation. In a series of cases reported by Lee and co-workers (195), a patient with acute focal bacterial nephritis progressed to abscess formation. Treatment includes hydration and intravenous antimicrobials for at least 7 days, followed by 7 days of oral antimicrobial therapy. Patients with bacterial nephritis typically respond to medical therapy, and follow-up studies will show resolution of the wedge-shaped zones of diminished attenuation. Failure to respond to antimicrobial therapy is an indication for appropriate studies to rule out obstructive uropathy, renal or perirenal abscess, renal carcinoma, or acute renal vein thrombosis. Long-term follow-up studies performed in a few patients with multifocal disease have demonstrated a decrease in renal size and focal calyceal deformities suggestive of papillary necrosis (62).

Emphysematous Pyelonephritis

Emphysematous pyelonephritis is an acute necrotizing parenchymal and perirenal infection caused by gas-forming uropathogens. The pathogenesis is poorly understood. Because the condition usually occurs in diabetic patients, it has been postulated that the high tissue glucose levels provide the substrate for microorganisms such as *E. coli,* which are able to produce carbon dioxide by the fermentation of sugar (303). Although glucose fermentation may be a factor, the explanation does not account for the rarity of emphysematous pyelonephritis despite the high frequency of Gram-negative urinary tract infection in diabetic patients, nor does it explain the rare occurrence of the condition in nondiabetic patients.

In addition to diabetes, many patients have urinary tract obstruction associated with urinary calculi or papillary necrosis and significant renal functional impairment. It seems

more reasonable to postulate that impaired host response caused by local factors, such as obstruction, or a systemic condition, such as diabetes, allows organisms with the capability of producing carbon dioxide to use necrotic tissue as a substrate to generate gas *in vivo.* Thus emphysematous pyelonephritis should be considered a complication of severe pyelonephritis rather than a distinct entity.

Clinical Findings

All of the documented cases of emphysematous pyelonephritis have occurred in adults (130). Juvenile diabetic patients do not appear to be at risk. Women are affected more often than men.

The usual clinical presentation is severe, acute pyelonephritis, although in some instances, a chronic infection precedes the acute attack. Almost all patients display the classic triad of fever, vomiting, and flank pain (303). Pneumaturia is absent unless the infection involves the collecting system. Results of urine cultures are invariably positive. *E. coli* is most commonly identified. *Klebsiella* and *Proteus* are less common.

Radiologic Findings

The diagnosis is established radiographically. Tissue gas that is distributed in the parenchyma may appear on abdominal x-ray films as mottled gas shadows over the involved kidney

(Fig. 4.13). This finding is often mistaken for bowel gas. A crescentic collection of gas over the upper pole of the kidney is more distinctive. As the infection progresses, gas extends to the perinephric space and retroperitoneum. This distribution of gas should not be confused with cases of emphysematous pyelitis in which air is in the collecting system of the kidney. Emphysematous pyelitis is secondary to a gas-forming bacterial urinary tract infection, often occurs in nondiabetic patients, is less serious, and usually responds to antimicrobial therapy.

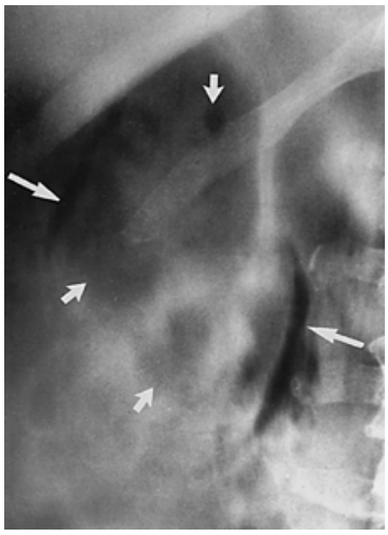

FIGURE 4.13. Emphysematous pyelonephritis; plain film. Extensive perinephric *(long arrows)* and intraparenchymal *(short arrows)* gas secondary to acute bacterial pyelonephritis.

Excretory urography is rarely of value in emphysematous pyelonephritis because the affected kidney usually is nonfunctioning or poorly functioning. Because of the significant risk of contrast nephropathy in critically ill, dehydrated diabetic patients with abnormal renal function, retrograde pyelography rather than excretory urography is advisable to demonstrate obstruction. Obstruction is demonstrated in approximately 25% of the cases. Ultrasonography usually demonstrates strong focal echoes suggesting the presence of intraparenchymal gas (27,53). CT is the imaging procedure of choice in defining the extent of the emphysematous process and guiding management (Fig. 4.14). An absence of fluid in CT images or the presence of streaky or mottled gas with or without bubbly and loculated gas appears to be associated with rapid destruction of renal parenchyma and a 50% to 60% mortality rate (19,376). The presence of renal or perirenal fluid, the presence of bubbly or loculated gas or gas in the collecting system, and the absence of streaky or mottled gas patterns is associated with a less than 20% mortality rate. A nuclear renal scan should be performed to assess the degree of renal function impairment in the involved kidney and the status of the contralateral kidney.

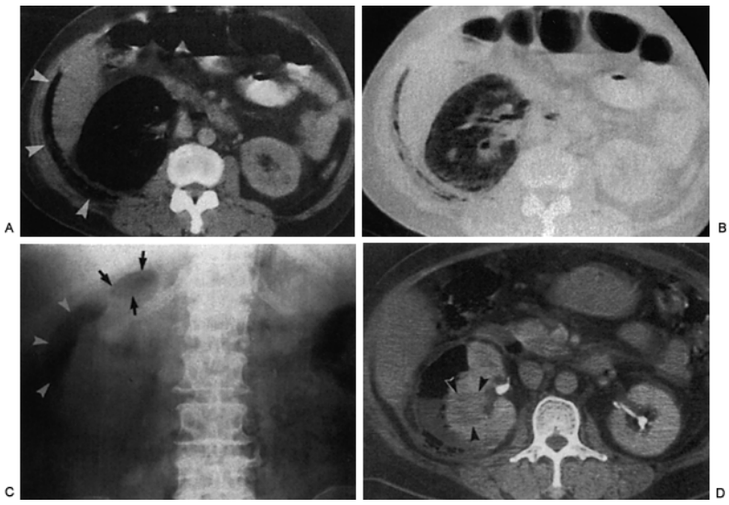

FIGURE 4.14. A, B: Type I emphysematous pyelonephritis (EPN) with complete renal destruction in a 49-year-old woman. **A:** Computed tomography (CT) scan of the right kidney shows complete destruction with gas *(arrowheads)* extending beyond the renal fascia. **B:** CT scan with a modified lung window display shows the characteristic streaky gas in the completely destroyed kidney. The patient died on arrival in the emergency department before nephrectomy was attempted. **C, D:** Type II EPN in a 57-year-old woman. **C:** Radiograph shows crescent-shaped *(arrowheads)* and loculated *(arrows)* gas in the right renal area. **D:** CT image obtained after administration of contrast material shows a low-attenuation area *(arrowheads)* in the right kidney due to acute pyelonephritis as well as a subcapsular abscess with fluid, bubbly, and loculated gas. The patient survived after percutaneous drainage was performed.

Management

Emphysematous pyelonephritis is a surgical emergency. Most patients are septic, and fluid resuscitation and broad-spectrum antimicrobial therapy are essential. If the kidney is functioning, medical therapy can be considered (19,376). Nephrectomy is recommended for patients who do not improve after a few days of therapy (73). If the affected kidney is nonfunctioning and not obstructed, nephrectomy should be performed because medical treatment alone is usually lethal. If a kidney is obstructed, catheter drainage must be instituted. If the patient's condition improves, nephrectomy may be deferred pending a complete urologic evaluation. Although there are isolated case reports of retention of renal function after medical therapy combined with relief of obstruction, most patients require nephrectomy (149).

Renal Abscess

Renal abscess or carbuncle is a collection of purulent material confined to the renal parenchyma. Before the antimicrobial era, 80% of renal abscesses were attributed to hematogenous seeding by staphylococci (36). Although experimental and clinical data document the facility for abscess formation in normal kidneys after hematogenous inoculation with staphylococci, widespread use of antimicrobials in the past 25 years appears to have diminished the propensity for Gram-positive abscess formation (57,64).

During the past two decades, Gram-negative organisms have been implicated in many adults with renal abscesses. Hematogenous renal seeding by Gram-negative organisms may occur, but this is not likely to be the primary pathway for Gram-negative abscess formation. Clinically, there is no evidence that Gram-negative septicemia antedates most lesions. Furthermore, Gram-negative hematogenous pyelonephritis is virtually impossible to produce in animals unless the kidney is traumatized or completely obstructed (57,362). The partially obstructed kidney rejects blood-borne Gram-negative inocula, as does a normal kidney. Thus ascending infection associated with tubular obstruction from prior infections or calculi appears to be the primary pathway for establishment of Gram-negative abscesses. Two-thirds of Gram-negative abscesses in adults are associated with renal calculi or damaged kidneys (290) (Fig. 4.15). Although the association of pyelonephritis with vesicoureteral reflux is well established, the association of renal abscess with vesicoureteral reflux has rarely been noted in the past (310). However, it has been observed that reflux often is associated with renal abscesses and persists long after sterilization of the urinary tract (362).

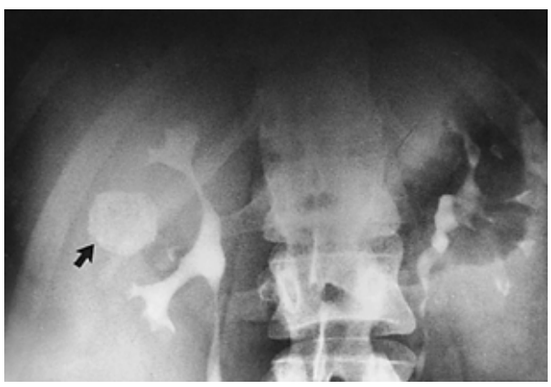

FIGURE 4.15. Renal abscess associated with infection stone. Excretory urogram. Twenty-minute film demonstrates a large, right midpole calculus *(arrow).* Abscess associated with this infection stone causes displacement of adjacent collecting system.

Clinical Findings

The patient's symptoms may include fever, chills, abdominal or flank pain, and occasionally, weight loss and malaise. Lower urinary tract infections, including cystitis, also usually occur. Occasionally, these symptoms may be vague and delay diagnosis until surgical exploration or, in more severe cases, at autopsy (5). A thorough history may reveal a Gram-positive source of infection 1 to 8 weeks before the onset of urinary tract symptoms. The infection may have occurred in any area of the body. Multiple skin carbuncles and intravenous drug abuse introduce Gram-positive organisms into the bloodstream. Other common sites are the mouth, lungs, and bladder (205). Complicated urinary tract infections associated with stasis, calculi, pregnancy, neurogenic bladder, and diabetes mellitus also appear to predispose the patient to abscess formation (5).

Laboratory Findings

The patient typically has marked leukocytosis. The blood cultures are usually positive. Pyuria and bacteriuria may not be evident unless the abscess communicates with the collecting system. Because Gram-positive organisms are most commonly blood borne, urine cultures in these cases will typically show no growth or a microorganism different from that isolated from the abscess. When the abscess contains Gram-negative organisms, the urine culture usually demonstrates the same organism isolated from the abscess.

Radiologic Findings

The urographic findings depend on both the nature and the duration of the infection. In patients in whom abscess formation has progressed from an episode of acute bacterial

nephritis or those in whom the kidney has been seeded by an outside infection, radiologic examination may demonstrate generalized renal enlargement with distortion of the renal contour on the affected side. There also may be renal fixation evident on inspiratory and expiratory films and obliteration of the corresponding psoas shadow. Scoliosis is often present, with a concavity of the curve facing the affected kidney. If renal involvement is diffuse, the nephrogram will be delayed or even absent. When an abscess is more localized, the findings may be similar to those of acute focal bacterial nephritis.

In a more chronic abscess, the predominant urographic abnormalities are those of a renal mass lesion (Fig 4.15). The calyceal system may be poorly defined or show distortion or even amputation. Nephrotomography usually reveals a relative radiolucency in the involved area. Occasionally, the excretory urogram will appear normal despite the presence of a renal abscess, particularly if the abscess involves the anterior or posterior portion of the kidney without impinging on the parenchyma or collecting system.

CT appears to be the diagnostic procedure of choice for renal abscesses because it provides excellent delineation of the tissue. On CT, abscesses are characteristically well defined both before and after contrast enhancement. Initially, CT shows renal enlargement and focal, rounded areas of decreased attenuation (Fig 4.16A). After several days of the onset of the infection, a thick, fibrotic wall begins to form around the abscess. CT of a chronic abscess shows obliteration of adjacent tissue planes, thickening of Gerota's fascia, and a round or oval parenchymal mass of low attenuation that forms a ring when the scan is enhanced with contrast material (Fig 4.17A). The ring sign is caused by the increased vascularity of the abscess wall.

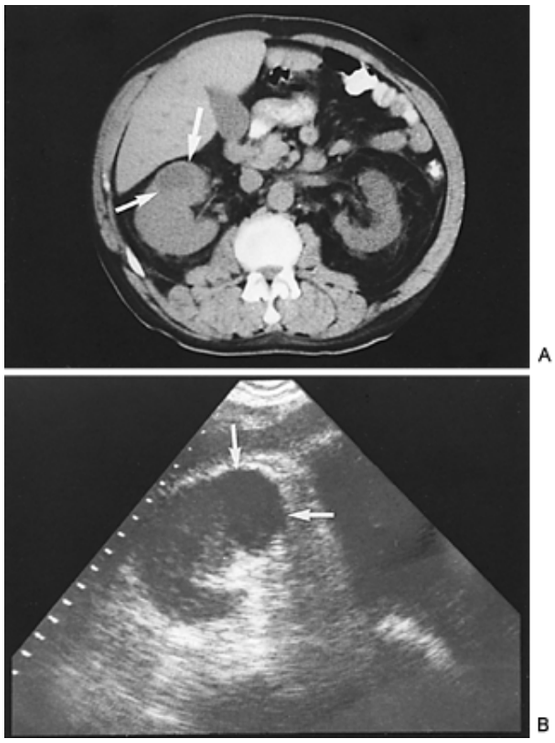

FIGURE 4.16. Acute renal abscess. **A:** Nonenhanced computed tomography scan through the midpole of the right kidney demonstrates right renal enlargement and an area of decreased attenuation *(arrows).* After antimicrobial therapy, follow-up scan showed complete regression of these findings. **B:** Ultrasound. Transverse scan of the right kidney demonstrates a poorly marginated rounded focal hypoechoic mass *(arrows)* in the anterior portion of the kidney.

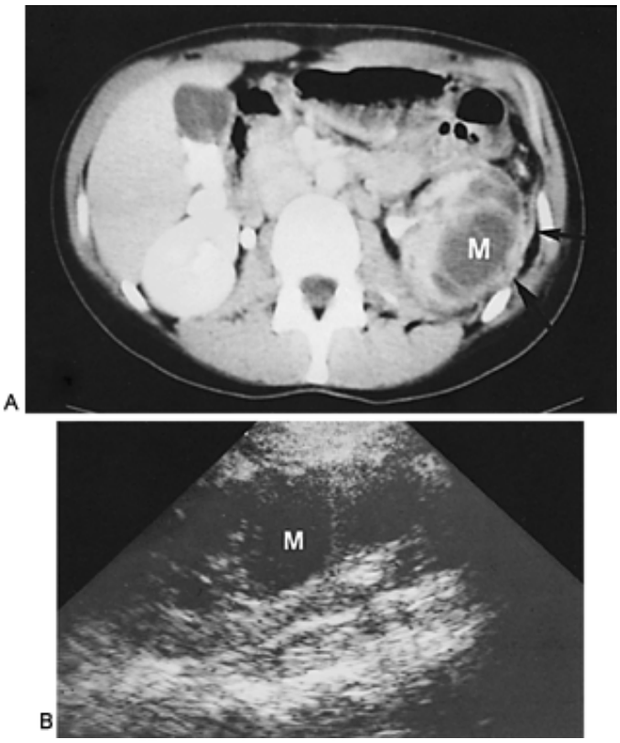

FIGURE 4.17. Chronic renal abscess. **A:** Enhanced computed tomography scan shows irregular septated low-density mass *(M)* extensively involving the left kidney. Note thickening of perinephric fascia *(arrows)* and extensive compression of the renal collecting system. Findings are typical of renal abscess. **B:** Ultrasound. Longitudinal scan demonstrates septated hypoechoic mass *(M)* occupying much of the renal parenchymal volume.

Ultrasonography is the quickest and least expensive method to demonstrate a renal abscess. An echo-free or low-echo-density space-occupying lesion with increased transmission is found on the sonogram. The margins of an abscess are indistinguishable in the acute phase, but the structure contains a few echoes, and the surrounding renal parenchyma is edematous (Fig 4.16B). Subsequently, the appearance tends to be that of a well-defined mass. However, the internal appearance may vary from a virtually solid lucent mass to one with large numbers of low-level internal echoes (Fig 4.17B). The number of echoes depends on the amount of cellular debris within the abscess. Presence of air results in a strong echo with a shadow. Differentiation between an abscess and a chronic tumor is impossible in many cases. Arteriography is used occasionally to demonstrate abscesses. The center of the mass tends to be hypovascular or avascular, with increased vascularity at the cortical margins and lack of vascular displacement and neovascularity.

Radionucleotide imaging with gallium or indium is sometimes useful in evaluating patients with renal abscesses. The exact mode of gallium-67 localization in tissues is not clear. Suggested possible mechanisms include concentration within labeled polymorphonuclear leukocytes, leakage of protein-bound gallium through capillaries, and increased vascularity of the lesion. Delayed imaging is often necessary. Gallium is a nonspecific method of identifying an inflammatory lesion; more important, it lacks anatomic detail. In addition, gallium is excreted into the colon and sequestered in postsurgical beds, inflammatory sites, and tumors; therefore the interpretation of gallium scans can be extremely difficult.

Indium-111–labeled leukocyte scanning is a clinically effective method for detecting inflammatory diseases and abscesses. Indium-111–labeled leukocytes accumulate only in sites of inflammation and not in normal kidneys or in tumors. Thus their presence appears highly specific for inflammation. However, the indium scan has limitations. Hyperalimentation and hyperglycemia can prevent the accumulation at the site of inflammation, and the distribution of leukocytes is altered in patients who have had splenectomy or bone marrow radiation. The necessity of high doses of radiation with indium scanning may make it unsuitable for pediatric patients (107).

Ultrasonography and CT identify more than 90% of abscesses (91,316). Ultrasonography demonstrates a hypoechoic mass with irregular walls and acoustic shadowing if gas is present. CT scan findings depend in part on the age and severity of the abscess (16).

Management

Although the classic treatment for an abscess has been incision and drainage, there has been good evidence that the use of intravenous antimicrobials and careful observation of a small abscess less than 3 cm in diameter, if begun early enough in the course of the process, may obviate surgical procedures (198).

When hematogenous dissemination is suspected, the pathogenic organism most commonly is penicillin-resistant *Staphylococcus,* and the antibiotic of choice therefore is a penicillinase-resistant penicillin (305). If a history of penicillin hypersensitivity is present, the recommended drug is either cephalosporin or vancomycin. Cortical abscesses that occur in the abnormal urinary tract are associated with more typical Gram-negative pathogens and should be treated empirically with intravenous third-generation cephalosporins, antipseudomonal penicillins, or aminoglycosides until specific therapy can be instituted. These individuals can have follow-up with ultrasonography or CT until the abscess resolves. A clinical course contrary to this should lead to the suspicion of misdiagnosis or an uncontrolled infection with development of perinephric abscess or infection with an organism resistant to the antimicrobials used in therapy. In these instances, drainage is usually necessary.

CT- or ultrasound-guided needle aspiration may be necessary to differentiate a small abscess from a hypovascular tumor. Aspirated material can be cultured and appropriate antimicrobial therapy instituted on the basis of the findings. Abscesses larger than 3 cm and smaller abscesses in immunocompromised hosts or those that do not respond to antimicrobial therapy should be drained percutaneously (91,316). However, surgical drainage currently remains the procedure of choice for most renal abscesses greater than 5 cm in diameter.

Infected Hydronephrosis and Pyonephrosis

If bacterial infection occurs in a hydronephrotic kidney, a purulent exudate will collect in the renal collecting system. Pyonephrosis refers to infected hydronephrosis associated with suppurative destruction of the parenchyma of the kidney, with total or near-total loss of renal function (Fig. 4.18).

The point at which infected hydronephrosis ends and pyonephrosis begins is difficult to determine.

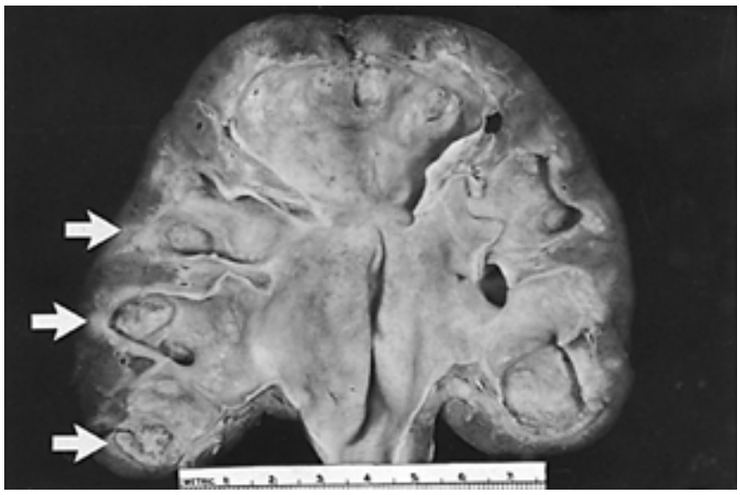

FIGURE 4.18. Pyonephrosis; gross specimen. Kidney shows marked thinning of renal cortex and medulla, suppurative destruction of the parenchyma *(arrows),* and distention of the pelvis and calyces. Previous incision released large quantity of purulent material. Ureter showed obstruction distal to the point of section.

Clinical Findings

The clinical presentation is variable, ranging from no complaints to urosepsis. However, many patients will be ill with fever, chills, and flank pain and tenderness. A history of urinary tract calculi, infection, or surgery is common. Bacteriuria may not be present if the ureter is completely obstructed. Wu and colleagues (398) observed significantly higher erythrocyte sedimentation rates and C-reactive protein levels in patients with infected hydronephrosis or pyonephroses compared with those with simple hydronephrosis. A cutoff of erythrocyte sedimentation rate greater than 100 mm per hour and C-reactive protein of 3 mg/dL yielded a specificity and sensitivity of 89% and 100%, respectively, and a diagnostic accuracy of 97%. Changes in these parameters can be used to evaluate the effectiveness of antimicrobial therapy.

Radiologic Findings

The ultrasonographic diagnosis of infected hydronephrosis depends on demonstration of internal echoes within the dependent portion of a dilated pyelocalyceal system. CT scan is nonspecific but may show thickening of the renal pelvis, stranding of the perirenal fat, and a striated nephrogram. The urographic findings are those of urinary tract obstruction and depend on the degree and duration of obstruction. Typically, the obstruction is longstanding, and excretory urography shows a poorly functioning or nonfunctioning hydronephrotic kidney. Ultrasound demonstrates hydronephrosis and fluid debris levels within the dilated collecting system (56) (Fig 4.19A). The diagnosis of pyonephrosis is suggested if focal areas of decreased echogenicity are seen within the hydronephrotic parenchyma.

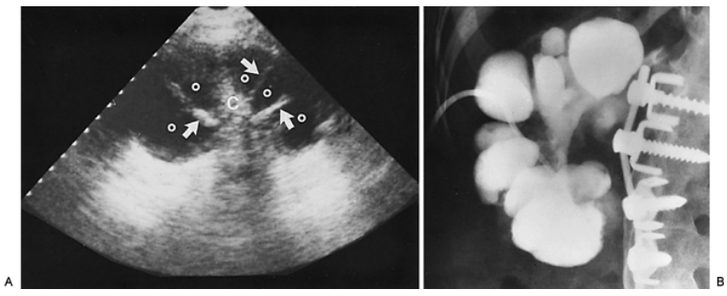

FIGURE 4.19. Pyonephrosis. **A:** Ultrasound. Longitudinal scan of the right kidney demonstrates echogenic central collecting complex *(C)* with radiating echogenic septae *(arrows)* and thinned hypoechoic parenchyma. Multiple dilated calyces *(o)* with diffuse low-level echoes are seen. **B:** Antegrade pyelogram performed through a percutaneous nephrostomy catheter correlates well with the ultrasound image. Dilated pus-filled calyces are demonstrated. The renal pelvis is obliterated by chronic scarring and stone disease. The kidney did not regain function.

Management

Appropriate intravenous antimicrobial therapy is important, but immediate drainage of the kidney is mandatory. Percutaneous nephrostomy (Fig. 4.19B) or retrograde ureteral catheterization (or, if necessary, open nephrostomy) must be performed. When the patient's condition has stabilized, appropriate corrective surgery or nephrectomy can be performed depending on the patient's age, the cause and type of obstruction, and the degree of renal function impairment.

Perinephric Abscess

Perinephric abscess (PNA) usually results from rupture of an acute cortical abscess into the perinephric space. Patients with pyonephrosis, particularly when a calculus is present in the kidney, are susceptible to perinephric abscess formation. Diabetes mellitus is present in approximately one-third of patients with perinephric abscess (70,361). In about one-third of the cases, perinephric abscess is caused by hematogenous spread, usually from sites of skin infection. A perirenal hematoma can become secondarily infected by the hematogenous route or by direct extension of a primary renal infection. Rarely, perinephric or psoas abscess may be the result of bowel perforation, Crohn's disease, or spread of osteomyelitis from the thoracolumbar spine. *E. coli, Proteus,* and *S. aureus* account for most infections.

Clinical Findings

The onset of symptoms is typically insidious. Symptoms have been present for more than 5 days in most patients with perinephric abscess compared with only about 10% of patients with pyelonephritis. The clinical presentation may be similar to that of pyelonephritis; however, more than one-third of patients may be afebrile. An abdominal or flank mass can be felt in about half of the cases. Psoas abscess should be suspected if the patient has a limp and flexion and external rotation of the ipsilateral hip. Laboratory features include leukocytosis, elevated levels of serum creatinine, and pyuria in more than 75% of cases. Edelstein and McCabe (70) showed that results of urine cultures predicted PNA isolates in only 37% of cases; a blood culture, particularly with multiple organisms, was often indicative of perinephric abscess, but identified all organisms in only 42% of cases. Therefore therapy based on the results of urine and blood cultures often may be inadequate. Pyelonephritis usually responds within 4 to 5 days of appropriate antibiotic therapy; perinephritic abscess does not. Thus perinephric abscess should be suspected in a patient with urinary tract

infection and abdominal or flank mass or persistent fever after 4 days of antimicrobial therapy.

Radiologic Findings

Excretory urography is abnormal in 80% of cases. However, the abnormalities are not specific. Classically, the radiographic features of perinephric abscess have been the absence of psoas shadow, a mass in the perirenal area often associated with indistinct renal outlines, and an elevated or immobile diaphragm. With large abscesses, the soft tissue density may extend to the pelvis following the renal fascia. In patients with perinephric abscess secondary to gas-forming organisms, bubbled collections of extraluminal gas are seen surrounding the kidney (203). CT is particularly valuable for demonstrating the primary abscess. In some cases, the abscess is confined to the perinephric space; however, extension to the flank or psoas muscle may occur (Fig. 4.20). CT is able to show with exquisite anatomic detail the route of spread of infection into the surrounding tissues. This information may be helpful in planning the approach for surgical drainage. Ultrasound demonstrates a diverse sonographic appearance ranging from a nearly anechoic mass displacing the kidney to an echogenic collection that tends to blend with normally echogenic fat within Gerota's fascia (56).

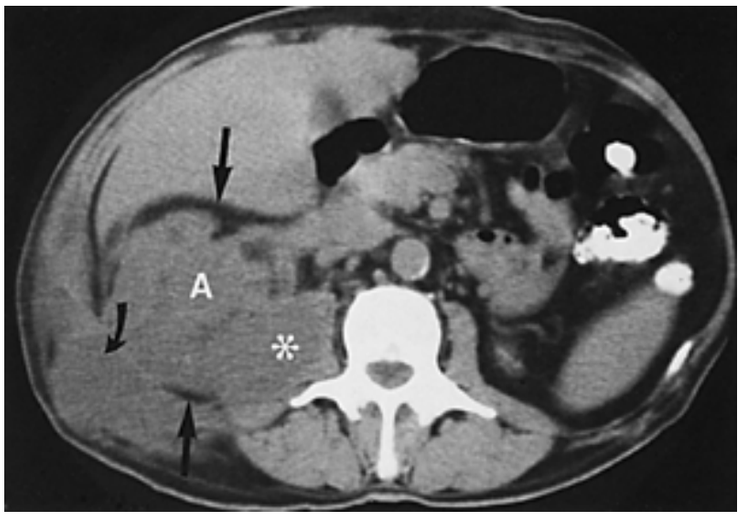

FIGURE 4.20. Extensive perinephric abscess. Nonenhanced computed tomography scan through the lower pole of the right kidney (previous left nephrectomy). Extensive abscess *(A)* distorts and enlarges renal contour, infiltrates perinephric fat *(arrows),* and also extends into the psoas muscle *(asterisk)* and the soft tissues of the flank *(curved arrow).* Also note that normal renal collecting system fat has been obliterated by the process.

Occasionally, a retroperitoneal or subdiaphragmatic infection may spread to the paranephric fat that is outside Gerota's fascia. The clinical symptoms of insidious onset of fever, flank mass, and tenderness are indistinguishable from those associated with perinephric abscess. Urinary tract infection, however, is absent. Ultrasonography and CT can usually delineate the abscess outside Gerota's fascia (Fig. 4.21).

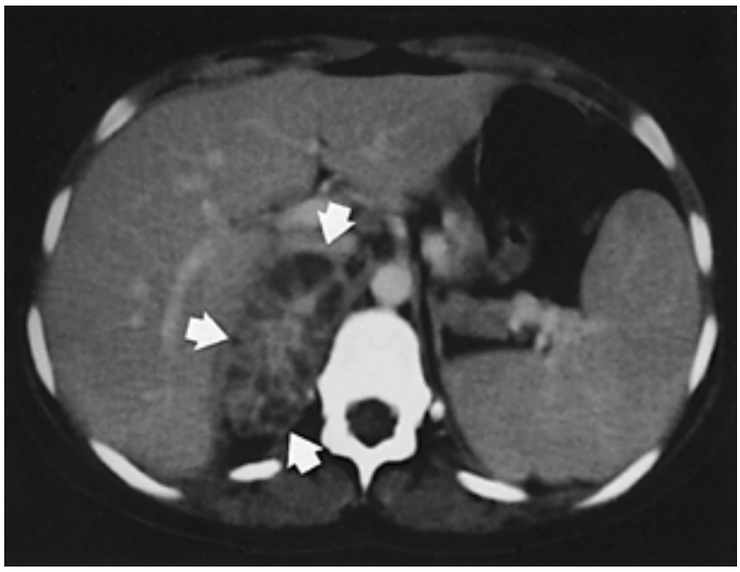

FIGURE 4.21. Perinephric abscess involving the right adrenal gland. Computed tomography scan. Large right pararenal mass *(arrows)* with multiple low-density areas within. At surgery, a large pararenal abscess with extensive involvement of the right adrenal was found.

Management

Once the diagnosis of perinephric or paranephric abscess is established, the primary treatment is surgical drainage. Gram stain identifies the pathogenesis and guides antimicrobial

therapy. An aminoglycoside together with an antistaphylococcal agent, such as methicillin or oxacillin, should be started immediately. If the patient has a penicillin hypersensitivity, cephalothin or vancomycin may be used.

Once the perinephric abscess has been drained, the underlying problem must be dealt with. Some conditions, such as renal cortical abscess or enteric communication, require prompt attention. Nephrectomy for pyonephrosis may be performed concurrent with drainage of the perinephric abscess if the patient's condition is good. In other instances, it is best to drain the perinephric abscess first and correct the underlying problem or perform a nephrectomy when the patient's condition has improved.

Chronic Pyelonephritis

In patients without underlying renal or urinary tract disease, chronic pyelonephritis secondary to urinary tract infection is a rare disease and an even more rare cause of chronic renal failure. In patients with underlying functional or structural urinary tract abnormalities, however, chronic renal infection can cause significant renal impairment. Hence, it is essential that appropriate studies be used to diagnose, localize, and treat chronic renal infection.

The prevalence of chronic pyelonephritis has also been assessed in patients undergoing dialysis for end-stage renal disease. Despite a 2% to 5% prevalence of bacteriuria in women, only 1,000 to 2,000 women have end-stage renal disease as a result of pyelonephritis. Schechter and colleagues (304) analyzed the cause for renal failure in 170 patients referred to them for dialysis. Chronic pyelonephritis was the primary cause of end-stage renal disease in 22 (13%) but was usually associated with an underlying structural defect. Unequivocal nonobstructive chronic pyelonephritis was not found. The authors also observed that symptomatic infections tended to occur before the onset of azotemia in most patients with chronic pyelonephritis. Similarly, Huland and Busch (151) evaluated 161 patients with end-stage renal disease and found that 42 had chronic pyelonephritis. However, in addition to a history of urinary tract infections, these 42 patients had complicating defects, such as vesicoureteral reflux, analgesic abuse, nephrolithiasis, or obstruction. Nonobstructive uncomplicated urinary tract infection alone was never found to be the cause of renal insufficiency. Thus, using end-stage renal disease seen at autopsy or at the dialysis clinic as an indicator, the prevalence of uncomplicated chronic bacterial pyelonephritis is rare.

In addition, the role of bacterial infection in development of chronic renal disease can be assessed in patients with renal interstitial and tubular damage similar to that which has classically been called *chronic pyelonephritis.* The frequency with which various potential causes of interstitial damage are operative in patients with interstitial nephritis was assessed by Murray and Goldberg (234). These investigators not only concluded that urinary tract infection is rarely the sole cause of chronic renal disease in the adult, but they also observed that 89% of their azotemic patients had a readily identifiable primary cause of their interstitial nephritis. Thus, when patients with a clinical diagnosis of chronic interstitial nephritis are selected as the starting point, it is easy to associate many factors with this disease, but urinary tract infection does not seem to be one of them.

Clinical Findings

There are no symptoms of chronic pyelonephritis until it produces renal insufficiency, and then the symptoms are similar to those of any other form of chronic renal failure. If a patient's chronic pyelonephritis is thought to be an end result of many episodes of acute pyelonephritis, a history of intermittent symptoms of fever, flank pain, and dysuria may be elicited. Similarly, urinary findings and the presence of renal infection correlate poorly. Bacteriuria and pyuria, the hallmarks of urinary tract infection, are not predictive of renal infection. Conversely, patients with significant renal infection may have sterile urine if the ureter draining the kidney is obstructed or the infection is outside of the collecting system.

The pathologic and radiologic criteria for diagnosing renal infection may also be misleading. Asscher (7a) has tabulated eight long-term follow-up studies from the literature on kidneys of adults with urinary tract infections. The data from these reports on 901 patients show that bacteriuria present in otherwise healthy adults for long periods may be associated with nonexistent or extremely minimum evidence of kidney damage. Conversely, patients who have chronic pyelonephritis may have negative urine cultures.

Radiologic Findings

The diagnosis of chronic pyelonephritis can be made with the greatest confidence on the basis of pyelographic findings. The essential features are asymmetry and irregularity of the kidney outlines, blunting and dilation of one or more calyces, and cortical scars at the corresponding site (Fig. 4.22). In the absence of stones, obstruction, and tuberculosis, and with the single exception of analgesic nephritis with papillary necrosis (which can be readily excluded by history), chronic pyelonephritis is virtually the only disease that produces a localized scar over a deformed calyx (331). In advanced pyelonephritis, calyceal distortion and irregularity together with cortical scars complete the picture. Hodson (135) pointed out that renal infarction, an extremely rare condition, may closely resemble pyelonephritic scars but that the renal pyramid remains with renal infarction in contradistinction to pyelonephritis.

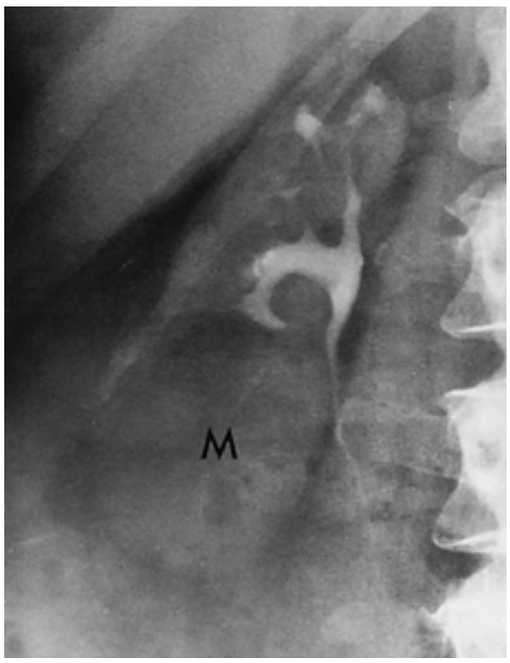

FIGURE 4.22. Chronic pyelonephritis. Excretory urogram. Ten-minute film demonstrates irregular renal outline with upper pole parenchymal atrophy. Note significant loss of renal cortical thickness over blunted and dilated calyces. Lower pole mass *(M)* is a simple cyst.

Management

Management of radiographic evidence of pyelonephritis should be directed at treating infection, if present; preventing future infections; and monitoring and preserving renal function. The treatment of existing infection must be based on careful antimicrobial susceptibility tests and selection of drugs that can achieve bactericidal concentrations in the urine and yet are not nephrotoxic. Achievement of acceptable bactericidal levels of a drug in the urine of a patient with chronic pyelonephritis may be difficult because the diminished concentrating ability of pyelonephritis may impair excretion and concentration of the antimicrobial agent. The duration of antimicrobial therapy is often prolonged to maximize the chance of cure. With patients in whom renal damage develops or progresses in the presence of urinary tract infection, the working hypothesis should be that there is an underlying renal, usually papillary, lesion or underlying urologic condition, such as obstruction or calculus, that has increased susceptibility to renal damage. Appropriate nephrologic and urologic evaluation should be undertaken to identify and, if possible, correct these abnormalities.

Bacterial "Relapse" from a Normal Kidney

The concept that bacteria persist in the renal parenchyma between bacteriuric episodes and cause "relapsing" urinary tract infections was based on a study by Turck and colleagues (366) that suggested that bacterial persistence could be recognized by simply identifying two consecutive recurrent infections with the same organism. Unfortunately, this study did not indicate whether the urine was cultured during therapy to ensure that the original infection had actually been eradicated. It is possible that some of these so-called relapses were in fact unresolved initial infections and that ureteral edema associated with catheterization may have impeded clearance of the initial infecting strain.

Subsequent studies summarized by Stamey (331) and Forland and associates (90) have shown that in a normal urinary tract recurrent infections are not caused by relapse from bacterial persistence in the kidney. With ureteral catheterization techniques, Cattell and associates (39) localized the site of bacteriuria in 42 patients who had follow-up for 6 months after therapy. They analyzed the response to antimicrobial therapy of 2 weeks' duration. Of the 26 patients who were cured of their initial infection, 16 had recurrence with the same organism; 8 had upper tract infections, and 8 had bladder bacteriuria.

If bacterial persistence in the kidney is a major problem after therapy, one would expect that patients who have more recurrent infections would also have more relapses than those who have less frequent recurrences. Mabeck (206) analyzed this, however, and found that with an increasing number of recurrences, the relationship among treatment failure, relapse, and reinfection remained unchanged. Thus bacteria do not persist in normal kidneys between recurrent urinary tract infections (331), and recurrences with the same strain are not caused by "relapse" from the kidney.

INFECTIOUS GRANULOMATOUS NEPHRITIS

Part of "4 - URINARY TRACT INFECTIONS "

Renal Tuberculosis

Tuberculosis is an acute or chronic infectious disease that in the United States is usually caused by *Mycobacterium tuberculosis. Mycobacterium bovis, Mycobacterium kansasii,*

and *Mycobacterium intracellulare* are rare causes of tuberculosis.

Mycobacteria customarily gain access to the human body by inhalation, although the bovine organisms may be acquired by ingestion of unpasteurized milk. After initiation of the tuberculous infection, a primary pathologic focus develops, which usually heals spontaneously. In addition, the primary infection often results in an initial silent bacillemia that is responsible for systemic spread of *Mycobacterium* with latent infection of many organs. These latent foci of tuberculous infection may break down and result in overt tuberculosis of the kidney or other organs many years later. Bacillemia and seeding of the kidneys or other organs may also occur from a focus of progressive primary or reactivation tuberculosis in the lung or from clinically evident secondary tuberculosis in other organs. Therefore any individual who has previously been infected with tuberculosis is at risk for developing renal involvement.

Renal infection is among the most common sites for extrapulmonary tuberculosis. Approximately 5% of the estimated 250,000 patients with active tuberculosis in the United States have cavitary tuberculosis of the genitourinary tract (236,323,381). Thirty percent to 50% of patients with renal tuberculosis have had previous tuberculous pulmonary disease documented by history or implied from chest roentgenograms (320). However, it is uncommon for pulmonary tuberculosis to be active at the time of diagnosis of renal tuberculosis. Although effective chemotherapy has resulted in a significant decrease in the prevalence of pulmonary tuberculosis, the frequency of renal tuberculosis has not declined significantly in recent decades (197,236).

Pathology and Pathogenesis

In the hematogenous phase that takes place after the primary infection, both kidneys are seeded with tubercle bacilli in 90% of cases. However, clinically apparent renal tuberculosis is usually unilateral. The initial lesions involve the renal cortex with multiple small granulomas in the glomeruli and in the juxtaglomerular regions. With patients in whom acquired cellular immunity develops, there is inhibition of bacterial multiplication and containment of the disease process to the renal cortex. Microscopic examination reveals central caseation necrosis surrounded by pink staining epithelial histiocytes, Langhans' giant cells, and more peripherally, lymphocytes and plasma cells (125). Most patients are asymptomatic and have normal findings on radiologic examination. The asymptomatic cortical disease may be stable for many years and an incidental finding at nephrectomy or autopsy. These early lesions may resolve completely either spontaneously or as a result of treatment.

In untreated patients who fail to heal spontaneously, the lesions may progress slowly and remain asymptomatic for variable periods. In most individuals, the latent period between initial exposure and reactivation of renal disease is 10 to 40 years (320) and may be increased by appropriate therapy (236). The cortical areas of infection may seed the glomerular filtrate, creating lesions in the tubules and Henle's loop, resulting in additional foci in the renal pyramid. As the lesions progress, they produce areas of caseous necrosis, chronic interstitial nephritis with papillary necrosis, and parenchymal cavitation (Fig. 4.23). Large, tumorlike parenchymal lesions or tuberculomas often have a fibrous wall and can resemble a solid mass lesion. Their content may vary from caseous to calcified material (125). Larger blood vessels may show obliterative arteritis.

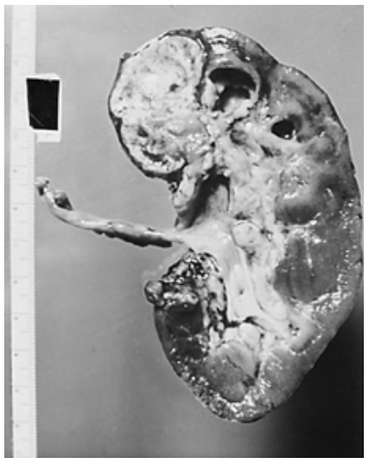

FIGURE 4.23. Tuberculoma, gross specimen. A destructive necrotic mass is present in the upper pole. (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

Once cavities form, spontaneous healing is rare and destructive lesions result. With necrotizing papillitis, there is spread of the infection to the renal pelvis, ureter, and bladder. The inflammation and edema produce obstruction of the infundibula and ureter, leading to caliectasis, calyceal clubbing, and ureteral strictures, with consequent pelvic and ureteral dilation. Extensive peripelvic fibrosis may cause a substantial decrease in the pelvic capacity (Fig. 4.24). With extensive renal tuberculosis, parenchymal calcification is often present, varying from faint punctate foci to a complete cast of the kidney. Total destruction of the kidney may occur, resulting in autonephrectomy (Fig. 4.25).

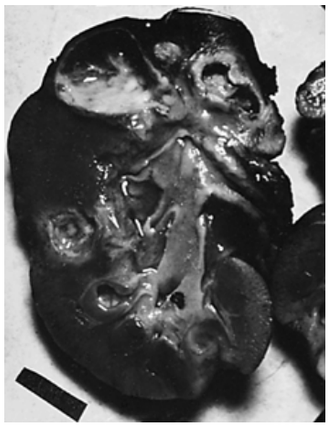

FIGURE 4.24. Tuberculosis with pelvic fibrosis. Gross specimen shows several large necrotic cavities. The peripelvic fibrosis has caused marked diminution in the pelvic volume. (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

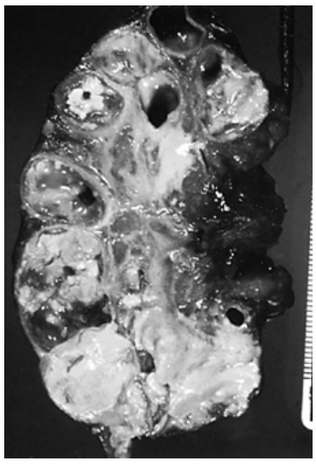

FIGURE 4.25. Tuberculosis, autonephrectomy. Gross specimen shows complete parenchymal destruction by extensive caseous necrosis. (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

Seeding of the urine may also result in involvement of the bladder and male genital organs. Tuberculous inflammation in the bladder produces necrosis, ulceration, and fibrosis, which result in a thick-walled sac of small capacity.

Clinical Findings

Renal tuberculosis is predominantly a disease of young to middle-aged adults. Approximately 50% of the patients are

20 to 40 years of age, and approximately 75% are younger than 50 years of age (247,381).

Because of the slow progression and variable course of the disease, there is no classic presentation. Approximately 20% of patients subsequently found to have tuberculosis will be symptom free. Tuberculous nephropathy is an insidious process that often goes unrecognized for long periods. Up to 70% of patients with even advanced cavitary tuberculosis of the kidney may have few diagnostic renal symptoms (22,193). Gross hematuria; dull, vague flank discomfort; and ureteral colic secondary to passage of clots, debris, or calculi are the most common renal symptoms. Constitutional complaints such as fevers, chills, night sweats, weight loss, and malaise are uncommon. It is only when the bladder is involved that the patients become severely symptomatic. Frequency is the most common presenting symptom and is often progressive and occurs during the day and at night. Pain, urgency, and dysuria are also common with bladder involvement.

The physical examination is usually not helpful diagnostically. A chronic draining fistula tract from previous renal surgery or palpably enlarged, firm seminal vesicles on rectal examination should arouse suspicion. Patients with chronic epididymitis unresponsive to therapy should also be evaluated for tuberculosis.

Patients may also have complications of renal tuberculosis, including draining sinus, hypertension, renal failure, secondary amyloidosis, and adenocarcinoma of the renal pelvis (20,88,187,352,383,392). A draining sinus or abscess cavity can occur many years after completion of chemotherapy even in the presence of sterile organs. Pyelocutaneous fistula is often associated with calculus obstruction of the ureteropelvic junction.

Hypertension is present in approximately 5% to 10% of patients with renal tuberculosis; the incidence in patients with unilateral nonfunctioning or poorly functioning kidneys is approximately 25%. Although some of these individuals have evidence of renal ischemia as determined by renal vein renin studies and normalization of blood pressure after nephrectomy, most patients appear to have hypertension that is not mediated by the renin-angiotensin system and is not cured by nephrectomy (246).

Laboratory Findings

The urinalysis is abnormal in 90% of the patients. The most common finding is sterile, acid pyuria, often accompanied by hematuria and proteinuria. Pyuria in the absence of a positive culture for the usual uropathogens should always warrant consideration of diagnosis of renal tuberculosis. Acid-fast smears of urinary concentrates are usually negative and are not totally reliable if positive because the saprophytic organism *Mycobacterium smegmatis* may contaminate the urine and is morphologically indistinguishable from *M. tuberculosis* on acid-fast smear.

The most important laboratory test is urine culture for

M. tuberculosis. Cultures are positive in approximately 90% of affected individuals (55). First-morning urine specimens are more reliable than 24-hour collections because they are easier to collect and there is much less chance of bacterial contamination. Because discharge of *M. tuberculosis* into the urine may be intermittent, it is advisable to collect morning urine specimens on a total of at least 3 separate days (236). Cultures should be obtained regardless of whether pus is present in the urine because positive cultures have been found in otherwise normal specimens (156). Susceptibility testing should be performed on isolated organisms.

Although the classic finding of renal tuberculosis is sterile pyuria, many patients have a concurrent positive culture for uropathogenic organisms at initial presentation. This finding should not preclude consideration of diagnosis of renal tuberculosis in the proper clinical setting. Such patients continue to demonstrate pyuria after the uropathogenic organism is eradicated by appropriate antimicrobial therapy.

The sealing off of cavitary lesions in chronic infections may in rare cases result in persistently negative findings on urine culture for tuberculosis and may mean that the disease in some patients remains undiagnosed despite repeated cultures (204). The tuberculin test, although not diagnostic, is of value only if positive.

Tuberculosis depresses renal function, but the damage has to be widespread before the serum creatinine level is elevated. Biochemical evidence of renal functional impairment is seen in less than 10% of patients with renal tuberculosis. Renal failure may be accentuated by obstructive uropathy that results from ureteral stricture or by secondary amyloidosis (210). Estimations of renal function are essential to preliminary assessment of patients with renal tuberculosis and determining the dose levels of antituberculous drugs. Wisnia and colleagues (392) showed that 58% of patients with renal tuberculosis had chronic renal failure at the time of diagnosis; 43% had subclinical impairment of creatinine clearance, 10% had compensated renal failure, and 5% had uremia.

It is apparent that the clinical presentation may be subtle, and therefore a high index of suspicion of renal tuberculosis is indicated in patients with a history of past or present tuberculosis, with chronic cystitis that fails to respond to adequate antimicrobial therapy, or with sterile pyuria accompanied by gross or microscopic hematuria.

Radiologic Findings

Approximately 90% of patients with renal tuberculosis will have abnormal excretory urograms. The roentgenographic findings vary according to the severity of the destructive process and the duration of the disease. Early changes in the radiologic appearance of the tuberculous kidney may be subtle and difficult to find; hence, a normal excretory urogram does not rule out renal tuberculosis.

The most suggestive urographic features of renal parenchymal tuberculosis are the presence of cavities that communicate with the collecting system and fill with contrast medium and dilation of part or all of the calyceal system (125,236). Initially, the cavities are small; appear as a slight irregularity of a minor calyx; and show a moth-eaten, feathery, irregular appearance (Fig. 4.26A). Fibrous stenosis may cause amputation of one or more calyces (Fig. 4.26B).

As the calyceal system becomes eroded, the parenchyma is destroyed by cavitation and the picture may closely resemble pyelonephritis (Fig. 4.27). The kidney will be either enlarged if caseous sacs are present or atrophic if there is longstanding infection. Parenchymal curvilinear or confluent calcifications in areas of caseous necrosis are common (Fig. 4.28). Autonephrectomy with complete nonvisualization of kidney may result from complete parenchymal destruction or hydronephrosis caused by stenosis of the renal pelvis or ureter (Fig. 4.29).

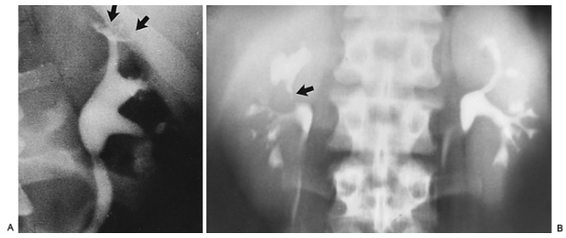

FIGURE 4.26. Tuberculosis. Early disease. Excretory urograms. **A:** Calyceal surface is irregular with linear rays of contrast material extending into the medulla(arrows). **B:** Tomogram demonstrates upper pole infundibular stenosis *(arrow).* No ureteral involvement is seen. (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

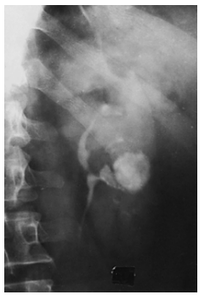

FIGURE 4.27. Tuberculosis, advanced disease. Excretory urogram shows a large cavity communicating with the calyx in the middle portion of the kidney. Note the irregularity and narrowing of the remainder of the collecting system. (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

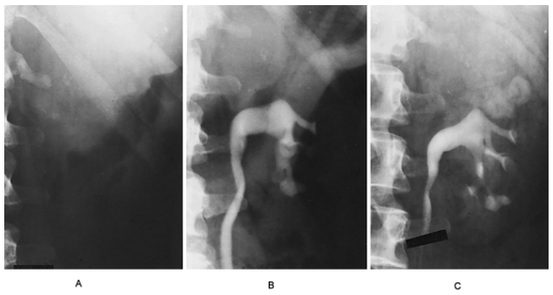

FIGURE 4.28. Tuberculoma. **A:** Faint calcification over the renal fossa. **B:** Fifteen-minute film from an excretory urogram shows "amputation" of the upper pole calyx in the region of calcification. **C:** Delayed film reveals contrast material filling the mass, indicating its communication with the collecting system. (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

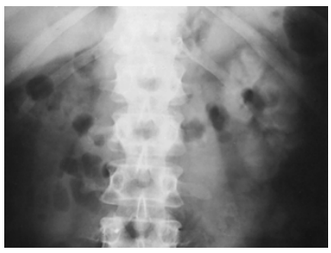

FIGURE 4.29. Tuberculosis, autonephrectomy. Extensive confluent calcifications in the renal fossa. The excretory urogram indicated no function. (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

Fibrosis may cause the volume of the renal pelvis to be markedly reduced (Fig. 4.30). Tuberculous ureteritis is common and results in rigidity and a beading or corkscrew appearance (Fig. 4.31). Ureterovesical junction obstruction is caused by tuberculous cystitis or strictures of the distal third of the ureter. Although not common, mural calcification in the wall of the calyces, pelvis, ureter, or bladder is extremely suggestive of renal tuberculosis (125).

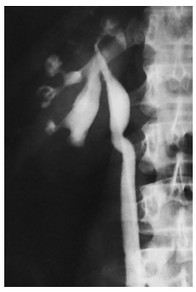

FIGURE 4.30. Tuberculosis with pelvic fibrosis. Retrograde pyelogram shows significant calyceal irregularity. The calyces come together and empty into the proximal ureter. (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

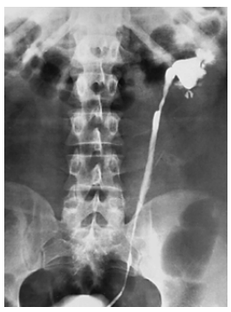

FIGURE 4.31. Tuberculosis, advanced disease. Retrograde pyelogram shows extensive ureteral changes including irregularity and rigidity, giving "pipestem" appearance. Note extensive distortion, irregularity, and amputation of the upper pole calyx.

Retrograde urography should be used in cases of nonvisualized or poorly functioning kidneys. A voiding cystogram may show a severely contracted bladder with vesicoureteral reflux in one or both sides.

Sonographic examination has limited diagnostic value. CT has several advantages; it can be used in nonfunctioning kidneys and is very sensitive for detecting calcifications and perinephric extension or perinephric hemorrhage that may complicate renal tuberculosis. CT is also

the best technique for demonstrating pelvic and ureteral mural thickening. Angiography has limited usefulness in diagnosing renal tuberculosis. Arterial fibrosis results in narrowing or amputation of the small intrarenal arteries (101,125).

Differential Diagnosis

If all of the radiographic findings are typical of renal tuberculosis, the diagnosis is straightforward. However, all of the classic findings are often absent, and the radiographs may suggest medullary sponge kidney, papillary necrosis, invasive transitional cell carcinoma, chronic pyelonephritis, or schistosomiasis. The pertinent radiologic discriminators have been summarized by Hartman (125).

Medullary sponge kidney and papillary necrosis demonstrate extracaliceal accumulations of contrast material and medullary nephrocalcinosis, but cortical calcification and parenchymal masses are rare. Ring calcification near a necrotic or sloughed papilla is extremely suggestive of papillary necrosis. Chronic urinary tract infection and pyelonephritis show distortion of the renal cortex and collecting system similar to tuberculosis, but calyceal, pelvic, and ureteral strictures are not commonly associated with typical urinary tract infections. Invasive transitional cell carcinoma may show infundibular narrowing or calyceal amputation and may be difficult to differentiate radiographically from tuberculosis. Transitional cell carcinoma is not associated with communicating cavities or parenchymal calcification. Infundibular narrowing and submucosal calcifications are seen in amyloidosis of the kidney, but amyloidosis is not associated with destructive communicating cavities or parenchymal calcification. *Schistosoma haematobium* infection of the urinary tract may cause ureteral and bladder calcifications. However, schistosomiasis does not involve the renal parenchyma primarily and is not associated with renal calcification. Schistosomiasis affects only the distal ureter,

whereas tuberculosis often involves the entire ureteral length.

Cystoscopy

In early cases of tuberculosis, the bladder is diffusely red and extremely sensitive. Bladder wall ulcerations, severe contracture of the bladder, and golf-hole ureteral orifices are seen in more advanced disease. Ulcerated areas in the bladder strongly suggest tuberculosis. Tuberculous ulcers are irregular and shallow with undermined edges, often well circumscribed from adjoining normal-appearing mucosa. Neoplasms may have a similar appearance and must be differentiated by biopsy.

Management

Appropriate management must be based on an accurate bacteriologic diagnosis and initial assessment of the extent of the disease, the level of renal function, and the nature and severity of ureteric obstruction. Renal tuberculosis in the absence of active pulmonary tuberculosis does not represent a significant infectious risk; therefore isolation is not required. Management always includes appropriate chemotherapy and surgery when indicated. With close and long-term follow-up, the overall mortality rate for renal tuberculosis has dropped from approximately 50% to 2%.

Table 4.5 gives an overview of agents available for treatment of tuberculosis. There is no uniformly recommended chemotherapeutic program. Patients with positive urine cultures but negative findings on urinalysis and normal urograms usually are treated with isoniazid and rifampin for 1 year. Patients with clinically manifest renal tuberculosis are usually treated with three antituberculous drugs such as isoniazid, ethambutol, and rifampin for 2 years (381). If the patient's initial urinary isolate is *M. tuberculosis* resistant to isoniazid or is one of the nontuberculous (atypical) mycobacteria, isoniazid therapy should be stopped and two other drugs chosen on the basis of *in vitro* susceptibilities. A short-term regimen of only 4 months' duration has been recommended by Gow (110) and is summarized in Table 4.6 . The initial results with this regimen appear promising, but longer follow-up is required.

Drug	Usual Dose	Route	Frequency	Adverse Effects
Isoniazid	300 mg/day	p.o.	Once daily	Hepatotoxicity, peripheral neuropathy, asymptomatic transaminase rise
Ethambutol	25 mg/kg/day 15 mg/kg/day	p.o. p.o.	Once daily for 60 days Once daily for remainder of treatment period	Optic neuritis seen at 25-mg/kg dose, less frequent at 15-mg/kg dose; usually reversible if drug is stopped immediately
Rifampin	600 mg/day	p.o.	Once daily	Hepatotoxicity, thrombocytopenia
Pyrazinamide	25 mg/kg/day	p.o.	Once daily	Hepatotoxicity: dose and duration related, hyperuricemia
Ethionamide	750–1,000 mg/day	p.o.	Divided doses, 250 mg each	Nausea, vomiting, anorexia, abdominal pain
Cycloserine	750–1,000 mg/day	p.o.	Divided doses, 250 mg each	Neurotoxicity: headache, drowsiness, convulsions, psychotic disturbance, peripheral neuropathy
Para-aminosalicylic acid	200 mg/kg/day	p.o.	2 divided doses	Gastrointestinal irritation, rash, and fever; hemolysis in glucose-6-phosphate dehydrogenase deficiency
Streptomycin	750–1,000 mg/day	i.m.	Once daily for 60–90 days and twice weekly thereafter	Ototoxicity, especially in older patients; rash and fever, nausea
Capreomycin	750–1,000 mg/day	i.m.	Once daily	Renal toxicity and ototoxicity, especially in older patients

Compiled from Kucers AM, Bennett N. *The use of antibiotics,* ed 3. London: Heinemann Medical Books, 1979, by Corigliano B, Leedom JM. Renal tuberculosis: part 2. In: Massry SG, Glassock RJ, eds. *Textbook of nephrology,* vol 1. Baltimore: Williams & Wilkins, 1983.

TABLE 4.5. COMMONLY USED AGENTS IN THE TREATMENT OF TUBERCULOSIS

Phase	Drug	Dosage (mg/day)	Frequency
Intensive phase (2 mo)	Isoniazid	300	Daily
	Rifampin	450	Daily
	Pyrazinamide	1,000	Daily
	Ethambutol	1,000	Daily
Continuation phase (2 mo)	Isoniazid	600	3 times/wk at night
	Rifampin	900	3 times/wk at night

Modified with permission from Gow JG. The management of genitourinary tuberculosis. *J Antimicrob Chemother* 1981;7:590.

TABLE 4.6. GOW'S SHORT-COURSE REGIMEN FOR TREATMENT OF RENAL TUBERCULOSIS

Usually, tuberculous bacilli disappear from urine immediately after initiating chemotherapy, but to monitor the drug's effect, repeated cultures should be done every 3 to 4 months. All of the antituberculous drugs have toxic effects when used continuously. Renal and hepatic function should be monitored during the treatment. Rifampin and isoniazid appear to be the safest drugs in the presence of impaired renal function (276).

Surgery was once commonly used in the treatment of renal tuberculosis, but since the advent of effective antituberculous chemotherapy, it is reserved primarily for

management of local complications, such as ureteral stricture or for treatment of nonfunctioning kidneys. If surgery is warranted, it is wise to precede the operation with at least 3 weeks and preferably 3 months of triple-drug chemotherapy.

The incidence of ureteral strictures has been reported to be as high as 10% in centers that treat large numbers of patients with urinary tuberculosis (248). The stricture may be present at the time of diagnosis of renal tuberculosis, but it often develops or progresses during otherwise effective treatment with chemotherapeutic agents (48). Recommended treatment of strictures includes ureteroneocystostomy, construction of a Boari flap, or transluminal balloon ureteral dilation (10,233,375). Success rates with these procedures have been reported at 60% to 90%.

Horne and Tulloch (146) added prednisolone 5 mg four times a day to the standard chemotherapy regimen in all patients with renal tuberculosis who had evidence of stricture formation at presentation or in whom it developed during treatment. No important side effects were noted. Of 29 patients so treated, 72% were relieved of obstruction and only 2 (7%) patients showed recurrence after withdrawal of steroids; both individuals responded to further courses of steroids. Success with steroid therapy has not been universal, however (48).

Removal of a nonfunctioning kidney is usually indicated for advanced unilateral disease complicated by sepsis, hemorrhage, intractable pain, newly developed severe hypertension, suspicion of malignancy, inability to sterilize the urine with drugs alone, abscess formation with development of fistula, or inability to have appropriate follow-up (194,201,236). Prophylactic removal of a nonfunctioning kidney to prevent complications, remove a potential source of viable organisms, and shorten the duration of convalescence and requirement for chemotherapy is advocated by some authors (88,252,394).

Others who have followed up a large series of patients treated with medical therapy alone have concluded that because the frequency of late complications is only 6%, routine nephrectomy should not be performed for every nonfunctioning kidney (194,380). These authors treated patients for 2 years. The merits of short-term therapy and prophylactic nephrectomy versus long-term, 2-year chemotherapy and selected nephrectomy warrant further study.

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis is a chronic inflammatory disease characterized by accumulation of lipid-laden foamy macrophages. It begins within the pelvis and calyces and subsequently extends into and destroys renal parenchymal and adjacent tissues. In most cases, xanthogranulomatous pyelonephritis is unilateral and results in a nonfunctioning, enlarged kidney associated with obstructive nephropathy secondary to nephrolithiasis. It has been known to imitate virtually every other inflammatory disease of the kidney, as well as renal cell carcinoma, on radiographic examination. In addition, the microscopic appearance of xanthogranulomatous pyelonephritis has been confused with clear cell adenocarcinoma of the kidney on frozen section and has led to radical nephrectomy (33).

Pathology and Pathogenesis

The kidney is usually massively enlarged and has a normal contour. Xanthogranulomatous pyelonephritis may be diffuse, as in approximately 80% of the patients, or segmental. In the diffuse form of the disease, the entire kidney is involved, whereas in segmental xanthogranulomatous pyelonephritis, only the parenchyma surrounding one or more calyces or one pole of a duplicated collecting system is involved. On sectioning, the kidney usually demonstrates nephrolithiasis and peripelvic fibrosis. The calyces are dilated and filled with purulent material, but fibrosis surrounding the pelvis usually prevents dilation. The papillae are often destroyed by papillary necrosis (109). In advanced stages of the disease, multiple parenchymal abscesses are filled with viscous pus and lined by yellowish tissue (Fig. 4.32A). The cortex is often thin and is often replaced by xanthogranulomatous tissue. The capsule is often thickened, and extension of the inflammatory process into the perinephric or paranephric space is common (109,115,219).

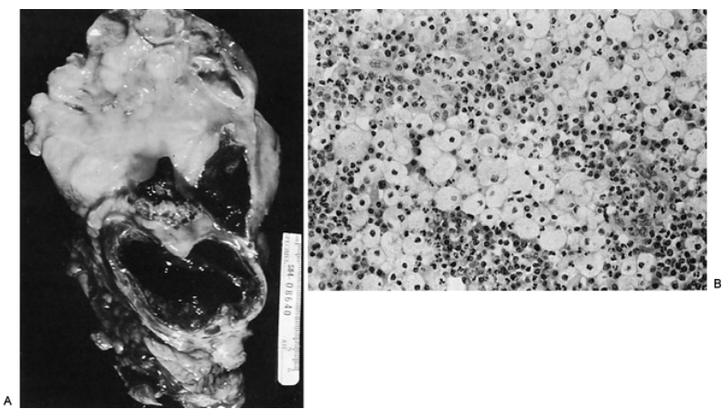

FIGURE 4.32. Xanthogranulomatous pyelonephritis. **A:** Gross specimen. Kidney is massively enlarged, measures 23 by 12 cm; the normal architecture is replaced by a shaggy yellow upper pole mass corresponding to xanthogranulomatous inflammation and numerous distorted and dilated calyces. **B:** Microscopically, the shaggy yellow tissue is composed primarily of lipid-laden histiocytes mixed with other inflammatory cells.

On microscopic examination, the yellowish nodules that line the calyces and surround the parenchymal abscesses contain dark sheets of lipid-laden macrophages (foamy histiocytes with small, dark nuclei and clear cytoplasm) intermixed with lymphocytes, giant cells, and plasma cells (Fig. 4.32B). Xanthogranulomatous cells are not specific to xanthogranulomatous pyelonephritis but may be present anywhere inflammation or obstruction coexists. The origin of the fatty substance is disputed. Cholesterol esters that

make up a part of the lipid might be derived from lysis of erythrocytes after hemorrhage (286).

The primary factors involved in the pathogenesis of xanthogranulomatous pyelonephritis are nephrolithiasis, obstruction, and infection (115). Nephrolithiasis has been noted in as many as 83% of the patients in various series; approximately half of the renal stones have been of the staghorn type (45,237,255). It has been proposed clinically and demonstrated experimentally that primary obstruction followed by infection with *E. coli* can lead to tissue destruction and collections of lipid material by histiocytes (271). The bacteria appear to be of low virulence because spontaneous bacteremia has rarely been described. Other possible interrelated factors include venous occlusion and hemorrhage, abnormal lipid metabolism, lymphatic blockage, failure of antimicrobial therapy in urinary tract infection, altered immunologic competence, and renal ischemia (99,109,219,226,363). The concept that xanthogranulomatous pyelonephritis is related to incomplete bacterial degradation and altered host response has received mixed support (176,254). Thus it appears that there is probably no single factor that is instrumental in the pathogenesis of this disease. Rather there is an inadequate host acute inflammatory response within an obstructed, ischemic, or necrotic kidney.

Clinical Findings

Xanthogranulomatous pyelonephritis should be suspected in patients with urinary tract infections and a unilateral enlarged nonfunctioning or poorly functioning kidney with a stone or a mass lesion indistinguishable from malignant tumor. Although it may occur at any age, the peak incidence of xanthogranulomatous pyelonephritis is in the fifth to the seventh decade. Women are more commonly affected than men. There is no predilection for either kidney.

Most patients have multiple, chronic symptoms that are variable and nonspecific. Patients usually have flank pain, fever or chills, malaise, weight loss, symptoms of cystitis, calculi or palpable mass, and a history of recurrent urinary tract infection. Many patients are admitted to the hospital for urosepsis. Less commonly, hypertension, hematuria, or hepatomegaly is the presenting complaint. The medical history is often positive for urinary tract infections and urologic instrumentation (69,89,109,111,209,237,260,400).

Laboratory Findings

Hematologic evaluation commonly shows anemia and leukocytosis. Diabetes mellitus is present in approximately 15% of the patients. Urinalysis reveals proteinuria and pyuria in nearly all cases. Urine cultures are positive in approximately 70% of patients. Although earlier reports indicated that *P. mirabilis* was the primary pathogen, in recent studies, *E. coli* was cultured in 40% of specimens, and *P. mirabilis* was cultured in approximately 30%. Other pathogens include *Klebsiella, Pseudomonas,* and *Bacteroides* (73). Anaerobes, most often bacteroids, have been isolated

in a small number of patients (45,69,111). Approximately 10% of the patients will have mixed cultures. It is noteworthy that about one-third of the patients have sterile urine, probably because many patients receive long-term antimicrobial therapy or are taking antimicrobials when the culture is obtained. The infecting organism may be revealed only by tissue cultures obtained during surgery.

Ballesteros and associates (14) reported accurate preoperative diagnosis of xanthogranulomatous pyelonephritis by serial urinary cytology in 80% of their cases. Subsequent investigators have sought but not found xanthogranuloma cells in the urine (45,69). Thus the diagnostic value of urine cytologic testing remains unclear.

Xanthogranulomatous pyelonephritis is usually unilateral; therefore azotemia or frank renal failure is uncommon (109,115). Reversible hepatic dysfunction has been observed in 20% to 40% of patients with diffuse xanthogranulomatous pyelonephritis (209,363). Liver enzymes return to normal after nephrectomy.

Radiologic Findings

Approximately 50% to 80% of patients show the classic triad of unilateral renal enlargement with little or no function and a large calculus in the renal pelvis (73). At times, the enlargement may be localized and resemble a renal mass. Less commonly, excretory urography demonstrates delayed function and hydronephrosis, which may be massive. Smaller calcifications within the mass are not uncommon but are much less specific (Fig. 4.33A). Although there is abundant intracellular fat, the plane almost never demonstrates significant lucency (126). Retrograde pyelography may show the point of obstruction and dilation of the renal pelvis and calyces. If there is extensive parenchymal damage, contrast studies may demonstrate an ulcerated pyelocalyceal system with multiple irregular filling defects.

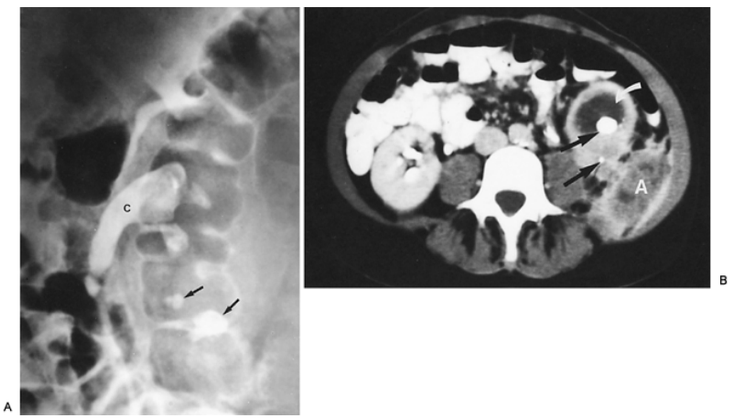

FIGURE 4.33. Xanthogranulomatous pyelonephritis. Excretory urogram. **A:** Ten-minute film shows lower-pole enlargement and nonfunction. Note a large pelvic calculus *(C)* and several smaller parenchymal calculi *(arrows).* The upper pole of the bifid collecting system functions normally. **B:** Enhanced computed tomography scan shows collecting system and parenchymal calculi *(arrows)* with lower pole pyonephrosis *(curved arrow)* and an irregular, predominantly low-density perinephric abscess *(A)* extending into the soft tissues of the flank.

Sonography usually demonstrates global enlargement of the kidney (225). The normal renal architecture is replaced by multiple hypoechoic fluid-filled masses that correspond to debris-filled, dilated calyces or foci of parenchymal destruction (78,127). With focal involvement, a solid mass involving a segment of the kidney is demonstrated with an associated calculus in the collecting system or ureter. Renal cell carcinoma and other solid renal lesions must be considered in the differential diagnosis (73).

CT is probably the most useful radiologic technique in evaluating patients with xanthogranulomatous pyelonephritis. CT usually demonstrates a large, reniform mass with the renal pelvis tightly surrounding a central calcification without pelvic dilation (69,108,126,326) (Fig. 4.33B). Renal parenchyma is replaced by multiple water density masses representing dilated calyces and abscess cavities filled with varying amounts of pus and debris. On enhanced scans, the walls of these cavities demonstrate a prominent blush resulting from the abundant vascularity within the granulation tissue. However, the cavities fail to enhance, whereas tumors and other inflammatory lesions usually do. The findings of focal xanthogranulomatous pyelonephritis often mimic

neoplasm. The CT scan is particularly helpful in demonstrating the extent of renal involvement and may indicate whether adjacent organs or the abdominal wall is involved (69,170).

Radionuclide renal scanning using ^{99}Te dimercaptosuccinic acid (DMSA) is used to confirm and quantify the differential lack of function in the involved kidney (115). Magnetic resonance imaging has not yet superseded CT in the evaluation of renal inflammation, but it provides some advantages in delineating extrarenal extension of inflammation (325). Lesions of xanthogranulomatous pyelonephritis may appear as cystic foci of intermediate intensity signal on T_1-weighted images and hyperintensity on T_2-weighted images. Angiography is seldom required for diagnosing xanthogranulomatous pyelonephritis. Most commonly, there is stretching and attenuation of vessels around avascular masses with an irregular nephrogram (73). Benign neovascularity, absence of irregular vessels, and arterial- venous shunting are also characteristic.

Differential Diagnosis

Diagnosis of segmental xanthogranulomatous pyelonephritis without calculi may be difficult. Xanthogranulomatous pyelonephritis in association with massive pelvic dilation cannot be distinguished from pyonephrosis. When xanthogranulomatous pyelonephritis occurs within a small contracted kidney, the radiographic findings are nonspecific and nondiagnostic. Renal parenchymal malakoplakia may show renal enlargement and multiple inflammatory masses replacing the normal renal parenchyma, but calculi are usually not present. Renal lymphoma may be associated with multiple hypoechoic masses surrounding the contracted, nondilated pelvis, but lymphoma is usually clinically obvious, and renal involvement is usually bilateral and not associated with calculi (126).

Management

The management of xanthogranulomatous pyelonephritis is usually surgical. Antimicrobial therapy may be necessary to stabilize the patient preoperatively; occasionally, long-term antimicrobial therapy will eradicate the infection and restore renal function (230). Nephrectomy is required for diffuse xanthogranulomatous pyelonephritis. Partial nephrectomy is the preferred treatment for focal xanthogranulomatous pyelonephritis if the diagnosis can be established preoperatively or, if necessary, by frozen section at the time of surgery (251,259). However, the lipid-laden macrophages associated with xanthogranulomatous pyelonephritis closely resemble clear cell adenocarcinoma and may be difficult to distinguish solely on the basis of frozen section. Furthermore, xanthogranulomatous pyelonephritis has been associated with renal cell carcinoma, papillary transitional cell carcinoma of the pelvis or bladder, and infiltrating squamous cell carcinoma of the pelvis (268,307,363). Therefore, if malignant renal tumor cannot be excluded, nephrectomy should be performed.

It is important to remove the entire inflammatory mass because in nearly 75% of patients, xanthogranulomatous tissue is infected. If incision and drainage alone are performed rather than nephrectomy, the patient may continue to suffer from protracted debilitating illness and may develop a renocutaneous fistula, and an even more difficult nephrectomy will be necessary (73). Extensive xanthogranulomatous pyelonephritis may make surgical dissection and ligation of the friable vascular pedicle particularly difficult. Extension of the inflammatory reaction to adjacent bowel, diaphragm, and aorta requires tedious dissection and at times resection of the involved tissues.

Renal Parenchymal Malakoplakia

Malakoplakia, from the Greek words meaning “soft plaque,” is an uncommon inflammatory lesion described originally by Michaelis and Gutmann (227). It was characterized by Von Hansemann (373) as soft, yellow-brown plaques with granulomatous lesions in which the histiocytes contain distinct basophilic inclusions or Michaelis-Gutmann bodies. Although its exact pathogenesis is unknown, malakoplakia probably results from abnormal macrophage function in response to a bacterial infection, which is most often *E. coli.* The inclusions probably represent calcification around incompletely digested bacteria (1,217).

The disease usually affects the lower urinary tract; only about 50 patients with renal parenchymal malakoplakia have been reported (216). Clinically, radiologically, and at surgery, malakoplakia often mimics a neoplastic growth. The mortality rate can exceed 50%, and morbidity can be substantial (347). Extension of renal parenchymal malakoplakia into the perirenal space is uncommon (6). Renal parenchymal malakoplakia may also be complicated by renal vein thrombosis and inferior vena cava thrombosis (128,216).

Concomitant nonrenal foci of malakoplakia are seen occasionally in patients with renal parenchymal malakoplakia (347). The most common locations of other foci are the bladder and ureter. Less common sites that have been reported include the retroperitoneum, abdominal wall, colon, testis and epididymis, lungs, scrotum, prostate, adrenal gland, lymph nodes, and diaphragm (216).

Pathology and Pathogenesis

Two basic patterns of renal parenchymal malakoplakia have been described: multifocal and unifocal. The multifocal pattern accounts for 75% of the reported cases and is bilateral in about half of the patients (128). The kidney is usually enlarged and contains multiple masses varying from

several millimeters to several centimeters. They are usually yellow, are well demarcated, and may have a focus of hemorrhage or suppuration (Fig. 4.34A and Fig. 4.34B). The masses often coalesce to form larger nodules. These nodules often project beyond the cortical margin, resulting in an irregular contour. Less commonly, the nodules are limited to the papilla or the medulla and occasionally mimic necrotizing papillitis, in which cases the renal contour is normal (26,66,125).

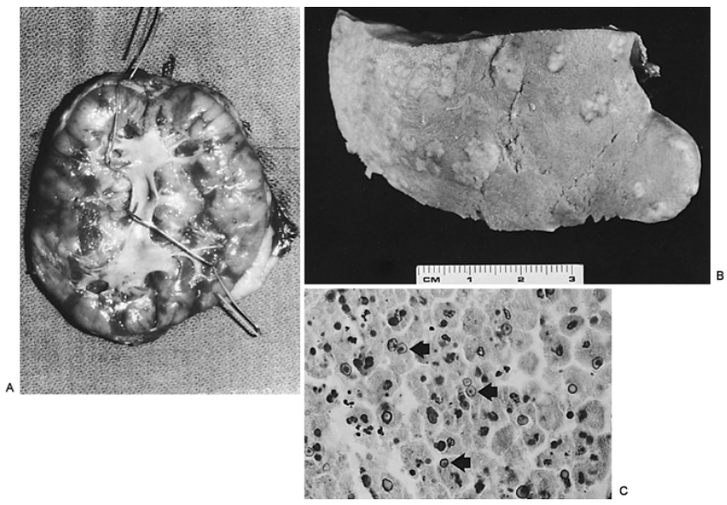

FIGURE 4.34. Renal parenchymal malakoplakia. **A:** Cut surface demonstrates extensive cortical and upper medullary replacement by multifocal, confluent, tumorlike masses. **B:** Cortical surface exhibits multiple, firm, plaquelike lesions. **C:** Hallmark of malakoplakia is demonstration of the Michaelis-Gutmann body *(arrows),* which represents incompletely destroyed bacteria surrounded by lipoprotein membrane (hematoxylin-eosin stain). (**A, B:** Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. I and II. *Monogr Urol* 1985;6:3.)

Unifocal disease usually appears as a large yellow-gray mass, 2.5 to 8 cm in diameter (128). The mass is usually smooth and well marginated, and central necrosis or cyst formation may be present. Calcification of the mass is unusual (309).

Microscopically, malakoplakia is characterized by the Von Hansemann histiocyte, a large polygonal cell with foamy eosinophilic cytoplasm and compact, dark nucleus admixed with intracellular and extracellular Michaelis-Gutmann bodies. The latter contain precipitated calcium phosphate crystals and iron so that both periodic acid–Schiff and von Kossa calcium stains and iron stains are useful in demonstrating the inclusions (202). They are slightly smaller than a red blood cell and are recognized by concentric laminations that impart a targetoid or owl's-eye appearance (102) (Fig. 4.34C). Histochemical and ultrastructural studies have shown that these Michaelis-Gutmann bodies represent incompletely destroyed bacteria surrounded by concentric lipoprotein membranes. Extracytoplasmic Michaelis-Gutmann bodies probably represent debris released from dead cells (216).

It has been shown that macrophages in malakoplakia involving the kidney and bladder contain large amounts of immunoreactive α-antitrypsin (35). The amount of α-antitrypsin remains unchanged during the morphogenetic

stages of the pathologic process. Macrophages from other pathologic processes, closely resembling malakoplakia but without Michaelis-Gutmann bodies, do not contain α-antitrypsin except for a few macrophages in tuberculosis and xanthogranulomatous pyelonephritis. Therefore immunohistochemical staining for α-antitrypsin may be a useful test for an early and accurate differential diagnosis of malakoplakia.

Megalocytic interstitial nephritis shows histologic changes that are similar to those of renal parenchymal malakoplakia, but the lesions are usually confined to the renal cortex and Michaelis-Gutmann bodies are less prevalent. Some authors believe that megalocytic interstitial nephritis and renal parenchymal malakoplakia represent two ends of the spectrum of a similar process (102,125,273).

The pathogenesis of malakoplakia is unknown. Almost all reported cases are associated with Gram-negative urinary tract infections, and one of the most popular theories is that malakoplakia results from incomplete resolution of the bacterial infection. Hematogenous dissemination of *E. coli* and subsequent foci of renal parenchymal malakoplakia may explain the finding of lesions limited to the cortex and medulla without renal-pelvic or lower tract disease. Patients with renal malakoplakia limited to the renal papilla or associated with contiguous renal pelvic involvement or obstructive uropathy probably have had an ascending infection (125).

The demonstration of bacteria within phagocytic vacuoles of histiocytes suggests an inability of the histiocyte to digest the bacteria. It is not clear, however, why a histiocyte response is found instead of the usual polymorphonuclear leukocyte response. The association of malakoplakia with debilitating diseases such as sarcoidosis, diabetes mellitus, and tuberculosis suggests an immunologic defect as a prerequisite for its development. Defective monocyte function has been demonstrated in one patient with malakoplakia (1). In this case phagocytosis was normal, but complete degradation of the bacteria was impossible because of low levels of cyclic guanine monophosphate, which may have resulted in decreased lysosomal degradation and inability of the cell to release the lysosomal enzymes. This defect appears to be reversible by cholinergic agonists that cause accumulation of cyclic guanine monophosphate in monocytes and enhance chemotaxis, but this finding has yet to be confirmed. At present, malakoplakia should be considered an unusual inflammatory lesion resulting from altered host macrophage or histiocytic response.

Clinical Findings

The diagnosis of renal parenchymal malakoplakia is difficult but should be suspected if there is substantial enlargement of the kidney in the presence of urinary tract infection. Renal parenchymal malakoplakia usually affects middle-aged women with recurrent urinary tract infections. The most common signs and symptoms are fever, flank pain, or a palpable flank mass (125,347). The most common pathogen is *E. coli,* which accounts for approximately 75% of the cases. *Aerobacter aerogenes, Klebsiella pneumoniae,* and *Proteus* are cultured less commonly (102,216). In addition, *E. coli* cultures have been obtained from the resected kidney, perinephric abscess, or blood or cerebrospinal fluid of affected patients. Renal failure without evidence of obstruction is not uncommon when malakoplakia is bilateral or occurs in a solitary kidney.

The association of some cases of malakoplakia with altered immune states, such as transplantation, sarcoidosis, hemolytic uremic syndrome, tuberculosis, steroid therapy, lymphoma, leukemia, alcoholism, or emaciation, is common (34,125). Nevertheless, many patients in whom malakoplakia occurs have no recognized defects.

Radiologic Findings

Multifocal malakoplakia on excretory urography typically manifests as enlarged kidneys with multiple filling defects (Fig. 4.35A). Renal calcification, lithiasis, and hydronephrosis are absent. The multifocal nature is best appreciated with ultrasonography, CT, or arteriography. Sonographic examination may demonstrate renal enlargement and distortion of the central echo complex. The masses are often confluent, resulting in an overall increase in the echogenicity of the renal parenchyma (128). CT often shows masses or enlargement of the kidneys. On CT, the foci of malakoplakia are less dense than the surrounding enhanced parenchyma (125). Arteriography typically reveals a hypovascular mass with peripheral neovascularity (Fig. 4.35B and Fig. 4.35C) (41,364).

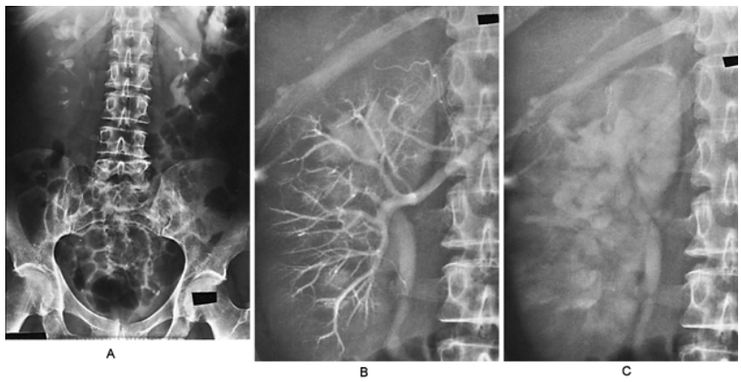

FIGURE 4.35. Multifocal renal parenchymal malakoplakia. **A:** Excretory urogram. The right kidney is enlarged (16.5 cm) with dilation of the upper pole calyces and poor filling of the renal pelvis. **B:** Early angiogram. Separation of the intrarenal vessels without neovascularity. **C:** Angiographic nephrogram. Multiple irregular filling defects located primarily within the cortex. (Courtesy of Charles E. Bickham Jr., MD, Bethesda, MD. Reprinted with permission from Hartman DS, Davis CJ, Lichtenstein JE, et al. Renal parenchymal malakoplakia. *Radiology* 1980;136:33.)

Intense renal uptake of gallium-67 in the clinical setting of fever, progressive renal failure, and nephromegaly strongly supports a diagnosis of renal parenchyma malakoplakia (147). Unifocal malakoplakia on intravenous urography manifests as a noncalcified mass that is indistinguishable from other inflammatory or neoplastic lesions. Ultrasound and CT may demonstrate a solid or cystic structure depending on the degree of internal necrosis. Angiography may demonstrate neovascularity (364). Extension beyond the kidney, which can occur with either multifocal or unifocal malakoplakia, is best demonstrated by CT.

Differential Diagnosis

The differential diagnosis includes renal cystic disease, neoplasia, and renal inflammatory disease (125). Malakoplakia should be considered when one or more renal masses are observed, particularly in female patients with recurrent urinary tract infections with *E. coli,* altered immune response syndromes, or cystoscopic evidence of malakoplakia or filling defects in the collecting system (43). Malakoplakia should also be suspected when these radiographic findings

occur in a renal transplant patient who has persistent urinary tract infection despite appropriate antimicrobial therapy. Cystic disease generally can be excluded by careful sonographic and CT evaluations. Renal involvement with metastatic disease or lymphomas usually occurs late in the course of the disease, which is well established. Multifocal renal cell carcinoma is most often seen in the context of von Hippel–Lindau disease with its other clinical manifestations. Patients with xanthogranulomatous pyelonephritis usually have signs and symptoms of urinary tract infection. As with malakoplakia, the involved kidney is enlarged, but renal calculi and obstruction are common. Multiple renal abscesses are often associated with hematogenous dissemination resulting from cardiac disease.

Management

Initial management is directed at controlling the urinary tract infection, correcting the immunologic defect, and improving renal function if necessary (125). Nephrectomy is usually performed for unilateral disease.

Long-term antimicrobial therapy, such as rifampin, TMP-SMX, and doxycycline, has been used successfully in approximately 10% to 15% of patients with renal parenchymal malakoplakia established by biopsy (347). Dramatic improvement has also been reported in patients with intraabdominal malakoplakia treated with cholinergic agents and ascorbic acid (1).

The long-term prognosis appears to be related most directly with the extent of disease. When parenchymal renal malakoplakia is bilateral or occurs in the transplanted kidney, death usually occurs within 6 months (26,66,134). Patients with unilateral disease usually have a long-term survival after nephrectomy.

Renal Echinococcosis

Echinococcosis is a parasitic infection caused by the larval stage of the tapeworm *Echinococcus granulosus.* The disease is prevalent in dogs, sheep, cattle, and humans in South Africa, Australia, New Zealand, Mediterranean countries (especially Greece), and some parts of the former Soviet Union. In the United States, the disease is rare; however, it is found in immigrants from Eastern Europe or other foreign endemic areas or as an indigenous infection among Native Americans in the southwest and Eskimos (269).

Pathology and Pathogenesis

Echinococcosis is produced by the larval form of the tapeworm, which in its adult form resides in the intestine of the dog, the definitive host. The adult worm is 3 to 9 mm long.

The ova in the feces of the dog contaminate grass and farmlands and are ingested by sheep, pigs, or humans, the intermediate hosts. Larvae hatch, penetrate venules in the wall of the duodenum, and are carried by the bloodstream to the liver. Those larvae that escape the liver are next filtered by the lungs. Approximately 3% of the organisms that escape entrapment in the liver and lungs may then enter the systemic circulation and infect the kidneys. The larvae undergo vesiculation, and the resultant hydatid cyst gradually develops at a rate of about 1 cm per year. Thus the cyst may take 5 to 10 years to reach pathologic size.

Echinococcosis cysts of the kidney are usually single and located in the cortex (235). The wall of the hydatid cyst has three zones: (a) a peripheral zone of fibroblasts derived from tissues of the host becomes the adventitia and may calcify, (b) an intermediate laminated layer that becomes hyalinized, and (c) a single inner layer that is composed of nucleated epithelium (called the *germinal layer*). The germinal layer gives rise to brood capsules that increase in number, become vacuolated, and remain attached to the germinal membrane by a pedicle. New larvae (scoleces) develop in large numbers from the germinal layer within the brood capsule (Fig. 4.36). The hydatid cyst is also filled with fluid. When brood capsules detach, they enlarge and move freely in the fluid and are then called daughter cysts. Hydatid sand is composed of free larvae and daughter cysts.

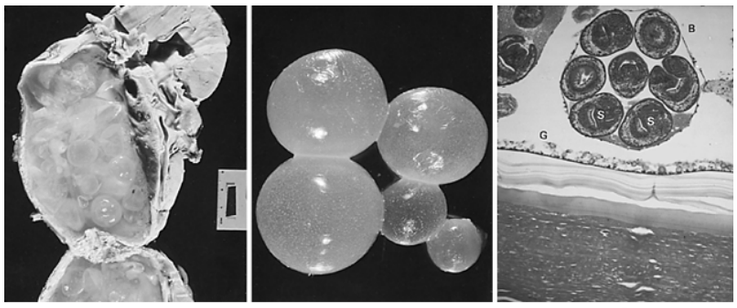

FIGURE 4.36. Echinococcosis. **A:** Gross specimen. A cystic mass 7 by 11 cm in lower pole. Smaller daughter cysts are identified within the larger cystic mass. **B:** Gross specimen. Daughter cysts represent brood capsules that have detached and move freely. **C:** Photomicrograph. Brood capsules *(B)* arising from the germinal layer *(G)* contain viable and degenerating scoleces *(S).* (Reprinted with permission from Hartman DS. Radiologic pathologic correlation of the infectious granulomatous diseases of the kidney. III and IV. *Monogr Urol* 1985;6:26.)

Clinical Findings

The symptoms of echinococcosis are those of a slowly growing tumor. Most patients are asymptomatic or have flank mass, dull pain, or hematuria (105,235). Because the cyst is focal, it rarely affects renal function. Rarely, the cyst ruptures into the collecting system, and the patient may experience severe colic and passage of debris resembling grape skins in the urine (hydatiduria). The cyst may also rupture into an adjacent viscus or the peritoneal cavity. The fluid is extremely antigenic (126).

Laboratory Findings

If cyst rupture occurs, the definitive diagnosis can be established by identifying daughter cysts in the urine or by identifying the laminated wall of the cyst (328).

Fewer than half of the patients have eosinophilia. The most reliable diagnostic test uses partially purified hydatid arc 5 antigens in a double diffusion test (51). Complement fixation, hemagglutination, and the Casoni intradermal skin tests are less reliable but, when combined, are positive in approximately 90% of patients (328).

Radiologic Findings

Excretory urography typically shows a thick-walled cystic mass, occasionally calcified (29). If the cyst ruptures into the collecting system, daughter cysts may be outlined in the pelvis as an irregular mass or as multiple solitary lesions (105). Occasionally, direct filling of the cyst with contrast medium occurs.

Ultrasonography and CT are useful in characterizing the mass; CT is more sensitive (314). Ultrasonography usually demonstrates a multicystic or multiloculated mass. A sudden

change in position may demonstrate bright falling echoes corresponding to hydatid sand, which can be observed during real-time evaluation of a hydatid cyst (287).

On CT, several patterns of renal echinococcosis may be recognized. The most specific is a cystic mass with discrete round daughter cysts and a well-defined enhancing member (214). The less specific pattern is that of a thick-walled multiloculated cystic mass (105). The presence of daughter cysts within the mother cyst differentiates the lesion from simple renal cyst and from renal abscesses, infected cysts, and necrotic neoplasm.

Both CT and ultrasound are useful in evaluating the liver. Angiography is seldom required. Diagnostic aspiration carries a high risk of rupture and spillage of the highly antigenic cyst contents and risk of fatal anaphylaxis (285). Nevertheless, Baijal and colleagues (11) described a percutaneous management of renal hydatidosis as a minimally invasive diagnostic and therapeutic option.

Management

The prognosis of echinococcosis is good but depends on the site and size of the cysts. Although there have been preliminary reports on the use of mebendazole in the treatment of hydatid disease, the results have been less than satisfactory (71).

Surgery remains the mainstay of treatment of renal echinococcosis (270). The cyst should be removed without rupture to reduce the chance of seeding and recurrence. If the cyst wall is calcified, the larvae are probably dead and the risk of seeding is low, although a daughter cyst may be viable. If the cyst ruptures or cannot be removed and marsupialization is required, the cyst contents initially should be aspirated and the cyst filled with a scolecoidal agent such as 30% sodium chloride, 0.5% silver nitrate, 2% formalin, or 1% iodine for approximately 5 minutes to kill the germinal portions (235,315,328).

BACTERIURIA IN PREGNANCY

Part of "4 - URINARY TRACT INFECTIONS "

Asymptomatic bacteriuria is one of the most common infectious complications of pregnancy. The overall prevalence of bacteriuria in pregnancy ranges from 2% to 7%, and the risk of acquiring bacteriuria during pregnancy increases with duration of pregnancy (37,243,351). Spontaneous resolution of bacteriuria in pregnant women is unlikely unless treated. Nonpregnant patients often clear their asymptomatic bacteriuria, but pregnant women become symptomatic more frequently and tend to remain bacteriuric (74). Pyelonephritis develops in 1% to 4% of all pregnant women (358) and in 20% to 40% of pregnant women with untreated bacteriuria (257,401). Treatment of asymptomatic bacteriuria found early in pregnancy has been shown to decrease the prevalence of subsequent acute pyelonephritis from 28% to less than 3% (358).

Pathogenesis

The anatomic and physiologic changes induced by the gravid state significantly alter the natural history of bacteriuria (256). The significant physiologic changes in pregnancy, which may develop as early as the first trimester, lead to urinary stasis and mild hydroureteronephrosis and contribute to development of pyelonephritis. Recent studies of *E. coli* adhesins and their respective specific tissue receptors have established an adhesin-based mechanism of pyelonephritis-induced preterm births and low birth weights in mice (172). There is a higher incidence of *E. coli* bearing Dr adhesins during the third trimester of pregnancy in women with gestational pyelonephritis (245) and an upregulation of Dr adhesin in the kidney, endometrium, and placenta during the third trimester of pregnancy (212). When infected intravesically with *E. coli*–bearing Dr adhesin, nearly 90% of mice that were hyporesponsive to bacterial lipopolysaccharide and had a deficient immune response delivered preterm, compared with 10% of mice infected with *E. coli* without Dr. Also, there was a significant reduction in fetal birth weight in the Dr-infected group. Bacterial tissue culture showed systemic spread of the Dr *E. coli* to the placentae and fetuses.

Management

In the preantibiotic era, pregnant women with symptomatic urinary tract infections and bacterial pyelonephritis were reported to have a high incidence of prematurity, low birth weight, and death (106). The relationship between asymptomatic bacteriuria and prematurity is less clear. Gilstrap and colleagues (106) found no difference in pregnancy among patients treated for asymptomatic bacteriuria as compared with nonbacteriuric controls. However, because women with asymptomatic bacteriuria are at higher risk for developing a symptomatic urinary tract infection that results in adverse fetal sequelae, all women with asymptomatic bacteriuria should be treated. The pathogens are similar to those seen in nonpregnant women (207).

An initial screening culture should be performed in all pregnant women during the first trimester (351). If the culture shows no growth, repeat cultures are generally unnecessary because patients who have no growth in their urine early in their pregnancy are unlikely to develop bacteriuria later (220,243). Pregnant women with a history of recurrent urinary tract infection or vesicoureteral reflux may benefit from antimicrobial prophylaxis (30).

If the culture is positive, special consideration must be given to the selection of antimicrobial agents chosen to treat infection to prevent fetal toxicity. Table 4.7 lists the antimicrobial agents and dosing for use in pregnancy. The aminopenicillins and cephalosporins are considered safe and generally effective throughout pregnancy. In patients with penicillin allergy, nitrofurantoin is a reasonable alternative. It may be used safely during the first two

trimesters in patients without glucose-6-phosphate dehydrogenase deficiency. Given the low efficacy of short-course ß-lactam therapy in nonpregnant women, it is prudent to describe a full 7-day course of therapy in pregnant women. Follow-up cultures should be obtained to document absence of infection. Pregnant women with acute pyelonephritis should be hospitalized and treated initially with parenteral antimicrobials. More than 95% of these patients respond within 24 hours using ampicillin and an aminoglycoside (59) or cephalosporins (291). Appropriate oral agents should then be given for at least 14 days (84). After the treatment course is completed, low-dose prophylaxis with nitrofurantoin, amoxicillin, or cephalexin has been shown to be effective in preventing reinfection (292,370). The efficacy of postcoital prophylaxis with either cephalexin (250 mg) or nitrofurantoin (50 mg) has been reported (264).

Drug	Dosage	Comments
Agents Considered Safe		
Penicillins		
Ampicillin	500 mg q.i.d.	Extensively used
Amoxicillin	250 mg t.i.d.	Safe and effective
Penicillin V	500 mg q.i.d.	Used less frequently, but achieves excellent urinary levels
Cephalosporins		
Cephalexin	500 mg q.i.d.	Extensively used
Cefaclor	500 mg q.i.d.	Somewhat more effective against Gram negatives
Agents That May Be Used with Caution		
Nitrofurantoin	100 mg q.i.d.	May result in hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency
Sulfisoxazole	1 g, followed by 500 mg q.i.d.	May cause kernicterus in the newborn; also may cause hemolytic anemia when glucose-6-phosphate dehydrogenase deficiency is present; especially avoid in last few weeks of gestation
Agents That Should Be Avoided		
Fluoroquinolones		Possible damage to immature cartilage
Chloramphenicol		Associated with gray-baby syndrome
Trimethoprim		May cause megaloblastic anemia because of antifolic action
Erythromycin		Associated with maternal cholestatic jaundice
Tetracyclines		May cause acute liver decompensation in the mother and inhibition of new bone growth in the fetus

TABLE 4.7. ORAL ANTIMICROBIAL AGENTS USED IN PREGNANCY

Drugs that are relatively contraindicated during pregnancy include the fluoroquinolones, TMP, chloramphenicol, erythromycin, tetracycline, sulfonamides, and nitrofurantoin. Fluoroquinolones are contraindicated because of their effects on immature cartilage. TMP may have teratogenic effects and should be avoided, especially in the first trimester. The “gray-baby syndrome” is a toxic effect of chloramphenicol on neonates resulting from the inability of the infant to metabolize or excrete the drug. Erythromycin may cause cholestatic jaundice in the mother. Tetracycline may cause fetal malformations and maternal liver decompensation. Sulfonamides may cause kernicterus and neonatal hyperbilirubinemia and should be avoided in the third trimester. Nitrofurantoin can cause hemolytic anemia in both mother and child when glucose-6-phosphate dehydrogenase deficiency is present.

BACTERIURIA IN THE ELDERLY

Part of "4 - URINARY TRACT INFECTIONS "

Urinary tract infections in the elderly are a common and expanding health problem (174). The prevalence of bacteriuria increases with age, institutionalization, and concurrent diseases and may exceed 50% in selective groups (23,297). Longitudinal studies have clarified the dynamic aspect of bacteriuria in the elderly with frequent, spontaneous alteration between positive and negative urine cultures (231). The incidence of asymptomatic bacteriuria is much more common than is apparent from a single survey, implying that most elderly will eventually have episodes of bacteriuria (24).

Pathogenesis

The pathophysiology of increased susceptibility is multifactorial and poorly understood. Age-related changes include decline in cell-mediated immunity, neurogenic bladder dysfunction, increased perineal soiling as a result of fecal and urinary incontinence, increased incidence of urethral catheter

placement, and in women, changes in the vaginal environment associated with estrogen depletion (274,297). Bacteriologic characteristics of infection in the elderly differ from those in younger patients (12). *E. coli* remains the most common uropathogen, but there is a significant increase in the incidence of *Proteus, Klebsiella, Enterobacter, Serratia,* and *Pseudomonas* species, as well as enterococci. *S. saprophyticus* is not seen in this population. Polymicrobial bacteriuria is more common among the elderly (240).

Diagnosis

Diagnosis of urinary tract infections in the elderly can be difficult. Urinary tract symptoms are often absent, and concomitant disease can mask or mimic urinary tract infection. Even severe upper tract infections may not be associated with fever or leukocytosis (12). Therefore a high index of suspicion is warranted, and diagnosis should rely on the results of a carefully obtained urinalysis and culture. The presence of greater than 10^5 CFU/mL of urine remains the standard for diagnosis in these patients. Pyuria alone is not a good predictor of bacteriuria in this population (253). Boscia and associates (25) reported that more than 60% of women with pyuria of 10 WBCs/mm^3 or greater (noted in midstream specimens) did not have a concurrent bacteriuria. However, the absence of pyuria was a good predictor of the absence of bacteriuria. Because urinary tract abnormalities can often predispose and complicate bacteriuria in the elderly, a thorough urologic evaluation is warranted. Commonly used studies include plain radiographs of the abdomen, renal and bladder ultrasonography, excretory urography, and cytoscopy.

Significance of Screening Bacteriuria

The significance of asymptomatic bacteriuria in the elderly is unclear (297). There is no documented relationship between asymptomatic bacteriuria and uncomplicated urinary tract infections and worsening renal function in this population. The treatment of asymptomatic bacteriuria to improve incontinence has not been justified (12). Although studies have demonstrated decreased survival in bacteriuric patients compared with nonbacteriuric control subjects, it is unclear whether increased mortality rates and bacteriuria are causally related (2,12). Nicolle and associates (240) randomized institutionalized women with bacteriuria to treatment or observation and followed these patients for more than 1 year. Treatment did not result in improved survival and was associated with a number of adverse effects.

Management

The exceedingly high prevalence of recurrent bacteriuria in this population, concern over the adverse actions of drugs, and the emergence of resistance associated with antimicrobial use make a universal recommendation to treat asymptomatic bacteriuria in the elderly unwarranted. However, asymptomatic patients with an alkaline pH and cultures indicating that urea-splitting organisms are present should be treated to prevent development of infection stones. When symptomatic infections are being treated, antimicrobial selections should take into account the potential for impaired metabolism and excretion of these drugs, as well as the greater likelihood of drug interactions in this population.

CATHETER-ASSOCIATED BACTERIURIA

Part of "4 - URINARY TRACT INFECTIONS "

Catheter-associated bacteriuria is the most common hospital-acquired infection, with an incidence of more than 1 million per year (121,342). The development of bacteriuria in the presence of an indwelling catheter is inevitable and occurs at an incidence of approximately 10% per day of catheterization. Intermittent catheterization has been associated with rates of bacteriuria of less than 1% in healthy individuals and 15% in elderly hospitalized patients (365). The most important risk factors associated with increased likelihood of developing catheter-associated bacteriuria are duration of catheterization, female gender, absence of systemic antimicrobials, and catheter-care violations (342). Most catheter-associated urinary tract infections are asymptomatic. In patients with short-term catheter placement, only 10% to 30% of bacteriuric episodes produce typical symptoms of acute infection (120,129). Similarly, although patients with long-term catheters are bacteriuric, the incidence of febrile episodes occurs at a rate of only 1 per 100 days of catheterization (378).

Pathogenesis

Bacteria enter the urinary tract of a catheterized patient by several routes. Bacteria can be introduced at the time of initial catheter placement by either mechanical inoculation of urethral bacteria or contamination from poor technique. Subsequently, the bacteria most commonly gain access via a periurethral or intraluminal route (342). In women, periurethral entry is the most prevalent. Daifuku and Stamm (60) found that among 18 women who developed catheter-associated bacteriuria, 12 had antecedent urethral colonization with the infecting strain. Bacteria may also enter the drainage bag and follow the intraluminal route to the bladder. This route is particularly common in patients who are clustered among other patients with indwelling catheters (208).

The urinary catheter system provides a unique environment that allows for two distinct populations of bacteria: those that grow within the urine and another population that grows on the catheter surface. A biofilm represents a microbial environment of bacteria embedded in an extracellular matrix of bacterial products and host proteins that often lead to catheter encrustation (342). Certain bacteria,

particularly of the *Pseudomonas* and *Proteus* species, are adept at biofilm growth, which may explain their higher incidence in this clinical setting (229). The uropathogens isolated from the catheterized urinary tract often differ from those found in noncatheterized ambulatory patients. *E. coli* is still the most common organism isolated, but *Pseudomonas, Proteus,* and *Enterococcus* species are very prevalent (378). In patients with long-term catheterization of more than 30 days, the bacteriuria is usually polymicrobial and the presence of four or five pathogens is not uncommon (379). Although certain species may persist for long periods, the bacterial populations in these patients tend to be dynamic.

Significant bacteriuria in patients with catheters is present when greater than 100 CFU/mL is present because even this low level progresses to greater than 10^5 CFU/mL in almost all patients (208,350). Pyuria is not a discriminate indicator of infection in this population.

Management

Careful aseptic insertion of the catheter and maintenance of a closed dependent drainage system are essential to minimize development of bacteriuria. The catheter–meatal junction should be cleaned daily with water, but antimicrobials should be avoided because they lead to colonization with resistant pathogens, such as *Pseudomonas.*

Incorporation of silver oxide (301) or silver alloy (288) into the catheter and hydrogen peroxide into the drainage bag has been reported to decrease the incidence of bacteriuria in some studies (301), but not in other populations (342). Concurrent administration of systemic antimicrobials transiently decreases the incidence of bacteriuria associated with short-term catheterization, but after 3 to 4 days, the incidence of bacteriuria is similar to the rate in catheterized patients not taking systemic antimicrobials, and the prevalence of resistant bacteria and side effects is substantial. The concept of instilling nonvirulent bacteria into the bladder to completely block colonization and infection by pathogens has been tested in patients with spinal cord injuries (152). Patients successfully colonized with the nonvirulent strain had reduced symptomatic urinary tract infection and a subjective improvement in quality of life.

In patients with indwelling catheters, urine cultures should be performed if they become febrile and require antimicrobial therapy. The antimicrobial should be discontinued within 48 hours of resolution of the infection. If the catheter has been indwelling for several weeks, encrustation may shelter bacteria from the antimicrobial; therefore the catheter should be changed.

When a catheter is to be removed and there is a high probability of bacteriuria, a culture should be obtained 24 hours before removal. The patient should be started on empiric antimicrobial therapy such as TMP-SMX just before decatheterization and maintained on therapy for 2 days. A posttherapy culture should be obtained 7 to 10 days later to confirm the eradication of the bacteriuria.

FUNGURIA

Part of "4 - URINARY TRACT INFECTIONS "

Funguria is usually associated with predisposing factors, including indwelling catheters, antimicrobial therapy, diabetes mellitus, hospitalization, and immunosuppressed states (184).

Clinical Findings

Fungi may invade the kidneys as the result of hematogenous spread from other sources of infection or the gastrointestinal tract. *Candida albicans* accounts for approximately 50% of positive fungal cultures. *Candida glabrata* is the second most common fungus, representing approximately 10% to 15% of positive fungal cultures (228). *C. glabrata* is a normal commensal organism of the gastrointestinal tract and vagina and probably colonizes the urinary tract by ascending infection.

Asymptomatic funguria, implying urinary colonization rather than infection, is common. Invasive infection is suggested by the presence of irritative voiding symptoms and pyuria. Renal or perinephric abscesses and fungus balls (also known as bezoars) may result from funguria. These patients may demonstrate symptoms suggestive of pyelonephritis with flank pain and fever. However, fungal balls may develop in the collecting system of asymptomatic patients.

Diagnosis

The criteria for diagnosis are unclear. Particularly in women, vaginal or perineal colonization may contaminate urine specimens. Microscopic examination can reveal fungi budding forms or pseudohyphae. The presence of pyuria does not correlate well with the presence of symptoms or the degree of funguria. Cultures of 10,000 to 15,000 CFU/mL have been suggested as cutoff points for infection (182). Regardless of the count, a positive culture requires evaluation.

Management

A treatment algorithm for genitourinary fungal infection has been presented by Wise (388) (Fig. 4.37). Before antifungal therapy, predisposing factors to funguria should be eliminated. Unnecessary indwelling catheters should be removed and the nutritional status should be optimized. Discontinuation of broad-spectrum antimicrobial agents reduces fungal colonization. If, after removal of the catheter, fungal infection persists, amphotericin B may be instilled intravesically for up to 1 week. Fifty milligrams of amphotericin B dissolved in 1 L of sterile water is introduced into

the bladder via a three-way catheter over a 24-hour period (390). Alternatively, 200 to 300 mL of irrigant may be instilled for 1 to 2 hours with clamping of the catheter. Miconazole (50 mg per liter per day) has also been shown to be effective as a bladder irrigant (391). Amphotericin B may also be instilled via nephrostomy tube for upper tract fungal infection. Oral fluconazole has been shown to be as effective and safe as amphotericin B bladder irrigation for treatment of older adults with funguria (160).

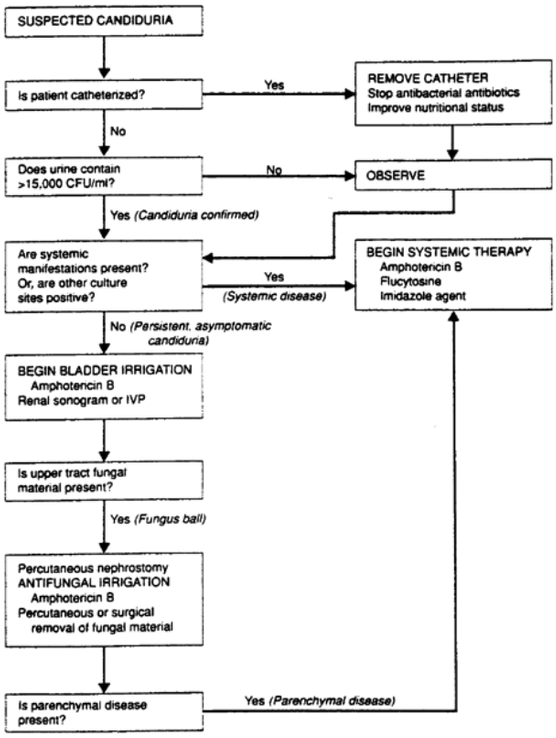

FIGURE 4.37. Treatment algorithm for management of suspected candiduria. IVP, intravenous pyelogram. (Reprinted with permission from Wise GJ. Amphotericin B in urologic practice. *J Urol* 1990;144:215.)

Funguria also may be treated effectively with oral agents. Flucytosine is readily absorbed from the gastrointestinal tract and is primarily excreted renally. A dosage of 100 to 200 mg/kg per day in four divided doses for 2 to 3 weeks is recommended. Dosing adjustments should be made for patients with renal insufficiency. Wise and associates (389) reported success (as defined by a decrease in colony counts or clinical improvement) in 212 of 225 patients treated for 21 to 28 days. Fungal resistance was reported in 14 of the patients. Flucytosine may be used in combination with amphotericin B bladder irrigation. Side effects include an elevation in liver function tests, diarrhea, and agranulocytosis.

Fluconazole is a triazole antifungal agent that is readily absorbed from the gastrointestinal tract and is excreted predominantly in unchanged form in the urine. Dosing is typically 200 mg for the first day followed by 100 mg daily for 10 to 14 days. Success rates of greater than 75% to 80% have been reported in studies treating *Candida* species with limited numbers of patients (15,221,242). The most common side effects present in 60% of patients include nausea, headache, skin rash, abdominal pain, vomiting, and diarrhea (113).

Patients with renal candidiasis and disseminated infection are usually treated with intravenous amphotericin B. Amphotericin B acts in a fungicidal fashion by binding to

the fungal-cell membranes, eventually resulting in disruption of the internal cellular components. Fungal resistance is uncommon. Because excretion is primarily biliary, amphotericin B may be administered to patients with renal insufficiency with caution because of its nephrotoxic effects, but without need for dosing adjustment. Side effects of significance with amphotericin B include chills, rigors, fevers, phlebitis, bone marrow toxicity, and potassium and magnesium depletion. After an initial dose of 1 mg, the dose may be increased gradually in daily increments of 5 mg to a maintenance dose of 0.3 to 1.2 mg/kg. Daily dosing should not exceed 50 mg. Although strict guidelines for duration of total amount of therapy do not exist, most renal infections require between 500 mg and 1.5 to 2 g over a 6- to 12-week period (223). Fluconazole has not been used extensively for upper tract infections, but when given intravenously, it has been shown to be effective in treating systemic candidiasis in critically ill patients (4,54,112,186).

The presence of fungal balls and accompanying obstruction should be assessed in patients with suspected upper tract funguria. Fungal balls typically involve *Candida* species because of their propensity to develop pseudohyphae. Patients with upper tract obstruction are especially prone to fungemia. The patients often require the placement of percutaneous nephrostomy tubes to relieve the obstruction. This tube may then be used to instill antifungal irrigant or to provide a tract for access for percutaneous endourologic removal of the fungal ball.

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5

MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY

Jay Y. Gillenwater

Jeffrey P. Weiss

J.Y. Gillenwater: Professor of Urology, University of Virginia Medical School, Charlottesville, VA 22908.

J.P. Weiss: Clinical Adjunct Assistant Professor of Urology, Weill/Cornell University Medical College, New York, NY 10595.

Contents

The urinary tract in pregnancy is of interest to the urologist because of the interesting physiologic changes that pose challenges in the management of its problems. In caring for patients during pregnancy, the urologist must always consider the effects of treatment on both the mother and the fetus. In this chapter, the marked changes in urinary tract anatomy and function during pregnancy are presented, as well as the clinical problems of urolithiasis, infection, hydronephrosis, coexistent renal diseases, and lower urinary tract dysfunction.

Physiologic changes during pregnancy include (a) an increase in renal blood flow of 60% to 80%; (b) increased glomerular filtration of 40% to 50%, with subsequent lowering of mean serum creatinine to less than 0.5 mg/dL; and (c) increases in cardiac output of 30% to 50%, associated with decreased peripheral resistance and increased stroke volume. Hydronephrosis of pregnancy is caused by both hormonal and mechanical factors. During pregnancy, there is net retention of sodium, potassium, and calcium. Urolithiasis has a similar incidence and causes as for nonpregnant patients, but it creates problems in the last trimester because one cannot safely operate or use shock wave lithotripsy on lower ureteral stones. Hypertension, renal insufficiency, and bacteriuria are major risk factors in fetal outcome. Pregnancy does not affect most renal diseases, and renal function usually increases temporarily in the diseased kidney during pregnancy. Acute renal failure of pregnancy, acute cortical necrosis, and idiopathic postpartum acute renal failure are problems seen in pregnancy. Pregnancy can be a success during dialysis or after renal transplantation. Excellent reviews have been published by Loughlin (148), Dafnis and Sabatini (51), Jungers and co-workers (118), and Weiss and Hanno (269).

RENAL PHYSIOLOGY IN PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Several changes in renal function normally occur owing to the gravid state; the one most relevant to urologists is dilation of the ureters, pelves, and calyces (146). Hydronephrosis of pregnancy may be attributed to a combination of factors, principally hormonal and mechanical. There is evidence that circulating estrogenic and progestational compounds produced by placentas in animals surgically lacking fetuses result in ureterectasis in the absence of mechanical obstruction (208,257,258). Prostaglandin E_2 has smooth muscle–relaxing properties that also contribute to hormonally induced hydronephrosis (217). Probably a greater contributing factor in physiologic hydronephrosis of pregnancy is stasis induced by the dextrorotating and enlarging uterus at midterm, explaining the proclivity for such obstruction to occur on the right. Experimental evidence for what otherwise may be taken as obvious is that differential pressure measurements in the ureter, above and below the pelvic brim, reveal a gradient at the level of the uterus in erect patients that resolves in the knee-chest position (165,219).

During pregnancy, cardiac output is increased. This is associated with decreased peripheral resistance and increased stroke volume. Initially, blood pressure decreases; later in pregnancy, the heart rate increases and stroke volume returns toward normal. Plasma volume increases 40%, and red blood cell volume increases 25% (141). Changes in the respiratory system include a 20% reduction in functional residual capacity by the fifth month of pregnancy (204). This is accompanied by a 15% increase in oxygen consumption, putting the mother at risk for developing hypoxemia during periods of hypoventilation.

There are gestational increases in both glomerular filtration rate (GFR) of 40% to 50% and renal plasma flow (RPF) of 60% to 80% (67). These changes occur in patients with either a solitary (native or transplant) kidney or two functioning kidneys (54,55). Increases in GFR and RPF also occur in the diseased kidney. An explanation for these hemodynamic and physiologic changes likely derives from increased cardiac output and decreased renal vascular resistance (133), as well as increased serum levels of aldosterone, deoxycorticosterone, progesterone, placental lactogen, and chorionic gonadotropin (146). A practical consequence of increased GFR is that plasma creatinine levels are reduced to a mean of 0.46 mg/dL during pregnancy because creatinine production is unchanged. Thus plasma creatinine concentrations that are normal for the general population are abnormally high in gravid patients and should signal a nephrologic evaluation for possible renal functional impairment (146,253). A corollary of increased RPF and glomerular filtration during pregnancy is the increase in urinary excretion of protein, glucose, amino acids, and vitamins (22,146,275).

An increase in renal volume as much as 30% is observed in pregnant patients in the absence of hydronephrosis. This is thought to be due to hemodynamic and hormonal factors, specifically increases in RPF and increased glomerular filtration surface area caused by a growth hormone–like effect of prolactin (38).

It has long been known that pregnancy is associated with hypercalciuria (129), a phenomenon attributed to increased GFR (163), increased calcium filtration (105), and excess intestinal calcium absorption secondary to high plasma levels of calcitriol (83). However, overwhelming evidence suggests that stone formation is not enhanced by pregnancy, and stone-formers who become pregnant do not incur a higher incidence of urolithiasis (103). Thus it may be assumed that pregnancy also occurs within a milieu of factors that mitigate the stone-forming effect of hypercalciuria, such as increased excretion of stone inhibitors (citrate, magnesium, and glycosaminoglycans) (20,80,179,180).

Pregnancy is associated with diminished plasma osmolality (60). A maximum decrease in osmolality of 10 mOsm/kg can be expected from week 10 of gestation until parturition. Although it is tempting to explain this finding in terms of altered vasopressin metabolism, no such evidence exists and the cause for the altered osmoregulation of pregnancy is obscure (56,58,59). On the other hand, renal handling of sodium during pregnancy is better understood.

A small quantity of sodium (950 mEq) is accumulated during pregnancy. Thus there must be factors accounting for this maintenance of sodium homeostasis in that the increase in GFR that normally accompanies pregnancy in and of itself would cause a loss of 5,000 to 10,000 mEq sodium daily as an additional filtered load (146). Tubular reabsorption accounts for preservation of the majority of this increased filtered sodium load (13). However, other factors, including hormonal and physical changes, result in sodium maintenance. Aldosterone production and excretion are known to increase to high levels as an offset to natriuresis during pregnancy (27). Deoxycorticosterone, another potent mineralocorticoid, likewise increases in pregnancy, especially during the third trimester (28,187,272). Further enhancing sodium retention are high levels of circulating estrogens in pregnancy (145,271). The antinatriuretic effect of estrogens is also enhanced by their induction of 21-hydroxylation of progesterone (a salt-wasting hormone), yielding salt-retaining deoxycorticosterone (155). Other potentially salt-retaining hormones of pregnancy include adrenocorticotropic hormone, cortisol, prolactin, growth hormone, and placental lactogen (146). Although circulating catecholamines may result in natriuresis via direct renal effects or indirectly through renal sympathetic innervation, levels of these compounds are variably and only slightly changed; thus their effects on sodium metabolism appear to be minimal (12). Renin and angiotensin II levels are distinctly elevated during gestation (15,106). The influence of the renin-angiotensin axis on sodium homeostasis is indirect, to the extent of its relation to aldosterone metabolism and volume status. It is currently theorized that gestational renin levels may be affected by increases in prostaglandin E_2 and prostacyclin produced by the uterus, resulting in general

vasodilation, decreased blood pressure, and augmented vascular volume during pregnancy (75,79).
The physical factors influencing sodium metabolism in pregnancy are increased ureteral pressure and increased uterine blood supply with its arteriovenous shunting characteristics (35,208). These physical factors are greatly influenced by position and levels of ambulation and generally are believed to result in sodium retention in the pregnant subject.
In summary, the tremendous potential for gestational salt loss owing to increased GFR is offset in multiple ways that are both hormonal and physical. These factors combine to the net observation that sodium is retained slightly during pregnancy.

UROLOGIC SYMPTOMS IN PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

The most common urologic symptom in pregnancy is frequency of voiding (nearly universal at term in primigravidas), followed by stress incontinence, 35% at term (237). Other symptoms often found include urgency, urge incontinence, poor stream, and incomplete emptying, although these are not typically found to be severe enough to warrant investigation with micturitional studies (49).

Hematuria may occur as a normal concomitant of pregnancy because of microanatomic changes in such (enlarged) kidneys that exhibit renal venous fragility in the collecting tubules or pelvis (264). Recurrent unilateral gross hematuria occurring during consecutive pregnancies has been reported to be related to renal varicosities owing to mechanical (uterine compressive) and hormonal factors causing pelvic venous congestion (52). Another common urologic gestational symptom is flank pain, which can be attributed to multiple underlying processes, such as hydronephrosis, pyelonephritis, urinary calculi, spontaneous renal rupture, or tumors.

USE OF MEDICATIONS DURING PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Urologists often are asked to treat pregnant patients for conditions that require prescriptions, such as pain relievers, antimicrobials, antipyretics, anesthetics, and anticholinergics. The potential for pharmaceutical teratogenicity behooves a detailed knowledge of medications safe for use in pregnancy.

Antibiotics (Table 5.1) and analgesics are the most commonly prescribed medications by urologists for pregnant women. Antimicrobials that are considered safe without reservation (barring allergies) include penicillins, cephalosporins, and erythromycin (133,182,276). Nitrofurantoin is regarded as safe in pregnancy because of low blood levels, although the rare complication of idiosyncratic pulmonopathy should be kept in mind with long-term administration (6,198). The safety of this drug during pregnancy should not be confused with its association with hemolytic anemia in breastfed infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Aminoglycosides may be safely administered during pregnancy (44) when used with the usual judicious attention to monitoring of renal function and serum peak and trough levels. Sulfonamides are safe until 28 weeks, after which time there is a risk of fetal kernicterus and

hemolysis in patients with G6PD deficiency (113,133). Trimethoprim/sulfamethoxazole is contraindicated because of possible teratogenicity and fetal folate antagonism (211). Tetracycline should be assiduously avoided to prevent dysgenesis of fetal limbs (weeks 0 to 12) and teeth, which results from competition with calcium for access into sites of bone development (87,113). Chloramphenicol is contraindicated near term because of potential bone marrow depression and fetal gray syndrome (113,267), although it may be used safely throughout most of gestation. Isoniazid may cause a number of congenital defects, such as infant encephalopathy; metronidazole must be used with caution during the second and third trimesters (37) in that rat lung adenomas and increased bacterial mutation rates have been found experimentally (113). Erythromycin and amoxicillin/clavulanic acid are considered safe in pregnancy, although formal human studies of the latter combination are lacking (2,113). Although ketoconazole as an antifungal has not been documented to cause fetal malformation, it is not recommended during pregnancy because of its association with teratogenicity in rats and an inhibitory effect on androgen and corticosteroid synthesis (168). Angiotensin-converting enzyme inhibitors cause neonatal renal failure and hypotension and should thus not be used.

TABLE 5.1. ANTIBIOTIC USE IN PREGNANCY

Antibiotic	Safety Margin (Barring Allergy)
Penicillins	Safe
Cephalosporins	Safe
Erythromycin	Safe
Nitrofurantoin	Safe (hemolytic anemia in breastfed infants with G6PD deficiency)
Aminoglycosides	Potential CNS toxicity, ototoxicity (monitor serum levels, renal function)
Sulfonamides	Safe until 28 weeks (thereafter risk hemolysis, kernicterus if G6PD deficiency)
Trimethoprim/sulfamethoxazole	Contraindicated (teratogenic, fetal folate antagonist)
Tetracyclines	Contraindicated (fetal limb, dental dysgenesis)
Chloramphenicol	Contraindicated near term (fetal bone marrow depression, "gray syndrome")
Isoniazid	May cause congenital defects (e.g., infant encephalopathy)
Metronidazole	Use with caution in second and third trimesters only (possibly mutagenic)
Amoxicillin/clavulanic acid	Formal studies lacking; safety unknown
Quinolones	Bone growth retardation
Ketoconazole	Contraindicated (teratogenic in rats; inhibits steroid synthesis)

CNS, central nervous system; G6PD, glucose-6-phosphate dehydrogenase.

Fortunately, a variety of analgesics may be used with a wide safety margin during pregnancy. Whereas acetaminophen is safe in pregnancy, aspirin is contraindicated, particularly during the third trimester, because of a propensity for causing newborn intracranial (subchoroidal) hemorrhage (41,220,231). However, prospective studies have failed to demonstrate an increased risk of aspirin-induced fetal malformations (231). From the maternal standpoint, aspirin may cause anemia, peripartum uterine hemorrhage, prolonged gestation, or labor (119). Although theoretically nonsteroidal antiinflammatory drugs may be thought to carry the same caveats as aspirin, they should be avoided, especially during the third trimester, to prevent premature closure of the ductus arteriosus, a prostaglandin-dependent phenomenon (144). For more severe pain, narcotic analgesics are considered safe without reservation when used short term before parturition (107). Under these circumstances, the urologist may prescribe appropriate dosages of morphine, meperidine, or oxycodone.

Although an exhaustive discussion of all pharmaceuticals is beyond the scope of this chapter, two specific substances deserve special mention. As surgeons, urologists will often need to use topical sterilizing agents. When administered near term, povidone-iodine may be absorbed vaginally or perineally to the extent that neonatal hypothyroidism and goiter may result (26,134). Hexachlorophene, another common topical antiseptic, is also of concern because of its association with neurotoxicity and white matter vacuolar degeneration (270). These substances should be used judiciously during pregnancy and should be rinsed thoroughly with sterile water where applied.

DECISION MAKING FOR GESTATIONAL URINARY TRACT IMAGING

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Paramount in the mind of the physician caring for a pregnant patient in need of roentgenographic imaging studies is radiation-dosage tolerance. Significant pelvic radiation dosages (5 to 15 cGy) during the first trimester increase the risk of teratogenicity from 1% to 3% (244). Putting this into perspective, a standard urogram renders 1.5 cGy to the fetus; however, prudence dictates the standard that limited exposure to two or three "shots" should be taken during a gestational urogram. These images include the plain film, a 30-minute exposure, and a 2- or 3-hour exposure if the diagnosis of obstruction remains in doubt. Because each plain abdominal film yields 0.2 cGy to the fetus, the two- or three-shot urogram is considered safe even during the first trimester (66,103,159). On the other hand, data exist to cause concern with even low doses of roentgen ray exposure to the fetus. Specifically, an average of 1 rad of fetal exposure has been correlated with a net 2.4-fold increase in the incidence of all childhood malignancies (99). However, it is not clear during which trimesters radiation exposure occurred. Although ultrasound is safe under all circumstances of pregnancy, its use in diagnosing obstruction is of limited value because of its suboptimal view of the ureter and presence of hydroureteronephrosis as a physiologic concomitant of pregnancy. Thus, because urography is found to have diagnostic value greatly in excess of sonography during pregnancy (103), it is recommended in the following situations: (a) persistent fever, (b) massive or increasing hydronephrosis as seen during serial urosonography, and (c) pain or emesis refractory to conservative therapy.

The theoretic risk of development of childhood cancer (not necessarily teratogenicity) should at all times be kept in mind when subjecting the fetus to roentgen ray exposure (156,177). In particular, there is no evidence that fetal radiation exposure below 5 rad causes congenital malformation, spontaneous abortion, or growth retardation (25). However, the relative risk of childhood leukemia occasioned by fetal exposure of 1 to 2 rad is increased from 1 in 3,000 (general population) to 1 in 2,000 (229). Put into perspective, the risk of leukemia for a sibling of a leukemic child is 1 in 700 (25).

In view of these data, it is useful to discuss radiation dosages received by the uterus owing to specific imaging studies. For example, cerebral angiography causes less than 10 mrad exposure to the uterus, a negligible dosage, due to the maximum distance of the collimated beam from the brain to the pelvis (262). In contrast, double-vessel coronary angioplasty provides 90 mrad uterine exposure (76,86), and barium enema causes 2 to 4 rad fetal exposure due to proximity of the study to the uterus (16). Other roentgen ray studies may be ordered during pregnancy. Computed tomography causes maximum radiation exposure at the skin level, with a progressive decrease toward the body interior.

Correspondingly, radiation dosage to the fetus diminishes with enlargement of the pregnancy and its investing tissues (48). Specifically, a ten-slice abdominal study causes 2.6 rad fetal exposure at weeks 0 to 14, whereas the same study provides only 1.7 rad to the conceptus at weeks 35 to 42 (48,207,228). Likewise, administration of radiopharmaceuticals may be safely done during pregnancy. Nuclear medicine studies of the brain, biliary system, skeleton, lungs, kidneys, abscesses, and heart may all be accomplished with fetal exposures varying from 40 to 1,100 mrad (48). In general, because radioactive iodine readily crosses the blood-placental barrier, isotopic iodine administration should be avoided during pregnancy (261). Magnetic imaging is thought to be safe during pregnancy because studies of static, gradient, and radiofrequency magnetic fields at strengths lower than 2 tesla have thus far failed to demonstrate mutagenic or other deleterious effects on the fetus (48,81,225,262).

In summary, it is useful to keep in mind the American College of Obstetricians and Gynecologists' guidelines for diagnostic imaging during pregnancy (5):

X-ray exposure under 5 rad has not been associated with increased fetal anomaly or spontaneous abortion.

Maternal health should not be compromised by irrational fears of the dangers of ionizing radiation to the fetus. However, alternative imaging procedures such as ultrasonography and magnetic resonance imaging (MRI) should be used instead of x-rays when applicable.

Although ultrasonography and MRI are unassociated with known adverse fetal effects, MRI to date is not recommended for use in the first trimester.

Radiologic consultation is advisable if it is deemed necessary to estimate fetal dose when roentgenologic procedures are performed during pregnancy.

Therapeutic radioactive iodine isotopes are contraindicated during pregnancy.

Ultrasound is the most common modality used in diagnosis of calculous disease in pregnancy. However, because most symptomatic gestational calculi will be in the ureter and hydronephrosis is a normal finding in pregnancy, in most cases, ultrasound and its suboptimal view of the ureter will fail to be diagnostic in this setting. Horowitz and Schmidt (103) performed 11 ultrasound examinations in six gravid patients with calculi and found this modality to be diagnostic only once. In comparison, excretory urography was diagnostic in six of ten pregnant patients. These authors use a two-shot urogram consisting of a plain film and 3-hour postcontrast film with the idea that clearance of contrast from the symptomatic side excludes significant obstruction. They specifically outline the following situations in which urography is indicated: (a) persistent pyrexia or positive urine culture despite 48 hours of intravenous antibiotics, (b) declining renal function, (c) massive hydronephrosis detected by sonography, and (d) unrelenting pain or vomiting. In conclusion, sonography is most useful in evaluating gravid patients thought to have acute symptomatic stone disease requiring further investigation with roentgenographic imaging studies (269).

Renal sonography can be used in serial fashion without concern of radiation-induced fetal injury in the pregnant patient. Muller-Suur and Tyden (178) found that 31 of 35 patients with flank pain had hydronephrosis. In this study, the upper limit of normal pelvic diameter was determined to be 17 mm. In asymptomatic patients, normal renal pelvic diameters during the first, second, and third trimesters were 5 ± 1 mm, 10 ± 3 mm, and 12 ± 2 mm, respectively, on the right side, and 3 ± 1 mm, 4 ± 1 mm, and 5 ± 1 mm, respectively, on the left. These parameters constitute a guide to selection of patients having ureteral colic for further study. Whereas neither parity nor a history of urinary tract problems is found to be related to the degree of dilation, the incidence of hydronephrosis as determined by ultrasound investigation is 90% on the right side and 67% on the left (197). When hydronephrosis is found sonographically during pregnancy, a question may arise as to whether it is caused by obstruction or normal physiologic changes of the gravid state. Such a distinction may be made by determination of internal vascular resistivity indices by use of renal Doppler duplex ultrasound. Statistically significant relation is made between elevation of resistivity index and pathologic upper tract dilation in symptomatic pregnant patients (101). In this fashion, duplex renal ultrasound may be used to attribute hydronephrosis caused by calculus as opposed to nonobstructive physiologic phenomena.

HYDRONEPHROSIS OF PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Obstructive changes in the upper tracts during pregnancy are attributable to evolution of a physiologic process. Stadfeldt (236) reported right hydroureteronephrosis caused by uterine compression of the ureter at the level of the iliac vessels as long ago as 1861. Although their subject matter was autopsies of women dying in late pregnancy, Harrow and colleagues (98) were able to draw the same conclusion 103 years later using data compiled from excretory urography. Further support for the direct compression theory derives from the observation that hydronephrosis tends not to occur in gravid women with either ectopic ureters or those placed ectopically as in patients with urinary diversion; in neither of these two cases do the ureters become compressed between the uterus and iliac great vessels (247). Clark (39) reported an alternative explanation for hydronephrosis of pregnancy; namely, ureteral compression is caused by a dilated right ovarian vein that crosses over the ureter on its way toward the vena cava, as opposed to the left ovarian vein that runs a more parallel course with its ureteral mate. Although both he and others (68) performed resection of the offending ovarian veins plus ureterolysis with

good results, this experience largely has not been found to be reproducible (214).

Hydroureterectasis in pregnancy first occurs as a simple consequence of ureteral compression above the pelvic brim by the enlarging, dextrorotating uterus at about midterm (70,269). Such rotation explains why hydronephrosis of pregnancy is usually found on the right. Hormonal factors may also contribute to this “physiologic” hydronephrosis. The elegant experiments in rhesus monkeys of Van Wagenen and Jenkins (257) and Van Wagenen and Newton (258) permitted the conclusion that in these animals, hormonal changes by a functioning placenta lacking a (surgically removed) conceptus induce ureterectasis. Whereas in the past these changes have been thought to be normal concomitants of pregnancy and not necessarily pathologic, current literature is replete with reports of obstructive uropathy in gravid women causing acute renal failure and polyhydramnios (71,102), acute pain (206), hypertension (138), and spontaneous renal rupture (88).

When symptoms of pain or infection are refractory to conventional nonoperative therapy with analgesics or antimicrobials, invasive manipulation of the hydronephrosis of pregnancy is indicated. The most commonly used method of temporary relief of this type of obstruction is placement of a ureteral stent or drainage catheter (19,71,112,138,151,184,240). Alternatively, for example, when ureteral tortuosity late in pregnancy precludes retrograde stent passage, percutaneous nephrostomy under either fluoroscopic (206) or sonographic (24,31,124,256) guidance may resolve symptomatic hydronephrosis. Indeed, for the tortuous ureter late in pregnancy, the straightening technique described by Pryor and Gillenwater (205) can be helpful in negotiating an otherwise unnavigable channel in stent passage. These authors suggest preliminary passage of a floppy-tip guidewire through a dual-channel cystoscope bridge to straighten the ureter in anticipation of catheter placement through the second channel. Stent passage also can be facilitated without the need for roentgenographic imaging through the use of endoluminal ultrasound (273). Goldfarb and associates (85) caution that pregnant stone-formers are at additional risk for development of concretions on indwelling stents. Thus increased fluid intake should accompany care of hydronephrosis of pregnancy treated with stenting.

Aside from the drainage procedures described previously, other solutions to the symptomatic hydronephrosis of pregnancy include epidural block (209) and delivery of the fetus at or near term, either by labor induction through amniotomy (192) or cesarean section (61). Bed rest in the contralateral position cannot be overemphasized to prevent complications of severe hydronephrosis of pregnancy, especially in patients with a solitary kidney (102).

An uncommon but potentially life-threatening complication of hydronephrosis of pregnancy is spontaneous renal rupture. The pathogenesis of this entity stems from increased hydrostatic pressure within the collecting structures that exceeds the holding capacity of the calyceal– renal capsular junctions resulting in extravasation (172). Kidneys with prior damage through infection, trauma, or surgery are particularly prone to rupture because of increased intracavitary pressure against noncompliant, scarred renal parenchyma. Symptoms occur between 18 weeks of gestation (172,258,278) and 1 day postpartum (61,121,172). Flank pain, hematuria, flank mass, and hypotension are harbingers of spontaneous renal rupture of pregnancy. Specific diagnosis may be carried out using sonography, limited excretory urography, and retrograde ureteropyelography. In addition, arteriography may be used to identify the source of hemorrhage in ruptured kidneys that have bled and caused hemodynamic instability (114). This technique may prove therapeutic with the addition of angioembolization, although radiation dosage for such a procedure is such that it cannot be recommended during the first trimester. Although most patients with hemorrhagic spontaneous renal rupture of pregnancy have required nephrectomy (172), timely use of rest in the contralateral decubitus position, ureteral stenting, or percutaneous nephrostomy may be expected to prevent this disastrous complication (64,132,162,189).

It should be noted that retroperitoneal hemorrhage may have origins in other than hydronephrosis of pregnancy as evidenced by the report of Plaus (202); he found hemorrhagic necrosis of metastatic renal choriocarcinoma related to a prior pregnancy in a patient with a positive pregnancy test and normal pelvic examination who was clearly not pregnant. A related problem is the rare spontaneous rupture of the ureter in pregnancy due to impacted proximal ureteral calculus (69).

URINARY CALCULOUS DISEASE IN PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Although symptomatic urinary calculi of pregnancy are vexing and pose problems that challenge all who treat them, they are neither more nor less common than their counterparts in the general population (103). This is accounted for in that the many determinants that tend to increase stone formation in pregnancy are offset by opposing factors. Hydronephrosis, decreased ureteral peristalsis, infection, and calcium supersaturation (159) all augment the stone-forming tendency of pregnancy, whereas increased excretion of stone inhibitors (magnesium, citrate, and glycosaminoglycans) works in the reverse (80). Although most researchers have found that calculi of pregnancy tend to occur in multiparas (9,47,170,191,227,235,241), a more recent study found primiparas to be more commonly afflicted (191).

Diagnosis of calculi in the pregnant patient begins with symptoms of flank or abdominal pain, urinary urgency, nausea, and vomiting. Because any of these symptoms are compatible with normal pregnancy, imaging studies

must be done for confirmation. Ultrasound may reveal hydronephrosis, but as discussed earlier, this finding is entirely consistent with physiologic dilation and may lack diagnostic capability. Even demonstration of the presence of a calculus in the renal collecting system may not be definitive because most symptomatic calculi during pregnancy are located in the ureter (269). A diligent sonographer may occasionally demonstrate a calculus in the ureter adjacent to a filled bladder; however, the unreliability of sonography in this setting leads to the conclusion that roentgenography is necessary to diagnose most symptomatic urinary calculi requiring intervention by the urologist, as discussed previously.

Because most symptomatic stones during pregnancy will pass spontaneously, the treatment of these stones is primarily expectant (62,100,103,240). This conservative posture is feasible because most calculi become asymptomatic after the first trimester (137,240), so stones that remain in the urinary tract but become asymptomatic can be “nursed along” until intervention may be undertaken without concerns for fetal health following parturition.

Similar to treatment for symptomatic hydronephrosis of pregnancy, intervention most commonly assumes the form of stent placement (66,103,150,158). It has been suggested that stents be changed monthly to prevent rapid encrustation in patients with chronic recurrent stone disease or in those with persistent infection (216). We consider it axiomatic that asymptomatic stone disease in women of childbearing age be treated prophylactically to preempt the dilemma of diagnosis and treatment of stones during pregnancy. Rittenberg and Bagley (213) recommend flexible ureteroscopy for both diagnosis and extraction of symptomatic calculi in pregnancy; however, narrow-caliber, semirigid fiberoptic telescopes have been useful in our experience, especially because most of these calculi are below the iliac crossover. Ureteroscopy is further facilitated during pregnancy by ureterectasis, both physiologic and obstructive in nature.

Alternative management options of calculi include placement of percutaneous nephrostomy tubes and open lithotomy (47,66,96), both considered safe in pregnancy. However, the position of extracorporeal shock wave lithotripsy (ESWL) in pregnant patients is less clear. Although female fertility is believed to be unaffected by ESWL (259), there is a dearth of information as to the safety of shock waves administered in the vicinity of a fetus. Ultrasound-guided shock waves during early pregnancy in Sprague-Dawley rats were not found to be harmful (232a). Certainly, the small but significant radiation dosage received by many patients from fluoroscopic imaging during ESWL would support the use of devices using ultrasound coupling to the shock wave energy source. Suffice it to say that the lack of mitigating data at present places pregnancy as a relative contraindication to ESWL.

Open surgery can be safely performed for stones in the kidney or upper ureter. Open surgery is *contraindicated* in the last half of pregnancy for lower ureteral stones. There is not enough room in the pelvis to operate, and it would be difficult to correct any surgical complications. In the past, some urologists approached lower ureteral stones through a small vaginal incision.

To continue medications for prophylaxis of stone disease during pregnancy is questionable. Gregory and Mansell (90) reported experience with 46 pregnancies in cystinuric patients. D-Penicillamine was continued during gestation (with the exception of weeks 6 through 20 to prevent mutagenicity) with no congenital defects identified. Sodium bicarbonate and potassium citrate were also continued throughout pregnancy with no ill effects on the fetus. However, thiazides are known to cross the placental barrier, causing fetal or neonatal jaundice and thrombocytopenia, thus creating a relative contraindication for pregnancy (93,269). Calcium-binding agents and low-calcium diets should be replaced with liberal fluid intake alone to prevent nutritional deficiencies in the evolving conceptus.

URINARY INFECTION IN PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Asymptomatic bacteruria is present in 4% to 7% of pregnancies, similar to the incidence in menstruating women generally (127,133,188,246). Thus, although pregnancy does not in and of itself cause bacteruria, the latter's association with pyelonephritis results indirectly in prematurity, low birth weight, and growth retardation (133,135,277,278). Kass (121,123) demonstrated that 20% to 40% of pregnant women with first trimester bacteruria acquire pyelonephritis in the third trimester. Conversely, successful treatment of bacteruria significantly lessens the progression to pyelonephritis of pregnancy and associated low birth weight, growth retardation, and premature labor (42,122). This is especially true in diabetic patients (176). It is therefore considered axiomatic that bacteruria of pregnancy be both screened for and treated. In a study of 3,254 patients screened for bacteruria of pregnancy (238), it was found that the risk of acquiring bacteruria increased with the duration of pregnancy, from 0.8% at the end of the first trimester to 1.93% at term. Because the risk of onset of bacteruria is highest between weeks 9 and 17 of gestation, it was suggested that week 16 is the optimal time for screening if considerations of economy dictate a single specimen be selected for this purpose. A meticulous, clean-catch midstream urine culture growing greater than 100,000 colony-forming units (CFU)/mm is considered significant for purposes of treatment and antimicrobial prophylaxis during pregnancy (196).

Offending microorganisms in the genesis of urinary tract infections during pregnancy are those causing infection in the general adult female population, primarily Gram-negative rods. *Escherichia coli* is the most common, followed by *Klebsiella, Enterobacter, Proteus,* Gram-positive cocci, and

enterococci (in order of frequency) (7,154). Stenqvist and colleagues (239) demonstrated that pregnancy does not diminish the virulence of *E. coli* strains that cause pyelonephritis compared with those causing only asymptomatic bacteruria, suggesting that pregnancy does not enhance host factors for resistance to upper urinary tract infection. Matorras and associates (164) found 20% of pregnant diabetic patients (twice as many as nondiabetic patients) to be colonized rectovaginally with group B streptococcus. However, group B streptococci did not cause more frequent urinary infection in diabetic than in nondiabetic patients. Urethritis caused by *Chlamydia trachomatis* occurs in 50% of women with dysuria, pyuria, and urinary frequency (266). In addition, chlamydial cervicitis was found in 21% of 11,544 women at their first prenatal visit; when untreated, it was associated with premature rupture of membranes, as well as low birth weight and decreased survival (221). Neonatal complications of chlamydial infection included nasopharyngitis, pneumonitis, and conjunctivitis. Thus *Chlamydia* is not “normal flora” and should be treated when discovered during pregnancy with erythromycin 500 mg four times daily for 7 to 10 days (266).

Once urinary tract infection is established in the pregnant patient, it becomes necessary to select both initial treatment and subsequent prophylaxis. Krieger (133) recommends full-dose antibiotic therapy for 7 to 10 days in treatment of gestational bacteruria. In addition, treatment for acute cystitis is the same as for asymptomatic bacteruria of pregnancy (169). However, regimens for initial treatment vary from single-dose to 3-day courses using amoxicillin (82,115), nitrofurantoin (97), and cephalexin (115,167). Angel and co-workers (8) found that in the absence of bacteremia, oral antibiotic therapy was as safe and effective as intravenous treatment for acute pyelonephritis during pregnancy.

Prophylaxis against recurrence of bacteruria for the remainder of pregnancy once the initial positive culture has been treated may be given as a daily or periodic dose of a suppressive antimicrobial agent. Van Dorsten and colleagues (254) used nitrofurantoin 50 mg three times daily as uroprophylaxis unless the initial posttreatment urine culture grew an organism resistant to that drug. Alternatively, Pfau and Sacks (201) use postcoital prophylaxis in the form of either cephalexin (250 mg) or nitrofurantoin (50 mg), similar to the case in nonpregnant patients. An intermediate prophylaxis regimen would be an equivalent dose of any antibiotics known to be safe and effective in pregnancy and for the particular microorganism in question as a nightly dose for the duration of the remainder of gestation (142,196,254). Close bacteriologic follow-up (e.g., semiweekly or monthly urine cultures) should follow initial treatment and be used to determine when additional bursts of full-course antibiotics should be prescribed.

Demonstration of persistent bacteruria during pregnancy is associated with structural urinary tract defects warranting thorough urologic evaluation postpartum (65). Austenfeld and Snow (10) found increased rates of urinary tract infection and miscarriage in women having undergone prior ureteroneocystostomy for childhood vesicoureteral reflux. Evaluation with early and repetitive urine cultures accompanied by prompt intervention with antimicrobials as described previously is appropriate in pregnant patients with any preexisting anatomic urinary anomaly.

RENAL FAILURE IN PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Chronic renal failure can be exacerbated by pregnancy, and acute renal failure (ARF) can be caused by pregnancy. Pregnancy is further complicated by end-stage renal disease (ESRD) treated either by dialysis or transplantation. These parallel management problems and counseling for women with renal disease facing pregnancy are now considered.

Renal failure resulting from pregnancy is classified into three etiologic categories: prerenal, renal, and postrenal. Prerenal states are caused principally by hypovolemia attributable to hyperemesis gravidarum and uterine bleeding (131). Hemorrhage in turn has three primary etiologies: abortion, placenta previa, and abruptio placentae. Unchecked by appropriate replacement of lost fluids, prerenal azotemia deteriorates into acute tubular necrosis (ATN), the most common cause of ARF in pregnancy (55). ATN and its counterpart, renal cortical necrosis (RCN), are the chief causes of ARF of pregnancy (Table 5.2). ATN and RCN are

distinguished from one another in that ATN occurs in a setting of preeclampsia (hypertension, proteinuria, and edema), eclampsia (preeclampsia plus seizure and coma), sepsis, and hemorrhage (215). In contrast, RCN follows disseminated intravascular coagulation (caused by amniotic fluid embolism, intrauterine fetal demise, or abruptio placentae), transfusion reactions, and sepsis (caused by chorioamnionitis, septic abortion, and pyelonephritis) (92,131). Clinically, ATN may be distinguished from RCN in that, whereas ATN rarely causes anuria and is usually reversible, RCN is manifested by anuria followed by irreversible renal damage accompanied by renal cortical calcification (269). RCN may occur during the puerperium as the syndrome of idiopathic postpartum renal failure. This rare syndrome is clinically characterized by oligoanuric acute renal failure following an otherwise uneventful pregnancy, which often progresses to RCN. [Three of five cases in a series of 57 cases of ARF in pregnancy were reported by Grunfeld and Pertuiset (92).] Although ARF occurs with an incidence of 1 in 2,000 to 5,000 pregnancies, more than 20% of cases of ARF in women are seen during pregnancy (92,131). Fortunately, ARF in females is declining as a result of improved obstetric care in general, and it has nearly disappeared late in the first trimester because of eradication of septic abortion (269).

Acute Renal Failure Etiology	Acute Tubular Necrosis	Renal Cortical Necrosis
Predisposing factors	Prerenal azotemia (hyperemesis gravidarum, uterine hemorrhage), preeclampsia, eclampsia, sepsis	Disseminated intravascular coagulation (amniotic fluid embolism, abruptio, intrauterine fetal demise), transfusion reactions, sepsis (chorioamnionitis, septic abortion, pyelonephritis)
Clinical manifestations	Nonoliguric renal failure	Oligoanuric renal failure; may occur as idiopathic postpartum renal failure
Outcome	Resolution of renal insufficiency	Chronic renal failure; renal cortical calcification

TABLE 5.2. ACUTE RENAL FAILURE IN PREGNANCY: ACUTE TUBULAR NECROSIS AND RENAL CORTICAL NECROSIS COMPARED

Whereas pregnancy may be a cause of acute renal disease, it may exacerbate preexisting renal disorders. Imbasciati and associates (109) reported 18 patients with serum creatinines more than 1.6 mg/dL underwent 19 pregnancies resulting in 13 live births, of which 50% were premature. Of the 18 patients, 14 were followed postnatally; 5 of 14 (36%) developed rapidly progressive renal insufficiency. Abe and colleagues (1) described renal deterioration in 25% of women with chronic renal disease in the midst of or following pregnancy. Others have recommended termination of pregnancy if the pregnancy causes progressive decline in renal function (152). Pregnancy does not seem to permanently influence kidneys with diabetic nephropathy, glomerulonephritis, renal transplants, or polycystic kidneys (136). However, manifestations of cystic renal disease, such as hypertension, infection, hematuria, and calculi, may cause management problems in pregnant patients with autosomal-dominant polycystic kidney disease (APCKD). In contrast, reflux nephropathy entails significant risk for acceleration of renal dysfunction during and after pregnancy. Becker and coworkers (14) reviewed 20 patients during a 10-year span and found 4 (20%) developing ESRD within 2 years of parturition, while 4 others who aborted went on to develop hypertension and ESRD. They conclude that patients with a history of reflux nephropathy incur a 50% risk of progression to end-stage renal failure. Patients with renal failure or hypertension are at greater risk for impairing renal function during pregnancy.

Although pregnancy might accelerate the progression of chronic renal disease toward the end stage, pregnancy remains a possibility for the patient with established ESRD. The first term pregnancy in a hemodialysis patient was reported in 1971 (43). A more recent series (210) describes nine births resulting from 14 pregnancies in 13 patients enrolled in dialysis programs (8 patients receiving chronic ambulatory peritoneal dialysis and 6 receiving hemodialysis). Although no congenital anomalies were identified, pregnancies tended to be complicated by exacerbation of hypertension and worsening residual renal function; babies were small for gestational age. These data support the general recommendation for allowing attempt of conception in the dialysis population with close medical surveillance.

If ESRD presents a set of risks to patients contemplating or facing pregnancy, renal transplantation becomes a “double-edged sword” in (to the positive) eliminating the azotemic state and (to the negative) causing fetal exposure to immunosuppressive drugs (63). It is now known that successful renal transplantation improves the likelihood of pregnancy from 1 in 200 (pretransplantation) to 1 in 50 (34). Conversely, pregnancy is unlikely to harm an adequately functioning renal graft (54). Specifically, only 15% of renal transplants will deteriorate as a result of pregnancy (226). However, in those few transplant patients experiencing increasing azotemia during pregnancy, termination has been recommended to prevent irreversible transplant damage (226). An interesting window of opportunity has been observed in transplant patients who become pregnant. That is, pregnancy occurring more than 5 years after transplantation causes permanent renal injury in 75% of cases (57). On the other hand, the outcome of pregnancy itself is superior at least 2 years after transplantation (34). These combined observations yield the conclusion that renal transplant patients should plan their pregnancies between 2 and 5 years after transplantation.

Pregnancy further affects renal transplant function in that the immunologically privileged state of gestation diminishes the incidence of transplant rejection (195). A corollary of this phenomenon is the occasional “rebound” of transplant rejection occurring postpartum. Immunosuppressive drugs (e.g., steroids, azathioprine, cyclosporine), although teratogenic at high dosages, are usually safe at moderate dosages during pregnancy (63,139,186). Although renal transplant patients must be monitored closely throughout pregnancy for development of hypertension, urinary infection, prematurity, and preeclampsia, transplant function is only minimally jeopardized during gestation (30,190).

UROLOGIC CONSIDERATIONS IN THE PREGNANT PATIENT WITH A SPINAL INJURY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Approximately 2,000 women of childbearing age sustain spinal cord injury annually in the United States alone (46). As a result of vastly improved rehabilitative measures, pregnancy has become a real possibility in such patients. Cross and associates (46) reported 25 pregnancies in 16 women

with cervical (7 patients) or thoracic (9 patients) spinal injuries. Twenty-two babies, four of whom were delivered via cesarean section, and three abortions resulted from these pregnancies. Eleven patients had symptomatic urinary tract infections, one had removal of a bladder calculus, and seven had autonomic dysreflexia (see also reference 265) related to a number of stimuli, such as a full bladder, enema, bowel movement, Foley catheter change (143), or uterine contraction. Greenspoon and Paul (89) recommend maintenance of a clean perineum to prevent ascent of bacteria from skin to bladder. The usual means of bladder drainage (e.g., intermittent clean catheterization, suprapubic catheterization, Credé maneuver) should be continued intrapartum. All spinal injury patients should be monitored closely and are at increased risk for asymptomatic bacteruria of pregnancy. Because most are managed with some type of catheterization, bacteruria is the rule in pregnant patients with a spinal injury; consequently, most will require antibiotic prophylaxis during pregnancy to reduce attendant complications, such as prematurity or low birth weight.

In the past, many patients with spinal injury or those with congenital spinal anomalies have been managed with extensive urologic surgical procedures to relieve obstruction or stasis in the upper or lower tracts. Such patients requiring delivery via cesarean section especially should be treated with great care, preferably with a team of operating gynecologic and urologic surgeons to avoid injury to bladder, ureter, or diversionary intestinal segment (212).

LOWER URINARY TRACT DYSFUNCTION IN PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Whereas urinary stress incontinence and frequency are common lower tract symptoms during pregnancy, gestational urinary retention is distinctly uncommon (237). The latter is thought to occur as a result of uterine retroversion during early pregnancy, a situation that tends to spontaneously reverse in the second trimester (95). That is, urethral obstruction caused by first trimester uterine retroversion resolves with backward cervical movement and fundal anteversion occurring at week 14 or 15 (84). Thus this form of urinary retention may be resolved by either temporary placement of a pessary or manual repositioning of the fundus (84,183,230). The problem may be circumvented by intermittent catheterization and voiding in the prone position (203).

Urinary retention may occur as a consequence of epidural block preceding delivery by cesarean section. This complication may be avoided by preoperative placement of a Foley catheter that is indwelling for several days postpartum. The incidence of urinary retention in this cohort is thereby reduced from 40% to zero (126). In patients with neurogenic urinary retention treated with indwelling bladder stimulator devices, there have been no adverse effects on the pregnancy or fetus (157,181).

Urinary stress incontinence occurs commonly both during and after pregnancy. The genesis of pregnancy-related stress incontinence remains controversial. It seems likely that myogenic or neurogenic damage to the urethral sphincter may occur after difficult vaginal delivery or that facilitated by application of forceps (245). On the other hand, Van Geelen and associates (255) found that neither functional urethral length nor urethral closure pressure changed significantly during pregnancy, nor was there a notable influence by either the duration of labor or the presence of an episiotomy on postpartum urethral pressure profiles. In the same study of 43 asymptomatic primigravidas, urethral closure response to stress maneuvers did not change during the course of pregnancy, nor did birth weight influence urethral pressure or length parameters postpartum in patients undergoing vaginal delivery. The conclusion was that inherent weakness in the sphincter mechanism rather than pregnancy itself caused stress incontinence.

In contrast, Iosif (110) found that only 4.9% of 1,411 patients developed permanent pregnancy-related stress incontinence, and of this 4.9%, most developed incontinence during their first pregnancy. Moreover, the incidence of stress incontinence in parous patients' mothers was greater by fivefold in incontinent patients as compared with that of controls. It was inferred that pregnancy itself rather than birth trauma was responsible for stress incontinence. The same author has studied stress-incontinent women urodynamically during and after pregnancy and has found that urethral closure pressure progressively diminishes during the course of gestation, as opposed to continent women, who exhibit an increase in both urethral length and urethral closure pressure as pregnancy proceeds (111). This finding supports the concept that physiologic changes in urethral function (or the lack thereof), as opposed to direct trauma to urethral smooth muscle or innervation during parturition, lead to stress incontinence. Petros and Ulmsten (200) propose an effect of relaxin, produced by the corpus luteum of pregnancy, on urethral collagen (depolymerization and resulting tissue softening) as causing reversible stress incontinence in a pregnant patient having had an intravaginal sling operation. Further studies will be necessary to confirm whether relaxin or other hormonal phenomena are responsible for temporary or permanent changes in urethral function during and after pregnancy.

UROLOGIC COMPLICATIONS OF CESAREAN SECTION AND VAGINAL DELIVERY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

The incidence of overall injuries to the urinary tract during caesarean section is less than 1%, although it is much higher if associated with cesarean hysterectomy (147). Ureteral injury during cesarean section occurs 0.1% of the time (148). Such injuries are most often repaired using ureteroneocystostomy facilitated by psoas hitch (148). Injury to the urinary bladder is the most commonly reported acute urologic

obstetric injury and is often caused by an opening in the bladder dome created during cesarean section (11,72,173). Repair is straightforward owing to the lack of involvement of the trigonal structures. However, low-segment cesarean section may injure the bladder base or ureters, risking vesicovaginal (0.7% incidence) or, more rarely, ureterovaginal fistula (4,104,147). Multilayer closure and omental interposition during repair is prudent in prevention of such complications. Rare urologic obstetric complications include urethral diverticula that may obstruct labor (174), atraumatic bladder or urethral rupture, necrosis of the anterior vaginal wall leading to vesicovaginal fistula secondary to obstructed labor (147), vesicouterine fistula following repeat cesarean section (250), loss of pelvic floor muscle tone after episiotomy and high forceps delivery (94,128,243,249), and trans-serosal invasion of the bladder by placenta percreta (222,232). Recent data suggest that repeat cesarean section has now become the principle cause of vesicouterine fistula due to altered vascularization of the supravaginal septum and distortion of bladder anatomy after primary section (116).

Vesical neck support and mobility are affected by both vaginal delivery and cesarean section, more so with the latter. Forceps delivery in particular may have profound effects on ability of women to contract their pelvic floor musculature. In addition, forceps delivery causes prolonged pudendal nerve terminal latencies as compared with vaginal delivery without forceps. Multiparity with or without forceps delivery results in pudendal nerve dysfunction similar to forceps delivery in primigravidas or in women having had a prolonged second stage of labor or high birth weight (3,233,242). Such pudendal nerve dysfunction may persist and worsen over the years following delivery (234). Cesarean delivery seems to preserve pudendal nerve function and, by extension, pelvic floor muscle tone. Similarly, noninstrumented vaginal delivery leads to transient but reversible pudendal nerve dysfunction (248). Thus it is clear that preservation of pelvic floor neuromuscular integrity is directly related to efforts to minimize the use of forceps and episiotomy in facilitating vaginal delivery, as well as limiting prolongation of the second stage of labor, prevention of third- and fourth-degree lacerations, and judicious application of cesarean delivery (94,250).

URINARY TRACT RECONSTRUCTION AND PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Pregnancy is possible in patients having undergone prior urinary tract reconstruction, whether for neurogenic bladder, tumor, or voiding dysfunction. Fenn and colleagues (74) described 19 pregnancies in 18 women ages 21 to 36 years having undergone clam enterocystoplasty for intractable detrusor instability. Pajor and colleagues (193) advocate lower urinary reconstruction with an ileocecal as opposed to ileal bowel segment to avoid uterine-induced mesenteric compromise during the course of pregnancy. Kennedy and co-workers (125) reported on successful pregnancies in four women with exstrophy having had flap vaginoplasty and creation of subsequent continent right colonic urinary reservoir with an orthotopic perineal stoma (Indiana pouch). The authors performed cesarean section and close monitoring for maternal or fetal distress in all cases. Creagh and colleagues (45) reported 34 pregnancies in 27 women with reconstructed lower urinary tracts who underwent either vaginal or cesarean delivery, indicated by specific obstetric considerations. Most of their patients (28 of 34) underwent successful vaginal delivery. Thus patients having undergone lower urinary reconstruction may safely deliver either vaginally or via cesarean section; attendance of the urologist is essential in all cases.

URINARY TRACT TUMORS DISCOVERED DURING PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Despite pregnancy being an immunologically impaired state, the incidence of malignancy is similar to that in the general population (185). A wide variety of urologic tumors have been reported to occur during pregnancy (149). Specifically, renal cell carcinoma is the most common renal neoplasm of pregnancy; because the latter is a condition of the young, angiomyolipoma occurs next in frequency (263). For the same reason, Wilms' tumor is known in pregnancy (23). Bladder cancer during pregnancy may take the form of adenocarcinoma (78), transitional cell carcinoma (18,19), or squamous cell lesions (120). Because electrical current may induce neighboring uterine contractions, obstetric treatment to diminish uterine smooth muscle reactivity may be helpful in reducing the possibility of premature labor from electroresection and cautery. Similarly, laser phototherapy is useful to treat bladder tumors of pregnancy while eschewing prematurity.

Adrenal tumors such as pseudocyst (251) and pheochromocytoma (29,224) are extant during pregnancy. Key issues in pheochromocytoma of pregnancy include diagnostic conundrum (symptoms and signs resemble those of preeclampsia, leading to mortality rate greater than 50% when undiagnosed), choice of α-blockade (prazosin, to avoid teratogenicity of phenoxybenzamine), means of imaging (MRI is especially useful for localizing pheochromocytoma and is free of ionizing radiation), timing of surgical resection (expeditiously), and route of delivery (vaginal preferred) (29,91,149,160,224,260).

TIMING OF ANESTHESIA DURING PREGNANCY

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

General anesthesia in and of itself does not entail a risk of adversity to pregnancy (48). This holds especially true when the (nonobstetric) procedure is complication free. A landmark

study from Scandinavia evaluated 5,405 incidental surgical procedures performed during all three trimesters of pregnancy. Although the incidence of low birth weight and prematurity was greater in these patients as compared with a large cohort of pregnancies, there was no tendency toward congenital malformation in the operated group. It was concluded that there is an increased risk of prematurity following intragravid surgical procedures requiring general anesthesia, which may be attributed to the underlying condition rather than the procedure or anesthetic itself (40,166).

Other considerations involving anesthesia during pregnancy include timing of semiurgent procedures that may not be postponed until parturition. There is evidence that nonobstetric surgical procedures are most safely performed during the second trimester owing to the increased risk of spontaneous abortion during the first trimester and induction of premature labor when procedures take place near term (108).

A related issue is the diminished requirement for both local and general anesthetics during pregnancy (149). Thus dosages of inhalation anesthetics such as halothane and isoflurane should be reduced in pregnancy to compensate for the sedative effects of progesterone (153,171,194). Likewise, the requirement for local anesthetics is decreased during the first trimester because of increased cell membrane receptor sensitivity to these agents, again a progestational-mediated phenomenon (53,73).

CONCLUSION

Part of "5 - MANAGEMENT OF UROLOGIC PROBLEMS IN PREGNANCY "

Urologic problems during pregnancy are often undertreated because of unfounded fears of causing fetal harm. An understanding of pathophysiologic changes in the urinary tract, as well as appropriate use of antimicrobials, anesthetics, imaging studies, and invasive procedures, will lead to resolution of most such problems while providing a margin of safety for both mother and child.

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6
UROLOGIC LASER SURGERY

Douglas F. Milam

Joseph A. Smith Jr.

D.F. Milam and J.A. Smith, Jr.: Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN 37232-2765.

Contents

The usefulness of an individual surgical laser is predicated by the unique tissue effect generated by thermal transformation of light energy. Lasers can be used to coagulate, incise, or vaporize tissue and, under certain circumstances, provide a combination of these processes. Selective absorption of laser energy by the target tissue is possible, thereby increasing the efficiency of therapy and decreasing the risk of side effects. The transmission of laser energy by small, flexible optical fibers facilitates energy delivery either directly or through an endoscope. Adaptations allowing side firing and diffuser tip emission of laser energy have further expanded the therapeutic capabilities for surgical lasers.

This chapter reviews the pertinent aspects of laser history, physics, and tissue interaction. To safely use laser energy, the surgeon must have an adequate understanding of methods to manipulate and influence tissue effects. Specific urologic applications of laser surgery are discussed in detail. No written document can be all-inclusive; nevertheless, detailed recommendations are provided for individual urologic problems in an effort to be a practical reference for the clinical surgeon.

LASER PHYSICS

Part of "6 - UROLOGIC LASER SURGERY "

Although the concept of stimulated emission of radiation was hypothesized by Einstein in 1917, the first beam of laser light was not generated until 1960 (69). Mulvaney and Beck used ruby laser and carbon dioxide (CO_2) lasers in urology and found them to have minimal value in destroying kidney stones but projected possible use for tumor ablation (91). It was not until the development of the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser and a suitable fiber delivery system that lasers began to play a role in urologic surgery.

To safely and effectively apply laser energy as a surgical tool, a basic understanding of laser physics and tissue effects is essential. The tissue-destructive properties of a laser beam can be therapeutically beneficial if properly used, but they can also produce unique complications if misdirected or applied with inadequate knowledge or experience.

The word *laser* is an acronym for “light amplification by stimulated emission of radiation.” White light from an incandescent bulb is a divergent mix of multiple wavelengths (colors). In contrast, laser light consists of nearly a single wavelength (monochromatic) that travels in a unidirectional manner (collimated) and can be deflected for projection onto tissue surfaces. In theory, the beam is nondivergent, although the angle of divergence from surgical laser fibers is at least 5 degrees and often much greater.

Surgical lasers are powered by electricity, which is used to ignite a flashlamp. Atoms of the active medium in the laser resonator are energized from the ground state to an excited state by photons produced by the flashlamp. When the atoms spontaneously decay to the ground state, a photon of specific wavelength is emitted (Fig. 6.1). The spontaneously emitted photon interacts with an excited-state atom, stimulating it to decay, and emits a second monochromatic photon. Because the original incident photon is also released, stimulated emission of radiation involves a factor of two energy gain with each atomic interaction (Fig. 6.2). A totally reflecting mirror at one end of the laser cavity and a partially reflecting mirror at the other preserve photons within the resonator. Photon reflection through the laser resonator substantially increases laser output because photons have greater opportunity to stimulate excited-state atoms to decay. Photons exit the resonator as a nearly nondivergent beam through the partially reflecting mirror at one end. The laser beam may pass directly from the laser or be coupled to a flexible, fused-silica glass optical fiber.

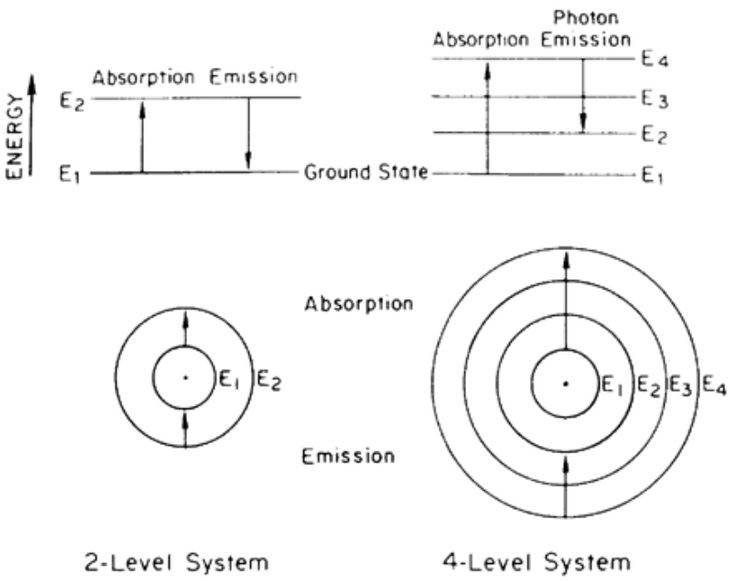

FIGURE 6.1. Diagram of energy states corresponding to electron energy levels. Laser wavelength is directly related to the energy released by electron decay from the excited to the ground state.

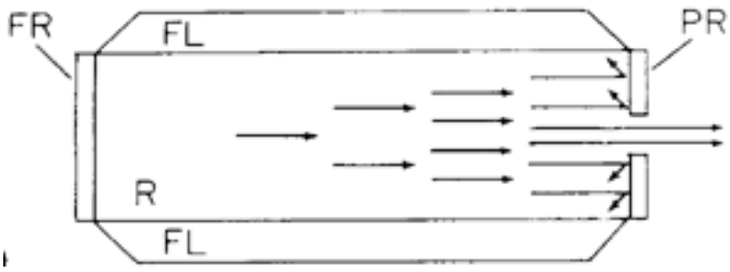

FIGURE 6.2. Laser design and energy gain. FL, flash lamp; FR, fully reflective mirror; PR, partially reflective mirror; R, laser resonator rod.

The active medium, that is, the source from which the photons are emitted, determines the wavelength of a particular laser. It may be a gas (CO_2, argon), a liquid (rhodamine-B, coumarin green), or a solid [neodymium, potassium titanyl phosphate (KTP)].

In general, minimum modifications are necessary to prepare an operating room or cystoscopic area for laser use. Electrical outlets [220 V (three-phase), 50 amp], ideally with isolated transformers, are required for argon and some older or high-energy Nd:YAG lasers. A 206-V (single-phase), 50-amp wall power source is optimal for most Nd:YAG, holmium, and KTP lasers. A few lower-power devices such as diode lasers, CO_2 lasers, and some newer Nd:YAG lasers require only a 110-V power source. When planning an operating room for laser surgery, one should have all three of the power outlets near each other in a convenient location. This includes a high-amperage 110-V power source; a three-phase 220-V, 50-amp power source; and a single-phase 206-V, 50-amp power source.

Lasers generate a large amount of waste heat that must be removed from the resonator cavity to prevent overheating. All currently available urologic lasers use an internal radiator and fan for cooling. Very-high-energy systems and older medical lasers may require cooling water obtained through a hose connected to a running water source. A wastewater drain is also required if external cooling water is used. Externally cooled systems are cumbersome and have limited portability.

Access to the operating room should be controlled to prevent accidental entry during laser use. Protective shades should cover all windows. As with any procedure using electrically powered equipment, the operating room floor

should be kept as dry as possible. Deflection of the laser beam into the eye can produce retinal injury with the Nd:YAG, argon, and KTP lasers and a corneal burn with the CO_2 or holmium laser. Therefore eye protection is mandatory for all persons in the operating room during laser use. Typically, glasses or goggles with green-tinted lenses are used for the Nd:YAG laser, amber lenses for the argon and KTP lasers, and clear lenses for the CO_2 and holmium lasers. Newer, more expensive clear lenses are available to protect the eye from Nd:YAG and KTP laser energy. During endoscopic laser surgery, the use of either a solid-state CCD camera or a wavelength-specific lens cap over the eyepiece of the telescope may suffice once the fiber is inserted into the cystoscope or laparoscope. One should never underestimate the amount of laser light that can be reflected backward from the end of the fiber through the cystoscope toward the surgeon's eye.

TISSUE EFFECTS OF LASER ENERGY

Part of "6 - UROLOGIC LASER SURGERY "

Tissue Optical Properties

Tissue optical properties control the transformation of laser light energy into heat (124). Cellular destruction generally is not evident when tissue temperatures less than 60°C are maintained for only a few seconds. Above 60°C, protein denaturation ensues, although minimum volatilization and tissue vaporization occur below 100°C. Above 100°C, cellular water evaporates and charring and tissue vaporization are observed.

Several important factors influence the extent of thermal destruction that occurs when a laser beam is projected onto tissue surfaces. The most easily controlled factor is laser wavelength. Body tissues contain chromophores, such as hemoglobin, that preferentially absorb certain wavelengths of light. The absorption characteristics of a particular laser wavelength depend on the relative tissue absorption and can vary significantly from one wavelength to another.

Absorption and scattering of laser light are important in determining the extent of tissue injury during laser surgery. As tissue is irradiated, light traveling through the tissue is attenuated by absorption and scattering. The proportionality constant describing the amount of light attenuated by absorption is the absorption coefficient (μ_a). The constant describing the attenuation of light due to scattering away from the direction of propagation is the scattering coefficient (μ_s). A third parameter, the anisotropy coefficient (g), describes the fraction of light scattered into any given direction and is assumed to be the average cosine of the scattering angle. These three coefficients are referred to as the *optical properties.* The propagation of light in tissue depends on three dimensionless parameters, one of which has already been discussed (g); the other two are based on the absorption and scattering coefficients. These are the albedo (a) and the optical depth (τ), defined as follows:

$$a = \mu_s/(\mu_a + \mu_s)$$

and

$$\tau = d(\mu_a + \mu_s)$$

where d is the sample thickness.

Because the distribution of light in tissue depends on tissue optics, much research on measuring the optical properties of tissues has been conducted and several methods have been introduced (98,123,127,130). A study of the optical properties of rat prostate tumor revealed values of 0.05 mm^{-1}, 27.0 mm^{-1}, and 0.98 for μ_a, μ_s, and g, respectively (4). Scientific studies into the tissue effects of various laser treatments must consider these factors.

Energy Density

In addition to wavelength and angle of incidence, other parameters can be used to predict and, to some extent, control the tissue effects and depth of penetration of a particular laser, including energy density. Stated simply, energy density is the amount of energy delivered to a given area of tissue. It is determined by the following formula:

Power (Watts) × Duration (seconds)/Area^2 (cm^2)

The power output of a particular laser is controlled from the instrument panel. Duration can be modified by controlling the time length of a particular pulse or by varying the speed with which the beam is moved across the tissue surface.

An influential component of the formula for energy density is the size of the treatment area. Treatment area is a function of offset distance and divergence angle:

Area = π × [Offset distance × tan(Divergence angle/2)]^2

Surgical laser fibers with a wide angle of divergence produce a lower energy density than nondivergent fibers by treating a larger surface area or spot size with the same amount of energy. The distance between the fiber tip and the tissue surface also influences the energy density by markedly changing the treated surface area. Contact techniques increase energy density by limiting the treatment surface area.

The angle of divergence from the fiber tip is unique to each device. The end-fire probes used over the last decade have an angle of divergence of only 5 to 15 degrees. Tissue injury from short-duration (2 to 3 seconds), high-energy density exposure may extend for several centimeters. Widely divergent beams (up to 90 degrees) produce a much lower energy density. Long-duration (60 to 90 seconds), low-power (40 to 60 W) exposure with these fibers can coagulate a large volume of tissue with coagulation depths of over 1 cm.

Optical properties of tissue have been shown to be temperature dependent. This is of concern because an increase in the absorption or scattering coefficient prevents light from penetrating deeper into the tissue, thus compromising laser treatment. Chambettaz and colleagues (21) measured temperature-dependent changes in total reflectance and transmittance while irradiating excised arterial wall specimens at 383 W/cm^2 and 191 W/cm^2. They found that with the higher irradiance, transmittance decreases rapidly with increasing temperature up to 51.4°C, followed by a rapid increase in transmittance as temperatures continued to increase. Reflectance measurements showed inverse responses. When the tissues were irradiated at 191 W/cm^2, changes in transmittance and reflectance occurred more slowly with their extrema occurring at 44.1°C. Another study reported a fourfold increase in the scattering coefficient (0.43 to 1.74 mm^{-1}) of porcine myocardium during coagulation, whereas the absorption coefficient remained relatively unchanged (0.04 to 0.05 mm^{-1}) (31). Splinter and colleagues (123) also demonstrated a twofold to threefold increase in the reduced scattering coefficient in canine and human coagulated myocardial tissue. Pickering and colleagues (99) found that the scattering coefficient of rat liver increased while the absorption and anisotropy coefficients decreased during tissue heating. They also noted that the rates of change in these properties were proportional to the amount of energy used to heat the samples.

Coagulation

When tissues are heated to less than 60°C for only a few seconds, tissue warming without irreversible damage is observed. Between 60° and 100°C, permanent protein denaturation occurs, causing tissue coagulation. Although this is irreversible and destructive, immediate tissue removal does not occur. The thermally injured tissue either sloughs or is reabsorbed by the body's inflammatory mechanism. Transurethral laser treatment of the prostate causes coagulation and delayed slough of tissue for 4 to 8 weeks (75). Tissue sloughed from the urinary tract is amorphous and does not cause urinary retention. Hemostasis both during and after treatment usually is excellent because the coagulation process extends to blood vessels within the volume of treated tissue. Poorly absorbed wavelengths, such as the 1,064-nm light produced by the Nd:YAG laser, primarily cause tissue coagulation. Coagulation rather than vaporization may be favored when using a given wavelength by lowering the energy density. In general, low-power, long-duration laser exposure through a large irradiated area such as that produced by diode lasers for interstitial laser prostatectomy increases the amount of coagulation and the depth of tissue injury compared with higher-power laser sources used for a short duration.

Vaporization

When high tissue temperatures (generally above 100°C) are achieved, immediate tissue vaporization ensues. Surface carbonization may be observed and a smoke plume generated. Some degree of coagulation accompanies carbonization, so hemostasis is usually adequate, although less than that observed with pure coagulation techniques. Carbonization significantly increases the tissue absorption coefficient, leading to further marked tissue heating in the small area of carbonized tissue. The total coagulation depth may actually be decreased by absorption of nearly all the laser light at the tissue surface.

Vaporization is more difficult to achieve under water than in an air environment. This is particularly pertinent for urologic endoscopic use because the irrigating fluid causes surface cooling. If desired, vaporization is facilitated by using highly absorbed wavelengths (CO_2 or holmium lasers), using a high laser power output, applying the energy pulse over a very brief period, or decreasing the treated surface area (as with contact tips).

Physics of Laser Prostatectomy

Side-firing Laser Prostatectomy

Side-firing laser coagulation prostatectomy involves disposition of laser light into tissue. The prostate, like other bodily tissues, is somewhat transparent to incident light. Photons of laser light experience three possible interactions during passage through tissue. Initially, photons pass through tissue in the original incident direction. This is termed *through transmission.* Interaction with tissue causes photons to be extensively scattered in directions other than the original incident direction. This process is wavelength dependent and causes the beam to form a plume with lateral width. Once a photon is *absorbed* by tissue, its energy is liberated as heat. Thermocoagulation will occur if enough laser energy is used to achieve tissue temperatures of 60° to 70°C for more than a few seconds.

Many factors affect tissue temperature distribution, including laser, optical, and thermal parameters. Laser parameters consist of wavelength, power, spot size, beam profile, and scanning velocity. The optical parameters of importance are surface reflection and the tissue absorption and scattering coefficients. Thermal parameters are the characteristics of the tissue, such as thermal conductivity, specific heat, tissue density, and convective heat transfer coefficient. Of these, thermal and optical properties depend on temperature and wavelength.

Tissue optical characteristics define the effect of a specific laser delivery system. Three parameters are most important: energy loss caused by urethral reflection, tissue absorption, and scattering coefficients. Loss caused by urethral reflection is largely unavoidable, although there is some evidence that incident beams normal to the tissue surface

transmit a higher portion of their energy into tissue-oblique beams.

Tissue absorption for a given wavelength is estimated by the Lambert-Beers law: $I_x = I_0 e^{-ax}$, where

I_0 = Incident beam intensity

I_x = Beam intensity at tissue depth × centimeters

a = Tissue absorption coefficient (μ_a)

x = Depth (cm)

The relatively low absorption coefficient at the 1,064-nm wavelength (Nd:YAG) permits deep tissue penetration and therefore deeper tissue heating and coagulation (Fig. 6.3). The greater absorption coefficient at the 532-nm (KTP) or the 633-nm wavelength (helium:neon) causes rapid tissue absorption. Absorption of most incident energy in a relatively small volume of tissue will cause rapid heating of superficial tissues. Several studies have demonstrated the wavelength dependency of the absorption coefficient in a typical biologic tissue (22,49). This is the principal mechanism causing differing tissue effects of lasers with different wavelengths. Rapid superficial vaporization seen with the CO_2 laser is a consequence of the tissue absorption coefficient being greater than 1,000 times that of the Nd:YAG laser operating at 1,064 nm.

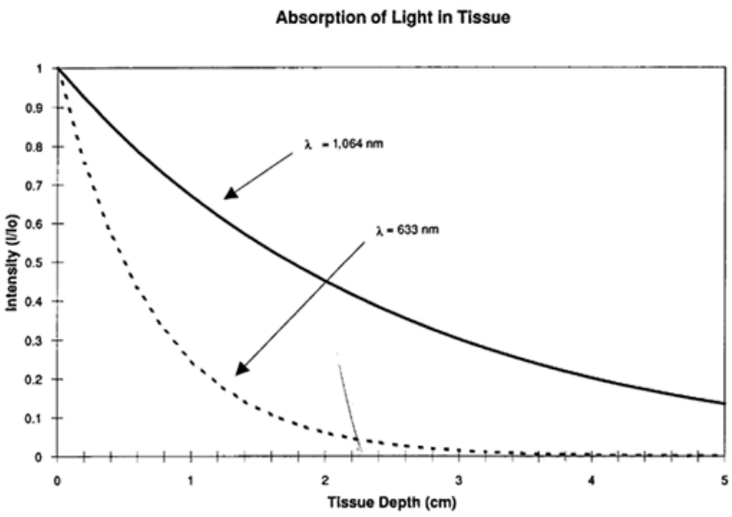

FIGURE 6.3. Relative intensity of light passing through tissue in canine prostatic tissue from two clinically important laser sources. Only the effect of the absorption coefficient (μ_a) is considered here.

Surface carbonization is one clinically important factor that markedly affects the tissue absorption coefficient. Carbon black is a near-perfect absorber of all visible and infrared wavelengths. Surface charring increases the absorption coefficient (μ_a) by several orders of magnitude. During Nd:YAG laser prostatectomy, surface char can alter the treatment session producing a superficial effect similar to the CO_2 laser. Surface charring should be avoided if possible during a side-firing coagulative treatment session. This has been theorized to be the causative mechanism of why, in one series, exposure at 40 W proved clinically superior to exposure at 60 W (54).

Tissue heating is also influenced by the light-scattering coefficient described previously (22,49,95). Scattering measures the propensity of the laser photons to reflect within tissue (Fig. 6.4). This process causes divergence from the original beam path and therefore increases the width of tissue injury from a given incident beam (100). Both laser wavelength and tissue temperature increase the scattering coefficient. The initial importance of light scattering at physiologic temperature during Nd:YAG lasing is limited. However, increasing tissue temperature during a treatment session greatly increases the scattering effect (94). Coagulated tissue volume is substantially increased because of tissue scatter when using the Nd:YAG laser.

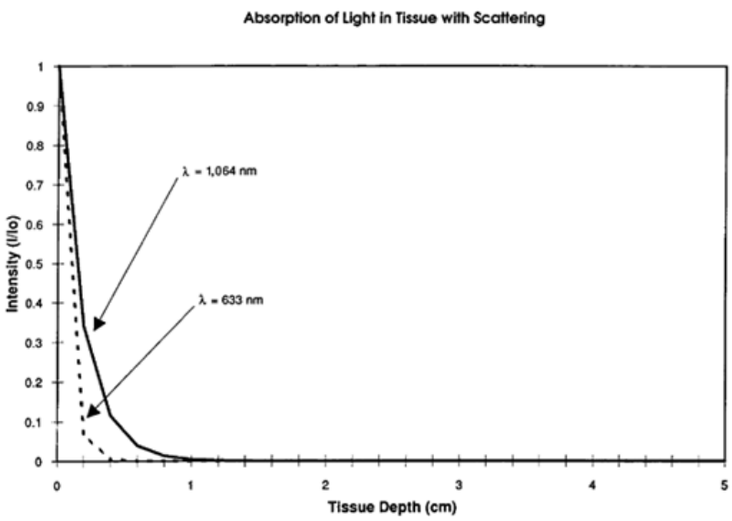

FIGURE 6.4. Laser scattering plays a critical role in depth-dependent attenuation of laser light. This figure describes light passage through canine prostatic tissue of two clinically important laser sources. Comparison with Fig. 6.3 clearly demonstrates the importance of light scattering.

Laser parameters, such as wavelength, power, spot size, beam profile, and scanning velocity, also substantially affect tissue treatment (102). The importance of wavelength is largely determined by tissue absorption and scattering coefficients as discussed earlier. Although near-infrared light

from the Nd:YAG (1,064 nm) laser provides good results, other sources in the range of 800 to 1,000 nm may also be used. High-power (25 to 50 W) diode lasers are competitive alternatives to the continuous-wave Nd:YAG laser source. Although diode lasers may achieve results comparable to the volume of prostatic coagulation achieved using the Nd:YAG laser, exposure at these wavelengths may not achieve superior clinical or experimental results. Other commonly available medical laser sources (CO_2, holmium, alexandrite, KTP, and argon) are too strongly absorbed by tissue (high μ_a) to be useful for side-firing, noncontact coagulation prostatectomy.

Laser power is an important determinant of the extent of tissue injury. Coagulation prostatectomy requires tissue temperatures of 60° to 70°C for about 3 seconds to effect reliable protein denaturation. It is important to differentiate between temperature and heat. The relationship between heat, or enthalpy, and tissue temperature is described by the following equation:

ΔH = (Enthalpy) the amount of heat in tissue = (Cp)(ΔT)

where *Cp* is the tissue heat capacity and Δ*T* is the tissue temperature change. From this equation, one could conclude that increased power would yield increased tissue coagulation. Surface effects negate this relationship, however. Extreme surface heating, as seen in high-power applications, causes surface charring. In the presence of char, laser light transmission deep into tissue is limited because of surface absorption. To overcome this effect, laser power must be increased substantially.

The extent of surface heating at a given power is also a function of spot size. Indeed, power density (power divided by spot size) and the prostatic optical absorption coefficient are the critical determinants of surface tissue heating. Side-fire laser beam profile is often considered analogous to spot size. This is an oversimplification based on the assumption that laser power is uniformly spread throughout the incident spot (25). Data have shown marked variations in visible laser beam profile between different side-firing devices. These data are useful for determination of optimal exposure techniques. Narrow beam–profile devices require different exposure techniques than those with widely divergent beams.

The importance of movement of the laser beam during prostatectomy is only now being understood. Initial laser prostatectomy studies were performed with a static exposure technique using a divergent laser fiber (low power density) (33,54). This technique treated a large volume of tissue, minimized surface charring, and facilitated laser scattering. Static treatment is clearly not appropriate for many of the newer fibers with a narrow divergence angle and, consequently, smaller spot size.

Several devices with narrow divergence angles have less than a 3-mm spot size. Laser light scattering at 1,064 nm throughout prostate tissue is not sufficient to ensure thorough coverage of an entire prostate without probe movement.

Analytic and finite element mathematical models for predicting optimum tissue exposure (94) predicted the volume of coagulated tissue (greater than 70°C) to be 36% to 109% greater with a laser scanning rate of 1 mm per second than an identically powered laser source where the beam is stationary for 60 seconds. Intuitively, the optimal scanning-rate speed would be as slow as possible without causing tissue charring.

In addition to a slow scan rate, optimal treatment depends on the initial static “dwell” period. During probe movement, tissue ahead of the probe is heated because of forward scatter of the laser light. Tissue treated at the beginning of a laser pass is not exposed to energy from prior forward scatter. Undertreatment of the initial region may occur unless the fiber is held static for 2 to 4 seconds before initiating movement. Mathematical modeling techniques have predicted the optimal dwell period (90). These data indicate that a dwell period of approximately 4 seconds is optimal. Intuitively, however, one should dwell for as long a period as possible without creating tissue carbonization.

Contact Vaporization Prostatectomy

Contact vaporization prostatectomy differs considerably from the coagulation procedures described previously and from techniques that use a holmium laser to resect the prostatic adenoma. During contact vaporization, ablation occurs in real time creating an open prostatic fossa similar to transurethral resection of the prostate (TURP). During vaporization prostatectomy, the structural components of tissue are carbonized and much of the water component is vaporized. Equipment unique to contact laser prostatectomy is required for the procedure.

Contact vaporization prostatectomy is most commonly performed using the Contact Laser system (SLT, Inc., Valley Forge, Pennsylvania). When using this system, a 7-mm diameter, round contact probe is threaded onto a 600-µm optical fiber (Fig. 6.5). A black, absorbent coating is deposited onto the probe surface during manufacture. This coating absorbs approximately 30% of the laser energy, causing intense probe heating. Contact between the hot probe and tissue produces tissue vaporization. Passage of laser energy through the probe into tissue further enhances vaporization and facilitates hemostasis because of subsurface tissue coagulation. The advantage of true tissue vaporization is not without cost. Contact prostatectomy requires considerably more time than coagulation techniques.

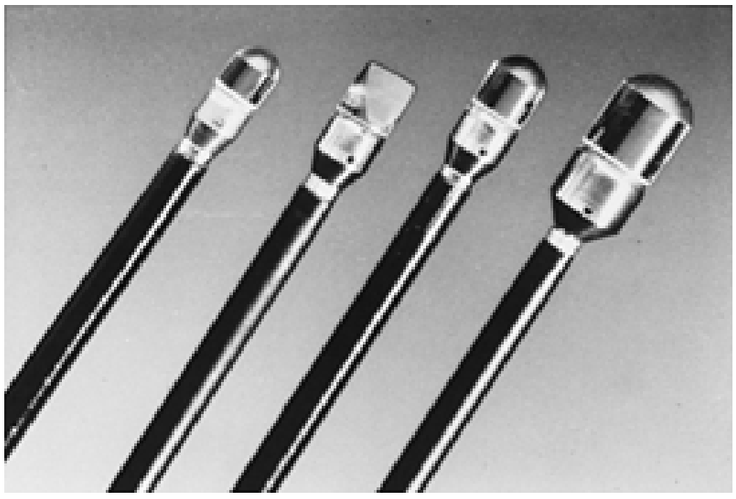

FIGURE 6.5. Contact laser prostatectomy devices. Reusable, fused-silica glass contact probes are threaded onto a semirigid, coaxial optical fiber. Several probe sizes are available; however, the larger probes produce more efficient tissue vaporization during contact laser prostatectomy.

Other Vaporization Techniques

Durable, side-firing laser fibers may also be used for tissue vaporization. Nonmetallic refractive fibers having a narrow divergence angle are used both in contact and slightly offset from tissue. Fournier and Narayan (35) have reported using the Ultraline fiber for contact and noncontact vaporization in the clinical and laboratory setting. These investigators reported superior vaporization when the fiber was used in contact with tissue because of the markedly increased power density during contact treatment. Fiber durability is an issue. The same authors reported consistent fiber tip etching at approximately 50,000 Joules (J) and recommended increasing laser output from 60 to 80 W to compensate for transmission loss at that point. Total device failure occurred after 150,000 J. Other nonmetallic fibers have not been tested as extensively in this application, but they may be useful. These data are particularly important in confirming the appropriateness of side-firing fibers for laser-vaporization prostatectomy. Physical laws involving the heat of vaporization of prostatic tissue apply to both the contact-probe and side-firing devices. Total energy requirements should be similar. Side-firing devices must be able to withstand at least 100,000 J to be useful for vaporization prostatectomy.

CHOICE OF LASER WAVELENGTH

Part of "6 - UROLOGIC LASER SURGERY "

Laser instruments differ primarily in the wavelength and pulse duration of the emitted light. Wavelength is a function of the chemical composition of the active medium in the resonator cavity, which may be a solid, liquid, or gas as described previously. In addition, a frequency-doubling crystal may be used to modify the wavelength of an existing laser source. An example of this is the KTP laser, which is a frequency-doubled Nd:YAG laser.

Argon Laser

Argon has several potential lasing lines between 488 and 514 nm. Light at this wavelength is poorly absorbed by water but strongly absorbed by body pigments, such as melanin and hemoglobin, and chromophores, such as hematoporphyrins.

Consequently, tissue absorption is intermediate between that of the poorly absorbed Nd:YAG and the strongly absorbed CO_2 laser. The selective absorption of argon energy by hemoglobin has led to its use for treatment of hemangioma. Commercially available surgical argon lasers have a relatively limited power output and generally can only be used for small (less than 1 cm in size) lesions. Use of argon lasers has been largely abandoned for treatment of superficial transitional cell carcinoma of the bladder. Other devices such as continuous-wave Nd:YAG, KTP, and holmium lasers are better suited for this application.

Argon Dye Laser

Dye lasers can be used to produce coherent monochromatic laser light over a wide range of wavelengths depending on the type of dye used. The argon-pumped dye laser uses an argon laser instead of a flashlamp to power a dye laser. By selecting the proper wavelength (choosing the proper dye), one can selectively excite a tissue chromophore. Hematoporphyrin derivative has been used in several studies because of selective uptake by carcinoma *in situ* in the bladder (15,16 and 17,42,101). Hematoporphyrin derivative is activated by wavelength-specific (630-nm) argon-pumped dye laser light. The use of an inefficient laser to pump another inefficient laser causes tremendous energy loss. For this reason, energy output of the argon-pumped dye laser is limited to 5 to 10 W. Most treatment protocols require bladder illumination time to be 1 hour or more. Research into selective absorption of chromophores by tumor cells and preferential laser destruction of those cells continues; however, these techniques have yet to find widespread acceptance.

Carbon Dioxide Laser

The 10,600-nm wavelength of a carbon dioxide laser is strongly absorbed by water. Thus the energy is rapidly absorbed at the tissue surface, creating high-temperature vaporization. The depth of CO_2 laser light penetration is limited, less than 1 mm. High-intensity vaporization coupled with superficial penetration can produce a scalpel-like effect. Carbonization will occur if the energy is applied to a cutaneous surface for more than a few seconds. A smoke plume is produced, and a dedicated smoke evacuator should be used if infectious material such as condyloma is being treated.

The relatively long wavelength of the carbon dioxide laser creates problems for transmission via flexible fibers. Wavelengths in the far-infrared position of the electromagnetic spectrum are absorbed by optical and most fiberoptic glass. Attempts have been made to develop cystoscopes using a series of reflecting mirrors. So far, however, a practical CO_2 laser cystoscope has not been developed, although specific optical devices to redirect the CO_2 laser beam have been designed for otolaryngologic applications. In urologic applications, the beam is delivered to tissue via a series of articulating arms and reflecting mirrors. CO_2 lasers have proven useful for first-line therapy of various lesions of the external genitalia and with open surgical applications.

Diode Laser

Diode lasers operate differently than the previously described lasers that generate laser light by illuminating a resonator cavity with a flashlamp. Monochromatic coherent light can be generated directly by semiconducting laser diodes. Low-power diode lasers are commonly used to read information from computer and audio discs. Diode lasers designed for urologic applications produce greater power than those found in consumer applications; however, maximum power output is less than that produced by most other laser sources. Current urologic diode lasers weigh less than 20 pounds, fit in a briefcase, and require only a 110-V electrical source. The most commonly used urologic application of the diode laser is transurethral interstitial laser therapy of the prostate. In this application, the laser is coupled to a fused silica glass fiber that incorporates a diffuser tip onto the distal end.

Holmium:Yttrium-Aluminum-Garnet Laser

The holmium:YAG laser emits light in the midinfrared region of the electromagnetic spectrum (2,100 nm). Unlike the continuous-wave lasers described previously, energy emission occurs in a rapid pulse over a few milliseconds. Holmium:YAG laser light is highly absorbed by water and produces explosive vaporization and cutting.

Several companies produce holmium lasers. All have pulse repetition rates of about 5 to 20 Hz, 3 to 5 J per pulse, each of which is delivered over approximately 500 microseconds. The light, invisible to the human eye, is readily transmitted through a flexible optical fiber. All manufacturers provide a range of optical fibers from 200 to 1,000 microns. The smaller fibers are particularly useful for ureteroscopic applications.

Unlike an electrohydraulic lithotripsy probe, the holmium laser fiber tip should be held in close approximation to the stone or tissue surface being treated. Otherwise, rapid attenuation of the laser light will occur because of absorption by water. When treating ureteral or renal stones, the clinician must take care to keep the fiber tip away from urothelial tissue. Unlike coumarin green-pulse dye lasers that were widely used in the 1990s, holmium laser light will cut ureteral tissue as well as fragment stones.

The hemostatic abilities of the holmium laser are less than a continuous-wave Nd:YAG laser because there is more vaporization of tissue. One should keep this in mind because once started, bleeding may be difficult to stop without switching to electrocoagulation. The holmium:YAG

laser has been extensively used for urinary tract stone fragmentation in addition to cutting and coagulation of soft tissue. Most urologists would agree that the holmium laser is the most used and most versatile laser for a wide range of urologic applications.

Potassium Titanyl Phosphate Laser

KTP lasers use a potassium titanyl phosphate crystal to double the frequency of Nd:YAG lasers, thereby producing 532-nm wavelength green light. Interaction of Nd:YAG light with the KTP crystal causes substantial energy loss. Therefore the energy output of the typical dual-wavelength laser in KTP mode is only approximately half that of the Nd:YAG mode. The 532-nm wavelength provides an intermediate level of vaporization and coagulation. The energy can be transmitted by the same standard optical fiber used for Nd:YAG treatment. Tissue effects are similar to those achieved with an argon laser, although greater power can be produced than with most surgical argon lasers. KTP lasers have been used for treatment of superficial transitional cell cancer in the bladder, ureter, and renal pelvis. In some circumstances, KTP lasers provide an increased safety margin compared with Nd:YAG lasers because of limited coagulation depth. However, treatment is slower than with Nd:YAG lasers, and treatment for large tumors may be more difficult. KTP lasers have also been used for treatment of external genital and urethral lesions.

Combined techniques for treatment of benign prostatic hyperplasia (BPH) using coagulating energy followed by vaporization of prostate tissue with a KTP laser have been described. Early studies clearly demonstrated the feasibility of this method; however, widespread acceptance of the technique did not occur because of the increased operative time and the need to use more than one modality. Higher-energy KTP lasers are now available that address these concerns.

Nd:YAG Laser

For many years since its introduction into clinical practice in 1979, the Nd:YAG laser was the most commonly used laser in urologic surgery. This continuous-wave laser produces an invisible 1,064-nm light that is nearly ideal for deep tissue coagulation. When used in a noncontact mode, tissue coagulation is complete and hemostasis is total. The Nd:YAG is the preferred laser source for coagulative destruction of vascular lesions of the urogenital tract. Because of this great utility, the Nd:YAG laser can be purchased coupled with a holmium laser source. Most urologic surgical laser applications can be performed using a single dual-wavelength Nd:YAG/holmium laser.

The active medium within the resonator cavity consists of neodymium atoms contained within a YAG lattice. The Nd:YAG laser emits invisible infrared 1,064-nm wavelength light. Light at this wavelength is poorly absorbed by water and body pigments. Because of poor absorption, the light penetrates deeper into tissue than other commonly used urologic lasers.

In a fluid environment, the poor absorption of the laser energy results in thermal coagulation of both surface and subsurface tissue. Structural and architectural integrity of the tissue is maintained. A certain percentage of the energy is transmitted through the target organ. Thus the thermal effects may extend to adjacent organs. After noncontact Nd:YAG laser treatment, hemostasis is usually total. The coagulated tissue takes on a white, fluffy appearance. The tissue sloughs secondarily over a several-week period, although complete healing may take up to 3 months (75).

CLINICAL APPLICATIONS OF LASER SURGERY

Part of "6 - UROLOGIC LASER SURGERY "

The thermal effects of laser energy have been used for the treatment of a variety of urologic lesions. In certain situations, lasers do not appear to be as effective as standard therapy or offer no particular advantages. In other circumstances, lasers provide substantial practical and therapeutic improvements over other treatment methods. The unique physics and tissue effects of laser energy have created new treatment opportunities for selected problems in urologic surgery. Table 6.1 indicates which lasers are used for various problems in urologic surgery.

	CO_2 Laser	KTP Laser	Nd:YAG Laser	Pulse Dye Laser	Holmium Laser
Genital condylomata	***	**			
Urethral/bladder condylomata		**	***		*
Penile carcinoma	*	**	***		
Urethral stricture		**	**		***
TUIP		**	**		***
Coagulation prostatectomy			***		
Prostatic resection		**	**		***
Urothelial hemangioma			***		
Bladder calculus				**	***
Bladder carcinoma		*	***		**
Ureteral/renal calculus				***	***
Ureteral carcinoma		***	**		*
Renal pelvic carcinoma		**	***		*
Calyceal diverticulum		*	***		*

Most frequently (***), frequently (**), and less frequently (*) used applications of urologic lasers.

TABLE 6.1. UROLOGIC LASER APPLICATIONS

Urinary Tract Stones

Successful treatment of urinary tract stones is the single largest reason for the popularity of the holmium laser. The holmium laser improved on the previously available coumarin green-pulse dye laser by producing more rapid and complete stone fragmentation. The coumarin green laser had the important limitation of frequently not fragmenting the hardest calcium oxalate monohydrate stones. With the holmium laser, this limitation has been overcome.

One group of investigators examined the end products of stone fragmentation (129). These authors found that after holmium laser treatment, calcium oxylate monohydrate produced calcium carbonate, cystine yielded cysteine and free sulfur, calcium phosphate produced calcium pyrophosphate, magnesium ammonium phosphate produced ammonium carbonate and magnesium carbonate, and uric acid yielded cyanide. The same group later examined in detail the conversion of uric acid to cyanide (126). No reports of adverse health consequences of cyanide exposure have been reported to this date.

Tissue cutting in addition to stone fragmentation is the principle disadvantage of the holmium laser for work in the ureter. Ureteral injury is avoided by careful placement of the optical fiber tip onto the stone surface and away from

the ureteral wall. Although laser energy settings for stone fragmentation are less than those used for transurethral incision of the prostate (TUIP) or most other cutting procedures, energy at these settings can do considerable damage to the ureteral wall if placed in direct contact. Laser energy settings for ureteral stone fragmentation typically range between 1 and 2 J with pulse repetition rates of between 5 and 15 Hz. Even the hardest stones fragment successfully with this amount of energy (65).

Some care should be taken to avoid head-on holmium laser exposure to ureteroscopic guidewires. Freiha and colleagues (36) demonstrated that it is possible to cut a guidewire with holmium laser energy. However, the authors found that the energy had to be applied directly and from a distance of less than 1 mm.

Renal and bladder stones are also effectively fragmented with the holmium laser. Given the larger size of those stones and the more open operative space, energy settings are often increased when treating renal and bladder stones. Treatment is more time efficient if peripheral stone tissue is treated first. One should avoid the temptation to break large stones into several pieces early in the treatment session. By staying on the periphery of a stone, one can continuously break off the superficial layers into dust or sand. Treatment continues until the stone has been completely ablated. Further details of stone management with the holmium laser are presented elsewhere in this text.

External Genitalia

Laser treatment of lesions of the external genitalia usually uses the CO_2, Nd:YAG, or KTP laser. Direct application of CO_2 laser energy to lesions of the external genitalia is performed either with a hand piece and a series of articulating arms and mirrors or a coupling microscope. Fiber-conducted light from a KTP or Nd:YAG laser can be directed using a hand piece. The choice of laser is based on the desired depth of tissue destruction. CO_2 lasers produce only superficial vaporization, KTP lasers produce a moderate level of coagulation, and Nd:YAG lasers produce the greatest depth of coagulation for tumor treatment.

Condyloma Acuminatum

Lasers are well established as effective treatment for condyloma acuminatum. CO_2, Nd:YAG, argon, and KTP lasers can be used, although most clinical experience is with CO_2 and Nd:YAG lasers (37,47). With a CO_2 laser the lesion is vaporized, and large amounts of smoke are produced. Proper smoke evacuation equipment must be available to prevent inhalation of viral particles that may be in the smoke plume. Application of laser energy to the skin is painful, and local anesthetics are injected subcutaneously before treatment. For large or more extensive lesions, a penile block may be preferable. The skin is cleansed with an iodine-based or equivalent compound. The power output chosen is based to some extent on the size of the lesion, but the lowest output that successfully vaporizes the condyloma is desirable. Usually, 5 to 10 W of power will suffice. Rosemberg and colleagues (105) described a technique of vertical, horizontal, and oblique application of the beam to ensure complete removal. As successive portions of the condyloma are treated, the carbonized surface is removed by wiping with a saline-soaked sponge. Bleeding does not occur until

the deeper layers of the dermis are reached. Care should be taken to avoid a full-thickness skin injury. The white dermal layer underlying the condyloma should be left intact. An antibacterial cream may be applied topically after treatment, but analgesics are usually unnecessary. Lesions of the urethral meatus can be treated satisfactorily with a CO_2 laser and nasal speculum, but the lack of a fiber delivery system has precluded treatment of more proximal urethral lesions.

Very large lesions should be treated in stages to prevent a large area of full-thickness burn. Bridges of either normal or pathologic tissue should remain intact between large treatment areas even if this commits the patient to a second treatment session. Untreated tissue bridges will hasten the healing process and lessen the chance that skin grafting of a large area will be required. In most patients, excellent cosmetic results can be anticipated.

Using the CO_2 laser, Lundquist and Lindstedt (68) treated more than 150 patients with condyloma resistant to podophyllin therapy. Ninety-five percent of patients were reported cured, although some required a second treatment. Similar results have been reported by Bellina (13). Rosemberg (103) found an 88% cure rate in 61 patients undergoing only a single treatment. More recently, others have used erbium and pulse dye lasers for condylomata (48). Tissue ablation with the erbium laser is extremely superficial, more so than the CO_2 laser. This laser offers a potential benefit relative to existing therapy. One other benefit is that the plume from erbium laser treatment apparently does not contain viable viral particles (48).

The Nd:YAG laser also has been shown to be effective in the treatment of condyloma acuminatum (72). Unlike after CO_2 laser treatment, the lesions do not undergo vaporization. Rather, they are coagulated and may be removed with forceps or allowed to slough secondarily. Treatment depth may be more difficult to control than with the CO_2 laser, but a treatment session proceeds more rapidly when large lesions are encountered.

Nd:YAG laser energy is applied with a power of 10 to 15 W until the lesion turns a pale white color. The epithelium surrounding the lesion should be treated for a distance of 2 to 3 mm to destroy the virus in adjacent areas. Care should be taken to avoid excessive energy density, which can result in third-degree thermal injury and full-thickness skin slough. One must also consider the location of the dorsal neurovascular bundles and underlying corporal bodies when using the Nd:YAG laser.

The oncogenic potential of certain subtypes of the human papillomavirus has been reported. Microscopic lesions can often be detected on the penis of sexual partners of women with carcinoma or carcinoma *in situ* of the cervix (6,8). Five percent acetic acid applied to the penis for 5 minutes on a soaked gauze wrap produces a white discoloration of small human papillomavirus lesions that can then be detected by examination with magnifying loupes (34). Carpiniello and associates (20) found a high recurrence rate of these lesions after CO_2 laser treatment despite the use of topical 5-fluorouracil cream after laser treatment. This and other studies have demonstrated that condylomata are difficult to eradicate. Previous studies probably overstated the cure rate by a substantial margin.

Carcinoma of the Penis

Laser treatment of selective carcinomas of the penis may avoid the need for partial penectomy in some patients. Although topical application of 5-fluorouracil cream seems to be the preferred initial treatment for erythroplasia of Queyrat, lasers have been effective in eliminating resistant lesions (70). Because this is a premalignant lesion that does not invade deeply into tissue, lasers with superficial penetration produce sufficient treatment. Good results have been achieved with the CO_2 laser.

For an invasive carcinoma, a greater depth of coagulation is advisable (Fig. 6.6). Appropriate patient selection is the key element determining success. Pretreatment biopsies of the lesion should be taken in order to assess tumor depth. In most situations, the Nd:YAG laser is preferable. Energy should be applied to the entire lesion, as well as the surrounding, more normal-appearing skin. Generally, 25 to 35 W of energy is used with the Nd:YAG laser. Iced saline applied to the surface of the lesion during treatment helps cool the superficial tissues and prevent carbonization. This avoids a smoke plume and increases the effective energy penetration because char at the tissue surface absorbs laser light. Treatment should continue until all areas of the lesion are coagulated. The tissue surface will remain intact.

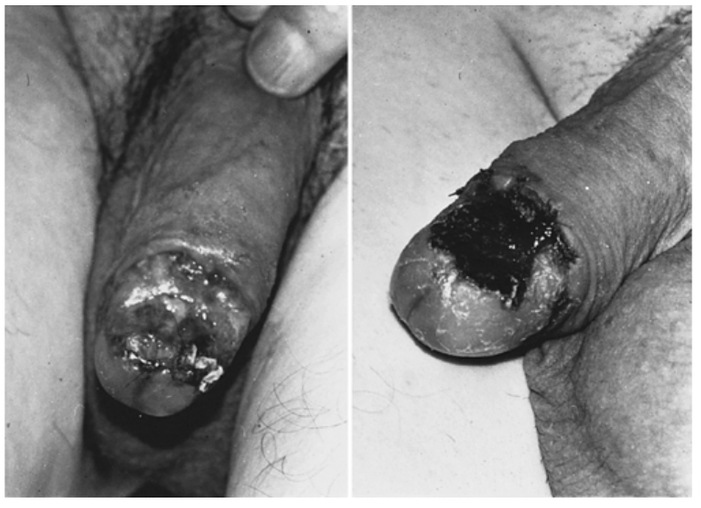

FIGURE 6.6. A: Invasive squamous cell carcinoma of the penis. **B:** After Nd:YAG laser treatment, the lesion has a coagulation eschar that may take up to 6 weeks for complete healing.

After treatment with the Nd:YAG laser using these energy parameters, a third-degree thermal injury is created. The lesion is usually painless, but slough of necrotic tissue and drainage may persist for up to 2 months. Eventually, reepithelialization will occur unless residual cancer is present. The necrotic lesion may result in secondary adenopathy, making the assessment of the inguinal lymph nodes during the healing process more difficult. Cosmetic results are good considering the other options. Most patients are left with a shallow divot and normal epithelial covering.

Results of laser treatment of carcinoma of the penis indicate that treatment generally can be successful in properly selected patients. Malloy and colleagues (73) have treated 23 patients with the Nd:YAG laser for carcinoma of the penis. Six patients had T_{is} and no evidence of recurrent cancer an average of 34 months after treatment. Of 15 men with T_1 tumors, 12 were cancer free with a mean follow-up of 31 months. Two men with T_2 cancer had reduction of the tumor mass but were not cured. Hofstetter (44) treated 17 patients with T_1 and T_2 tumors. With follow-up of 3 to 6 years, only one patient had died from metastatic disease.

The obvious advantage of laser treatment of penile cancer is preservation of the phallus. Although efforts to avoid partial or total penectomy ultimately should not compromise

the chances for cure, not all patients with squamous cell cancer require amputation. Laser therapy plays an important role in the management of properly selected patients with carcinoma of the penis.

Urethral Stricture Disease

Lasers have been extensively used for incision and coagulation of urethral scar tissue. The Nd:YAG laser has been used with or without contact tips. More recently, the holmium laser has been extensively used for both incision and ablation of urethral stricture tissue.

Animal data suggest that tissue treated with Nd:YAG laser light heals with more elastic fibers and less collagen deposition than comparable electrosurgical injury. In addition, there is less bleeding into the tissues, with possibly less secondary scarring. These ideas have formed the basis for laser treatment of benign urethral strictures. There is no doubt that laser energy can cut urethral strictures, but delayed results have been mixed.

Holmium:YAG laser properties are nearly optimal for urethral stricture incision. Under direct vision, the fiber tip is placed immediately adjacent to the scar. One should not push the optical fiber tip into tissue because that maneuver may result in deep bleeding that cannot be stopped with further laser energy. Laser power is set at 1 to 3 J per pulse and the pulse rate at about 5 Hz. Absorption of holmium laser light by superficial scar tissue results in cellular disruption and cutting. Given appropriate power, tissue injury is limited to a 1- to 2-mm coagulation zone below the cleavage zone. Cutting proceeds until the appropriate depth is reached. Holmium laser urethrotomy produces less deep tissue injury than Nd:YAG laser urethrotomy.

Several techniques for Nd:YAG laser treatment of urethral strictures have been described. A metal guidewire is inserted through the urethral lumen to maintain orientation. Circumferential laser energy may be delivered to the entire stricture in anticipation of secondary slough of this tissue and normal healing (Fig. 6.7). With this technique and no postoperative Foley catheter, Smith and Dixon (120) reported a recurrence rate of 56% at 6 months and considered this method generally to offer no advantages over standard therapy. Shanberg and Tansey (113) described radial incisions through the stricture with direct contact between the fiber and the tissue. Results in five patients with bladder neck contractures were good. However,

recurrences were noted in 58% of the patients with urethral strictures.

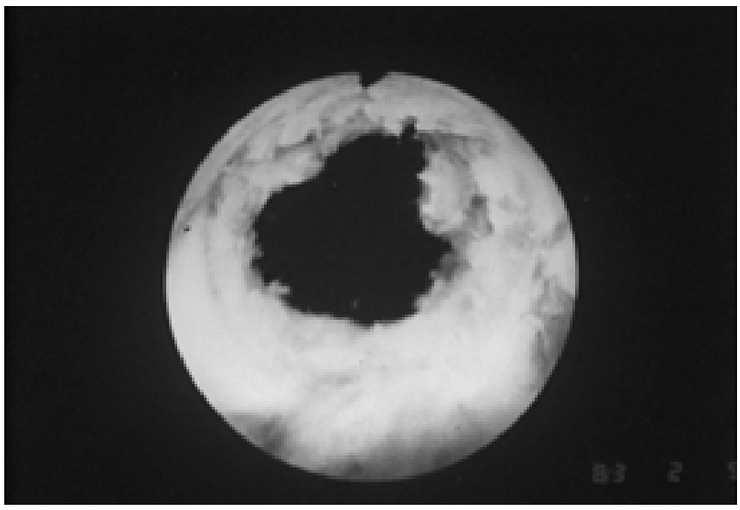

FIGURE 6.7. Urethral stricture after circumferential Nd:YAG laser application. The coagulated tissue sloughs secondarily.

Merkle (87) described short-duration (0.2-second) pulses of 25 W placed at multiple sites of the stricture. A catheter was left indwelling for 2 weeks. Successful results (no recurrence of the stricture) were reported in 90% of patients, but others have not reproduced this experience.

Tips for laser fibers may be designed for direct contact between the tissue and the fiber tip. These can be constructed of various materials in differing geometric configurations. By concentrating the energy density, they increase the cutting effect. Smith (118) conducted a prospective study with sapphire contact-tip Nd:YAG laser fibers in 20 men with benign urethral strictures. The cutting effect was unsatisfactory in half of the patients, and recurrence was seen in 13.

The argon laser has been used in other series (1). Rothauge and colleagues (107) treated 41 patients, but longterm results were not reported. The coagulative effects on the tissue would be similar to those obtained with a KTP laser (111,128), but the limited power output of an argon laser appears to make the procedure tedious and technically unsatisfactory for strictures with dense scar tissue.

On the basis of physics and tissue effects, a CO_2 laser is the most appealing laser for the treatment of urethral strictures. Theoretically, the scar could be vaporized with little effect on the underlying urethra. However, until a contact CO_2 laser fiber or cystoscope is perfected, treatment requires gaseous distention of the urethra, a setting in which fatal air embolus has been reported.

Benign Lesions of the Bladder

Lasers are the preferred treatment for patients with bladder hemangioma (121). Although this is an unusual lesion, it can be a particularly debilitating and difficult problem, especially in patients with various congenital venous anomalies such as the Klippel-Trenaunay-Weber syndrome. Nd:YAG laser treatment has been performed in these patients with excellent results, and there have been no reported instances of serious bleeding induced by the laser (Fig. 6.8).

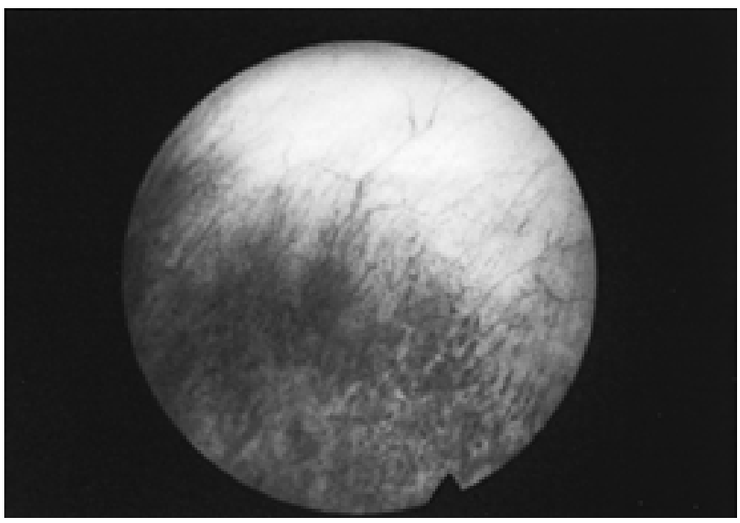

FIGURE 6.8. Hemangioma of the bladder 3 months after Nd:YAG laser application contrasting the treated area *(upper right)* with the nontreated region.

Laser treatment for control of chronic bleeding from radiation cystitis or Cytoxan-induced cystitis has been less successful. Nd:YAG lasers are capable of ablating focal areas of bleeding from cystitis, but the diffuse nature of these diseases is the primary limitation of therapy. Unlike hemangioma or arterial venous malformations, hemorrhagic cystitis is a diffuse condition that is not well treated by local methods.

The success that some have reported with Nd:YAG laser treatment of interstitial cystitis is intriguing but somewhat difficult to explain. In some series, 60% to 70% of patients experience significant pain relief and improvement in their irritative voiding symptoms after laser treatment of active Hunner's ulcers and areas of the bladder most intensely involved with the process (110). Virtually all patients treated had failed multiple alternative treatments. Symptomatic recurrence is common some 8 to 10 months after laser treatment, but successful results can be achieved with a second laser treatment. At this point, laser therapy for interstitial cystitis has not been shown to be more effective than more conventional therapy or placebo.

Bladder Cancer

Since they were first introduced into clinical practice almost 15 years ago, lasers have been used for ablation of transitional cell carcinoma of the bladder. Justification for the use of lasers as an alternative to standard methods of electrocautery resection has been based on theoretic therapeutic advantages, as well as an observed decrease in

treatment-related morbidity. The development of new laser wavelengths and instrumentation has facilitated and expanded the use of lasers in a number of areas of urologic surgery, including treatment of bladder cancer.

Patient Selection

Although some investigators maintain that tumor recurrence rate is decreased after laser treatment compared with electrocautery resection (43), laser therapy of superficial bladder cancer is performed most often to decrease or eliminate the need for inpatient hospitalization. Commonly, patients with bladder cancer of low invasive potential undergoing laser treatment have previously undergone resection or biopsy of recurrent, low-grade papillary transitional cell carcinoma. When papillary tumors of low invasive potential are seen on routine surveillance cystoscopy, laser treatment can be an effective, low-morbidity treatment.

Laser vaporization or coagulation results in tumor destruction that does not allow retrieval of tissue for adequate histologic examination. Preoperative, cold-cup biopsies can partially address this issue and allow pathologic examination to determine tumor grade and give some staging information. In general, though, sessile-appearing tumors or those with broad stalks should be treated by electrocautery resection with biopsies of the underlying bladder muscle wall. Some investigators believe that first-time tumors should be treated by electrocautery resection rather than laser treatment so that adequate histologic material is available (116).

Tumor size is another consideration. Lesions greater than 1 to 2 cm in size are difficult to treat with laser alone and may require a debulking electrocautery resection before a laser treatment of the tumor base. However, this may obviate many of the practical advantages of laser if electrocautery resection is required anyway.

Tumor location is a relatively minor issue. Virtually all parts of the bladder are accessible for laser treatment. Extra caution is appropriate for tumors on the bladder dome where loops of small bowel may be adjacent. Small bowel thermal injury and perforation with intact bladder wall has occurred. Treatment of tumors overlying the ureteral orifice appears to be associated with a very low risk of stricture and ureteral obstruction.

Treatment Technique

A number of different treatment techniques have been described for laser destruction of bladder tumors. Differences exist depending on the laser wavelength. The amount and manner of energy delivery depend on the preoperative assessment of tumor stage.

Superficial Tumors of Low Invasive Potential

Laser treatment of superficial transitional cell carcinoma of the bladder (stages T_a to T_1) is usually performed on an outpatient or ambulatory surgery basis. When treatment is performed without anesthesia, the patient is able to perceive the laser energy and often describes it as a burning type of discomfort. However, treatment is tolerated better than electrocautery resection. The exact reason for this is uncertain. However, laser energy probably results in rapid heating and destruction of nerve fibers in a well-defined volume of tissue. Electrocautery resection is associated with more irregular propagation of the energy along nerve and muscle bundles. The decision to perform laser therapy with general or regional anesthesia is based primarily on the surgeon's experience; the patient's personality; and the size, number, and location of the tumors.

When a rigid cystoscope is used, the patient is placed in a standard lithotomy position. Most cystoscope instrument companies offer a laser bridge that adapts to the standard cystoscope with either a 19- or 21-Fr sheath. The laser insert allows stabilization of the fiber tip and a watertight entry port. The optical fiber is inserted through the channel, and the tip of the laser fiber is positioned just beyond the end of the visualizing telescope. Fiber tip placement is especially important when using the holmium:YAG laser because treatment energy may destroy the telescope lens if the two are in close proximity.

Nd:YAG and holmium lasers are the most commonly used lasers for treatment of bladder carcinoma. Both lasers can be used satisfactorily. One needs to know the relative merits of each laser, however. Noncontact treatment with the Nd:YAG laser results in tumor coagulation and preservation of the underlying bladder wall. As mentioned, underlying small bowel injury may occur, but the mechanical integrity of the bladder wall is almost always preserved. The holmium laser, on the other hand, produces tissue cutting at even moderate settings. Aggressive resection may result in bladder wall perforation.

For a noncontact technique with the Nd:YAG laser, a standard 400- or 600-micron end-fire optical fiber is used. The fiber tip is positioned 3 to 5 mm from the tumor surface with the aiming beam illuminating the region of intended treatment. With the Nd:YAG laser, 20 to 30 W of energy usually is sufficient for complete tumor coagulation. The duration of the treatment usually is controlled by the speed with which the aiming beam is moved across the tumor surface. The laser can be operated in a continuous mode whereby energy is emitted whenever the foot pedal is depressed. An aiming beam, either from a flashlamp or a helium neon laser, marks the point of impact (the Nd:YAG laser beam is invisible to the human eye). Sterile water, normal saline, or amino acid solutions can be used for irrigation. A continuous-flow system is not required; the irrigant usually can be turned off during treatment because bleeding is usually nonexistent.

Laser treatment is best performed as a dynamic process rather than a series of adjacent, static impulses. The beam is slowly moved across the surface of the tumor in a “painting”

fashion. The tumor undergoes a white discoloration indicative of adequate thermal coagulation (Fig. 6.9). Care should be taken to avoid excessive laser energy application in any given area. Usually 2 to 3 seconds of duration is required in a given area for complete thermal coagulation to be evident. Techniques have been described wherein a ring of coagulated tissue is created around the tumor base to seal blood and lymphatic vessels. In practice, this is unnecessary because bleeding does not occur even if the energy is applied initially to the center of the exophytic portion of the tumor.

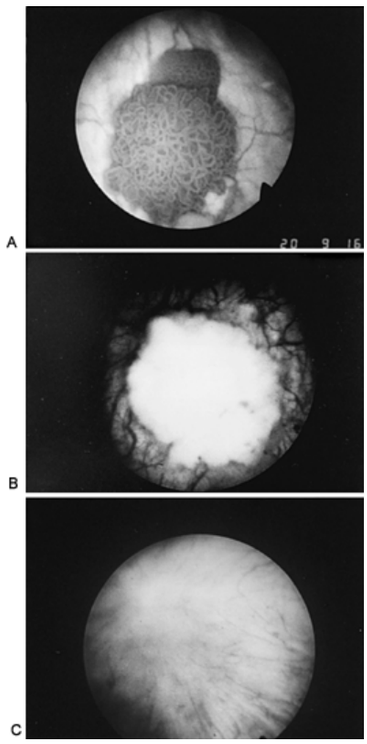

FIGURE 6.9. A: Papillary transitional cell carcinoma of the bladder. **B:** After Nd:YAG laser treatment, the lesion undergoes a white discoloration indicative of adequate thermal necrosis. **C:** Six weeks later, complete bladder healing is evident.

It is not necessary to treat the tumor base initially, but it is important to make certain that all aspects of the lesion have been thermally coagulated. After the papillary frondular tissue is coagulated, it usually can be dislodged with the tip of the fiber or the cystoscope to expose deeper portions and the tumor base. Treatment is best performed with the bladder as empty as possible to avoid excessive thinning of the bladder wall. This allows an added margin of safety for underlying small bowel. If the tumor is located in the air bubble, either the air can be evacuated or the patient can be tilted to remove the tumor from the air bubble. If this proves to be difficult, treatment can be performed through the air bubble itself, but there is usually some surface carbonization and smoke production. The temperature of the irrigating fluid does not seem to be a major factor in determining tissue or treatment effect.

Subsurface boiling may be observed during treatment, producing a popcornlike effect. These microexplosions, although sometimes dramatic, carry no particular significance. If the fiber tip inadvertently touches the bladder wall, there usually is some superficial carbonization and a cratering effect. The foot pedal is released and the fiber withdrawn from the tissue surface. If there is any tissue adherent to the fiber tip, it should be wiped away with a moist sponge before proceeding with therapy. If necessary, cleavage of the fiber tip and stripping of the outer sheath will restore the fiber to original condition.

The depth of coagulation cannot be monitored satisfactorily intraoperatively. In general, coagulation depth is predicted preoperatively based on known characteristics of the wavelength, power, duration of laser output, and spot size. In most circumstances, 3 to 5 mm of complete tissue coagulation can be anticipated.

If a small amount of bleeding occurs, especially after a cold-cup biopsy, hemostasis usually is accomplished in the course of laser treatment. However, even a relatively small amount of blood undergoes rapid carbonization and can both obscure and prevent effective energy delivery to the tumor surface.

Superficial tumors in bladder diverticula can be treated satisfactorily with a laser. Even though, by definition, there is no muscular backing to a diverticulum, actual free perforation of the diverticulum and bladder wall is uncommon. Usually, there is some shriveling of the mucosa of the diverticulum as the coagulation process occurs. The iliac blood vessels and obturator nerve are often adjacent to diverticula, but if appropriate energy densities are used, direct injury is unlikely. The obturator nerve is not stimulated by laser energy. Obturator spasm and a leg jerk, as may be observed with electrocautery, do not occur.

Treatment of tumors directly overlying the ureteral orifices is performed in the same manner as if the tumor were

located elsewhere in the bladder. Stents should be removed from the ureteral orifice before treatment is performed because the laser energy may melt the stent itself. Metal guidewires can be used alternatively. After an extensive treatment overlying the ureteral orifice, postoperative management with a stent may be advisable because of temporary edema. However, the long-term risk of ureteral stenosis appears to be low.

A postoperative Foley catheter is usually not necessary because of the lack of bleeding. The thermally coagulated tissue either sloughs as imperceptible particles or is resorbed. If the treatment is thought to be adequate, follow-up cystoscopy can be performed as per the routine for a particular patient depending on tumor grade, stage, and prior history.

Intravesical drugs can be used after laser treatment, and the indications for their use should be the same as after electrocautery resection. However, because raw surfaces of the bladder wall are not exposed after laser treatment, intravesical drugs, such as bacille Calmette-Guérin (BCG) or chemotherapy, can be introduced more rapidly after treatment with an apparent decreased risk of systemic absorption (24).

Muscle-invasive Tumors

The ability of Nd:YAG lasers to produce transmural coagulation without perforation has allowed laser treatment of some invasive bladder cancers. Even in a controlled setting, however, the treatment depth is variable (122). However, application of energy to both the inner and outer bladder wall through both a cystoscope and a laparoscope allows overlapping zones of thermal necrosis and complete transmural coagulation (108). When treated with this technique, the bladder wall maintains structural integrity because of rapid fibroblast infiltration and collagen deposition (108). The location of most invasive bladder tumors near the trigone makes laparoscopic visualization and energy application somewhat difficult.

Patients being considered for laser treatment of invasive bladder cancer should first undergo a standard transurethral electrocautery resection. This accomplishes two purposes. First, it allows accurate histologic examination for tumor staging. Second, resection debulks the surface of the tumor. Logically, if laser therapy is considered a method for extending the margin of resection, the electrocautery resection should extend deeply into the bladder muscle.

Under most circumstances, it is best to delay laser treatment for at least 3 to 5 days after an electrocautery resection. This allows any bleeding to cease and any overlying clot to lyse. Active bleeding or blood clot interferes with delivery of energy. General or regional anesthesia is required because relatively large amounts of laser energy are needed. The irregular appearance of the resection crater does not allow visual determination of treatment adequacy. Therefore systematic application of laser energy to the entire resection crater, as well as an adequate surrounding margin, should be performed.

Because the goal of treatment is transmural necrosis, energy output up to 45 or 50 W may be appropriate. When an end-fire fiber with a 5- to 15-degree angle of divergence is used, the energy is maintained in a given area for 2 to 3 seconds. If a laparoscope has been inserted, the small bowel can be displaced from the treatment area. After adequate energy has been applied through the cystoscope, the Nd:YAG laser fiber can be inserted through the laparoscope and energy can be applied to the intraperitoneal surface of the bladder in the same region, if visualization is adequate. Steaming or subtle coagulation of the intraperitoneal bladder surface behind the tumor can often be seen laparoscopically during cystoscopic Nd:YAG laser therapy. Otherwise, the intended treatment site may be difficult to determine.

The most appropriate patients for laser treatment of invasive bladder cancer are those with minimally invasive lesions (11,117). Lasers have been used to treat bulky, invasive bladder cancers. However, the surface effect that is obtained in this circumstance usually offers no demonstrable benefit compared with electrocautery debulking and cauterization of the tumor surface.

A catheter is not required postoperatively but may be used depending on the amount of the bladder surface area requiring treatment. Follow-up cystoscopy is performed after 1 month to assess healing and to detect any obvious residual tumor. Reepithelialization of the bladder surface overlying residual cancer is feasible, but most often, there is no residual tumor present when complete reepithelialization occurs within 2 to 3 months of treatment.

Complications of Bladder Treatment

Laser treatment of bladder cancer is used because of the observed decrease in patient morbidity and treatment-related complications. Usually, there is minimal discomfort after treatment. A distinct advantage is the almost complete lack of bleeding that occurs with coagulative procedures. Bleeding that may be present from a preoperative biopsy usually is coagulated adequately during the course of energy application. The coagulation that occurs from the laser energy itself causes virtually no bleeding either as an immediate or a delayed phenomenon.

The most feared complication of laser treatment of bladder cancer is perforation of an adjacent viscus. The small bowel or colon may lie in direct approximation with the peritoneal surface of the bladder. Thus the risk for bowel perforation is greatest with laser treatment on the posterior bladder wall or dome. Hofstetter and colleagues (43) treated more than 500 tumors and reported only two incidences of small bowel perforation, in at least one of which excessive energy levels were used inadvertently. Smith (116) has had no cases of small bowel perforation

in over 150 laser treatments of superficial bladder tumors.

Most patients with bowel perforation develop signs and symptoms within 8 to 24 hours of treatment, but symptomatic presentation has been delayed for as long as 2 weeks. Abdominal pain, physical examination findings consistent with an acute abdomen, and free intraperitoneal air are all associated with bowel perforation from laser therapy. It is important to recognize that bowel perforation may occur in the absence of bladder perforation. A cystogram may be normal. The thicker muscle wall of the bladder makes it less prone to perforation, and forward scatter of the energy can place the bowel at risk.

Immediate laparotomy is indicated if small bowel or colon perforation is suspected. The site of laser energy is identified. The zone of tissue injury may be far greater than is visibly evident, so resection of the affected site is indicated.

Results

Initially, laser treatment of superficial bladder cancer was promoted as a means to decrease the recurrence rate (45,74). Indeed, both Nd:YAG and holmium laser treatments have low local recurrence rates at the site of prior resection. Modern thinking about urothelial field change disease has produced serious questions about whether any therapy directed toward specific lesions can affect the eventual rate of recurrence, however.

Both prospective and retrospective clinical series have, in general, failed to support a favorable effect of laser treatment on recurrence rate of bladder cancer (12,50). In most retrospective series, the patient population under study is one of the most influential factors in determining recurrence rate. This complicates comparisons of laser-treated patients to historical series of those undergoing electrocautery resection. Prospective studies have shown no apparent salutary effect of laser treatment on the overall recurrence of superficial bladder cancer.

On the other hand, there is good evidence attesting to the effectiveness of laser therapy in eradicating existing and visible superficial bladder tumors. Multiple series have shown a local recurrence rate of around 5% to 10%, a figure that compares favorably with electrocautery resection. In a randomized, prospective study, Beisland and Seland (12) found a local recurrence rate of 43% for stage T_1 transitional cell carcinoma treated with electrocautery resection alone compared with only 7% for Nd:YAG laser treatment.

There are no studies comparing various laser fibers, wavelengths, or contact versus noncontact treatment of superficial bladder tumors. There have been published reports of holmium:YAG treatment of bladder tumors (50). If adequate vaporization or coagulation of the lesion occurs, good results can be anticipated in terms of local eradication of visible tumors with any of the laser wavelengths. Overall, though, the Nd:YAG laser has proven to be the most versatile and produces the most complete hemostasis. There is no evidence that other laser treatment techniques offer an increased margin of safety.

Laser therapy is firmly established as an effective treatment for superficial bladder cancer of low malignant potential. The ability to eradicate existing, visible tumors is comparable or, perhaps, superior to results obtained with electrocautery resection. Overall, though, there is no demonstrable favorable effect on tumor recurrence. Therefore the indications for adjuvant intravesical treatment with either BCG or cytotoxic drugs are unchanged after laser therapy compared with standard treatment recommendations.

Laser treatment of superficial bladder cancer has been associated with an observed decrease in treatment-related morbidity. Bleeding is almost nonexistent, and catheter drainage of the bladder is not required. Treatment can be performed on an ambulatory basis. A complication unique to laser therapy, perforation of an adjacent viscus, is unusual if appropriate treatment parameters are used. A number of laser wavelengths and fibers have been used successfully to treat superficial bladder cancer. One has not been proven to be inherently superior to another, although the Nd:YAG laser used in a noncontact manner produces optimum coagulation. Holmium laser energy may also be safely used to cut and coagulate bladder tumors. The primary limitations of laser treatment of superficial bladder cancer are the lack of tissue available for histologic examination and the difficulty in treating tumors that are larger than 2 cm with laser alone. Laser treatment of invasive bladder cancer is limited by difficulties and inaccuracies with clinical staging of invasive transitional cell carcinoma and by the inability to predict and control the depth of coagulation.

Benign Prostatic Hyperplasia

Lasers exert their therapeutic effects on tissue through transformation of light energy into heat. Contemporary BPH treatment methods rely on various modifications of laser parameters to produce a desired therapeutic effect. Modifications in instruments for delivery of energy have facilitated treatments that rely on coagulation (e.g., side-firing refractive, reflective free-beam techniques), vaporization (e.g., contact tips, holmium desiccation), or cutting (e.g., holmium laser resection of the prostate). Coagulation is associated with superb hemostasis but results in minimal immediate tissue removal. Obstructive voiding symptoms usually worsen for several days because of postoperative tissue edema. Irritative voiding symptoms also may be prolonged and problematic in some patients. Cystoscopy as long as 3 months after coagulation laser prostatectomy may show residual shaggy gray necrotic tissue (75). On the other hand, vaporization techniques with current instrumentation are slow, and hemostasis is less secure.

The techniques and results that have been reported for laser treatment of BPH are discussed next. Despite the considerable differences between some techniques, similar satisfactory results have been reported. Laser prostatectomy is a compromise procedure in which one attempts to achieve most of the benefits of TURP with decreased morbidity.

Historical Perspective

Early attempts at laser treatment of the prostate met with some anticipated limitations because of difficulty in energy delivery. We and others observed that noncontact laser coagulation of prostatic tissue using conventional end-fire probes resulted in unsatisfactory removal of prostatic tissue (83,119). There was no immediate relief of obstructive symptoms. In fact, some of the edema that occurred secondary to the laser treatment resulted in a temporary increase in symptoms and often urinary retention.

In 1982, McPhee and colleagues developed a modified cautery resectoscope that enabled the simultaneous availability of both electrical (cautery resection/coagulation) and Nd:YAG laser energy. Eleven patients (five with prostatic cancer and six with BPH) underwent transurethral resections using laser irradiation alone for hemostatic control. From 12 to 45 g of tissue was resected using 9,600 to 17,200 J of laser energy at dose ranges of 60 to 90 W for a duration of 1 to 3 seconds. All patients had a satisfactory postoperative voiding pattern, although one patient had bleeding on the third postoperative day, requiring a 3-unit transfusion. The technique was cumbersome, and difficulty was encountered in controlling bleeding of large vessels at the bladder neck when an exaggerated oblique angle of laser application was required (82).

When an end-fire probe is used, obtaining hemostasis on actively bleeding vessels often is difficult. Hemoglobin absorbs Nd:YAG laser energy and effectively diminishes penetration of the laser beam into the tissue. Direction of the beam to the end of the bleeding vessel can be problematic. Thus, although the Nd:YAG laser is an excellent device for coagulating tissue with virtually complete hemostasis during treatment, it is less useful as an instrument to stop active bleeding.

Littrup and colleagues (67) performed percutaneous ablation of the canine prostate using transrectal ultrasound guidance, ethanol injection, and Nd:YAG laser ablation. Transrectal ultrasound guidance was used to direct treatment. Ethanol injections produced an intraglandular hemorrhagic necrosis that extended in some animals to the external prostatic sphincter and the mucosa of the urethra and bladder. Ninety-two percent (11 of 12) of the laser ablations produced intraglandular foci of thermal tissue damage that had distinct margins of transition between necrotic and viable cells. Ultrasound visualized the areas of ablation well, and it was believed that ultrasound could be used as a real-time, intraoperative monitor of treatment effects. However, no follow-up clinical trials have been published.

Although limited success was reported in some of these series, historically laser treatment achieved a very minor role in the management of prostatic obstruction. End-fire probes created access difficulty, tissue coagulation and vaporization was suboptimal, and laser treatment was inferior to electrocautery in gaining hemostasis of actively bleeding vessels. The side-firing laser device altered significantly the methodology for laser treatment of the prostate and improved clinical results.

One of the earliest side-firing techniques to report the results of a controlled study was the transurethral laser-induced prostatectomy (TULIP) (IntraSonix, Burlington, Massachusetts) (106). The system combined a real-time ultrasound transducer and Nd:YAG laser delivery system contained within a 22-Fr urethral probe (5). The laser energy was delivered through a 600-micron, fused-silica fiber that, at the distal end, was coupled to a novel, right-angle microprism integrated into a probe. A 2.8-mm spot size was produced on the tissue surface when the probe was centered inside a 36-Fr balloon. The ultrasound scanner produced a 90-degree real-time sector scan using a 7.5-MHz transducer. Angular resolution was approximately 2 mm, and the depth of view could be set from 2 to 5 cm. A sweep rate of 2 Hz was used in initial studies. A polymer balloon transparent to Nd:YAG laser frequency light encloses the fiber tip and the deflecting prism. This allows the prism to be surrounded by pure degassed water and prevented fouling of the tip by contact with surrounding tissue. The procedure was performed by imaging the bladder neck with ultrasound and slowly withdrawing the laser beam from the bladder neck to the apex of the prostatic urethra using ultrasound guidance. Multiple passes are made depending on the size of the prostate. Laser power in the 20- to 40-W range at a pull rate of approximately 1 mm per second was used in most treatments (77).

Takahashi and colleagues (125) followed 30 patients after a TULIP procedure for symptomatic BPH. At 3 months, flow rate increased from 7.9 to 14.5 mL and remained at 14.7 mL at 1 year. Prostate volume was not significantly different than the pretreatment value when examined at 1 year. Using a modified Boyarsky Symptom Score, there was a mean decrease from 18.4 preoperatively to 7.6 at 3 months after treatment, 6.2 at 6 months, and 6.2 at 12 months. The changes at all three of these intervals are statistically significant (P <.05). Peak flow rates did not improve immediately, but they improved progressively over time. The mean peak flow rate increased from a preoperative level of 7.2 mL per second to 12.4 mL per second at 3 months, 13.1 mL per second at 6 months, and 11.1 mL per second at 12 months. Again, all of these changes are statistically significant (P <.05).

None of the patients undergoing the TULIP procedure in the clinical trial required a blood transfusion, although

1.5% required cystoscopy after treatment for irrigation of bladder clots (78). Urethral strictures were observed in 9.8% of patients and impotence in 4.6%. Only 5.2% of patients reported retrograde ejaculation. Persistent problems with incontinence have been observed in 4.6% of the patients undergoing the TULIP procedure. Most of these complications or adverse treatment effects are well within the ranges reported for series of patients undergoing electrosurgical transurethral prostatectomy. The mean blood loss of less than 16 mL for the procedure clearly is less than that observed after comparable patient groups undergoing transurethral prostatectomy.

The primary limitation of the TULIP procedure was the delayed time until optimal treatment results were achieved. In fact, most patients had aggravation of symptoms during the first several weeks after treatment until laser-induced edema and tissue effects resolved. Although the duration of hospitalization was short, most patients required bladder drainage via a urethral catheter or suprapubic tube for 1 to 2 weeks, and irritative voiding symptoms often persisted for 6 weeks or longer. The TULIP device never was marketed in the United States. Nevertheless, the clinical trial was one of the most carefully conducted multicenter trials of laser BPH therapy.

Contemporary Techniques

Technologic improvement and methodologic changes have altered significantly the manner in which laser treatment of the prostate is performed. The theoretic basis for treatment is more substantially founded than with the techniques described previously. Promising clinical results have emerged.

It is important to recognize that the term *laser prostatectomy* encompasses a wide variety of instruments, laser wavelengths, and techniques. Often, the described methodology bears little resemblance to alternative techniques. Therefore it is invalid to discard all methods of laser prostatectomy simply because one described technique may not achieve satisfactory clinical results. Likewise, promising results or advantages with one particular method of laser prostatectomy may not be applicable to other techniques.

Each of the various methods of laser prostatectomy is described categorically. Clinical techniques and postoperative results are discussed in detail. Laser prostatectomy methods are continuously evolving, and it is not possible to define the optimal method, if any, for laser treatment of the prostate.

Clinical and Laboratory Studies

Right-angle Delivery Systems

The Urolase fiber (C.R. Bard, Covington, Georgia) was the first side-firing optical fiber to experience widespread use for laser prostatectomy. Although it is no longer available, a large part of the total laser prostatectomy literature describes results using this device. This fiber originally was developed for use in gynecology to ablate the endometrium. However, Johnson and associates (52) performed laboratory dosimetry studies and canine experimentation for potential use in the prostate. They found no evidence of tissue penetration beyond the prostatic capsule in their initial study.

In a follow-up study, Johnson and associates (53) performed serial gross and histopathologic examinations of the prostate following transurethral laser prostatectomy in the canine model. Gross examination of the prostate immediately after treatment showed acute swelling of the prostate, causing an overall increase in size of 25% to 35%. The acute swelling regressed rapidly as evidenced by an increase in the size of the urethral lumen at 3 hours. A urethral catheter was left indwelling for 7 to 10 days following the laser treatment to prevent postoperative urinary retention. Within 24 hours, the well-demarcated sphere of thermal necrosis measuring 2.7 cm in diameter had begun liquefaction and cavitation. By the end of 1 week, a central cavity had been formed with a peripheral rim of viable tissue. Within 5 weeks, reepithelialization of the central cavity was observed. The findings were reproducible despite variability in the flow of irrigation and difficulty maintaining a consistent distance between the fiber tip and the prostatic urethral lumen.

Various methods are used to create angled or side-firing laser fibers. Many fibers have a wide angle of divergence, allowing noncontact coagulation of large volumes of prostate tissue. In general, low-power, prolonged-duration exposure generates deeper tissue coagulation than high-power, shorter-duration exposure (19). Using a Urolase fiber, Kabalin and Gill (55) found maximum tissue coagulation with 40 W applied for 90 seconds in both a canine model and an *in vivo* human prostate model. The mean depth of tissue ablation was 16 mm with a mean volume of tissue ablation of 5.5 mL. A plateau effect was observed wherein longer exposure or higher power did not appreciably extend the depth of injury.

Shanberg and associates (112) applied laser energy transurethrally before radical prostatectomy with a Prolase II fiber. Sixty Watts applied for 60 seconds had the greatest treatment depth, and coagulation necrosis extended a mean of 1.75 cm into tissue.

Most of the clinical and laboratory studies using side-firing lasers have involved noncontact application resulting in coagulation necrosis. When placed in direct contact with tissue, energy density is increased. Using high power output and tissue contact, Fournier and Narayan (35) evaporated canine prostate tissue with an Ultraline fiber (Hereaus, LaserSonics, Milpitas, California) (Fig. 6.10). This potentially allows bulk tissue removal for immediate voiding.

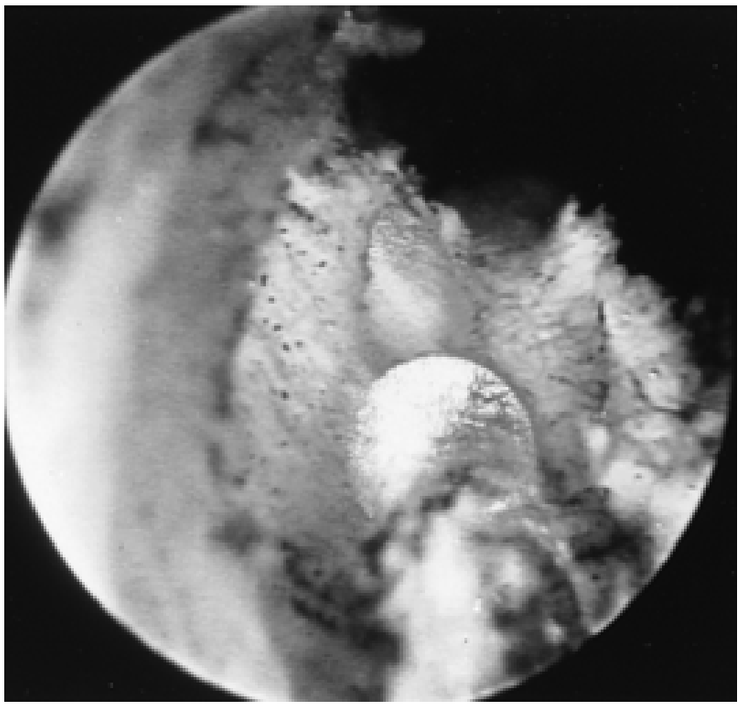

FIGURE 6.10. Side-firing refractive laser prostatectomy.

It is important to recognize that differences exist between various fibers, and the optimal energy parameters for one fiber may not apply to others. Furthermore, laser tissue

effects in dog prostates are different and, usually, exaggerated compared with a human prostate. Differences in the stromal-to-epithelial ratio may account partly for the lack of direct comparability (32).

Costello and associates (26,27) initially published results of small, clinical series of patients undergoing laser prostatectomy with a Urolase fiber (visual laser ablation of the prostate [VLAP]). The patients underwent epidural anesthesia; a 23-Fr cystoscope with a deflecting mechanism was used. The fiber was positioned approximately 5 mm beyond the end of the telescope just proximal to the verumontanum. Either glycine or water was used for irrigation. The metal alloy tip of the laser delivery system was placed approximately 1 mm away from the prostatic urethra.

In the initial pilot study, energy was delivered at 60 W continuous wave for 1 minute in each of four quadrants, including the roof of the prostatic fossa, the floor, and both lateral lobes. However, subsequent improvements in the reflectivity of the fiber tip decreased the treatment time to 15 to 30 seconds in four quadrants (27). For patients with significant median lobe enlargement, laser energy was applied for approximately 30 seconds to the bladder neck. Treatment was continued until the circular fibers of the bladder neck were visually apparent. Visible vaporization of the lateral lobes was observed.

Subsequent clinical trials generally used longer treatment times than the 15 to 30 seconds reported in this study. An average of 18,000 J of laser energy was delivered per patient with a mean treatment time of 4.2 minutes. Six weeks after treatment, the mean symptom score fell from 15 to 4, and the mean peak flow increased from 5 to 9 mL per second. Of 12 patients treated, postoperative urinary retention developed in one patient; 2 subsequently required TURP because of persistent symptoms; and one underwent a bladder neck incision. A Foley catheter was left indwelling postoperatively for 2 to 3 days.

Norris and associates (97) reported results in 108 patients treated on an outpatient basis using a Urolase fiber with energy parameters of 60 W for 60 seconds. An average of 19,457 J of energy was applied. Preoperative American Urological Association (AUA) symptom score was a mean of 22.3 compared with 9.2 postoperatively. The peak flow rate increased from a mean of 7.56 to 12 mL per second. No blood transfusions were required, and none of the patients developed a urethral stricture. Seventeen percent of patients required reinsertion of a Foley catheter for urinary retention, and four subsequently required a TURP. Visually, the prostatic fossa eventually resembles a post-TURP appearance (75).

Kabalin (54) reported his initial experience using 40 W of power for 30 to 60 seconds. Total energy ranged from 7,200 to 19,200 J. In 25 patients, peak urine flow rates increased 120% and 141% at 3 and 6 months, respectively, and symptom scores decreased 66% and 78%, respectively. Treatment modifications occurred, and subsequent experience in more than 250 patients has shown no transfusion requirement. Re-treatment has been required in only 5 of the last 150 patients (3.3%). A power of 40 W for 90 seconds has been used with a total energy of a mean of 44,000 J. Peak flow increased from 6.7 mL per second preoperatively to a mean of 18.5 mL after 1 year of follow-up (55).

Dixon and colleagues (33) reported the initial results of a randomized, prospective double-blind study of TURP versus laser prostatectomy using a side-firing, noncontact technique. At 12 months, 16% of the laser group had failed and required an additional procedure compared with 4% for TURP. This re-treatment rate is higher than that reported in comparable series. Symptom score was decreased 30% for laser and 59% for TURP, whereas flow rate increased 82% in the laser group and 147% for TURP. The number of patients randomized at the time of the report (56) was too small for a meaningful comparison of side effects.

A common theme throughout these clinical series is objective and subjective treatment response that approaches that of TURP. However, laser-treated patients have a higher rate of recatheterization, prolonged voiding symptoms, and repeat procedures. In turn, bleeding is almost nonexistent with laser, the risk of urethral stricture is diminished because of the use of smaller instruments, and antegrade ejaculation is preserved in many patients. Coagulative side-firing laser prostatectomy can be performed safely in anticoagulated patients (18). Furthermore, the lack of bleeding facilitates performance of laser prostatectomy on an outpatient basis (66), although TURP also can be performed successfully without hospitalization (63).

Other Side-firing Devices

Numerous side-firing devices have been produced for laser prostatectomy. The number of such devices changes frequently

and precludes complete listing. All major urologic laser manufacturers offer side-firing fibers that can be used for laser prostatectomy.

Most practitioners use a scanning technique. Probe movement occurs at the slowest possible rate while avoiding carbonization. A methodical, cylindric treatment pattern satisfactorily ensures thorough exposure of the entire prostate. Each pass through the prostate begins with a dwell period as long as possible while avoiding carbonization.

Other investigators have used high-power exposure. These techniques involve a combination of both coagulation and vaporization. Slow fiber movement allows surface heating sufficient to ablate superficial tissue. With sufficient energy input, the Nd:YAG laser may be used to bore cavities into the prostate. This technique requires far greater energy use and therefore longer treatment time than pure coagulation prostatectomy. Decreased postoperative obstruction is a potential benefit, however.

Clinical results from other side-firing devices are similar to those achieved with the Urolase device. Patients experience symptom score decreases similar to those of TURP, uroflow increases about two-thirds those of TURP, frequent urinary retention, and decreased procedure-related morbidity (23).

Contact Vaporization

Contact laser systems use a conventional fiberoptic waveguide with a fused-silica glass or synthetic-sapphire contact tip coupled to the fiber. Because energy density is inversely related to the square of the radius of the spot size, contact fibers greatly increase the energy delivered for a given volume of tissue. This facilitates tissue vaporization. The contact probes initially developed could tolerate only limited power output without melting. In addition, these devices proved to be relatively inefficient for incising or vaporizing large tissue volumes as is required for treatment of prostatic enlargement (118). Recent advances in contact-probe development have increased efficiency, however. Absorptive coatings added to the contact-probe surface increase direct thermal heating.

Similar to TURP, contact prostatectomy demands considerable understanding of the treatment procedure. The procedure begins using the Nd:YAG laser in continuous-wave mode at 40- to 80-W output. Under cystoscopic visualization, the hot contact probe is pushed into prostatic tissue. Knowledge of anatomic landmarks is critical for efficient tissue vaporization. For that reason, the procedure begins at the bladder neck (Fig. 6.11). Initial short passes are repeated over 360 degrees to open the bladder neck. Subsequent longer passes vaporize progressively more distal tissue (Fig. 6.12). The procedure is repeated until an open prostatic fossa is created to the verumontanum. Contact vaporization prostatectomy causes minimal bleeding but is not bloodless. It is important to vaporize tissue in a methodical fashion to maintain adequate visualization. As discussed previously, increased vaporization sometimes implies decreased coagulation and hemostasis. However, this has not been a practical problem with contact laser treatment of the prostate. Adequate hemostasis occurs during treatment. The primary limitation has been that, even with some of the design changes and improvements, vaporization of the prostate is relatively slow and tedious. Milam (88) has calculated that nearly 50,000 J of energy must be converted to heat and effectively transferred to the prostate in order to vaporize 20 g of tissue. Considering inefficiencies in the system that result in loss of nearly 50% to 90% of the energy before

reaching the prostate, total laser outputs of over 100,000 J may be necessary to completely vaporize 20 g of prostatic tissue. Thus further improvements in energy delivery are necessary.

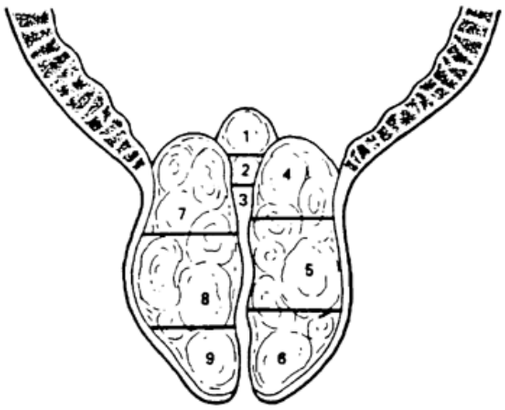

FIGURE 6.11. The sequence for contact laser vaporization of the prostate. Initial vaporization of the median lobe and bladder neck region facilitates improved visualization during the procedure. The procedure extends distally until the entire prostate is vaporized.

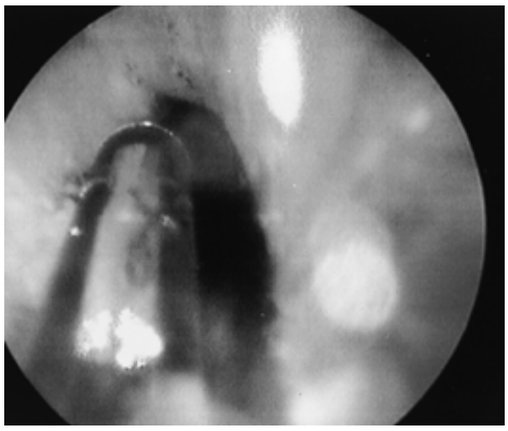

FIGURE 6.12. Contact vaporization of prostatic tissue.

Contact laser treatment of the prostate theoretically is appealing because the technique results in immediate tissue vaporization. Thus therapeutic results do not depend on secondary tissue slough. The immediate voiding problems experienced by some patients after noncontact laser treatment methods may be avoided with contact lasers. This, coupled with the excellent hemostasis observed during treatment, minimizes the need for postoperative Foley catheter drainage of the bladder. Most investigators routinely remove the catheter on the morning of the first postoperative day. Although hemostasis is good, the procedure is not bloodless. Unlike side-firing coagulation prostatectomy, contact prostatectomy should not be performed on anticoagulated patients.

Anson and associates (3) found earlier voiding in their patients compared with noncontact treatment. Aleida (2) used contact laser tips as an adjunct to electrocautery and thought that the combination allowed earlier hospital discharge (29).

Narayan and co-workers (93) performed prostatectomy using direct contact with a side-firing Ultraline fiber. The fiber has a beam divergence of only 17 degrees. Tissue vaporization was achieved using 60 to 80 W of power and dragging the fiber tip through tissue. Mean total energy for glands 20 to 40 g in size was 42,024 J and 95,732 J for those more than 40 g. The prostatic fossa healed completely by 6 months with a decrease in ultrasound-measured prostate volume of 34%. Only 2 of 61 patients subsequently required a TURP, and no significant bleeding occurred. Peak flow was increased 164% at 12 months.

Interstitial Fiber Placement

It has been known for many years that application of low-power laser energy to a given location within a solid organ over several minutes will induce a 1- to 2-cm zone of coagulation necrosis. By using several fiber placements, nearly the entire prostate can be treated while preserving the urethral lining. This principle is used in interstitial laser coagulation (ILC) of the prostate.

ILC has become popular due to the technical ease of treatment, low morbidity, outpatient nature of therapy, and relatively low cost of equipment acquisition. Most described laser treatments of the prostate involve transurethral application of the laser energy. Just as with transurethral electrocautery resection of the prostate, laser injury to the urethral mucosa accounts for some of the treatment-related morbidity. A procedure that preserves the integrity of the prostatic urethra conceivably could decrease or eliminate any treatment-related bleeding, as well as postoperative, irritative voiding symptoms.

As discussed previously, Littrup and colleagues (67) performed interstitial treatment of the canine prostate using the Nd:YAG laser. Placement of the laser fiber was monitored by transurethral-ultrasound guidance. They observed pathologically a homogeneous zone of thermal necrosis and concluded that this technique may be useful for treatment of benign prostatic hypertrophy. However, no follow-up clinical studies have been reported.

McPhee and associates (85) performed studies on interstitial application of laser irradiation using hematoporphyrin-derivative photosensitized Dunning R-3327 prostate cancers. They showed a beneficial effect of treatment on tumors, with either arrest of tumor growth or a decrease in tumor size in most animals. However, the photosensitizers currently available are retained in malignant or dysplastic cells and require systemic administration. Therefore this technique would have no utility for treatment of benign prostatic hypertrophy. Nonetheless, there is at least the potential for the future development of photodynamic therapy of the benign prostate using locally administered photosensitizers.

Johnson and associates (51) placed a frosted Nd:YAG laser fiber interstitially in dog prostates and delivered 10 W of power for 5 minutes to each lobe. Coagulation necrosis followed by interstitial cysts 6 weeks later was observed. A subsequent study using a cylindrically diffusing tip and 25 W for 10 minutes showed large areas of liquefaction necrosis followed by cystic cavitation (28).

McNicholas and associates (81) used interstitial Nd:YAG laser fibers placed percutaneously with low-power (1 to 2 W), long-duration (400 to 1,500 seconds) exposure in dogs. Coagulation necrosis followed by liquefaction and cystic degeneration was observed. Muschter and colleagues (92) reported 15 patients with symptomatic BPH treated with interstitial Nd:YAG laser application and subsequently have accumulated a much larger experience. Five Watts of energy was applied for up to 10 minutes, creating tissue temperatures exceeding 100°C. By 2 months, prostate size measured by ultrasound had decreased from an average of 63 to 44 g and peak flow had increased from 6.6 to 15.2 mL per second. A follow-up report of 42 patients from the same group showed a 30% decrease in prostate size 3 months after treatment (92). The same authors went on to investigate diffuser tip probes coupled to a lightweight diode laser source. This device is now known as the Indigo Laser System (Johnson and Johnson, Superior, Colorado). Many practitioners have used this device with good results. One group found that symptom scores using the AUA symptom index fell from 20.2 to 9.8 at 9 months after treatment and that the uroflow rate increased from 4.4 to 6.2 mL per second over the same period (40). An indwelling catheter was used in all patients postoperatively and was removed between day 3 and day 7. Interstitial laser coagulation appears to produce results similar to those reported with noncontact techniques. One potential advantage is

urethral preservation, although urinary retention remains a problem.

Holmium Laser Resection

Holmium laser resection of the prostate (HoLRP) differs substantially from the techniques described previously in this chapter. As noted, the holmium:YAG laser at greater than 1 J per pulse is an excellent cutting laser. HoLRP uses this property to cut and resect rather than coagulate or desiccate tissue. Much like TURP, there is a substantial learning curve. With experience, however, the urologist can learn to resect a volume of tissue similar to that removed during TURP (57,58,64). Unlike coagulation prostatectomy with a side-firing device, tissue is immediately removed, symptom scores drop rapidly, and postoperative urinary retention due to tissue edema is not a problem. Properly performed, HoLRP results in immediate tissue resection similar to TURP with improved hemostasis. Unlike coagulation techniques, though, HoLRP is not bloodless.

HoLRP has been compared with VLAP in a small multicenter study of experienced investigators (39). Forty-four men were randomized to either HoLRP or VLAP. There were no significant differences between the preoperative patient groups. Mean total operative time was longer with HoLRP than with VLAP, 52 versus 41 minutes, respectively. Catheterization time differed considerably, 1.4 days for HoLRP versus 11.6 days for VLAP. There were no significant differences in postrecovery AUA symptom score; however, PdetQmax and Schafer grade measurements at 3 months showed greater relief of obstruction in the HoLRP group. The Qmax did not differ statistically.

Matsuoka and associates (76) evaluated 103 patients treated with HoLRP. They used a high-power laser and a forward-firing 550-micron optical fiber. Symptom score, Qmax, and quality of life were significantly improved at the 1-week visit. Similar results were maintained for up to 36 months postoperatively.

Carcinoma of the Prostate

Laser therapy has never been proved effective for curative treatment of adenocarcinoma of the prostate and is not advocated. An investigative method for endoscopic laser treatment of carcinoma of the prostate has been described, and initial clinical results are available (9,10). An “extended” or “radical” transurethral resection with electrocautery was performed with the intent of removing all prostatic tissue (80). Six to ten weeks after the resection, laser treatment was performed with the Nd:YAG laser. A power output of up to 70 W was used and applied to the entire prostatic capsule. The laser fiber tip was positioned 1 to 2 mm from the tissue surface.

McNicholas (79) has treated 30 patients by this method. Ultrasound follow-up has shown a nearly 75% reduction in the overall volume of the prostate, but it is uncertain how much of the reduction in size is secondary to the transurethral resection as opposed to the laser therapy. Fifty-four percent of patients had an undetectable postoperative prostate-specific antigen (PSA) level, whereas 14% of patients had a PSA level outside the normal range. Undoubtedly, further follow-up will be necessary to assess the efficacy of this technique. The multifocal nature of prostatic adenocarcinoma makes one question whether this type of ablative therapy has promise.

Ureter

The small diameter and flexibility of laser fibers allow their use through either rigid or flexible ureteroscopes (115). Flexible 200- to 400-micron fibers are particularly suited for ureteroscopic application. Larger-diameter fibers may pass through the working ports of several small ureteroscopes, but the rigidity of a 400- to 600-micron fiber inhibits active deflection of the ureteroscope tip. Nd:YAG, KTP, and holmium lasers may all be used on the ureter for soft tissue ablation. KTP and holmium lasers have a theoretic advantage over the Nd:YAG laser for treatment in the thin-walled ureter. Both lasers produce more superficial zones of tissue injury than the Nd:YAG laser.

In highly selected patients with low-grade transitional cell carcinoma of the ureter, successful treatment can be achieved with endoscopic Nd:YAG, KTP, or holmium laser therapy (62,72) (Fig. 6.13). Several authors have reported extensive single-institution experience.

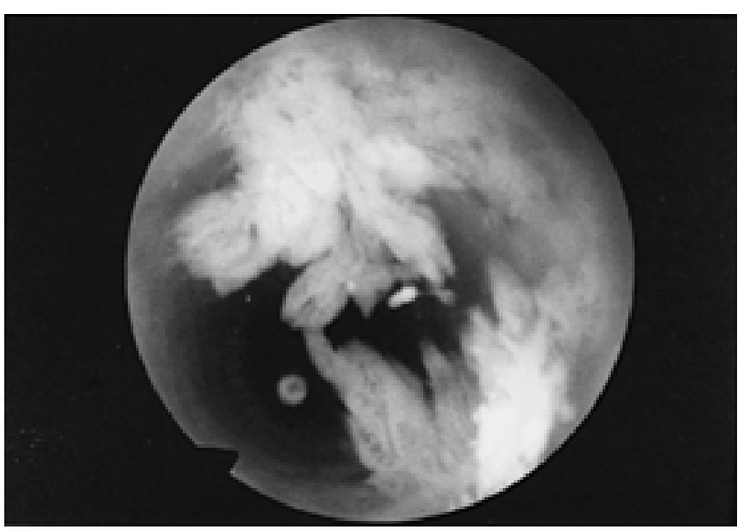

FIGURE 6.13. Papillary transitional cell carcinoma of the ureter. Nd:YAG laser energy can be applied via a small fiber inserted through either a flexible or rigid ureteroscope.

Schmeller (109) treated 18 patients using the Nd:YAG laser. Treatment was not feasible in three patients because of tumor size or location. Of the remaining 15 patients, 14 had no evidence of recurrence with a variable but generally

adequate length of follow-up after laser treatment. Ureteral strictures developed in three patients in whom circumferential treatment was performed.

Kaufman and Carson (61) reported nine patients with ureteral tumors treated with the Nd:YAG laser. No patient had a recurrence, and no strictures were observed. Gaboardi and colleagues (38) treated 18 patients with biopsy-confirmed ureteral tumors with Nd:YAG laser energy applied through a ureteroscope (25 to 30 W for 3 seconds). Eight patients developed a recurrence that was subsequently treated with a repeat Nd:YAG laser application. Nephroureterectomy was required in one patient for tumor control.

Thirty-eight patients with upper tract transitional cell carcinoma were treated in one series using both Nd:YAG and holmium lasers (62). Patients underwent ureterorenoscopy every 6 to 12 weeks until they were proven to be tumor free. Seventy-five percent of recurrent tumors were not identified radiographically. Patients were treated with the Nd:YAG laser or later with the holmium laser. Median follow-up was 35.1 and 26 months, respectively. High tumor grade, size, and multifocality were associated with tumor persistence and recurrence. The authors concluded that endoscopic management of upper tract transitional cell carcinoma is reasonable in selected patients. No significant difference was noted between the Nd:YAG and holmium laser–treated groups.

Kidney

Lasers have not proven to be particularly beneficial for partial nephrectomy. The hemostasis achieved with the CO_2 laser is suboptimal (7,104). The Nd:YAG laser is a poor cutting instrument and is not useful for incising the renal parenchyma (14). When combined with an ultrasonic surgical aspirator, the Nd:YAG laser does appear to be capable of decreasing the blood loss associated with partial nephrectomy (86). However, this technique requires the combination of two cumbersome instruments, and the inconvenience may outweigh the benefits.

The Nd:YAG laser has been useful when the surgical margins are precarious after treatment of a renal cell carcinoma. After enucleation of a renal tumor or a compromised partial nephrectomy, Nd:YAG laser energy can be applied to further extend the margin some 5 mm and help gain hemostasis (71). Virtually no patient morbidity is involved in this technique, and it seems to be a potentially beneficial use of the Nd:YAG laser.

The Nd:YAG laser has been used for percutaneous thermoablation of inoperative renal tumors. The investigators treated three patients using real-time guidance in an open-access interventional magnetic resonance imaging (MRI) scanner (30). Ablation and necrosis of target tissue was confirmed by follow-up gadolinium-enhanced MRI. Whether this type of treatment affects patient outcome remains to be seen. Nevertheless, the authors have demonstrated the concept of percutaneous ablation of malignant renal tissue with the Nd:YAG laser.

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7

GENITOURINARY MALIGNANCY: ETIOLOGY AND MOLECULAR GENETICS, NATURAL HISTORY, AND TREATMENT

Mcclellan M. Walther

Fredrick Leach

David K. Ornstein

Norman Zambrano

W. Marston Linehan

M.M. Walther, F. Leach, D.K. Ornstein, and W.M. Linehan: Urologic Oncology Branch, National Cancer Institute, Bethesda, MD 20892.

N. Zambrano: Department of Urology, Catholic University of Chile, Santiago, Chile; Urology Service, Sotero Del Rio Hospital, Puente Alto, Santiago, Chile.

Contents

Kidney cancer, prostate cancer, and bladder cancer affect more than 250,000 people annually in the United States, and nearly 56,000 die from these diseases each year. Significant and dramatic improvements have been made in the last decade in both the diagnosis and the treatment of these malignancies. However, despite these remarkable advances, most patients with advanced renal, prostate, or bladder cancer still die from these diseases. We have witnessed a dramatic biotechnologic revolution over the past two decades, which has provided significant opportunities for the development of better methods for diagnosis, prevention, and treatment of these genitourinary malignancies. Many scientists and clinicians believe that the key to the development of rational and effective forms of therapy for patients with advanced genitourinary malignancies lies in the understanding of the fundamental basis of these cancers, that is, in identification of the genes that cause these cancers and elucidation of the molecular genetic basis for their progression. Examples of molecular therapeutics have proven this principle, and it is the hope of scientists and clinicians that understanding the molecular genetic basis of genitourinary cancers and their molecular pathways will lead to even better methods for diagnosis, prevention, and treatment of these cancers.

RENAL CELL CARCINOMA: ETIOLOGY, NATURAL HISTORY, AND MOLECULAR GENETICS

Part of "7 - GENITOURINARY MALIGNANCY: ETIOLOGY AND MOLECULAR GENETICS, NATURAL HISTORY, AND TREATMENT "

Renal cell carcinoma is a historical term that has been applied to a number of renal parenchymal tumors of different histopathologic types. An attempt to classify renal cell carcinomas was begun by Grawitz (160) in 1883, when the origin of renal tumors was attributed to an ectopic adrenal rest and named “hypernephroma.” Understanding of the genetic abnormalities found in renal tumors has led to a recognition of distinctive histologic types of tumors. Kovacs (245) classified genetically similar renal cell tumors and divided them clinically into four groups: those with papillary growth or nonpapillary pattern, chromophobe renal cell carcinomas, and renal oncocytomas. Papillary renal cell carcinomas were defined by the presence of at least 75% of the tumor with a papillary pattern (245).

Recently, a division of renal cell tumors into benign and malignant categories has been proposed (462). Benign tumors were subclassified into oncocytoma, papillary renal adenoma, and metanephric adenoma. Malignant tumors were subclassified into conventional (clear-cell) renal carcinoma; papillary renal carcinoma; chromophobe renal carcinoma; collecting duct carcinoma; and renal cell carcinoma, unclassified.

Incidence and Time Trends

Malignant tumors of the kidney account for about 3% of cancer incidence in the United States. Approximately 30,800 new cases of renal cancer were estimated to occur in the United States in the year 2001, and 12,100 patients were predicted to die of their disease (163a). Generally, renal cancers occur at a median age of 65 years, and men are affected 1.5 times as frequently as women (163).

The incidence of renal cancer in the United States has been increasing over the last 65 years (69). The age-adjusted incidence rates for renal cancer over approximately the last 20 years have been 9.6 per 100,000 person-years for Caucasian men, 11.1 for African-American men, 4.4 for Caucasian women, and 4.9 for African-American women (69). Annual incidence rates in these groups have risen from 2.3% to 4.3% per year. Increases occurred in all stages, the largest occurring in patients with localized renal tumors (rising from 3.8% to 5.6% per year during the same period). The development of new imaging technologies has not accounted for all of these changes (69). Trends in 5-year relative cancer survival rates have been increasing for both Caucasians and African-Americans (163).

Etiology

Environmental and hereditary genetic factors have been associated with the development of the renal cell carcinomas, although individual toxins have not been linked to specific histologies. Environmental factors thought to confer risk include cigarette smoking, petrochemicals, cadmium, and thorium dioxide. Other related factors include obesity and long-term renal dialysis for the treatment of end-stage renal disease. Hereditary forms of most of the histologic types of renal cell carcinoma have also been described.

The increasing incidence of renal cell carcinoma in the United States has been attributed to increased obesity and protein intake, rising incidence of hypertension in the increasing obese and elderly populations, and increasing exposure to toxic environmental agents. Smoking has been on the decline, and this may contribute to a smaller proportion of patients developing renal cancer in the future.

Cigarette Smoking

Case-control studies generally report an association between cigarette smoking and the development of renal cancer (relative risk of 1.35 to 2.2) (255,289,299,300,415,458,461) with risk related to duration of exposure (300,317). The risk attributed to cigarette smoking has been shown to increase with increasing number of cigarettes smoked per day (461). The dose-response relation observed further

substantiates this association (48,255,289,300). The lack of association in some studies has been attributed to lack of power secondary to small sample size or biased samples with a high prevalence of smoking in the control group, such as hospital controls (413). With cessation of smoking, the risk of renal cell carcinoma decreases, as much as 30% to 50% at 10 to 25 years (299,461). Gender and presence of a filter on the cigarette have not been found to alter risk. It has been estimated that 24% of female and 30% of male renal cell carcinomas (24) to approximately 18% overall may be caused by cigarette smoking (300a).

In patients with renal cancer, it has been suggested that patients who smoke have more advanced disease at diagnosis and shorter survival than nonsmokers (411).

Obesity

The presence of obesity has been highly correlated with the development of renal cell carcinoma in case-control studies (317,415). The question of whether the risk of renal cell carcinoma is attributed to obesity alone or obesity-related food pattern remains to be answered. Obesity is linked to dietary intake. The incidence of renal cell carcinoma has been positively correlated with intake of fat-containing foods (fats, oil, meat, milk, sugar) and negatively correlated with cereals and vegetables (36,289).

Case-control studies and cohort studies have shown increased risk of developing renal cancer related to high caloric intake (relative risk of 1.7), high intake of fatty foods (relative risk of 1.90), and high protein intake (relative risk of 1.71) (11,36,289,456). Decreasing risk was seen with increasing intake of fruit (relative risk of 0.4 to 0.85) and vitamin C (relative risk of 0.62) (36,456). Studies controlling for caloric intake, body mass, and smoking show protein intake as an independent risk factor (11). It has been estimated that 21% of renal cell carcinoma in the general population is attributed to excess body weight (24).

Hypertension

Cohort studies have been performed to evaluate the association of hypertension and associated medical treatment with the development of renal cancer (186,373,415). Hypertension alone does not appear to be associated with such a risk (186). Although not entirely consistent, the accumulated data suggest that diuretics may increase the risk of renal cancer, especially among women. Increase usage or duration of use was associated with greater risk. The use of ß-adrenergic blockers has also been suggested to be associated with the development of renal carcinoma (odds ratio of 1.5 to 3.0) (415). It has been estimated that 18% of renal cell carcinoma is attributable to hypertension (24).

Occupation

Case-control and cohort studies have shown that exposure to various chemicals is significantly linked to the development of renal cancer (294,301,433). Significant associations have been reported in the blast-furnace and coke-oven industries (odds ratio of 1.7 to 2.0); in the iron and steel industry (odds ratio of 1.6 to 2.5); among firefighters (odds ratio of 3.5), glassworkers (odds ratio of 3.5), chemical processors (odds ratio of 2.6), photographers (odds ratio of 2.1), and painters (odds ratio of 1.6); and for exposure to asbestos (odds ratio of 1.4 to 1.6), cadmium (odds ratio of 2.0), dry cleaning solvents (odds ratio of 1.4 to 1.5), gasoline (odds ratio of 1.6 to 2.1), petroleum products (odds ratio of 1.6), carbon tetrachloride (odds ratio of 2.5), and tetrachlorethene (odds ratio of 10.8) (98,294,301,433).

Carcinogenesis is thought to occur secondary to exposure to toxic metabolites of the environmental agents. A common mechanism of metabolism is enzymatic conjugation with glutathione, which facilitates further processing. Further conjugation with cysteine adducts allows acetylation to mercaptic acids, which are excreted in the urine, or cleavage by kidney tubular epithelium to highly reactive chlorinated thioketenes. *In vitro* and *in vivo* studies suggest that these metabolites are highly genotoxic (171,229).

End-stage Renal Disease

The development of cystic disease in kidneys of patients undergoing hemodialysis was first observed by Dunnill (108) in an autopsy study in 1977. Cystic disease has subsequently been found in patients with chronic renal failure and undergoing dialysis. Patients with end-stage renal disease maintained by dialysis have an 18% to 88% incidence of acquired renal cystic disease and a 1% to 7% incidence of renal cancer (187,348,364). Risk of cystic disease appears to increase with duration of dialysis (364,432). The renal cancer histology that is clinically apparent has most frequently been clear cell. Clinically inapparent cancers, that is, microscopic papillary renal cancers, have also been reported with some frequency (187,348).

Male patients may be more frequently affected (187,348). Patient survival appears to be related to tumor stage (348). Overall survival in patients reviewed in the literature was 70% at 1 year, 35% at 5 years, and 10% at 10 years (298).

Medical and Family History

A single first-degree relative affected with renal cancer is associated with an increased familial risk of developing renal cancer (relative risk of 1.6) (373). Thyroid disease was also associated with the development of renal cancer (relative

risk of 1.6) (373). A significant trend in risk was reported with number of childbirths in women (272). Use of oral contraceptives has also been associated with a reduced risk of renal cancer in nonsmoking women (272). No association has been reported with estrogen replacement therapy in women (272).

Polymorphic Xenobiotic-metabolizing Enzymes

Environmental toxins may be directly toxic, or they may require metabolic activation by oxidative (phase I) enzymes, such as members of the cytochrome P450 family (CYP), to be transformed into toxic metabolites. Removal of most carcinogens starts with the conjugation action of phase II enzymes, such as the glutathione-S-transferase (GST) and arylamine *N*-acetyltransferases (NAT) families of enzymes.

A wide range of metabolizer enzyme activity in each gene family has been described, ranging from a polymophism associated with loss of the involved gene to a gene with full enzymatic activity. These naturally occurring genetic polymorphisms could infer great interindividual variation in susceptibility to develop cancer after exposure to environmental toxins. Polymorphisms of these types have been shown to be associated with development of bladder and head and neck cancers in patients who smoke (195,256).

The ability to metabolize environmental toxins may be protective for the development of renal cancer. Presence of the 1A1 allele of CYP has been associated with an increased risk of developing renal cancer (283). Presence of the CYP1A1allele with either the TT1 or TP1 alleles of GST or the NAT2 (slow acetylator) polymorphism has been reported to further increase this risk (283). Patients with loss of the Mu1 allele of GST (null polymorphism) and presence of π1 GST polymorphism have even higher risk if the CYP1A1 or NAT2 (slow acetylator) is also present (283).

Hereditary Forms of Renal Cancer

Renal cell carcinoma can occur in an inherited form, similar to retinoblastoma, breast cancer, prostate cancer, and colon cancer. As many as 4% of renal cancers may be inherited (275). Inherited renal cancers are characterized by early age of onset of bilateral, multifocal renal tumors. Two forms of clear-cell renal cancer have been described. Von Hippel–Lindau disease (VHL) is an autosomal dominant inherited multiorgan tumor syndrome in which 40% to 45% of affected individuals develop clear-cell renal tumors (Fig. 7.1) (150,349). Its incidence has been estimated as 1:36,000 (291). Individual families have also been described with reciprocal germline chromosome 3 translocations that are associated with the development of clear-cell renal tumors (35,74,240,248,271,449).

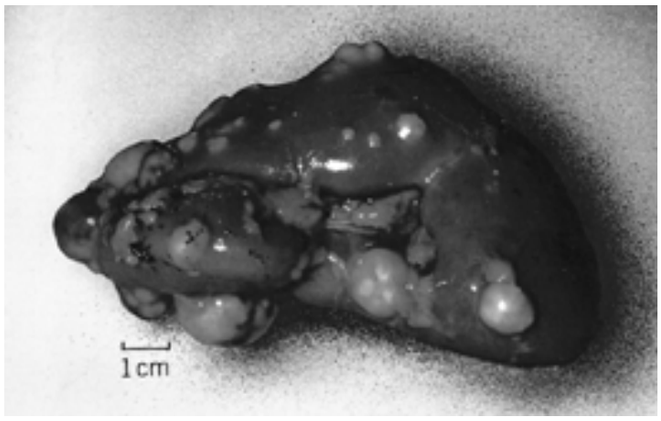

FIGURE 7.1. Von Hippel–Lindau (VHL) disease is characterized by the development of multiple bilateral clear-cell renal cancers and cysts over the course of the patient's life. A typical VHL kidney is shown here.

Hereditary basophilic papillary renal cell carcinoma (Fig. 7.2) (463,464) and hereditary renal oncocytoma (453) have also been described, both manifesting with autosomal dominant inheritance of bilateral, multifocal renal tumors.

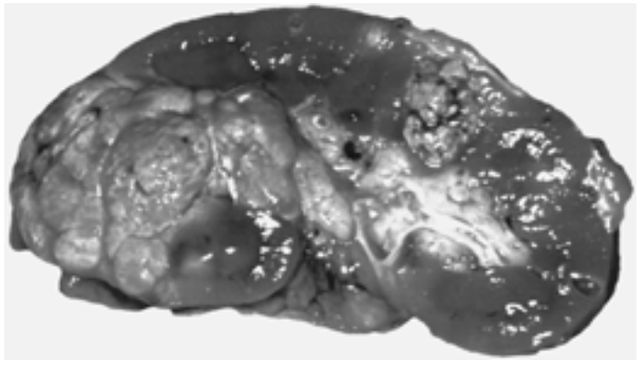

FIGURE 7.2. Hereditary papillary renal cancer is characterized by the development of bilateral basophilic (type 1) papillary renal cell cancers over the course of the patient's life. Cystic disease does not occur as part of HPRC. A typical HPRC kidney is shown here (463).

Birt-Hogg-Dubé syndrome (BHD) is characterized by the clinical manifestations of skin fibrofolliculomas and pulmonary cysts leading to spontaneous pneumothorax. Recently, it has been observed that renal tumors of several histologic tumor types can develop in these patients. This syndrome is currently being characterized (428).

Natural History

Patient survival is strongly associated with tumor stage. Five-year disease-specific survival has been reported as 91%, 74%, 67%, and 32% for tumor, node, metastasis (TNM) stages I, II, III, and IV lesions (69,430). Tumor characteristics similarly correlated with a 5-year survival rate of 83% for stage T_1, 57% for stage T_2, 42% for stage T_3, and 28% for stage T_4 disease. Tumor grade is also associated with

patient survival: 89% 5-year survival for grade 1, 65% for grade 2, and 46% for grades 3 and 4. Overall, TNM stage and tumor grade were the most important prognostic indicators, whereas the Eastern Cooperative Oncology Group (ECOG) performance status was a less significant predictor and tumor stage was not an independent predictor (209,216,316,430).

Evaluation of prognosis associated with different tumor histopathologies suggests that some renal cancer types may be more aggressive than others. In patients with similar size renal tumors, those with clear-cell renal cancer had metastases at the time of diagnosis more frequently than patients with papillary or chromophobe renal tumors (37% versus 16% versus 8%, p = .044 and .048, respectively) (280). Patients with papillary and chromophobe renal cancer also had longer survival.

Clinical parameters at initial presentation have also been correlated with survival. Symptomatic presentation and significant weight loss have been associated with decreased survival (144). Shortened survival has been associated with the laboratory findings of elevated serum lactate dehydrogenase, C-reactive protein, erythrocyte sedimentation rate, and alkaline phosphatase; low hemoglobin; and hypercalcemia (144,297,316).

Molecular Genetics

Renal carcinoma may occur in both inherited and noninherited forms. As many as 4% patients with renal carcinoma may carry an inherited factor (275). Inherited renal cancer gives special insight into the earliest genetic changes required for the different histologic types of renal cancer to develop. Clinically, patients with familial renal cancer are characterized by early age at presentation of multiple, bilateral renal tumors. New renal tumors can develop over the course of the patient's life.

The best-characterized hereditary renal cancer is VHL (151), in which as many as 45% of affected individuals develop clear-cell renal carcinoma (151,349). Individual families have also been described with hereditary clear-cell renal cancer associated with the reciprocal germline translocation of chromosome 3 to 8 (74,271,449), chromosome 3 to 6 (248), or chromosome 3 to 2 (35,240). Hereditary papillary renal cell carcinoma is a familial form with autosomal dominant transmission, but at a reduced penetrance in comparison with VHL and familial clear-cell cancer (463). Hereditary renal oncocytoma has been described in a number of families (453) BHD is a hereditary renal syndrome characterized by autosomal dominant inheritance of multiple bilateral chromophobe renal tumors, spontaneous pneumothorax, and characteristic cutaneous trichofolliculoma (34,362,428).

The study of inherited forms of renal tumors allows the use of the powerful tools of linkage analysis to localize and identify the initial genetic abnormality leading to a specific histologic subtype of renal cancer. Identification of these genes may be useful clinically in the diagnosis of renal tumors and their metastases.

HISTOPATHOLOGIC CLASSIFICATION OF RENAL TUMORS

Part of "7 - GENITOURINARY MALIGNANCY: ETIOLOGY AND MOLECULAR GENETICS, NATURAL HISTORY, AND TREATMENT "

Renal tumors have been classified based on cytomorphologic characteristics and presumed cellular origin. Thoenes and colleagues (422) developed one of the first modern classifications of benign and malignant renal tumors based on these features. Renal tumors were categorized as (a) clear cell, (b) chromophil, (c) chromophobe, (d) spindle shaped or pleomorphic, or (e) oncocytoma. The study of tumor genetics has led to the recognition of distinctive types of renal tumors: carcinoma with papillary morphologic pattern, carcinoma with nonpapillary pattern, chromophobe renal cell carcinoma, and renal oncocytoma (245).

Storkel and colleagues (406) and Kovacs and colleagues (243) proposed a histopathologic classification of renal tumors based on the underlying genetic abnormalities of the different subtypes. Both classifications recognize benign and malignant renal neoplasms. Malignant tumors were classified into conventional or clear-cell, papillary, chromophobe, collecting duct, and unclassified renal cancer. Benign tumors were classified into metanephric adenoma and adenofibroma, papillary renal cell adenoma, and renal oncocytoma. A European and American joint working group adopted a similar histologic classification system in 1997 (Table 7.1) (406,462).

Malignant Neoplasms
1. Conventional (clear-cell) carcinoma
2. Papillary renal carcinoma
3. Chromophobe renal carcinoma
4. Collecting duct carcinoma
5. Renal cell carcinoma, unclassified
Benign Neoplasms
1. Oncocytoma
2. Papillary adenoma
3. Metanephric adenoma

Histologic classification of renal tumors by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer.

TABLE 7.1. UICC CLASSIFICATION OF RENAL TUMORS

GENETIC CLASSIFICATION OF RENAL NEOPLASMS

Part of "7 - GENITOURINARY MALIGNANCY: ETIOLOGY AND MOLECULAR GENETICS, NATURAL HISTORY, AND TREATMENT "

Hereditary Conventional Renal Cancer

Germline mutations in the VHL gene (chromosome 3p25) lead to conventional (clear-cell) renal cancer, the most

common form of inherited renal cancer. Single families with reciprocal germline translocations involving chromosome 3 have also been described to develop a hereditary form of conventional renal cancer (35,74,240,248,271,449). Evaluation of tumors from these patients reveals both copies of the VHL gene to be inactivated. One copy of the gene has the germline mutation and the second copy has a somatic (acquired) mutation (35,154,271,377). Inactivation of both copies of a gene in this fashion is characteristic of a tumor-suppressor gene. These findings support mutation of the VHL gene as the initial genetic event in the development of clear-cell renal cancer.

Clear-cell Renal Carcinoma

Conventional, or clear-cell, renal carcinoma makes up 70% to 80% of renal tumors (462) and is the most studied renal tumor. Conventional renal carcinoma is believed to derive from proximal renal tubular epithelial cells (25,129). These tumors consist predominantly of cells with clear cytoplasm, although foci of cells with eosinophilic cytoplasm are common. Tumor architecture is usually solid and cystic, and tumors have a characteristic delicate branching vasculature. Approximately 5% of these tumors develop high-grade, sarcomatoid changes (406,462).

Sporadic Clear-cell Renal Cancer

Similar to inherited conventional (clear-cell) renal cancer, sporadic conventional renal cancer is thought to arise from loss of function of both copies of the VHL gene. In sporadic tumors, both mutations occur as somatic events. Ninety-eight localized and advanced conventional renal tumors analyzed by Gnarra and colleagues (154) had loss of one copy of the VHL gene [loss of heterozygosity (LOH)]. The second copy of the VHL gene was mutated in 57% of the tumors. These findings have been confirmed by other reports of chromosome 3p LOH and by cytogenetic studies (10,154,227).

An alternative mechanism of inactivation to LOH, hypermethylation, has also been described. Chromosomal regions rich in groups of CpG, termed *CpG islands,* are often found in the 5´ regulatory areas of genes, where hypermethylation could render the genes inactive (33). Hypermethylation of the VHL gene was reported in 11% (149) to 19% (191) of sporadic conventional renal tumors. Hypermethylation of the VHL gene has been associated with loss of expression of the VHL gene by Northern blot analysis (191).

These data show a very high degree of loss of one copy of the VHL gene by LOH, and at least 53% to 76% inactivation of the second copy, in conventional renal cancers (154,191,227,410). Inactivation of the VHL gene has been associated specifically with conventional renal cancers (154,227) and suggests the requirement of inactivation of both copies of the VHL gene for the development of conventional renal cancer.

Other Early Genetic Changes

Loss of function of the VHL tumor-suppressor gene has been associated with increased expression of transforming growth factor-α (TGF-α) (234). Northern blot mRNA expression of TGF-α and TGF-β_1 has been reported elevated in 60% of undefined sporadic renal cancers when compared with normal kidney (156). As many as 75% of undefined sporadic renal cancers have increased expression of the *myc* oncogene (232,452).

Late Events or Progression

Higher clinical stage, higher tumor grade, and poor prognosis have been associated with the expression of specific genetic abnormalities. The best-characterized changes have been in the p53 (chromosome 17p13) tumor-suppressor gene. P53 is the most commonly mutated gene in human cancer and is linked to control of cell cycling from G_1 to S phase. Oda and colleagues (329) studied both carcinomatous and high-grade sarcomatous portions of 14 sarcomatoid renal cancers by polymerase chain reaction, subcloning and sequencing the p53 gene. Sarcomatoid tumors had a high mutation rate for the p53 gene (78.6%), compared with a low p53 mutation rate (14.3%) in carcinomatous tumors. Immunohistochemical studies of p53 in these tumor types has demonstrated similar findings (196).

Thirty-seven percent of conventional renal cancers examined with dual-color fluorescence in situ hybridization had loss of chromosomes 14q (457). This loss was significantly correlated with higher stage, higher histologic grade, and worse patient outcome. Similar studies have shown loss of chromosome 14q correlated with higher nuclear grade and advanced tumor stage (379). Smaller studies have shown loss of genetic material on chromosome 2 (351) correlated with higher tumor stage and gain of chromosomes 12 and 20 (102) with higher nuclear grade. Increased expression of type IV collagenase in renal cancer cell lines from patients with metastatic renal cancer has correlated with shortened survival (445) Larger studies are required to corroborate these findings.

Loss and mutations of the VHL gene in all stages of conventional renal carcinoma, as well as in familial forms, indicates that the VHL gene is central to the origin of this tumor (154,259).

Papillary Renal Cell Carcinoma

The second most common cancer of the kidney is papillary renal cancer, accounting for 10% to 15% of renal neoplasms(245,422).

Papillary renal cancer has distinct morphologic and cytogenetic features that distinguish it from conventional (clear-cell) and chromophobe renal cancer (99,245,422).

Papillary renal cancer is defined by the presence of at least 75% of the tumor composed of papillary or tubulopapillary architectural pattern (6,99,422). Papillary tumors are chromophilic, describing their characteristic uptake of dyes, and are subdivided into eosinophil, basophil, and duophil tumors (422). Basophilic tumors contain small cells with scanty amphophilic cytoplasm and small, low-grade nuclei (244,422). Eosinophilic tumors are characterized by large cells with abundant eosinophilic cytoplasm and large nuclei. Delahunt and Eble (99) proposed to classify papillary renal cancer into type I and type II, corresponding to chromophil-basophilic and chromophil-eosinophilic tumors (422).

Papillary renal cancer occurs more often in men, with a 5:1 to 8:1 preponderance (245,247). Basophilic papillary renal cancer occurs about twice as frequently as the eosinophil variant (99). The incidence of eosinophil papillary renal cancer is higher in patients with end-stage renal disease than in the general population (203,250). Survival rates for patients with all types of papillary renal cancer are higher than those for patients with conventional renal cancer (6,172,358).

Hereditary Papillary Renal Cancer

A hereditary form of basophilic papillary (type I) renal cancer has been described, characterized by multiple bilateral renal tumors inherited in an autosomal dominant fashion (376). The hereditary papillary renal cell carcinoma gene is the protooncogene, *c-met*, located on chromosome 7q31.1-34 (374). Missense mutations in the tyrosine kinase domain of the *c-met* gene have been identified in the germline of affected family members.

Sporadic Papillary Renal Cancer

Approximately 80% of sporadic papillary renal cancers contain multiple copies of genes. Trisomy or tetrasomy of chromosome 7 and trisomy of chromosome 17 have been found in 45% to 100% and in 64% to 100% of papillary renal cancers, respectively (27,101,203,246,462). Sporadic papillary renal carcinomas have been shown to contain mutations of the *c-met* gene (374,375). Introduction of mutant *c-met* will transform cells *in vitro* and is tumorigenic in nude mice (217), findings typical of a tumor oncogene. The chromosome 7 mutations have been observed in all stage and grade tumors, suggesting that *c-met* oncogene expression is an initial event in the development of basophilic papillary renal cancer. Early molecular events in eosinophilic papillary renal cancers are not well described, although there has been an associated with the 1:X translocation (221,390,454).

Trisomy of chromosome 17 may occur as a later abnormality (27,101). No p53 mutations have been reported in these tumors, suggesting that other genes in this chromosome are involved in tumor progression (78,101). Other DNA losses described include LOH on chromosomes 9p, 11q, 14q, 21q, and 6p in 43%, 43%, 37%, 37%, and 33% of the tumors, respectively (425). In addition, Y chromosome loss has been observed in 80% to 90% of papillary renal cancers from males (101,202,252).

Mutations in the *c-met* oncogene differentiate papillary renal tumors from conventional tumors on a genetic basis. Chromosome 3p and VHL gene abnormalities are not important in the development of this neoplasm (10,132,425).

Chromophobe Renal Cell Carcinoma

Chromophobe renal cancer accounts for approximately 5% of renal neoplasms (90,422). Chromophobe renal cancer is characterized histologically by compact growth pattern of large polygonal cells with pale reticular cytoplasm and prominent cell membranes (423). Chromophobe cells often have numerous cytoplasmic vesicles by electron microscopic analysis (31,90). Compared with conventional renal cancer, these cells have low glycogen content. Another diagnostic finding in chromophobe renal cancer is lack of cytoplasmic staining with routine dyes. A diffuse, strong cytoplasmic staining with Hale's colloid iron stain has been suggested to be characteristic for chromophobe renal cancer (427). This tumor, however, may be composed of so-called eosinophilic chromophobe cells, which have a large number of mitochondria and few cytoplasmic vesicles (421). The presumed progenitor cells for chromophobe renal cancer are the intercalated cells of the collecting duct (337,420).

Five-year survival has been reported as 92% for chromophobe and 62% for conventional renal cancer of equal nuclear grade (423). Other studies, however, demonstrated similar 5-year survival rates between chromophobe and conventional renal cancers of nuclear grade II and Robson clinical stage I (85% and 84%, respectively), perhaps because most chromophobe renal cancers were stage I (86%) or were discovered incidentally (53%) (90).

Karyotypic changes in chromophobe renal cancers included monosomies of chromosomes 1, 2, 6, 10, 13, and 17 (211,242,251). Molecular genetic studies have confirmed these findings, with loss in 54% to 95% of tumors (50,382,398). Chromosome 3p loss of heterozygosity was observed in 25% of chromophobe tumors, with only rare mutations in the VHL gene (227,389).

Mutations in the p53 gene were identified in 30% of chromophobe renal cancers studied, whereas LOH on chromosome 17p was detected in 78% of tumors. The lack of

correlation of p53 mutations with LOH suggested the presence of a second genetic abnormality on chromosome 17 (78).

No genetic change has been observed to occur in all tumor nuclear grades or clinical or pathologic stages, suggesting the initial genetic occurrence characteristic of this tumor type.

Collecting Duct Carcinoma (Bellini Duct Carcinoma)

Collecting duct carcinoma (CDC) makes up approximately 0.4% to 2.6% of renal cancers (243,406,462) and is thought to arise from the medullary collecting ducts (420). Collecting duct carcinomas are usually centrally located, arising in the renal medulla, are white-gray in color, and demonstrate a tubulopapillary growth pattern and a microcystic and solid pattern. Microscopic findings are high-grade cytologic atypia and stromal desmoplasia with dysplastic changes in the neighboring medullary renal tubules. Strong positivity for intracytoplasmic mucin is seen on appropriate stains (228). Collecting duct cancer may be more aggressive in clinical behavior than other renal cancers (14,103). Local invasion or lymph node metastases are common (228).

Few chromosomal studies have been performed on CDC. The most frequently described karyotypic abnormalities have been monosomy of chromosomes 18, 21, and Y (57,165). Other findings include gain of chromosomes 7, 12, 17, and 20. Loss of heterozygosity has been found on chromosome 1q in 57% to 69% of CDC, especially in the region of 1q32 (346,405). LOH has also been detected on chromosomes 8p (48%), 6p (45%), 21q (40%), and 13q (50%). Forty-five percent of tumors have amplification of the oncogene *c-erbB* (383). All patients with this finding died within 1 year, whereas half of patients without amplification were alive after a mean follow-up of 42 months (383).

Renal medullary carcinoma (RMC) may be a variant of CDC (243,406) first described by Davis and colleagues (93) in 1995. RMC has been reported only in African-American patients with sickle cell trait or hemoglobin–sickle cell disease (92,93). Karyotypic findings were loss of chromosome 11 in four of six tumors examined (13). This finding is noteworthy for the presence of the ß-globin gene on chromosome 11p (97).

Renal medullary cancer manifests in the second or third decade of life, usually with metastatic disease (92,93). Mean patient survival has been reported as 3.5 months after diagnosis (135,194).

Mean tumor size at presentation has been 7 cm in diameter, located primarily in the renal medulla (92,93). There is a characteristic infiltrative growth pattern (92) with peripheral satellite tumors in the renal cortex and venous and lymphatic invasion. RMC demonstrated a reticular, yolk sac–like, or adenoid cystic appearance, frequently with poorly differentiated areas in a highly desmoplastic stroma.

Renal Oncocytoma

Renal oncocytomas make up 3% to 5% of renal tumors and are thought to originate from the distal renal tubule (7,420). Renal oncocytomas are predominantly composed of eosinophilic cells arranged in a characteristic nested or organoid fashion (7,341). Oncocytomas are usually well circumscribed, beige or mahogany brown tumors that lack areas of necrosis. A gross or microscopic central scar may be present. Renal oncocytomas have nuclei that are round with uniform contours. About half of tumors have prominent nucleoli. A high content of cytoplasmic mitochondria is characteristic of oncocytoma (115). Renal oncocytoma lack significant necrosis, mitosis, or conspicuous papillary formations (7). The eosinophilic (granular) cytoplasm of oncocytomas may appear similar to that found in other renal neoplasms such as chromophobe, conventional, and papillary renal cancer (341). Typical renal oncocytomas are considered a benign neoplasm (7,304,406).

Three types of genetic abnormalities of oncocytoma have been observed: (a) numerical anomalies, including loss of chromosomes Y and 1 (46,188,426); (b) translocations involving the breakpoint region 11q13 [t(5;11)(q35;q13) and t(9;11)(p23;q13)] (323,393); and (c) a variety of other genetic abnormalities, including chromosomal monosomies (164), trisomy 1, 7, 12, and 14 (434), and loss of heterozygosity of chromosomes 17p, 17q, 10q, and 3p (414). Genetic abnormalities in patients with hereditary forms of renal oncocytoma have not been described (453) (Fig. 7.3).

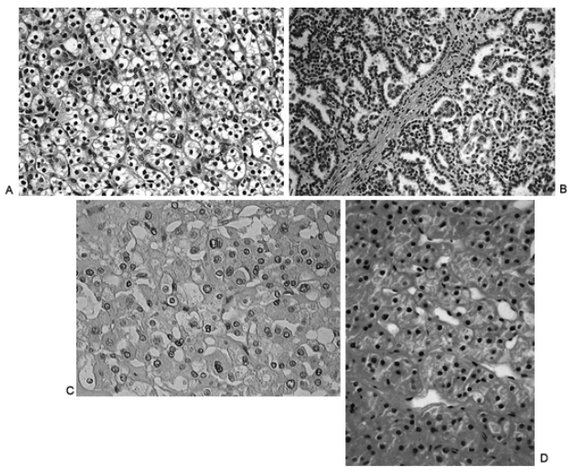

FIGURE 7.3. A: Clear-cell renal carcinoma (characterized by VHL gene mutation) (153,274). **B:** Papillary type 1 renal carcinoma (464) from patient with hereditary papillary renal carcinoma (374) characterized by *c-met* mutation (375). **C:** Chromophobe renal carcinoma. **D:** Oncocytoma, as seen in patients affected with Birt-Hogg-Dubé syndrome (428).

Papillary Adenoma

The most common renal neoplasm is papillary adenoma, occurring in as many as 20% of patients (166). Papillary adenomas are solid-tubular-papillary structures consisting of small “blue” cells (basophilic) or large eosinophilic cells, similar to low-grade papillary renal cancers. Papillary adenomas are usually less than 5 mm in diameter (246,406). There are no cytologic criteria to distinguish papillary adenomas from small papillary renal cancers, suggesting that papillary adenoma could represent early papillary renal cancer (45). Genetic findings are trisomy or tetrasomy 7, trisomy 17, and loss of the Y chromosome (246,249).

Metanephric Adenoma

Renal metanephric adenomas are rare, benign, well-circumscribed tumors that may represent the benign counterpart of Wilms' tumor (143,356). Histologically, metanephric adenomas are composed of uniformly small epithelial cells forming tubules or tubulopapillary structures. They are characterized by an unusual degree of cell

maturation and differentiation. Rosette-like configurations with no evidence of necrosis or cellular atypia can be present. The cell nuclei are oval, smooth, and without mitosis. Only rare cytogenetic studies have been reported (143,356).

OVERVIEW

Part of "7 - GENITOURINARY MALIGNANCY: ETIOLOGY AND MOLECULAR GENETICS, NATURAL HISTORY, AND TREATMENT "

The initial genetic changes important for the development of each histologic tumor subtype appear to be unique to each tumor type and may be useful in molecular diagnosis of renal tumors or their metastases (Table 7.2). Characterization of these genetic anomalies will allow more accurate diagnosis and prognostic evaluation and may help in planning therapy. The identification of familial forms of these tumors is an important tool in the identification of hereditary forms of renal cancer. Identification of germline mutations in these families allows earlier diagnosis with an associated wider range of treatment options. The identification of secondary genetic markers, such as mutations of p53, duplication of chromosome 5q22, loss of chromosome 14q, and overexpression of collagenase type IV, will contribute to prognostic planning of individual patients' tumors in the future.

Pathologic Subtype Findings	Initial Findings	Later Findings
Conventional (clear-cell) carcinoma	3p LOH VHL gene mutation	+5q −8p, −9p, −14q p53 mutation C-erbB-1 oncogene expression
Papillary renal carcinoma	+7, +17 −Y Met gene mutation	+12, +16, +20 −9p, −11q, −14q, −17p, −21q PRCC-TFE3 gene fusion
Chromophobe renal carcinoma	−1	−1p, −2p, −6p, −13q, −21q, −Y p53 mutation
Collecting duct carcinoma	−18, −Y	−1q, −6p, −8p, −11, −13q, −21q C-erbB-1 oncogene expression
Oncocytoma	−1, −Y, 11q rearrangement*	
Papillary adenoma	+7, +17 −Y	—

Genetic findings and pathologic subtypes of renal tumors. Common genetic abnormalities, or abnormalities not associated with stage, were assumed to occur early. Other abnormalities were assumed to occur later, possibly associated with progression. −, Loss of chromosomal segment; +, gain of chromosomal segment; LOH, loss of heterozygosity. Unclassified renal cell carcinoma and metanephric adenoma are not characterized sufficiently to identify common genetic abnormalities.
*Not enough data to assign abnormality as an early or late event.

TABLE 7.2. COMMON GENETIC FINDINGS IN PATHOLOGIC SUBTYPES OF RENAL TUMORS

CLINICAL MANAGEMENT OF HEREDITARY RENAL CANCER

Part of "7 - GENITOURINARY MALIGNANCY: ETIOLOGY AND MOLECULAR GENETICS, NATURAL HISTORY, AND TREATMENT "

Types of Hereditary Renal Cancer

The best-characterized form of hereditary renal cancer is von Hippel–Lindau disease (VHL). VHL is an autosomal dominant inherited disorder caused by a defect in the VHL gene, located on chromosome 3p25, resulting in the development of clear-cell tumors (259). Mutations in the VHL

gene predispose patients to develop retinal angiomas, central nervous system hemangioblastomas, endolymphatic sac tumors, renal cysts and cancers, pancreatic cysts and islet cell tumors, pheochromocytomas, and epididymal cystadenomas (32,257,295,447). Patients with VHL demonstrate variable clinical penetrance of these tumors.

From 24% to 45% of patients with VHL have been reported to develop renal cell carcinoma (64,257,292). However, of patients in the 60- to 70-year-old age group, 90% to 95% develop cystic or solid renal lesions (64). Affected patients with VHL usually develop multiple, bilateral clear-cell renal tumors and can develop new tumors over the course of their life. Patients develop VHL and renal cancer at a mean age of 39 years, 10 to 20 years younger than patients with sporadic renal cancer (151) (Fig. 7.4).

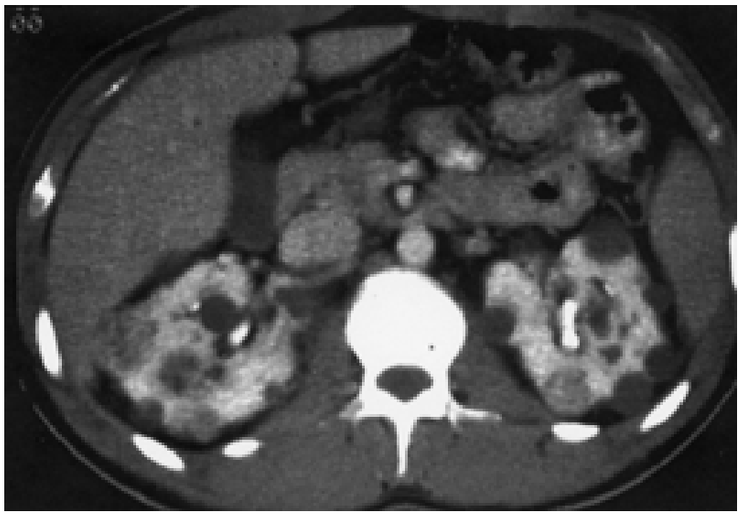

FIGURE 7.4. Abdominal computed tomography of renal masses in a patient with Von Hippel–Lindau disease.

A hereditary form of basophilic papillary renal cancer (type 1) has been also been described. Hereditary papillary renal cancer (HPRC) is inherited in an autosomal dominant fashion and, like all other forms of hereditary renal tumors, is characterized by multiple, bilateral renal tumors. Other associated tumors are not known to occur in patients with HPRC. HPRC is caused by germline mutations in the *met* gene, located on chromosome 7q31 (463,464).

Familial renal oncocytoma (FRO) is characterized by multifocal, bilateral renal oncocytoma (453). Few FRO families have been identified, and the clinical manifestations of this entity are not well characterized. Familial linkage and tumor loss of heterozygosity studies have not suggested the location of a responsible gene. Affected patients have a lifelong risk of recurrent tumors (453).

BHD comprises characteristic skin lesions (fibrofolliculomas), renal tumors, and pulmonary cysts predisposing patients to spontaneous pneumothorax. Renal tumors in BHD are usually chromophobe tumors. A unique aspect of this form of hereditary renal tumor syndrome is the development of other histologic tumor types, although at a low frequency (428).

Treatment Options in Patients with Hereditary Renal Cancer

Patients with hereditary forms of renal cancer are predisposed to develop multiple bilateral renal tumors over the course of their lives. Although radical nephrectomy will cure patients with localized disease, there are quality-of-life issues associated with renal replacement therapy. The largest experience in treating patients with hereditary renal cancer is in patients with clear-cell renal cancer associated with VHL. Management approaches used in VHL patients with renal tumors have ranged from observation to bilateral nephrectomy with renal replacement therapy to renal-sparing operations (80,137,155,200,327,339).

Although observation of patients with renal cancer is not traditionally recommended, there is historical experience with this approach. In the era before the use of abdominal computed tomography imaging, patients were followed with intravenous pyelogram (IVP) imaging studies. IVP

studies do not detect small tumors and even some larger tumors. During this era, 23% to 45% of patients with VHL were reported to develop renal cell carcinoma, similar to recent reports, and about one-third of these patients died of metastatic disease (70,126,151,257).

A second approach has been to perform bilateral nephrectomy, removing all renal tumors and their associated risk of metastases (80,155,200). Unfortunately, there is little experience in treating VHL patients with renal replacement therapy. Survival of non-VHL patients managed with dialysis or transplant is only 65% at 2 years (1). Similar treatments of small groups of patients with VHL have had a similar outcome (343). Some transplant centers, however, consider the presence of or potential for VHL-related tumors (renal and extrarenal) a contraindication for renal transplantation.

A third treatment option is renal parenchymal-sparing surgery. Patients with hereditary forms of renal tumors have been predicted to have hundreds or thousands of microscopic tumors present in the normal renal parenchyma (336,446). Surgery in these patients is not thought of as being curative, but rather as “resetting the clock” until small microscopic tumors grow to become clinically detectable. The decision of when to operate can be somewhat arbitrary in these patients.

In patients with sporadic renal tumors, the risk of metastases has been correlated with size of the primary tumor (22,116,133). Small renal cancers were even historically termed *adenomas* to emphasize their benign clinical course (26). Based on these observations, the management of patients with hereditary renal cancer has evolved to use size criteria as an indication for surgery. A French group follows renal tumors in patients with VHL until they reach 2.5 cm in diameter before recommending surgery (63,72); the National Cancer Institute (NCI) group uses 3 cm (193); and a German group uses 6 cm (324).

The large numbers of tumors that are often present in these patients do not allow traditional partial nephrectomy with margin of 1 cm or more of normal renal tissue. Rather, simple enucleation is used to remove the many tumors present (448). Small tumors are easily removed by this technique, but even tumors larger than 3 cm in diameter have been managed in this fashion. The NCI has reported the largest follow-up of patients with VHL treated in this fashion (193).

At the NCI, VHL patients with solid renal tumors were followed with serial imaging studies until the largest solid tumor reached 3 cm in size. At that time, surgery was recommended to remove all solid lesions and all accessible cystic lesions in the kidney. Renal cystic disease was not included in a patient's evaluation for surgery. In addition, the cystic component of solid renal masses was subtracted out when measuring tumor growth toward the 3-cm cutoff.

VHL patients with renal tumors less than 3 cm in diameter followed for a median of 60 months did not develop metastases or require renal replacement therapy (443). VHL patients with larger renal tumors had a risk of developing metastases related to tumor size (Table 7.3) (443). Similar management strategy has been used in patients with other hereditary forms of renal cancer.

Frequency of Metastases	Tumor Diameter (cm)
0/52 (0%)	≤3.0
1/17 (6%)	3.2–4.0
2/10 (20%)	4.1–5.5
4/12 (33%)	6.0–10.0
4/5 (80%)	≥11.0

Comparison of tumor size and the development of metastases in patients with von Hippel–Lindau (VHL). VHL patients with renal tumors larger than 3 cm had an increased risk of developing metastases with increasing tumor size.

TABLE 7.3. COMPARISON OF TUMOR SIZE AND THE DEVELOPMENT OF METASTASES IN PATIENTS WITH VHL

Planning Surgery in Patients with Hereditary Renal Cancer

Patients with VHL develop multiple tumor types, which can cause problems during an operation. Pheochromocytoma can be associated with hypertensive crisis, retinal angioma can bleed during periods of hypertension or with the use of anticoagulation, and central nervous system (CNS) hemangioblastomas can be at risk for bleeding or CNS herniation. Preoperative evaluation of all VHL manifestations is performed to identify tumors in the brain, eye, pancreas, and adrenal. CNS tumors may require treatment before abdominal surgery can be safely performed. Medical blockade of pheochromocytoma is necessary before surgery. Once the patient is cleared for abdominal surgery, a multispecialty approach can allow simultaneous treatment of renal, adrenal, and pancreatic tumors.

Renal angiography has not been helpful for diagnosis of renal tumors, with identification of only 16% of the multiple, small renal tumors present (308). Renal angiography is helpful in defining renal arterial anatomy, including small polar branches, which could be damaged during initial or repeat renal operations.

The multiple tumors found in patients with hereditary renal cancer syndromes do not allow partial nephrectomy with a wide resection of normal tissue around each tumor. Pathologic evaluation of renal tumors in patients with VHL consistently reveals a fibrous pseudocapsule margin (349). The multiple renal tumors and fibrous pseudocapsule lend these tumors well to enucleation (448). Patients with other hereditary tumor syndromes have been well managed with similar surgical treatment (193).

Patients with VHL also develop multiple simple and complex renal cysts. Although these lesions behave in a

benign fashion, microscopic examination reveals that at least 21% contain foci of renal cell carcinoma (349). Based on these findings, surgical removal of cystic lesions has been recommended when extensive injury of normal renal parenchyma is not necessary to remove the cysts.

Color Doppler intraoperative ultrasound has been an important contribution to the management of patients with hereditary renal cancer. Additional tumors were found in 25% of patients with intraoperative ultrasound, contributing to a more thorough evaluation and treatment of each kidney (71).

Results of Surgery in Patients with Hereditary Renal Cancer

The largest single-institution experience treating patients with hereditary renal cancer is at the NCI. There, 28 men and 22 women were reported undergoing a total of 71 surgical procedures (193). Affected patients were identified by screening affected families. Sixty-eight patients had pathologic stage T_1, one had stage T_2, and two had stage T_{3b}. Two patients with pathologic stage T_1 renal cancer had tumor thrombus in minor renal veins. No patient had lymph node or other metastases.

Fifty-three kidneys were treated with enucleation, five with partial nephrectomy, six with enucleation plus partial nephrectomy, and nine with nephrectomy. Patients underwent a median of one renal operation (range of one to four). During a median overall follow-up of 80 months, eight kidneys underwent repeat renal parenchymal-sparing surgery a median of 31 months after the first operation. Forty percent of renal parenchymal-sparing operations were performed with cold renal ischemia (Table 7.4). Eight patients with VHL underwent resection of VHL-associated tumors at the same time, including enucleation of pancreatic neuroendocrine tumors (*n* = 4), bilateral adrenalectomy for pheochromocytoma (*n* = 2), and unilateral adrenalectomy for pheochromocytoma (*n* = 2). The most notable complications were renal atrophy in 3 of 65 kidneys (4.6%) treated with renal parenchymal-sparing surgery and a single intraoperative myocardial infarction resulting in postoperative death. Urinary leakage persisting longer than 30 days occurred in three patients. Similar complications have been encountered in previous series, with the exception of renal failure, which was lower in the NCI series (64,403). No patient in the NCI series treated with renal parenchymal-sparing surgery has required dialysis. Thirty-five percent of kidneys undergoing renal parenchymal-sparing surgery developed a recurrence during the 80-month follow-up.

Surgical Characteristics			
Parameter	***N***	**Mean**	**Range**
Lesions resected per kidney	65	14.7 ± 1.3 lesions	1–51 lesions
Cold renal ischemic time	26	51.1 ± 5.6 minutes	10–120 min
Operative time	71	354.5 ± 19.0 minutes	117–830 min
Estimated blood loss	71	2885.1 ± 494.5 mL	150–23,000 mL
Blood units transfused	71	4.3 ± 0.9 units	0–34 units

TABLE 7.4. THE NCI RENAL PARENCHYMAL-SPARING SURGICAL EXPERIENCE IN PATIENTS WITH HEREDITARY FORMS OF RENAL CELL CARCINOMA

The use of nephrectomy was reduced in the NCI experience. Seven nephrectomies were performed in the first 5 years, with only two in the second 5 years (444). The use of nephrectomy in this series was lower than previously reported (12% versus 26%) in multiinstitutional reports, even accounting for differences in stage (403). This lower rate of nephrectomy may be related to the broad use of the enucleation technique, regardless of number of tumors or location of renal tumors.

Follow-up After Renal Parenchymal-sparing Surgery

Among 65 kidneys managed primarily using enucleation techniques, 35% developed recurrent tumors during 80 months of follow-up, similar to previous studies (403). This high recurrence rate is not surprising, because there are reports of many microscopic tumors in normal renal parenchyma of VHL and HPRC patients (336,446). Evaluation of normal VHL renal tissue predicts 600 microscopic clear-cell renal tumors and 1,100 clear-cell cysts in the average VHL kidney undergoing surgery. Similar evaluation of HPRC patients predicts 3,400 microscopic papillary renal tumors per kidney. These findings support the strategy of watching renal tumors grow to a predetermined size because renal surgery in these patients is not curative in the traditional sense. They also emphasize the need to search for the smallest tumors present during exploration to best treat these patients. Intraoperative ultrasound has been extremely useful for maximizing the number of lesions identified at the time of surgery (71,444). Disease-specific survival in these patients was excellent and may reflect the early detection of small tumors by periodic screening.

The treatment strategy applied to these patients with hereditary renal tumor syndromes is not curative, but is designed to “reset the clock” relative to the time required for microscopic tumors to grow to a size at which they present a significant metastatic risk. This management approach balances the goals of minimizing the risk of renal cell carcinoma metastasis while preserving renal function. Additionally, this approach attempts to minimize the total number of surgeries a patient will require in a lifetime.

MOLECULAR GENETICS OF PROSTATE CANCER

Despite significant improvements in early detection and local curative therapies, carcinoma of the prostate remains a major public health issue. Prostate cancer is now the most common noncutaneous malignancy in the United States and is the cause of more cancer-related deaths in men than any human malignancy other than lung cancer (162). Because of this, we must strive to improve the accuracy of diagnostic tests and prognostic measures. We must improve efficacy while reducing morbidity of local therapies, and we must devise methods to effectively prevent or treat hormone-refractory prostate cancer. A better understanding of the underlying molecular genetic events responsible for prostate cancer initiation and progression will enhance our chances for achieving these goals. This basic knowledge should allow us to develop better diagnostic tests that will eliminate false-positive results of prostate-specific antigen (PSA) screening. In the future, molecular pathology should also be able to accurately distinguish between “clinically indolent” and potentially lethal prostate cancers so that aggressive treatment is prescribed only to those who require it. We should be able to use this knowledge to design therapies that prevent progression of androgen-dependent to androgen-independent disease. Ultimately, we should be able to custom design effective treatments and prevention strategies based on a man's specific genetic makeup, the molecular abnormalities of his tumor, or both.

Currently, our understanding of the molecular genetics of prostate cancer is in its infancy. There is compelling evidence that a small proportion of prostate cancers (approximately 10%) is inherited but that the remaining 90% is caused by a complex interplay between environmental factors and somatic genetic molecular events (56). Several known tumor-suppressor genes (TSGs) are thought to play a role in a subset of prostate cancers, and alterations in various oncogenes, growth factors, and apoptotic pathways have been implicated as well. Recent advances in molecular technology that enable accurate, high-throughput analysis of genomic structure, as well as gene expression profiles, will almost certainly facilitate efforts to understand prostate cancer biology. This section reviews what we currently know about potential genomic and somatic events that may be responsible for prostate cancer development and then discusses the application of genomics and proteomics to prostate cancer investigation.

Hereditary Prostate Cancer

Several epidemiologic studies have demonstrated a familial clustering of a subset of prostate cancer cases, and some investigators have suggested that patterns of affected men can be explained by dominant inheritance of a rare high-risk allele (55,56,169,404). Studies suggest that hereditary cases account for 40% of cases of early-onset prostate cancer (i.e., age less than 55 years) but only 9% of other cases (56,168). There is a familial aggregation of prostate cancer, and an individual man's risk increases with the number of affected family members. Prostate cancer risk is increased twofold to threefold for men with one affected first-degree relative and elevenfold for men with three affected first-degree relatives (442).

To date, linkage analysis has identified four separate prostate cancer susceptibility loci (HPC1 on 1q24-25, PCAP on 1q42-43, CAPB on 1p36, and HPC on Xq27-28) (Table 7.5) (30,146,395,459). Positional cloning efforts are currently underway to identify these specific genes. Although it appears that each one of the genes will only be responsible for a subset of hereditary prostate cancers, their identification will provide important information regarding the underlying biologic mechanism of prostate cancer development.

Chromosomal Band	Locus
1q24-25	HPC1
1q42-43	PCAP
Xq27-18	HPCX
1p36	CAPB

TABLE 7.5. HEREDITARY PROSTATE CANCER SUSCEPTIBILITY LOCI

Genetic Polymorphisms

It has been estimated that 1 in every 300 to 500 bases in the human genome is a single nucleotide polymorphism and that some of these single-base pair differences may alter protein function, contributing directly to a trait or disease phenotype (77). One of the must highly characterized polymorphisms in prostate cancer is within a gene in the chromosomal Xq11-12 region encoding the androgen receptor. Androgen responsiveness of prostate cancer is well documented, and circulating androgens are necessary for prostate cancer development (96). It has been suggested that the length of the highly polymorphic region of the CAG repeat coding for the polyglutamine chain in the androgen receptor inversely correlates with an individual's prostate cancer risk (147,378,401). Data from two separate large, population-based, case-controlled studies have demonstrated this relationship. In the Physicians Health Study, men with an androgen-receptor CAG repeat length of less than 18 had a 50% increased risk of developing prostate cancer compared with those men with CAG repeat lengths greater than 26 (147). A study using a population identified from the Surveillance, Epidemiology, and End Results (SEER) program showed that men with two short repeat lengths (CAG less than 22 and GGN less than 16) had a twofold higher prostate cancer risk than men with longer repeat lengths (401). Epidemiologic studies of CAG repeat lengths in different racial populations support these findings. That is, African-American men (the racial group with

the highest prostate cancer incidence) have on average the shortest CAG repeat length, whereas Asian-American men (the racial group with the lowest prostate cancer incidence) have on average the longest CAG repeat length. Caucasians as a group have an intermediate prostate cancer incidence and have an intermediate CAG repeat length (73,368). Studies have also shown that among prostate cancer patients, those with shorter CAG repeat lengths are more likely to develop prostate cancer at a younger age (180) and are more likely to have aggressive prostate cancer with unfavorable pathologic features compared to those with longer CAG repeats (147). The underlying biologic mechanism for this relationship is not known. *In vitro* studies have demonstrated that transactivation of the androgen receptor is inversely related to its polyglutamine length, and some have hypothesized that increased androgen responsiveness predisposes prostate epithelium to malignant transformation. More study is needed to determine whether a short polyglutamine length directly increases prostate cancer risk or is merely associated with this phenotype.

There is epidemiologic evidence suggesting that decreased vitamin D levels, either from reduced exposure to sunlight or conversion of 7-dehydrocholestrol to vitamin D, may predispose to prostate cancer development (81,179). Several *in vitro* studies have also suggested that vitamin D may act as a tumor inhibitor for prostate cancer. Interestingly, different polymorphisms in the vitamin D receptor gene have been reported to be associated with either an increased or a decreased prostate cancer risk (176,208).

Other potentially important genetic polymorphisms associated with prostate cancer development have been observed in members of the glutathione S-transferase family. It has been shown that a single nucleotide polymorphism (SNP) in the glutathione S-transferase Pi gene, resulting in an amino acid change, alters prostate cancer risk by an odds ratio of 0.4 (182). In addition to SNPs, homozygous deletions within the human genome are also commonly observed (354). One of these, at the glutathione S-transferase-0 (GSTT1) locus on chromosome 22q11.2, occurs in 20% to 30% of Caucasian men in the United States. Studies have shown that men who do not have a homozygous deletion at GSTT1 are at increased risk of developing prostate cancer (354).

In the near future, molecular epidemiologic studies will define many more genetic polymorphisms that either predispose to or protect from the development of prostate cancer. It is likely that a man's prostate cancer risk will ultimately be determined by a panel of different genetic polymorphisms and that this information will be critical for designing and executing effective prostate cancer prevention strategies.

Chromosomal Abnormalities

Alterations in chromosomal number and structure are common findings in all human cancers. Cytogenetic studies of prostate cancer have demonstrated alterations on multiple different chromosomes, but the most common finding is loss or rearrangement of sequences on the short arm of chromosome 8 and gain of sequences on the long arm of chromosome 8 (67,290,438). In fact, studies have shown that 8p loss and 8q gain are associated with more aggressive disease (437). PSCA and c- *myc* are two genes located on 8q whose amplification may play a role in prostate cancer progression. The responsible genes on 8p have yet to be determined. Microsatellite-based LOH analysis is a powerful molecular tool used to define regions of genetic loss in attempts to discover TSGs. LOH studies of nonmetastatic prostate cancer revealed a deletion frequency of as high as 86% on the short arm of chromosome 8 and have suggested the presence of at least three separate TSGs located on this chromosome (438). Chromosomal bands 8p21-12, 8p22, 8p23, and 8q12-13 are regions with high rates of LOH (28,342,438). LOH at chromosomal bands 13q, 6q, 16q, 18q, 9p, and 7q31 have been observed less frequently (260,437).

Researchers have found a homozygous deletion in a metastatic tumor focus that maps to 12p12-13, suggesting that there is a prostate cancer metastasis suppressor gene in this region (230). One intriguing candidate gene in this region is p27. This gene encodes a cyclin kinase inhibitor that induces cell cycle arrest in the G_1 phase. This mechanism prevents DNA replication in cells with substantial DNA damage (15). Several studies have shown that reduced levels of p27 are associated with aggressive and metastatic prostate cancers (84,174,460). Other studies have shown that LOH at 8p22 is a common finding in metastatic prostate cancer, suggesting that this region also contains a metastasis suppressor gene (269).

Contemporary scientific data suggest that there are multiple genes responsible for development and progression of prostate cancer and that multiple different genetic pathways for this common human malignancy exist. Defining any of these genetic defects will provide researchers tremendously important insight into the underlying biology of prostate cancer. Examples of some potential candidate genes on chromosome band 8p include FEZ1 (212), NKX3.1 (185), N33 (429), and Dematin (286), among many others. Currently, efforts to determine which genes have tumor-suppressor function in prostate cancer now focus on further defining areas of minimal deletion and sequence analysis of candidate genes within regions of high LOH.

Promoter Methylation

Methylation of cytosine bases in CpG-rich promoter regions is an important mechanism to regulate tissue-specific gene expression. Alterations in methylation patterns are commonly observed in multiple different human malignancies. Reduction in gene expression can be the result of promoter hypermethylation, whereas promoter hypomethylation

can cause increases in gene expression. In fact, extensive methylation of the glutathione S-transferase Pi (GSTP1) promoter region is the most common somatic genomic alteration described in prostate cancer to date (265). Immunohistochemical analysis of GSTP1 expression has demonstrated that promoter methylation does in fact correlate with reduced protein expression. Studies of radical prostatectomy specimens have demonstrated loss of GSTP1 expression in the vast majority of invasive prostatic carcinomas and high-grade prostatic intraepithelial neoplasia lesions (44). Researchers have proposed that because GSTP1 functions as a detoxification enzyme, loss of GSTP1 activity can predispose prostate cells to accumulate damaged DNA, leading to malignant transformation. If loss of GSTP1 is an important event leading to prostate carcinogenesis, medication or dietary supplements with detoxification functions may be effective prostate cancer prevention strategies.

It appears that prostate cancer is associated with methylation changes within promoter regions of several other genes as well (Table 7.6). For example, it has been shown that hypermethylation of the CD44 promoter region is a common finding in high-grade localized and metastatic human prostate cancer (284). CD44 is a transmembrane glycoprotein involved in cell-cell and cell-matrix interactions that suppresses metastasis in a highly metastatic prostate cancer model (Dunning rat) (142). Hypermethylation of the p16/CDKN2 gene, which encodes an inhibitor of cyclin-dependent kinase 4, has been observed in a limited number of prostate cancers (189,190,305). It has been shown that inactivation of the p16/Rb pathway can result in cellular immortalization (215). Methylation of the endothelin B receptor gene in prostate cancer has also been reported, and it has been suggested that this event may be responsible for endothelin-1 secretion (215). It has been shown that exposing androgen receptor–negative prostate cancer cell lines to a demethylating agent increases androgen receptor expression. It has been suggested that promoter methylation may be a cause of heterogeneous androgen receptor expression observed with hormone-refractory prostate cancer (214). It is clear that altered promoter methylation of a variety of genes is a common event in prostate cancer, but it remains to be seen which gene alterations are responsible for prostate cancer development and progression and which merely are associated with the malignant phenotype.

GSTP1	E-cadherin
CD44	Endothelin B
P16	Androgen receptor
PTEN	Loci D17S5 on 17p

TABLE 7.6. GENES WHOSE EXPRESSION IS ALTERED BY METHYLATION IN PROSTATE CANCER

Tumor-suppressor Genes

A tumor-suppressor gene responsible for early prostate cancer development has yet to be discovered. However, there are several known TSGs that may play a role in prostate cancer progression. The gene for PTEN maps to chromosomal band 10q23.3. The protein product of the PTEN gene is a dual-specific phosphatase with documented tumor-suppressor function in some cultured cells and nude mice (141). Within cancerous prostate cells, PTEN can be inactivated by multiple different mechanisms, including genomic deletions, point mutation, and hypermethylation (53,161,409,450). In general, PTEN inactivation is far more common among high-grade or advanced prostate cancers than in lower-grade and earlier-stage disease (105,161). In fact, the vast majority of PTEN mutations have been found in patients without organ-confined prostate cancer (105,161). Collectively, these data suggest that PTEN may be an important metastasis-suppressor gene, but it probably does not play an important role in prostate cancer initiation.

Likewise, p53 mutations are far more common in high-grade metastatic prostate cancer than in earlier lesions (110,307). Clinical studies have shown that the presence of p53 mutations in prostate cancer correlates with poorer cure rates for both radiotherapy and radical prostatectomy (65,66,320).

The WAF1 gene is the primary target of the transcription activation by P53 and is also an important regulator of cell cycle kinetics (111). P21, the product of the WAF1 gene, inhibits the activity of cyclin E and cyclin D, which prevent cells from entering the S phase of the cell cycle (181). A few small preliminary studies suggest that overexpression of the P21 or cyclin D1 protein is associated with higher tumor grade and adverse clinical outcome (2,365).

Growth Factors

Alterations in a variety of growth factors and their receptors have been implicated in prostate cancer growth and progression. Among the most widely studied growth factor in prostate cancer are members of the epidermal growth factor family, epidermal growth factor (EGF) and TGF-α. Within normal prostates, EGF expression is restricted to stromal cells (134), and epidermal growth factor receptor (EGFR) expression is restricted to basal cells of prostatic epithelium (305). Immunohistochemical analysis of benign prostatic hyperplasia demonstrates overexpression of EGF in hyperplastic glands. In contrast, immunohistochemistry has demonstrated that both EGF and EGFR levels are upregulated in malignant prostate epithelium (95). Studies of prostate cancer cells suggest that EGF and TGF-α play a role in upregulation of EGFR mRNA and protein (384). Furthermore, there is evidence that a variant EGFR (EGFRvIII), lacking the external domain of the native receptor, is overexpressed in prostate cancer cells, and that aberrant expression of EGFRvIII is associated with more aggressive disease (330).

Collectively, these studies suggest that autocrine expression of EGF and TGF-α signaling through the EGFR may contribute to the autonomous growth and invasiveness of human prostate cancer cells (231).

The HER-2/neu (erbB-2) gene encodes for another tyrosine growth factor receptor that is a member of the EGFR family. Interestingly, gains in genomic content of the HER-2/neu gene are observed in 40% to 60% of high-grade prostate cancers (361,381). It has been demonstrated that overexpression of HER-2/neu restores androgen-receptor functions in androgen-independent prostate cancer xenograft model (88).

Overexpression of several fibroblast growth factor (FGF) family members has been associated with prostate cancer progression. Studies have shown that FGF8 mRNA expression is increased in prostate cancer (266) and that overexpression correlates with higher Gleason grade and advanced tumor stage (106). Overexpression of growth factors by prostatic stromal cells may also play a role in prostate cancer progression. For example, expression of FGF2 is restricted to stromal fibroblasts and endothelial cells, and expression levels are greatly enhanced within cancerous glands (148). Interestingly, the receptor for FGF2 is overexpressed in malignant prostate epithelium (148).

Insulin growth factor (IGF) may also play a role in prostate cancer development and progression. IGF-II mRNA is expressed by some prostate cancer cells, and it has been suggested that it may function as an autocrine growth factor (167). All studies have suggested that alteration in the IGF binding proteins may alter bioavailability of IGF and play a role in prostate cancer progression (125). Results of a large retrospective study demonstrated a correlation between higher serum IGF levels and increased prostate cancer risk (61). In this study, men with serum IGF levels in the highest quartile had a 2.4 times greater chance of being diagnosed with prostate cancer compared with age-matched men with lower IGF levels. Prospective studies are needed to determine whether elevated serum IGF levels predispose to prostate cancer development and whether lower serum IGF levels could be an effective prostate cancer prevention strategy.

Other growth factors that have been implicated to play a role in prostate cancer include transforming growth factor-ß (TGF-ß) (54), hepatocyte growth factor (HGF) (326), nerve growth factor (NGF) (9,397), bone morphogenetic proteins (BMPs) (12,207,424), and platelet-derived growth factor (PDGF) (394), among others. The role of TGF-ß in prostate cancer is not entirely clear, because TGF-ß inhibits prostate cancer growth *in vitro* (407) but promotes growth and metastasis *in vivo* (18). This paradoxic response may be explained by data suggesting that prostate cancer cells downregulate TGF-ß receptors so that increased expression of TGF-ß induces host effects that facilitate cancer progression and metastasis (173). Among the metastasis-promoting effects attributed to TGF-ß are immunosuppression, angiogenesis, and extracellular matrix deposition (455). HGF ("scatter factor") is secreted almost exclusively by prostatic stromal cells and binds to the product of the *c-met* protooncogene expressed on prostate epithelium (205). Preliminary data suggest that expression of *c-met* is elevated in prostate cancer and increases with increasing grade, thereby enhancing mobility and cellular scattering (344). BMP and NGF have been implicated in development of bony metastasis and hormone-independent growth, respectively (12,91).

The realization that alterations in growth factors and growth factor receptors may play a role in prostate cancer progression has led to development of novel therapeutic strategies. A recombinant anti–HER-2/neu antibody (Herceptin) that inhibits growth of breast cancer cells that overexpress HER-2/neu has been developed (122,201) and is now approved for the treatment of human breast cancer (39). Studies of two prostate cancer xenograft models have shown that Herceptin provides synergistic antitumor activity when combined with paclitaxel chemotherapy (5). Another potential therapeutic strategy explored by researchers relies on EGFR blockade. Interestingly, *in vitro* studies have shown that blockade of the EGFR not only attenuates the actions of EGF, but also IGF-I (352). This suggests that it may be possible to reverse several functional autocrine growth factor pathways by blocking a single receptor site. Although the efficacy for human prostate cancer therapy remains to be seen, both Herceptin and EGFR receptor blockade are good examples of how understanding alterations in growth factors and their receptors can lead to the design of novel targeted prostate cancer therapies. Therapeutic approaches directed at physiologic pathways altered in cancer will likely provide the cornerstone for treatment of hormone-refractory prostate cancer in the future.

Apoptosis

Programmed cell death (apoptosis) is an important regulator of cellular hemostasis, and alterations in apoptotic pathways have been implicated in prostate carcinogenesis. Bcl-2, Bcl-x, and Mcl-1 are proteins that inhibit apoptosis, and Bax is a protein that induces apoptosis (19). Immunohistochemical studies have demonstrated overexpression of Bcl-2 in 25% and Mcl-1 in 81% of prostate cancers (253). Studies have shown that overexpression of Bcl-2 is a predictor of poor clinical outcome in patients undergoing radical prostatectomy or radiation therapy for clinically localized prostate cancer (41,372,400). It has also been suggested that the ratio of Bcl-2/Bax immunohistochemical staining correlates with poor response to radiotherapy (288).

Animal studies have shown that overexpression of Bcl-2 protein augments growth of LnCaP tumors (21), and these findings have been used to design a novel prostate cancer

therapy. In preclinical studies, researchers have shown that antisense Bcl-2 oligonucleotides inhibited growth of LnCaP and Shinogi and prevented PSA progression both *in vitro* and in castrated mice with subcutaneously implanted tumors (309). Chemosensitivity to taxol and mitoxanthrone was also enhanced. A phase I clinical trial using antisense Bcl-2 alone or in combination with mitoxanthrone is currently in progress (335).

Angiogenesis

Angiogenesis may play an important role in prostate cancer progression. Both *in vitro* and *in vivo* studies of LnCaP cells demonstrate that cells expressing higher levels of vascular endothelial growth factor (VEGF) exhibit enhanced metastatic potential (17). VEGF is the best-characterized angiogenesis factor to date (109,123), and one immunohistochemical study demonstrated positive staining for VEGF in 80% of prostate cancers compared with only 18% of benign glands (123,124). Some studies of human prostate cancer have shown that increased microvascular density in localized prostate cancer specimens predicts advanced pathologic stage and treatment failure (408), but other studies have failed to demonstrate this relationship (145,363).

Blocking tumor angiogenesis is a potentially exciting new approach to cancer therapy (131). The discovery and characterization of two potent endogenous angiogenesis inhibitors, angiostatin and endostantin, will facilitate the development of prostate cancer therapies targeting angiogenesis (37,119,396). Animal studies using these agents are currently underway (335).

Cell Adhesion Molecules

Alterations in cell adhesion molecules may also play a role in prostate cancer progression. The genes encoding two important cell adhesion molecules, E-cadherin and KAI-a, map to chromosomal bands 16q24 and 11p11.2, respectively. Both regions are frequently deleted in metastatic prostate cancer (104,270), and expression levels of E-cadherin can also be reduced in prostate cancer by promoter methylation (159). Animal studies suggest that KAI-1 can suppress prostate cancer metastasis (206). Likewise, E-cadherin plays an important role in establishing and maintaining ordered intercellular connections and morphogenesis (311). *In vivo* studies of the Dunning rat prostate tumor showed that transfecting tumor cells with E-cadherin downregulates matrix metalloproteinase 2 expression (another factor implicated in prostate cancer progression) and reduces cellular invasiveness (285). Immunohistochemical studies of human prostate cancer tissue have suggested that reduced levels of E-cadherin expression correlate with higher Gleason score and advanced pathologic stage (94). Restoring functional cell adhesion molecules to prostate cancer cells may be one possible strategy that could be used to prevent tumor progression and metastasis.

New Frontiers in Molecular Profiling of Human Malignancies

By the year 2003, the complete map and sequence of the entire human genome will be known, and sequencing of cDNA's coding for all human genes will be completed shortly thereafter (77). This information will provide us with the “periodic table of life” and will be the foundation for understanding both normal and diseased cellular functions. Over the past several years, we have witnessed tremendous advances in gene expression technology. In the near future, it will be possible to rapidly assess expression patterns of virtually all genes and proteins within a particular population of human cells. Advances in microdissection and cell-sorting technology allow one to isolate pure populations of cells from human tissue sections and then extract DNA, RNA, and protein. Differential display and cDNA microarrays are evolving technologies that facilitate high-throughput mRNA expression analysis. Advances in proteomic techniques have also made it possible to assess expression patterns of a large number of proteins simultaneously. Combining new approaches for “molecular profiling” with the complete human genome sequence will provide new opportunities to understand the underlying mechanism responsible for human malignancy. This knowledge should ultimately revolutionize diagnosis and treatment of men and women with cancer.

Tissue Processing and Procurement of Pure Populations of Cells

One of the major limitations to the direct study of molecular changes in human malignancy has been the challenge to obtain pure populations of malignant and benign cells. This difficulty arises because of cellular heterogeneity such as is seen in prostate cancer or the presence of inflammatory cells that infiltrate certain tumors such as renal cell carcinoma. To overcome this investigative hurdle, different microdissection techniques have been developed for the purpose of procuring pure or semipure populations of cells from human tissue sections. One methodology relies on ablating all the unwanted tissue with a laser and then isolating the macromolecules from the remaining tissue. Another methodology, laser capture microdissection (LCM), is currently the most widely used technique (113). LCM allows researchers to visualize a tissue section via light microscopy and then procure the desired cells by activating a 7.5- to 30-micron-diameter infrared laser beam. The laser beam melts an ethyl-vinyl-acetate film in contact with the tissue section, thereby capturing the cells of interest. Lifting up the cap pulls these cells out of the tissue sections. Intact DNA, RNA, and protein can then be extracted from the cap using

various lysing buffers and analyzed by conventional methods. The advantage of this technology is that it allows for simple, fast, and reliable microdissection of human tissue sections. This technology facilitates *in vivo* molecular analysis of defined populations of human cells.

High-throughput Gene Expression Analysis

Rapid advances in high-throughput gene expression analysis technology are making it possible to analyze expression patterns of a large number of human genes simultaneously and to study how these patterns are altered in different stages of malignancy. Currently, the most widely used method to analyze gene expression patterns in cancer is through cDNA microarrays (47,100). This technology involves labeling a sample of cDNA, representing the expressed genes from a population of cells, with a radioactive or fluorescent probe. The probe is then hybridized to a nylon filter or glass array slide containing cDNA fragments representing several thousand human genes of interest. Analysis of these experiments allows one to determine relative expression levels for different genes within the same population of cells or different genes within different populations of cells. Researchers have begun to apply this technology to the study of prostate cancer. Using cDNA microarrays to compare gene expression in the androgen-independent and androgen-dependent tumors in CWR22 xenograft model yielded 37 candidate genes that were upregulated by more than twofold in the androgen-independent state (49). Although the biologic relevance of these differentially expressed genes remains to be determined, the use of cDNA microarray will be an important approach to the study of prostate cancer progression. One important caveat to this study and many others is that they use xenograft or cell culture models that may not accurately represent *in vivo* gene expression in human prostate cancer. This is a particularly important problem when it comes to the study of premalignant lesions and early-stage prostate cancer because few good animal models or cell lines are available. The recent development of LCM technology and the ability to isolate RNA from specific populations of LCM-procured cells should facilitate the *in vivo* study of gene expression in human prostate cancer. In fact, preliminary data suggest that this approach can be used to identify several (approximately 40 genes in one experiment) differentially expressed candidate genes (75). Limitations of cDNA microarray technology include potential for artifacts (particularly if using PCR amplification) and the fact that the only genes that will be studied are those that have been placed on the array filter.

Another technique used to determine genes that are important in prostate cancer development and progression rely on generating cDNA libraries from defined populations of cells (279,321,322). This strategy allows one, in theory, to study all genes (both known and unknown) expressed by a particular population of cells. The NCI-sponsored Cancer Genome Anatomy Project (CGAP) has used both bulk tissue and microdissected procured cells to create cDNA libraries from several common human cancers and corresponding normal tissue (www.ncbi.nih.gov//ncicgap/) (112). The primary goals of the project are twofold: (a) aid in discovering new human genes and (b) profile gene expression patterns for particular human cancers and tissue types. It has been estimated that more than 50% of the approximately 100,000 human genes will have been discovered through this initiative (112). This information will be a critical foundation for future prostate cancer studies. The use of microdissected-derived samples has been the cornerstone of the gene-profiling aspect of the CGAP project. In regard to prostate cancer, twelve microdissected-based libraries have been produced from epithelial components of radical prostatectomy specimens, including normal epithelium, premalignant foci, locally invasive cancers, and metastatic lesions (112). This will allow us to define all of the genes that are expressed in normal prostate (prostate unigene set) and those genes whose expression is altered in different stages of malignancy. Research efforts will focus on correlating gene expression profiles with pathologic and clinical outcomes. Ultimately, this strategy will allow us to understand how alteration in a complex network of genes leads to prostate cancer development and progression.

Although gene expression analysis holds great promise for understanding the molecular events underlying prostate cancer progression, the malignant phenotype is ultimately the reflection of quantitative and qualitative changes in cellular proteins. Therefore many researchers believe that proteomic analysis of human cancers provides unique and complementary information to genomic DNA and gene expression studies (8,107). Two-dimensional gel electrophoresis (2D-PAGE) is a highly effective and widely used means of separating a large number of proteins. Advances in 2D-PAGE technology and protein staining methods have greatly improved the reproducibility and sensitivity of protein analysis. It is now possible to separate as many as 10,000 different protein forms with high-resolution 2D-PAGE, and computer software can be used to compare spot patterns between different gels (59,60,441). One of the major advantages of 2D-PAGE protein analysis is that it allows for relatively easy identification of specific protein spots. Unknown proteins can be identified by utilization of an electrospray that can be used to generate additional partial-sequence information. One major limitation with proteomic studies of prostate cancer has resulted from difficulty in obtaining enough material from pure populations of cells. Cell lines are a good source of pure populations of cells, but recent studies suggest that protein expression patterns of cultured tumor cells may differ substantially from those of the same cells *in vivo* (58). One potential strategy to overcome these problems is to analyze proteins isolated from microdissected populations of cells. In fact,

researchers have shown that highly reproducible protein profiles can be generated using cellular lysates from populations of benign and malignant prostate epithelium procured by LCM, and that differentially expressed proteins can be identified by this approach.

Although significant technologic advances have been made, the major shortcoming of 2D-PAGE protein analysis remains sensitivity. Therefore cancer researchers should combine these robust proteomic techniques with more sensitive mRNA expression analysis. In the future, advances in technology may allow proteomic analysis of all cellular proteins, even the least abundant ones.

Conclusions

Although current understanding of the underlying biologic mechanisms responsible for prostate cancer development and progression is at a relatively rudimentary stage, there is overwhelming hope and optimism for the future. There has been tremendous progress in the search for genomic alteration associated with prostate cancer development, and it is likely that in the very near future, several specific “prostate cancer genes” for both hereditary and sporadic prostate cancer will be identified. As more genetic polymorphisms are linked with prostate cancer, there will be new opportunities to assess prostate cancer risk with more certainty, and to design rational and effective prevention strategies. The completion of the human genome sequence combined with the revolution in gene and protein expression analysis technology should allow us to classify different prostate cancers more accurately based on molecular and histopathologic features. Ultimately, an improved understanding of prostate cancer biology should be used to improve quality of life for all men with prostate cancer, as well as those at risk for this disease.

MOLECULAR GENETICS OF BLADDER CANCER

Part of "7 - GENITOURINARY MALIGNANCY: ETIOLOGY AND MOLECULAR GENETICS, NATURAL HISTORY, AND TREATMENT "

Bladder cancer is the second most common urologic cancer and fifth most common malignancy in the United States (163a). Furthermore, bladder cancer is 2.5 times more common in men than women and is the second most prevalent malignancy in older men (130). More than 50,000 patients were diagnosed with bladder cancer in the year 2000, and although the mortality rate from bladder cancer is declining, more than 10,000 deaths were expected (163a). In the United States, urologists are the primary referral for patients with unspecified microscopic and gross hematuria. As a result, the diagnosis and treatment of most bladder cancers is left almost exclusively to the practicing urologist. Our current diagnostic algorithm and treatment options for bladder cancer result in very few cases of undiagnosed and untreated bladder cancers found at autopsy (233). Fortunately, most patients (70% to 80%) have superficial (non–muscle-invasive) tumors that can be managed with bladder-sparing procedures, intravesical agents, and surveillance cystoscopy and cytology. As a result, the majority of patients treated for bladder cancer survive but require diligent follow-up because more than two-thirds of superficial tumors recur and a large percentage of high-grade tumors progress to muscle-invasive disease (192).

In contrast to superficial involvement of the bladder wall, the presence of muscle invasion makes bladder cancer a life-threatening condition. Approximately 50% of patients with muscle-invasive disease will have occult or overt metastases at the time of presentation, and the majority of these patients will die from their disease. Patients with muscle-invasive bladder cancer are managed aggressively with radical cystectomy alone or with adjuvant chemotherapy, radiation, or both for patients with advanced disease. Patients with localized muscle-invasive bladder cancer can enjoy long-term survival, and the use of orthotopic neobladders and nerve-sparing approaches has improved quality of life in appropriate surgical candidates (183). Still, approximately half of patients with muscle-invasive bladder cancer will develop overt metastases within 2 years of treatment. Metastatic bladder cancer is always associated with a high mortality rate despite aggressive chemotherapeutic regimens, and the urologic management of patients with metastatic transitional cell carcinoma usually consists of palliative procedures with or without cystectomy. Although new chemotherapeutic regimens are being investigated (435,439), treatment of metastatic transitional cell carcinoma is clearly an opportunity for molecular biologists and physicians to develop novel treatment regimens based on genetic changes that occur in these highly aggressive and lethal tumors.

Urothelial malignancies have diverse clinical and histologic presentations (114,314). Some patients have large, solitary, noninvasive papillary lesions (pTa); others have multiple noninvasive tumors. Some patients have low- or high-grade papillary or sessile lesions invading into the lamnia propria (pT_1) but not into the detrusor muscle layer of the bladder. Still others have diffuse high-grade flat lesions, carcinoma in situ (CIS, pTIS), confined to the urothelium that are associated with synchronous muscle-invasive lesions (pT_{2-4}) or progression to muscle-invasive lesions. Although the majority (60% to 70%) of patients with low-grade papillary urothelial malignancies experience a recurrence, a significant percentage do not. Some tumors respond to intravesical agents such as bacille Calmette-Guérin (BCG) or mitomycin C; others are resistant. Many patients are treated for years for multiple recurrent tumors that do not progress, but a significant percentage of patients with superficial high-grade disease progress to muscle-invasive or metastatic disease (192).

Transitional cell carcinoma (TCC) of the bladder is the most common histologic type and location of urothelial malignancy in the United States. However, squamous cell carcinoma (SCC) of the bladder is more common in areas inhabited by the microorganism *Schistosoma haematobium* (313).

In these areas, bladder cancer is the most common malignancy and provides clues to the importance of inflammation and chronic infection in the etiology of bladder cancer (359). Other tumors, such as adenocarcinomas, neuroendocrine tumors, lymphomas, and pheochromocytomas, are rare primary bladder malignancies. The genetic abnormalities responsible for the histologic diversity in bladder cancer are not clearly defined, and molecular studies have not demonstrated consistent genetic differences between the common histologic types (177,385). Urothelial malignancies affecting the upper tracts of the urinary system (renal pelvis and ureter) are comparatively rare and assumed to have similar genetic changes as bladder cancer. TCC of the renal pelvis accounts for only 10% of renal tumors, and TCC of the ureter is uncommon (4% of urothelial malignancies). However, a hereditary cancer predisposition syndrome known as hereditary nonpolyposis colon cancer (HNPCC) or the Lynch II syndrome is associated with an increased incidence of upper tract urothelial malignancy (287,451). This syndrome and the association with upper tract TCC are discussed later in this chapter.

Oncogenes and Urothelial Cancer

Oncogenes are altered human genes that dominantly transform cells. Unaltered oncogenes (protooncogenes) are involved in important cellular functions such as cell surface signaling, apoptosis, cell cycle regulation, and gene expression or function as growth factors or growth factor receptors. Many protooncogenes were first described in their altered form as part of an oncogenic retrovirus that caused tumors in rodents or birds. The human homologs were subsequently isolated and the corresponding oncogene identified in human malignancies, including bladder cancer. Oncogenes often belong to families of homologous genes, and the three oncogenes to be discussed in urothelial malignancy, ras, myc, and bcl-2, are no exceptions. The genetic alterations in some oncogenes are tumor specific. For instance, c-myc is a DNA-binding nuclear protein associated with chromosome 8q amplifications and overexpression in bladder tumors (278,370), n-myc is associated with amplification on chromosome 2 in neuroblastomas (380), and l-myc is amplified in lung cancer (319). In contrast, mutations in all members of the ras gene family have been described in bladder cancer (121,139,355,387).

Unlike TSGs (described in the following section), alterations in oncogenes usually involve point mutations or chromosomal amplifications associated with increased transcription, increased stability, or increased activity. Inactivating point mutations, intragenic deletions, or gross chromosomal alterations generally do not occur in protooncogenes unless they result in increased stability or increased expression. Two classic examples of gross chromosomal alterations resulting in the protooncogene activation are bcl-2 located on chromosome 18q and c-myc on chromosome 8q. A translocation event between chromosomes 14 and 18 t (14,18) in follicular B cell lymphomas causes deregulation of bcl-2 due to approximation of an immunoglobulin heavy chain enhancer and the bcl-2 transcription unit (431). A similar type of translocation event has been described for c-myc in Burkitt's lymphoma (89). Therefore gross chromosomal alterations are an apparently common mechanism for oncogene activation in lymphoma.

The Harvey ras gene (H-ras) and other members of the ras gene family are involved in cell surface signaling through a variety of pathways including growth factor and growth factor receptor interactions (306). Ras proteins are activated by binding to guanosine triphosphate (GTP) and inactivated when GTP is dephosphorylated by GTPases. Characteristic ras point mutations at codons 12, 13, and 61 in bladder cancer and other malignancies are associated with unregulated activation of ras proteins potentially causing unregulated signaling for cell proliferation via growth factors (417). Mutations in H-ras were initially described in the bladder cancer cell line T-24 (355) and subsequently shown to be mutated in primary bladder tumors (121). Mutations in Kirsten ras (K-ras) and n-ras have also been described in bladder cancer, but K-ras mutations are more common in colon cancer and n-ras mutations in lymphoid malignancies. The ras protooncogenes are highly homologous, and activation of any ras protein is likely to cause a similar mechanism of cellular transformation. H-ras activation commonly occurs due to point mutations in codon 12 (38), and mutations affecting any ras codon have been described in up to 40% of bladder tumors (128,139,140).

The c-myc, n-myc, and l-myc protooncogenes are well studied and have contributed extensively to our understanding of DNA binding proteins and protein-protein interactions (76). The importance of c-myc in a variety of human malignancies has been reported and usually involves gene amplification or rearrangements as described previously. The c-myc gene is expressed in proliferating cells (226). The myc proteins are transcription factors associated with increased expression of genes involved in DNA replication and cell growth (76,241). Amplification and alterations of the c-myc locus in cancer have been described (29,370); however, the role of c-myc in bladder cancer is not well understood. Although overexpression and amplification of the homologous n-myc gene in neuroblastoma has prognostic implications (380), a similar role for c-myc in TCC has not been demonstrated (278). However, low-level amplification and overexpression of c-myc in TCC has been described and correlated with progression in one study (370).

Overexpression of the bcl-2 protooncogene prevents apoptosis, a form of programmed cell death that involves activation of cellular proteases known as caspases (328). Inhibition of cell death is important in tumorigenesis for several reasons. First, the homeostatic balance is shifted

toward cellular accumulation; second, apoptosis removes genetically defective cells that may become malignant if allowed to expand; and third, the toxic effect of chemotherapeutic agents on malignant cells may be abrogated. Bcl-2 is normally located in mitochondrial membranes, where it regulates pore formation. Mitochondrial pores are important in regulating free radical formation and ion fluxes and maintaining membrane potentials within the cell. Intracellular fluxes mediated by these pores can signal caspase activation and initiate the cascade of proteolytic events leading to DNA fragmentation and irreversible cell death. Some caspases are specific for cleavage of bcl-2 whereas others have a more general proteolytic spectrum. Bcl-2 prevents the initiation of these events by blocking the transduction of apoptotic signals to trigger the caspase proteolytic cascade. Therefore decreased bcl-2 expression would be associated with apoptosis and increased expression with resistance to apoptosis.

Expression of bcl-2 has been investigated in bladder as a prognostic marker and as a target for apoptotic directed therapy for bladder cancer (152,225). The tumor-suppressor protein, p53 (discussed later), is an important negative regulator of bcl-2 expression, and molecular studies demonstrate increased expression of bcl-2 in the absence of wild type p53 (223). Other members of the bcl-2 family of genes have apoptotic promoting and apoptotic preventive effects. One example, bax, binds to bcl-2, preventing it from functioning and thereby promoting apoptosis. Bax is transcriptionally activated by p53 and is therefore an effector of p53 regulated apoptosis (223). Other bcl-2–related proteins such as bcl-xL prevent apoptosis, and bcl-xs, bad, and others promote apoptosis. The mechanism of action of bcl-2 and related proteins is incompletely understood, but its location in mitochondrial membranes and regulation of pore formation are important aspects of function.

Tumor-suppressor Genes and Urothelial Cancer

Oncogenes were the first human cancer genes discovered and investigated in detail, but genetic alterations in TSGs appear to be the more common mechanism leading to human malignancies (392). Oncogenes promote tumorigenesis in a dominant fashion, and TSGs prevent or slow tumorigenesis in a dominant fashion. Classically, one allele of a protooncogene acquires an activating mutation, whereas both alleles of a TSG must be inactivated for tumorigenesis (120,239). Unlike protooncogenes, large deletions and chromosomal alterations are common events leading to TSG inactivation. One TSG allele may be completely lost while a point mutation inactivates the remaining allele (16). This phenomenon can be detected through the use of polymorphic markers and is known as loss of heterozygosity (LOH) because one allele of a marker is missing when tumor DNA is compared to normal (germline) DNA in the same patient.

TSGs can be artificially classified into two groups. The first group consists of TSGs associated with hereditary cancer predisposition syndromes and in these kindreds are associated with an inherited mutation in one allele (238). Group one TSGs were initially suspected because of increased occurrence and autosomal dominant inheritance of tumors such as retinoblastomas in affected families. Linkage analysis confirmed the presence of a cancer-predisposing gene and resulted in cloning of the inherited mutated allele (136). Once identified, TSGs are often found to be mutated in sporadic tumors, as was the case for retinoblastoma. Other TSGs were identified as mutated genes in sporadic malignancies and subsequently identified as the altered gene in a cancer predisposition syndrome (293). Investigation of these genes in transgenic mice with homozygous inactivation of the target gene confirmed importance in cell growth and tumorigenesis. The second group consists of candidate TSGs that are located in areas of LOH in sporadic cancers. Members of this second group have not yet been linked with inherited mutations in familial cancer syndromes. These TSGs are located within a common genetically altered region but have not been conclusively shown to be the target of complete inactivation in tumor cells. Several genes in this group are being investigated in bladder cancer (235,236).

TSGs that belong to the first group are retinoblastoma (Rb), p53, adenomatous polyposis coli (APC), VHL, neurofibromatosis type 1 (NF-1), neurofibromatosis type 2 (NF-2), Wilms' tumor (WT-1), tuberous sclerosis complex–1 (TSC-1), and tuberous sclerosis complex–2 (TSC-2). The first TSG products identified in this group were p53 and Rb. Rb was identified by its association with inherited retinoblastoma and subsequently shown to be inactivated in bladder cancer (213,412). The p53 TSG was shown to be mutated in colon cancer (16) and then identified as the inherited and mutated gene in the Li-Fraumeni cancer predisposition syndrome (293). Although these two important TSGs were identified by different approaches, Rb and p53 are functionally linked in suppression of cell growth by blocking the progression through the cell cycle.

Unphosphorylated Rb suppresses tumorigenesis by sequestering a transcription factor known as E2F-1 (236). E2F-1 causes transcriptional activation of genes involved in DNA synthesis and progression through the cell cycle (219,281). When RB is phosphorylated by an assembly of proteins that includes cyclins and cyclin dependent kinases (cdk), it can no longer sequester E2F-1. The result is progression of cells into the DNA synthesis (S) phase of the cell cycle from a growth or gap (G_1) phase. This block in the cell cycle at G_1 is known as a cell cycle checkpoint, and Rb is an important effector of G_1 cell cycle arrest. Cyclin D1 (CCND1) is also important at this checkpoint by its ability to regulate Rb phosphorylation through its association with

cdk-4 and -6 (315). Amplification and overexpression of CCND1 has been described in cancers such as bladder (42,264,318,465) and has prognostic significance. CCND1 overexpression can overcome the G_1 cell cycle checkpoint by promoting unregulated phosphorylation of RB and causing increased bioavailability of E2F-1. The ability of cyclin D1 and other cyclins to dominantly promote tumor formation by promoting cell proliferation makes them potential oncogenes in bladder carcinogenesis (315,353,388).

The important and versatile TSG, p53, is mutated in over 50% of human malignancies, including TCC (4,197). The normal or wild type p53 protein has many important functions in suppressing tumorigenesis, such as growth arrest and apoptosis (267,268). Transactivation of a gene known as p21/waf-1/cip-1 by p53 causes inhibition of cdk-dependent phosphorylation of RB and thereby causes inhibition of E2F-1–mediated cell cycle progression (111). As mentioned previously, p53 transcriptionally activates genes such as bax that promote apoptosis and transcriptionally represses bcl-2 that prevents apoptosis (223). Other genes transcriptionally activated by p53 such as GADD45 and FAS/Apo1 also play a role in growth arrest or apoptosis (223). An important signal for many p53 functions is DNA damage from a variety of causes such as chemotherapy or radiation. These agents can block progression through cell cycle checkpoints influenced by DNA repair (222).

Another protein, p14ARF (called p19ARF in mouse) on chromosome 9p and within the same transcription unit as p16 (discussed in the next section), is transcriptionally activated by E2F-1 (20,347). The p14ARF protein interacts with a protein known as mouse double minute–2 (mdm-2), causing it to be degraded (254,347,466). The mdm-2 gene on chromosome 12 is transcriptionally activated by p53 but negatively regulates p53 by binding and targeting p53 for ubiquitin-mediated degradation (184). Mdm-2 is often amplified and overexpressed in tumors (175,262,331) and has oncogenic properties through its physical interaction with the tumor-suppressor properties of p53 (175,332). The interaction of p14ARF with mdm-2 allows increased activity of p53 and negatively regulates progression through the G_1 checkpoint. This entire process serves as a negative feedback loop for E2F-1–mediated cell cycle progression and potentiates the action of other cdk inhibitors such as p21/waf-1/cip-1. Therefore p53 and Rb are functionally related through their effects on the cell cycle. Inactivating mutations that affect either p53 or Rb promote unregulated cell growth, and mutations in both may be synergistic (83,86,170).

The role of Rb and p53 expression in bladder cancer has been a very active area of research. The p53 gene is often mutated in bladder cancer and associated with high-grade invasive lesions (117,118,138,333). Other studies have investigated the role of p53 in tumor recurrence, progression, and response to treatment such as radical cystectomy, radiation, chemotherapy, or intravesical therapy (85,263,276,366,367). Using immunohistochemistry, p53 expression generally correlates with poor outcome in terms of recurrence, progression, resistance, and survival. However, immunohistochemical analysis of p53 has caused some discrepancies when used as the sole assay for p53 mutational analysis in these studies.

Immunohistochemistry correlates with mutations that increase stability of the altered p53 protein product (118). Mutations in p53 correlated with immunohistochemistry when 20% of cells demonstrated nuclear staining in one large bladder cancer series (276). However, a positive immunohistochemical result may not be specific for the mutant protein due to biologic factors (178). This observation, combined with the technical limitations of immunohistochemistry, has led to different results using p53 as an independent variable for clinical outcome in bladder cancer (402). The clinical response of bladder cancer patients to chemotherapy is one recent example. In one study, mutant p53 (as determined by immunohistochemical analysis) was associated with favorable outcome when cystectomy was combined with adjuvant chemotherapy (87), while in another study immunohistochemical staining of p53 was associated with decreased response to neoadjuvant chemotherapy (367).

The underlying hypotheses for each result is the ability of wild type p53 to induce apoptosis when using agents such as MVAC that cause DNA damage. Tumors with increased p53 staining (mutant p53) cannot undergo p53-mediated apoptosis induced by the chemotherapeutic agents and are therefore resistant. Alternatively, the absence of p53-mediated G_1 arrest may allow tumor cells with damaged DNA to proceed through S phase but arrest at mitosis and subsequently undergo apoptosis (440). Tumor cells with normal p53 presumably repair DNA damage before entering S-phase and then undergo mitosis. The true mechanism is currently unknown and may be dependent on the status of other proteins such as Rb, mdm-2, p21, or proteins involved in DNA repair. In addition, experimental and study design differences may prove to be the most important factor. Although p53 mutation is independently associated with higher grade, stage, and progression in most studies and may have clinical applications in the future, the practicality of using p53 immunohistochemistry instead of routine pathologic staging and grading has not been definitively proven (436).

Immunohistochemical analysis of Rb expression has also been extensively investigated in bladder cancer (82,282). Although mutations in Rb have not been associated with increased reactivity using immunohistochemistry, increased expression has been observed in some tumors (86). Absent or altered Rb staining is associated with muscle-invasive disease, and studies have associated abnormal Rb expression with poor outcome (82,86). Moreover, loss or abnormal expression of Rb combined with p53 immunoreactivity has independent and prognostic value in some studies (83,170).

Investigation of p53 and Rb proves that development of bladder cancer is complex and dependent on accumulation of mutations in multiple targets. Mutations in parallel pathways may be important for development and progression of high-grade malignancy, whereas single pathway alterations are necessary for low-grade tumors.

Many chromosomal regions are associated with high rates of LOH in bladder cancer (40,52,199,236,237,310,345,350,360). However, most common and consistent area of LOH in bladder cancer are the long and short arms of chromosome 9 (224,236). At least three genes in this region are important in tumor suppression via their effect on progression through the cell cycle. The ink4a (p16, mts-1, ckn2a), and ink4b (p15, mts-2) genes encode inhibitors of cyclin-dependent kinases, and ink4a/ARF encodes a peptide that regulates p53 activity, as discussed previously. This region has a high rate of homozygous deletions in cell lines and primary tumors (51,220). Methylation and transcriptional repression may also be an important mechanism of inactivation of these genes (158). Moreover, these genes are associated with hereditary melanomas fulfilling the criteria as group one TSGs described previously.

LOH on the short and long arms of chromosome 9 is common in bladder cancer. Over 50% of superficial and invasive TCCs have LOH on chromosome 9 (235). Unlike p53 and RB, where LOH on chromosomes 17p and 13q, respectively, usually occur in high-grade lesions (52,333), chromosome 9p losses occur early and are associated with low-grade superficial TCC in addition to high-grade lesions. These findings suggest that 9p genes are important initiators in TCC, allowing growth advantage until other genetic events select more aggressive clones. Genetic alterations affecting Ink4a appear to be common in tumorigenesis (51,158,334), but the mechanism of inactivation implies that all genes in this region are important TSGs. Both p15 and p16 proteins are cdk inhibitors that function in G_1 (68). By inhibiting cdks, p16 prevents RB phosphorylation, E2F-1 remains sequestered and cells are prevented from entering S-phase. Loss of p16 and p15 activity by homozygous deletion of ink4a and ink4b allows unregulated phosphorylation of Rb and increased E2F-1 activity. Furthermore, loss of ink4a/ARF results in increased mdm-2 (due to the lack of ink4a/ARF-mediated mdm-2 degradation) and increased ubiquinin-mediated degradation of p53. Therefore homozygous deletion of these three genes affects Rb and p53 regulation of the cell cycle.

Regions on chromosomes 3p, 4q, 9q, 8p, 11q, 14q, and 18q are also associated with high rates of LOH in bladder cancer and are undoubtedly locations of group two TSGs (40,52,62,199,236,237,345,350,360). In addition, candidate TSGs on chromosomes 4 and 9 have been identified and are currently being investigated (23,198,236,345,386). The pattern of LOH and gene mutations in bladder cancer suggests a model of tumorigenesis in which inactivation of genes on chromosome 9p and 9q are early events and associated with low-grade papillary lesions (357,399). These tumors have a growth advantage but tend to remain localized to the urothelial mucosa. High-grade lesions such as CIS are associated with early 13q and 17p losses, and progression may be associated with these and other TSGs (310). The important role of TSGs in bladder cancer is well established, and the discovery of other TSGs will most likely enhance our understanding of bladder cancer pathogenesis.

Growth Factors and Growth Factor Receptors

Growth factors and their receptors have been investigated in human bladder cancer (306,392). The met gene (chromosome 7) and its ligand hepatocyte growth factor were described in another section. Trisomy of chromosome 7 in bladder tumors has been described, and therefore met gene alterations may play a role in these tumors. However, the factors most extensively studied in bladder cancer are EGF, EGFR, and ERB-B2 (a 185-kD transmembrane protein homologous to the EGFR) also known as HER-2/neu. Growth factors and their receptors have a normal role in promoting growth, and therefore most alterations cause increased expression by increasing copy number or transcription similar to oncogenes. In addition, alterations in growth factor receptors can affect intracellular signaling (418).

EGF has been studied extensively in bladder cancer and normal urothelium (306,391). Studies have shown increased expression of EGF in the basal layers of normal urothelium and increased expression in TCC. Increased levels of EGF have been detected in the urine of patients with TCC but do not correlate with tumor grade or stage (402). The EGF receptor is an independent predictor of poor survival when overexpressed in TCC (277,303). ErbB-2 is amplified and often overexpressed in bladder tumors (72,302,369). In breast cancer, erbB-2 amplification has been well documented and shown to have prognostic implications (29). Conflicting results have been reported as to the importance of amplification of this gene in bladder cancer progression (371,416).

Hereditary Predisposition and Urothelial Cancer

Although environmental agents such as smoking, organic compounds, and phenacetin have been implicated in the development of bladder cancer, hereditary bladder cancer syndromes have not been clearly defined. Clustering of TCC in families has been described, but linkage to a specific gene(s) had not been described until recently (273,340). Lynch and colleagues (287,451) described an increased incidence of upper tract TCC in an inherited cancer predisposition syndrome known as hereditary nonpolyposis colon cancer (HNPCC). Although colon cancer is the predominant

malignancy found in these kindreds, extracolonic tumors, including upper tract TCC, are also prevalent in a subset of families.

The mutated genes responsible for HNPCC are highly conserved genes involved in mismatch repair (MMR) (43,127,261,325,338). At least nine human MMR genes have been identified, and several have been shown to be mutated in families with hereditary predisposition to cancer (hMSH2, hMSH6, hMLH1, PMS-1, and PMS-2); however, the most commonly mutated MMR genes in hereditary and sporadic tumors are hMSH2 and hMLH1 (338). MMR-deficient tumors have a characteristic phenotype referred to as microsatellite instablility (MSI) due to alterations in dinucleotide and trinucleotide repeats (3,210,419).

Several features of MMR in urologic malignancies deserve special attention. As mentioned previously, HNPCC is the only well-characterized hereditary cancer predisposition syndrome with increased risk of TCC. The absence of increased bladder TCC risk in HNPCC is surprising but may reflect subtle differences in cell biology of upper tract and bladder urothelium. Alternatively, the association of an increased incidence of upper tract TCC with HNPCC may have been more easily established due to the low incidence of upper tract TCC in the general population. HNPCC patients develop bladder cancer, and it would be interesting to determine if bladder tumors in HNPCC patients exhibit MSI due to inactivation of the wild type MMR gene allele.

Approximately 10% to 15% of sporadic colon cancers have MMR mutations (3). However, only about 3% of superficial bladder tumors showed MSI (157). An immunohistochemical analysis of hMSH2 expression identified 25% of TCC with reduced expression of hMSH2 and complete absence of expression in 2% (218). Decreased hMSH2 expression was predominantly found in high-grade and recurrent tumors, suggesting that alterations in MMR activity may be involved in recurrence and progression. In addition, cell lines deficient for MMR are resistant to DNA alkylating agents (204). This finding may be important for urothelial malignancies because alkylating agents are sometimes used in the treatment of superficial bladder tumors and MMR deficiency may be important for resistance to other chemotherapeutics.

INFECTIOUS AGENTS AND UROTHELIAL CANCER

Part of "7 - GENITOURINARY MALIGNANCY: ETIOLOGY AND MOLECULAR GENETICS, NATURAL HISTORY, AND TREATMENT "

Bladder cancer associated with chronic irritation, inflammation, and certain infections usually has the histologic appearance of SCC. The schistosome *S. haematobium* is one of four schistosome species that infects humans (312) and the only schistosomal infection associated with development of bladder cancer. The etiology of the SCC is related to the intense inflammatory response to the *S. haematobium* eggs deposited within the bladder wall. Molecular analysis of SCC from individuals infected with *S. haematobium* suggests that the genetic alterations are similar to nonbilharzial tumors (385). SCC development using *S. haematobium* as a model system could be useful for investigation of immune response initiation of these tumors and response to treatment.

Markers in Urothelial Cancer

An important area in bladder cancer research is development of markers for early detection of primary or recurrent tumors, progression, and prognosis. Currently, cystoscopy with cytology is an essential component for diagnosis of urothelial malignancies. Insufficient sensitivity for low-grade cancer does not allow cytology to be used independent of cystoscopy. As a result, a number of markers have been developed and assessed for detection of urothelial malignancies (402). Currently, no single marker or test has sufficient sensitivity and specificity to replace cystoscopy and cytology in diagnosis or surveillance of bladder cancer patients.

A novel approach to detection of urothelial malignancies uses the detection of genetic alterations in the form of LOH and MSI (296). The clonal nature of tumors expands and propagates genetic alterations that can be detected using a panel of molecular markers. High sensitivity and specificity has been achieved using this technique in urothelial malignancies. However, sensitivity is achieved by screening large numbers of markers and may be impractical for routine clinical use. Similar approaches using gene expression may prove less cumbersome, but these tests have not been proven useful in a large series. In addition, tests that can predict or direct responses to standard or novel anticancer agents will need further investigation.

Conclusion

Urothelial malignancies are common due to environmental, infectious, and genetic factors. Bladder cancer is the most common manifestation of urothelial malignancy and usually exists as two histologic and pathologic diseases. Superficial disease is easily treated, but recurrence and progression are of major importance. Invasive disease is aggressive and potentially lethal because of high metastatic potential. However, the natural history of bladder cancer and its treatment makes this disease an excellent model for cancer recurrence, progression, and response to treatment. Urologists should be instrumental in the investigation of bladder cancer because management of localized disease is completely within the field of urology. Our goals as urologists, molecular biologists, and physician scientists are to develop better treatment options for advanced and metastatic urothelial malignancies and develop markers for recurrence and progression.

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8

CALCULUS FORMATION

Alan D. Jenkins

A.D. Jenkins: Department of Urology, University of Virginia, Charlottesville, VA 22908.

Contents

Most patients who have passed a kidney stone do not understand the nature of their disease and want to know why they form kidney stones. Other patients may have an easily identifiable cause such as cystinuria or renal tubular acidosis (RTA) for their stone formation. Specific and effective medical treatment programs exist for these patients. Other patients may benefit from simple measures such as increased fluid intake and dietary moderation. Patients with recurrent stone formation require a medical regimen that is designed to correct any physicochemical abnormalities.

This chapter imparts an understanding of the basic pathophysiology of urinary tract stone formation and enables the urologic practitioner to blend the medical and surgical management of urolithiasis patients.

BASIC PRINCIPLES

Part of "8 - CALCULUS FORMATION "

Biologic mineralization involves the precipitation of a poorly soluble salt, usually in association with an organic matrix. Supersaturation (SS) of the precipitating phase must be present before crystallization can occur. If at least local SS is not present, then crystallization is thermodynamically impossible. Most medical treatment programs depend on a reduction of SS to prevent further stone formation. The solubility concept is one of the most important aspects of biologic mineralization (262).

The physical chemistry of ions in an aqueous solution involves four basic concepts: ion activity, ion pairing, solubility, and relative supersaturation (RSS). The effective concentration of an ion, such as calcium (Ca^{2+}), in solution is different from its actual concentration. This effective concentration, the chemical activity, depends on the ionic strength of the solution. Through electrical field effects, the other ions in the solution affect the true chemical activity of a particular ion. The ionic strength is a measure of the magnitude of this electrical field and increases as the concentration of ions increases and their valence or charge increases. The activity of an ionic species decreases as the ionic strength increases. For a given total calcium concentration, the activity of Ca^{2+} would be greater in distilled water, which contains only the Ca^{2+} and its accompanying anions, than in urine, which contains many different ions.

The relation between ion activity, $\{Na^+\}$, and ion concentration, $[Na^+]$, is given by the following equation:

$$\{Na^+\} = [Na^+] \times a_1$$

where a_1 is the activity coefficient for Na^+. Activity coefficients are always less than 1 and approach unity as the concentration of the solution decreases. The ionic strength of a physiologic salt solution, such as urine, is approximately 0.15 M. The corresponding activity coefficients for the divalent ions Ca^{2+} and $C_2O_4^{2-}$ (oxalate) are approximately 0.3. The activity of each of these ions is less than one-third of the concentration.

Specific ions of opposite charge, such as Ca^{2+} and sulfate (SO_4^{2-}), can interact to form soluble ion pairs or complexes. These interactions effectively reduce the "ionized" concentrations of the ions involved. Many such interactions are possible in urine. Ionized calcium can be measured directly with an ion-selective electrode, but no satisfactory method has been developed to measure the free ion concentrations of those anions (especially oxalate) that participate in urinary tract mineralization.

Computer programs have been written to calculate the free ion concentrations of the major ionic species in urine, given the total concentrations of the ions, the pH, and the stability constants of the various ion pairs (94,361). (The stability constant is a measure of the strength of the association between the ions forming an ion pair.) These algorithms also permit the calculation of ionic strength, activity coefficients, and activity products. The activity product of a salt such as sodium chloride (NaCl) is given by the product of the activities of Na^+ and Cl^-: $\{Na^+\} \times \{Cl^-\}$. An estimate of SS can be made if the activity product is compared with the thermodynamic solubility product.

A solid salt added to an aqueous solution dissolves to an extent determined by the thermodynamic solubility product of the particular compound. If the solution is at equilibrium with the solid phase, the numeric value of the solubility product is equal to the product of the activities of the constituent ions of the salt. The equation for NaCl solubility is as follows:

$$K_{sp} = \{Na^+\} \times \{Cl^-\}$$

where $\{Na^+\}$ and $\{Cl^-\}$ are the activities of Na^+ and Cl^- in equilibrium with pure, solid NaCl. Potassium (K_{sp}) is a constant at a given temperature and pH.

Within the range of physiologic urine pH, the solubilities of two common stone salts, calcium phosphate and uric acid, are pH sensitive. The equation for calcium phosphate solubility is as follows:

$$Ca_5(PO_4)_3OH = 5Ca^{2+} + 3PO_4^{3-} + OH^-$$
$$K_{sp} = \{Ca^{2+}\}^5 \times \{PO_4^{3-}\}^3 \times \{OH^-\}$$
$$H_2PO_4 = HPO_4^{2-} + H^+$$
$$HPO_4^{2-} = PO_4^{3-} + H^+$$

As the pH increases, $\{OH^-\}$ increases and hydrogen ion activity (H^+), decreases. More phosphate exists as PO_4^{3-}, and the solubility of $Ca_5(PO_4)_3OH$ decreases. Clinically, calcium phosphate urolithiasis tends to occur in alkaline urine.

The pKa at 38°C of the first dissociable proton in uric acid is 5.5 (98). In an aqueous solution of uric acid at pH 5.5 and 38°C, half exists as dissolved uric acid (HU) and half exists as urate ion (U^-): $HU = H^+ + U^-$. This physicochemical property of uric acid is responsible for the sensitive pH dependence of uric acid solubility in urine. As urinary pH increases, more of the uric acid exists as urate ion, and urate is more soluble than uric acid. The solubility of uric acid as a function of pH is shown in Table 8.1 . The dramatic increase of uric acid solubility with increasing pH is the cornerstone of the medical treatment of uric acid lithiasis.

pH	Solubility (mg/L)
5.0	60
6.0	200
7.0	1,600

TABLE 8.1. SOLUBILITY OF URIC ACID AS A FUNCTION OF pH

The ratio of the calculated activity product *(AP)* to

the thermodynamic solubility product *(K_{sp})* is the relative supersaturation *(RSS or SS):*

$$RSS = AP \div K_{sp}$$

If solid crystals of a salt are added to a solution of the salt, they will dissolve if SS is less than 1 and will grow if SS is more than 1. If SS is 1, the crystals will not grow or dissolve. SS (RSS ratio more than 1) of the precipitating salt must be present for stones to form and grow.

The initial step in the actual formation of a crystal is nucleation or the birth of crystals from solution (356). If the supersaturated solution is pure, nucleation may occur homogeneously at a critical level of SS. However, urine contains many foreign surfaces, such as cell membranes, that can act as heterogeneous nuclei. Heterogeneous nucleation occurs at a lower level of SS than does homogeneous nucleation and is the most common, if not the only, type of nucleation that occurs in biologic systems (104). The level of SS at which nucleation occurs often is referred to as the *formation product.* The formation product is not as precisely defined as the solubility product and is most accurately described as a range of SS that permits nucleation.

The range of SS between the solubility product and the formation product is called the *metastable zone* (Fig. 8.1). Spontaneous nucleation does not occur in this zone, but preformed crystals grow until the RSS is reduced to 1.

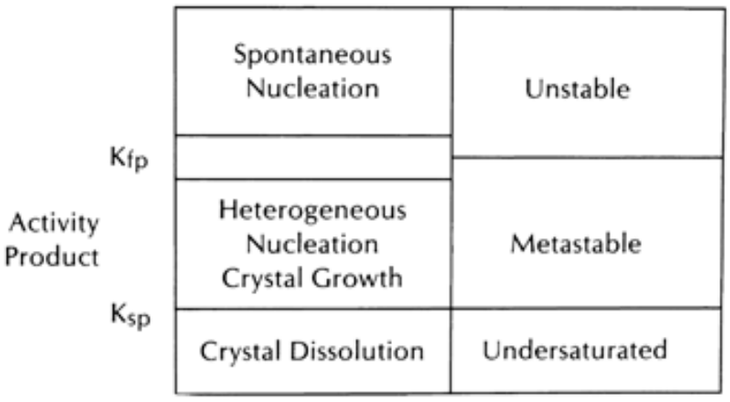


FIGURE 8.1. Schematic representation of states of saturation. K_{sp}, solubility product; K_{tp}, formation product (range).

Ideal crystals are composed of identical units arranged in a repetitive pattern. These units may be atoms, molecules, ions, or groups of these particles. In real crystals, these units are not always identical, and the pattern is not strictly repetitive. Deviations from periodicity, called *dislocations,* commonly occur in crystals formed in biologic systems. However, all crystalline substances have an approximate periodic structure, or lattice, that can be characterized with x-ray diffraction. If the lattice structure of one crystal is similar to that of a different crystal, the second crystal may be able to nucleate and grow on the first crystal. This oriented overgrowth is called *epitaxy* (179,203). The concept of epitaxy was offered several years ago as a possible explanation for the growth of mixed urinary stones. The clinical association of disorders of uric acid metabolism (hyperuricosuria and hyperuricemia) with calcium oxalate urolithiasis motivated the intensive study of a possible epitaxial relation between urate crystallization and calcium oxalate crystallization (56,164,225). Other investigators have questioned the specific importance of epitaxial crystal growth in clinical urolithiasis (33,195,196). It is likely that mixed stone formation in the urinary tract occurs by heterogeneous nucleation and overgrowth, not by the highly specific mechanism of epitaxy.

More recent *in vitro* studies have shown that the promotion of calcium oxalate crystallization by dissolved urate is not caused by the epitaxial nucleation of calcium oxalate or by the inactivation of urinary glycosaminoglycans (119). A “salting out” mechanism may be responsible for the promotion of calcium oxalate crystallization by dissolved urate (279).

Nuclei will grow to form larger crystals if the urine remains supersaturated for the precipitating phase. The growth units of the crystal are added to growth sites on the crystal surface (216). Available evidence suggests that the growth sites of urinary crystals are screw dislocations (Fig. 8.2). As the crystal grows, the step winds itself into a spiral with the center fixed at the dislocation. Because the step does not disappear during growth, the crystal can grow continuously at a low SS. The crystal grows as long as the bathing solution remains supersaturated for the precipitating phase.

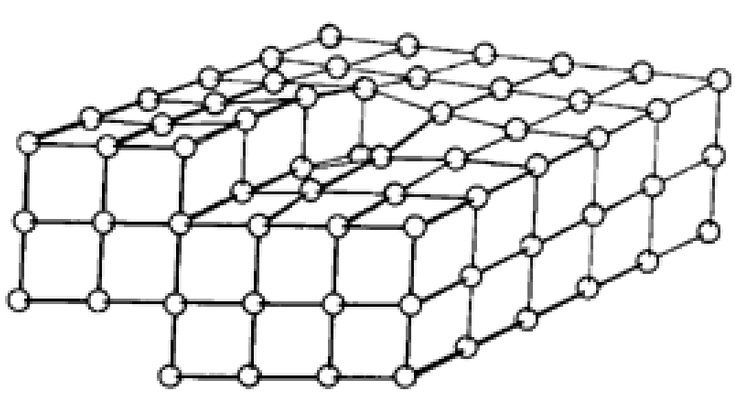


FIGURE 8.2. Schematic representation of a crystal with a screw dislocation.

Many collisions occur between the small crystals in an aqueous solution. Some of these crystals may stick together to form larger crystalline masses. This process is called *aggregation* or *agglomeration;* it is another mechanism by which crystals can increase in size to form a stone. Crystal growth produces a more dense particle than does aggregation (95). The density of actual uroliths is similar to that of pure stone crystals. This implies that urinary tract stones increase in size primarily through crystal growth, not aggregation. However, initial particle retention could still involve crystal aggregation.

CLINICAL STONE FORMATION

Why do some people form many kidney stones? Four factors are involved: urinary SS, inhibition and promotion, particle retention, and matrix (34). Our understanding of the pathophysiology and effective treatment of urolithiasis is based on these four factors.

Supersaturation

Urinary SS for the precipitating stone salt is a necessary condition for stone formation. It is thermodynamically impossible for a stone to grow if the urine is not supersaturated for the particular salt, but continuous SS does not have to be present. Urine may become supersaturated after meals. This effect may be accentuated after the evening meal, because the lack of fluid consumption during sleep permits a decrease in overnight urine volume. Stone growth can occur only at night, even though daytime fluid intake is sufficient to prevent SS.

Inhibitors and Promotors

Urinary SS alone does not explain the presence of stone disease in some individuals and its absence in others. Urine commonly is supersaturated for stone salts, especially calcium oxalate (110,270). Small urinary crystals often are passed by individuals who have never formed a stone (271,359). One explanation for this apparent paradox is the presence of crystallization inhibitors in urine (100). Inhibitors of crystal growth and aggregation have been isolated from human urine, and inhibitors of nucleation may exist (272,280); inhibitors of crystal growth have received the most attention (101). Inhibitors usually are classified according to their ability to inhibit the growth of calcium phosphate or calcium oxalate. Pyrophosphate, citrate, and magnesium are known inhibitors of calcium phosphate crystal growth. Pyrophosphate and citrate also inhibit calcium oxalate crystal growth (299), but most of the calcium oxalate crystal growth inhibition in urine is provided by larger-molecular-weight polyanions: glycosaminoglycans and RNA fragments (21,37,197,293). Heparin, although not found in urine, is a potent inhibitor of *in vitro* calcium oxalate crystal growth.

Acidic glycoproteins have been isolated from human urine and human kidney tissue culture medium (141,212,213). Evidence shows that patients with calcium oxalate nephrolithiasis have intrinsically abnormal acidic glycoproteins (210). These glycoproteins from healthy persons contain γ-carboxyglutamic acid and are strong inhibitors of calcium oxalate crystal growth at low concentrations (10 to 7 M). Glycoprotein crystal growth inhibitor from patients does not contain γ-carboxyglutamic acid and is a functionally poor inhibitor.

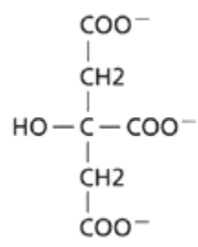
This glycoprotein inhibitor of calcium oxalate crystal growth has been named *nephrocalcin* (209). Nephrocalcin has been isolated from human calcium oxalate renal stones (211) and appears to localize to the proximal tubule cells of the human kidney (312). The γ-carboxyglutamic acid residues of nephrocalcin are synthesized by the addition of a carboxyl group to the γ-carbon of glutamic acid residues after messenger RNA translation. The same investigators have reported that nephrocalcin and Tamm-Horsfall glycoprotein inhibit calcium oxalate crystal aggregation at concentrations as low as 2×10^{-9} M and 1×10^{-8} M (132).

Tamm-Horsfall protein is a glycoprotein that is produced in the thick ascending limb of Henle's loop. It inhibits calcium oxalate monohydrate crystal aggregation at a low ionic strength and a high urinary pH (131). In highly concentrated urine, Tamm-Horsfall protein readily polymerizes, thereby overwhelming other urinary inhibitors and promoting the agglomeration of calcium oxalate monohydrate crystals (118,294).

Uronic acid–rich protein, another glycoprotein that has been isolated from human urine, also exhibits inhibitory activity against crystal growth (8). It appears to be a more potent inhibitor than nephrocalcin.

Patients who form stones appear to excrete more lipids or acid phospholipids than normal individuals. Urinary excretion of glycolipid, cholesterol, and cholesterol esters also was higher in stone-formers (154). The greater excretion of lipids may reflect sloughing of tubular cells in response to a challenge by oxalate or calcium oxalate crystals. Acid phospholipids from cellular membranes may be involved with crystal nucleation and retention.

Citrate, through its ability to complex calcium and inhibit the growth of calcium salts, may play a role in the pathogenesis of calcium urolithiasis. Citrate is a tricarboxylic acid that, when totally ionized above pH 6.5 at 37°C, has a charge of minus 3:



The following reactions occur with calcium in urine at a physiologic pH:

$$Ca_3Cit_2 \rightarrow Ca^{2+} + 2CaCit^{2-}$$
$$CaCit^{-} \rightarrow Ca^{2+} + Cit^{3-}$$

As the concentration of citrate increases, the reaction is shifted toward the left with increased complexation of calcium. This effect decreases calcium oxalate SS and the potential for crystallization. Citrate weakly inhibits the

growth of preformed calcium oxalate crystals, but this action is not as important as complexation.

Citrate is filtered at the glomerulus and reabsorbed primarily in the proximal tubule (309). The ability of renal mitochondria to metabolize citrate by means of the tricarboxylic acid cycle is thought to control the renal clearance of citrate. Metabolic acidosis increases the entry of citrate into the matrix space of mitochondria and decreases the exit of citrate from mitochondria, thereby allowing mitochondrial oxidation of citrate. Cytoplasmic citrate levels decline, reabsorption of citrate from tubular fluid is enhanced, and less citrate appears in the final urine. Metabolic alkalosis has an opposite effect.

The luminal membrane of the proximal tubules (brush border membrane) is equipped with a Na^+}-gradient–dependent transport system that is highly specific for intermediates of the tricarboxylic acid cycle, including citrate (157). Metabolic acidosis caused by dietary acid loading increases the intrinsic capacity of proximal tubular brush border membrane to transport citrate from the tubular lumen into the cell interior (143). A corresponding decrease in urinary citrate excretion was seen. A dramatic increase in urinary citrate excretion was seen with dietary alkali loading (with $NaHCO_3$), but brush border membrane transport of citrate was unchanged. These studies demonstrate that urinary citrate excretion is exquisitely sensitive to manipulation of systemic acid–base balance through effects on renal cellular function.

Urine from patients with recurrent calcium oxalate nephrolithiasis tends to have greater calcium oxalate SS and lower inhibitor levels than urine from healthy individuals (76,271), but considerable overlap exists. It is impossible to predict consistently on the basis of SS or inhibition alone who will and who will not recurrently form calcium oxalate stones. A combination of these two factors, the saturation-inhibition index, has discriminated between healthy individuals and patients with recurrent stone formation (269). The saturation-inhibition index is a mathematic combination of relative calcium oxalate and inhibition of crystal growth and aggregation (as measured by the change in particle-size distribution in an *in vitro* crystal growth system). Patients with the greatest saturation-inhibition indexes had the highest recurrence rates. Because SS and inhibition are difficult to measure, this method has not had widespread clinical application.

The concept of urinary risk factors is an extension of the saturation-inhibition index. This concept attempts to account for the multifactoral nature of calcium urolithiasis by considering six factors (236,266,267): urine volume, urine pH, urinary excretion of oxalate, uric acid, calcium, and alcian blue precipitable polyanions (a measure of acid mucopolysaccharides or large-molecular-weight inhibitors). Although no solitary abnormality may distinguish a stone-former, clear discrimination can be made by the presence of several risk factors. A low urine volume has the greatest risk, followed by a high urinary oxalate excretion. A high urine pH or uric acid excretion is associated with a higher probability of forming stones. Hypercalciuria is the least important risk factor.

Crystal Retention

Freshly voided urine samples from most healthy persons intermittently contain small crystals (usually calcium oxalate dihydrate), but only 5% to 10% of such persons will ever develop an actual kidney stone. These crystals probably form in the papillary collecting ducts and are flushed out with the urine before they grow large enough to become lodged in the lumen. Anatomic abnormalities or adherence to the epithelium may prevent these particles from leaving the kidney. This increased particle retention permits the crystals to grow larger, further reducing the likelihood that they will be passed spontaneously (35). This condition could easily predispose an individual to the formation of kidney stones. An attractive hypothesis is that patients with stone disease may have an increased particle retention time, possibly resulting from an abnormal tendency for small crystals to adhere to the epithelial lining of the upper urinary tract.

Two theoretical mechanisms have been proposed for crystal retention: free particle or fixed particle. The free particle mechanism assumes that nucleation and initial crystal growth occur in the tubular lumen. The crystalline particles grow with such sufficient rapidity that they become trapped in the papillary collecting ducts, where they grow to form a macroscopic stone (350). Estimates of calcium oxalate crystal growth rates in the distal tubule have cast doubt on the ability of these crystals to grow rapidly enough to occlude the lumen before they are washed out of the collecting ducts (97). Some investigations have suggested that rapid aggregation of small crystals would permit free particle trapping to occur.

More support exists for the second theory, a fixed particle mechanism. Rats with magnesium deficiency develop nephrocalcinosis and stone formation (219). Small stones were found attached to normal-appearing tubular epithelium near the bend of Henle's loop. This intranephronic calculosis may have occurred by crystal nucleation on the luminal membrane or attachment of a passing crystalline particle. Carr (38) suggested that crystals floating in the renal pelvis could be trapped in forniceal lymphatic vessels and grow to macroscopic size. Papillary tip stones could originate from crystals that had become attached to the epithelial lining of the distal collecting ducts and had grown out of the lumen to form a papillary cup (351). Randall's plaques (254) are macroscopic subepithelial deposits of calcium crystals. Although older studies found a poor correlation between the incidence of stone disease and the incidence of Randall's plaques, it was still hypothesized that the epithelium over the plaque could erode, and a calyceal stone could develop

from crystal growth on the plaque (252). More recent studies of Randall's plaques have found that they are not just subepithelial deposits (326); they appear to extend deep into the papilla and are intimately associated with collecting tubules and vasa recta. These same investigators found that papillary plaques were more common in patients with calcium oxalate and calcium phosphate stones than in patients without a history of stone disease (180). Endoscopic examinations found that most patients with calcium stone disease had Randall's plaques.

Investigators have induced calcium oxalate nephrolithiasis in rats with intraperitoneal injections of oxalate (146,151). Calcium oxalate crystals were found in the tubular lumina, in the intercellular spaces between cells, and attached to the tubular epithelial basal lamina. Necrosis of tubular cells was responsible for exposure of the tubular basal lamina. Oxalate itself may be toxic to renal epithelium (166,331), and renal tubular epithelial damage can result in the shedding of membranous cellular debris, thereby providing a substrate for heterogeneous nucleation (153).

The attachment of crystals to the kidney epithelium may involve a specific molecular interaction between stone crystals and the epithelial membrane. Rat renal inner-papillary collecting tubule cells have been isolated in primary cultures and used as a model for the study of crystal-membrane interactions (358). Riese and colleagues (258) developed a mathematic model of the binding of calcium oxalate crystals to these cells. This binding is location specific, saturable, and inhibitable. Calcium oxalate crystal binding appears to be related to cell membrane polarity (259). This binding is enhanced if a monolayer of cultured cells is depolarized by disrupting the normal intercellular tight junctions. These results suggest that the crystals preferentially attach to a basolateral cell membrane component. Renal epithelial cells also can endocytose calcium monohydrate crystals (175). Other studies continue to confirm the ability of calcium oxalate monohydrate crystals to specifically bind to cultured renal epithelial cells (22,163,176).

The most provocative hypothesis regarding stone formation involves nanobacteria (147). Nanobacteria are sterile-filterable, Gram-negative, atypical bacteria that have been detected in bovine and human blood. They produce carbonate apatite on their cell walls and could potentially act as nidi for the precipitation of other stone salts, such as calcium oxalate. The smallest apatite units in kidney stones resemble the site and morphology of nanobacteria by scanning electron microscopy (48). One investigator has isolated nanobacteria from more than 90% of nonstruvite kidney stones.

Meticulous work by Delatte and associates (72) revealed that small calcium oxalate stones are not uniformly round but have one surface with a concave depression. A small crystalline aggregate of calcium phosphate sometimes was found in this depression. Clinically significant growth of calcium oxalate stones may be initiated by epithelial precipitation of calcium phosphate that subsequently is overgrown with calcium oxalate (114,124,341).

Matrix

Kidney stones contain a variable amount of organic material called *matrix.* The matrix content of most urinary calculi is 2.5% by weight (25). Cystine stones contain approximately 10% matrix. The rare matrix calculus is a soft, radiolucent body that occurs in patients whose upper urinary tracts are infected with urea-splitting bacterial organisms (253). The matrix content of these calculi averages 62%.

Macroscopic examination of whole renal calculi reveals concentric laminations and radial striations (25). Scanning electron microscopic studies of fractured calcium oxalate calculi demonstrate fibrous material bridging adjacent crystals (321). These findings support the proposal that matrix acts as a ground substance (153).

Other investigators believe that the presence of matrix in urinary stones is serendipitous (99). Nonspecific physical adsorption of organic compounds on growing crystals may account for at least some of the matrix found in calculi (169). Electron microscopic examination of calcium oxalate crystals incubated with γ-globulin or albumin has revealed an amorphous coat of material covering the crystals (146). This continuous coat is consistent with simple adsorption.

Few studies have attempted to isolate and precisely identify the chemical composition of matrix. The best known investigations found similarities between urinary mucoproteins and matrix material that was extracted from renal stones with ethylenediaminetetra-acetic acid (EDTA). A mucoprotein material, matrix substance A, was identified in urine from patients with recurrent stone disease (27). This organic compound constituted approximately 85% of the total organic matrix of kidney stones. One-third of matrix substance A was carbohydrate and two-thirds was protein. Aspartic and glutamic acids were the most common amino acids found in the protein component. The carbohydrate component contained galactose, mannose, methylpentose, glucosamine, and galactosamine (24). Studies of dialyzed ultrafiltrates of matrix also found aspartic and glutamic acids. Alkaline hydrolysis revealed the presence of γ-carboxyglutamic acid (174). Proteins containing this amino acid have a strong affinity for calcium ions.

Urinary stone protein, or uropontin, is an aspartic acid–rich glycoprotein that is found in stone matrix (161). It binds calcium and has the same structure as osteopontin, which is found in bone and other mineralized tissue (36). Increased staining of distal renal tubular cells for this glycoprotein is seen in rats that have been induced to form stones by the administration of glyoxylic acid (160).

Uropontin also has been isolated from urine and is a potent inhibitor of the nucleation, growth, and aggregation of calcium oxalate crystals and the binding of these crystals to renal epithelial cells (202). Uropontin concentration in

urine appears to vary inversely with urine volume. Its ability to prevent calcium oxalate crystallization would increase as urinary concentration increases.

EPIDEMIOLOGY

Part of "8 - CALCULUS FORMATION "

In the United States and in other technologically developed countries, urolithiasis commonly occurs as upper tract stones. Bladder stones are more common in less-developed countries (7). Epidemiologic data suggest that climate, geography, and diet are important factors in the pathogenesis of urolithiasis (261). The best-known example of this influence is the apparent existence of “stone belts.” These are geographic areas that are associated with a high prevalence of stone formation (134). A questionnaire survey of hospitals estimated that, during 1952, 0.95 persons per 1,000 population were admitted to a hospital with a diagnosis of urinary calculi (26). A rate of 1.93 per 1,000 population in South Carolina and 0.43 per 1,000 in Missouri provided evidence of geographic variability. Each of the southeastern states had a high rate of urinary calculi. A more recent study found that 1.64 persons per 1,000 population were admitted to a hospital with the diagnosis of urolithiasis, an increase of 75% over the 22-year period (303). High rates were again found in the southeastern states, especially in the Carolinas (North Carolina, 3.0 per 1,000 population; South Carolina, 2.7 per 1,000 population), but the differences were not statistically significant.

Studies of hospitalization rates may underestimate the number of patients with urolithiasis because not all patients with stones are hospitalized (145). A study of residents of Rochester, Minnesota, found that 51% of patients with stone disease were seen only as outpatients. These investigators precisely defined their epidemiologic terms and the population under study. *Incidence* was defined as the first symptomatic and diagnosed episode in a person's life. The *incidence rate* was the ratio of the number of persons who experienced such initial episodes during a specified period to the size of the population at the midpoint of the period. *Prevalence* was the number of people who had had at least one symptomatic episode, whereas *recurrence* referred to episodes that followed the initial episode. Patients with asymptomatic stones, urinary tract infections, or struvite calculi were excluded from this study.

Six hundred seventy-two persons had their first episode of symptomatic urolithiasis while a resident of Rochester, Minnesota: 468 (70%) men and 204 (30%) women. The first episode tended to occur between the ages of 30 and 60 years. The annual age-adjusted incidence rate for males was 1.1 per 1,000 population and for females it was 0.36 per 1,000 population. The incidence rates for females were stable over the 25-year study period (1950 to 1974), but the male rate per 1,000 population increased from 0.8 to 1.24. This increase was statistically significant and most apparent in the group of men aged 50 to 70 years. Prevalence was estimated to increase to a peak of approximately 12% in males older than age 70 years. Prevalence in females was less than 5%. Recurrences tended to occur during the first year: 15.9% in males and 12.4% in females. Annual recurrence rates for subsequent years was 3.7% for males and 2.0% for females.

Studies of racial differences in the incidence of urolithiasis have been inconsistent. A retrospective review found that the frequency of urinary stones in Caucasian patients was three to four times that in African American patients (289). More African American women than African American men formed stones, and the most common type of stone formation in African American patients was struvite and carbonate apatite. Stones tended to occur at a younger age in African American males.

Normal pregnancy causes hypercalciuria, but pregnancy is not a stone-forming condition (57,182). Abnormal crystalluria is not seen in pregnant patients, and more frequent stone production is not seen in stone-formers who become pregnant. A prospective study of 11 women revealed no change in urine volume (183). Although citrate excretion increased during pregnancy, this increase was not proportional to the increase in urinary calcium. Citrate failed to increase in parallel with calcium excretion, even though the urine pH rose. SS for calcium oxalate and brushite was as high in pregnancy as in patients with proven calcium nephrolithiasis. One explanation for the lack of clinical stone formation is the relatively short duration of pregnancy. Another explanation is an increase of protective mechanisms, such as crystal growth inhibition. Nephrocalcin excretion may increase during pregnancy.

Many explanations have been offered for the increasing incidence of kidney stones in the world population. These include increased dietary protein intake, increased intake of refined sugar, decreased dietary fiber, and increased affluence. Recurrent stone formation is associated with a greater expenditure on food (378). There is a positive correlation between monthly income and urinary excretion of calcium, uric acid, and inorganic phosphorus. Stone-forming patients may consume less dietary fiber than those who do not form stones (260). One explanation is that fiber, possibly through its phytate content, binds calcium in the gastrointestinal (GI) tract and prevents its absorption. The relationship between stone disease and sugar consumption is more controversial. Increased dietary sugar can increase urinary calcium excretion (338), but epidemiologic data show an inverse relationship between sugar consumption and hospitalization rates for stone disease (260).

High consumption of animal protein seems to correlate best with affluence and stone disease (266,268). Individuals on a high-protein diet excrete more urinary calcium, cyclic adenosine monophosphate, and hydroxyproline (93). The increased fixed acid load provided by a high-protein diet may cause mild resorption of bone and reduced renal

tubular reabsorption of calcium. GI absorption of calcium is not affected. Calculated urinary SS for calcium oxalate does not change, but urinary citrate excretion and pH decrease. The reduced effectiveness of crystal growth inhibitors at the lower urinary pH would allow the growth of larger crystals.

Salt abuse also is a risk factor for kidney stone formation (111). A high sodium intake significantly increases urinary sodium, calcium, and pH, and decreases urinary citrate (283). Urinary saturation of calcium phosphate and monosodium urate increases, and inhibitor activity against calcium oxalate crystallization increases. The net effect is a higher likelihood for the precipitation of calcium salts in urine.

The relation between the composition of drinking water and urolithiasis has been examined in several studies. Dissolved calcium and magnesium are responsible for the hardness of water. The incidence of urolithiasis tends to be higher in areas of the United States that have softer drinking water (44,304). Another study examined two specific geographic regions: North and South Carolina, which had soft water and a high stone incidence, and the Rockies (Colorado, Idaho, Montana, Nevada, Utah, and Wyoming), which had hard water and a low stone incidence (300). No significant differences were found for the concentration of calcium, magnesium, or sodium in home tap water. An incidental finding was that individuals drinking private well water had a greater risk of stone formation than those drinking public water. The authors concluded that water hardness should be a minor concern with respect to stone formation.

Patients with calcium stone formation often are advised to limit their intake of dietary calcium. This advice is based on the presence of hypercalciuria in up to half of patients with idiopathic calcium urolithiasis (ICU). However, restriction of dietary calcium may increase the risk of stone formation by enhancing dietary oxalate absorption and urinary oxalate excretion (188). A prospective study in a cohort of 45,619 men without a history of kidney stones found an inverse relationship between the relative risk of kidney stone formation and dietary calcium intake (62). Stone formation was negatively correlated with fluid intake but positively correlated with intake of animal protein.

The inverse relationship between stone formation and dietary calcium content is consistent with the hypothesis that mild hyperoxaluria is more important than hypercalciuria in the pathogenesis of urolithiasis (263). One of the determinants of urinary oxalate excretion is intestinal oxalate absorption. Intestinal oxalate absorption is influenced by the oxalate-to-calcium ratio of the diet, because oxalate that is bound to calcium is not absorbed. Enhanced absorption of “free” oxalate could occur if dietary calcium is restricted or intestinal absorption of calcium is enhanced (108).

Oxalobacter formigenes is a specific oxalate-degrading, anaerobic bacterium that colonizes the GI tracts of vertebrates, including humans. It appears to maintain a symbiotic relationship with its host by regulating oxalate absorption (2). It catabolizes free oxalic acid, thereby preventing absorption, and also enhances oxalate secretion from plasma. Fecal samples from patients with Crohn's and other inflammatory bowel diseases lack *O. formigenes* and have a low rate of oxalate degradation (3). When noncolonized laboratory rats were colonized with live bacteria or treated with a preparation of oxalate-degrading enzymes derived from *O. formigenes,* they developed increased resistance to a subsequent high oxalate challenge, excreted far lower levels of oxalate, and did not develop crystalluria, as seen in control animals (302).

Excessive sweating also may contribute to stone formation. Moderate physical exercise lowers urinary pH and citrate excretion due to a mild metabolic acidosis (285). Although the total excretion of stone-forming salts decreases, the greater decrease in urine volume results in an increase in urinary calcium oxalate SS and the concentration of undissociated uric acid (secondary to an increase in total uric acid concentration and a fall in urinary pH). Nephrolithiasis is more prevalent in machinists chronically exposed to a hot environment (e.g., a glass plant) (23). These individuals had higher urinary uric acid concentrations than individuals who worked in an environment with a normal temperature. This biochemical difference was clinically expressed by uric acid stone formation in 39%.

Another study found a positive association between urinary stone disease and consumption of carbonated beverages (e.g., sugared cola) (301). A negative association existed between coffee and beer consumption and stone disease in the Rockies. Primary intake of milk, water, or tea was not associated with urinary stone disease.

The widespread consumption of iced tea has been suggested as a reason for the high incidence of urolithiasis in the southeastern United States. Although dietary oxalate is responsible for only 10% to 15% of total urinary oxalate (138), urinary oxalate excretion increases after the ingestion of oxalate-rich foods such as spinach (330). A case-control study from Newfoundland examined tea consumption in stone-formers but found no evidence to support the suggestion that tea drinking is a risk factor for calcium oxalate urolithiasis (46). These investigators calculated that 1 cup of tea would add only 0.5 mg of oxalate to total urinary excretion.

ETIOLOGY

Part of "8 - CALCULUS FORMATION "

A classification of causes of urolithiasis is given in Table 8.2 . The syndrome of ICU accounts for 70% to 80% of stone disease in industrialized nations. Inherited enzyme disorders or renal tubular syndromes are found in fewer than 1% of stone-forming patients. Primary hyperparathyroidism is the most common hypercalcemic condition associated with

urolithiasis and is responsible for stone formation in 5% of patients.

Renal tubular syndromes	Enzyme disorders
Renal tubular acidosis	Primary hyperoxaluria
Cystinuria	Xanthinuria
Hypercalcemic disorders	2,8-Dihydroxyadeninuria
Primary hyperparathyroidism	Secondary urolithiasis
Immobilization	Enteric hyperoxaluria
Milk-alkali syndrome	Infection
Sarcoidosis	Obstruction
Hypervitaminosis D	Medullary sponge kidney
Neoplastic diseases	Urinary diversion
Cushing's syndrome	Drugs
Hyperthyroidism	Idiopathic calcium urolithiasis
Uric acid lithiasis	Hypercalciuria
Idiopathic	Normocalciuria
Gout	
Low urine output states	
Myeloproliferative diseases	

TABLE 8.2. CAUSES OF UROLITHIASIS

Renal Tubular Acidosis

RTA is a syndrome of disordered renal acidification that causes a hypokalemic hyperchloremic metabolic acidosis (156). The inability to excrete normal amounts of acid into the urine may be responsible for the entire syndrome, because the administration of sodium bicarbonate corrects the hyperchloremic acidosis and the excessive urinary losses of potassium, calcium, and phosphorus (297).

Two basic types of defective urinary acidification have been identified in these patients. Patients with type 2 RTA (proximal) have a defect in the reabsorption of filtered bicarbonate, a process that occurs in the proximal tubule (204). When the plasma bicarbonate is reduced only moderately, the urinary pH is inappropriately high, but with the development of a more severe systemic acidosis the bicarbonaturia disappears and the urinary pH decreases to a normal minimum. Patients with the most frequently studied disorder, type 1, or classic, RTA (distal) have a normal capacity to reabsorb filtered bicarbonate but cannot lower the urine pH below 6.0, regardless of the severity of the systemic acidosis (325).

Classic RTA may exist as a primary or secondary form. The primary form may be subdivided into infantile or adult types. Adult, or persistent, primary RTA occurs predominantly in females. Most of the cases are sporadic, but the disease may be inherited as an autosomal-dominant trait (32). The reclamation of filtered bicarbonate is intact in the proximal tubules, but the distal tubule is unable to generate or maintain steep lumen-peritubular hydrogen ion gradients.

The electrolyte abnormalities are responsible for the symptoms. Chronic acidosis may contribute to the impaired growth of children with type 1 RTA (191), because the retained acid is buffered in bone (86). Although urinary wasting of calcium and phosphorus may lead to osteomalacia, the hyperchloremic acidosis is so readily detected that patients rarely are left untreated long enough to develop this complication. Urinary potassium wasting may result in severe hypokalemia and a flaccid paralysis.

Nephrolithiasis occurs in 70% of patients with distal RTA (142,347). Multiple calculi usually are present in both kidneys. Nephrocalcinosis is found in approximately three-fourths of adults with type 1 RTA (28). Stone formation is related to hypercalciuria, relatively alkaline urine, and low urinary citrate excretion. Reduced urinary excretion of pyrophosphate, sulfate, and inhibitors of hydroxyapatite and of crystal growth also may contribute to clinical stone formation.

The diagnosis of distal RTA is made when systemic acidosis (serum bicarbonate less than 20 mEq/L) is present and urine pH is greater than 5.5 (42,167). An ammonium chloride (NH_4Cl) load often is used as a stress test to confirm the diagnosis. Liquid NH_4Cl (100 mg/kg as a 5% solution) is given in the evening; the patient voids at 6 AM on the following day, drinks three 8-ounce glasses of water, and voids again at 7:30 AM. The pH of this latter urine specimen is measured with a pH meter. The pH of this urine sample is between 5.0 and 5.5 in a healthy individual. If the pH is greater than 5.5 and the serum bicarbonate is greater than 20 mEq/L, the NH_4Cl load is repeated. The urinary pH measurement is repeated in 4 hours.

The distal tubular acidification mechanism is intact in type 2 or proximal RTA, but the reabsorption of filtered bicarbonate is reduced in the proximal tubule (205). Proximal RTA usually is associated with an underlying disorder of proximal tubular function, such as Fanconi's syndrome, hereditary fructose intolerance, Wilson's disease, or multiple myeloma. The most common cause of proximal RTA in adults is intestinal malabsorption that leads to vitamin D deficiency, hypocalcemia, secondary hyperparathyroidism, and hypophosphatemia (207). Proximal RTA is not associated with stone formation.

Previously, infants and children with a distal acidification defect and bicarbonate wasting were believed to have had type 3 RTA. This term is no longer used because the bicarbonate wasting is thought to reflect the same defect in renal acid excretion that causes type 1 RTA in adults (192). The reduction in acid excretion is secondary to the renal bicarbonate wasting as a cause of the acidosis. Adults with type 1 RTA excrete 1% to 3% of filtered bicarbonate, whereas infants and children with this disorder excrete 6% to 14% of filtered bicarbonate.

The term *type 4 RTA* has been applied to an acidification defect that may accompany a reduction in the renal clearance of potassium. This disorder is thought to involve the cation-exchange segment of the distal nephron, where aldosterone

stimulates hydrogen ion secretion. Type 4 RTA may be the most common form of RTA, and often is associated with the syndrome of hyporeninemic hypoaldosteronism (18). Hyperkalemic distal RTA also has been found in patients with obstructive uropathy (18). Type 4 RTA is not associated with nephrolithiasis.

Some patients with recurrent calcium urolithiasis are not systemically acidotic but are unable to lower their urine pH after an NH_4Cl load (31). Both proximal and distal acidification defects have been identified in stone-formers with the syndrome of incomplete RTA (10,221,337). Patients with these disorders tend to develop stone disease at an earlier age, have more frequent recurrences, and grow larger stones. Hypocitruria and hypercalciuria usually are present. The hypercalciuria is unexplained because these patients do not have systemic acidosis. Serum electrolyte concentrations are normal, and a standardized acid loading study is required for the diagnosis of incomplete RTA.

Urolithiasis is a complication of long-term treatment with carbonic anhydrase inhibitors (241,336). Carbonic anhydrase, which catalyzes the hydration of carbon dioxide, is present in both the proximal and distal nephrons. Because carbonic anhydrase aids the proximal reclamation of filtered bicarbonate and the distal secretion of hydrogen ions, the administration of an inhibitor of the enzyme, such as acetazolamide, causes a proximal and distal RTA. Treatment with acetazolamide produces alterations in the ionic composition of urine, such as a low citrate concentration, which closely resemble those found in untreated distal RTA (126,308). All of the changes can be reversed by stopping administration of the carbonic anhydrase inhibitor.

Cystinuria

Cystine is a disulfide composed of two cysteine molecules (Fig. 8.3), and its pKa is 8.0. Cystinuria is an inherited disorder of amino acid metabolism in which transport of *c*ystine, *o*rnithine, *l*ysine, and *a*rginine in the renal tubule and GI tract is defective. (The mnemonic "COLA" or "COAL" can be used to remember these four amino acids.) The defect is transmitted as an autosomal-recessive trait. This disorder would be a metabolic curiosity if it were not for the relative insolubility of cystine in urine (61,63). Approximately 300 mg of cystine is soluble in 1 L of urine at a pH of 7.0; the solubility of cystine more than doubles as the pH rises above 7.5 (Fig. 8.4). Homozygotes excrete large amounts of cystine, lysine, arginine, and ornithine in their urine.

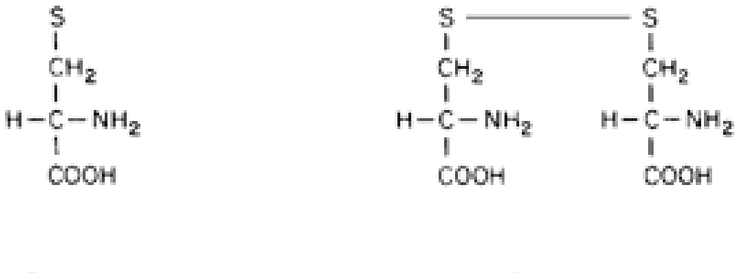


FIGURE 8.3. Structures of cysteine and cystine (a disulfide).

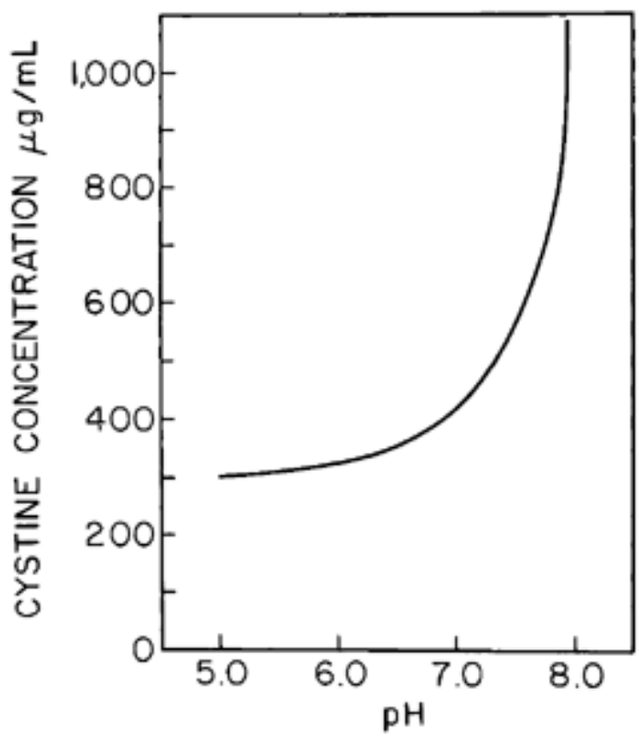


FIGURE 8.4. The pH dependence of the solubility of cystine. (Modified from Dent CE, Senior B. Studies on the treatment of cystinuria. *Br J Urol* 1955;27:317, with permisison.)

Cystinosis, another recessively inherited metabolic disorder, may be confused with cystinuria. Cystinosis is characterized by the intracellular accumulation of excessive quantities of cystine (291). Crystal deposition occurs in the cornea, conjunctiva, bone marrow, lymph nodes, leukocytes, and internal organs. All patients with nephropathic cystinosis have a generalized amino aciduria, but the daily excretion of cystine is only 5% to 10% of that found in patients with cystinuria. Children with cystinosis tend to produce a relatively alkaline urine, and stone formation rarely occurs.

Cystinuria is manifested clinically by the formation of homogeneous radiodense calculi that may have a branched configuration. Multiple small satellite stones may accompany a large stone. The stones have the gross appearance of maple sugar and tend to be hard and tough. Hexagonal cystine crystals may be present in a voided urine sample, especially one that is concentrated and acidified. The diagnosis is confirmed by the analysis of a stone and the finding of increased urinary cystine on an amino acid analysis. Urine can be screened with the cyanide-nitroprusside test, which is positive if more than 75 to 125 mg of cystine per gram of creatinine is present (63). This test does not differentiate homozygotes from heterozygotes. A new test kit based on the reaction of cystine with nickel ion and sodium hyposulfite has been marketed by Mission Pharmacal Company (107). This convenient method can be used to screen patients who are interested in extracorporeal shock wave lithotripsy (ESWL), but whose stones have a radiographic appearance strongly suggestive of cystine.

Urinary excretion of cystine is less than 30 mg per day in healthy adults. Heterozygous adults excrete less than 400 mg of cystine per day and usually do not form stones. Daily urinary cystine excretion is usually greater than 400 mg in homozygous cystine stone-formers. No overlap in cystine excretion has been demonstrated between well-confirmed homozygotes and heterozygotes (60).

Hypercalcemic Disorders

Primary hyperparathyroidism is the most common disorder associated with hypercalcemia and urolithiasis. It is found in approximately 5% of patients with stone disease (6). The diagnosis is based on the presence of hypercalcemia with an inappropriately elevated parathyroid hormone (PTH) level.

PTH is synthesized in the chief cells of the parathyroid gland and is split into at least two major fragments after being secreted into the circulation (148). The N-terminal fragment is responsible for the biologic activity and has a short half-life. The C-terminal fragments have longer half-lives but no biologic activity. PTH increases bone resorption, increases renal reabsorption of calcium, decreases renal absorption of phosphate, and augments renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, thereby increasing intestinal absorption of calcium (177,320). All of the effects of PTH tend to increase the serum concentration of calcium, which exerts negative feedback control over the secretion of PTH. The phosphaturia in patients with primary hyperparathyroidism may lead to hypophosphatemia, but most patients have normal serum phosphate concentrations. A liberal dietary phosphate intake may compensate for the phosphaturia.

A single adenoma, usually chief cell, is responsible for the disease in 80% of patients (113). Chief cell hyperplasia is found in most of the remaining 20%. The hypercalcemia and inappropriately high PTH levels found in patients with primary hyperparathyroidism are caused by the relatively autonomous function of the adenomatous or hyperplastic tissue.

The clinical presentation of primary hyperparathyroidism has changed over the past 20 years. Generalized osteitis fibrosa cystica is extremely rare, and the incidence of urolithiasis has decreased. A population study in Rochester, Minnesota, from 1965 through 1976, found that the average annual incidence of cases of primary hyperparathyroidism increased from 7.8 persons per 100,000 population to 51 per 100,000 population (127). This dramatic increase in the apparent incidence occurred immediately after routine measurement of serum calcium was begun in 1974. The frequency of urolithiasis decreased from 51% to 4%. The proportion of patients without symptoms or complications increased from 18% to 51%. A more recent study found that fewer than 2% of patients with renal stones had primary hyperparathyroidism (295). Bone demineralization occurs with a similar frequency in patients with and without stone disease (306).

The reason for stone formation in patients with hyperparathyroidism and urolithiasis is not known. Patients have urine that is supersaturated with respect to calcium stone salts whether or not stone disease is present (233), and the magnitude of SS is not greater for patients with stones. Patients with hyperparathyroid-induced stone formation may have been predisposed to form stones. One study found that hyperparathyroid stone-formers excreted less citrate than non—stone-formers (4).

Immobilization may be complicated by hypercalcemia, hypercalciuria, and stone formation. The hypercalcemia and hypercalciuria may be especially severe in adolescents with active bone growth. Approximately 10% of patients with traumatic spinal cord injuries develop renal calculi (77). The risk of stone formation is greatest during the first 3 months after injury. Urinary calcium excretion exceeds normal levels at approximately the fourth week of immobilization and reaches maximum levels at 16 weeks. The hypercalciuria may persist for 12 months but resolves by 18 months. Resorption of bone appears to be the primary process. Serum calcium levels are elevated or in the high-normal range. Hypercalcemia and nephrolithiasis also have been reported in patients with multiple fractures (218).

Hypercalciuria and hyperphosphaturia occur during the weightlessness of space travel, but there has been no evidence of clinical stone formation (181). Long-term bed rest is used as a model to study the effects of weightlessness on metabolism. Such studies at simulated high altitudes disclosed that urinary losses of calcium were significantly smaller at a higher altitude. Exercise does not prevent hypercalciuria (140).

Nephrocalcinosis and renal insufficiency may occur with the milk-alkali syndrome and vitamin D intoxication. Stone formation also occurs in sarcoidosis, where there is increased intestinal calcium absorption, hypercalcemia, and hypercalciuria (39,128). Hypercalcemic patients with sarcoidosis have elevated serum levels of 1,25-dihydroxyvitamin D. Healthy persons produce this active metabolite of vitamin D only in the renal tubule. There is evidence that patients with sarcoidosis convert 25-hydroxyvitamin D to the active compound in the granulomas (171). Hypercalcemia also occurs in patients with other granulomatous diseases, such as tuberculosis, berylliosis, and coccidioidomycosis.

Uric Acid Lithiasis

Uric acid is the endproduct of purine metabolism in humans. Uric acid has two dissociable protons (Fig. 8.5), the first with a pKa of 5.5 and the second with a pKa of 10.3 (98). The limited solubility of this weak acid accounts for its propensity to form renal calculi (Fig. 8.6). Uric acid solubility is approximately 15 mg/dL at a pH of 5, but is 200 mg/dL at a pH of 7.

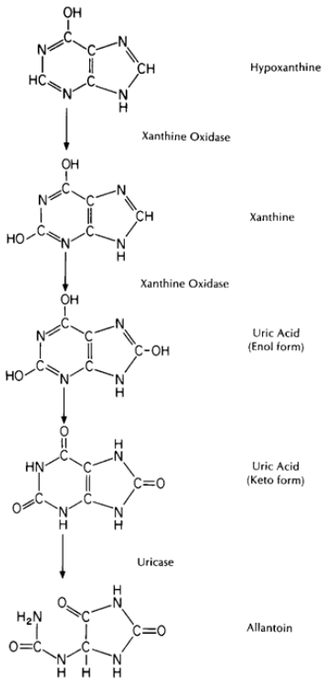


FIGURE 8.5. Metabolic pathway for conversion of hypoxanthine to xanthine and uric acid. Most ureotelic mammals, except humans, have hepatic uricase that converts uric acid into the more soluble allantoin.

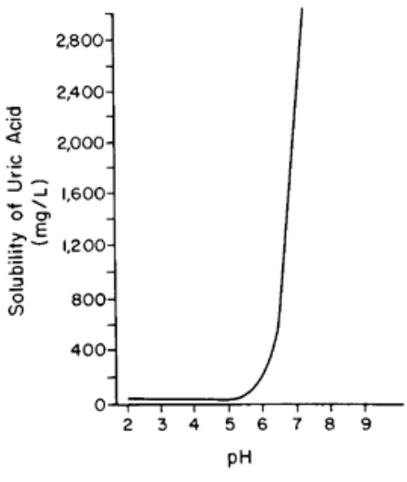


FIGURE 8.6. The pH dependence of the solubility of uric acid at 38°C. (Modified from Finlayson B, Smith A. Stability of first dissociable proton of uric acid. *J Chem Eng Data* 1974;19:94, with permission.)

Uric acid excretion depends on the biosynthesis of new purines and, to a lesser extent, on preformed dietary purines (90,121). A series of enzymatic reactions leads to the formation of the mononucleotide, inosine monophosphate. Dietary nucleic acids can be catabolized to form two other mononucleotides: adenosine monophosphate and guanine monophosphate. Cleavage of the phosphate group by nucleotidases forms the corresponding nucleosides: inosine, guanosine, and adenosine. The action of nucleoside phosphorylases forms the purine bases: hypoxanthine (from inosine), guanine, and adenine. Xanthine oxidase converts hypoxanthine to xanthine and uric acid (Fig. 8.5). The purine salvage enzymes, hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) and adenine phosphoribosyltransferase, can reconvert the purine bases to the mononucleotides. This is the purine salvage pathway.

An X-linked deficiency of HGPRT is responsible for two clinical syndromes (370). Enzyme activity is virtually absent in the Lesch-Nyhan syndrome, a disease characterized by uric acid overproduction and a central nervous system disorder (e.g., mental retardation, spasticity, choreoathetosis, self-mutilation). HGPRT activity is partially deficient in the second syndrome, which is characterized by uric acid overproduction and severe gout, but no neurologic abnormality. Uric acid lithiasis may occur in both syndromes.

Biosynthesis of purines from amino acids also provides a way to eliminate waste nitrogen as uric acid (121). This is the major pathway of waste nitrogen disposal in birds and uricotelic reptiles. Loss of water and electrolytes is minimized by discharging a semisolid uric acid mass through a cloaca. In most ureotelic mammals, except humans, urate that enters the glomerular filtrate is reabsorbed in the proximal tubule and recycled through the liver for conversion to water-soluble allantoin by hepatic uricase. Allantoin is freely excreted by the kidney. Uricase is not present in humans, and uric acid cannot be converted to the more soluble allantoin. Plasma and urine uric acid levels in humans are an order of magnitude greater than those in most mammals. The high concentrations of uric acid are precariously held in solution, a situation that predisposes humans to gout and uric acid lithiasis.

The dalmatian coach hound also is predisposed to uric acid urolithiasis (377). Normal quantities of uricase are present in the liver, but uric acid conversion to allantoin is slow and incomplete. This, together with defective tubular reabsorption of urates, leads to hyperuricosuria and stone formation.

Uric acid lithiasis accounts for 5% to 10% of stones formed in the United States. Approximately one-fourth of patients with primary gout develop uric acid stones. Uric acid lithiasis is found in approximately 40% of stone-forming persons in Israel (9). Uric acid bladder calculi are a common problem in children of rural Southeast Asia.

Patients with uric acid lithiasis may excrete too much uric acid or excessively acidic urine (259). Overproduction of uric acid, as occurs in some patients with gout, may be responsible for the hyperuricosuria. Purine and protein gluttony also may increase uric acid excretion. Most patients with uric acid lithiasis do not have gout or any recognizable disorder of purine metabolism. Serum and urine uric acid levels are usually normal in patients with idiopathic uric acid urolithiasis. Many of these patients have a persistently low urine pH. Although some investigators have found an isolated defect in renal tubular ammonia secretion, the mechanism of the low urinary pH is still poorly understood. Urinary pH also tends to be low in gout (120).

Gouty patients who are treated with uricosuric agents may be at risk for uric acid stone formation. This can be prevented with an increased fluid intake and urinary alkalinization. Patients with myeloproliferative disorders are also at risk for uric acid stone formation, especially with the initiation of chemotherapy or radiotherapy. The increased purine load may even lead to intratubular precipitation of uric acid and anuria.

Disorders that reduce urine volume are associated with uric acid precipitation in an acid urine. Patients with ileostomies or chronic diarrhea can lose large amounts of fluid and bicarbonate. Maintenance of an adequately dilute urine can be difficult for these patients because oral fluids and electrolytes are not well absorbed. The diarrhea or ileostomy output may increase as fluid intake increases. Small bladder calculi composed of uric acid may be found in men with prostatism. These patients reduce their urinary frequency by reducing their fluid intake. Pure uric acid is radiolucent, but gradual incorporation of impurities (usually metals such as calcium) makes larger stones (more than 2 cm diameter) faintly radiopaque. Identification of smaller stones can be accomplished with excretory urography, sonography, or computed tomography (CT). Large uric acid stones may have a branched configuration (Fig. 8.7).

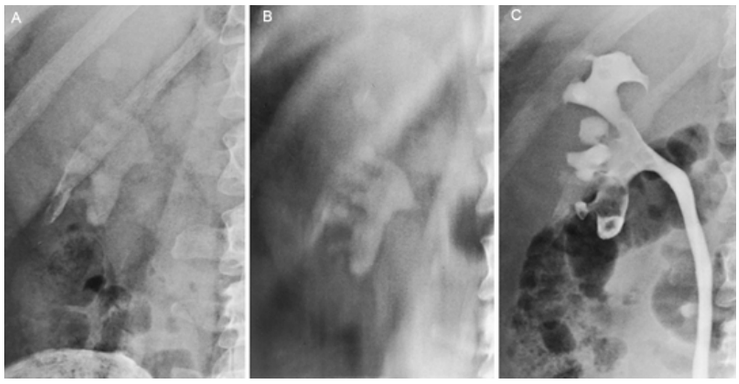


FIGURE 8.7. A: Plain abdominal radiograph that demonstrates a large branched right renal calculus. **B:** Plain tomographic film. **C:** Retrograde pyelogram that demonstrates a filling defect. Analysis of the removed stone material revealed 98% uric acid.

Xanthinuria

Xanthine is less soluble than uric acid (Fig. 8.4). Its solubility increases with rising urine pH, but the effect is not as great as that with uric acid. The pKa of the first dissociable

proton of xanthine is 7.7. Like uric acid, xanthine is radiolucent. Xanthine calculi have been reported to occur in xanthinuria, a rare, inherited deficiency of xanthine oxidase (75). Serum and urine uric acid levels are low, but urinary excretion of hypoxanthine and xanthine is elevated. Stone formation has occurred in approximately one-third of patients.

Urinary excretion of hypoxanthine and xanthine is more commonly elevated in patients who are being treated with a xanthine oxidase inhibitor such as allopurinol (Fig. 8.8). Xanthine stone formation during allopurinol administration has been reported in patients with Lesch-Nyhan syndrome and in patients with myeloproliferative disorders who are receiving chemotherapy (29).

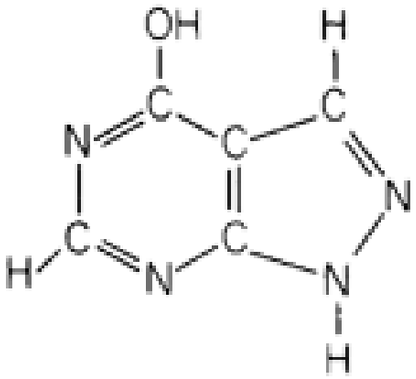


FIGURE 8.8. Structure of allopurinol, an analog of hypoxanthine and xanthine.

2,8-Dihydroxyadeninuria

2,8-Dihydroxyadeninuria is an inherited disorder caused by a defect of the purine salvage enzyme, adenine phosphoribosyltransferase (105,372). Adenine is converted to 2,8-dihydroxyadenine (2,8-DHA), which is insoluble over a wide range of urinary pH. Stone formation and renal failure have been described, usually in children (102). Like uric acid, 2,8-DHA stones are radiolucent. Uric acid stones are hard and yellowish, whereas 2,8-DHA stones are friable and brown or gray. Enzymatic analysis with uricase avoids mistaken identification as uric acid, and infrared spectroscopy or x-ray crystallography confirms the diagnosis. "Uric acid" stones in children must always be suspect and subjected to a sophisticated analysis. The failure to diagnose this disorder can lead to needless recurrent stone formation and even renal failure (40).

Primary Hyperoxaluria

Primary hyperoxaluria is a rare, inherited disorder of glyoxylate metabolism. Clinical manifestations include recurrent calcium oxalate nephrolithiasis, nephrocalcinosis, and chronic renal failure. Extrarenal deposits of oxalate, or oxalosis, develop in the presence of renal failure.

Approximately 10% of oxalate excreted in urine is absorbed from the GI tract. The remainder is derived from endogenous metabolism. Oxalate is produced in mammals as an endproduct of the oxidative metabolism of ascorbic acid (Fig. 8.9) and by oxidation of glyoxylic acid (Fig. 8.10). The major precursor of oxalate in humans is glyoxylate.

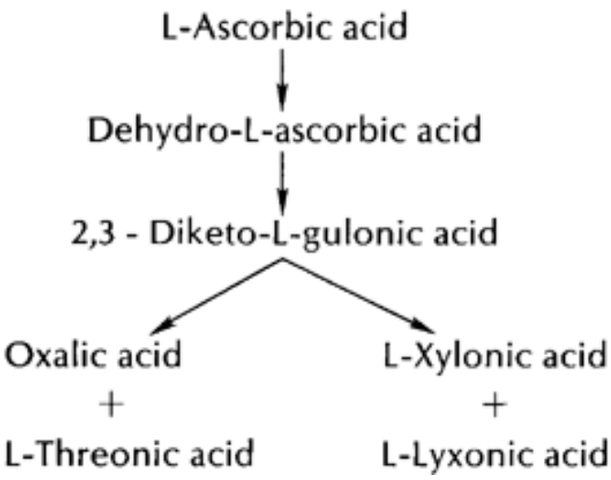


FIGURE 8.9. Oxidative metabolism of ascorbic acid leads to the production of oxalate.

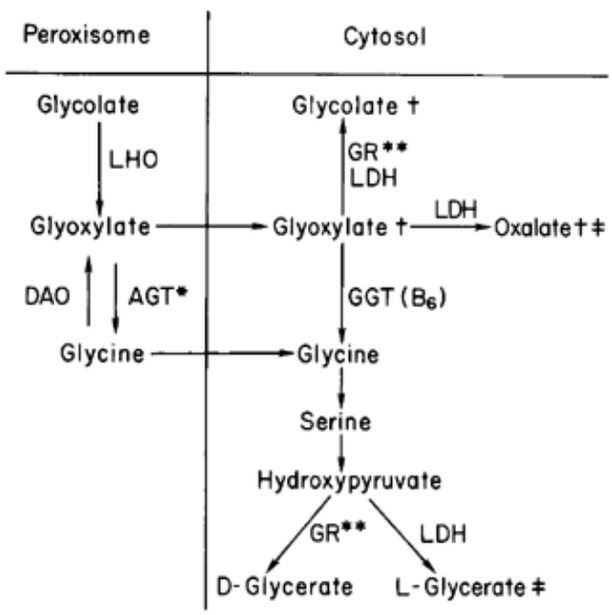


FIGURE 8.10. Pathways of oxalate metabolism in humans. A deficiency of peroxisomal AGT* is responsible for primary hyperoxaluria type 1 (67,68) and results in elevated urinary levels of glycolate †, glyoxylate†, and oxalate†. A deficiency of cytoplasmic GR** is responsible for primary hyperoxaluria type 2 and results in elevated urinary levels of L—glycerate‡ but normal levels of glycolate and glyoxylate. *Peroxisomal enzymes:* LHO, L-α-hydroxy acid oxidase/glycolate oxidase; DAO, D-amino acid oxidase/glycine oxidase; AGT, alanine: glyoxylate aminotransferase/serine: pyruvate aminotransferase. *Cytosolic enzymes:* GGT, glutamate: glyoxyl aminotransferase/alanine:2-oxoglutarate aminotransferase (pyridoxine is a cofactor); GR, glyoxylate reductase/D-glycerate dehydrogenase; LDH, lactate dehydrogenase.

Type 1 primary hyperoxaluria, or glycolic aciduria, was thought to be caused by deficiency of the cytoplasmic enzyme α-ketoglutarate-glyoxylate carboligase (367). More recent investigations have shown that this disorder is caused by a deficiency or functional abnormality of peroxisomal alanine-glyoxylate aminotransferase in the liver (Fig. 8.10) (67,68 and 69). This enzyme acts on glyoxalate and alanine in peroxisomes to produce pyruvate and glycine. Glutamate-glyoxylate aminotransferase is a cytoplasmic enzyme that

acts on cytoplasmic glyoxylate and glutamate to form glycine and 2-oxoglutarate. Pyridoxine (vitamin B_6) is a cofactor in this latter reaction. Urinary excretion of oxalate, glyoxalate, and glycolate is elevated in type 1 primary hyperoxaluria, which is the most common form of the disease.

Type 2 primary hyperoxaluria, or L-glyceric aciduria, is caused by a deficiency of the enzyme glyoxylate reductase/ D-glycerate dehydrogenase (Fig 8.10) (43,366). Urinary excretion of oxalate and L-glyceric acid is elevated, but glycolate excretion is normal, as is that of glyoxylate.

Primary hyperoxaluria is a rare disorder. An extensive review in 1964 reported on 63 typical and 47 atypical cases (137). The disease had become clinically manifest in more than half of the patients by age 4 years. Almost half had died of renal failure by 20 years of age.

The disease should be suspected in patients who are young, have a family history of urolithiasis, and have nephrocalcinosis or large, radiodense calculi on plain abdominal radiographs. Urinary oxalate excretion generally is greater than 100 mg per 24 hours, except in the presence of renal failure. Differentiation between types 1 and 2 is made with urinary glycolate measurements. Glycolate excretion is normal in type 2 but elevated in type 1.

Secondary Urolithiasis

Stone formation may be associated with a group of unrelated conditions: small bowel dysfunction; urinary tract infection with bacterial organisms that produce urease; obstructive uropathy; structural anomalies such as medullary sponge kidney; urinary diversion; and pharmacologic agents. Although all of these disorders may be associated with stone formation, they may not be its primary cause. It is important to search for underlying disorders, such as primary hyperparathyroidism, cystinuria, RTA, or idiopathic hypercalciuria. Prevention of further stone formation requires treatment of any underlying metabolic disorder and the immediate cause of stone formation.

Enteric Hyperoxaluria

Dietary oxalate is a relatively minor source of urinary oxalate in healthy persons, but patients with small bowel disorders may develop hyperoxaluria and recurrent calcium oxalate stone disease. GI absorption of dietary oxalate is more avid in these patients. Enteric hyperoxaluria was first described in the early 1970s and was partly responsible for the abandonment of jejunoileal bypass surgery as a means to control obesity (217,317). Major sources of dietary oxalate are the green leafy vegetables such as rhubarb, spinach, and kale. Tea, cocoa, chocolate, and pepper also have a high oxalate content. The average daily diet contains 100 to 900 mg of oxalate (365).

The acid medium in the stomach releases oxalate from foodstuffs. After combining with free dietary calcium in the alkaline medium of the small intestine, most of the oxalate exists as insoluble calcium oxalate. The small amount of free oxalate that does exist can be absorbed. The colon seems to be the major absorptive area. Patients with ileostomies rarely develop hyperoxaluria (83). The reaction between intestinal calcium and oxalate prevents the absorption of no more than 10% of dietary oxalate by healthy persons.

Patients with a variety of chronic GI disorders such as small bowel resection, inflammatory small bowel disease, chronic pancreatitis, or a jejunoileal bypass may malabsorb fat. The intraluminal concentration of fatty acids increases and calcium is bound to form calcium–fatty acid soaps (85). Less calcium is available to bind oxalate, and more free oxalate is available for absorption. Evidence also shows that malabsorbed fatty acids or bile acids increase colonic permeability to oxalate (82). Patients with enteric hyperoxaluria may absorb up to one-third of their dietary oxalate.

The incidence of nephrolithiasis in inflammatory bowel disease is 2% to 3%, but ileal resection increases the risk to 10% (81). The primary risk factor is increased urinary excretion of oxalate. In comparison with the primary hyperoxalurias, excretion of L-glyceric acid and glycolic acid is normal.

Elevated urinary oxalate is not the only risk factor in these patients (319). The multiple risk factors are shown in Table 8.3 . All factors increase the propensity for calcium oxalate precipitation. Reduced urinary volume and pH may promote uric acid stone formation.

Malabsorbed Component	Urine Composition
Fatty acids, bile acids	Increased oxalate
Water	Decreased volume
Electrolytes	Decreased ionic strength
Bicarbonate	Decreased pH, decreased citrate
Magnesium	Decreased magnesium
Protein	Decreased sulfate, decreased phosphate, decreased pyrophosphate

Modified from Smith LH, Werness PG, Wilson DM. Enteric hyperoxaluria: associated abnormalities that promote formation of renal calculi. In: Rose GA, Robertson WG, Watts RWE, eds. *Oxalate in human biochemistry and clinical pathology.* London: Wellcome Foundation, 1979:224, with permission.

TABLE 8.3. ENTERIC HYPEROXALURIA RISK FACTORS FOR UROLITHIASIS

Another form of enteric hyperoxaluria is that possibly associated with ascorbic acid (310,344). The metabolic pathway for *in vivo* conversion of ascorbate to oxalate is shown in Fig. 8.6 . *In vitro* conversion of ascorbate to oxalate may occur in saline solutions or pooled urine samples, especially those that have not been acidified (278). This may produce a factitious hyperoxaluria in patients who are

consuming large quantities of vitamin C. A further confounding factor is that some methods used to measure oxalate may not be able to distinguish ascorbate metabolites from oxalate (122). Patients should be advised not to take large amounts of vitamin C when they are collecting a 24-hour urine specimen for chemical analysis.

Infected Renal Lithiasis

Infected renal lithiasis refers to the pathologic occurrence of stones composed of magnesium ammonium phosphate ($MgNH_4PO_4 \cdot 6H_2O$, or struvite). Stones caused by infection are not pure struvite—careful crystallographic analysis of infected stone material from humans has revealed a mixture of struvite, carbonate apatite [$Ca_{10}(PO_4)_6 \cdot CO_3$], and hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] (116).

Infection of the urinary tract with urease-producing bacterial organisms is a necessary prerequisite for the formation and growth of struvite stones (117). The enzyme urease catalyzes the formation of ammonia and carbon dioxide (CO_2) from urea:

$$(NH_2)_2CO + H_2O \rightarrow 2NH_3 + CO_2$$

The formation of ammonia leads to an increase in urinary pH:

$$NH_3 + H_2O \rightarrow NH_4^+ + OH^-(pK = 9.0)$$

When urine is physiologically alkaline, ammonia levels are low, but when urease is present, the urine is alkaline and ammonia levels are high.

The higher pH also leads to the further dissociation of phosphate:

$$H_2PO_4^- \rightarrow H^+ + HPO_4^{2-}(pK = 7.2)$$

$$HPO_4^{2-} \rightarrow H^+ + PO_4^{3-}(pK = 12.4)$$

Under these conditions, urine is supersaturated for magnesium ammonium phosphate, and precipitation of this material occurs.

Because all of the reactions occur in aqueous solution, CO_2 exists as carbonic acid:

$$CO_2 + H_2O \rightarrow H_2CO_3$$

In the presence of an alkaline pH, the carbonic acid dissociates to form bicarbonate:

$$H_2CO_3 \rightarrow H^+ + HCO_3^-(pKa = 6.3)$$

and the bicarbonate dissociates to form carbonate:

$$HCO_3^- \rightarrow H^+ + CO_3^{2-}(pKa = 10.2)$$

The CO_3^{2-} can precipitate with PO_4^{3-} and Ca^{2+} to form carbonate apatite.

Proteus species most commonly are associated with infection stones, but some species of *Klebsiella, Pseudomonas* and *Staphylococcus* may produce urease (116). Virtually all *Proteus* species produce urease, whereas *Escherichia coli* never produces urease. *Ureaplasma urealyticum* will induce alkalinization and crystallization of magnesium ammonium phosphate and calcium phosphates in synthetic urine, and a recent clinical review found this organism in 25% of patients with infection stones (19). Even some anaerobic bacterial organisms produce urease.

Infection stones account for 15% to 20% of all urinary stones. Struvite stones frequently have a branched or staghorn configuration, but not all branched calculi are infection induced. Cystine and uric acid stones also may have a branched configuration.

Some patients with metabolic stone disease may have urinary tract infections with bacteria that do not produce urease. The stones do not contain struvite, and the infection is not responsible for the stone formation. The infection can be treated successfully with antibiotics alone in half of these patients.

Some patients with metabolic stone disease may develop recurrent urinary tract infections with urease-producing bacterial organisms. Struvite may then precipitate on a core of calcium oxalate or cystine. Some investigators have found an underlying metabolic disorder in more than 50% of patients with struvite stone formation (256,296). Prevention of further stone formation requires the identification and treatment of any such metabolic disorder. Other investigators found that recurrent stone formation was negligible in a group of patients who had operative removal of their stone material, specific antimicrobial therapy, and postoperative irrigation of the collecting system with hemiacidrin solution (307). This study implies that metabolic disorders are relatively unimportant in the pathogens of struvite urolithiasis.

Obstruction

Stone formation may be associated with obstructive uropathy. The most common example is uric acid bladder stone formation with bladder outlet obstruction, usually from prostatic hyperplasia. Upper urinary tract obstruction may delay the normal washout of crystal aggregates and gravel. These particles may continue to grow and form macroscopic stones. Persistent infection with urease-producing bacterial organisms may occur in the presence of urinary stasis and result in struvite stone formation. Most patients with obstruction do not form kidney stones.

Medullary Sponge Kidney

Medullary sponge kidney is characterized by dilated collecting tubules in one or more renal papillae. In the absence of complications, it is an asymptomatic and benign condition, but urinary tract infection and nephrolithiasis are frequent complications (373). The diagnosis is made by excretory urography; linear or spherical tubules in the renal papillae are filled with contrast medium.

The role of medullary sponge kidney in the pathogenesis of nephrolithiasis has not been clarified, but 20% of patients with calcium urolithiasis may have this disorder (373). Other investigators found medullary sponge kidney in fewer than 5% of their calcium stone-forming patients (220). Medullary sponge kidney is found more commonly in women than in men. Patients with medullary sponge kidney and nephrolithiasis have the same spectrum of metabolic abnormalities as the overall population of calcium stone-formers (220,243). Calcium oxalate is the most common stone salt found in patients with medullary sponge kidney (125).

Polycystic Kidney Disease

Nephrolithiasis occurs in approximately 20% of patients with autosomal-dominant polycystic kidney disease (ADPKD). Approximately half of the patients are symptomatic, even though most of the stones are in calices or attached to the papillary tips. Careful intravenous urography or CT is required to distinguish stones from parenchymal or cyst wall calcification. Tubular ectasia is found in 15%, but the relationship of this radiographic finding to the pathogenesis of the stone formation is unknown.

Most of the calculi are composed of uric acid, often in association with calcium oxalate. The distorted renal anatomy and urinary stasis may contribute to stone formation, but most patients have concurrent metabolic abnormalities. A retrospective review at the Mayo Clinic found hypocitraturia in 67% of patients, hyperuricemia in 19%, hyperoxaluria in 19%, hyperuricosuria in 15%, hypercalciuria in 11%, and primary hyperparathyroidism in 5% (342). A defect in the transfer of ammonium to the final urine may prevent patients with ADPKD from responding appropriately to acidosis. This would explain the hypocitraturia found in a majority of patients.

Urinary Diversion

Stone formation and recurrent infections may be associated with urinary tract diversion. Urease-producing bacterial infections may lead to struvite stone formation. The diversionary procedure also may produce metabolic abnormalities that encourage stone formation. GI bicarbonate loss and hyperchloremic acidosis are known side effects of ureterosigmoid anastomoses (189). The systemic acidosis may lead to hypercalciuria and hypocitruria. Osteomalacia has been reported to develop in patients with ureterosigmoidostomies and a metabolic acidosis (305). Occasional patients with ileal conduits develop a hyperchloremic acidosis (84,159). Most stones form in the presence of *Proteus* infections and are composed of struvite. Because excess conduit length may contribute to the bicarbonate loss and chloride absorption, these metabolic derangements may occur more frequently with the new continent diversionary procedures. The use of nicotinamide to block intestinal chloride transport may be a useful preventive measure (158).

The incidence of calculus formation after augmentation cystoplasty has been reported to be as high as 50% (239). Urinary tract infection, mucus production, foreign bodies, and hypocitraturia have been identified as potential risk factors (155). The acidic environment provided by gastrocystoplasty retards mucous production and bacterial overgrowth (240). As expected, stone formation occurs less frequently than after enterocystoplasty.

Drugs

The metabolic effects of some drugs lead to stone formation. Acetazolamide, a carbonic anhydrase inhibitor, produces changes in urine composition that are similar to those found in distal RTA. Kidney stones have formed in patients who have received this drug for the treatment of glaucoma. Nephrolithiasis also has been reported in patients who have received long-term acetazolamide for the treatment of periodic paralysis and myotonia (336).

Drugs or their metabolites may have limited solubility in urine. These compounds may be absorbed onto calculi already present in the urinary tract or may precipitate to form new stones. Approximately 50% of an ingested dose of allopurinol is excreted as oxypurinol, an oxidative metabolite. Oxypurinol, like xanthine, is less soluble than allopurinol or hypoxanthine. The solubility of oxypurinol decreases with a decrease in pH. Radiolucent oxypurinol stone formation has been reported in a patient with regional enteritis who was receiving allopurinol for the prevention of recurrent uric acid lithiasis (327). Persistent oliguria and aciduria contributed to the precipitation of oxypurinol. Rarely, xanthine stones have formed in patients treated with allopurinol.

Triamterene and its metabolites have been identified in renal calculi. Some investigators have suggested that their precipitation may be a causative factor in the formation of calcium stones (364). Other investigators found that triamterene and its metabolites adsorb to stone matrix (360). Because stones that contain triamterene have an unusually high matrix content, triamterene and its metabolites may be a passive constituent of renal calculi. Clinical studies of patients receiving a combination of triamterene and hydrochlorothiazide (Dyazide) suggest that nephrolithiasis is not a clinically significant side effect (144).

Sulfonamides were one of the first classes of drugs to precipitate in the urinary tract, but numerous other drugs and their metabolites have been identified in renal calculi (70). Sulfadiazine urolithiasis has been reported in patients with AIDS who have received this drug for the treatment of toxoplasmosis (41,199). Another example is the report of several ceftriaxone stones in a 13-year-old boy treated for acute bacterial meningitis (51). Infrared spectrophotometry

found that 92% of the stone material was ceftriaxone disodium; calcium oxalate monohydrate and protein comprised the remaining 8%.

Indinavir is a protease inhibitor used for treating HIV-1 (288). Indinavir was the third such drug introduced into the United States and is the most widely prescribed drug in this class of retroviral agents. Indinavir therapy has been associated with a 4% incidence of nephrolithiasis. Indinavir crystalluria (platelike rectangles and fan-shaped or starburst forms) can be found in 20% of patients and often is associated with irritative voiding symptoms (162).

Pure indinavir stones cannot be seen with CT scanning unless intravenous contrast is used (332). Symptomatic urolithiasis usually can be treated with hydration alone.

Several factors can predispose an individual to the urinary precipitation of a drug: a high renal excretion rate, a low solubility of a drug or its metabolites, a low urine volume, and prolonged treatment at a high dose. The appearance of synthetic compounds in renal calculi is to be expected as new drugs are introduced and analytic methods of stone analysis become more sophisticated.

Urinary calculi also may form on foreign bodies in the urinary tract (65). Foreign-body stones in the upper urinary tract have been associated with ureteral catheters, nephrostomy tubes, sutures, biliary calculi, shrapnel, and acupuncture needles. Renal papillary necrosis with calcification of the sloughed papillae may mimic nephrolithiasis (Fig. 8.11).

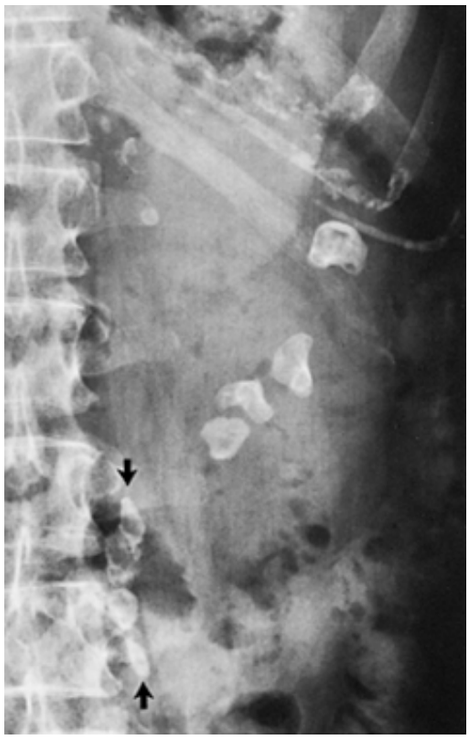


FIGURE 8.11. Multiple calcified bodies in left kidney and ureter *(between arrows).* The radiolucent centers could represent uric acid or necrotic renal papillae *(arrows).* Histologic examination revealed necrotic calcified renal papillae.

Ammonium acid urate calculus formation has been reported in women with a history of laxative abuse (79). Urinary volume over 24 hours and excretion of sodium, potassium, and citrate were low. GI loss of fluid and electrolytes led to chronic extracellular volume depletion and intracellular acidosis (low urinary citrate and potassium).

Idiopathic Calcium Urolithiasis

The diagnosis of ICU is one of exclusion and is applicable in 70% to 80% of North American and Western European patients with urolithiasis. If pure uric acid lithiasis, cystinuria, RTA, primary and secondary hyperoxaluria, and hypercalcemia have been excluded in a patient with calcium oxalate or mixed calcium oxalate and/or calcium phosphate stone formation, this diagnosis may be applied. However, a patient may have more than one disorder. Primary hyperparathyroidism and ICU or cystinuria and ICU may occur in the same patient.

Careful metabolic studies of patients with ICU reveal a multiplicity of abnormalities: hypercalciuria, mild hyperoxaluria, hyperuricosuria, crystal growth–inhibitor deficiencies, hypocitruria, and “incomplete” RTA. One or more of these abnormalities may be found in the same patient, and some of the abnormalities may be related to the others, such as hypocitruria to incomplete RTA. Some patients with ICU may have no clearly recognizable disorder other than calcium stone formation.

Between 50% and 70% of these patients have hypercalciuria (264). Most healthy men receiving a 1-g calcium diet excrete less than 275 mg of calcium over 24 hours. The corresponding figure for women is 250 mg per 24 hours. A more convenient way to remember is that urinary calcium excretion should not exceed 4 mg/kg per 24 hours. Most patients with ICU and hypercalciuria are thought to have primary intestinal hyperabsorption of dietary calcium (234). Increased absorption of dietary calcium may slightly increase the serum calcium concentration and suppress PTH secretion. The increased filtered load of calcium and decreased tubular reabsorption results in hypercalciuria. The urinary calcium loss compensates for the enhanced intestinal absorption, thereby maintaining serum calcium within a normal range. In the past, patients with absorptive hypercalciuria have been separated into three categories that depended on the serum phosphorous level and the level of dietary calcium at which hypercalciuria ensued.

A positive correlation exists between urinary calcium excretion and sodium excretion (255). Another study found that a group of hypercalciuric subjects on a 200-mEq sodium diet converted to normocalciuria on an 80-mEq sodium diet (208). The sensitive relationship between urinary

calcium and sodium and the normal day-to-day variation of sodium intake may confound the results of standard 24-hour urine collections.

It is not known if absorptive hypercalciuria is caused by a primary intestinal defect or by a more complex metabolic disorder. Several investigators have found elevated vitamin D metabolites in one-third to one-half of patients with absorptive hypercalciuria (298). Some patients with absorptive hypercalciuria have low serum phosphorus levels. The stimulation of 1,25-dihydroxyvitamin D synthesis in the kidney by hypophosphatemia could lead to increased intestinal calcium absorption (115); the primary event would be a “renal leak” of phosphate. However, other investigators do not think that vitamin D and its metabolites play a critical role in the pathogenesis of absorptive hypercalciuria (215,222).

Two sources exist for calcium that appears in urine: GI absorption and bone resorption (172). Augmentation of intestinal absorption of dietary calcium is responsible for most of the increase in urinary calcium. Increased bone resorption is an unlikely primary source because the magnitude and duration of the hypercalciuria would lead to overt bone disease. Nevertheless, calcium balances are slightly but significantly negative in patients with idiopathic hypercalciuria. The existence of a generalized disorder of calcium homeostasis is further supported by an elevation of urinary hydroxyproline excretion that is seen in some patients. This reflects bone resorption. Lumbar bone density is significantly lower in patients with absorptive or fasting hypercalciuria compared with normocalciuric stone-formers (246). Bone loss in these patients also may be related to environmental factors such as intake of sodium or animal protein.

A familial basis of some types of hypercalciuria is supported by a high frequency of calcium stone disease and hypercalciuria in first-degree relatives of stone-formers (89). Most family studies of idiopathic hypercalciuria are broadly consistent with an autosomal-dominant mode of inheritance. However, the complexity and high variability of the inheritance patterns suggest that idiopathic hypercalciuria is a polygenic trait and involves alleles at several loci.

A smaller group of patients with hypercalciuria may have impaired renal tubular reabsorption of calcium (53,222). Fasting urinary calcium excretion is elevated, the serum concentration of calcium is reduced, and parathyroid function is stimulated. The elevated PTH level tends to restore serum calcium to normal levels by mobilizing bone calcium and enhancing intestinal absorption. Renal hypercalciuria and absorptive hypercalciuria are differentiated by measuring PTH levels and fasting urinary calcium excretion. PTH levels should be elevated in renal hypercalciuria but normal in absorptive hypercalciuria. Fasting urinary calcium excretion should be high in renal hypercalciuria but normal in absorptive hypercalciuria.

Early studies found renal hypercalciuria in more than 50% of patients with hypercalciuria, but this proportion decreased to 10% with later studies. This discrepancy may have been the result of differences in the specific immunoassays used to measure PTH. More intensive fasting tends to reduce the proportion of patients with renal hypercalciuria. Renal and absorptive hypercalciuria may represent extremes of a variable disorder rather than distinct clinical entities. A uniform elevation of intestinal calcium reabsorption may better explain the data than separate absorptive and renal forms of hypercalciuria (54).

Many studies have examined calcium metabolism in nephrolithiasis, but relatively few have investigated the role of oxalate in ICU. The paucity of such studies is related to the difficult nature of oxalate measurement in urine. Several investigators have found a mild but definite increase in urinary oxalate excretion in a subset of patients with ICU (12,265). A mildly elevated urinary oxalate is a greater risk factor for the precipitation of calcium oxalate than is a mildly elevated urinary calcium, because normal urinary oxalate levels are tenfold lower than normal urinary calcium levels. A small increase in urinary oxalate leads to the precipitation of a greater volume of crystals than does a comparable increase in urinary calcium.

Patients with mild hyperoxaluria do not appear to have a specific disturbance of glyoxylate metabolism. The hyperoxaluria is thought to be secondary to intestinal hyperabsorption of oxalate and calcium (186). The mechanism is analogous to that for enteric hyperoxaluria, but intraluminal intestinal calcium is reduced by hyperabsorption, not by complexation with fatty acids. Less calcium is available to bind oxalate, thereby permitting more avid absorption of free oxalate. A similar situation may occur when patients with recurrent calcium lithiasis are instructed to limit their dietary intake of foods that contain calcium. Isolated dietary calcium restriction may increase the risk of stone formation by allowing oxalate excretion to increase without a commensurate decrease in calcium excretion (17).

Intestinal hyperabsorption of oxalate may not be solely secondary to calcium hyperabsorption and reduced complexation. A more widespread defect in cellular transport of oxalate may exist. Transport of oxalate across red blood cell membranes differs in healthy persons and patients with recurrent calcium oxalate nephrolithiasis (13,14,103). The mean transmembrane oxalate flux rate in stone-forming patients was triple that in healthy control subjects. This meant that oxalate could cross the red blood cell membrane faster in patients with ICU. A similar situation in the luminal membrane of the GI tract could provide another mechanism for oxalate hyperabsorption.

Some patients with ICU have a concurrent disorder of uric acid metabolism. These patients tend to have a more severe form of stone disease, manifested by more frequent stone formation and a greater need for surgical intervention (52). Specific epitaxial overgrowth of calcium oxalate on uric acid or monosodium urate has been suggested as a possible explanation, but it is doubtful that this occurs in

the urinary tract. Heterogeneous nucleation could occur, but freshly voided urine specimens from patients with ICU rarely contain uric acid or urate crystals (359). The binding of macromolecular inhibitors by another form of urate (colloidal) was proposed and has been supported by some studies (281). The reduction of hyperuricosuria with allopurinol also increased calcium oxalate–crystal growth inhibition (226), and hyperuricosuric calcium oxalate nephrolithiasis has been treated successfully with alkalizing agents (235).

A quantitative or qualitative disorder of crystal growth inhibition has been proposed as a possible reason for stone formation in patients with ICU. As discussed in the section on clinical stone formation, citrate is a complexor of calcium and a weak inhibitor of calcium oxalate crystal growth. Some investigators have found a subgroup of patients with ICU who have low urinary citrate levels (194,277). Hypocitnaturia in patients with distal RTA may enhance stone growth. Although the most beneficial action of citrate is through complexation of calcium, its weak inhibitory effects would help prevent further stone formation. Pharmacologic citrate preparations, through their alkalizing property, have successfully prevented further stone formation in patients with hypocitraturic calcium lithiasis (236).

Persistently alkaline urine has been found in another subset of patients with ICU but no clearly identifiable acid–base disorder (273). Careful analysis of stone material formed by patients with ICU reveals the presence of calcium phosphate, albeit in small amounts, in most of the stones. Because calcium phosphate preferentially precipitates at an alkaline pH, small calcium phosphate crystals may provide heterogeneous nuclei for the overgrowth of calcium oxalate. This mechanism may become more important as alkalizing agents are more commonly used to treat patients with ICU.

Patients with incomplete RTA are not systemically acidotic, but they have an impaired ability to acidify their urine after an ammonium chloride load. This implies the presence of a renal tubular defect in hydrogen ion secretion. The hypocitruria found in some patients with ICU may be the result of a subtle intracellular acidosis.

Defective tubular reabsorption of calcium is thought to be the cause of renal hypercalciuria. All of these disorders may be different manifestations of a more widespread tubular dysfunction. Evidence for this was provided by a study of the effects of hydrochlorothiazide and acetazolamide on the urinary excretions of calcium, sodium, and magnesium (334). These diuretic agents were chosen for their known actions at different sites in the nephron. Hydrochlorothiazide augmented sodium, calcium, and magnesium excretion to a greater extent in patients with ICU than in control subjects. With acetazolamide, the increase in sodium excretion was less in the patients than in the control subjects. The abnormal responses to both diuretics were most significant in patients with hypercalciuria during fasting. Such studies implicate a disorder of renal tubular transport as the primary abnormality in ICU. GI hyperabsorption of calcium would be a secondary phenomenon.

EVALUATION

Part of "8 - CALCULUS FORMATION "

The goal of a metabolic evaluation is to identify any physiologic or environmental factors that could be responsible for or exacerbate clinically active stone formation. No single approach is universally accepted, but it is possible to provide the general principles of a practical and efficient evaluation. The specifics of three different approaches were presented at a recent National Institutes of Health Consensus Development Conference on Prevention and Treatment of Kidney Stones (247,369,376).

History

The clinical history may help determine the cause of stone formation. The important elements in the history are outlined in Table 8.4 . Inherited disorders, such as primary hyperoxaluria, cystinuria, and RTA, are clearly associated with urolithiasis, but even ICU tends to occur within families. Idiopathic stone formation and uric acid lithiasis are more common in males, whereas primary hyperparathyroidism and RTA are more common in females. Although ICU is the most common type of stone disease in children and adults, the classic inherited disorders associated with stone formation are more common in children than in adults.

Age at onset	Diet
Sex	Medications
Family history	Previous stone passage
Geographic residence	Interventional procedures
Occupation	Previous stone composition
Fluid intake	Urinary tract infections

TABLE 8.4. CLINICAL HISTORY

Residence in a geographic area with a high incidence of stone disease, such as the southeastern United States, may have some epidemiologic importance, but temporary residence in an arid climate may be more pertinent. People who are not acclimated to these conditions may have a low urine-output state as a result of large fluid losses from perspiration and respiration. Long-distance runners may have the same problem. Evidence suggests that stone formation may be more common in marathon runners than in the general population (201). Urine volume tends to be low in patients who must perform manual labor in a hot environment. Easy access to fluids and bathroom facilities may not be possible with some occupations. A low urine-output state is a byproduct of many occupations.

Excess dietary intake of calcium, oxalate, or protein and a low fluid intake may encourage the formation of stones. Stone formation also is associated with certain medications: vitamin D, absorbable alkali (calcium carbonate), and carbonic anhydrase inhibitors (acetazolamide). Patients need not consistently overindulge to form a stone. Brief periods of dietary indiscretion or poor fluid intake may initiate crystallization. A similar consideration applies to medications, particularly those associated with a nutritional fad.

A patient's past experience with stone formation and passage may provide clues about the cause of the stone disease and the patient's motivation to pursue a lifelong treatment program. A history of multiple stone passages and rapid recurrent stone formation may indicate a fundamental metabolic cause such as primary hyperparathyroidism or RTA. The necessity for multiple interventional procedures implies the growth of larger stones. Struvite lithiasis should be suspected if the patient has a history of infection with urease-producing bacterial organisms. The composition of previously analyzed stones should be sought. If old stones have not been analyzed, they should be examined and sent for formal analysis. It often is possible to determine a stone's composition just by looking at it. Cystine and uric acid stones are good examples.

Physical Examination

Recognizable physical abnormalities may be present in a few disorders associated with urolithiasis (Table 8.2): sarcoidosis, Cushing's syndrome, hyperthyroidism, and gout. Patients with neurogenic bladder dysfunction may be at risk for recurrent urinary tract infections and infected stone formation. Calcium stones may form in a recently immobilized patient. Extensive abdominal scarring is seen in some patients with small bowel disorders and should raise the possibility of enteric hyperoxaluria. Most patients do not have physical findings related to their stone disease, and laboratory studies are required to uncover the cause.

Laboratory Evaluation

The extent of the laboratory evaluation of a particular patient depends on the severity of the stone disease. A 40-year-old man who has passed several dozen calculi over the past 10 years needs a more extensive metabolic evaluation than a 60-year-old woman who has a 1-cm asymptomatic renal pelvic stone but no previous history of stone disease. Patients who have formed a single calcium stone have the same range of metabolic abnormalities as do patients with recurrent stone formation (224,328). Hypercalciuria was present in 50% to 75% of patients; approximately 5% had primary hyperparathyroidism, and 20% to 30% had no identifiable metabolic disorder. The patients with single stones were older when they passed their stones, had a higher incidence of urinary tract infection, and were more likely to have had surgical or endoscopic intervention. These authors recommended that single-stone-formers have the same evaluation and be treated no differently from other patients with stone disease.

Patients who have formed a single stone may be willing to modify their diet and increase their intake of fluids, but are unwilling to take a medication for several years. The benefit of an extensive metabolic evaluation in such a patient is not readily apparent. A utilitarian evaluation of a single-stone-former would include an assessment of calcium metabolism and renal function (usually obtained as a multichannel chemical analysis of serum), a urinalysis and culture, and a stone analysis. These studies should detect obvious hyperparathyroidism, infected stone formation, and most of the disorders for which specific therapy is especially beneficial (e.g., uric acid lithiasis and cystinuria). A more extensive evaluation usually is reserved for those patients who prove to have metabolically active stone disease.

A complete metabolic workup should include the studies listed in Table 8.5 . An isolated elevated serum calcium level should be confirmed on two or three separate occasions. The normal range varies among laboratories, but one should be suspicious of a serum calcium level greater than 10.1 mg/dL. Total serum calcium includes ultrafilterable calcium and protein-bound calcium. Ultrafilterable calcium, that which enters the glomerular filtrate, is composed of ionized calcium and a small amount of complexed calcium. Approximately half of total serum calcium is protein bound, primarily to albumin. The critical fraction that is controlled by the homeostatic mechanisms of the body is ionized calcium, but it is difficult to measure reliably ionized calcium. Total serum calcium usually is measured and corrected for serum albumin.

Serum	Urine chemistry (24-hr volume)
Calcium	Calcium
Phosphorus	Phosphorus
Uric acid	Uric acid
Creatinine	Oxalate
Alkaline phosphatase	Cystine
	Citrate
Urine	Sodium
Urinalysis	Magnesium
Culture	
Fasting pH	Stone analysis
24-hr volume	

TABLE 8.5. LABORATORY EVALUATION

Serum phosphorus varies with age, sex, renal function, and diet, but may be low in patients with primary hyperparathyroidism and some patients with ICU. Serum alkaline phosphatase activity may be elevated in patients with hyperparathyroidism. Elevated serum uric acid levels are found in some patients with uric acid lithiasis, but calcium

stone-formers also may have hyperuricemia. A serum bicarbonate measurement usually is included in a multichannel analysis and may be decreased in patients with RTA or with small bowel disorders associated with malabsorption.

A urinalysis should be performed promptly after collection. The pH is best measured in a morning urine specimen after an overnight fast. A pH less than 5.5 eliminates distal RTA. A short urinary acidification test can be performed if the pH is not less than 5.5. Uric acid stone-formers may have a persistently low pH. A high urine pH (more than 8.0) is found if the urine is infected with a urease-producing bacterial organism. The infection must be eliminated to accurately assess the pH. Ingestion of alkali or citrate preparations also raises the pH.

Red blood cells and white blood cells usually are seen with urolithiasis, and bacteria may be visible if an infection is present. A urine culture will confirm the presence of an infection, but some patients with struvite stone formation will have negative bladder urine and even renal pelvic urine cultures. Bipyramidal-shaped calcium oxalate dihydrate crystals can be found in healthy persons. Multiple small, platelike or dumbbell-shaped calcium oxalate monohydrate crystals often are found in patients with hyperoxaluria, usually the primary disorder. Calcium oxalate monohydrate crystals are birefringent and will appear as bright specks with polarized microscopy. The presence of hexagonal cystine crystals is virtually diagnostic of cystinuria. A 24-hour urine collection is the traditional mainstay of a metabolic stone evaluation. The most important and often most neglected measurement is the volume. Many patients with recurrent calcium stone formation have a 24-hour urine volume that is approximately 1 L. The basic principles of the medical treatment of urolithiasis are dietary moderation and a consistently high urine volume. Patients can easily monitor their progress by measuring their 24-hour urine volume at home.

Urinary excretion of calcium, phosphorus, oxalate, and uric acid is a function of dietary intake. Increased urinary oxalate is found in patients with primary or secondary hyperoxaluria. Dietary oxalate content has its greatest impact in patients with enteric hyperoxaluria. Uric acid excretion may be elevated in uric acid or calcium oxalate stone-forming patients. Urinary calcium excretion has received much attention. Elaborate protocols have been devised to differentiate the renal and absorptive hypercalciurias and the various types of absorptive hypercalciuria (231). The goal has been to institute specific pharmacologic therapy, but these calcium tolerance tests have achieved limited clinical utility (170).

Urinary cystine excretion can be screened with the traditional cyanide-nitroprusside reaction or newer spot tests (107). A positive reaction should be followed by a quantitative amino acid analysis. Urinary citrate excretion is decreased in patients with distal RTA and intestinal malabsorption. Citrate is low in the presence of a urinary tract infection because bacteria metabolize citrate. Urinary magnesium excretion is of some interest to investigators but is not clinically useful. Urinary sodium excretion may be elevated in some patients with hypercalciuria.

Computer programs have been written to calculate urinary saturations for the major stone-forming salts (94,262) and are available commercially (237). These programs are useful in research, but their widespread clinical utility has not been demonstrated. Examination of the 24-hour urine volume and the total excretions of the major ions should provide enough information to make sound clinical decisions.

Stone material that has been passed or removed should be analyzed. Many different crystalline components have been identified in urinary calculi (Table 8.6), and several methods have been used to identify accurately these constituents (333). The composition of some calculi, such as cystine, can be identified with simple macroscopic or microscopic analysis. Whole stones covered with calcium oxalate dihydrate crystals have a burr or “hair-on-end” appearance. If the whole stone is available, an attempt should be made to separate the nucleus from the rest of the stone because the composition of the nucleus may differ from that of the outer layers. Optical properties (i.e., crystal system, optical sign, refractive index, angle of extinction, and birefringence) can be measured with polarization microscopy (251). The limited number of crystalline components in urinary calculi can be identified from these optical properties. X-ray powder diffraction has been the standard method for stone analysis because it enables almost absolute identification of crystalline materials and mixtures of these materials (206). The equipment is expensive, and the procedure is time-consuming.

Substance	Mineralogic Name	Formula
Calcium oxalate monohydrate	Whewellite	$CaC_2O_4 \cdot H_2O$
Calcium oxalate dihydrate	Weddellite	$CaC_2O_4 \cdot 2H_2O$ (to $2.5H_2O$)
Magnesium hydrogen phosphate trihydrate	Newberyite	$MgHPO_4 \cdot 3H_2O$
Magnesium ammonium phosphate hexahydrate	Struvite	$MgNH_4PO_4 \cdot 6H_2O$
Hydroxyapatite	Hydroxyapatite	$Ca_{10}(PO_4)_6(OH)_2$
Carbonate-apatite	Carbonate-apatite	$Ca_{10}(PO_4)_{6-x}(OH)_{2-y}(CO_3)_{x-y}$
Calcium hydrogen phosphate dihydrate	Brushite	$CaHPO_4 \cdot 2H_2O$
Tricalcium phosphate	Whitlockite	$\beta\text{-}Ca_3(PO_4)_2$
Octacalcium phosphate		$Ca_8H(PO_4)_3 \cdot 2.5H_2O$
Uric acid		$C_5H_4N_4O_3$
Uric acid dihydrate		$C_5H_4N_4O_3 \cdot 2H_2O$
Ammonium acid urate		$C_5H_3N_4O_3NH_4$
Sodium acid urate monohydrate		$C_5H_3N_4O_3Na \cdot H_2O$
Cystine		$[\text{-}SCH_2CHNH_2COOH]_2$
Xanthine		$C_5H_4N_4O_2$
Calcium sulphate dihydrate	Gypsum	$CaSO_4 \cdot 2H_2O$

Modified from Sutor DJ, Scheidt S. Identification standards for human urinary calculus components, using crystallographic methods. *Br J Urol* 1968;40:22, with permission.

TABLE 8.6. CRYSTALLINE CONSTITUENTS OF HUMAN URINARY CALCULI

Infrared spectroscopy is becoming the most widely used method of stone analysis (20,133,363). Finely powdered stone material is pressed into a transparent tablet with optically pure potassium bromide. The infrared spectrum is recorded and compared with a library of standard spectra. Infrared spectroscopy is rapid and relatively inexpensive, and it permits the identification of noncrystalline components and artifacts. This method is especially useful for identifying drugs and their metabolites. Other methods of stone analysis such as thermogravimetric technique (275), scanning electron microscopy with energy dispersive x-ray analysis (150), and CT (136) have been proposed, but they appear to have limited applicability.

Activity

The propensity to form stones varies from patient to patient as well as in a particular patient over time. An arbitrary method for assessing activity was developed at the Mayo Clinic (315). The concept of stone activity enables one to evaluate the need for long-term pharmacologic therapy and the response to such therapy. Two basic categories of activity are defined: surgical and metabolic. A patient with

renal colic, obstruction, or infection associated with a stone has surgically active urolithiasis.

Metabolic activity refers to the precipitation of stone material. Urolithiasis is metabolically active in patients who have had growth of old stones, formation of new stones, or the passage of gravel within the past year. These criteria must be documented radiographically. If a patient's stone disease meets none of these criteria, the urolithiasis is metabolically inactive. If previous radiographs are unavailable or of poor quality, the metabolic activity is said to be indeterminate. Such patients are instructed to increase their fluid intake and avoid dietary excesses. They receive follow-up until the metabolic activity can be determined.

The distinction between surgical and metabolic activity is important because a symptomatic stone may have formed several years before. No specific medical treatment may be needed after the immediate surgical problem is resolved. Metabolically active urolithiasis may exist without symptoms. No surgical intervention may be needed, but specific medical therapy may be required to prevent further stone formation.

One of the goals of urolithiasis research has been the development of a method to predict stone activity when a patient is first evaluated (123). Several measures have been proposed, including the previously discussed saturation-inhibition index, but none has had greater utility than this simple, time-dependent method of assessing activity. Recurrent stone formation is common, but it cannot be predicted from standard laboratory evaluations in individual patients (178).

Radiographic Evaluation

The assessment of metabolic activity depends on the availability of high-quality radiographs. Tomographic views provide more detail than standard radiographs because the overshadowing effects of bowel gas and intestinal contents are lessened. Spiral CT scans have virtually replaced intravenous pyelography in the evaluation of patients with ureteral calculi (64,352). Renal calculi can be seen easily on such studies, but plain or tomographic radiographs usually are easier to use for longitudinal follow-up. Relatively radiolucent stones such as uric acid or cystine are best monitored with ultrasonography or CT scanning.

The radiographic appearance of a stone depends on the composition of the stone, its thickness and orientation, surrounding tissues or bowel contents, and radiographic technique. A stone may rotate and give the illusion of a change in size. This rotation cannot be prevented, but its possible occurrence should be remembered when radiographs are examined. All stones, except uric acid, are clinically radiopaque. Even large uric acid stones appear faintly radiopaque from incorporated impurities. Small cystine and struvite stones may be difficult to see on plain radiographs. Relative radiodensities of the common stone salts have been measured and, in decreasing order, are apatite, whitlockite, brushite, whewellite, weddellite, cystine, struvite, and uric acid (276).

MEDICAL MANAGEMENT

Part of "8 - CALCULUS FORMATION "

With few exceptions (dissolution of uric acid and cystine stones), the goal of medical treatment is to prevent the formation of new stones or the further growth of old stones. This prophylaxis must be effective and continuous. Patients must understand that prevention of further stone formation probably will require lifetime treatment.

The therapy of urolithiasis is based on two principles: a reduction of urinary SS, and an increase in net inhibitory

activity. The latter can be achieved by increasing the quantity of inhibitors, by increasing the potency of inhibitors, or by corresponding decreases in promoter activity.

The purpose of a high fluid intake is to lower urinary SS. The dilution reduces ionic strength, complexation, and the concentration of inhibitors, but these side effects are more than offset by the reduction of SS. It is impossible for stone formation to occur in urine that is undersaturated for the particular stone salt. All patients with renal calculi should be counseled to increase their fluid intake. An 8-ounce glass of fluid should be consumed hourly while awake, and 8 to 16 ounces of fluid should be consumed if the patient is up at night. Approximately half of the fluid should be water. The patient should produce at least 2,500 mL of urine per 24 hours. The fluid intake should be consistent. A liberal intake of fluids during the day but poor intake during the night does not uniformly lower SS, especially after a heavy evening meal. Patients can use a container of known volume to inexpensively monitor their 24-hour urine output. A fixed numeric goal is helpful because most patients are poor estimators of their fluid intake and urine output.

A dietary history should be taken and dietary excesses eliminated (238). The traditional recommendation has been a low-calcium diet, but this may increase urinary oxalate excretion. Urinary SS can be lowered with a low-calcium, low-oxalate diet, but patients are less likely to adhere to a more complex program. The same criticism applies to a low-carbohydrate diet, a high-fiber diet, and a low–animal protein diet, although the last may be useful in the treatment of idiopathic uric acid lithiasis. Because dietary therapy requires long-term patient compliance, the encouragement of dietary moderation may be the best advice (135).

Fluid and dietary therapy should be used in all patients with urolithiasis and should be the only initial therapy in patients with ICU. One hundred eight patients with ICU of indeterminate metabolic activity were treated initially with fluid and dietary therapy at the Mayo Clinic (139). No stone growth or new stone formation was seen in 58% of these patients during a mean follow-up period of more than 5 years. Of those patients with hypercalciuria alone, 70% proved to have metabolically inactive stone disease. The existence of metabolically active stone formation should be proved before a patient is committed to lifelong pharmacologic therapy (314).

Renal Tubular Acidosis

The metabolic abnormalities of patients with distal RTA are corrected with replacement of sodium, potassium, and bicarbonate. Daily, 90 to 150 mEq of base usually is required and may be given as sodium bicarbonate or citrate (Bicitra, Polycitra, or Urocit-K). Total body potassium levels are low in untreated patients, and the serum potassium level may decrease as the acidosis is corrected. Potassium should be replaced while monitoring serum levels. Urinary calcium excretion decreases, and urinary citrate increases to a normal level with correction of the systemic acidosis.

Sodium bicarbonate, sodium citrate, potassium bicarbonate, and potassium citrate are equally effective in increasing urinary citrate (30). The advantage of citrate is that it produces a more even and longer-lasting effect on renal citrate excretion than bicarbonate. The advantage of potassium citrate over sodium citrate is that a long-term reduction of urinary calcium is seen with the former but not the latter (249,250).

Cystinuria

The goal of therapy is to reduce the urinary SS of cystine (130). Urine volume over 24 hours should be maintained at 3 to 4 L. The solubility of cystine in normal urine is approximately 300 mg/L but increases as the pH increases (Fig. 8.4). If the 24-hour urinary cystine excretion of a patient is known, the information in Fig. 8.4 can be used to calculate the urine volume and pH required to solubilize adequately all of the cystine. The pH usually must be increased to 7.5 to 7.8. This degree of alkalinization may be difficult to maintain and can promote the coprecipitation of calcium phosphate.

A carbonic anhydrase inhibitor such as acetazolamide can be used to maintain urinary alkalinity throughout the night, but these agents probably should be avoided because they induce changes in urinary composition that favor the precipitation of calcium phosphate. If a cystine stone becomes covered with a layer of calcium phosphate, further attempts at dissolution will be fruitless.

Cystine is two cysteine molecules linked by a disulfide bond (Fig. 8.3). The drug D-penicillamine (Cuprimine) reacts with cystine to form penicillamine-cysteine, a mixed disulfide that is more soluble than cystine in urine. The dose of D-penicillamine is 250 to 500 mg four times daily. It is given 30 minutes before meals and at bedtime. D-penicillamine is a potentially toxic drug that should be used for attempted stone dissolution or in patients whose disease cannot be controlled with hydration and alkalization. Adverse reactions include skin rashes, fever, arthralgias, and lymphadenopathy. A potential pyridoxine deficiency can be avoided with prophylactic pyridoxine (50 mg twice daily) therapy. Stone dissolution may require several months to 1 or 2 years.

Urinary cystine excretion also can be lowered by limiting dietary methionine. This therapy severely limits protein intake and is rarely, if ever, used.

α-Mercaptopropionylglycine (α-MPG, or Thiola) shares chemical properties with D-penicillamine but appears to have fewer adverse effects (230). A multicenter study of 66 patients with cystinuria found that the effectiveness of α-MPG in reducing cystine excretion was equal to that of D-penicillamine. A mean dose of 1,193 mg of α-MPG per

day maintained daily cystine excretion at 350 to 560 mg. In 59 patients who had taken both drugs, adverse reactions forced 31% to stop taking α-MPG and 60% to stop taking D-penicillamine.

Captopril, an angiotensin-converting enzyme inhibitor, contains a sulfhydryl group that can participate in a thiol exchange reaction to form captopril-cysteine that has a 200-fold greater solubility than cystine (313). Captopril further lowers urinary cystine excretion by a mechanism other than thiol exchange. Captopril may be a useful drug for the treatment of cystinuria (245,329), but a sufficient dose may cause orthostatic hypotension. Other physicians question the clinical utility of captopril (59).

Other metabolic disturbances may occur in patients with cystinuria. A comprehensive metabolic evaluation of 27 patients with homozygous cystinuria revealed that 19% had hypercalciuria and 22% had hyperuricosuria (286). Hypocitruria was found in 44%. Recurrent stones in cystinuric patients may be composed of calcium or uric acid, not cystine. It is important to remember that multiple metabolic abnormalities may exist in a single patient.

Hypercalcemic Disorders

The primary cause of hypercalcemia determines the therapy. If surgical treatment of a stone is contemplated in a patient with primary hyperparathyroidism, a parathyroidectomy should be the first procedure, although concomitant parathyroidectomy and ESWL, ureteroscopic stone removal, or percutaneous stone removal have been performed safely (349). Patients should have careful follow-up after parathyroidectomy to ensure that the hypercalcemia has been corrected and stone formation has ceased. Persistent stone growth may be caused by another disorder.

An adequate intake of fluids should be encouraged in all immobilized patients. Oral orthophosphates decrease urinary calcium excretion in immobilized patients and may be used if fluid therapy is unsuccessful (112). Corticosteroids should reduce the hypercalciuria in patients with sarcoidosis.

Uric Acid Lithiasis

The medical treatment of uric acid lithiasis is satisfying because uric acid stones can be dissolved. Fluid intake should be increased to achieve a 24-hour urine output of 3 L. The solubility of uric acid can be increased 10-fold by raising the urine pH to 6.5 (Fig. 8.6). A sodium bicarbonate or citrate preparation can be used to accomplish this (130). A daily dose of 300 mg of allopurinol, a xanthine oxidase inhibitor (Fig. 8.5 and Fig. 8.8), reduces the amount of uric acid excreted in the urine.

When all three elements of this program are used, most uric acid stones can be dissolved within 3 months. The allopurinol can be stopped after the stones are dissolved. New stone formation usually can be prevented by maintaining an alkaline urine. Overexuberant alkalization may precipitate a layer of calcium phosphate over the stone. Dissolution then becomes impossible. Use of carbonic anhydrase inhibitors should be avoided for the same reason.

Xanthinuria

Patients who form xanthine calculi while taking allopurinol should discontinue the drug. Patients with xanthinuria secondary to an inherited deficiency of xanthine oxidase should maintain a high urine volume and restrict their dietary intake of foods that contain purine. Because the pKa of the first dissociable proton of xanthine is 7.7, the solubility of xanthine cannot be increased significantly by physiologic alkalization.

2,8-Dihydroxyadeninuria

Xanthine oxidase is responsible for the oxidation of adenine to 2,8-DHA (40,102,106). Treatment consists of fluids and allopurinol without urinary alkalization. The solubility of 2,8-DHA is not affected by urinary pH. Dietary adenine may contribute to stone formation and should be reduced. Lentils and other grains have a high adenine content (50).

Primary Hyperoxaluria

Large doses of pyridoxine (50 mg four times daily) reduce oxalate excretion in 20% to 50% of patients (109). Neutral orthophosphate (1.5 to 2.0 g per 24 hours of elemental phosphorus in four divided doses) may halt the growth of existing stones and prevent the formation of new stones (318). Sodium citrate increases urinary citrate excretion, reduces calcium oxalate saturation, and reduces stone formation in patients with primary hyperoxaluria (173).

Renal transplantation has been attempted in patients with primary hyperoxaluria and renal failure, but oxalate mobilization from preexistent oxalosis may lead to deposition of oxalate in the transplanted kidney (71). Transplantation should be performed soon after the onset of renal failure, because oxalate is not removed efficiently by hemodialysis (73,185).

Hepatic or combined hepatic-renal transplantation has been performed for the treatment of primary hyperoxaluria (190,357). This aggressive approach corrects the enzymatic defect. Urinary oxalate and glycolate return to normal levels, and extrarenal deposits of oxalate are mobilized.

Enteric Hyperoxaluria

Dietary intake of oxalate and fat should be restricted. An additional advantage of a low-fat (50 g) diet is that bothersome steatorrhea is reduced. Dietary calcium supplementation has been used to increase precipitation of calcium

oxalate within the GI lumen (324), but this may increase urinary calcium. Stone disease usually can be controlled without resorting to calcium supplementation. Cholestyramine (12 g daily in three or four divided doses) binds acidic compounds, including oxalate, in the colonic lumen. Oxalate absorption decreases, steatorrhea decreases, and water absorption and urine volume may increase. Intestinal bicarbonate loss reduces urinary pH and citrate excretion. Some patients may even have a mild metabolic acidosis. These abnormalities can be corrected with base replacement. If metabolically active stone formation persists in patients with an ileal bypass, the normal anatomy of the GI tract should be restored (80).

Infection Stones

Surgical removal of a struvite stone generally is necessary to preserve renal function and reduce long-term morbidity and potential mortality (256). Urine cultures should be obtained and specific bactericidal therapy should be started 48 hours before surgery. All infected stone material should be removed. Antibiotic treatment should be continued for 10 to 14 days after surgery. Postoperative irrigation of the collecting system with hemiacidrin has been advocated to dissolve any minute retained stone fragments (5,214).

The patients should be maintained on antibacterial prophylaxis for 3 to 12 months. Adjunctive urinary acidification with ammonium chloride (2 g per day) has been used in conjunction with long-term antimicrobial therapy (379). Small retained fragments may dissolve with this regimen. The proper antibacterial agents suppress bacterial growth, and because of the decrease in urease production, urinary acidification can be achieved with ammonium chloride. Ammonium chloride (1.5 to 3 g per day) is a more effective urinary acidifier than either methenamine hippurate (2 g per day) or ascorbic acid (1.8 g per day) (355).

Acetohydroxamic acid, a urease inhibitor, may prevent the further growth of struvite stones and rarely may lead to dissolution of the stone material (368). Up to 50% of patients may experience side effects from the drug, including tremulousness, headache, or deep vein thrombosis.

The Shorr regimen combines a low-phosphorus diet with aluminum hydroxide capsules to achieve selective dietary phosphorus depletion (168). A few uncontrolled studies suggest that the Shorr regimen is an effective therapy for struvite urolithiasis, but the diet is difficult to follow. Low-phosphorus diets also increase urinary calcium excretion and promote crystalluria (362).

Most investigators report recurrent stone growth in 25% to 30% of patients (116). If recurrent metabolic stone formation is excluded, recurrent struvite stone formation occurs in 10% to 15% of patients. The lowest reported recurrence rate was only 2% (307).

Idiopathic Calcium Urolithiasis

Patients who consume adequate amounts of fluid and in whom dietary excesses have been eliminated may continue to have metabolically active stone formation. Several effective treatment programs are available.

Thiazide Diuretics

Thiazide diuretics are particularly effective when significant hypercalciuria is present. Hydrochlorothiazide 50 mg twice daily or trichlormethiazide 2 mg twice daily will reduce urinary calcium excretion, crystalluria, and urinary SS for calcium oxalate and calcium phosphate (374). The mechanism of action is thought to be stimulation of renal tubular calcium reabsorption, possibly by extracellular volume contraction (165). A high-sodium diet can blunt or prevent the hypocalciuric effect of thiazides. Moderate sodium restriction may be needed to reduce urinary calcium excretion. Up to 90% of patients who are treated with thiazides cease further stone formation.

Thiazides also may prevent stone formation in normocalciuric persons. This is a controversial finding, but may be related to a reported reduction in oxalate excretion after long-term thiazide therapy (58,375). Another study found that hydrochlorothizide did not reduce oxalate excretion, at least in patients with renal leak hypercalciuria (343). Side effects, including fatigue unrelated to the hypokalemia; hypomagnesemia; muscle weakness and cramping; decreased libido; impotence; and abnormalities in serum calcium, glucose, and uric acid, occur in up to 10% of patients.

There is some evidence that the treatment of all hypercalciuric patients with thiazide diuretics may be inappropriate (248). These investigators examined the effect of hydrochlorothiazide in 12 patients with absorptive hypercalciuria and in 10 patients with renal hypercalciuria. At short-term (3 to 6 months) follow-up, urinary calcium was significantly decreased in both groups. At long-term (30 to 120 months) follow-up, half of the patients with absorptive hypercalciuria were again hypercalciuric. The increased long-term stone formation seen in those patients with absorptive hypercalciuria was not statistically significant.

Yet another study found that chlorthalidone at a daily dose of 25 or 50 mg reduced the predicted rate of calculous events by 90% (87). This was a double-blind, randomized study that did not differentiate the mechanism of the hypercalciuria.

Orthophosphate

Orthophosphate has been the treatment of choice in patients with normocalciuria (314). It also may be effective in patients with hypercalciuria. Orthophosphate decreases urinary calcium excretion and increases inhibitor activity (371). Increased calcium complexation and decreased free

calcium ion activity are a result of increased urinary phosphate, citrate, and pH. Calcium oxalate SS decreases, but the SS of hydroxyapatite or brushite does not change. Excretion of the inhibitors, pyrophosphate and citrate, increases, and the more alkaline pH increases the potency of pyrophosphate as a crystal growth inhibitor. Orthophosphate also may reduce 1,25-dihydroxyvitamin D synthesis (348).

Orthophosphate usually is given as the neutral or mildly alkaline salt. The total daily dose should provide 1.5 to 2.0 g of elemental phosphorus. Patients may lose previously formed stone material during the first 3 to 6 months of therapy. If radiographs document that stone mass is being lost and no new stone material is precipitating, patients should be reassured that the medication is preventing further stone growth and that the troublesome stones were formed before drug therapy was started. Calcium stone formation ceases in 90% of patients taking orthophosphate (339).

Diarrhea is the most common complication of orthophosphate therapy. The dose may be halved until the diarrhea subsides, and then gradually increased to a therapeutic level. Orthophosphates should not be used in the presence of secondary urolithiasis resulting from infection or obstruction or in the presence of renal failure (glomerular filtration rate, less than 30 mL per minute).

Cellulose Phosphate

The purpose of cellulose phosphate therapy, unlike orthophosphate therapy, is not to provide absorbable phosphate. Cellulose phosphate binds calcium in the intestinal lumen and decreases calcium absorption (227). Cellulose phosphate should be used only in patients with absorptive hypercalciuria, because it may result in a negative calcium balance in those patients with normal intestinal calcium absorption or renal hypercalciuria. The usual dose is 5 g two or three times daily.

When given alone, cellulose phosphate may be ineffective or even increase calcium oxalate crystalluria (10). Urinary oxalate excretion increases with cellulose phosphate therapy alone, probably because intestinal absorption increases. Less calcium is available to complex dietary oxalate in the intestinal lumen. Cellulose phosphate also binds magnesium and decreases urinary magnesium excretion. Supplementation of cellulose phosphate therapy with magnesium (1 to 1.5 g magnesium gluconate per day), a low-oxalate diet, and a high fluid intake will effectively halt stone formation in almost 80% of patients (223).

Magnesium

Magnesium oxide (193) and magnesium hydroxide (66) have been advocated for the treatment of ICU, but the effectiveness of this therapy has not been demonstrated systematically. [The same criticism may be applied to clinical trials of thiazides and orthophosphates (45).] Anticipated benefits of increased magnesium excretion are increased complexation of oxalate and phosphate and a slight increase in crystal growth inhibition. Some investigators have reported prevention of recurrent stone formation in 80% of treated patients. Approximately 1 g of magnesium oxide or 250 to 750 mg of magnesium hydroxide have been given in two or three divided daily doses.

Ettinger and colleagues (87) used a prospective, double-blind, randomized clinical trial to examine the effectiveness of chlorthalidone or magnesium hydroxide in the prevention of recurrent calcium oxalate stone formation. The duration of the study was 3 years. Compared with historic control subjects (pretreatment rates of stone formation), all of the treatments, including placebo, appeared to prevent recurrent stone formation. With appropriate controls, chlorthalidone was more effective than placebo or magnesium hydroxide. The placebo groups had 56% fewer stones than predicted; the low-dose magnesium hydroxide group had 62% fewer stones. Both low-dose and high-dose chlorthalidone reduced the predicted rate of new stone formation by 90%.

The pitfalls of clinical trials of thiazides have been reviewed by Churchill and Taylor (47). Without a control group, it is difficult to determine how much of a decrease in new stone formation is caused by regression to the mean and how much is a result of treatment.

Allopurinol

The use of allopurinol in patients with hyperuricosuric calcium urolithiasis has been controversial (96). Early reports were encouraging (55), but later reports were less optimistic (198). Two adverse effects of hyperuricosuria have been proposed: heterogeneous nucleation of calcium oxalate on urate crystals and binding of large-molecular-weight calcium oxalate–crystal growth inhibitors to colloidal urate (91). An allopurinol-induced reduction of urate excretion could preclude either mechanism. Allopurinol has even been reported to decrease urinary oxalate excretion (292). Allopurinol does not appear to have a direct effect on calcium oxalate precipitation. The most conservative approach may be to use allopurinol as a secondary drug in those patients who have abnormal uric acid metabolism. Tiselius and colleagues (340) concluded that empiric allopurinol is ineffective in the treatment of recurrent calcium oxalate stone disease in the absence of hyperuricosuria or hyperuricemia.

Between 10% and 20% of patients with idiopathic calcium urolithiasis have hyperuricosuria as an isolated metabolic abnormality. Ettinger and colleagues (88) found that allopurinol effectively prevented recurrent stone formation in this subset of patients. They recommended allopurinol instead of thiazides for patients with isolated hyperuricosuria,

even though thiazides can be as effective. The risk of allergic reactions is increased with the simultaneous administration of thiazides and allopurinol.

Potassium Citrate

Potassium citrate has been used to treat patients with ICU and hypocitruria (228). The alkalizing effects of citrate increase urinary pH and urinary citrate excretion. Complexation of calcium with citrate increases, and ionized calcium and calcium oxalate SS decrease. Inhibition and calcium oxalate crystal growth increases slightly (increased citrate excretion and greater potency of pyrophosphate at a more alkaline urinary pH). In a study by Pak and Fuller, further stone formation ceased in almost 90% of ICU patients with hypocitruria. Citrate excretion increased to the normal range, whereas urinary pH was maintained at 6.5 to 7.0.

Several liquid preparations of citrate contain sodium. The effects of sodium citrate and potassium citrate on urine composition have been compared (284). Urinary pH and citrate excretion increased with both compounds, but calcium excretion decreased only with potassium citrate. The higher urinary pH increased brushite (calcium phosphate) saturation in both groups of patients, but a supersaturated condition was obtained only in those patients treated with sodium citrate. The failure to reduce urinary calcium excretion may have contributed to this latter effect.

In a trial by Pak and associates, long-term treatment with potassium citrate (20 mEq three times daily) reduced stone formation in 98% of patients, and stone formation ceased in 80% (236). Minor GI complaints were the most common side effects. No patients had melena or occult fecal blood. Although potassium citrate therapy of ICU is becoming more popular, not all investigators think that it is more beneficial than thiazides or even a placebo (242).

Pak and Fuller (228) studied 37 adults with a history of recurrent calcium oxalate stone formation. Seventeen had hypocitruria as an isolated abnormality, 18 had absorptive hypercalciuria, and 2 had hyperuricosuria. Potassium citrate (30 to 80 mEq per day) was administered to 25 patients. Twelve patients took thiazide, allopurinol, or both. Sustained increases in urinary citrate, potassium, and pH were seen with potassium citrate therapy. Only 4 patients continued to form stones, for a remission rate of 89%.

In spite of some early skepticism, studies continue to support the clinical effectiveness of potassium citrate (1,129). A randomized, double-blind study in patients with idiopathic hypocitraturic calcium nephrolithiasis found that, compared with a placebo, potassium citrate (30 to 60 mEq daily in wax matrix tablets) significantly reduced stone formation (16). This reduction in clinical stone formation was accompanied by increases in urinary citrate, pH, and potassium. Citrate has even been used to prevent the deposition of calcium oxalate on fragments that remain after ESWL (335).

Potassium citrate may be useful in patients who do not respond to thiazides (236). Thirteen patients had hypercalciuria that was corrected by thiazide treatment, but stones continued to form. The addition of potassium citrate to thiazide therapy prevented the development of hypokalemia and caused a sustained increase in urinary citrate and pH. Urinary calcium, oxalate, sodium, or volume did not change. Stone formation was reduced in all patients, and a complete remission occurred in 77%.

Citrus fruit juices are rich sources of potassium and citrate. The ingestion of these juices potentially represents an alternative to potassium citrate in the management of hypocitraturia calcium and uric acid nephrolithiasis. A study of eight healthy men and three men with hypocitraturic nephrolithiasis found that, compared with potassium citrate, orange juice delivered an equivalent alkali load and caused a similar increase in urinary pH (354). Orange juice increased urinary oxalate without altering calcium excretion, whereas potassium citrate decreased urinary calcium without altering urinary oxalate. Orange juice lacked the ability of potassium citrate to reduce calcium oxalate saturation. Nevertheless, orange juice should be beneficial in the treatment of calcium and uric acid lithiasis.

Other Agents

Some patients with ICU and mild hyperoxaluria have been treated with pharmacologic doses of pyridoxine (200 to 400 mg per day) (15). Oxalate excretion decreased by approximately one-third. The proposed mechanism is stimulation of pyridoxal-5-phosphate–dependent transaminases that are responsible for the conversion of glyoxalate to glycine (Fig. 8.10). Less glyoxalate would be available for conversion to oxalate. Pyridoxine also decreased urinary glycolate excretion and increased erythrocyte glutamic oxaloacetic transaminase activity. Individuals who consume large quantities of pyridoxine (2 to 6 g per day) may develop a sensory neuropathy (290).

Pentosan polysulfate is a structural analog of heparin but has little anticoagulant activity (282). Up to 4% of an oral dose is excreted in the urine. This agent was used initially to treat patients with interstitial cystitis (244). Pentosan polysulfate is also a potent inhibitor of calcium oxalate crystal growth (187). A 50% reduction in the rate of calcium oxalate crystal growth was achieved with a concentration of 2.4×10^{-9} M. A daily dose of 300 mg should provide a urinary concentration of 10 mg/L and increase inhibition by one-third. A recent clinical trial of this compound found no difference in the rate of stone formation before and during treatment, although patients who continued to form stones reported that they were smaller and more easily passed spontaneously (92).

Potassium-magnesium citrate is similar to potassium citrate, but the magnesium may lower urinary oxalate by binding oxalate in the intestinal tract (232). It also causes a

greater rise in urinary citrate and pH. Consequently, it may be more effective than potassium citrate in inhibiting the crystallization of uric acid and calcium oxalate in urine.

BLADDER CALCULI

Part of "8 - CALCULUS FORMATION "

Bladder calculi commonly are found in children who live in lesser developed countries and in men with bladder outlet obstruction. Bladder stones usually are freely movable in the bladder, but may be fixed to a bladder wall suture placed during a previous surgical procedure. The usual symptoms of bladder outlet obstruction may be present: urinary hesitancy, frequency, and nocturia. Patients also may have hematuria, dysuria, suprapubic pain that often radiates to the tip of the penis, and an interrupted urinary stream.

The diagnosis of a bladder stone usually is confirmed by radiographic examination, ultrasonography, or cystoscopy. Because many bladder stones are composed of radiolucent uric acid, the absence of a radiopaque shadow on a plain abdominal radiograph does not exclude the presence of a stone.

PROSTATIC CALCULI

Part of "8 - CALCULUS FORMATION "

Most prostatic calculi are found in men aged 50 to 65 years. Prostatic calculi are formed by the deposition of calcium salts on corpora amylacea. Corpora amylacea are laminated organic structures that are thought to form around desquamated epithelial cells in prostatic alveoli. Prostatic calculi may be associated with prostatic hyperplasia or prostatitis or may be asymptomatic. They may be seen on a plain roentgenogram of the pelvis and frequently can be palpated by rectal examination. Asymptomatic prostatic calculi require no treatment, but they often are removed during a transurethral prostatectomy for benign prostatic hyperplasia.

URETHRAL CALCULI

Part of "8 - CALCULUS FORMATION "

Urethral stones may form in the urethra or may migrate from the bladder or upper urinary tract. Primary or native urethral calculi usually are associated with chronic stasis and infection. Virtually all urethral calculi in women have been found in a urethral diverticulum. Men with urethral stones often have urethral strictures, a history of prostatic surgery, or coexistent bladder stones. Calcium phosphate and calcium carbonate are the most common chemical constituents.

Primary urethral calculi may be asymptomatic because they grow slowly with the urethral lumen or a diverticulum. Migrant stones may become symptomatic when they drop into the prostatic urethra. Patients may have dysuria, a weak urinary stream, or retention. Two-thirds of urethral stones are found in the posterior urethra, and one-third are found in the anterior urethra.

Fewer than half of urethral stones are diagnosed radiographically. Retrograde urethrography can define urethral anatomy in men but usually does not reveal a urethral diverticulum in women. Cystourethroscopy confirms the diagnosis.

CHILDHOOD UROLITHIASIS

Part of "8 - CALCULUS FORMATION "

Bladder stone disease was common in children in 18th century Europe (274). Boys younger than 10 years of age typically were affected. The prevalence of pediatric bladder stone disease became less common as Europe became industrialized. The occurrence of bladder stones in children was virtually unknown in Norway by 1831 (287). The disappearance of this disease is probably related to the concurrent improvement in nutrition. The disease still exists in less well-developed nations in Asia and the Middle East.

Bladder stone disease has been studied extensively in Thailand (78,346). Boys younger than age 10 years usually are affected. The stones are composed of a mixture of calcium oxalate and ammonium acid urate. Concurrent renal lithiasis typically is not present. A low intake of breast milk and early rice supplementation provide a diet low in protein and minerals. Urinary excretion of phosphate, sulfate, sodium, potassium, and magnesium is low. Urinary excretion of oxalate, calcium, uric acid, and ammonia is high. The high oxalate excretion is thought to be caused by consumption of local vegetables and plant leaves that have a high oxalate content. The hot climate and low fluid intake also contribute to crystallization.

Of patients with urinary calculi, 2% to 3% are children (345). Bladder stone disease is now uncommon in Europe and the United States. Most children with urolithiasis present with renal or ureteral calculi. Most patients have stones composed of calcium oxalate, calcium phosphate, or mixtures of these stone salts (184,311). Most children with urolithiasis have bacteriuria that is secondary to stone formation, but most of these organisms do not produce urease. One study found struvite stone formation in one-third of the patients (184). All had a history of multiple urologic procedures, diversionary procedures, or indwelling drainage devices. *Proteus* was the most common bacterial organism. Other investigators found a lower incidence of infection-induced stone formation.

The spectrum of causes is the same in children as it is in adults. One-third to one-half of patients have ICU. One study reported finding primary hyperparathyroidism in 6% of the pediatric patients (184), but most authors think that hyperparathyroidism as a cause of urinary stone formation in children is extremely rare. Some of the discrepancy may be explained by the rarity of any kind of urolithiasis in

children. Other metabolic causes of stone formation in children are distal RTA, cystinuria, and primary hyperoxaluria. Inflammatory bowel disease also is responsible for recurrent calcium oxalate stone formation in children (49). The pathophysiology is the same as that for enteric hyperoxaluria in adults.

A subsequent review of 221 pediatric patients referred to the Mayo Clinic found an almost even split between boys and girls (108 versus 113, respectively) (200). Analysis of stone material from 122 of the patients revealed calcium oxalate in 45%, calcium phosphate in 24%, cystine in 8%, struvite in 17%, and uric acid in 2%. A metabolic predisposition to form stones was found in 52%: hypercalciuria in 34% and hyperoxaluria in 20%. Other factors predisposing to stone formation were structural abnormalities or chronic infection.

Episodic gross hematuria may precede overt urolithiasis in children with hypercalciuria (323). Hypercalciuria was present in approximately 40% of children with gross hematuria but without urinary infection or proteinuria. Many children had concurrent abdominal or suprapubic pain, dysuria, and urinary frequency. Three-fourths of the children with hypercalciuria had a family history of urolithiasis. The hematuria resolved during anticalciuric therapy with hydrochlorothiazide or dietary calcium restriction.

The frequency and prognostic importance of hypercalciuria in children with hematuria were examined in a prospective multicenter study (322). Hypercalciuria was found in 76 (35%) of 215 patients (aged 3 to 18 years) who had unexplained isolated hematuria. No patient had proteinuria, urolithiasis, infection, or a systemic disorder. The children with hypercalciuria tended to be white males, have a family history of urolithiasis, and have gross hematuria with calcium oxalate crystalluria. Oral calcium loading tests showed renal hypercalciuria in 26 patients, showed absorptive hypercalciuria in 15 patients, and were not diagnostic in 35 patients. One week of dietary calcium restriction normalized urinary calcium excretion in those patients without renal hypercalciuria. During the follow-up period of 1 to 4 years, more hypercalciuric than normocalciuric children developed urolithiasis or renal colic. The authors also concluded that oral calcium loading tests offered little diagnostic benefit over 24-hour urinary calcium excretion measurement after dietary calcium restriction. Hydrochlorothiazide will correct the hypercalciuria (353).

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9

SURGICAL MANAGEMENT OF CALCULUS DISEASE

Stevan B. Streem

Glenn M. Preminger

S.B. Streem: Urological Institute, The Cleveland Clinic Foundation, Cleveland, OH 44195.

G.M. Preminger: Division of Urologic Surgery, Duke University Medical Center, Durham, NC 27710.

Contents

The surgical management of urinary calculus disease has evolved considerably over the past two decades. Twenty years ago, open procedures for stones were some of the most frequently performed urologic operations. Since then, however, stone management has been at the forefront of “minimally invasive” intervention. Specifically, the introduction and refinement of percutaneous and ureteroscopic access to the upper tracts, along with the nearly simultaneous development of both extracorporeal and intracorporeal lithotripsy, has relegated the role of open surgery to less than 1% of patients undergoing intervention for their stone disease. This chapter reviews the indications to intervene for urinary calculi, the basic physics of the most frequently used devices for both extracorporeal and intracorporeal lithotripsy, and the respective roles of extracorporeal and intracorporeal lithotripsy with percutaneous or ureteroscopic access and open surgery. The results and complications associated with each of these forms of intervention are reviewed as well.

PATIENT EVALUATION

Part of "9 - SURGICAL MANAGEMENT OF CALCULUS DISEASE "

Radiographic Evaluation

A thorough radiologic evaluation is one of the most important aspects of the overall investigation of urinary stone disease. These studies are invaluable aids in assessing three major issues that must be addressed before selecting appropriate

treatment: stone burden and location, urinary tract anatomy, and overall and ipsilateral renal function.

Plain Abdominal Radiography

More than 90% of stones within the urinary tract are radiopaque, and a plain film of the kidney, ureter, and bladder (KUB) is often the initial radiographic examination obtained in patients with nephrolithiasis. The KUB should be performed before any subsequent films that use contrast media because contrast may prevent the visualization of any calculi.

It is important not to overlook stones that may be obscured when they overlie bony structures, such as the sacrum or transverse processes of the lumbar vertebrae. These stones can be more easily identified using oblique views in addition to those obtained in the anteroposterior position. In addition, nephrotomograms can also be used to assist in the identification of small, less radiopaque calculi within the kidneys.

Intravenous Pyelography

An intravenous pyelogram (IVP) can be instrumental in defining the relationship of calculi to the pyelocalyceal system and ureter. The exact location of the stones, the presence or absence of obstruction, and renal or ureteral anomalies are important pieces of information that can be gleaned from the IVP. In addition, the IVP can approximate renal function in both the affected and the contralateral kidney as suggested by the promptness of contrast excretion, thickness of renal parenchyma, and amount of pyelocaliectasis. However, for more precise information on renal function, a differential renal scan should be obtained.

For patients with an apparent ureteral calculus, delayed films are obtained for as long as necessary to specifically identify their location and to prove their presence within the urinary tract. An IVP may also suggest the presence of radiolucent stones, and it may also identify anatomic abnormalities that contribute to stone formation such as a ureteropelvic junction obstruction or calyceal diverticula.

Renal Ultrasonography

Ultrasonography (US) can be used as a screening tool for hydronephrosis or stones within the collecting system. Additional information provided by sonographic examination of the kidneys includes an estimate of the amount of renal parenchyma present and identification of otherwise radiolucent calculi, because a classic “sonographic shadow” will often clearly identify stones that may not be visualized on standard plain films. However, the middle ureter and distal ureter are often not satisfactorily visualized on US due to the presence of bowel gas anteriorly and the bony pelvis posteriorly. US may also be useful in the acute setting to rule out other causes of abdominal pain and during follow-up of patients with recurrent nephrolithiasis because its use avoids x-ray exposure.

Computed Tomography

Computed tomography (CT) scanning is particularly useful in helping identify the etiology of otherwise radiolucent filling defects within the renal pelvis or ureter. In addition, obstruction, anatomic anomalies, or other urologic problems such as a vascular insult that can mimic ureteral colic can also be easily identified.

Nonenhanced spiral CT is currently the preferred diagnostic tool in the assessment of patients with acute flank pain (182). This technique is more sensitive than either simple radiography or US. All stones, with the exception of certain drug-related crystals, are visualized by this method, which is also fast and cost-effective. Moreover, other manifestations of obstruction, such as periureteric and perinephric stranding, and periureteric edema and hydronephrosis are easily identified (Fig. 9.1). Finally, spiral CT scan has the advantage of being able to definitively identify other causes of acute flank or abdominal pain such as appendicitis, diverticulitis, cholecystitis, or abdominal aneurysmal disease.

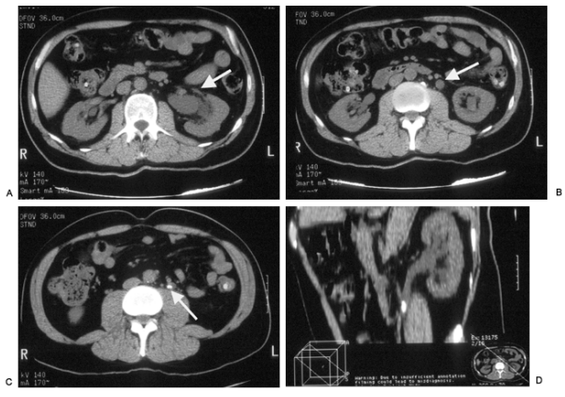

FIGURE 9.1. A: Dilation of left renal collecting system *(arrow)*. **B:** Dilated left ureter overlying psoas muscle *(arrow)*. **C:** Calculus in proximal ureter *(arrow)*. **D:** Reconstructed computed tomography imaging confirms partially obstructing proximal ureteral calculus.

Radionuclide Evaluation

Renal radionuclide studies provide rapid and safe information about total and differential renal function. These tests are specifically advantageous because they are noninvasive, require no bowel or other specific preoperative preparation, subject the patient to only minimal radiation exposure, and are apparently free of allergic complications. A differential renal scan should be performed in those patients in whom an obstructing stone might have resulted in a permanent and significant reduction in renal function, because nephrectomy may be the procedure of choice for kidneys that, after relief of obstruction, will supply less than 10% to 15% of overall function.

THE ACUTE STONE EPISODE

Part of "9 - SURGICAL MANAGEMENT OF CALCULUS DISEASE "

Classic symptoms associated with an acutely obstructing urinary stone include colicky flank pain with or without nausea or vomiting. The pain may radiate anteriorly or even to the groin, ipsilateral testicle, or labia. Stones in the distal ureter may also result in frequency, urgency, and dysuria. If the obstruction is associated with infection, high-grade fever or even sepsis may ensue. If a patient demonstrates these classic findings and has a previous history of recurrent radiopaque nephrolithiasis, further studies are warranted to address the size and location of the stone to determine the appropriate course of treatment. Stones 4 mm or smaller in

largest diameter have a greater than 90% rate of spontaneous passage with conservative measures alone; however, stones 6 mm or larger have only a 10% rate of spontaneous passage (121).

For patients who lack classic symptoms and are experiencing their first stone episode or who are known to form radiolucent stones, either a nonenhanced spiral CT or an IVP should be performed. Sonography may be used to assess hydronephrosis and intrarenal calculi, but it may be especially insensitive for the diagnosis of ureteral stones.

If the patient is clinically stable and has no evidence of systemic infection, progressive obstruction, or obstruction of a solitary kidney, conservative management may be offered with pain medications alone such as nonsteroidal antiinflammatory drugs or narcotic analgesics. However, in the presence of obstruction with infection, unrelenting pain, or significantly compromised renal function, urinary drainage should be instituted on an emergent basis, either as ureteral stent placement or as percutaneous nephrostomy drainage.

INDICATIONS FOR INTERVENTION

Part of "9 - SURGICAL MANAGEMENT OF CALCULUS DISEASE "

Although the use of newer, less invasive modalities has become the standard of management for nearly all patients requiring intervention for stones, the indications to intervene have remained essentially unchanged. These include chronic or progressive obstruction from the stone; pain, infection, or hematuria associated with the stone; or active stone growth despite appropriate medical management (Table 9.1). In addition, even in the absence of an otherwise clear indication, stone removal should be considered for any “high-risk” patient, such as an airplane pilot, who cannot afford to experience an inopportune episode of renal colic.

Chronic or progressive obstruction from the stone
Pain, infection, or hematuria associated with the stone
Active stone growth despite appropriate medical management

TABLE 9.1. INDICATIONS FOR INTERVENTION

SHOCK WAVE LITHOTRIPSY

Part of "9 - SURGICAL MANAGEMENT OF CALCULUS DISEASE "

Since the first patient was successfully treated with shock wave lithotripsy (SWL) in 1980, rapid acceptance and widespread use have made this form of stone therapy the treatment of choice for more than 80% of all patients undergoing intervention for renal and ureteral calculi. Although the basic principles of SWL remain unchanged, a number of technologic advances and modifications in currently available lithotripters have significantly expanded the clinical applications of lithotripsy. The rapid acceptance and widespread application of SWL have also led to many advances in lithotripsy technology and have stimulated numerous studies to better understand the basic physics and the bioeffects of this modality.

Following the initial success of the first-generation lithotripter (Dornier HM-3), more than 20 different models of second-generation lithotripters were developed, utilizing various energy sources, focusing schemes, coupling media, and stone localization techniques (135,144). Moreover, several "third-generation" lithotripters, characterized by their dual imaging and variable power capabilities, have recently been developed and are either commercially available or undergoing clinical trials both in Europe and the United States (14,92,104,152). Although the fundamental principles of SWL remain unchanged, these advances in lithotripsy technologies have generally led to improved safety and, in some cases, improved cost-effectiveness of urolithiasis treatment.

Basic physics and animal studies performed in the past two decades have greatly advanced our understanding of the mechanisms of stone fragmentation, as well as tissue injury and renal functional alterations, induced by SWL. A basic understanding of the physical and biologic effects of high-intensity shock waves is important to ensure the safety and efficacy of SWL treatment. This knowledge is essential for the optimization of SWL technology to achieve maximal efficacy of stone fragmentation while minimizing adverse effects on renal tissue.

Not all stones are amenable to SWL, and clinical studies have demonstrated that the size and composition of the calculi, along with location and renal and ureteral anatomy, all significantly affect successful stone fragmentation and clearance. This section provides a critical review of our current understanding of SWL and offers insights into the future of this innovative technology.

Historical Aspects

Physicists at Dornier Systems, Ltd., and Friedrich Shafen, Germany, began experimenting with shock waves and their travel through water and tissue in 1963. Throughout the 1970s, numerous experimental lithotripters were developed that used new methods of transmitting shock waves, as well as different techniques of stone localization. In addition, experimental studies were being performed both *in vitro* and *in vivo* examining the effects of shock waves on various organs and tissues.

In 1980, Chaussy and associates successfully treated the first human patient, and they then reported their initial series of 72 patients in 1982 (25). Subsequently, nearly 2,000 articles have been published in the peer-reviewed literature detailing the use of SWL for the management of renal and ureteral calculi. Moreover, numerous second- and third-generation devices have been introduced and are currently being used throughout the world. Enhancements in these newer lithotripters may ultimately prove to facilitate stone fragmentation while reducing tissue injury.

Lithotripsy Design

All lithotripters share four main features: an energy source, a focusing device, a coupling medium, and a stone localization system (Table 9.2). The original Dornier HM-3 design uses a spark plug energy generator with an elliptical reflector for focusing the shock waves. A water bath transmits the shock waves to the patient with stone localization provided by biplanar fluoroscopy. Modification of the four basic components of this first-generation lithotripter has provided the development of second- and third-generation devices, of which more than ten machines are currently either available commercially or undergoing clinical trials (136).

Shock wave generator	Coupling medium
Shock wave focusing	Stone localization

TABLE 9.2. MAIN LITHOTRIPTER COMPONENTS

Shock Wave Generation

All lithotripters share the four aforementioned features, but it is the mode of shock wave generation that determines the actual physical characteristics of that particular lithotripter. The objectives for using different types of energy sources include maximum efficacy (the overall stone-free rate) and maximum efficiency (cost-effectiveness, including need for secondary treatments). The two basic types of energy sources for generating shock waves are point sources and extended sources. The electrohydraulic machines use point sources for energy generation, whereas extended sources are incorporated into the piezoelectric and the electromagnetic devices.

Electrohydraulic Generators

The electrohydraulic generator is located at the base of a water bath and produces shock waves by an electric spark gap of 15,000 to 25,000 volts and 1 μs duration. This high-voltage spark discharge results in the rapid evaporation of water, which generates a shock wave by expanding the

surrounding fluid. The spark plug is located in an ellipsoidal reflector that concentrates the reflected shock waves at a second focal point, F_2, with F_1 being the origin of the primary shock waves (Fig. 9.2). The spark-gap method of shock wave generation was pioneered by the first-generation Dornier HM-3 lithotripter and is also used in the Direx, Medstone, Northgate, and Technomed machines, among others.

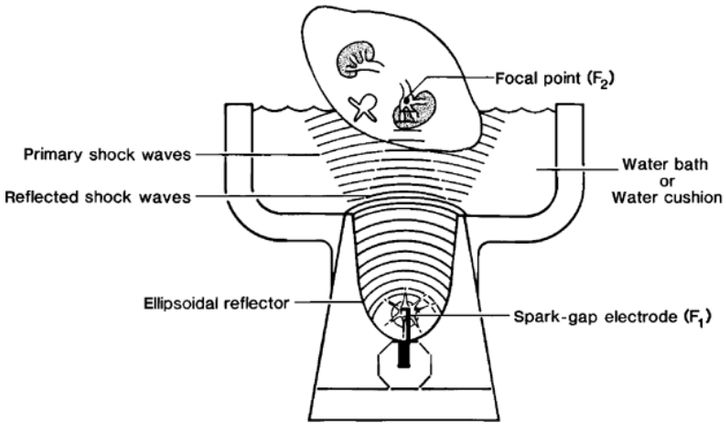

FIGURE 9.2. Schematic of electrohydraulic shock wave generator.

Piezoelectric Generators

Piezoelectric shock waves are generated by the sudden expansion of ceramic elements excited by a high-frequency, high-voltage pulse. Thousands of these tiny elements are placed along the inner surface of a hemisphere at the base of a pool of water. Although each of these ceramic elements moves only slightly in response to a pulse of electrical energy, the summation of the simultaneous expansion of multiple elements results in a high-energy shock wave directed to the focal point at the center of the sphere. The shock wave is propagated through either a small water basin or a water-filled bag to the focal point, F_1 (Fig. 9.3). The spherical focusing mechanism of the piezoelectric lithotripters provides a wide point of shock wave entry at the skin surface and a very small focal point.

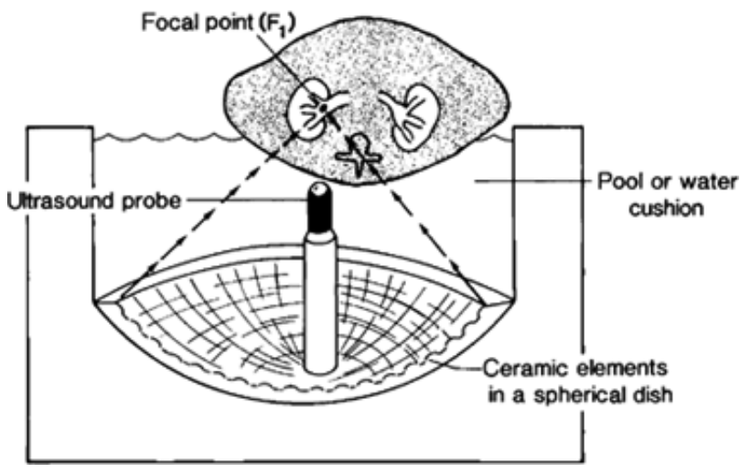

FIGURE 9.3. Schematic of piezoelectric shock wave generator.

Electromagnetic Generators

In electromagnetic devices, shock waves are generated when an electrical impulse moves a thin, circular metallic membrane, which is housed within a cylindric “shock tube.” The resulting shock wave, produced in the water-filled shock tube, passes through an acoustic lens and is thereby directed to the focal point, F_1 (Fig. 9.4). The shock wave is coupled

to the body surface with a moveable water cushion and coupling gel.

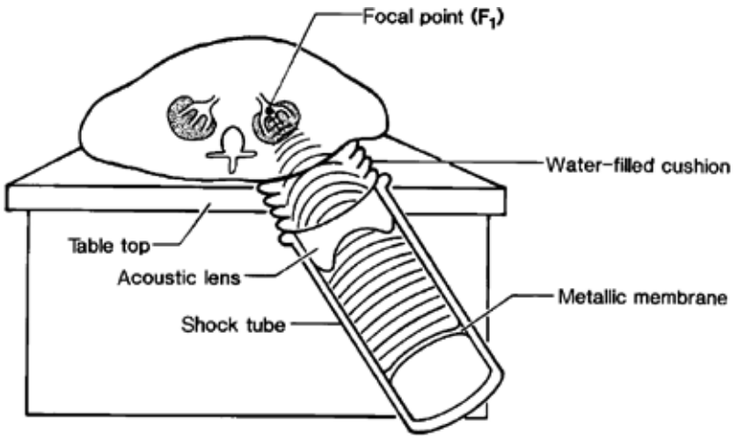

FIGURE 9.4. Schematic of electromagnetic shock wave generator.

Shock Wave Focusing

Shock waves must be focused to concentrate their energy on a target such as a calculus. The type of shock wave generation dictates the method of focusing used. Machines that use point sources, such as spark-gap electrodes, generate shock waves that travel in an expanding circular pattern. All of these machines use ellipsoid reflectors for focusing the shock waves at the second focal point, F_2.

Because a single piezoelectric element produces a very small amount of energy, larger transducers with multiple ceramic elements are required for piezoelectric lithotripters. The array of ceramic elements is positioned in a spherical dish that allows focusing in a very small focal region, F_1. The vibrating metal membranes of the electromechanical lithotripters produce an acoustic plane wave that uses an acoustic lens for focusing the shock wave at F_1.

Coupling Medium

The original Dornier HM-3 machine uses a 1,000-L water bath to transmit the shock waves to the patient. This method of coupling requires unique positioning of the patient, because the anesthetized subject has to be lowered into the tub and the calculus accurately positioned at the second focal point. Remote monitoring and the physiologic effects of almost total body immersion thus produced unique challenges for the anesthesiologist. Second-generation lithotripters were designed to alleviate the physiologic, functional, and economic problems of the large water bath, and current models use an enclosed water cushion, or a totally contained shock tube, to allow simplified positioning and “dry” lithotripsy.

Stone Localization

Stone localization during lithotripsy is accomplished with either fluoroscopy or US. Fluoroscopy provides the urologist with a familiar modality and has the added benefits of effective ureteral stone localization. Moreover, fluoroscopy allows the use of contrast material to help delineate the anatomy of the collecting system. However, fluoroscopy requires more space, carries the inherent risk of ionizing radiation to both the patient and medical staff, and is not useful, without adjunctive contrast injection, in localizing radiolucent calculi.

Sonography-based lithotripters offer the advantages of stone localization with continuous monitoring and effective identification of even radiolucent stones, without radiation exposure (135). In addition, US has been documented to be effective in localizing stone fragments as small as 2 to 3 mm and is as good as or better than routine KUB to assess patients for residual stone fragments following lithotripsy (1). The major disadvantages of US stone localization include the basic mastery of the use of ultrasonic techniques by the urologist and difficulty in localizing minimally obstructing or nonobstructing ureteral stones.

Anesthesia Requirements

Three factors contribute to the need for anesthesia during SWL: shock wave pressure (power), area of the shock wave at its skin entry site, and size of the shock wave focal point. The intensity of the shock wave is determined by the type of generator used and the amount of power (usually electrical charge) supplied to the shock wave generator. The original electrohydraulic design delivers the most powerful shock waves but also causes the greatest amount of discomfort for the patient. Therefore either general, regional, or local anesthesia is used in the original spark-gap machines. Recent studies have demonstrated the ability to reduce anesthesia requirements with the first-generation electrohydraulic devices (123).

The size of the focal point and the area of shock wave entry at the skin are both determined by the configuration of the focusing device (Fig. 9.5). The increased area of skin entry and diminished focal size have lessened the need for general or regional anesthesia in patients treated with second- or third-generation lithotripters. Currently, variable-power electrohydraulic lithotripters provide the advantage of a wide range of shock wave intensities to allow for either a reduction in anesthesia requirements or increased fragmentation efficacy with higher power under general or regional anesthesia. Using the lower power setting, however, causes the overall stone-free rate to decrease, while increasing the number of shocks required per treatment and the re-treatment rate. Therefore, to achieve an anesthesia-free status, one must expect the number of secondary treatments to increase. Therefore the efficiency of that lithotripter will be diminished.

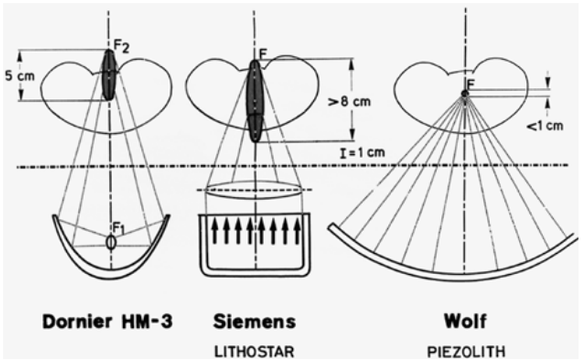

FIGURE 9.5. Configuration of focal regions for three types of shock wave generators.

Shock waves generated by a piezoelectric source tend to be less powerful than those from an electrohydraulic source. This leads to a higher re-treatment rate, but when combined with other design modifications, it allows treatment of stones without anesthesia (135). The wide aperture of the focusing sphere, the larger skin entry zone, and the small focal point combined with lower peak pressures make piezoelectric machines truly anesthesia free.

Design characteristics of the electromechanical lithotripters tend to place them between the other two machine types in terms of anesthesia requirements. The electromagnetic devices have a relatively small skin entry site and a large focal area. Electromagnetic lithotripsy is usually performed with intravenous or oral sedation, with or without the use of local anesthesia at the skin entry site. A transcutaneous electrical nerve stimulator may provide adequate analgesia during lithotripsy with electromagnetic lithotripsy (31).

Indications and Contraindications

Indications for SWL in urinary tract stone management are the same as the indications for surgical intervention. These include renal colic or chronic pain, urinary obstruction, infection, or decreasing renal function. Relative contraindications to SWL include large stone size (i.e., calcium oxalate stones greater than 2.5 cm in diameter or struvite stones greater than 5.0 cm in diameter), most cystine stones, active infection, proximate calcified abdominal aortic or renal artery aneurysms, distal obstruction, pregnancy, and poorly informed patients (167) (Table 9.3).

Large stone	Active infection
Calcium oxalate >1.5 cm	Proximate calcified abnormal aortic or renal artery aneurysm
Struvite >3 cm	
Significant dilation of collecting system	Pregnancy
Distal ureteral obstruction	Poorly informed patient
Untreated coagulopathy	

TABLE 9.3. RELATIVE CONTRAINDICATIONS TO SHOCK WAVE LITHOTRIPSY

Results: Clinical Considerations

Efficiency Quotient

The determination of lithotripter efficiency with regard to adequate stone fragmentation requires a delicate balance between the completeness of stone fragmentation and the need for anesthesia or analgesia. As the shock wave intensity is decreased to allow for “anesthesia-free” lithotripsy, the ability to adequately fragment stones is also reduced, thereby decreasing lithotripter efficiency. Diminished efficiency can be seen as an increase in the number of treatments needed to render a patient stone free or as an increased need for auxiliary procedures before or following lithotripsy. Auxiliary procedures would include placement of a percutaneous nephrostomy tube, formal percutaneous nephrostolithotomy, ureteropyeloscopy, or placement of a ureteral stent.

An “efficiency quotient” can be calculated by determining the stone-free rate obtained by various lithotripters in relation to the need for repeat lithotripsy, as well as the number of auxiliary procedures performed to render patients stone free (40). Using this efficiency quotient, one can make more valid comparisons between different types of first- and later-generation lithotripters.

Reports for many second-generation lithotripters have revealed stone-free rates similar to those obtained from the original electrohydraulic lithotripsy devices. If one also considers the need for repeat lithotripsy as well as the number of auxiliary procedures performed, however, the efficiency quotients of the lower-power, second-generation devices and the original electrohydraulic machines might not be equivalent. The efficiency quotient offers the urologist a more reliable gauge for comparing the effectiveness of individual lithotripters than does the stone-free rate alone (144).

With their higher re-treatment rate, second-generation lithotripters increase the time commitment necessary for both patient and treating physician. However, the decrease in stone fragmentation efficiency may be compensated by the fact that many of the second-generation devices allow

for office-based lithotripsy and require no hospitalization or intravenous lines, no anesthesia or analgesia, and no recovery room charges. Therefore some physicians and patients may accept the inconvenience of multiple repeat treatments if the safety and ease of operation of the second-generation machines outweighs the disadvantage of diminished lithotripsy "efficiency." In fact, it is probably not possible to have true anesthesia-free capability with a lithotripsy device that rates high on an efficiency quotient scale. To achieve anesthesia-free status, one has to expect the number of secondary treatments to increase, and therefore the efficiency quotient of that lithotripter will be diminished.

"Small" Calculi

The first-generation Dornier HM-3 represents the gold standard in terms of efficacy (overall stone-free rate) in stone fragmentation. As the shock wave pressure and focal point area of second- and third-generation machines have been reduced, so has the requirement for anesthesia or analgesia. However, the price paid for anesthesia-free lithotripsy is an increase in the secondary treatment rates and a subsequent reduction in efficiency. Although there is a compromise in efficiency with the piezoelectric lithotripters, the decreased efficiency may be balanced by the fact that each treatment can be performed as an "office" procedure, without anesthesia or analgesia. Electromagnetic lithotripsy, usually performed with intravenous or oral sedation, has been found to require a mean of approximately 3,600 shock waves per treatment, with stone-free rates of 69% to 80% and re-treatment rates of 7% to 21%.

"Large" Calculi

With increased stone volume, the efficacy of all lithotripters decreases significantly. With a Dornier HM-3, the stone-free rate may be as low as 30% for patients with a dilated collecting system and a stone or group of stones with total volume greater than 3 cm (105). Although the stone-free rate for large calculi is approximately 70% for patients with normal collecting system anatomy, many clinicians advocate the use of percutaneous nephrolithotripsy as the initial form of therapy in this setting (120,158).

In some situations, the combination of percutaneous nephrolithotripsy and SWL can be more effective than SWL alone. With this type of combination therapy, stone-free rates approaching 85% to 90% have been reported, even for large calculi (168).

Stone Location

Stone location in the collecting system is another important determinant of the outcome of SWL. Treatment of renal pelvic and upper ureteral stones may result in stone-free rates of 85% to 92% (91). In contrast, stone-free rates for patients with lower calyceal calculi are less than 60%, compared with 75% to 80% for those with middle and upper calyceal stones (106). Recent studies have also documented the importance of lower pole renal anatomy and its impact on stone clearance following SWL (49).

Stone-free rates of 65% to 70% for lower ureteral calculi (below the pelvic brim) have been achieved through various modifications in patient positioning and lithotripter design. However, ureteroscopy for the management of calculi in a similar location is successful in 95% to 100% of patients, and ureteroscopic extraction is now generally considered the first line of therapy for stones in the distal ureter (190).

Stones in calyceal diverticula have long been a source of treatment controversy. SWL provides improvement or resolution of symptoms in many patients but is generally unsuccessful in rendering such patients stone free. Percutaneous management of these stones, by contrast, produces significantly higher stone-free rates (12,87). These data suggest that stones in calyceal diverticula should be managed with SWL only when specific criteria regarding stone size and diverticular emptying are met (169).

Stone Composition

As the stone composition varies, so does the efficacy of SWL. "Harder" stones such as calcium oxalate monohydrate and cystine require an increased number of shock waves at higher intensity levels to achieve adequate fragmentation. Even at these higher settings, however, results with cystine calculi have been inferior to those with calcium oxalate stones (30). Most investigators advocate the use of percutaneous or "combination" therapy for large cystine calculi (27).

Auxiliary Procedures

Another area of controversy has been the efficacy of, and indications for, the use of ureteral stenting before SWL. Although some reports advocate the liberal use of ureteral stents before lithotripsy, the benefits of anesthesia-free lithotripsy would be diminished if an anesthetic or analgesia were required for stent placement. In fact, a recent clinical series evaluating the use of ureteral stents with lithotripsy found no improvement in stone-free rates or postlithotripsy complications in patients with ureteral stents. However, use of stents was associated with a significantly higher incidence of patient morbidity, including discomfort, frequency, urgency, and hematuria (109,137). Urologists generally exercise their own judgment regarding the merit of ureteral stenting in individual patients, and patients with large calculi or those requiring general or regional anesthesia for lithotripsy are more likely to undergo stent placement.

Current Lithotripters: Limitations

In the two decades since the first clinical application of SWL by Chaussy and associates (25), technical refinements have

produced more than 15 second- and third-generation devices. These designs have concentrated on altering the methods of shock wave generation, focusing, coupling, and localization, with the primary goal of equaling the stone-free rate of the Dornier HM-3 while increasing the safety, convenience, and cost-effectiveness of treatment. The new devices are designed to offer equivalent or better stone fragmentation, to decrease or eliminate anesthesia requirements, and to decrease radiation exposure from x-rays. Despite great technical progress, however, these new machines still have important shortcomings.

In general, second-generation lithotripters can be divided into a higher-power electrohydraulic and electromagnetic group and a lower-power piezoelectric group. Disadvantages of the first group include pain and attendant anesthesia requirements and as yet poorly quantified renal tissue damage. Disadvantages of the second group include a small focal size of the shock wave, with the need for a greater total number of shock waves, and a higher re-treatment rate.

The apertures of the electrohydraulic and electromechanical lithotripters are relatively small, leading to a smaller skin entry site and larger focal zone. This creates the need for general or regional anesthesia or heavy intravenous sedation. The larger aperture of the treatment dish of the piezoelectric lithotripters results in a large area of skin entry and a small focal zone. The discomfort produced by treatments with these machines is minimal enough to allow for anesthesia-free lithotripsy (135).

The relatively large focal region of electrohydraulic lithotripters exposes a larger amount of normal renal tissue to maximal shock wave pressures, and both animal and clinical studies have demonstrated more acute renal parenchymal injury from electrohydraulic and electromagnetic lithotripters when compared with piezoelectric units. However, one drawback of the small focal region in the piezoelectric machines is that it mandates constant monitoring of the effects of treatment on the targeted calculus. Accurate focusing of the shock wave is mandatory, because there is a rapid dropoff in pressure outside the small focal zone. The requirement of exact focusing is not necessary with the electrohydraulic or electromagnetic machines, which have a much larger area of maximal shock wave energy. As noted previously, for the advantage gained by performing anesthesia-free lithotripsy, one loses efficiency of stone fragmentation. Currently, it appears that it is not possible to have true anesthesia-free capabilities with a very “efficient” lithotripter.

Additional limitations of current lithotripsy devices relate to the method of stone localization. Although lithotripters using fluoroscopy can visualize the entire urinary system, they have the disadvantage of exposing the patient to a significant amount of radiation. In addition, it is often difficult, if not impossible, to identify small calculi within the kidney or ureter, or any radiolucent stones without the aid of contrast injection.

The devices that use sonography for stone localization potentially can be used for both renal and biliary lithotripsy, and they pose no risk of radiation exposure. Their main disadvantage is that they offer poor visualization of middle and lower ureteral stones. Efforts to develop echogenic ureteral stents, as well as new modes of sonography to aid in ureteral stone localization, are now in progress.

The Ideal Lithotripter

SWL can be used effectively to treat most renal and ureteral calculi with minimal morbidity and convalescence. Research in lithotripter design is ongoing, however, with attempts to improve performance and ultimately to design the “ideal lithotripter.” Such a device should be physically compact and portable, thereby allowing a lithotripter to be transported or shared between smaller institutions. In fact, a number of mobile lithotripsy units are currently in operation. The ideal lithotripter should also be adaptable for other endourologic procedures, as well as for biliary lithotripsy. Many of the current machines that use fluoroscopic stone localization can be used for percutaneous or ureteroscopic stone removal, and the US-based machines can easily be used for both urinary and biliary calculi.

By having an adjustable energy source, the ideal lithotripter would allow for anesthesia-free treatment of smaller or “routine” calculi, yet would have the potential power required to fragment either very hard or large renal or ureteral stones. This capability would allow for effective and efficient lithotripsy treatments, with the knowledge that in some cases, sedation or anesthesia must be administered to allow the use of the more powerful shock wave energy.

Finally, the ideal lithotripter should be economical to install and operate. This would entail minimal site renovations before installation of the lithotripter and little or no daily operating costs once the machine is on-line and running.

New-generation Lithotripters

A number of new-generation lithotripters have incorporated many of the characteristics of the ideal lithotripter (28). The basic design of these third-generation machines includes dual imaging capabilities, as well as variable shock wave power (Table 9.4). Currently, a number of third-generation lithotripters are currently in use across the globe. These include the Dornier MFL 5000 (HM5), Dornier Compact S, Siemens Lithostar Plus, Storz Modulith

SL20 and SLX, and Wolf Piezolith 2500 (77,93,107,118,138,177).

Dual imaging	Ultrasonography
Fluoroscopy	Variable power

TABLE 9.4. NEW-GENERATION LITHOTRIPTERS

Dual Imaging

Dual imaging capability entails having both fluoroscopic and sonographic localization systems available in the same machine. Such a design has the advantage of using fluoroscopy for imaging stones within the kidney and the ureter, while having the option to use sonography for the identification of radiolucent renal or biliary calculi. Another advantage of a sonographic localization system is that it allows the operator to target a stone using fluoroscopy initially, and then to switch to sonography to avoid excessive use of ionizing radiation.

Interestingly, while the Dornier, Siemens, and Storz machines have all added US capabilities to provide dual imaging, none of these systems provides “in-line” imaging for both the fluoroscopic and sonographic localization devices. For example, with the Dornier and Siemens devices, one can use sonography to target a radiolucent or biliary tract calculus, yet the patient must be moved “blindly” to the fluoroscopy unit, which is in line with the shock wave generator. Alternatively, one can use the fluoroscopic localization system with the Storz machine, yet only the US is in line with the shock wave generator. The Wolf Piezolith 2500 is currently the only third-generation device that has both fluoroscopy and sonography in line with the piezoelectric shock wave generator (Fig. 9.6). This permits rapidly changing from fluoroscopic to sonographic stone localization, without moving the patient off the treatment dish.

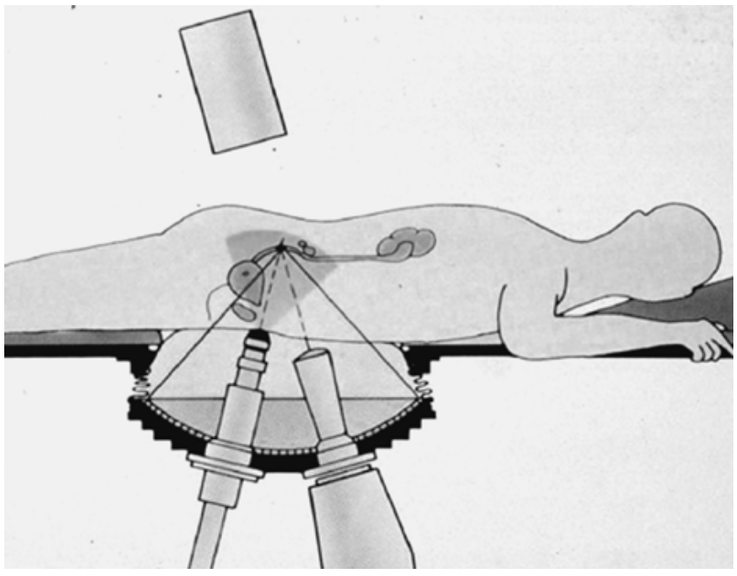

FIGURE 9.6. Illustration of dual imaging capabilities (fluoroscopy and ultrasonography) in newer-generation lithotripters.

Variable Power

All of the third-generation devices discussed here have variable-power shock wave generators. This capability allows the shock wave energy to be tailored to the requirements of a particular stone. The operator can turn down the generator power to provide significantly reduced anesthesia and analgesia requirements with the Dornier, Siemens, and Storz machines, as well as to provide totally anesthesia- and analgesia-free lithotripsy with the Wolf device. Moreover, the shock wave intensity can be increased with all these machines to allow adequate fragmentation of extremely hard or large calculi. However, when used in the high-power mode, these lithotripters will require some form of anesthesia or analgesia.

The ideal shock wave machine that allows anesthesia-free lithotripsy with maximum efficiency has yet to be developed. However, by varying the shock wave energy, a highly efficient shock wave can be administered, with the understanding that anesthesia or analgesia will be required when high shock wave pressures are used. Alternatively, with a

small or fragile stone, the shock wave energy can be significantly decreased to allow the use of minimal analgesia or even anesthesia-free lithotripsy. With the availability of variable-powered lithotripters that use electrohydraulic, electromagnetic, or piezoelectric energy sources, urologists must continue to monitor the amount of energy delivered to limit the incidence of potentially significant renal injury.

Conclusions

SWL has revolutionized the treatment of urinary calculi, and this technology can be considered the treatment of choice for almost any renal calculus smaller than 2 cm and for most nonimpacted ureteral calculi. Under these circumstances, stone-free rates approaching 90% can be expected, although for larger renal stones or impacted ureteral calculi, endoscopic technique should probably be considered first-line therapy.

Whereas the original lithotripter design requires general anesthesia, requires a 1,000-L water bath, and subjects patients to fairly high doses of ionizing radiation, second-generation devices incorporate technical refinements that increase the safety and convenience of this procedure. Although a decrease in shock wave pressure and focal point size has diminished or eliminated anesthesia requirements, this development has been associated with a rise in the re-treatment rate. An efficiency quotient can be used to compare the relative benefits and disadvantages of various second-generation machines. Current lithotripters do not seem to have the ability to rate high on the efficiency quotient scale while still maintaining anesthesia-free capabilities. Third-generation machines, however, with modifications to allow variable shock wave power and dual imaging capabilities, may represent a step toward achieving this goal. As research continues and new devices become adaptable to multiple tasks, we will come closer to making the “ideal lithotripter” a reality.

In the past decade, significant progress has also been made in the realm of basic SWL physics research. The majority of this effort has been devoted to further characterization and better understanding of the dynamics of cavitation bubbles induced by SWL, as well as the role of cavitation in both stone fragmentation and tissue injury. There is now increasing evidence to suggest that appropriate control of cavitation during SWL can lead to significantly improved stone fragmentation or reduced tissue injury, and this topic should be a major focus of SWL research in the near future. In addition, several new competing mechanisms of tissue injury have been proposed, and their validity will be tested by carefully designed experiments both *in vitro* and *in vivo.* For improved SWL therapy, it is also important to understand the stress wave propagation and the corresponding dynamic fatigue process of both stones and tissue during SWL. Knowledge gained from SWL basic research will become indispensable for the improvement of SWL technology and for the design of better clinical treatment protocols for SWL.

PERCUTANEOUS STONE EXTRACTION

Part of "9 - SURGICAL MANAGEMENT OF CALCULUS DISEASE "

Historical Aspects

Rupel and Brown (151) used an operatively established nephrostomy tract to extract an obstructing renal calculus in 1941. Nearly 15 years later, Goodwin and associates (63) reported the use of percutaneous nephrostomy drainage to provide relief of obstruction and infection. However, removal of a renal calculus via a percutaneous tract established specifically for that purpose was not performed until Fernstrom and Johansson (54) used such a technique successfully in three patients 20 years later. Subsequently, safe and effective means to fragment even large calculi were introduced, and percutaneous stone extraction gained acceptance as the procedure of choice for management of most patients with upper tract calculi in the late 1970s and early 1980s. As such, during that era, any patient who would have otherwise required open stone extraction was instead considered a potential candidate for percutaneous management, and the indications for this procedure were essentially identical to the indications to intervene for any stone.

Contemporary Indications and Contraindications

SWL has significantly affected the general indications for percutaneous stone management. These indications are now well defined and are nearly identical to the contraindications to SWL. As such, most of these indications are more relative than absolute. As the twenty-first century begins, the indications for percutaneous management of upper tract calculi include unusual body habitus precluding SWL, obstruction distal to the stone, cystine stones, stones associated with upper tract foreign bodies, and large or otherwise complex stones. Relative indications for percutaneous management rather than SWL may include the presence of an implanted cardiac pacemaker or defibrillator and a proximate calcified aortic or renal artery aneurysm. Another important indication for percutaneous management is failure of SWL. Currently, the only absolute contraindication to percutaneous stone extraction is an irreversible coagulopathy.

In 1987, Leroy and associates (103) at the Mayo Clinic reported a contemporary experience with percutaneous stone management in the era of SWL. During 1 year at their tertiary care center, 854 patients were managed with SWL while 143 with renal or upper ureteral calculi were managed percutaneously. In regard to their current indications and results for percutaneous management, the authors concluded that despite the increased complexity of patients undergoing percutaneous management, excellent results could still be achieved with acceptably low morbidity.

Patient Preparation

As with any intervention, the patient should be apprised of the potential risks and benefits of percutaneous lithotomy as compared with the applicable alternatives. In these often complex cases, this should include the risks of requiring secondary intervention, transfusion of blood products, infection, or rarely, emergent open operative intervention. Although complications can occur, most patients will ultimately benefit from a percutaneous procedure by experiencing a relatively short hospital stay and period of convalescence, especially compared with open operative intervention (17,19,20,139).

Standard preoperative preparation includes assurance of the availability of blood for possible transfusion with a blood type and screen, although formal crossmatching is generally not necessary. Patients with urinary tract infection are treated for approximately 1 week with sensitivity-specific antibiotics on an outpatient basis and are then intravenously “on call” to the procedure. The need for prophylactic antibiotic in the face of a sterile urine is unproven (24), although we generally use a “short course” protocol in this setting that consists of a first-generation cephalosporin given just before percutaneous access and continued for 24 hours following stone extraction.

Technique

The exact technique of percutaneous stone extraction used is specific to the size, location, configuration, and presumed composition of the stone. However, the procedure is always performed with the same four sequential steps: establishment of percutaneous access, dilation of the tract, stone manipulation with fragmentation and extraction, and postextraction drainage and tamponade of the tract. Techniques of percutaneous access are addressed elsewhere in this volume. As such, the percutaneous procedures described herein start with the assumption that access has been established.

The patient is in a prone or slightly oblique position with the ipsilateral side elevated to approximately 20 degrees (Fig. 9.7). For patients with rotational anomalies such as horseshoe kidneys, the contralateral side is elevated instead to allow a more medial rotation of the otherwise anteriorly projected renal pelvis. This allows the posterior infundibula and calices to project more laterally, thus fluoroscopically simulating a more orthotopic position of the kidney. At this point, before percutaneous stone manipulation, a second wire should be placed as a safety wire using a 9- or 10-Fr introducer set. Over the remaining “working” wire, the tract is dilated to 30 Fr using either sequential fascial dilators or, preferably, a 10-Fr, 12-cm balloon over which is back-loaded a 30-Fr working sheath (Fig. 9.8). At this point, then, a 30-Fr working sheath will be in place with a safety wire alongside.

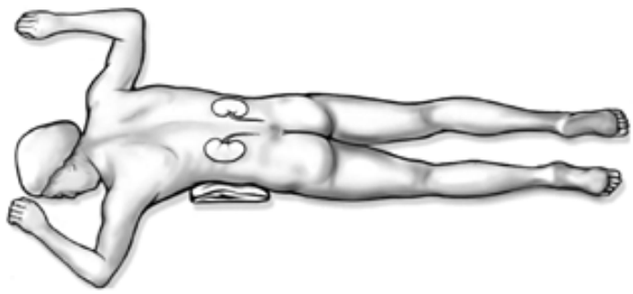

FIGURE 9.7. A prone-oblique position is standard for percutaneous procedures.

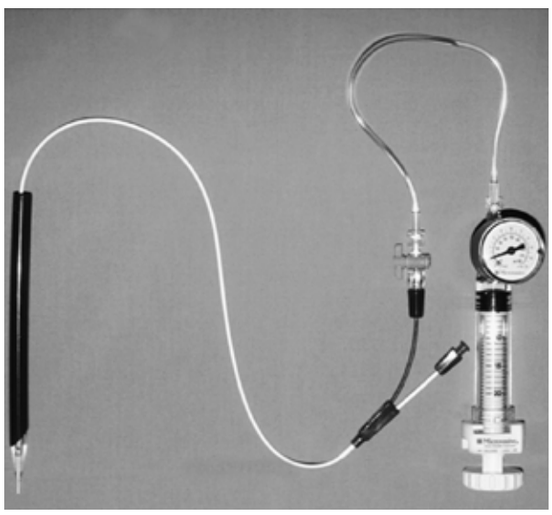

FIGURE 9.8. A 30-Fr working sheath back-loaded over a 10-Fr, 12-cm balloon dilator.

Stone extraction itself can be accomplished with a variety of techniques using direct vision through a nephroscope along with fluoroscopic guidance. At most centers, percutaneous stone extraction is accomplished using ultrasonic lithotripsy guided by direct vision through a rigid nephroscope. This approach was first described by Alken and colleagues (2) in Germany and Marberger and colleagues (115) in Austria, and it was subsequently popularized in the United States by Segura and associates at the Mayo Clinic (159) and Clayman and associates at the University of Minnesota (32).

The nephroscope is readied by attaching the light, suction, and irrigation, and it is then inserted through the working sheath. Once proper positioning in the pyelocalyceal system is ensured, the working wire, which is still within the sheath, is removed, taking care to keep a safety wire in place alongside the sheath. The irrigant of choice for percutaneous nephroscopy is normal saline. This prevents

the possibility of hyponatremia that might result from intravascular absorption if hyposmotic solutions are used (155). At the outset of nephroscopy, vision may be obscured by blood clots, which are easily evacuated by adjusting the irrigation and suction from the nephroscope sheath or by using suction through the US wand while ultrasonic energy is being applied to the clot.

Stones with a smallest diameter less than 9 or 10 mm are small enough to extract intact through an appropriate-size working sheath. Such stones are simply grasped under direct vision using rigid graspers or endoscopic forceps passed via the working port of the nephroscope (Fig. 9.9). However, most stones managed percutaneously are too large to be extracted intact, and intracorporeal lithotripsy will be required. The most commonly used modality for this has been ultrasonic lithotripsy (33). The US wand (Sonotrode) with its own suction attachment is introduced via the working channel of a rigid nephroscope (Fig. 9.10). Under direct vision, the tip of the Sonotrode is pressed against the stone while suction is applied through the hollow Sonotrode, holding the stone in place. This allows the stone pieces to be evacuated via the Sonotrode as fragmentation proceeds. Fragments that are too large to pass through the Sonotrode, but now measure less than 9 mm, are easily extracted using grasping techniques via the nephroscope under direct vision, bringing the pieces out through the working sheath that remains in place. The process of ultrasonic fragmentation with suctioning of fragments or forceps extraction continues until all visible stone has been removed.

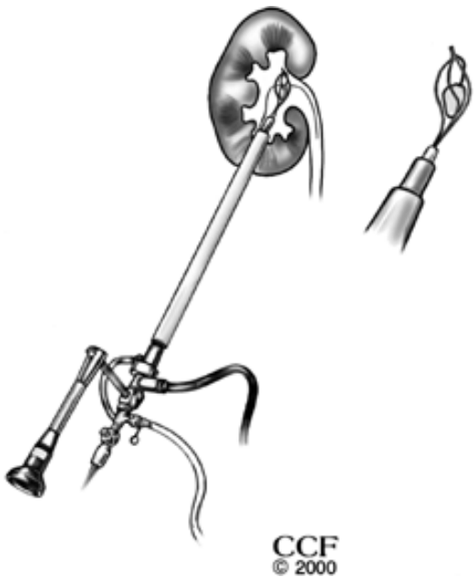

FIGURE 9.9. Small stones—those less than 10 mm—can often be extracted intact using graspers or baskets passed via the working port of the nephroscope under direct vision.

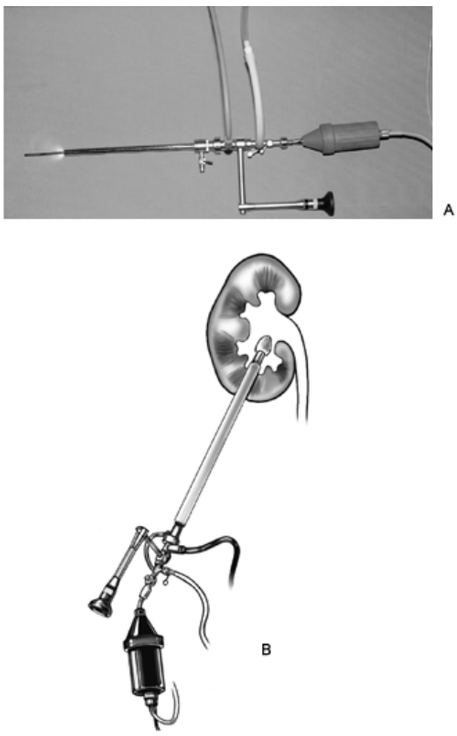

FIGURE 9.10. A: Rigid nephroscope with offset lens allows passage of a rigid Sonotrode. **B:** The nephroscope and ultrasound wand are placed through the working sheath. The ultrasound wand is abutted against the stone and ultrasonic energy applied, with simultaneous suction of fragments through the hollow Sonotrode.

Although ultrasonic lithotripsy can reliably fragment most stones, some stones are physically too hard to fragment with this modality. For the most part, this includes large calcium oxalate monohydrate stones, which often appear extremely dense and homogenous on plain radiographs, and some mixed calcium oxalate–uric acid stones. In such patients, intracorporeal lithotripsy can be performed effectively with several alternative modalities, including electrohydraulic lithotripsy (EHL), which has proven both safe and effective in this setting (116,141). The EHL probe is passed through the working port of the nephroscope under direct vision, and the stone is fragmented into smaller pieces, which are individually grasped and removed, or further fragmented and suctioned out with a US wand. Newer, even more contemporary alternatives to both electrohydraulic lithotripsy and ultrasonic lithotripsy include the holmium

laser (175) and variations of electromechanical lithotripsy such as the Lithoclast (41).

For infundibular or calyceal calculi lying at acute angles to the percutaneous tract, visualization, fragmentation, and extraction often require flexible nephroscopy (101,146). Although flexible nephroscopy can be successful when used during the initial percutaneous procedure, even a moderate amount of bleeding may obscure vision. As such, flexible nephroscopy will often be even more successful when performed via a mature tract. In either case, a working sheath is again in place and the flexible nephroscope is passed through this under direct vision (Fig. 9.11). Fluoroscopic guidance is even more important during flexible nephroscopy than rigid nephroscopy to ensure proper orientation. When the stone is visualized, a grasping forceps, prongs, or basket can be passed through the working port of the flexible scope and the stone engaged and withdrawn intact. Alternatively, larger stones can be fragmented with either the holmium laser or EHL, both of which allow intracorporeal lithotripsy via these flexible instruments.

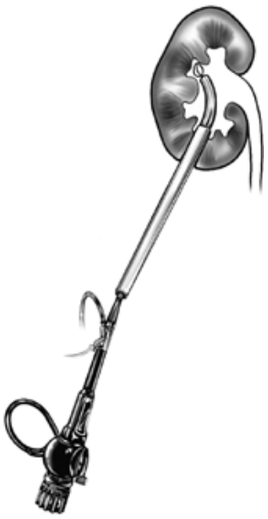

FIGURE 9.11. Flexible nephroscopy performed through a working sheath allows access to stones lying in otherwise inaccessible infundibulocalyces.

When visual and radiographic control ensure that all accessible stone has been extracted, nephrostomy drainage is instituted. Our preference is to pass a 24-Fr nephrostomy tube through the working sheath and position it fluoroscopically with its tip in the renal pelvis, at which time the working sheath is removed. The remaining safety wire is then used to pass a pyeloureteral catheter with its distal tip in the distal one-third of the ureter and the proximal end coiled at skin level (Fig. 9.12). This pyeloureteral catheter is secured in place and acts as a precautionary measure that allows rapid access back to the pyelocalyceal system should that be required before elective removal of the nephrostomy tube.

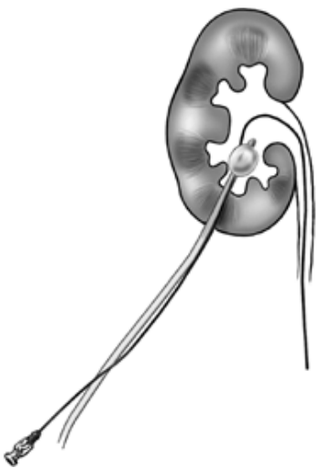

FIGURE 9.12. At the completion of the procedure, a 24-Fr nephrostomy tube is positioned in the renal pelvis, and a 6-Fr pyeloureteral catheter is left in place alongside.

Specific Indications

Body Habitus Precluding Shock Wave Lithotripsy

Patients in whom an unusual body habitus precludes SWL provide some of the most challenging indications for percutaneous stone extraction. This indication occurs most frequently in patients with morbid obesity to the extent that the stone cannot be positioned at the focal point or within the “power path” of an extracorporeally generated shock wave (179). In these patients, both the percutaneous access and tract dilation are more difficult, at least in part because fluoroscopic imaging is compromised. Furthermore, once an adequate tract has been established, stone fragmentation and extraction can be severely hampered by limitations in the length of available instrumentation.

In many cases, the limitations in length of instrumentation can be overcome by allowing the tract to mature for several days following the initial dilation and placement of a large-caliber nephrostomy tube. During this time, the kidney tends to fall back posteriorly toward skin level such that access with standard nephroscopic instrumentation can then be accomplished. Furthermore, a mature tract can be used to pass readily available alternative instruments such as standard flexible cystoscopes or even rigid cystoscopes, which are longer than most available nephroscopes. Working

laparoscopes may also be of value in this setting because of their length (60).

Kerbl and associates (89) have proposed using a flank position for percutaneous management of patients with morbid obesity. A suggested advantage of this position is that it may result in less restriction of pulmonary dependent chest wall movement, which then facilitates both anesthesiologic access and ventilation. Furthermore, the flank position allows the abdominal pannus to fall anteriorly, which may result in a decrease in the amount of tissue to be traversed to access the kidney. Overall, although there are clearly difficulties inherent in percutaneous stone management in morbidly obese patients, there may be little difference in overall success rates and ultimate morbidity compared with nonobese patients, at least when the procedure is performed by those experienced in these techniques (22,129).

Another contraindication to SWL regarding body habitus is occasionally seen in patients with severe scoliosis or body contractures preventing adequate positioning of the stone. In these patients, access may be difficult because of the altered anatomy. In some, the kidney may be located in a relatively anterior position, such that prevention of injury to adjacent solid or hollow viscera becomes an important consideration. Skoog and associates (164) have suggested using CT guidance to obtain access in patients with horseshoe kidneys or other fusion anomalies, and we have also found CT or US guidance valuable in preventing injury to adjacent organs in patient with severe scoliosis or other related anatomic abnormalities (Fig. 9.13).

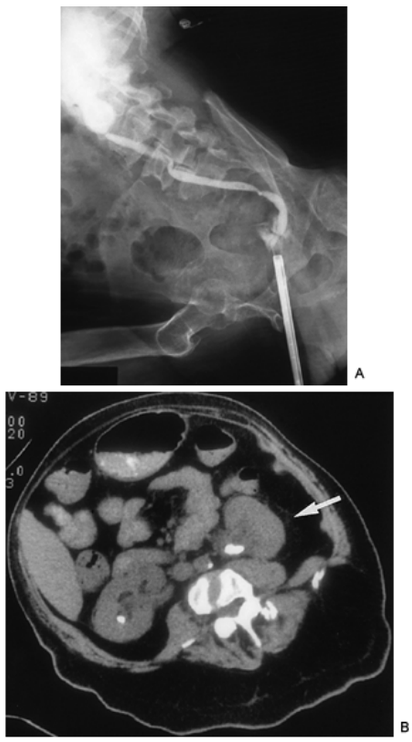

FIGURE 9.13. A: Retrograde study reveals renal pelvic stones that are difficult to see because they overlie the spine in this patient with severe body contractors. **B:** Computed tomography scan without contrast shows bilateral renal pelvic calculi and suggests an appropriate “window” *(arrow)* for safe percutaneous access.

Cystine Stones

Although small cystine stones can at times be managed successfully with SWL, in our experience, most cystinuric patients requiring intervention have larger stones at the time of presentation, and these tend to respond poorly to that modality. Fortunately, however, cystine stones are very amenable to most forms of intracorporeal management, including ultrasonic and holmium laser lithotripsy. At our center, percutaneous ultrasonic nephrolithotomy remains the preferred approach for the majority of cystinuric patients requiring intervention (27), although at a few centers, a ureteroscopic approach is being used with increasing frequency, even for pyelocalyceal cystine stones (64).

Upper Tract Foreign Bodies

Urologic practice has seen an increasingly frequent use of self-retaining stents, nephrostomy tubes, and dilating balloons, and this has led to a corresponding increase in the number of patients requiring management of “retained” upper tract foreign bodies. In many cases, these foreign bodies can be managed with retrograde endoscopy using standard ureteroscopic instrumentation. However, a ureteroscopic approach may be precluded by a prior urinary diversion, making access difficult if not impossible or by the formation of calculi on the foreign body that are too large for ureteroscopic management. When ureteroscopic management has failed or is contraindicated for any of these reasons, a percutaneous approach is indicated (Fig. 9.14) (180). For these patients, the site of the access to the foreign body is chosen as for any stone, and this then depends on its size and location within the pyelocalyceal system. Standard nephroscopic instrumentation, including forceps, graspers,

or baskets, may be used in conjunction with any form of currently available intracorporeal lithotripsy.

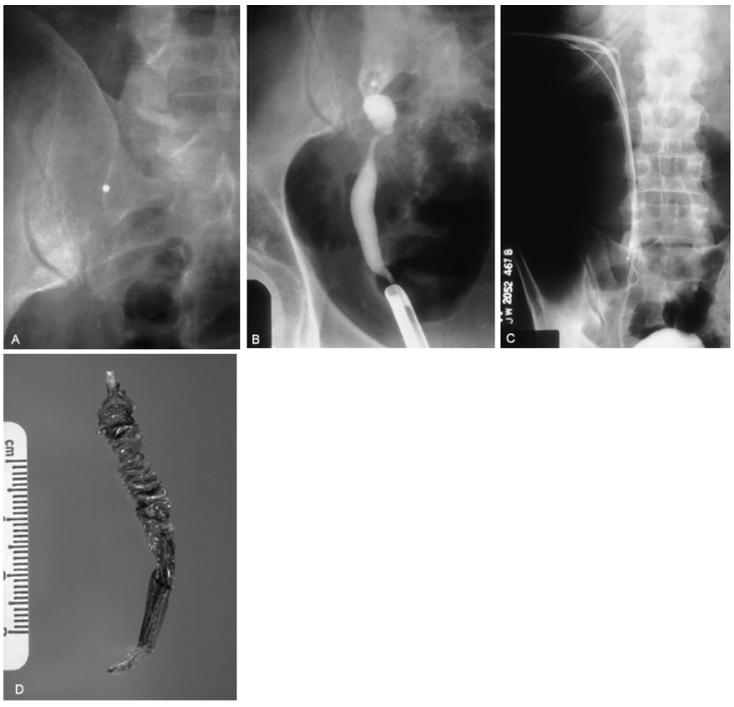

FIGURE 9.14. A: Plain radiograph reveals a metallic foreign body over the iliac bone. This represents the tip of a balloon catheter that became dislodged during an attempted balloon dilation for a ureteral stricture. **B:** Retrograde study confirms ureteral stricture below the level of the foreign body, which precludes its removal via retrograde ureteroscopic access. **C:** Antegrade approach using flexible instrumentation. **D:** The foreign body was extracted intact via an antegrade approach. The ureteral stricture was subsequently managed in an antegrade endourologic fashion.

Distal Obstruction

Successful SWL requires spontaneous passage of the resulting stone fragments. As such, obstruction distal to the targeted stone is a contraindication to SWL as primary treatment. For most affected patients, the distal obstruction will relate to the ureter or ureteropelvic junction (UPJ), although the same principle applies to stones in calyceal diverticula or those in calices associated with true infundibular stenosis. In these patients, percutaneous management is ideal because it provides an opportunity both to remove the stone and provide permanent relief of obstruction as described herein.

Calyceal Diverticular Calculi

Stones in calyceal diverticula are often amenable to a percutaneous approach (11,13,85,162). Ideally, the access should involve direct puncture of the diverticulum containing the stone (Fig. 9.15). Working and safety wires can either be coiled within the diverticulum or occasionally, under fluoroscopic control, passed through the diverticular neck, into the main pyelocalyceal system, and down the ureter. The tract is dilated and a working sheath placed. Nephroscopic

stone removal proceeds in a standard fashion following which the diverticular neck is often better visualized. If a wire has not already been passed across the neck, it can often be done at this time and the diverticular neck subsequently dilated. When the neck has been managed with dilation, a nephrostomy tube is left across it into the main pyelocalyceal system for several days. An adjunct to help identify the diverticular neck in these patients is cystoscopic placement of an open-end ureteral catheter up to the renal pelvis at the outset of the procedure. During nephroscopic visualization of the calyceal diverticulum, dilute methylene blue can be injected in a retrograde fashion through the ureteral catheter, and this often allows ready identification of the diverticular neck.

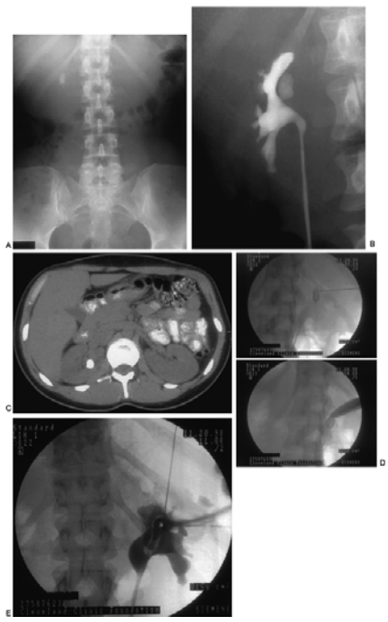

FIGURE 9.15. A: Plain radiograph reveals a 1.5-by-1-cm calcific density in the area of the right kidney. **B:** Retrograde study reveals this to be a stone in a calyceal diverticulum that does not fill with contrast. **C:** Computed tomography scan without contrast reveals a somewhat posteromedial location of the diverticulum, which as such can be managed percutaneously. **D:** Fluoroscopic control of direct percutaneous access to the diverticulum and dilation of the tract. **E:** Diverticular neck has been dilated and a 24-Fr nephrostomy tube left across it with its tip in the renal pelvis.

An alternative to dilation of the diverticular neck, especially when it cannot be visualized directly or intubated fluoroscopically, is simple fulguration (122). A nephrostomy tube is left in place in the diverticulum, but not across the neck. This acts to "marsupialize" the diverticulum, which does not have secretory urothelium.

Infundibular Stenosis

Stones located in calices drained by long, narrow infundibula or those in calices associated with true infundibular stenosis often require percutaneous management, and the best approach is again a direct one to the involved calyx (Fig. 9.16). In a situation analogous to stones in calyceal diverticula, subsequent access through the involved infundibulum at times cannot be obtained until the stone is extracted. Therefore the working and safety wires may be coiled in the involved calyx and then passed under direct vision once the nephroscope has been introduced.

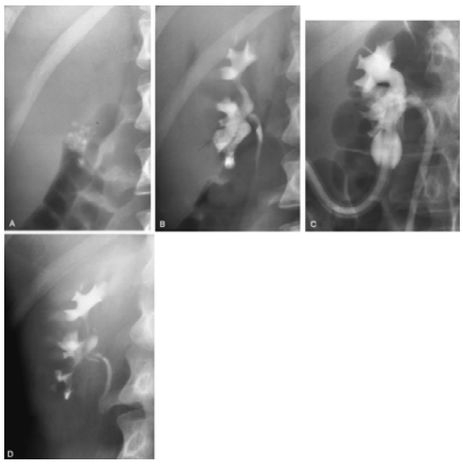

FIGURE 9.16. A: Plain radiograph reveals multiple stones in the lower pole of the right kidney following failed shock wave lithotripsy performed 2 years earlier. **B:** Intravenous pyelography reveals dilation of the involved lower infundibulocalyceal system as a result of localized infundibular stenosis. **C:** Direct access to the involved infundibulum allows direct stone removal. The infundibulum was then dilated percutaneously and a nephrostomy tube left across the infundibulum into the renal pelvis. **D:** Follow-up urogram reveals complete resolution of the localized hydrocalices following percutaneous dilation of the infundibular stenosis.

In contrast to management of calyceal diverticular necks, a stenotic infundibulum should always be dilated rather than fulgurated because the calyx contains secretory urothelium. The infundibulum can be dilated using sequential fascial dilators or a balloon catheter under direct vision, fluoroscopic control, or both. Following stone extraction and dilation of the infundibulum, a large-caliber nephrostomy tube is left indwelling across the infundibulum into the renal pelvis.

Ureteropelvic Junction Obstruction

The association of upper tract stones with ureteropelvic junction obstruction provides an ideal setting for percutaneous management because this allows simultaneous extraction of the stones and relief of obstruction (126). Percutaneous management of the stones is performed in a standard manner with the caveat that for this procedure, percutaneous access is best accomplished via a more superolateral calyx or infundibulum that will allow direct endoscopic access to the ureteropelvic junction with rigid instrumentation (Fig. 9.17). However, stone extraction should precede the actual endopyelotomy incision to prevent extravasation

of irrigant or stone particles during stone fragmentation and removal. At completion of the stone removal and endopyelotomy, a relatively large-caliber stent is left indwelling for approximately 4 weeks.

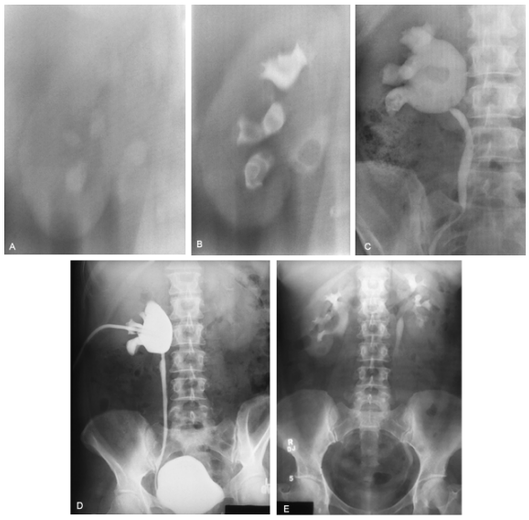

FIGURE 9.17. A: Opaque radiodensities overlying the right renal outline. **B:** Following intravenous contrast injection, dilated calices are visualized with the stones appearing as relatively radiolucent filling defects. **C:** Retrograde study confirms the stones to be associated with primary ureteropelvic junction obstruction. **D:** Percutaneous management of the stones has been performed via superolateral access, which allows direct visualization of the ureteropelvic junction for simultaneous percutaneous endopyelotomy. This follow-up nephrostogram shows resolution of the stones and patency of the endopyelotomy stent such that the nephrostomy tube is removed at this time. **E:** Follow-up intravenous pyelogram performed 1 month after stent removal confirms resolution of the stones and the obstruction.

Transplanted and Pelvic Kidneys

Stones in renal allografts or autografts require several management considerations, including the facts that they are generally solitary kidneys and that retrograde access to the ureter may be impossible following the requisite ureteral reimplantation. Relatively small stones (less than 1 cm) may often be treated with SWL, but consideration should be given to percutaneous management for even moderate-size stones. This is because of the inherent difficulty of obtaining retrograde access in the face of potential obstruction from post-SWL fragments and the need to ensure a stone-free result.

Percutaneous access to transplanted kidneys is generally straightforward because the kidney lies at near skin level. The only real difference from the procedure performed in native kidneys is that the patient is in a supine rather than prone position. When renal function is adequate, access can be obtained with standard fluoroscopic imaging after intravenous contrast injection, although US or CT guidance may otherwise be necessary. Once the tract is established, the procedure proceeds as for native kidneys with standard tract dilation, stone manipulation, and nephrostomy drainage (Fig. 9.18).

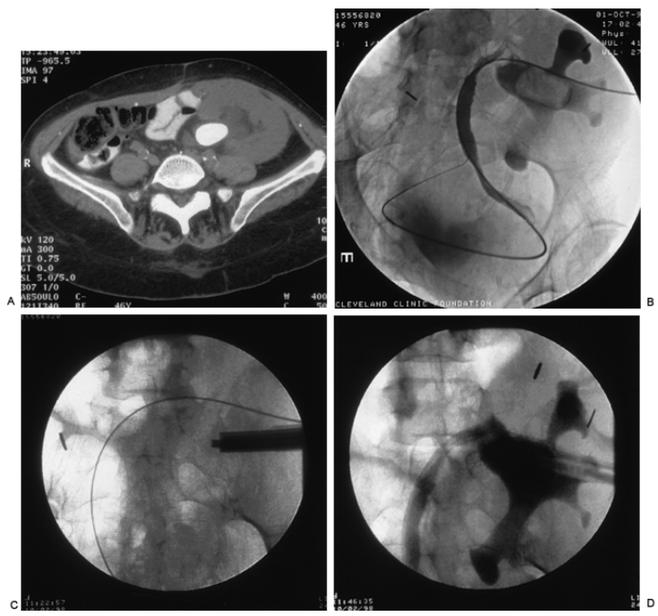

FIGURE 9.18. A: Computed tomography scan without contrast in this combined pancreas-kidney transplant patient reveals a large stone in the transplant renal pelvis on the left side. **B:** Percutaneous access is straightforward, although the patient is in the supine rather than prone position. **C:** As for native kidneys, rigid nephroscopy with ultrasonic fragmentation and suction is generally the preferred form of management. **D:** Follow-up nephrostogram shows resolution of the stone without any obstruction or extravasation.

Management of stones in congenital pelvic kidneys poses different problems. In contrast to transplanted kidneys, congenitally pelvic kidneys are deeper within the pelvis, and peritoneal contents, including small and large intestines, may be interposed. In such cases, percutaneous access may safely be obtained using laparoscopic control.

Proximate Calcified Arterial Aneurysms: Cardiac Pacemakers and Defibrillators

A cardiac pacemaker or implanted defibrillator is no longer an absolute contraindication to SWL (29,36). However, the presence of an implanted cardiac defibrillator may preclude such treatment because the stone is often obscured from vision in at least one plane by the defibrillator. In such cases, percutaneous management often becomes the primary modality of choice for these patients. Likewise, the presence of a proximate calcified aortic or renal artery aneurysm is at times considered a contraindication to SWL, and therefore an indication for percutaneous management (21). When SWL is considered inappropriate in any of these circumstances, percutaneous management is accomplished in a straightforward fashion using standard techniques as described earlier.

Large or Complex Calculi

Some patients with large, extensively branched, or otherwise complex stones may be managed definitively with a percutaneous approach alone (Fig. 9.19) (35,59,165,188). The best candidates are those in whom the stone burden is primarily central rather than peripheral, and our preference is to use percutaneous monotherapy for those patients in whom the stone can be safely accessed via one or two tracts. For patients with more extensively branched and peripherally located stones in whom complete extraction would require more than two or three tracts, percutaneous management can be used as a primary approach for "debulking" before adjunctive SWL as part of a planned, combination "sandwich" approach (Fig. 9.20) (88,156,170). In such cases, the initial percutaneous debulking reduces the stone burden for subsequent SWL. Furthermore, the placement of a large-caliber nephrostomy tube at completion of the primary percutaneous procedure allows proximal diversion with prevention of obstruction and subsequent bacteremia or sepsis from passage of fragments subsequent to SWL. A secondary percutaneous procedure can then be done via the mature tract or tracts within 24 to 48 hours of the shock wave procedure to hasten clearance of stone fragments and allow early nephrostomy tube removal (171).

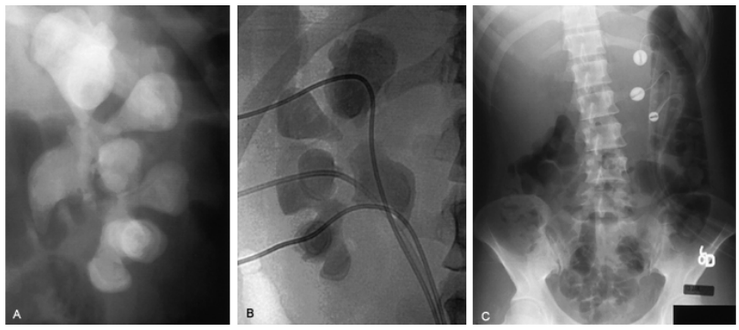

FIGURE 9.19. A: Plain film in this 22-year-old woman with recurrent proteus urinary infection reveals a complete, fully branched staghorn calculus overlying the left kidney. **B:** Reverse fluoroscopic view of percutaneous access via three tracts. **C:** Plain film from follow-up nephrostogram shows complete resolution of the stones.

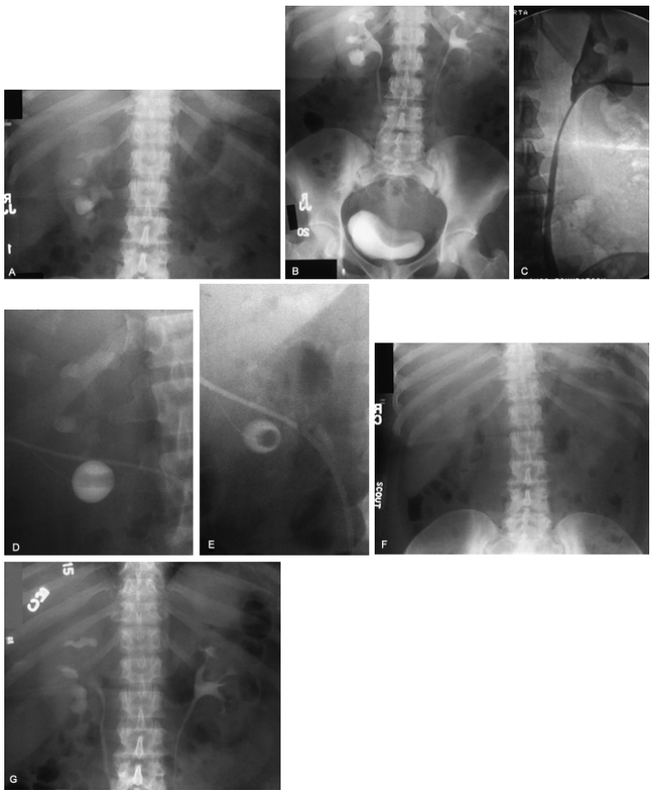

FIGURE 9.20. A: Plain film reveals a complete staghorn calculus filling the collecting system of the right kidney. **B:** Intravenous urography confirms an otherwise well-functioning kidney. Note that the kidney is "high riding" such that percutaneous access to the upper infundibulocalyceal portion of the stone would require access above the eleventh rib with subsequent risk of hydrothorax or pneumothorax. **C:** As an alternative, percutaneous debulking is performed via a lower infundibulocalix allowing access to the pelvic and lower infundibulocalyceal portions of the stone. **D:** Scout film from initial nephrostogram reveals mid and upper infundibulocalyceal fragments remaining that are inaccessible to rigid access via the lower-pole percutaneous tract. These inaccessible residual fragments are treated with shock wave lithotripsy. **E:** Twenty-four hours following shock wave lithotripsy, the previously inaccessible upper infundibulocalyceal fragments have migrated to the renal pelvis, where they are easily managed with second-look nephroscopy. **F:** Scout film from follow-up intravenous pyelogram 6 weeks later reveals no residual stone fragments. **G:** Following contrast injection, the kidney is seen to be well functioning.

Failed Shock Wave Lithotripsy

Percutaneous management can be used as a "salvage" procedure for essentially any patient who has failed SWL. When failure of SWL has led to obstruction resulting from ureteral stone fragments, initial percutaneous drainage allows recovery of function and treatment of any associated infection. When the patient is stable, tract dilation and stone manipulation can proceed in a standard fashion. Following percutaneous management of any pyelocalyceal stones, remaining ureteral fragments can be extracted in an antegrade or retrograde fashion ureteroscopically using flexible or semirigid instrumentation.

Postoperative Care

An estimate of the volume of irrigation and output should be kept during stone extraction. Generally, furosemide 20 mg is given intravenous at termination of the percutaneous procedure. Vital signs are monitored closely, and serial blood counts are obtained as determined by the clinical course. For the first 24 hours postoperatively, intravenous fluids are administered at a rate fast enough to ensure a sustained diuresis. For patients with documented urinary infection associated with the stone disease, sensitivity-specific antibiotics are continued intravenously for at least 48 to 72 hours while the patient is in the hospital and then orally until the first follow-up visit, at which time the need for chronic antibiotic prophylaxis is determined. In patients without a history of infection, prophylactic antibiotic coverage can be discontinued within 48 hours of an uncomplicated percutaneous stone extraction.

One to two days after stone removal, a nephrostogram is obtained and any residual fragments seen on this study

that appear accessible to the percutaneous tract are managed with repeat rigid or flexible nephroscopy, often performed with light intravenous sedation. If there are no residual stones and no obstruction or extravasation is noted on the nephrostogram, the pyeloureteral catheter is removed and the nephrostomy tube clamped for approximately 12 hours. The tube is removed if there has been no flank pain, fever, or increased drainage around the tube during that time. The patient is then discharged home and allowed to return to full prehospitalization activity 7 to 10 days later.

If extravasation or obstruction is noted on the initial nephrostogram, the nephrostomy tube is left to provide drainage and serial studies are obtained. Ureteral obstruction found at this time usually results from blood clots or edema, either of which should resolve spontaneously within 24 to 48 hours. Occasionally, obstruction results from small stone fragments in the ureter that often pass spontaneously, or they may be managed with antegrade or retrograde manipulation.

Complications of Percutaneous Stone Removal

Hemorrhage

Bleeding is one of the most significant complications associated with percutaneous stone removal. At least some bleeding is apparent in all cases, and it can become evident at any time during or after the procedure. Management then depends on timing and severity of the bleeding.

Bleeding during access or tract dilation generally responds to placement of the next size dilator, which effectively tamponades the tract. The more recent use of balloon dilation, rather than sequential fascial dilation, may decrease the incidence of bleeding during this step. If significant bleeding occurs during stone manipulation, the procedure should be temporarily halted and nephrostomy drainage instituted for a couple of days.

Bleeding through the nephrostomy tube is often evident at the completion of even a relatively uncomplicated procedure. Successful management in almost all such cases can be achieved by temporarily plugging the nephrostomy tube and allowing the collecting system to tamponade. Generally, the nephrostomy tube can be unplugged several hours later, at which time effluent will be markedly clearer. Bleeding that occurs during removal of the nephrostomy tube is best managed by immediate reinsertion. When the tract has matured for even 24 hours, fluoroscopic control is generally not required for this. Delayed hemorrhage (bleeding occurring several days following removal of the nephrostomy tube) is best managed conservatively, that is, with close monitoring of vital signs, bed rest, hydration, and transfusion as necessary.

Bleeding at any time that does not respond to conservative measures that include transfusion is best managed by renal angiography and selective or even superselective arterial embolization. Open operative exploration should be reserved only for failure of all other modalities because such surgery generally leads to partial, or more likely total, nephrectomy (90).

Extravasation

Extravasation of irrigating solution, contrast, or urine is perhaps the most frequent complication of percutaneous technology. Obviously, some degree of extravasation of all of these occurs during any percutaneous procedure; fortunately, in a control setting, this is generally a benign and self-limiting problem. Extravasation does imply urothelial disruption, which may be minor or more severe. However, the ability of the collecting system to repair itself in the setting of proximal diversion and drainage is remarkable.

Obviously, the collecting system is purposely perforated to obtain access to the pyelocalyceal system. Unplanned perforation generally occurs at the medial pelvic wall or ureteropelvic junction and may be the result of access, tract dilation, or stone manipulation. Potential adverse effects of this injury can be minimized by maintaining a sterile urine, carefully monitoring irrigation input and output during the procedure, use of a safety wire at all times to ensure access back to the collecting system, and perhaps most important, use of normal saline as the irrigant of choice rather than distilled water. In that way, the potential complicating effects of hyponatremia are essentially obviated; otherwise, large amounts of hypotonic solution may be absorbed.

Essentially all minor degrees of extravasation and even some major ones can be managed with nephrostomy drainage alone as long as the nephrostomy tube is confirmed to be in the collecting system, urine is aggressing, and the patient is clinically stable. In such cases, especially when the injury occurs in the renal pelvis or at the ureteropelvic junction, it is preferable to have a stent across the ureteropelvic junction either as a percutaneous pyeloureteral catheter or as an indwelling ureteral stent in addition to the nephrostomy tube. Again, as long as the patient is stable, serial nephrostograms can be obtained and the nephrostomy tube removed as soon as the extravasation is no longer radiographically evident and distal patency is ensured. When satisfactory drainage cannot be ensured, or when the patient is clinically unstable, open operative exploration and repair is indicated.

Extrarenal Organ Injury

Injury to a hollow or solid organ other than the kidney occurs in 1% to 5% of patients. Intraperitoneal extravasation can occur from breaching the peritoneum, and the

treatment is generally conservative, although paracentesis may be required. On the right side, injury to the liver can occur; this will usually respond to conservative measures because analogous percutaneous intervention is often performed purposely for such procedures as percutaneous biliary drainage. On the left side, splenic injury can occur, and although initial management is again conservative, open operative exploration and repair may be required.

With the recent increasing use of upper pole and supracostal access, hydrothorax, hemothorax, and pneumothorax are becoming more frequent. Management depends on the patient's clinical picture. If the patient is completely stable with no ventilatory or respiratory embarrassment, observation alone may allow spontaneous resolution. Alternatively, simple aspiration on a one-time basis may be adequate, although placement of a chest tube for a few days may be required.

Duodenal or colonic injury may also occur (191). In many cases, even when such injury involves the colon, conservative management may again be successful and consists of withdrawing the nephrostomy tube back to the colon to provide percutaneous colostomy drainage. An internal stent should also be placed into the involved collecting system to separate the colonic and urinary streams. In all cases, conservative management should also include the use of intravenous antibiotics. The patient should initially be placed on nothing-by-mouth status, and this should be followed by a low-residue diet.

Another important consideration in determining whether the patient is a candidate for further conservative management versus open operative repair is whether the injury is intraperitoneal or extraperitoneal. In most cases, this can be determined on the radiographic study used to initially make the diagnosis, whether it is a nephrostogram or a CT scan. Generally, extraperitoneal injuries can be managed using these nonoperative techniques. However, injuries that are intraperitoneal should be given careful consideration for immediate open operative repair.

Results

Percutaneous nephrolithotomy has been documented to be both safe and efficacious. In a community setting, approximately 90% of targeted stones can be removed successfully, and at experienced subspecialty care centers, this rate can approach 100% (9,102,147,160). Furthermore, morbidity for the procedure is acceptably low, even in patients with comorbid medical conditions and complex stones (22,103), and early return to prehospitalization employment and recreational activities can be expected for most patients, especially in comparison with open operative intervention (17,19,20,139). Most important, both functional and morphologic studies have repeatedly shown that percutaneous nephrolithotomy has little if any clinically significant adverse effect on renal function (58,117,119,154,184), even in patients with preexisting renal insufficiency or anatomically solitary kidneys (23,172).

URETEROSCOPY

Part of "9 - SURGICAL MANAGEMENT OF CALCULUS DISEASE "

The advent of ureteroscopy has significantly affected the management of ureteral calculi. Semirigid ureteroscopy can be used in conjunction with pneumatic, laser, and electrohydraulic lithotripsy probes to successfully fragment ureteral calculi (81,112,132), and flexible, actively deflectable ureteropyeloscopes have made access to the upper ureter and intrarenal collecting system a safer, and at times less tedious, procedure (4,6,140). These instruments can be advanced under direct vision or fluoroscopic guidance directly to the level of the stone, which may be fragmented or, when especially small, extracted intact.

Ureteroscopy is a versatile technique that can be used to treat stones throughout the urinary tract (52,161), although a small working channel (2.4 to 4.0 Fr) often limits the size and usefulness of the adjunctive instrumentation that is used for actual stone retrieval. This limitation on available instrumentation has necessitated the use of intracorporeal lithotripsy for the management of most ureteral and intrarenal calculi, and various modalities for intracorporeal stone fragmentation such as the holmium laser, pneumatic lithotripter, and electrohydraulic lithotripter can be used to fragment stones. Although the choice of intracorporeal fragmentation technique is often based on the location and composition of the stone, the experience of the physician and availability of equipment more often dictate this decision (173).

The major advantage of ureteroscopy compared with open operative or percutaneous intervention is decreased morbidity and trauma for the patient because most ureteroscopic cases are performed as an ambulatory surgical procedure with the patient returning to work within 1 to 2 days (78).

Semirigid Ureteroscopy

The technique of rigid transurethral ureteroscopy has undergone significant refinements. Early ureteroscopes were large, fixed-lens systems that, although smaller than the cystoscopes of the day, were still cumbersome to use due to their large (11- to 13-Fr) size, and ureteral dilation was often required for instrument insertion (15). The current generation of semirigid ureteroscopes incorporates fiberoptic light and image bundles into small metal frames (Fig. 9.21) (46,55,82). This miniaturization of the ureteroscope often obviates the need for ureteral dilation, which saves time and allows the visualization of ureteral mucosa unaltered by the trauma of dilation.

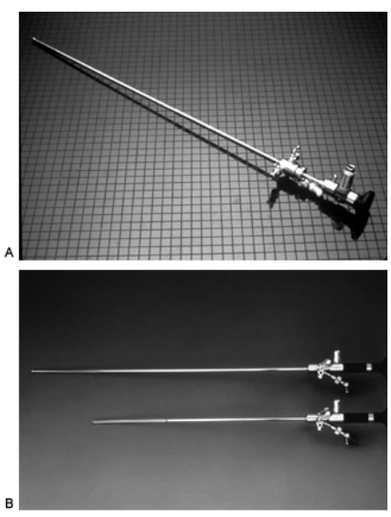

FIGURE 9.21. A: Semirigid ureteroscope. (Karl Storz Endoscopy, Inc., Culver City, California.) **B:** Semirigid ureteroscopes. (Richard Wolf Medical Instruments, Vernon Hills, Illinois.)

Semirigid ureteroscopes using fiberoptic image and light bundles were introduced in the late 1980s. These mini-ureteroscopes

were initially designed for use with laser lithotripsy of ureteral calculi. Initial ureteroscope design used two 2.1-Fr channels for both irrigation and instrument passage. Although these channels were too small to allow use of standard 3-Fr ureteroscopic accessories, they would easily accept laser lithotripsy fibers and guidewires. Since the first mini-ureteroscope was introduced, a number of other semirigid fiberoptic ureteroscopes have been developed that use either one or two working channels. All share the benefits of significantly reduced outer diameter and increased ease of passage (Fig. 9.22).

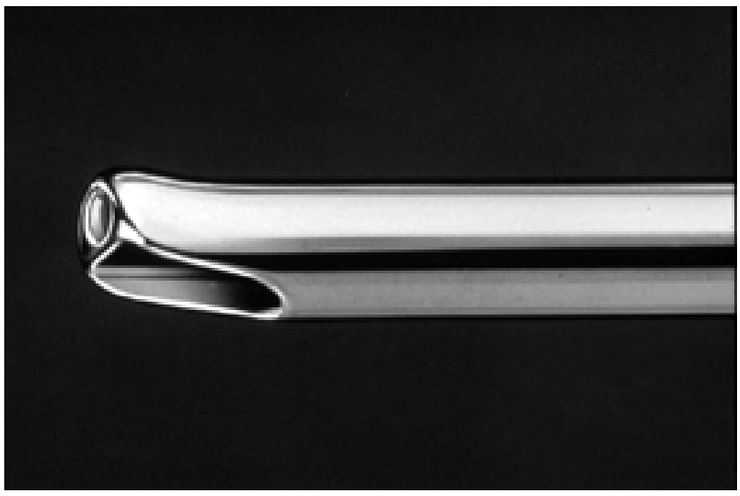

FIGURE 9.22. Distal tip of semirigid ureteroscope. (Richard Wolf Medical Instruments, Vernon Hills, Illinois.)

Indications

Semirigid mini-scopes are ideally suited for both diagnostic and therapeutic maneuvers performed in the lower half of the ureter. The semirigid mini-scopes are somewhat easier to manipulate in the distal portion of the ureter and therefore allow more rapid ureteroscopic procedures. However, the flexible ureterorenoscope is the ideal instrument to access the proximal half of the ureter, as well as lesions within the renal collecting system. Therefore a combination approach with both instruments is thought to allow easy and safe access to the entire upper urinary tract.

Technique

The standard technique involves passage of a 0.038-inch floppy-tipped guidewire under both cystoscopic and fluoroscopic guidance at the outset of the procedure. The semirigid ureteroscope is then passed under direct vision alongside the guidewire to the level of interest. If the ureteral orifice will not accept the ureteroscope, ureteral dilation is performed with a 10-Fr introducing catheter or, if necessary, a standard 15- to 18-Fr ureteral dilating balloon (34,83,86). Instruments used with the semirigid mini-ureteroscopes include stone baskets, grasping forceps, electrohydraulic lithotripsy probes, laser lithotripsy fibers, Bugbee electrodes, biopsy forceps, and brushes.

The most common indication for use of semirigid ureteroscopy is for the management of symptomatic ureteral stones. However, further refinements in the semirigid endoscope and holmium laser technologies now allow management of other forms of ureteral pathology, including ureteral obstruction and urothelial tumors (55,57,65,127,163).

Complications

Complications of semirigid ureteroscopy are usually minor and in most cases can be treated with placement of an indwelling ureteral stent (71). The most common complication developing during ureteroscopy is ureteral perforation, which has been reported in 2% to 6% of contemporary cases (97). The perforation is usually a result of stone fragmentation (EHL or laser lithotripsy) as opposed to passage of the ureteroscope. Occasionally, stone material may migrate through a ureteral perforation. Several studies have suggested that there are no long-term sequelae if a non–infection-related stone has migrated completely through the wall of the ureter (51,98,109,124). However, if stone fragments remain within the wall of the ureter, a ureteral

granuloma with subsequent stricture formation may result (45,66,148).

The most significant complication of ureteroscopic stone retrieval is ureteral avulsion. This complication is usually a result of basketing a stone that is too large to be extracted intact. When in doubt, intracorporeal stone fragmentation should obviate the possibility of avulsion. Although endourologic techniques have been used to manage ureteral avulsion, essentially all of these significant complications will require ureteral reconstruction (113,134,189).

Flexible Deflectable Ureterorenoscopy

Innovations in fiberoptic technology have propelled the further development of flexible ureteropyeloscopes. The widespread use of these new instruments has enabled diagnostic and therapeutic procedures to be performed routinely within the upper ureter and kidney. With the addition of active deflection capabilities, these newer endoscopes are often able to access the entire upper urinary tract, including all of the intrarenal collecting system (7,8,67) (Fig. 9.23), and even lesions or stones located in the lower pole or extremely lateral calyces can now be reached.

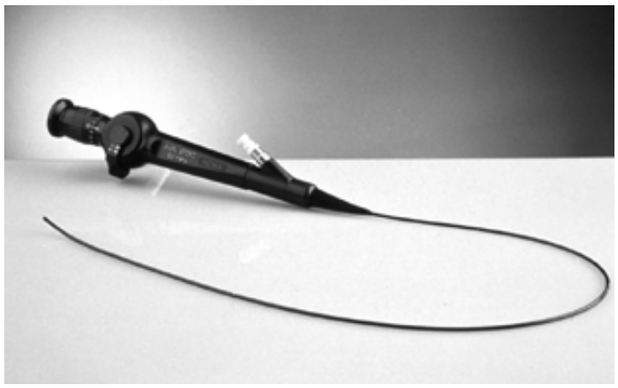

FIGURE 9.23. A 7.5-Fr flexible ureterorenoscope. (Karl Storz Endoscopy, Inc., Culver City, California.)

In addition to the more conventional uses of flexible deflectable ureteropyeloscopes, many special applications of these instruments have and will be used to take advantage of their unique capabilities. However, many of the attributes that make flexible ureteropyeloscopy a useful and effective tool can lead to potential complications, as discussed later in this chapter.

Technique

Perhaps the most difficult aspect of flexible ureteropyeloscopy is introducing the instrument into the distal ureter, because the flexibility of these small instruments, which allows their manipulation throughout the entire upper tract, may also act as an impediment to their passage. Appropriate dilation of the intramural ureter and introduction of the instrument are integral factors for the performance of flexible ureteropyeloscopy (Table 9.5).

Initial retrograde pyelogram
Passage of two 0.038-inch guidewires (safety and working wire)
Dilation of intramural ureter
Passage of flexible ureteroscope over working wire
Passage alongside wire if using access sheath
Use of fluoroscopic monitoring to confirm position of wires and scope

TABLE 9.5. PASSAGE OF FLEXIBLE URETEROSCOPE

Dilation of the Intramural Ureter

The majority of actively deflectable, flexible ureteropyeloscopes measure between 7.5 and 9.0 Fr in diameter, thus requiring some dilation of the intramural ureter. Dilation can be accomplished successfully with metal cone-tipped bougies, graduated flexible dilators, flexible olive-tipped metal dilators passed over a guidewire, or a ureteral dilating balloon. Currently, balloon dilators are the quickest, most effective, and potentially safest method to perform dilation of the intramural ureter (48).

Introduction of the Flexible Ureterorenoscope

Several techniques can be used to pass the flexible ureterorenoscope into the distal ureter. Most of these scopes can be passed directly over a guidewire that has been placed in the collecting system. This procedure is similar to other endourologic or radiologic techniques that use a guidewire for instrument passage. Care must be taken to follow the instrument fluoroscopically, prevent kinking of the wire, and avoid coiling of the flexible scope in the bladder.

Our current procedure for passage of an actively deflectable, flexible ureteropyeloscope entails initial placement of a 0.038-inch floppy-tipped wire up to the renal pelvis, usually using a 6-Fr open-end ureteral catheter to help guide the floppy guidewire into the ureteral meatus. Intermittent fluoroscopic monitoring during the entire case is an integral part of the procedure that allows confirmation of ureteroscopic position at any time. After the ureteral catheter has been removed, a second guidewire, or safety guidewire, is passed alongside the original (working) guidewire. Fluoroscopy should again be used to confirm that both wires are coiled within the renal pelvis.

If necessary, a 10-Fr introducing catheter or a 5-mm balloon dilator is passed over the working guidewire. Again, fluoroscopic visualization combined with direct view through the cystoscope will confirm inflation of the balloon with adequate dilation of the intramural ureter.

After removal of the balloon dilator, the flexible ureterorenoscope is passed directly over the working guidewire. Using both direct vision through the ureteropyeloscope

and fluoroscopic monitoring, the flexible ureteropyeloscope is passed up to the area of interest either in the ureter or renal collecting system. Once the area of interest has been reached, the working guidewire can be removed and the working port used either for irrigation or passage of adjunctive diagnostic or therapeutic instruments. The safety guidewire remains coiled within the renal pelvis at all times.

Flexible guide tubes made of Teflon or similar materials are also available to assist in passage of flexible ureteropyeloscopes. These guide tubes can be easily placed over a flexible dilator similar to the placement of a nephroscopy sheath during percutaneous endoscopic procedures (3,166). Early versions of these flexible guide tubes were limited by kinking in the bulbar urethra. However, newer ureteral access sheaths may further facilitate passage of the flexible ureteropyeloscope (Fig. 9.24) (94).

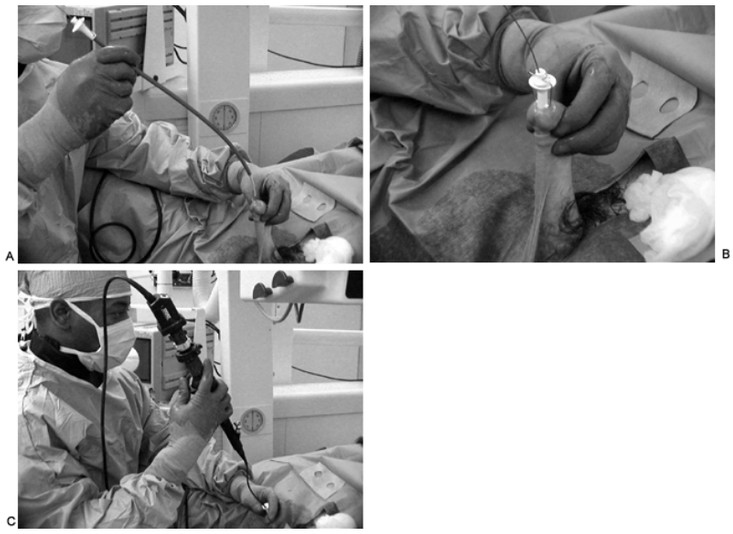

FIGURE 9.24. A: Ureteral access sheath passed over safety guidewire. (Applied Medical Resources, Laguna Hills, California.) **B:** Ureteral access sheath in place. **C:** Flexible ureteroscope passed alongside guidewire within access sheath.

Whatever method is used, it is strongly recommended that fluoroscopy and a safety guidewire be used in every case. These two modalities will allow continuous monitoring of the procedure and provide access to the renal pelvis should a problem occur during passage of the telescope. As long as safety guidewire access is maintained, a ureteral stent can usually be placed in the event of a complication.

Current Applications

The most common indication for flexible ureteropyeloscopy is for removal of symptomatic calculi located throughout the ureter or within the intrarenal collecting system. Under direct vision, various intracorporeal lithotripsy devices, stone baskets, grasping forceps, or snares can be manipulated to fragment or entrap ureteral or renal calculi or fragments under direct vision with fluoroscopic monitoring. During withdrawal, distal progression of the scope is monitored fluoroscopically and with visual documentation of the moving ureteral mucosa. This helps ensure that the ureter is not entrapped as the stone or fragment is being extracted.

Limitations

With the development of flexible deflectable ureteropyeloscopes, ureteral and renal calculi can often be accessed successfully. However, a major limiting factor in using these

smaller endoscopes to manage urinary stones is the small size of the working channel; the currently available flexible deflectable ureteropyeloscopes have working ports ranging from only 3.6 to 4.0 Fr in diameter. Current instrumentation to be used through the working ports of these instruments includes a vast number of baskets, graspers, electrodes, and laser fibers. Unfortunately, not all urologists have access to the myriad number of accessories that are available for use through the flexible deflectable ureteropyeloscope.

The limited size of the working channels of these flexible deflectable ureteropyeloscopes not only limits the instrumentation that can be used but also severely restricts irrigant flow, and this will have a negative impact on visualization during the actual therapeutic procedure. Studies have demonstrated that irrigant flow through a flexible deflectable ureteropyeloscope with a 3.6-Fr working channel is only 32 mL per minute with gravity irrigation, which is only 40% of the total flow that can be achieved through a 13-Fr rigid ureteroscope (186). Moreover, when placing a 3-Fr instrument through the 3.6-Fr working channel, the gravity irrigant flow will be reduced to only 2 mL per minute, which will significantly affect visualization.

Two potential ways to augment irrigant flow, and thereby enhance visualization during flexible ureteropyeloscopic procedures, would be to either limit the size of the instrument used through the working channel or to forcefully inject irrigant fluids. By reducing the instrument size to approximately 1 Fr (about the size of a laser fiber or small electrohydraulic lithotripsy probe), one can increase irrigant flow to 24 mL per minute with gravity irrigation, a 1,200-fold increase (187).

Raising the irrigant pressure, either by using a mechanical pump or forceful hand irrigation, can also significantly increase irrigant flow. However, one should be aware of the potential deleterious effects that can be induced by forceful hand irrigation because studies have demonstrated that this maneuver can raise intrarenal pressures to more than 400 mm Hg, and these pressures have been demonstrated to cause rupture of the intrarenal collecting system in animal studies (157). One must be cognizant of the potential deleterious effects of such high intrarenal pressures generated by forceful hand irrigation, and consider using a “pop-off” valve or, alternatively, a mechanical irrigator that will limit the amount of irrigant pressure (50,187).

Intracorporeal Lithotripsy

The extremely small working channels of the semirigid and flexible endoscopes, which range from 2.4 to 4.0 Fr, has limited the size and usefulness of instruments that can be passed and used for stone removal. For larger stones, baskets or grasping forceps are often inadequate and potentially dangerous to accomplish successful stone extraction. This limitation of available instrumentation has prompted the use of intracorporeal lithotripsy for the management of most larger ureteral and intrarenal calculi.

Even with the availability of SWL for the management of urinary tract stones, intracorporeal lithotripsy still provides significant advantages in select cases. Because fragmentation is performed under direct vision, the stone can be entirely removed and there is no need to wait for fragments to pass, as with SWL (Table 9.6). Although the choice of intracorporeal fragmentation is often based on the location and composition of the stone to be treated, the experience of the clinician and availability of equipment often dictate this decision.

Electrohydraulic lithotripsy	Laser lithotripsy
Ultrasonic lithotripsy	Pneumatic lithotripsy

TABLE 9.6. INTRACORPOREAL LITHOTRIPSY MODALITIES

Selection of Modality

A number of modalities can be used for intracorporeal lithotripsy of both urinary and biliary tract calculi. Although there is no “best” device, considerations for choosing a specific technology include efficacy, safety, and cost. Electrohydraulic lithotripsy, using the small EHL probes, offers a combination of low cost and flexible endoscopic delivery. However, if a holmium laser is available, this multipurpose laser offers perhaps the best option. Both ultrasonic and pneumatic lithotripsy offer the advantage of rapid fragmentation, even with very large or hard stones, but use is limited to rigid or semirigid delivery systems.

Modalities

Electrohydraulic Lithotripsy

The principles of electrohydraulic lithotripsy were initially described and developed by a Russian engineer in 1950 (147). This technology had been used extensively for the destruction of bladder stones, and in 1975, reports were published on its use for the fragmentation of ureteral stones (142,143). The EHL unit consists of a probe, a power generator, and a foot pedal. The probe is made up of a central metal core and two layers of insulation with another metal layer between them. Probes are flexible and available in varying sizes. Commercially available EHL units are manufactured with power up to 120 volts. The electrical discharge is transmitted to the probe where a spark is generated at the tip. The intense heat production in the immediate area surrounding the tip of the probe results in a cavitation bubble, which produces a shock wave that radiates spherically in all directions (193). Collapse of the bubble causes a second shock wave. These shock waves,

repeated at a frequency of 50 to 100 per second, result in destruction of the stone.

EHL will effectively fragment all kinds of urinary calculi, including cystine, uric acid, and calcium oxalate monohydrate stones (178). Because the probes are small and flexible, they can be used through flexible endoscopes to fragment stones that are inaccessible for ultrasonic lithotripsy through a rigid instrument. The primary disadvantage of EHL is that in general, the resultant fragments have to be either washed out during intraoperative irrigation, or grasped with forceps or baskets.

The first experience with electrohydraulic lithotripsy in the ureter entailed a 6-Fr EHL probe that was fluoroscopically guided to the obstructing calculus. The most common cause of failure in this early experience was the operator's inability to pass the probe to the level of the stone. Additional early experience with EHL in the ureter described the use of a 9-Fr probe that provided excellent fragmentation of the stone, although 40% of the patients had ureteral extravasation following the procedure. This high complication rate was believed to be mainly attributable to the large probe size. The use of a smaller 5-Fr EHL probe through a rigid ureteroscope was compromised by decreased stone visualization because the probe occupied the majority of the working channel of the rigid ureteroscope (70).

The development of an even smaller 3-Fr EHL probe used through a flexible endoscope was first reported in 1988 (10,42,53). Recently, 1.2- to 1.9-Fr EHL probes have been developed that have been effective in fragmenting ureteral, intrarenal, and biliary tract stones. An additional benefit of these small-caliber probes is that they allow improved visualization through the flexible endoscope because a larger portion of the working channel is available for irrigation (80,133).

Power settings of the EHL unit normally range from 60 to 90 volts, and normal saline irrigation can be used with modern units. Excellent fragmentation of most ureteral calculi is to be expected, and intracorporeal lithotripsy with EHL for both urinary tract and biliary calculi offers a safe, effective, and cost-efficient modality when small-caliber, flexible lithotripsy probes are used.

Ultrasonic Lithotripsy

Ultrasonic energy was first used to fragment kidney stones in 1979. Commercially available units consist of a power generator combined with a US transducer and a probe that form the Sonotrode. A piezoceramic element in the handle of the Sonotrode is stimulated to resonate, and this converts electrical energy into US waves (23,000 to 27,000 Hz), which are transmitted along the hollow metal probe creating a vibrating action at its tip. When the vibrating tip is brought in contact with the surface of a stone, the stone can be disintegrated. The probe must be rigid because sound waves cannot be transmitted without energy loss along flexible probes. The probes come in varying sizes and are passed through the straight working channel of a rigid endoscope with a 30- or 90-degree-offset lens. Suction tubing can be connected to the end of the Sonotrode probe, thus converting the unit into a “vacuum cleaner” for stone fragments (62,84,185). Smaller 2.5-Fr solid US probes are available for use through rigid ureteroscopes (26), and these can be used for rare cases in which fragmentation of large, distal ureteral calculi with EHL or laser lithotripsy has been ineffective. In all cases, normal saline at body temperature should be used as irrigant.

We continue to use US mainly for the fragmentation of large renal calculi during percutaneous nephrolithotripsy procedures. The large, hollow US probes offer the advantage of effective stone fragmentation while allowing simultaneous aspiration of the fragments. This is especially useful when treating renal calculi in which a large volume of stone must be removed. US is now used only rarely via a ureteroscopic approach.

Laser Lithotripsy

The development of the pulsed dye laser for fragmentation of ureteral calculi was initiated in 1986 (47,183). Significant advances in laser fibers and power generation systems have propelled laser lithotripsy to the treatment of choice for fragmentation of most ureteral stones. The pulsed dye laser delivers short, 1-μs energy pulsations at 5 to 10 Hz produced from a coumarin green dye. Instantaneous fluid evaporation causes a plasma at the stone surface, resulting in a highly localized shock wave. The 504-nm wavelength produced by the pulsed dye laser is selectively absorbed by the stone, but not the surrounding ureteral wall. Because the energy is delivered in short pulses, minimal heat is generated, again protecting the ureteral mucosa. Initial experience yielded stone fragmentation rates ranging from 64% to 95% (68,80).

Failures are often related to equipment malfunction (4% to 19%) or to resistant stone composition. As such, the use of EHL had often been necessary as an adjunctive measure with the pulsed dye laser. However, use of the pulsed dye laser in the ureter appears to be safe, because no significant intraoperative or postoperative complications have been noted from the laser energy alone.

The primary advantages of laser fragmentation were initially thought to be its increased safety during stone fragmentation and increased irrigant flow through the flexible endoscope due to the small diameter of the laser probes. However, the smaller electrohydraulic lithotripsy probes have been proven to be just as safe and almost as small in diameter as some laser fibers. The major drawback of pulsed dye laser lithotripsy had been the high purchase price of the laser, as well as the need for relatively expensive ongoing maintenance and regular dye changes.

Recently, new solid-state lasers have been developed (Q-switched yttrium-aluminum-garnet, alexandrite, and holmium lasers) for the fragmentation of ureteral calculi.

These solid-state systems offer better efficacy rates than the pulsed dye lasers and are significantly less expensive to acquire and to maintain (130).

The holmium laser is the newest laser to be introduced for stone fragmentation. The holmium wavelength is not selectively absorbed and works equally well to fragment stones of varying color and composition (153,176,194). Moreover, the holmium laser has the advantage of being a multipurpose laser system. Not only can it be used for stone fragmentation, but it can also be used for its hemostatic and tissue effects, including incision of urinary tract strictures and prostatic resection (99,145). One potential limitation of the holmium device is its "drilling action" on hard stones. This can often be particularly time consuming when using the smaller holmium fibers (100,181). Moreover, the tissue effects demand a greater degree of caution because injury to the urothelium or damage to the guidewire or endoscope can occur during stone fragmentation.

Our own experience with the holmium laser shows it to be ideal for use through all kinds of flexible endoscopes, and we now use it almost exclusively as our fragmentation modality of choice with both semirigid and flexible ureteroscopes.

Pneumatic Lithotripsy

Another new technique developed for the fragmentation of ureteral, renal, and bladder calculi is pneumatic lithotripsy. The first pneumatic device, the Lithoclast, consists of a pneumatically driven piston that fragments stones by direct contact (Fig. 9.25) (43,74). A major advantage of this device is its efficiency in breaking up calculi of all composition. Pneumatic lithotripters use a semirigid probe and therefore can only be passed through instrumentation with a straight working channel (Fig. 9.26). At present, the smallest pneumatic probe is 0.8 mm, which can be used with the small semirigid ureteroscopes.

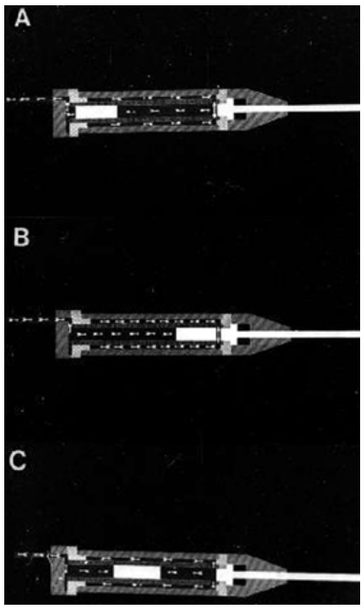

FIGURE 9.25. A–C: Schematic of projectile within handle of pneumatic lithotripsy probe.

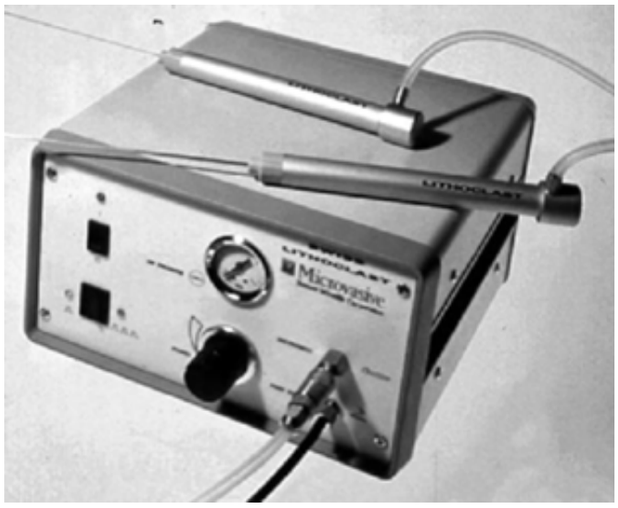

FIGURE 9.26. Pneumatic lithotripter. (Lithoclast, Microvasive Urology, Natick, Massachusetts.)

A number of basic science and clinical studies have demonstrated the safety and efficacy of the pneumatic device (44,72). In a randomized, prospective trial, Hofbauer and colleagues (75) compared the fragmentation of distal ureteral calculi with both EHL and pneumatic lithotripsy. Although the fragmentation rates for both devices were similar (85% fragmentation for EHL and 90% fragmentation for pneumatic lithotripsy), ureteral perforation was noted in only 2.6% of the patients undergoing pneumatic lithotripsy, and there was a 17% incidence of perforation in the EHL group. In a clinical experience using pneumatic lithotripsy, successful fragmentation of stones of varying composition located in the kidney, ureter, and bladder was achieved, although ureteral stone migration was a problem in a limited number of patients who had significantly dilated proximal ureters (178).

Two recent innovations have expanded the use of pneumatic lithotripsy for the intracorporeal fragmentation of ureteral calculi. A suction device (Lithovac) has been developed

to aid in removal of stone fragments during pneumatic lithotripsy (Fig. 9.27) and limit the proximal migration of ureteral calculi (39,73). In addition, flexible pneumatic probes are under development that will allow the use of pneumatic lithotripsy with flexible ureteroscopes (108,174,195).

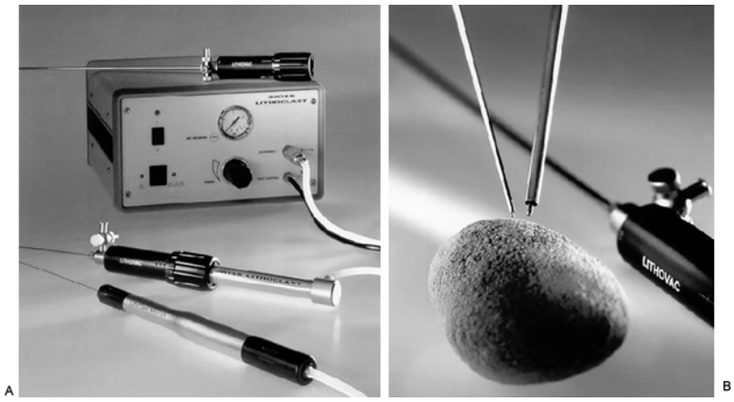

FIGURE 9.27. A: Lithovac suction device with Lithoclast. (Microvasive Urology, Natick, Massachusetts.) **B:** Close-up view of pneumatic probe within 5-Fr Lithovac and 9-Fr Lithovac. (Microvasive Urology, Natick, Massachusetts.)

Ureteroscopic Management of Renal Calculi

Most renal calculi are currently treated with SWL. However, certain predictors of inadequate fragmentation or clearance of residual fragments preclude successful treatment with this modality. The factors that may predict a poor outcome of SWL for management of renal calculi include large stone size (greater than 1.5 cm), “hard” stone composition (calcium oxalate monohydrate or cystine), distal ureteral obstruction, and “adverse” intrarenal anatomy.

Limitations of Shock Wave Lithotripsy

The size and composition of renal calculi are obvious predictors of SWL success or failure, but the impact of renal anatomy combined with stone location is less well defined. Recent studies have suggested that for larger stones located in lower pole calices or calyceal diverticula, or for those associated with significant dilation of the intrarenal collecting system, clearance of fragments will be less predictable. For most of these conditions, percutaneous nephrolithotomy is often the best alternative to both access the stone and achieve complete clearance of all fragments. However, certain instances may preclude the use of percutaneous stone removal, and thus favor ureteroscopic management. These factors include the coexistence of ureteral calculi or strictures in addition to the renal calculi, irreversible bleeding diatheses, renal anomalies, or morbid obesity (Fig. 9.28).

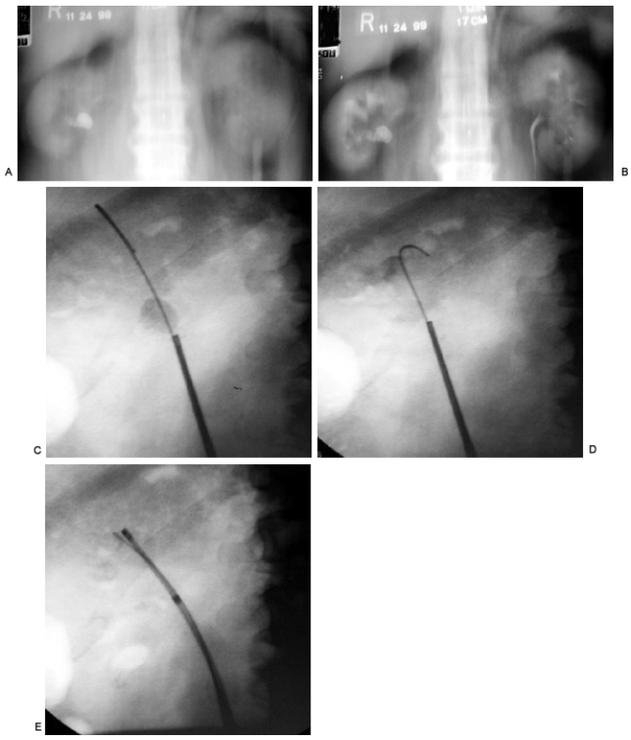

FIGURE 9.28. A: KUB of obese (205-kg) woman with 2-cm stone at ureteropelvic junction. **B:** Intravenous pyelogram showing obstruction of right collecting system. **C:** Ureteropelvic junction stone initially accessed with semirigid ureteroscope and 320-micron holmium laser fiber. **D:** Proximal migration of large stone fragment. **E:** Residual stone easily fragmented with flexible ureterorenoscope and 200-micron holmium laser fiber.

A major factor that now allows for routine ureteroscopic access and management of intrarenal calculi has been the introduction of holmium:yttrium-aluminum-garnet (Ho:YAG) laser lithotripsy. The holmium laser is an efficient and relatively safe device that will fragment stones of any composition. The major advantage of the holmium laser is that these small fibers can be placed through small, flexible ureteropyeloscopes. Both the 200- and 365-micron fibers can be placed through a flexible ureterorenoscope, although the 200-micron fiber is preferred when managing intrarenal calculi because the smaller fiber diameter allows for greater ureteroscopic deflection (100,194). However, the smallest EHL probes are even more flexible, and they may be beneficial in some instances

requiring very acute ureteroscopic flexion for stone visualization.

Our preferred settings for the holmium laser are 0.6 to 0.8 joules at 6 to 8 Hz. Studies have demonstrated that increasing the power to more than 1 joule will rapidly damage the small-caliber 200-micron fiber. Moreover, the relatively low power required to fragment calculi also allows the use of low-power holmium lasers. These low-power units provide 25 to 30 W of power, at a significantly reduced cost as compared with the high-power, 80-W lasers (95).

As mentioned, even though the 200-micron fiber is highly flexible, one can still lose anywhere from 10 to 45 degrees of tip deflection of a 7.5-Fr flexible ureteroscope when a 200-micron laser fiber is placed through the working channel (100,133). Another recent innovation, in the form of nitinol baskets and graspers, now allows for virtually full deflection of the flexible ureteroscopes such that a 3-Fr nitinol basket or grasper can be passed through a deflected endoscope with minimal loss of tip deflection (Fig. 9.29) (76,96).

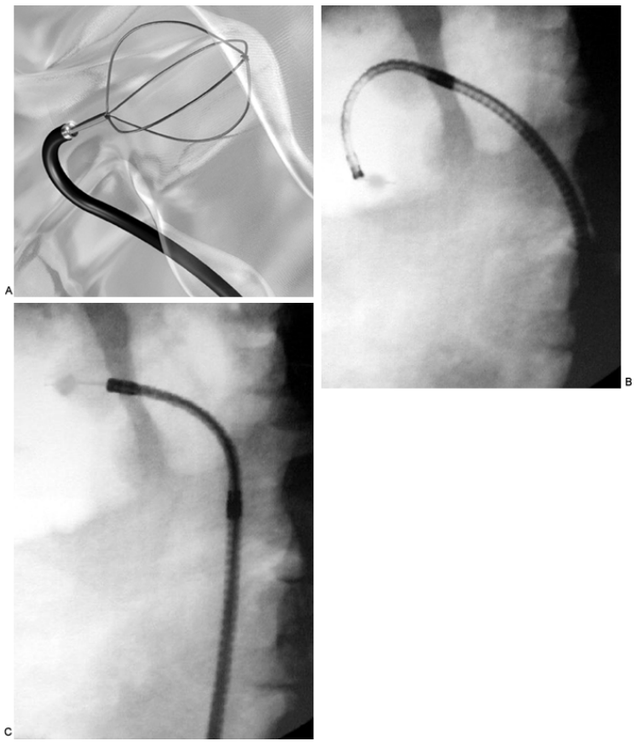

FIGURE 9.29. A: Nitinol stone grasper. (Microvasive Urology, Natick, Massachusetts.) **B:** Nitinol grasper can be passed through a fully flexed flexible ureteroscope to access lower pole renal calculus. **C:** Lower pole calculus repositioned into lateral calyx to allow for laser fragmentation with a 200-micron holmium laser fiber.

One useful technique for stones that are difficult to access is utilization of a nitinol basket or grasper to reposition them. For example, lower pole calyceal stones can be brought back up to a less dependent portion of the collecting system, such as the renal pelvis or an upper pole calyx, and this then allows for easier fragmentation with a holmium fiber.

OPEN OPERATIVE INTERVENTION

Part of "9 - SURGICAL MANAGEMENT OF CALCULUS DISEASE "

Contemporary Indications

Whereas the indications to intervene for stones have not changed significantly with the advent of new technology, the indications for open operative intervention have narrowed considerably (128). Currently, these indications include an associated anatomic abnormality that would best be managed with open operative intervention at the time of stone extirpation, a failure of or a contraindication to both SWL and percutaneous management, or in the urologist's judgement, a stone so large and complex that a single open operative procedure would more likely render the patient stone free, with less risk, than would the option of a complicated percutaneous procedure with or without adjunctive SWL.

The type of open operative intervention planned takes into consideration several factors, the most important of which are stone size, configuration, and location relative to the pyelocalyceal system. The approaches to be discussed in this section include standard and extended pyelolithotomy, simple nephrolithotomy, coagulum pyelolithotomy, calyceal diverticulolithotomy, anatrophic nephrolithotomy, partial nephrectomy, and nephrectomy.

Specific Techniques

Pyelolithotomy

A pyelolithotomy had been perhaps the most commonly performed open operative procedure for patients with renal calculi, but this was supplanted almost 20 years ago by the advent of percutaneous and shock wave technology. Currently, the only indications for this procedure are a failure of or contraindication to both SWL and percutaneous nephrolithotomy or the presence of an associated abnormality such as ureteropelvic junction obstruction, which could then be managed simultaneously. However, even in that setting, open pyelolithotomy is performed less often today because percutaneous stone management can be combined with percutaneous endopyelotomy.

Czerny (37) is credited with performing the first removal of a stone via an incision in the renal pelvis in 1880. However, that approach remained controversial because most surgeons of the time favored nephrolithotomy. In 1913, Lower (111), at The

Cleveland Clinic, popularized a vertical pyelolithotomy, which remained the preferred approach to uncomplicated renal pelvic calculi for many years. In 1965, Gil-Vernet (61) advocated a transverse rather than a vertical pyelolithotomy based on his studies of the functional anatomy of the renal pelvic musculature.

Standard Pyelolithotomy

Today, almost any patient whose stone could be managed via a pyelotomy incision can and should be managed with either percutaneous or shock wave technology such that the role of pyelolithotomy is now extremely limited. Currently, then, the indications for a standard pyelolithotomy, within the context of the limited indications for open operative intervention, include stones limited to the renal pelvis with minimal or no branching (Fig. 9.30). The procedure is performed through a standard flank incision, generally with twelfth-rib resection, or through a dorsal lumbotomy. Either of these approaches allows rapid access to the renal pelvis posteriorly.

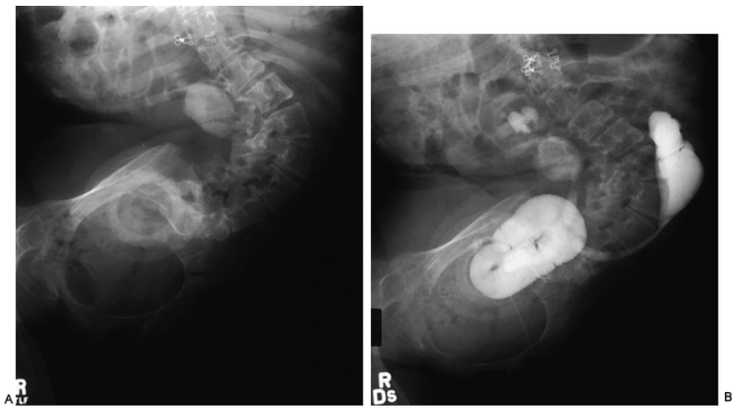

FIGURE 9.30. A: Plain film in this myelodysplasia patient status post–urinary diversion reveals a large calcification filling the right upper quadrant. **B:** Loopogram reveals free reflux into a nonfunctioning shell of a left kidney and hydronephrosis on the right associated with the large renal pelvic calculus. Percutaneous access to this stone is hindered by the severe scoliosis and would require supracostal puncture with risk of injury to the pleura or liver on the right. Open pyelolithotomy was indicated with consideration for simultaneous left nephrectomy.

The retroperitoneum is entered and Gerota's fascia opened posteriorly at the lower pole of the kidney. The proximal ureter is identified and surrounded with a vessel loop. This aids dissection and prevents distal stone migration during the subsequent procedure. The dissection is then carried proximally along the posterior aspect of the ureter, up toward the renal pelvis. Once the pelvis is exposed posteriorly, stay sutures are placed in preparation for the transverse pyelotomy. This incision is made well away from the ureteropelvic junction itself, and it is carried as far laterally on the pelvis as is necessary to extract the stone under direct vision (Fig. 9.31A). The stone is removed with a Randall's forceps and the vessel loop on the ureter is relaxed (Fig. 9.31B). An 8-Fr red rubber catheter is then passed antegrade down the ureter to the bladder to ensure

ureteral patency. The renal pelvis is thoroughly irrigated and the catheter removed. The pyelotomy is then closed in a single layer using running or interrupted 4-0 absorbable suture placed full thickness through the posterior renal pelvic wall such that peripelvic adventitia, musculature, and mucosa are all encompassed with each bite (Fig. 9.31C). In all cases, external drainage is provided with a Penrose or closed-suction drain placed near but not on the pyelotomy incision.

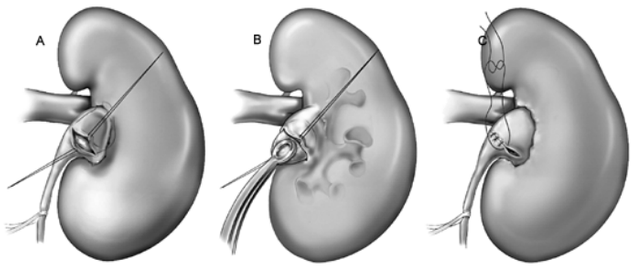

FIGURE 9.31. A: The pyelotomy incision is performed horizontally on the renal pelvis between stay sutures, taking care to avoid the ureteropelvic junction. **B:** The stone is extracted under direct vision with standard stone forceps. **C:** The pyelotomy incision is closed with full-thickness, interrupted, absorbable suture.

In uncomplicated cases, there is no need for an internal stent, although this should be considered in the presence of recent infection or if there is any question of residual calculi. Nephrostomy tubes are indicated only in the most complicated cases, such as in the setting of previous surgery with intense inflammation and scarring or if there is a question of ureteral patency or residual calculi. This allows excellent access for antegrade radiographic studies in the postoperative period.

Extended Pyelolithotomy

In 1891, Disse described fibrous extensions from the renal capsule that extended to the posterior renal pelvis and normally acted to separate the renal sinus from the retroperitoneal space. An extended pyelolithotomy, as advocated by Gil-Vernet in 1965 (61), takes advantage of dissection into the renal sinus to gain access to the intrarenal collecting system. This approach gained favor in Europe even for management of some extensive staghorn calculi. In general, though, its use had been limited to management of relatively large renal pelvic stones with or without extension into one or more infundibula, but without dumbbell-shaped calyceal extensions or associated infundibular stenosis (Fig. 9.32). However, these indications are now considered only within the narrower context of current indications for open operative intervention.

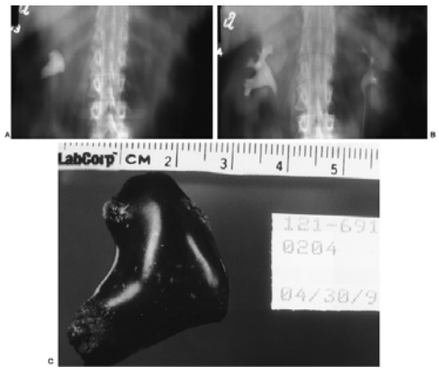

FIGURE 9.32. Intravenous urogram. **A:** Scout film. **B:** Following contrast injection, a large renal pelvic calculus is revealed extending from the upper to the lower infundibula. The patient had failed percutaneous management elsewhere and was adamant in her request for open operative intervention. Anatomically, this patient is a good candidate for an extended pyelolithotomy. **C:** Stone removed from this patient with an extended pyelolithotomy incision.

The posterior aspect of the renal pelvis is exposed as described for a standard pyelolithotomy. Dissection is then carried into the renal sinus by incising the fibrous tissue between the posterior hilar lip of renal parenchyma and the renal pelvis itself, and the plane between the renal pelvis and peripelvic fat is entered. Further exposure of the intrarenal collecting system can then be accomplished using vein retractors, or specifically designed Gil-Vernet renal sinus retractors, to elevate the posterior parenchymal lip. Dissection into the sinus then continues using a moist gauze or Kittner sponge (Fig. 9.33A). As described by Wulfsohn (192), temporary occlusion of the renal artery done in association with local hypothermia can serve to soften the renal parenchyma and allow further exposure of the intrarenal collecting system, which may be necessary in select cases.

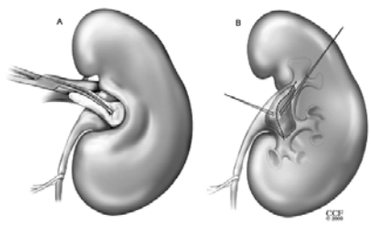

FIGURE 9.33. A: A moist gauze or sponge is used to develop the avascular plane posteriorly between the renal pelvis and parenchyma. **B:** An extended pyelolithotomy requires a curvilinear incision that extends from the upper infundibulum across the renal pelvis and into the lower infundibulum.

A curvilinear transverse pyelotomy is then performed between stay sutures, taking care to keep well away from the ureteropelvic junction. The pyelotomy is then extended along both the upper and lower infundibula, thus creating a renal pelvic flap, which affords access to even large calculi with early branch formation (Fig. 9.33B). Any infundibular extensions that remain after extraction of the renal pelvic stone can be removed using Randall's forceps.

For more extensive stones, this approach can be combined with a simple or lower pole nephrotomy. For dumbbell-shaped calyceal extensions near the mid or superior poles that cannot be withdrawn via the infundibulum, a nephrotomy incision is made directly over the stone. This approach is best reserved for those patients in whom the stone is associated with cortical loss and local cortical thinning.

Lower pole infundibulocalyceal extensions of pelvic calculi can be managed by extending the inferior aspect of the pyelotomy incision onto the posterior renal parenchyma itself as a pyeloinfundibulotomy, directly over the involved lower infundibulum (Fig. 9.34). The infundibulonephrotomy incision thus performed is in an avascular plane between the junction of the posterior and basilar segments of the kidney.

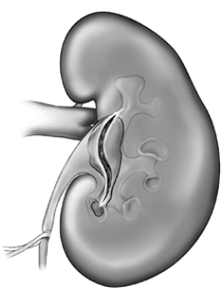

FIGURE 9.34. A pyeloinfundibulonephrotomy incision can be made on the anterior aspect of the kidney through a relatively avascular plane between the junction of the posterior and basilar segments of the kidney. Such an incision can be used to manage renal pelvic calculi extending into the lower infundibulocalyceal system.

As for a simple pyelolithotomy, on removal of all visible and palpable stone material, a catheter is passed antegrade down the ureter and the intrarenal collecting system is thoroughly irrigated. If multiple stones have been present, intraoperative radiography, fluoroscopy, US, or pyeloscopy should be performed to exclude the presence of residual calculi.

The pyelotomy incision is closed as for a standard pyelolithotomy. For cases requiring extensive dissection, placement of an internal stent may be desirable. External drainage is routinely provided.

Coagulum Pyelolithotomy

In 1943, Dees (38) combined human fibrinogen and clotting globulin to form an extractable cast of the upper collecting system, which he used to remove multiple renal calculi. Several authors have since reported their own modifications of the coagulum "recipe" to both simplify the procedure and reduce the risk of complications. At the authors' institution, we have used the technique described by Fischer and associates in 1980 (56). In that protocol, cryoprecipitate is the fibrinogen source and is converted to fibrin using thrombin as the active catalyst. Calcium chloride in the mixture serves to increase the tensile strength of the coagulum by neutralizing the citrate already present in the cryoprecipitate and by acting as a cofactor in the conversion of prothrombin to thrombin. To further obviate the risk of transmission of blood-borne disease, McVary and O'Conor (114), in 1989, reported the use of autologous cryoprecipitate in this setting.

The contemporary indication for a coagulum pyelolithotomy is the presence of multiple stones scattered throughout the collecting system, again in context of the otherwise

limited contemporary indications for open operative intervention. Stones in calices drained by relatively narrow infundibula cannot be extracted with this method because the dumbbell-shaped calyceal extensions of the coagulum would simply break off as the pelvic portion is removed. However, any residual coagulum left within the collecting system is of no consequence because it will dissolve spontaneously in 24 to 48 hours in response to urokinase normally present in the urine.

Exposure of the renal pelvis is accomplished as described for pyelolithotomy. Again, an occluding vessel loop is placed about the proximal ureter to prevent distal migration of either stone fragments or the coagulum itself. The volume of the pyelocalyceal system is now estimated by puncturing and draining the renal pelvis with a 14-gauge angiocatheter. The pelvis is filled to capacity with a measured amount of saline, and the volume of coagulum prepared is then based on the amount of saline required for gentle distention. The estimated amount of required cryoprecipitate is then drawn up into one large syringe while the requisite volume of thrombin and calcium chloride is combined together in a second syringe. The amount of each constituent required is based on a ratio of 1 mL of cryoprecipitate to 2 units of thrombin and 1 mg of calcium chloride.

At this time, the angiocatheter that had been left in place in the renal pelvis is used to again completely drain the pyelocalyceal system. The thrombin and calcium chloride are then injected into the syringe containing the cryoprecipitate, and the complete mixture is injected into the renal

pelvis within 45 seconds (Fig. 9.35A), after which time clotting will have irreversibly begun. At this point, assuming the measured capacity was correct, there will be complete filling and gentle distention of the renal pelvis. Care should be taken not to overdistend the system because this could result in pyelovenous backflow of the cryoprecipitate, and rarely, a pulmonary embolus can develop in this setting as reported by Pence and colleagues in 1981 (131).

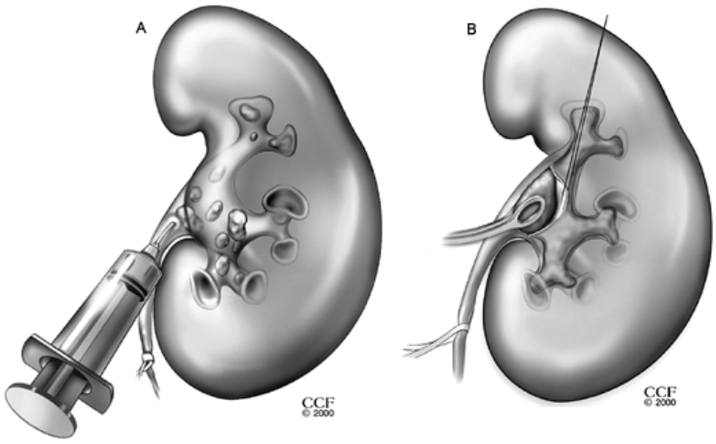

FIGURE 9.35. A: The proximal ureter is secured with a vascular tape as the coagulum, consisting of cryoprecipitate, bovine thrombin, and calcium chloride, is injected into the collecting system. **B:** A pyelotomy incision is made and the coagulum is extracted.

After 5 to 10 minutes, the coagulum should be well established. A standard or extended pyelotomy incision is made and the coagulum extracted (Fig. 9.35B). If the procedure has been performed correctly, the coagulum has formed a cast of the collecting system and multiple stones will be trapped within the substance of the coagulum (Fig. 9.36).

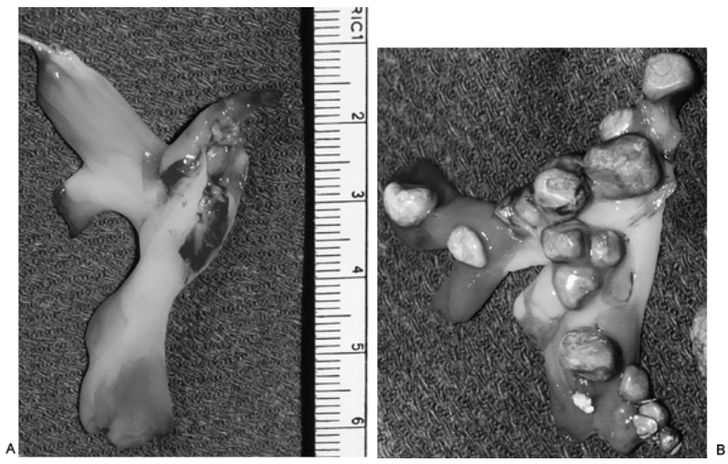

FIGURE 9.36. A: The coagulum has assumed the shape of the pyelocalyceal system. **B:** Multiple stones entrapped within the substance of the coagulum.

As for any procedure involving a patient with multiple stones, intraoperative radiographs, fluoroscopy, US, or pyeloscopy is then performed as necessary to exclude the presence of residual calculi. Because the procedure is always performed in patients with multiple calculi, it is generally prudent to leave an internal stent at this time to prevent migration of any potentially unrecognized residual stones in the early postoperative period. External drainage is routinely provided with a Penrose or closed-suction drain.

Calyceal Diverticulolithotomy

Calyceal diverticula are transitional epithelium-lined cavities in the renal parenchyma. Communication with a calix or infundibulum is implied by definition, although that communication may not be demonstrable at the time the patient is initially examined. Because some calyceal diverticula are associated with localized urinary stasis, they may be a source of stone formation, although as reported by Hsu and Streem (79), metabolic factors also play a role. The indications to intervene for calyceal diverticular stones are the

same as for any upper tract stones, although the indications for open operative intervention are considerably narrower. In highly select patients, SWL can be successful (169), although ureteroscopic and percutaneous techniques are generally considered more definitive (11,13,85,162). When these techniques are contraindicated or have failed, open operative intervention may be considered.

Preoperative planning generally includes a CT scan for three-dimensional radiographic localization (Fig. 9.37). The kidney is exposed via a standard flank incision. Generally, the diverticulum is readily apparent by inspection and palpation, although intraoperative localization can be performed when necessary with intraoperative fluoroscopy or US. In all cases, confirmation that the suspicious area represents the diverticulum can be performed by using a small-gauge needle to aspirate urine from the diverticulum or to "sound" the calculus.

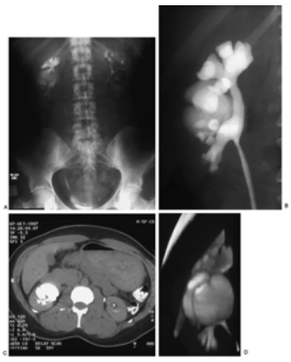

FIGURE 9.37. A: Intravenous urogram in this patient with chronic right flank pain suggests the presence of a large calyceal diverticulum in the central aspect of the kidney. **B:** Retrograde study confirms filling of a central calyceal diverticulum. **C:** Computed tomography reveals the diverticulum to be located anteriorly with thinning of the overlying parenchyma. **D:** Three-dimensional reconstruction confirms the anterior location of the diverticulum and allows better evaluation of the relationship to the collecting system. The anterior location of this diverticulum and the thin overlying parenchyma suggest that the best approach is either open or laparoscopic diverticulolithotomy.

When the diverticulum is associated with thinning of the overlying parenchyma, appropriate management is marsupialization. The thin parenchyma overlying the diverticulum is excised, and the calculi are removed. The diverticular neck can then be identified and is oversewn with absorbable suture or simply fulgurated. The lining of the diverticulum may also be fulgurated either with electrofulguration or an argon beam coagulator. The rim of remaining parenchyma is then oversewn with absorbable suture or simply fulgurated.

Occasionally, identification of the diverticular neck may be difficult. This can be circumvented with placement of a ureteral catheter at the outset of the procedure. Dilute methylene blue can then be injected retrograde via the ureteral catheter, and the diverticular neck is identified as the methylene blue flows into the diverticulum.

In some cases, the diverticulum may be located deep within the renal parenchyma. With the aid of intraoperative US, the area containing the diverticulum can easily be identified. In such cases, however, rather than unroofing, a local wedge resection is more appropriate. In all cases, a Penrose or closed-suction drain is placed near the site of excision, and the wound is irrigated and closed in a standard fashion.

Although open calyceal diverticulolithotomy and diverticulectomy should be a part of the urologic armamentarium, many patients who otherwise would have required open operative intervention because of a failure of or contraindication to less invasive techniques can and should be managed with a laparoscopic approach as described by Ruckle and Segura in 1994 (150).

Anatrophic Nephrolithotomy

Most opaque staghorn calculi are composed of magnesium-ammonium-calcium phosphate and are associated with urinary infection that will always recur as long as the stone is present. In 1994, the American Urological Association (AUA) Nephrolithiasis Clinical Guidelines Panel made recommendations regarding the management of these branched, infection-related stones (158). The AUA Nephrolithiasis Clinical Guidelines Panel stressed that left untreated, these stones are invariably associated with recurrent infection, loss of renal function, and high rates of renal-related morbidity and even death. In reviewing outcome probabilities for management of such stones, the AUA Nephrolithiasis Clinical Guidelines Panel concluded that any newly diagnosed struvite staghorn calculus was an indication for intervention. The AUA Nephrolithiasis Clinical Guidelines Panel further recommended that most such stones could be managed with percutaneous nephrolithotomy or SWL, either alone or in combination. However, open operative intervention was recommended as an appropriate option in cases where the stone was so extensive that an unreasonable number of percutaneous or shock wave procedures would be required to achieve a stone-free result.

In affected patients, the most common relative indication for open operative intervention is the finding of a massively sized, complete, fully branched staghorn calculus with multiple dumbbell-shaped infundibulocalyceal extensions associated with relatively narrow infundibula (Fig. 9.38). Multiple areas of true infundibular stenosis would also be a relative indication for open operative intervention so that this anatomic abnormality could be managed simultaneously. In such cases, the most appropriate open operative approach is generally anatrophic nephrolithotomy as initially described by Boyce and Smith in 1967 (16). With this procedure, the stones are removed through an incision that is least traumatic to overall renal function, that is, an incision through a relatively avascular plane in the kidney. The renal artery will temporarily be occluded during the procedure to provide a bloodless field in which to work, and the kidney must therefore be protected from the resulting ischemic insult. Finally, areas of true, functionally significant infundibular stenosis are addressed such that adequate drainage is provided from all parts of the collecting system.

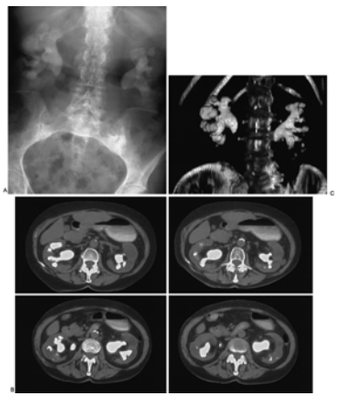

FIGURE 9.38. A: Plain abdominal film in this patient with significant renal insufficiency and proteus urinary infection reveals extensive, fully mature staghorn calculi bilaterally. Anatrophic nephrolithotomy is a reasonable approach compared with the option of multiple percutaneous and shock wave procedures. **B:** Standard computed tomography scan without contrast helps delineate the stone and the thickness of the overlying parenchyma. **C:** More recently, three-dimensional reconstruction has been used for more precise anatomic definition.

Our preference is a flank approach with resection of the eleventh or twelfth rib, with medial extension of the incision to the lateral border of the rectus muscle. The peritoneum is reflected medially, and access to the retroperitoneum is attained. The proximal ureter is surrounded with a vessel loop to prevent distal migration of stone fragments during the subsequent procedure. The kidney is then completely mobilized and the renal pedicle isolated. The renal artery is surrounded with a vessel loop and mannitol, 12.5 g, is given intravenously for protection during the subsequent renal ischemic episode (Fig. 9.39). Further dissection of the renal artery is accomplished until the anterior and posterior divisional branches are identified. The first major branch of the renal artery generally represents the posterior division (Fig. 9.40).

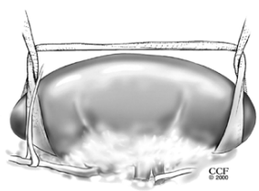

FIGURE 9.39. The kidney is mobilized and the renal artery identified and surrounded with a vessel loop. The kidney may be elevated into the wound using a Jones roll as a sling.

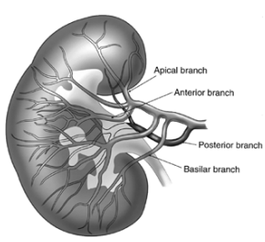

FIGURE 9.40. The first major branch of the renal artery generally represents the posterior division.

As described by Brodell in 1901 (18) and subsequently by Graves in 1954 (69), there is an avascular plane between

the junction of the blood supply to the anterior and posterior segments of the kidney. At the surface of the kidney, this generally lies on the posterior aspect approximately two-thirds of the way from the renal hilum to the true lateral border of the kidney. When desired, this can be further delineated by temporarily placing a vascular clamp on the anterior division of the renal artery (Fig. 9.41). Ten milliliters of methylene blue is then injected intravenously into the systemic circulation. This will stain the posterior renal segment and thus help identify the appropriate line of incision and further dissection into the renal parenchyma. Although delineation of the arterial blood supply in this manner may be useful, it may not be a requisite for a successful nephron-sparing result (125).

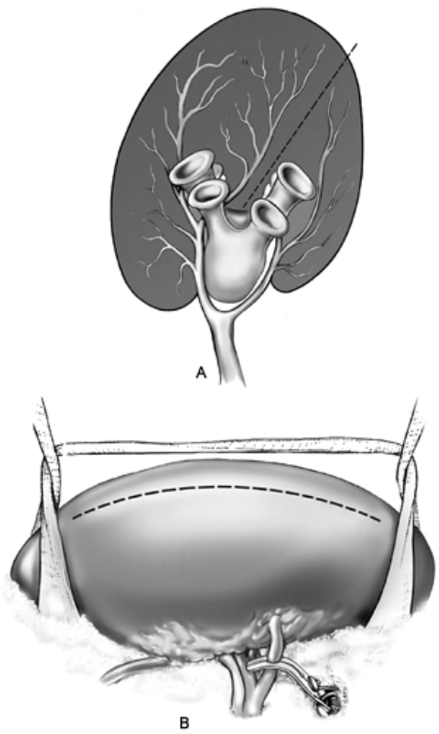

FIGURE 9.41. A: An avascular plane exists between the junction of the blood supply to the anterior and posterior segments of the kidney, and this plane generally provides the correct line of dissection for anatrophic nephrolithotomy. **B:** Temporary occlusion of the posterior branch of the renal artery can help delineate the optimal line of incision in this plane.

A bowel bag is the placed beneath the kidney and wrapped around the pedicle as a reservoir for ice slush. An additional 12.5 g of mannitol is given, and the main renal artery is subsequently occluded with a vascular clamp. At this point, the renal vein may also be occluded to ensure a blood-free surgical field. The kidney is packed with slush with a goal of obtaining a core temperature of 10°C as protection from the subsequent renal ischemic insult.

Once the kidney has reached core temperature, the capsule is incised longitudinally between the anterior and posterior segments, but extended only to the apical and basilar renal segments. The incision through parenchyma continues in a plane along the line of demarcation between the anterior and posterior arterial segments, down toward the renal pelvis. The correct plane generally runs

just anterior to the posterior row of infundibula and calices. If small arterioles or venules are cut and identified during this incision or during the subsequent dissection, these are managed using fine chromic figure-of-eight absorbable suture.

The stone is now identified either by palpation in one of the involved posterior infundibula or calyceals or by direct visualization. Once the initial stone-bearing infundibulocalix is open, a longitudinal infundibulotomy is performed and extended down to the renal pelvis (Fig. 9.42). Similarly, each involved posterior infundibulocalix is subsequently opened longitudinally as far as necessary to extract any stone, and the infundibulotomy is carried down its anterior aspect toward the renal pelvis.

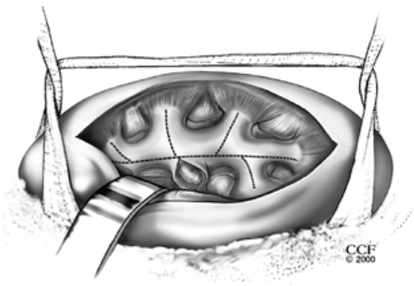

FIGURE 9.42. The collecting system is entered with an incision into one of the involved posterior infundibulocalyces containing stone.

Once the pelvic and posterior infundibulocalyceal aspects of the stone are identified, the anterior and polar portions are exposed, again with sequential longitudinal infundibulotomies. However, these are performed on the posterior aspect of the anterior segmental infundibula and central aspects of the polar infundibula. The infundibulotomies should begin at each infundibulopelvic junction and extend outward toward the calix as far as necessary to provide adequate exposure for stone removal.

Eventually, the entire staghorn calculus is exposed and ready for removal (Fig. 9.43). In some cases, the entire stone can be delivered intact, but piecemeal extraction is usually required. Infundibulocalyceal extensions may break off due to a relatively soft and friable intrinsic nature of the stone, or alternatively, the entire stone may not have been in continuity to start. If infundibulocalyceal extensions of the stone are not extracted with the main portion, the involved infundibulum should be dilated or further incised out toward the calix to ensure complete visualization and stone removal.

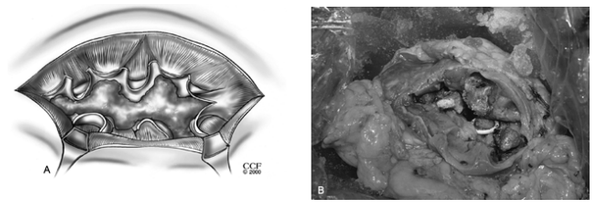

FIGURE 9.43. A: The entire stone is now exposed after performing sequential longitudinal infundibulotomies and opening the lateral portion of the renal pelvis. **B:** Intraoperative view of completed anatrophic incision with entire collecting system exposed. Note the bloodless field availed by clamping of the renal artery. The kidney is packed in ice slush to minimize the adverse effect of renal ischemic injury.

Once the bulk of the stone is removed (Fig. 9.44), each infundibulocalix is individually explored both visually and with palpation to exclude residual fragments. Occasionally, residual fragment can be palpated through thin parenchyma, but the infundibulum leading to the stone cannot be visualized. In such cases, a small nephrotomy made directly over the palpable stone is acceptable. The stone is extracted, and the nephrotomy is closed with absorbable sutures. The entire collecting system should now be thoroughly lavaged with iced saline using appropriately sized red rubber catheters placed sequentially into each infundibulocalix.

FIGURE 9.44. Staghorn calculus removed with anatrophic nephrolithotomy.

Because an optimal result requires removal of all stone fragments, several adjunctive maneuvers can be performed to identify and remove any potential residual stones, including intraoperative static radiography (Fig. 9.45A), fluoroscopy (Fig. 9.45B), US, and intraoperative pyeloscopy using flexible instrumentation (Fig. 9.45C).

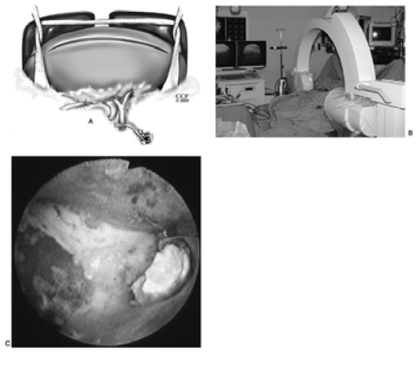

FIGURE 9.45. A: Intraoperative organ films had been a standard part of the procedure to exclude the presence of residual fragments. In general, such static radiography has been replaced with more contemporary adjunctive techniques such as intraoperative real-time fluoroscopy, ultrasound, or pyeloscopy. **B:** Intraoperative fluoroscopy has become a standard part of these stone procedures to exclude the presence of residual fragments and to help locate them for removal. **C:** Residual calyceal stone identified during intraoperative flexible pyeloscopy.

When all identifiable stone has been removed, a red rubber catheter is passed antegrade down the ureter, and the ureter is irrigated with saline. An internal stent may be placed at this time, and although this is not mandatory, it should be considered in those patients who may have residual fragments and in patients with compromised renal function. Nephrostomy tubes are used even less frequently and generally only for patients with severely compromised renal function and thinned parenchyma.

The collecting system is now reconstructed using fine absorbable suture (Fig. 9.46A). In areas of significant infundibular stenosis, infundibulorrhaphy is performed by suturing the adjacent borders of involved infundibula on their mirror-image sides, thus converting two or more stenotic infundibulocalyceal systems into one larger portion of the renal pelvis (Fig. 9.46B). Alternatively, isolated infundibular stenosis or polar infundibular stenosis can be managed with an individual infundibulorrhaphy that involves horizontal closure of the initial vertical infundibulotomy in a Heineke-Mikulicz fashion (Fig. 9.46C). However, when no infundibular stenosis is present, separate closure of the collecting system may not be necessary (125).

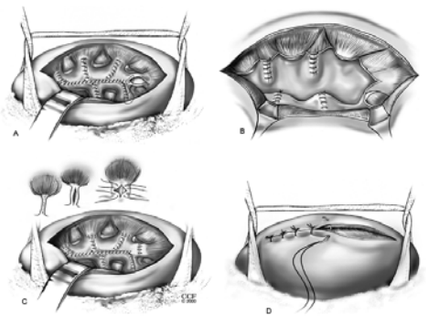

FIGURE 9.46. A: Closure of the collecting system begins with reconstruction of the incised infundibula and continues until the pelvis has been reapproximated. **B:** Infundibular stenosis is managed with infundibulorrhaphy. The lateral aspects of two adjacent infundibula are sutured to one another, creating widely patent, compound infundibulocalyces. **C:** Isolated polar infundibular stenosis is managed with a Heineke-Mikulicz infundibulorrhaphy. **D:** The renal capsule is approximated using running or interrupted mattress 3-0 chromic sutures taking a small bite of renal parenchyma.

The renal capsule is now approximated with running or interrupted 3-0 chromic sutures incorporating only a very small bite of renal parenchyma (Fig. 9.46D). At this time, an additional 12.5 g of mannitol is given intravenously and the vascular clamps are removed. Perirenal fat can be reapproximated over the nephrotomy incision, and external drainage is provided with a Penrose or closed-suction drain placed near, but not directly on, the nephrotomy incision itself.

Partial Nephrectomy

A partial nephrectomy is considered when stone disease is associated with a localized area of irrevocably poor renal function as can occur in the setting of chronic obstruction, especially with infection (Fig. 9.47). In such cases, removal of the diseased portion of the kidney along with the stone may be the best option, especially when localized xanthogranulomatous pyelonephritis may be present.

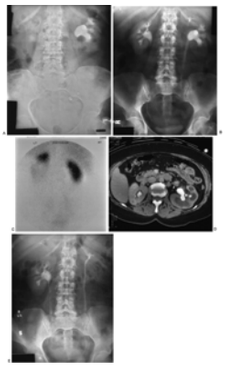

FIGURE 9.47. A: Plain film in this patient with recurrent urease-producing infection reveals a fully branched staghorn calculus overlying the left kidney. **B:** Intravenous urogram suggests contrast excretion from the lower pole, although this is a partially duplicated system, and function in that portion of the kidney was not proven on this study. **C:** Nuclear renogram reveals function only in the upper portion of the collecting system on the left side. The contrast in the lower pole on the left seen on the intravenous pyelogram was due to a "yo-yo effect" in the partially duplicated ureters. **D:** Computed tomography scan reveals thinning of the parenchyma in the involved lower portion of the collecting system. **E:** Following lower-pole partial nephrectomy, a well-functioning upper-pole system remains, as seen on this postoperative pyelogram.

Nephrectomy

Nephrectomy is indicated only rarely for management of renal calculi. The specific indication is stone disease associated with a nonfunctioning or poorly functioning kidney that is irrevocably damaged and would be unlikely to support life off dialysis should it be the sole kidney (Fig. 9.48). This generally implies renal function less than 10% to 15% of overall function, or a glomerular filtration rate of less than 15 mL per minute. In these cases, salvageability of the kidney is best determined preoperatively with radiographic evaluation that includes a differential nuclear scan. We have also found CT scanning to be especially useful in determining the residual cortical thickness and to search for evidence of xanthogranulomatous pyelonephritis, which is best managed by nephrectomy. If there is any question as to recoverability of function in the setting of chronic obstruction, placement of percutaneous nephrostomy provides temporary relief of obstruction and allows follow-up differential renal functional studies.

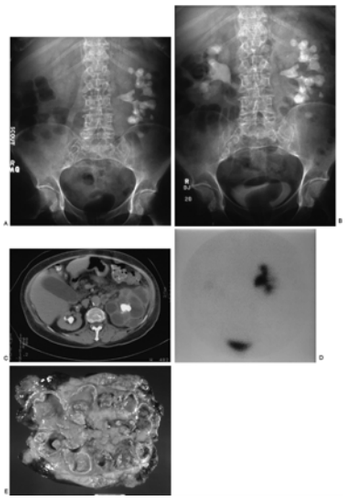

FIGURE 9.48. A: Scout film reveals a large, extensively branched staghorn calculus overlying the left kidney in this patient with recurrent urinary infection. **B:** Intravenous urogram shows prompt function on the right. However, there is no evidence of contrast excretion on the left side. **C:** Computed tomography scan in this same patient shows marked thinning of parenchyma and multiple cystic areas in the kidney consistent with local hydrocalices, and suggestive of xanthogranulomatous pyelonephritis. **D:** Renal scan shows essentially no function in the left kidney (posterior view). **E:** Nephrectomy specimen reveals chronic pyohydronephrosis. Pathologic examination confirmed xanthogranulomatous pyelonephritis.

Ureterolithotomy

Open ureterolithotomy is rarely performed in contemporary practice. Essentially, the only indication today is a failure of, or a contraindication to, all less invasive procedures, including SWL, retrograde ureteroscopic management, and percutaneous antegrade management. In such cases, an extraperitoneal approach is used with the incision positioned at the level of the stone. The peritoneum is reflected medially, the ureter is identified, and the stone is palpated. Generally, extensive ureteral mobilization is not necessary and should be avoided whenever possible. The ureter proximal to the stone is controlled by placement of a vascular tape (Fig. 9.49A). This prevents proximal migration of the stone up into the dilated ureter during the subsequent procedure. A longitudinal ureterotomy is then made directly over the stone using a "banana blade." The stone is extracted with an appropriate-size stone forceps (Fig. 9.49B). The ureter is then thoroughly irrigated distally and proximally with a small-caliber red rubber catheter, and distal patency is ensured by passage of the catheter all of the

way into the bladder. The ureterotomy is closed with interrupted fine absorbable suture (Fig. 9.49C) and the area drained with a Penrose drain. In the face of extensive ureteral edema or infection, strong consideration should be given to leaving an internal stent placed intraoperatively before closure of the ureterotomy.

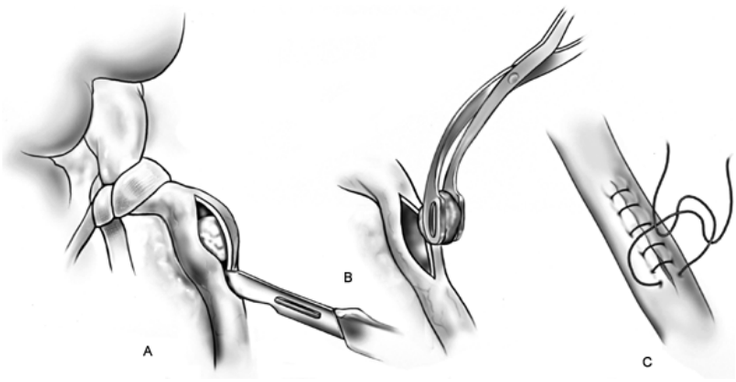

FIGURE 9.49. A: The ureter is isolated and controlled proximal to the stone using a vessel loop. **B:** A longitudinal ureterotomy is made directly over the stone, and the stone is extracted. **C:** The ureterotomy is closed using fine, absorbable interrupted suture to approximate the seromuscular layer.

Complications

Retained calculi can occur in up to 20% of patients, and when such retained stones are symptomatic or associated with infection or obstruction, further intervention is required. Fortunately, today, almost all such retained stones can be managed with SWL or percutaneous techniques, although these procedures should be delayed at least 4 to 6 weeks after the initial open operative intervention.

Persistent urinary drainage is uncommon and generally implies a local area of devascularization or distal obstruction. In most cases, such fistulae resolve spontaneously with conservative measures, including provision of local drainage and assurance of distal patency, at times with placement of an internal stent.

Bleeding into the collecting system or around the kidney almost always resolves spontaneously, and conservative, supportive measures are the initial treatment. When bleeding results in the need for multiple transfusions or an unstable cardiovascular status, intervention is indicated. In most cases, the treatment of choice is selective angiographic embolization because open surgical exploration generally results in nephrectomy (5).

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10

PERIOPERATIVE CARE

W. Scott McDougal

W.S. McDougal: Department of Urology, Harvard Medical School; Department of Urology, Massachusetts General Hospital, Boston, MA 02111.

Contents

The risk of an operative procedure must be weighed against its benefit so that the patient can be given a realistic view of the probable outcomes of both the nonoperative and the operative approaches. Although determining risk is simple in theory, it is extremely difficult in practice. Because of the wide variety of surgical procedures performed and the uniqueness of each patient, attempts to quantitate the risk factor have not met with great success. Many investigations have been unable to correlate accurately risk with any specific factor; however, a loose association has been shown with poor general health, advanced

age, emergency operation, and the site of the surgical procedure (41).

In an attempt to quantitate the risk associated with an anesthetic, irrespective of procedure performed, the American Society of Anesthesiologists (ASA) has proposed a classification of physical status: Class I is a normal healthy person, class II is used for patients with mild to moderate systemic disease, class III represents patients with severe systemic diseases that are not incapacitating, class IV indicates an incapacitating systemic disease that is a constant threat to the patient's life, and class V denotes a moribund patient not expected to survive more than 24 hours without an operation. This classification allows a general assessment but is not specific enough to accurately quantitate risk.
The most important factor in evaluating the risk of an operation is the functional status of the cardiovascular system. Pulmonary function also significantly affects the risk of anesthesia; perhaps the most common postoperative complication involves the respiratory tract. Hypoxemia secondary to respiratory dysfunction, when combined with myocardial disease, significantly increases the risk of myocardial infarction and death following the procedure.
The death rate from anesthesia, taking into account all operative procedures, has been estimated to be approximately 0.3%. Of patients who die as a result of the anesthetic and operative procedure, approximately 10% die in the period of induction, approximately 33% during the operative procedure, and the remainder within the first 48 hours after operation (32). The death rate attributed to anesthesia in patients who are ASA class I or II is much less and is estimated to be about 1 in 500,000 (27).
Preoperative assessment is undertaken to determine the risk of the proposed procedures and to identify abnormalities that can be corrected to reduce morbidity and mortality. The assessment should include an evaluation of the blood count and blood volume; the integrity of the hemostatic mechanisms; an evaluation of the cardiac function; an assessment of pulmonary function; and a review of the metabolic status, which should include an assessment of the liver, the kidneys, the immune system, the patient's nutritional status, the integrity of the adrenal glands, and an evaluation of any systemic diseases, such as diabetes, obesity, and thyroid disease.

BLOOD COUNT

Part of "10 - PERIOPERATIVE CARE "

All preoperative patients in whom a significant blood loss is anticipated or who are suspected of having an abnormal blood count require determination of a packed cell volume or hematocrit level. A value between 30% and 50% is acceptable. As the hematocrit level falls below 30%, the viscosity of the blood is reduced and flow characteristics through the small vessels improve. However, this is offset by the decreased oxygen-carrying capacity of the blood. Patients with chronic renal failure often have hematocrit levels of 20% to 24% and tolerate surgery well, provided there has not been a recent short-term change in the hematocrit level. The disadvantage is that there is little margin for error in terms of major blood loss. Patients with hematocrit levels above 55% have marked increased viscosity in their blood and are prone to thrombosis during periods of major fluid shifts. Therefore, except under extenuating circumstances, a hematocrit level between 30% and 50% should be sought in the preoperative preparation of the patient.

BLOOD VOLUME

Part of "10 - PERIOPERATIVE CARE "

The status of the patient's blood volume also must be assessed. Hypovolemia may be a consequence of secondary hyperaldosteronism, Addison's disease, acute blood loss, vomiting, diarrhea, pancreatic fistula, ileostomy, intestinal obstruction, pheochromocytoma, and neuroblastoma, among others. When these disorders are present, the blood volume must be restored through preoperative fluid administration and/or pharmacologic manipulation. α-Adrenergic blockade allows for volume expansion through relaxation of peripheral vasoconstriction with homeostatic volume restoration over a several-week period in patients with a pheochromocytoma and in hypertensive patients with a neuroblastoma. Fluid loss into the bowel, as occurs in bowel obstruction, diarrhea, or hemorrhagic blood loss, is not appropriately corrected by pharmacologic means; however, drugs may be used as temporary blood pressure stabilizers—intravenously (IV) when such losses are sufficient to cause cardiovascular instability—until fluid volumes can be restored generally.

The central venous pressure (CVP) is an indirect measure of the blood volume and competency of the heart to receive and propel blood. Provided heart disease is not significant, it is an accurate measure of volume status. A normal CVP ranges between 4 and 8 cm H_2O with reference to the left atrium (4 cm below the angle of the sternum). A low CVP suggests hypovolemia, and an elevated CVP suggests volume overload. A pulmonary artery catheter (right sided, Swan-Ganz) is necessary to determine accurately the volume status in patients with cardiac disease, those with chronic obstructive pulmonary disease, and patients in whom the CVP does not correlate with the clinical status (a high CVP in the presence of hypoperfusion). Although the CVP is adequate, a pulmonary artery catheter may be preferred in the patient with multisystem trauma, septic shock, decompensated cirrhosis, severe pancreatitis, or peritonitis, as well as in those receiving massive transfusions. In these circumstances, major fluid shifts can be more accurately titrated with a right-sided heart catheter. A normal pulmonary wedge pressure ranges between 12 and 15 cm of H_2O. This catheter also allows for the measurement of cardiac output and peripheral vascular resistance. Restoration of circulating volume and correction of metabolic disorders may require several weeks of proper

fluid and pharmacologic manipulation. The use of right-sided heart catheterization to monitor fluid administration in critically ill patients has been questioned recently. In one study in which similarly critically ill patients were compared, those who had right-sided heart catheterization had a higher mortality and greater utilization of resources than those who were managed without a cannula in the pulmonary artery (16).

A kidney in the diuretic state is less prone to injury; therefore patients who have operations on their urinary tract should be volume replete before and during surgery. The usual practice of nothing by mouth past midnight requires an intraoperative catch-up of fluids. Most patients tolerate this quite well; however, in the critically ill or those who are severely compromised, maintenance of normal fluid balance minimizes postoperative complications. This can be accomplished by beginning the IV fluid administration the night before surgery and giving the patient normal replacement fluids (see Fluids and Electrolytes).

HEMOSTASIS

Part of "10 - PERIOPERATIVE CARE "

The competency of the hemostatic mechanisms is assessed by history that addresses bleeding tendencies, bruisability, or a family history of bleeding disorders and serum studies. *A platelet count, a prothrombin time (PT), and a partial thromboplastin time (PTT) serve as good screening tests for major surgery.* PT and PTT are thought by many to be unnecessary in patients when there is no reason to suspect a coagulation problem. It is important to remember that there may be a qualitative platelet defect such as occurs in uremic patients and those taking aspirin, which would not be picked up by a routine platelet count.

RENAL FUNCTION

Part of "10 - PERIOPERATIVE CARE "

It has long been known that the onset of acute renal failure in the critically ill patient is a poor prognostic sign with an excessively high mortality. Many believed that acute renal failure was merely an indication of systemic organ failure accounting for the increased mortality. However, more recent data suggest that renal failure alone increases mortality, even if the degree of insufficiency is not enough to require dialysis. This makes it imperative to aggressively treat patients who have even modest elevations of their serum creatinine (5).

CARDIAC FUNCTION

Part of "10 - PERIOPERATIVE CARE "

Cardiac function is evaluated by history, physical examination, an electrocardiogram (ECG), and in select cases, a gated blood pool scan to provide ejection fraction. A previous myocardial infarction is of particular significance. *As a group, patients with a history of a myocardial infarction have a tenfold increase in the probability of having a subsequent postoperative infarction. A further analysis reveals that the time elapsed since the infarction is of prime importance.* One-third of patients who have operations within 3 months of their myocardial infarction will have another. Patients who have operations 6 months or longer after their myocardial insult have their risk of postoperative infarction reduced to approximately 6% to 8%. A postoperative infarction generally occurs within the first 7 postoperative days and has a 50% to 75% mortality (91). Other factors that appear to be particularly important in predicting myocardial dysfunction in the operative and perioperative period include (a) an S_3 gallop and/or jugular venous distention; (b) a preoperative cardiac rhythm other than sinus; (c) more than five premature ventricular contractions per minute; (d) an intraperitoneal, intrathoracic, or aortic operation; (e) an age greater than 70 years; (f) aortic valvular heart disease; (g) the necessity for an emergency operation; and (h) a poor general medical condition as reflected by an arterial blood gas abnormality, decreased renal function, and/or evidence of hepatic disease (40). Clearly, the most important predictors are the presence of congestive heart failure with jugular venous distention and/or an S_3 gallop and a history of a myocardial infarction within the preceding 6 months. These two findings carry with them a significant risk of death from the anesthetic.

Hypertension also increases the risk of an operative procedure, particularly if associated with coronary artery disease. Hypertensive patients have wider and more frequent blood pressure swings during anesthesia and are more likely to have associated cerebral vascular and coronary artery blood flow compromise.

Patients should continue antihypertensive medicine if they are normotensive, or the dosages should be adjusted to achieve a normal blood pressure. In general, medications should not be discontinued in the preoperative period. The monoamine oxidase (MAO) inhibitors may be an exception because they can interfere with anesthetic management.

Patients thought to have severe cardiac disease are best prepared preoperatively with a right-sided heart catheter placed in the pulmonary artery, inotropics or antiarrhythmics given as needed, and careful fluid resuscitation. An evaluation of cardiac and respiratory status can be performed by noting the patient's resting pulse, having him or her walk briskly a short distance, and then rechecking the pulse. If the pulse rate does not rise to twice the resting level, the patient is probably not at significant risk.

An excellent assessment of cardiac reserve can be accomplished by the determination of the ejection fraction. This may be performed by an isotopic method or by ultrasound. If the ejection fraction exceeds 50%, it is likely that the patient's heart will tolerate the procedure well. If the ejection fraction is between 40% and 50%, the patient is at increased risk for myocardial dysfunction but is still acceptable from a cardiac

standpoint. If the ejection fraction is less than 40%, the patient is at an increased risk and requires exceedingly close monitoring for cardiac malfunction, which is likely.

The need for sufficient cardiac reserve is made apparent by the fact that in the critically injured patient, a high normal or moderately increased cardiac output and oxygen consumption portends a much better prognosis with significantly reduced mortality compared with those in whom little increase is noted (5).

RESPIRATORY FUNCTION

Part of "10 - PERIOPERATIVE CARE "

Respiratory status is evaluated by history and determination of exercise tolerance. A smoking history of more than 20 pack-years is particularly significant. If the respiratory status is at all questionable, simple spirometry is an excellent screen. If the forced expiratory volume in 1 second (FEV_1) is under 15 mL/kg and the vital capacity is less than 1.5 L or the maximum voluntary ventilation is under 50%, further pulmonary function tests and additional preoperative preparation are in order.

METABOLIC STATUS

Part of "10 - PERIOPERATIVE CARE "

The metabolic status of the patient is assessed with regard to the hepatic, renal, and immune function, as well as the nutritional and adrenal status. If indicated by history, hepatic function is determined by evaluation of liver enzymes, PT, and albumin. In patients with compromised hepatic function, preoperative preparation includes improving the nutritional status (see Nutrition) and, in those with an impaired clotting mechanism, the administration of fresh-frozen plasma and vitamin K. Cirrhotic patients with ascites are prepared preoperatively by improving nutritional status, limiting sodium intake to 1 to 2 g per day, and reducing ascitic fluid by judicious use of spironolactone with or without other diuretics. Renal dysfunction is addressed in another chapter; however, renal function abnormalities generally do not significantly impair the operation, provided fluid and electrolyte balance is corrected. It still has a significant impact on postoperative survival in the critically ill though (5).

The patient's immune status, if in question, may be examined by determining whether the patient is allergic to cutaneous skin tests. Unfortunately, little can be done to alter the immune status unless it is caused by nutritional deficiency. A nutritional assessment also should be performed (see Nutrition). Medications of particular significance include antihypertensives and steroids. Adrenal insufficiency resulting from intrinsic disease or suppression secondary to exogenous steroid administration demands administration of preoperative, intraoperative, and postoperative steroids. The dose should be approximately ten times the resting nonstressed level and administered in three equally divided doses. Because the normal basal production of cortisol is about 35 mg per day, a replacement of an equivalent of approximately 300 mg of cortisone is indicated. Cortisol equivalent (100 mg) is administered several hours before the operation, 100 mg intraoperatively and 100 mg 8 hours postoperatively. The dosage is gradually tapered to maintenance levels over several days, or if the adrenal glands function normally, it may be discontinued altogether. If postoperative complications occur, however, the ten-times basal level dosage should be continued until the complications have resolved. All patients who have taken steroids preoperatively do not of necessity require preoperative, high-dose steroid replacement. In one study, patients who received less than 5 mg of prednisolone per day had a normal pituitary-adrenal axis. If the adrenal gland's ability to respond to stress is at all questionable, an adrenocorticotropic hormone (ACTH) stimulation test may be performed.

SYSTEMIC DISEASE

Part of "10 - PERIOPERATIVE CARE "

The evaluation of systemic disease generally involves a determination of the carbohydrate (diabetes) and thyroid status. In diabetic patients, it is important to avoid hypoglycemic ketosis or hyperosmolarity. This is best accomplished if the blood glucose level is maintained between 125 and 250 mg/dL. If the patient is taking insulin, half the usual dose is given on the morning of surgery and an IV dextrose-containing solution is begun. During the operative procedure, blood glucose levels are determined and regular insulin administered as necessary. In the postoperative period, blood glucose levels must be determined every 4 hours and regular insulin administered IV or subcutaneously for diabetic patients with major alterations in glucose metabolism. For patients who are particularly labile, an insulin infusion pump may be used in the postoperative period. Continuous monitoring of blood glucose levels must be performed throughout the period of administration, particularly when metabolic aberrations, sepsis, and trauma coexist, because these can significantly alter glucose utilization and cause wide fluctuations in serum levels.

METABOLIC RESPONSE TO INJURY

Part of "10 - PERIOPERATIVE CARE "

Basal Metabolic Rate

Uninjured humans at rest expend a definable amount of energy to perform physiologic work—the work required to maintain cardiac output, endocrine function, body temperature, hepatic function, respiration, renal function, and so on. The amount of energy required to maintain these functions at rest is called *basal metabolic rate* and is expressed in calories per hour per square meter of body surface. Basal

metabolism is the energy expended by the cells that constitute the active mass of the body; fat, extracellular fluid, and bone make no direct contribution to the metabolic rate. The energy used in physiologic work is derived from chemical energy, which in the course of the performance of the work is converted to heat and lost from the body. Therefore the basal metabolic rate, or energy expenditure, may be determined by direct calorimetry in which the heat lost from the body is directly measured. Direct calorimetry is difficult to perform and often impractical in the critically ill. Thus indirect methods of estimating the basal metabolic rate are more commonly used. The heat lost may be indirectly estimated from (a) oxygen consumption, carbon dioxide (CO_2) production, and nitrogen excretion; (b) measurement of energy intake and losses, coupled with the measurement of changes in body composition; or (c) measurement of insensible water loss, assuming that this represents 25% of the total heat loss. The basal metabolic energy requirement depends on patient age, sex, and lean body mass. A 1-month-old infant requires about 40 kcal/kg body weight per day. The requirement increases with age and body mass, so boys between the ages of 15 and 18 years consume 1,700 kcal per day and girls between the ages of 12 and 18 years require 1,400 kcal per day. The energy requirement remains relatively stable during the active years of life. With progressive aging, however, it decreases to 1,300 kcal per day for men and 1,100 kcal per day for women (74). The difference in metabolic rate between men and women probably relates to the fact that women have a larger proportion of fat per unit body weight. Indeed, if basal metabolic rate is expressed per unit fat-free body weight, it is remarkably similar for both males and females over an age span of 20 to 60 years (1.3 kcal/kg per hour).

Hypermetabolism

The response to injury is characterized by an increase in the basal metabolic rate, even though the patient remains at rest. The intensity of this hypermetabolic response depends on the severity of the injury, the patient's nutritional status, and the presence or absence of infection. Patients in good nutritional balance undergoing an elective operation will have a change in metabolic rate of no more than 10% in the postoperative period, provided there are no complications. In contrast, patients with multiple fractures have an increase of their resting energy expenditure by 10% to 25%, those with major infections by 20% to 50%, and those with major thermal burns by 50% to 125%. In the early posttraumatic period, satisfaction of these energy demands results in degradation of body protein (manifested by a negative nitrogen balance), depletion of energy reserves, and loss of body weight. The initial catabolic response in which body protein, fat, and carbohydrate are depleted is gradually reduced and reversed later in the recovery period. An anabolic phase ensues, provided adequate nutritional intake occurs, in which new protein is laid down and carbohydrate and fat reserves are repleted. The hypermetabolic response also gradually diminishes as the wounds heal and as infection is eradicated.

In the early postinjury period, energy requirements are satisfied by glucose, derived mainly from liver and muscle glycogen and by fatty acids released from adipose tissue. Glycogen reserves are rapidly depleted (usually within 48 hours). Fat stores, however, which supply the bulk of the energy requirement during this period, continue to supply fatty acids for many days. Protein catabolism also occurs, even though it may not serve as a primary energy source. Amino acids are released primarily from skeletal muscle at rates three to four times normal and are essential for maintenance of cellular metabolism. Moreover, the gluconeogenic amino acids serve as a source of new glucose and provide the basic glucose structure that is necessary for normal metabolism. Alanine is the most important gluconeogenic amino acid, and its principal site of uptake is the liver. It is part of the glucose-alanine cycle in which its deamination in the liver results in new glucose formation. When glucose undergoes anaerobic glycolysis in muscle, the resultant pyruvate is transaminated, producing alanine and completing the cycle. Rapid depletion of glucose stores coupled with the inability of the two carbon fragments of the fatty acids to serve as a source for gluconeogenesis make protein the only available substrate from which new glucose can be synthesized. Protein catabolism can be reduced but not eliminated by providing exogenous glucose (nitrogen-sparing effect of glucose). Also, certain amino acids can be used as energy sources thus sparing glucose. For example, glutamine from muscle is taken up by the intestine where it is used as respiratory fuel (94).

Catecholamines and Glucocorticoids

Posttraumatic catecholamine levels are elevated and promote hepatic glycogenolysis, inhibition of insulin release, stimulation of glucagon production, and stimulation of fat hydrolysis with the release of free fatty acids. This hormone is produced almost exclusively by the adrenal medulla and has been implicated as the mediator of the hypermetabolic response in injured patients (94).

Glucocorticoid levels are also characteristically elevated and remain so throughout the recovery period. The increased production is the direct result of an increased ACTH secretion by the anterior pituitary. It is presumed that the pituitary is stimulated to release ACTH by the action of the nerves from the periphery responding to the traumatic injury and perhaps by a direct effect of the elevated epinephrine levels. Patients who have sustained severe trauma that requires a prolonged period of convalescence, such as thermal burns, often have marked adrenal hyperplasia. Glucocorticoids promote gluconeogenesis and inhibit the action of insulin.

Insulin

Immediately after injury, circulating levels of insulin and glucose are elevated. Insulin facilitates glucose transport across cell membranes and inhibits both the release of amino acids from muscle and the release of free fatty acids from adipose tissue. In the posttraumatic period, hyperglycemia is common, possibly as a result of the development of insulin resistance. Glucose tolerance curves performed during this period simulate those observed in diabetes and have led many to refer to this state as the *diabetes of injury* (49).

However, the mechanism of the hyperglycemia may not be one of insulin resistance. More recent evidence indicates that glucose oxidation is unimpaired and that the hyperglycemia is caused by an increase in gluconeogenesis rather than a reduction in peripheral utilization. Moreover, glucose flow studies have clearly demonstrated that glucose turnover rate is increased above normal (59,95). Others suggest that the amount of circulating insulin is inadequate for the concentration of glucose.

Glucagon

The increased production of catecholamines after injury is known to stimulate the α-cell of the pancreatic islets, resulting in increased circulating levels of glucagon, a hormone that promotes glycogenolysis and gluconeogenesis. The relation between the concentration of insulin and glucagon (the insulin-to-glucagon molar ratio) determines whether the major influence is toward glucose breakdown or glucose formation. Early after injury, although the level of insulin is elevated, glucagon is disproportionately increased, and the ratio of the two favors gluconeogenesis at the expense of protein formation. As healing occurs, the molar ratio reverses, favoring glycolysis and protein formation. After injury, the hypermetabolic response and hormonal balance direct the metabolism and utilization of carbohydrate, fat, and protein. They set the stage for a negative nitrogen balance and weight loss, both of which are related to the extent of injury. The protein that is catabolized to satisfy energy and substrate requirements is derived mainly from skeletal muscle. Alanine and glutamine released from the muscle are transported to the liver, where they are converted to glucose (gluconeogenesis). With protein breakdown, urinary excretion of nitrogen (predominantly as urea), potassium, phosphate, creatinine, magnesium, zinc, and sulfate are greatly increased, reflecting catabolism of protoplasmic mass.

NUTRITION

Part of "10 - PERIOPERATIVE CARE "

The metabolic response to the trauma of operation or injury is characterized by hypermetabolism, which if left unchecked, results in increased tissue breakdown, loss of lean body mass, and depletion of essential intracellular constituents. The prevalence of malnutrition in hospitalized patients has been said to range between 30% and 50%. Protein-calorie malnutrition is characterized by (a) weight loss, (b) hypoalbuminemia, (c) decreased skeletal muscle mass, (d) reduced fat stores, and (e) decreased total lymphocytes (92).

Malnutrition has increased the incidence of clean-wound infections, prolonged postoperative ileus, impaired wound healing, depressed immunocompetence, increased the patient's susceptibility to sepsis, inhibited vital organ function, and increased the risk of respiratory infections and respiratory insufficiency (56,64,89). Moreover, severe malnutrition results in loss or malfunction of various intestinal enzymes. Lactase seems to be particularly sensitive to variations in nutritional status. Thus a patient who develops a lactase deficiency because of malnutrition will be incapable of absorbing supplements that contain milk or milk by-products. This greatly limits the type of supplements that can be administered orally.

If malnutrition is allowed to persist, morbidity and mortality significantly increase. Loss of body protein appears to be the critical factor determining the point at which the nutritional depletion compromises the ability of the host to respond appropriately to the injury. Mortality and morbidity associated with weight loss and starvation are directly related to the loss of essential protein stores: Death occurs with the loss of 25% of body nitrogen or 33% total body weight (68). Therefore it is essential to limit and ultimately reverse the loss of body protein to promote early recovery and reduce the incidence of life-threatening complications.

Nutritional Requirements

The daily caloric requirement for resting humans is approximately 25 kcal/kg body weight. Hypometabolic, starved humans may require somewhat less, but it is generally at the expense of limited organ function. Most surgical patients are hypermetabolic and require an additional 5 to 60 kcal/kg body weight. *Thus, when the total caloric requirement in the average surgical patient are calculated, 30 to 35 kcal/kg body weight is used.* Daily protein intake requirements are normally about 0.8 g/kg body weight per day, but under conditions of acute stress, they may be as high as 2.5 to 3.5 g/kg body weight per day. Although protein provides only 4 kcal/g, it is the number of grams of protein that is important, with satisfaction of caloric requirements being provided by the addition of carbohydrate or fat. For each gram of protein administered, 25 kcal (carbohydrate or fat) should be provided. Protein consists of amino acids that are either essential or nonessential. The former cannot be manufactured by the body, whereas the latter can.

In selected circumstances, it may be important to limit the total intake of protein or to alter the protein composition of the infusion. In patients with renal and hepatic failure, excessive amounts of protein may result in an

excessively elevated blood urea nitrogen (BUN) and/or serum ammonia level with systemic manifestations of uremia in the former or hepatic encephalopathy in the latter. In these cases, 0.5 to 1.0 g protein/kg body weight may be appropriate.

Alteration of the composition of the protein infusion also may be helpful. Essential amino acid infusions without their nonessential counterparts may lessen the rise in serum urea in patients with acute renal failure, and branched-chain amino acids, which are metabolized by muscle and do not require the liver for metabolism, may be more appropriate in patients with hepatic disease. Certain amino acids also have been added to nutritional regimens because they appear to play a more central role during injury than their counterparts. Glutamine serves as a vehicle for nitrogen transfer between tissues; it is also the most important substrate for renal ammoniagenesis, a regulator of protein synthesis, and an essential precursor in nucleic acid biosynthesis (76,93). Glutamine-supplemented nutritional regimens improve nitrogen balance (88). Glutamine may be administered in its more stable form as the dipeptide alanyl-glutamine or glycyl-glutamine. Arginine has potent secretagogue activity, and its administration may have trophic effects in the immune system and, when given, has been shown to improve weight gain and wound healing (4).

Fats have a high caloric value and provide 9 kcal/g. They also are classified as either nonessential or essential, depending on whether the body can manufacture them. Fats that cannot be manufactured by the body include linoleic, arachidonic, and linolenic. Only linolenic is absolutely essential because a fatty acid deficiency will not develop if it alone is provided. Vitamins must be provided daily, particularly the water-soluble vitamins, because they are depleted rapidly. Sodium, potassium, calcium, magnesium, and phosphate also must be provided in sufficient quantities on a daily basis. Trace elements, such as zinc, copper, iodine, manganese, and selenium, must be provided regularly over long-term periods.

A stable weight is often a good indication that basal needs are being met, provided that loss of lean body mass is not hidden by an increase in extracellular water. If the patient is incorporating exogenous protein into endogenous stores, he or she is said to be in a positive nitrogen balance. Nitrogen balance may be grossly calculated by assuming that 1 g per day of nitrogen is lost in the feces, if the patient is stooling, and about a quarter of a gram of nitrogen is lost through the skin. The remaining nitrogen loss occurs in the urine. Approximately 80% of the nitrogen lost in the urine is lost as urea nitrogen. Therefore it becomes apparent that the nitrogen balance of any patient may be calculated quickly by measuring the 24-hour urine and its urea content. The amount of urea nitrogen excreted is multiplied by 1.25 to give the total nitrogen excreted in the urine. If an additional 1 to 2 g is added for skin and stool loss and this quantity is subtracted from the protein nitrogen intake, a positive or negative number is obtained. These urine collections are appropriate for patients in whom bowel is not interposed in the urinary tract. Patients with bowel interpositions alter urea excretion so that this measurement cannot be performed accurately. If the nitrogen balance is positive, the patient is lying down or retaining protein (anabolism); if negative, body protein is being broken down for energy requirements (catabolism).

Nutritional Status

Several modalities have been used to determine whether the patient is malnourished and, if so, to quantitate the degree of nutritional deprivation. Among the indices most often used are weight loss, reactivity to skin-test antigens, creatinine excretion index, middle-arm circumference measurement, tricep skinfold thickness, the measurement of lymphocyte count, serum albumin, serum transferrin, retinal-binding protein, and thyroxine-binding prealbumin. A history of a recent weight loss is particularly important in determining current nutritional status. It must be remembered, however, that this may underestimate loss of lean body mass, because when body protein is metabolized, there is an obligate increase in extracellular fluid. Therefore the weight loss may not accurately reflect the loss of lean body mass. A patient who has lost fewer than 10 pounds in the preceding 3 months is said to be mildly malnourished; between 10 and 20 pounds moderately malnourished; and more than 20 pounds, severely malnourished. A patient's current weight can be compared with height/weight tables and a percentage deviation from normal obtained.

Reactivity to skin-test antigens has been used frequently to determine a patient's immune status. Indirectly, the response to these antigens reflects the patient's nutritional status. If a patient is known to be allergic to one of the antigens and is anergic when tested or if anergic to agents that normally cause a response, severe malnutrition is present. Antigens commonly used are dermatophytin, mumps, purified protein derivative (PPD), streptokinase, and streptodornase. The importance of this index is illustrated by the fact that in several series, cancer patients did not respond effectively to chemotherapy or surgery if their skin-test antigens were negative. However, if the patients were nutritionally repleted, approximately half converted to a positive status and then responded to either chemotherapy or surgery (18,22). More recent data have called into question the reliability of skin-test antigens in critically ill patients. The creatinine excretion index measures the lean body mass or muscle protein stores as does a measurement of middle-arm circumference. Triceps skinfold measurements indicate the status of fat stores. Lymphocyte count is a measure of visceral protein status and should normally be above 2,000 cells/mm^3. If the lymphocyte count is between 1,200 and 2,000 cells/mm^3, the patient is said to be mildly nutritionally depleted; between 800 and 1,200 cells/mm^3,

moderately nutritionally depleted; lower than 800 cells/mm^3, severely nutritionally depleted.

Albumin levels are another measure of visceral protein status. Serum albumin has been demonstrated to accurately reflect the patient's nutritional status. In one series, the only parameter that correlated with an increased hospital stay in nutritionally depleted patients was their albumin status (2). Others have found it to be an accurate predictor of the success of a nutritional regimen and an indicator of the degree of nutritional repletion (12). There is a 20% increase in wound infections if the serum albumin concentration is less than 2.9 g/dL (78). If the albumin level is between 3 and 3.5 g/dL, the patient is said to be mildly nutritionally depleted; between 2.5 and 3.0 g/dL, moderately nutritionally depleted; less than 2.5 g/dL, severely nutritionally depleted.

Serum transferrin levels also have been used as an indicator of visceral protein status. Transferrin determinations may not be readily available but can be calculated if one obtains a total iron-binding capacity (TIBC). The formula for calculation is as follows:

Serum transferrin = (0.8 × TIBC) – 43

If the level is between 150 and 200 mg/dL, the patient is mildly nutritionally depleted; between 100 and 150 mg/dL, moderately nutritionally depleted; less than 100 mg/dL, severely nutritionally depleted. Retinal-binding protein and thyroxine-binding prealbumin are also measures of visceral protein status and are helpful in select cases.

In practice, it is often difficult for the busy clinician to seek out the various tables required for a complete nutritional assessment. *Three modalities are conveniently used to assess the patient's status: weight loss, lymphocyte count, and albumin level.* With these indices, the patient can be placed into one of four categories: normal nutritional status or mildly, moderately, or severely nutritionally depleted. If one is still unsure, skin-test antigens may be used. If the patient is anergic to a battery of skin-test antigens, he or she is considered severely malnourished irrespective of the previously mentioned indices (Table 10.1).

TABLE 10.1. NUTRITIONAL ASSESSMENT: THE CATEGORIZATION OF PATIENTS INTO MILD, MODERATE, OR SEVERELY NUTRITIONALLY DEPLETED

Measurement	Mild	Moderate	Severe
Weight loss (lb)	<10	10–20	>20
Lymphocyte count (cells/mm^3)	1,200–2,000	800–1,200	<800
Albumin (g/dL)	3.0–3.5	2.5–3.0	<2.5
Serum transferrin (mg/dL)	150–200	100–150	<100
Skin-test antigens	+	+	Anergy

The amount of calories required per day for repletion also must be calculated so that appropriate amounts may be administered. The patient's weight times 25 gives the basal metabolic requirement of the patient. Depending on the severity of the insult, an additional 5 to 60 kcal/kg is added. In children, the amount of kilocalories metabolized varies according to weight. For the first 10 kg, 100 kcal/kg is metabolized; for the second 10 kg, 50 kcal per kg; and for each kilogram over 20, 20 kcal/kg (Table 10.2). The success of the regimen is determined by the return of the serum values to normal; the return of an allergic response to the skin-test antigens, if previously anergic; and weight gain. Moreover, periodic, crude measurements of nitrogen balance as previously described, if positive, will confirm that the amount and composition of the calorie load are appropriate. Having determined how much the patient requires, one must determine the route of administration: enteral, IV, or a combination.

TABLE 10.2. BASIC CALORIC REQUIREMENTS OF UNINJURED HUMANS AT REST

	Body Weight (kcal/kg)
Children	
First 10 kg (0–10)	100
Second 10 kg (10–20)	50
Each additional kg >20	20
Adults	25

Enteral Feedings

Enteral feedings are preferred if possible because complications are decreased and a more balanced, physiologic diet can be provided. Enteral diets are either nonelemental or elemental. Nonelemental enteral feedings consist of undigested and minimally digested protein hydrolysates, fat, and carbohydrates, whereas elemental diets consist of medium-chain triglycerides, glucose, and amino acids. *Enteral feedings can be provided either by a small feeding tube, a gastrostomy, or a feeding jejunostomy. Generally, nonelemental enteral feedings are preferred, provided the gut is not diseased, because they have lower osmolality and are cheaper.* The advantages of an elemental diet include its bulk-free and lactose-free composition (30). Therefore patients with severely diseased bowels or patients who have been chronically starved are probably better served with an elemental diet—at least at the outset.

One should begin with the enteral feeding diluted to half strength at a rate of 50 to 75 mL per hour in the adult. If this is tolerated, the volume is increased to 2,500 to 3,000 mL per 24 hours, and if tolerated, osmolality is increased to full osmotic content (i.e., approximately 1 kcal/mL will be administered at 500 to 1,000 mOsm/kg). Complications include abdominal cramps, diarrhea, and diaphoresis. If any of these symptoms occur, the infusion is slowed, the osmolality

is reduced, or both. Once the symptoms disappear, a gradual return to the strength and rate desired is begun. If diarrhea continues to be poorly controlled, the administration of paregoric 5 mL in divided doses may be helpful.

Isosmotic Intravenous Nutrition

Carbohydrate, protein, and fat substrates may be infused individually or in combination in near-isosmotic concentrations. Because of their isosmotic character, not only may they be administered by peripheral vein but also the rate of administration may be rapidly changed to satisfy a change in fluid requirements or even stopped so that medications, colloid, and blood may be administered. These properties make such solutions advantageous during periods of critical care when instability of the patient is not uncommon.

An understanding of the metabolic effects of each type of caloric source with respect to energy provision and its potential for endogenous protein preservation and maintenance of optimum organ function is essential if the proper substrate or combination of substrates is to be administered to acutely ill patients. The provision of glucose in dosages up to 100 g per day decreases protein loss as measured by the loss of urinary nitrogen. This protein-sparing effect is directly proportional to the quantity of calories administered. Infusion of larger quantities of glucose results in disproportionately lesser reductions in nitrogen losses. Supplying 700 protein-free calories to fasting normal humans results in maximum reduction of protein losses. Increasing the nonprotein caloric intake is without further effect in the sparing of body protein. Indeed, positive nitrogen balance cannot be achieved even with high-dose glucose infusions. Starved, unstressed humans given approximately 700 g of glucose maintain a negative nitrogen balance of about 1.5 g/m^2 per day. If the same total caloric load is given, however, but part of the glucose calories are replaced by an equivalent amount of amino acid calories, the negative balance is eliminated (96). Supplying dietary protein with calories further improves nitrogen balance. Thus, on a fixed adequate protein intake, energy level is the deciding factor in nitrogen balance, and at a fixed adequate caloric intake, nitrogen intake is the determinant of nitrogen balance (9). Similarly, in critically ill, traumatized patients and in those with superimposed bacteremia, at low-dose levels (or those that can be easily achieved employing isosmotic solutions), glucose has the same effect on nitrogen sparing as does an equivalent caloric load of amino acids (63). Thus, at low-dose levels, total caloric load, whether derived from protein or carbohydrate, determines the degree of nitrogen sparing, whereas when the caloric load is increased, amino acid intake becomes a more dominant determinant of nitrogen balance.

Fat emulsions also may be administered by peripheral vein and have the advantage of providing high caloric loads in relatively small volumes because fat provides 9 kcal/g, whereas glucose and protein provide a little less than 4 kcal/g. The effect of fat emulsion on nitrogen sparing, however, is not equivalent to equal caloric amounts of glucose or amino acids. In normal unstressed humans, equivalent caloric amounts of infused fat emulsion and glucose result in a lesser degree of nitrogen sparing for the former. When amino acids are added to equivalent caloric amounts of fat emulsion or glucose, the latter combination results in a less negative nitrogen balance. In severely injured humans some investigators failed to observe any reduction in nitrogen sparing with the infusion of large doses of soybean fat emulsions. Conversely, more recent studies have demonstrated adequate utilization of fat calories in the immediate posttraumatic and postoperative period. In view of the degree of nitrogen sparing observed in normal and injured humans, when used in combination with amino acids, fat emulsions seem helpful in sparing nitrogen, but glucose and amino acids are more effective than fat, calorie for calorie.

Although there are no distinct differences in nitrogen balance in comparing low-dose isosmotic administration of glucose and amino acids, there are clear advantages to infusing a medium-dose combination of the two substrates. First, their effect is augmentative, and the impact on calories is not limited when protein is provided. Second, amino acids administered alone cause a constant rise in BUN that is not observed when glucose is added. Third, altered hepatic and renal transport occur in critically ill patients who are given amino acids as their sole caloric source. The altered transport properties may be restored to normal by the addition of glucose. An appropriate combination that provides maximum nitrogen sparing per gram of nutrient administered while maintaining optimal hepatic, renal, and cardiac function consists of a liter solution in which half is provided as 10% dextrose and the other half as a 7% to 8% amino acid solution. Fat emulsions given in 500-mL amounts once or twice a day provide additional calories. Because these solutions may be administered by peripheral vein and because alterations in infusion rate and even abrupt cessation of infusion can be accomplished without untoward effects so that blood, antibiotics, and other medications can be given, these infusates are an ideal means of preserving normal metabolic function of vital organs while limiting nitrogen loss in early posttraumatic, postoperative, and unstable critically ill patients. Unfortunately, it is generally not possible to achieve positive nitrogen balance with isosmotic solutions because the amount of calories required would necessitate excessive fluid administration. If illness is protracted and oral alimentation is not possible, positive nitrogen balance is achieved by administration of hyperosmotic solutions (hyperalimentation).

Hyperosmotic Intravenous Nutrition

Hyperosmotic IV solutions, which are capable of providing enough nitrogen and calories in an acceptable volume, are made up of equivalent amounts of a 50% dextrose and 7% to 8% amino acid solution, providing approximately 1 kcal/mL

of solution. Electrolytes including potassium, sodium, calcium, magnesium, and phosphate are added as required (Table 10.3). Trace elements (zinc, copper, manganese, chromium) and multivitamins also are added as required. In addition, essential fatty acids are provided by the administration of 500 mL of fat emulsion two to three times a week.

Ingredient	Concentration
Amino acid (7%–8%)	500 mL
Dextrose (50%)	500 mL
Potassium (KCl)	60–150 mEq
Sodium (NaCl)	60–180 mEq
Calcium (Ca gluconate)	5–15 mEq
Magnesium ($MgSO_4$)	8–24 mEq
Phosphate (K_2HPO_4)	15–20 mmol
Trace elements	—
Multiple vitamins	—

TABLE 10.3. COMPOSITION OF HYPERALIMENTATION SOLUTIONS

Because the hyperalimentation solution is hyperosmotic, it must be administered through a central venous line and its rate of administration rigidly controlled. If long-term or home hyperalimentation is to be administered, the solution should be given through a long-term indwelling catheter, such as a Broviac or Hickman catheter. The catheters are placed in the superior vena cava, tunneled subcutaneously under the skin beneath the anterior chest wall, and brought out at about the level of the nipple—between it and the sternum. We have kept catheters functional as long as 21 months in adults and 14 months in children. In most cases, hyperalimentation will be administered for limited periods, and a percutaneous central line is placed. The central venous line must be placed and maintained with an assiduously sterile technique; otherwise, infection will invariably follow. The IV line is placed in the superior vena cava, either by a subclavian or internal jugular puncture. A sterile dressing is applied with an antibiotic ointment placed over the catheter entrance site. On alternate days, the dressing is changed and a new sterile dressing, iodophor preparation, and iodophor ointment are applied. A millipore filter is placed in line. The filter is changed and cultured every 24 hours. The IV tubing is changed with each bottle. The hyperalimentation solutions are made fresh daily and stored refrigerated. No medications, blood, or other fluid should be administered through the hyperalimentation line, nor should CVP measurements be made using the catheter through which the hyperalimentation solution is being administered. Fluid should be administered initially at low rates (50 mL per hour) until tolerance has been achieved (blood glucose remains below 200 mg/dL), after which the rate of infusion may be gradually increased until the proper caloric load is achieved. Usually, 3 to 4 L per day is given, providing 3,000 to 4,000 kcal per 24 hours. Blood must be monitored for glucose concentration periodically, when high, either the infusion rate must be reduced or insulin administered.

Blood glucose levels may be particularly difficult to control in the immediate postoperative and posttraumatic period. Insulin given IV every 4 hours, adjusting it to blood glucose levels, usually suffices. Occasionally, blood glucose levels can be better controlled with a continuous insulin infusion. Two to three units of regular insulin are administered per hour in a concentration of 1 U/mL of saline solution. If these simple measures do not control the glucose level or large amounts of insulin are required, the solution should be tapered or fat should be substituted for the glucose. It is apparent that high-dose insulin can lower serum glucose, but it is probable that under these conditions abnormal metabolism at the mitochondrial level occurs, obviating any beneficial effect of lowering the serum glucose.

Similarly, after IV fat administration, the serum must be observed for clearance. Normally, immediately after the infusion of IV lipid, the serum is lipemic. It should be totally clear approximately 8 hours after infusion. This may be checked by obtaining serum cholesterol and triglyceride levels, or grossly, at the bedside by drawing a blood sample, spinning it down, and observing the serum for lipemia. Plasma osmolality and sodium, potassium, chloride, CO_2, BUN, creatinine, calcium, phosphate, and glucose also should be monitored on a frequent periodic basis—initially daily. Magnesium levels should be monitored regularly, but somewhat less frequently.

When discontinuing the infusion, the clinician should gradually taper the rate over 24 to 36 hours. A prolonged infusion should never be stopped abruptly because severe hypoglycemia may ensue. On the other hand, many patients with home hyperalimentation tolerate abrupt cessation of the infusion well. These patients generally infuse their hyperalimentation solution over a 12-hour period while sleeping and immediately cease infusion when ambulatory. Critically ill and hospitalized patients are generally better served by tapering rather than abrupt cessation. Complications are not uncommon with hyperalimentation and can be life-threatening. Placement of the central venous catheter has resulted in pneumothorax, hemothorax, hydrothorax, brachial plexus injury, venous thrombosis, and embolism. Because of the nature of the solution infused and the central venous location of the catheter, infectious complications have been reported and must be recognized and immediately corrected. Alterations in glucose metabolism may result in hyperglycemia, glucosuria with an osmotic diuresis, and in severe cases, hyperosmolar nonketotic dehydration and coma. The mortality in the last situation can be as high as 50%.

Early recognition of hyperglycemia and its treatment by reducing the rate of infusion and/or administration of insulin correct these complications. A sudden change in glucose concentration in a patient who is receiving hyperalimentation should suggest sepsis. Patients with nonketotic

hyperosmolar coma characteristically have blood glucose levels in excess of 500 mg/dL and must be treated aggressively, often with large doses of insulin and fluid. Ketoacids in diabetic patients given inadequate insulin for the additional carbohydrate load and postinfusion hypoglycemia resulting from rapid withdrawal of glucose in the face of persistently elevated endogenous insulin levels also may occur and are treated by increasing insulin and glucose infusions, respectively. Rarely, the complete metabolism of glucose for energy needs results in an elevated partial pressure of CO_2 (P CO_2) and CO_2 narcosis with respiratory insufficiency. Blood gas determinations confirm the diagnosis. Treatment is directed at reducing the amount of CO_2 produced for energy requirements by providing a greater share of the caloric load as fat. Alterations in amino acid metabolism may result in hyperchloremic metabolic acidosis, plasma and amino acid imbalances, hyperammonemia, and elevated BUN levels (26). Alterations in the content of the infusion or rate of infusion must be made. Hypophosphatemia and hypercalcemia and hypocalcemia are corrected by addition or removal from the infusate of the appropriate inorganic ion. Vitamin deficiencies; essential fatty acid deficiencies; trace mineral deficiencies; and abnormal plasma potassium, sodium, and magnesium levels have been reported and are corrected by appropriate addition or removal of the particular substance. Trace minerals and essential fatty acid deficiencies are not encountered when fresh-frozen plasma and fat emulsions are administered as previously described. Finally, alterations in liver enzymes, cholestatic jaundice, and fatty infiltration of the liver complicate long-term administration. Indeed, the administration of more calories than required results in lipogenesis and fatty infiltration of the liver. This may be eliminated in patients receiving long-term hyperalimentation by administering it in a cyclic manner. Glucose is periodically withheld, and only amino acids and fats are infused for an 8-hour period. This has reduced and, in fact, cleared fatty livers.

Once the amount of calories for maintenance of basal needs and restitution of adequate nutrition is determined, the route may be chosen. If the amount of calculated calories can be administered by oral or tube feedings, this is preferred. It appears that patients require fewer calories to maintain body functions and normal weight status if they are given orally rather than IV. If the gut cannot be used and the total caloric requirements must be replaced, IV hyperosmolar solutions must be used. If the gut is temporarily unavailable and will be functional soon, isosmotic IV solutions may be used to limit catabolism until the gut is functional.

Perioperative Total Parenteral Nutrition

The benefits of perioperative nutrition have been difficult to assess in properly controlled studies. It has been shown conclusively to be of benefit only in severely malnourished patients. For all others, it seems to add risk rather than benefit. Indeed, overfeeding can be detrimental because it increases septic complications and compromises immune and hepatic function. In the severely malnourished patient who cannot take oral alimentation, total parenteral nutrition should be administered 7 to 10 days preoperatively. This reduces complications by 10%. The enteral route is preferred, if possible, because it reduces septic complications and maintains structure and functional integrity of the gastrointestinal tract (92).

Intravenous Nutrition for Specific Organ Malfunction

Surgical patients who have sustained acute renal failure have been successfully managed by providing them with hyperalimentation solutions. Providing adequate amounts of calories in these patients can be difficult because fluid administration may be limited. This can be obviated by either frequent dialyses or continuous plasma filtration. Unfortunately, dialysis and plasma filtration result in 6 to 10 g of amino acids lost per day. This amount must be added to the usual requirement to attain optimum balance. Mortality in surgical patients with acute renal failure is exceedingly high. According to some reports, mortality may be reduced significantly by the provision of adequate calories and essential amino acids (1). Hyperalimentation in patients with acute renal failure unfortunately does not reduce the frequency of dialyses, although it may have some effect on lessening the duration of renal failure. Essential amino acids have been found to be more efficacious than a combination of essential and nonessential regimens by some groups. It appears that those given essential amino acids have a less rapid rise in BUN and reduced mortality compared with a similar group given essential and nonessential amino acids in the hyperalimentation solution (36).

Patients who have hepatic failure or hepatic encephalopathy are often nutritionally depleted. Straight-chain amino acids are metabolized by the liver, whereas branched-chain amino acids are metabolized by muscle. Amino acid profiles examined in patients with hepatic failure reveal that the concentrations of straight-chain amino acids are elevated, whereas the branched-chain amino acids are diminished. The assumption is that of the two major sites of amino acid metabolism, liver and muscle, the liver is incapable of metabolizing amino acids. Moreover, it has been proposed that if the amino acids the liver metabolizes are withheld while those metabolized by muscle are given, the nutritional status of the patient might be improved. In one series, patients with cirrhosis given branched-chain amino acids had an 87% improvement in their condition, and 75% of those with hepatitis were improved after the administration of branched-chain amino acids (37). Patients with significant hepatic disease probably should have a limited protein intake, ranging between 0.5 and 1 g/kg body weight. Simultaneous administration of oral neomycin and

lactulose, by reducing gut flora and ammonia metabolism, may enhance protein tolerance.

More directed use of nutrients are currently being studied. L-Arginine and L-glutamine stimulate host defenses and increased wound healing. Glutamine may preserve the intestinal barrier in stressed patients and essential fatty acids and polyribonucleotides may enhance immune function in cancer patients. Thus in the future, it may be possible to assess a patient's specific needs and provide a selected nutrient regimen to meet these needs (78).

FLUIDS AND ELECTROLYTES

Part of "10 - PERIOPERATIVE CARE "

Body Fluid Compartments

The treatment of many fluid and electrolyte disorders requires a knowledge of the body fluid compartments and the ability to calculate them in a given individual. Specific therapy of postobstructive diuresis, dehydration, hypovolemia, and water intoxication requires that knowledge for appropriate therapy. *Total body water constitutes approximately 60% of the body weight in males and 50% in females.* For a lean person, 10% is added; for an obese person, 10% is subtracted because muscle cells contain the greatest fraction of water. *The total body water is divided into compartments: extracellular, intracellular, and transcellular* (Table 10.4). *The extracellular fluid compartment composes approximately 20% of the body weight and is divided into plasma (4.5%), interstitial fluid (16%), and lymph (2%). Because the blood volume is made up of solids and plasma, it can be calculated by multiplying the body weight by 7%.* Intracellular fluid composes 30% to 40% of the total body weight and is accessible only by freely diffusible molecules. Transcellular fluid constitutes 1% to 3% of the total body weight and is composed of pleural, peritoneal, cerebrospinal, intraocular, salivary, and digestive secretions. It is in equilibrium with the extracellular fluid and in disease conditions may increase in amount, particularly during trauma. This is the so-called third space, fluid that is unavailable to the intravascular compartment in situations of injury.

TABLE 10.4. BODY FLUID COMPARTMENTS

Compartment	%
Total body water	50–60
? Extracellular fluid	20–22
?? Blood plasma	4.5
?? Interstitial fluid	16
?? Lymph	2
? Intracellular fluid	30–40
? Transcellular fluid	1–3

The osmolality of the plasma is an indication of the endogenous substances contained in that compartment and is helpful clinically in situations of dehydration and hypervolemia. The osmolality is generally measured by freezing-point depression but can be calculated conveniently by doubling the sum of the sodium and potassium concentrations and adding to that quantity the blood glucose level divided by 20 plus the blood urea level divided by three. These latter two substances are osmotically active and may contribute significantly to the total osmotic content.

The amount of fluid necessary to maintain homeostasis is equivalent to the urine output plus insensible loss plus abnormal losses minus the water produced by the metabolism of fat, carbohydrate, and protein (Table 10.5). Each of these entities must be calculated for the individual patient if optimum fluid balance is to be achieved.

TABLE 10.5. FLUID REQUIREMENTS

	Requirement
Urine output (UO)	= 30–50 mL/hr (adult) 1–2 mL/kg/hr (child)
Insensible loss	= 10–15 mL/kg/24 hr (adult) 25–45 mL/100 kcal (child)
Abnormal loss	= Measured external or estimated third-space loss
Water of metabolism	= 0.1 × 25 × body weight (adult) 0.1 × kcal met (child)

Note: Basic fluid requirement = (UO + Insensible loss + Abnormal loss) – H_2O metabolism.

The amount of urine necessary to maintain proper balance is dictated by the physiologic limits of the kidney for solute and water excretion. *In resting humans, the products of normal metabolism produce a solute load that requires a minimum of 400 to 600 mL of urine for excretion.* Traumatized and critically ill patients are hypermetabolic and may produce twice the normal solute load, necessitating a minimum of 800 to 1,200 mL of urine excretion per day. Conversely, excessive output may lead to a washout of the renal medullary osmotic gradient, resulting in impaired concentrating capabilities of the kidney. The fluid intake required to produce large urine outputs also may result in fluid retention and vascular overload. Thus there are limits between which urine output should be maintained. The adult kidney is most efficient in maintaining balance when fluid intake is sufficient to produce a urine output of 800 to 1,200 mL per day, or 30 to 50 mL per hour. Urine output in children should be maintained between 1 and 2 mL/kg body weight per hour.

Insensible loss refers to the water lost from the respiratory tract and skin. The amount lost depends on the ambient temperature and humidity, as well as the patient's body surface area and body temperature. *The normothermic adult in a comfortable environment loses 800 to 1,000 mL per day (10 to 15 mL/kg of body weight per 24 hours).* Insensible losses

in children are conveniently related to caloric consumption. A child will lose 25 to 45 mL of H_2O for each 100 kcal metabolized. The amount of calories consumed per day may be calculated by multiplying the body weight by 100 for each of the first 10 kg, by 50 for each of the second 10 kg, and by 20 for each additional kg body weight in excess of 20 kg (Table 10.2). Therefore a 10-kg child loses about 350 mL per day and a 20-kg child about 420 mL. Insensible losses increase by about 10% for each degree centigrade of temperature elevation above normal.

The water produced by metabolism is calculated from the caloric expenditure of the patient. The amount of water produced in milliliters is numerically equal to 10% of the total amount of kilocalories consumed. The resting adult metabolizes approximately 25 kcal/kg of body weight per 24 hours, whereas the child's caloric expenditure is calculated on a graduated basis as previously described. *An 80-kg adult who consumes 2,000 kcal (25 kcal/kg × 80 kg) produces 200 mL of H_2O, whereas a 12-kg child who consumes 1,100 kcal (10 kg × 100 kcal/kg + 2 kg × 50 kcal/kg) produces 110 mL of H_2O.* Because these volumes are small, the water of metabolism is often disregarded in total fluid calculations in patients with functioning kidneys.

Abnormal losses refer to fluids lost from the body by nasogastric suction, fistula drainage, vomiting and diarrhea, or the vascular system by third-space sequestration (e.g., retroperitoneal edema, operative trauma, ascites, bowel obstruction). The volumes of these losses are measured when external drainage occurs or estimated when sequestration is present and added to the total daily fluid requirements.

The total daily fluid requirement in an adult is calculated by adding the desired urine output, the insensible loss adjusted for temperature elevations, and measured or estimated abnormal losses. By monitoring the patient's urine output and weight, the clinician can determine the appropriateness of the calculated fluid requirement. The patient who is not receiving total caloric replacement should lose approximately 1 pound per day unless, as in the immediate postoperative period, obligate third-space sequestration of fluid is occurring. If the urine output or weight status is inappropriate, the fluid administered is adjusted accordingly. An example of total fluid replacement calculation follows: an 80-kg febrile (38°C) adult with a nasogastric tube draining 400 mL per day would require 1,200 mL urine output (50 mL per hour × 24 hours) plus 1,320 mL insensible loss (15 mL per kg of body weight per 24 hours × 80 kg + 10% of this quantity for the 1° temperature elevation) plus 400 mL abnormal loss (nasal gastric output) for a total of 2,920 mL per 24 hours.

Total fluid replacement in children may be calculated from the calories metabolized. One milliliter of fluid is administered for each kilocalorie metabolized. *Thus a 25-kg child would require 1,000 mL for the first 10 kg, 500 mL for the second 10 kg, and 100 mL for the final 5 kg, for a total of 1,600 mL per day* (Table 10.2).

Basic Electrolyte Requirements

The average young adult eating a regular diet receives approximately 70 to 120 mEq of sodium, 60 to 80 mEq potassium, 15 to 24 mEq of magnesium, and 80 to 140 mEq of chloride per day. Although the kidney is extremely effective in conserving sodium because it can reabsorb in excess of 99% of that filtered, total renal function is better preserved if enough sodium is administered so that maximum conservation of that filtered is unnecessary. Potassium, on the other hand, is not as efficiently conserved and therefore must be provided to avoid potassium depletion. Because magnesium is stored, patients who are in good nutritional balance before their illness do not require replacement, provided the period of IV therapy is limited. Patients whose nutritional status is marginal or who have alcoholic cirrhosis often require magnesium replacement at a rate of 5 to 20 mEq per day. IV sodium, potassium, and chloride requirements may be satisfied by providing the adult with about 75 mEq of sodium chloride and 40 mEq of potassium chloride per day.

Baseline electrolyte requirements for children are best calculated on the basis of caloric expenditure. Minimum 24-hour requirements are 3 mEq of sodium per 100 kcal, 2 mEq of chloride per 100 kcal, and 2 mEq of potassium per 100 kcal. Thus the 30-kg child would require 1,700 kcal. The sodium requirement is 17 × 3 = 51 mEq, the chloride requirement is 17 × 2 = 34 mEq, and the potassium requirement is 17 × 2 = 34 mEq.

Abnormal losses must be added to these basic requirements. The fluid lost from the body may be analyzed for its electrolyte content to determine accurate replacement (Table 10.6). Fluid sequestered in a third space generally mimics the electrolyte content of plasma and therefore can be replaced accordingly.

	Sodium	Potassium	Chloride
Gastric	60	10.0	90
Jejunum	105	5.0	100
Ileum	120	10.0	105
Cecum	80	20.0	50
Bile	175	5.0	100
Pancreas	170	4.5	75

TABLE 10.6. AVERAGE ELECTROLYTE CONTENT OF GASTROINTESTINAL LOSSES

Anuria

The fluid and electrolyte requirements for patients who are anephric or anuric are calculated from insensible and abnormal losses. *With insensible loss, an adult should receive 10 to 15 mL/kg of body weight per 24 hours, whereas a child should receive 25 mL of fluid per 100 kcal expended.* The caloric

expenditure is estimated on the basis of weight as previously described. Half of the fluid is administered as 10% dextrose in water and the other half as 5% dextrose in 0.2N saline solution. Potassium is generally not administered unless serum studies indicate the need for replacement. Abnormal losses are added to these basic requirements. These calculations are merely estimates of the patient's needs; therefore fluid and electrolyte therapy must be continuously adjusted according to serum electrolyte analyses, patient weight, and when appropriate, urine output.

Volume and Sodium Disturbances

Dehydration

When the patient's minimum fluid requirements are not met, a water deficit accompanied by weight loss occurs. A 4% loss of body weight resulting from a water deficit requires emergent rehydration. A 6% loss of body weight caused by lack of hydration results in a life-threatening condition often manifested by signs and symptoms of shock. The water lost may be relatively isotonic, in which case the dehydration is normonatremic, or hypotonic, which causes hypernatremia to occur.

Dehydration in urologic patients may be caused by postobstructive diuresis, prolonged vomiting and diarrhea, and diabetes insipidus. Postobstructive diuresis may be either physiologic or pathologic. Physiologic diuresis occurs when volume overload precedes the relief of the obstruction or when serum urea is elevated. The kidney responds appropriately when it is unobstructed by excreting the excess volume in the former circumstance or undergoing an osmotic diuresis as a result of the excess urea in the latter situation. The diuresis is self-limited because it ceases when the kidney has returned the body to a homeostatic condition. Rarely, a pathologic diuresis is superimposed on the physiologic diuresis and occurs as a result of specific defects that cause a decreased proximal and distal tubule sodium reabsorption and lack of concentrating capabilities of the kidney, resulting from a reduced medullary osmotic gradient (65). Such patients do not respond to antidiuretic hormone (ADH) or mineralocorticoid administration. Appropriate therapy consists of replacing insensible losses as previously outlined in addition to measured losses. Because the sodium content in the urine usually ranges between 50 and 70 mEq/L, urine output is replaced with 0.5N saline solution. It is important not to overhydrate these patients because such therapy often perpetuates the pathologic diuresis and prevents reestablishment of the medullary osmotic gradient, prolonging the concentrating defect. As the concentrating ability of the kidney returns, fluid therapy is reduced accordingly. It is often helpful in patients who have severe diuresis to follow serum osmolalities and daily weights, adjusting therapy accordingly.

Gastric losses are repleted with 0.5N saline or normal saline solution to which potassium chloride is added. Diarrheic losses are replaced with lactated Ringer's solution. Diabetes insipidus may occur as a result of a lack of ADH, collecting duct unresponsiveness to endogenous ADH, or lack of a medullary osmotic gradient. Patients are often slightly hypernatremic and mildly dehydrated. The urinary sodium content is generally low. Fluid administered should have a relatively modest sodium content until results of urinary electrolytes become available. The diagnosis should be sought expeditiously because specific therapy will often correct the disorder.

Volume Excess

Volume overload may be the result of either hypotonic or isotonic fluid excess. Hypotonic fluid excess results in the water intoxication syndrome manifested by clouded sensorium, irrational behavior, changing neurologic signs, stupor, seizures, and coma. Water intoxication most commonly occurs as a result of hypotonic irrigant absorption through the prostatic bed in patients undergoing transurethral resections. The first signs of volume overload are usually a rising CVP and mental confusion. Blood pressure changes are not often noted initially. If a minimum amount of water is absorbed and central nervous system (CNS) symptoms are not present, fluid restriction with judicious use of diuretics will suffice. In more severe cases in which significant hyponatremia and CNS disorders occur, the treatment should include fluid restriction coupled with hypertonic sodium chloride (3%) administration. Diuretics are not effective in the presence of significant hyponatremia and should be used sparingly until the serum sodium is returning to normal. Inappropriate secretion of ADH, often as a consequence of malignant tumors, is another cause of hypotonic fluid excess and also may result in hyponatremic fluid overload. These patients are often successfully managed by fluid restriction.

Isotonic fluid excesses are usually iatrogenic and are a consequence of excessive administration of fluids that contain sodium. The development of congestive heart failure, inappropriate weight gain, or peripheral edema depends on the severity of the overload. Such patients are treated with diuretics and fluid restriction.

Potassium Disorders

Hyperkalemia usually occurs in urologic patients as a result of acute renal insufficiency, addisonian crisis, trauma, shock, and diabetic acidosis. Life-threatening elevations in serum potassium often produce significant ECG alterations. *Peaking of the T wave, lengthening of the PR interval, prolongation of the QRS complex, and loss of the P wave occur with progressive hyperkalemia.* As potassium continues to rise, the ECG may ultimately resemble a sine wave. Calcium gluconate protects the heart from the adverse effects of potassium

and may be administered in severe cases of hyperkalemia. *Treatment consists of IV administration of hypertonic sodium bicarbonate, which results in a shift of hydrogen ion out of the cell and concomitant movement of potassium into the cell, causing a temporary lowering of serum potassium.* Glucose and insulin therapy (10 units of regular insulin plus 50 g of glucose) are recommended only in extremely urgent situations. Potassium is temporarily bound during glucose transport, thus effectively removing it from the serum. Because these measures are only temporary, simultaneous institution of therapy to lower the serum potassium permanently is mandatory. This may be accomplished with ion exchange resins (Kayexalate given by mouth or by rectum), peritoneal dialysis, or hemodialysis.

Hypokalemia usually results from excessive upper gastrointestinal losses, diuretic therapy, steroid administration, and hyperaldosteronism. Metabolic alkalosis is often associated. Therapy is directed at eliminating the disorder and replacing the loss. Administration of solutions that contain sodium in the face of hypokalemia may promote renal potassium loss, particularly in patients with primary hyperaldosteronism. When sodium losses occur concomitantly with potassium deficits, both must be replaced simultaneously. If rapid replacement therapy is required, the ECG should be continuously monitored. If ECG changes occur, the infusion must be slowed or stopped until the abnormalities resolve.

Hypercalcemia

Hypercalcemia in urologic practice is generally the result of metastatic tumor to bone, hydrochlorothiazide therapy, or hyperparathyroidism. The symptoms of hypercalcemia include anorexia, weakness, somnolence, polyuria, and coma. Initial therapy involves the establishment of a sodium diuresis by administering IV saline solution and nonthiazide diuretics. If the diuresis must be prolonged, careful monitoring of serum potassium and magnesium concentrations is essential to prevent deficiencies.

Inorganic phosphate administration will rapidly lower serum calcium but results in metastatic calcification of soft tissues. Ethylenediamine tetraacetic acid (EDTA), a chelating agent, also rapidly lowers serum calcium but has many associated complications. These two agents should not be used unless life-threatening hypercalcemia occurs. On rare occasions, emergency therapy is required in patients with hyperparathyroidism who have uncontrollable serum calcium levels.

Mithramycin and steroids also have been used to control hypercalcemia. With both agents a decrease in serum calcium does not usually occur for 24 to 48 hours. Mithramycin, a cytotoxic agent used in the treatment of malignancies, has many serious side effects including bone marrow depression, renal failure, and hepatic toxicity. It should be used only in patients with neoplasms and then only when more conventional methods fail. The dosage is 1 to 2.5 mg per day for 3 days. Steroids are somewhat less effective and are best used in disorders in which vitamin D sensitivity is etiologic. Dialysis also may be used, particularly in patients with associated renal failure.

Bone resorption and release of calcium may be controlled by the oral or IV administration of etidronate disodium. This drug is useful for controlling hypercalcemia in patients with metastatic disease. It is not useful for treating an acute hypercalcemic crisis. In this situation, saline infusion and diuretics are indicated. Etidronate disodium may be added to the regimen to allay the recurrence of hypercalcemia. If used, adequate renal function and urine output must be present because the drug is excreted in the urine.

A saline diuresis should be the first modality tried, reserving the other forms of therapy for specific indications. It is important that diagnostic studies be instituted early to define the cause of hypercalcemia so that definitive therapy may proceed without delay.

Hypermagnesemia

Hypermagnesemia interferes with neuromuscular transmission both peripherally and centrally. The signs and symptoms include deterioration of mental function, drowsiness, muscular paralysis, and in severe cases, coma. Nausea, vomiting, peripheral vasodilation, and hypotension also may occur. The ECG shows prolongation of the QT interval. Persistent hypermagnesemia may cause soft tissue calcification and interfere with bone mineralization. Hypermagnesemia rarely occurs with normal renal function. Patients with decreased renal function who ingest medications that contain magnesium may be particularly prone to the disorder. Urologic patients in whom magnesium-containing solutions are used to irrigate the urinary system for dissolution of stones also may manifest hypermagnesemia. This is particularly true when the irrigant, such as Suby's solution G or citric acid, glucono-delta-lactone magnesium carbonate (Renacidin), is used at increased pressures in areas where vascular beds are exposed. When the symptoms are severe, emergency treatment with calcium gluconate may be necessary. In patients with normal renal function, however, hydration and furosemide administration generally suffice. Rarely, patients with decreased renal function or those with severe neurologic symptoms require hemodialysis to return magnesium levels to normal.

Hypomagnesemia may be a complication of aminoglycoside therapy, hepatic disease, or nutritional deficiency. Symptoms include somnolence and weakness.

Anion Gap

The anion gap is the difference between the sum of the major cations, sodium and potassium, minus the sum of the major anions, bicarbonate and chloride, and is normally about

16 mEq/L. The anion gap is of considerable importance in distinguishing among several types of acid–base disturbances. Most of the acidoses commonly found in urologic practice do not have an increased anion gap: hyperchloremic metabolic acidosis, renal tubular acidosis, uremic acidosis, and the acidosis accompanying diarrhea or excessive ileostomy drainage. An increased anion gap is most commonly associated with ketoacidosis; lactic acidosis; hyperosmolar, hyperglycemic, and nonketotic coma; and occasionally, uremic acidosis. Rarely, hyperchloremic metabolic acidosis caused by enteric urinary absorption may present with an anion gap.

Acid–Base Disturbances

Acid–Base Balance

Under normal dietary conditions, humans generate acid at 70 to 100 mEq per day, equal to 1 mEq/kg of body weight per 24 hours. This acid load is buffered by both extracellular and intracellular buffers that include hemoglobin, protein, inorganic phosphate, organic phosphate, and the bicarbonic–carbonic acid buffer system. Organic phosphate represents the principal intracellular buffer, whereas the bicarbonic–carbonic acid buffer system constitutes the major extracellular buffer. Under normal circumstances, these buffers can accommodate approximately 15 mEq/kg of body weight of hydrogen ion without causing major shifts in systemic pH. *Acid–base disturbances are classified into one of four basic types: (a) metabolic acidosis, (b) metabolic alkalosis, (c) respiratory acidosis, and (d) respiratory alkalosis.* Irrespective of the primary cause of the acid–base abnormality, the body compensates by establishing an acid–base disturbance. Thus, in patients with metabolic acidosis, there is compensatory respiratory alkalosis, and in those with respiratory alkalosis, there is compensatory metabolic acidosis, and so on. The compensatory mechanisms are generally incomplete, so despite compensation, the pH generally remains on the side of the primary disturbance. Therefore, if the pH is below 7.38, the primary disorder is acidosis; if above 7.42, the primary disorder is alkalosis. The Pa CO_2 distinguishes between respiratory and metabolic. A patient with a pH of 7.44 and a P CO_2 of 48 would have a primary alkalosis, which would be metabolic in view of the elevated P CO_2. The disturbance is a primary metabolic alkalosis with a secondary compensatory respiratory acidosis. The lungs are the primary mediator of the respiratory compensation and the kidneys the mediator of metabolic compensation. Clinically, the four types of acid–base disturbances are not classified as pure and are generally compensated as described. For illustrative purposes, however, each is discussed individually.

Metabolic Acidosis

Metabolic acidosis may be caused by a decreased extracellular bicarbonate concentration or may be a consequence of an increased extracellular volume without a proportional increase in bicarbonate content. The latter explains the acidosis of dilutional hyponatremia and water intoxication. A shift in hydrogen ion from the cell to the extracellular fluid compartment and net loss of body bicarbonate account for the acidosis. Decreased extracellular bicarbonate concentration may be caused by either a decrease in renal bicarbonate reclamation or by the consumption of serum bicarbonate resulting from an excessive acid load to the systemic circulation. In the former, the acidosis develops slowly, whereas in the latter it has an acute onset. Decreased generation of bicarbonate by the kidney occurs in uremic acidosis, renal tubular acidosis, and aldosterone deficiency. An increased production of metabolic acid may occur because of increased protein intake or an increased rate of tissue catabolism; increased production of endogenous organic acids, such as lactic acid (shock) and ketoacids (diabetes); the administration of exogenous acids, such as ammonium chloride; and finally, extrarenal losses, such as gastrointestinal losses of bicarbonate in patients with diarrhea or an ileostomy.

Excessive drug ingestion (salicylate intoxication) also may cause an acidosis. The effects of an acute acidosis include dilation of arterioles, impairment of cardiac contractility, and systemic venous constriction, whereas chronic acidosis results in depletion of bone alkaline stores caused by the buffering capacity of the bone. The bone generally buffers 30 to 40 mEq of acid per day in chronic acidotic states. The differential between a renal or extrarenal cause can conveniently be made by checking the urinary pH. If the acidosis is caused by exogenous or nonrenal mechanisms, the urinary pH is acidic. Conversely, if the mechanism is caused by a lack of bicarbonate generation and reclamation, the urinary pH is persistently alkaline.

Metabolic Alkalosis

When metabolic alkalosis occurs, there is a net addition or increase in extracellular bicarbonate concentration. Because the kidney has a great capacity to excrete bicarbonate, two conditions must be met for metabolic alkalosis to occur. First, there must be a mechanism for increasing extracellular bicarbonate concentration, and second, there must be a mechanism to prevent the kidney from excreting the excess bicarbonate. This may occur as a result of increased loss of hydrochloric acid from the stomach after vomiting or nasogastric tube drainage; increased loss of hydrochloric acid in the stool of patients who have a defect in chloride reabsorption in the ileum and colon (congenital chloridorrhea); potassium depletion, which results in a shift of hydrogen ion into the cell; contraction of the extracellular volume without a proportional decrease in bicarbonate content; an increased renal production of bicarbonate resulting from the use of a diuretic; respiratory acidosis; primary hyperaldosteronism; and hypoparathyroidism. Excessive ingestion of alkali, such as the milk alkali syndrome, also may be causative.

Respiratory Alkalosis

Hyperventilation results in respiratory alkalosis and is always caused by stimulation of the respiratory center. This may be the result of hypoxia, drugs, toxins, CNS disorders, or psychogenic causes, or hyperventilation may occur as a compensatory mechanism for metabolic acidosis. When primary, sepsis always must be suspected.

Respiratory Acidosis

Respiratory acidosis results from hypoventilation and may be caused by depression of the respiratory center from CNS disease, drugs, defects in nerves and muscles of the respiratory center as a result of disease or injury, thoracic cage disorders, airway obstruction, or chronic pulmonary disease.

FLUID AND ELECTROLYTE ABNORMALITIES ASSOCIATED WITH GENITOURINARY IRRIGANTS

Part of "10 - PERIOPERATIVE CARE "

Water Intoxication

Water intoxication in urologic practice is generally a result of excessive nonelectrolyte irrigant absorption during endoscopic or endourologic procedures. As the nonelectrolyte fluid is absorbed, volume expansion and dilutional hyponatremia occur. The clinical manifestations of this syndrome (TUR syndrome) were first described in 1946 after a transurethral resection (TUR) of the prostate in which the patient was noted to become restless. There was dark red discoloration of the serum, progressive oliguria, azotemia, and pulmonary edema, followed by death. The development of the syndrome was associated with an 18.5% mortality (20). As more experience has been gained with TURs, this syndrome has become better defined. After substantial volume expansion with resultant hyponatremia, patients generally complain of nausea, become mentally confused or restless, and have sensory disturbances; if allowed to progress, blindness, convulsions, hypotension, coma, oliguria, and death supervene.

During a TUR, some fluid is invariably absorbed; however, the amount is usually insufficient to cause the clinical manifestations of water intoxication. The amount of fluid absorbed is directly related to (a) the pressure of the irrigant, which is a function of the height the bag is placed above the prostatic fossa; (b) the intravesical pressure; (c) the intraprostatic pressure; and (d) the CVP. The duration of the resection, the size of the gland, the quality of resection, and the type of resection equipment used also play a role. Blood loss, like volume absorption, has been correlated with the time of resection. As a rule, 20 mL per minute of fluid are absorbed and 2 mL per minute of blood are lost during resection. A continuous-flow resectoscope is more likely to produce significant water intoxication than the inflow–outflow method. Perhaps most important is the quality of resection because frequent capsular penetration and entrance into venous sinuses predispose the patient to the development of water intoxication. The first sign that should arouse suspicion is an increase in CVP or left atrial pressure (Swan-Ganz). A change in blood pressure is generally not an early sign and in fact may not be noted, even when the syndrome is severe enough to cause blindness.

The pathophysiology of the TUR syndrome has been reasonably well elaborated. After nonelectrolyte irrigant absorption, serum sodium and chloride fall as volume overload occurs. Tachypnea, hypertension, and subsequent bradycardia resulting from the carotid reflex may occur. As electrolyte changes occur from dilution, cardiac output falls, plasma volume is variable, and body weight increases. As the extracellular osmolality decreases, cerebral edema occurs, causing confusion, seizures, and blindness. Pulmonary edema also may occur with hypoxemia, cyanosis, and acidosis, and alteration of the clotting factors may occur with hemorrhage, hemolysis, anemia, and shock. Patients at increased risk for development of this syndrome are those who have cardiac disease and have been on a low-salt diet with diuretic supplementation and patients with hydronephrosis, salt-losing nephritis, urinary retention, or chronic illness and malnutrition.

Treatment of Water Intoxication Syndrome

Patients who are symptomatic and manifest severe neurologic abnormalities require rapid correction of their electrolyte status. This may be accomplished by the simultaneous administration of a potent diuretic, such as furosemide, with the restoration of serum sodium content by the infusion of hypertonic saline solution. The sodium deficit is calculated by subtracting the current serum sodium from the desired serum concentration and multiplying the value by the quantity 0.2 × body weight in kilograms (extracellular fluid volume). This gives the milliequivalent amount required to return the serum sodium to the desired value. Half of this amount is administered rapidly, after which a second serum sodium concentration is obtained and the therapy modified accordingly. If the patient has neurologic symptoms or signs, 3% sodium chloride is used. On the other hand, if neurologic abnormalities are absent, normal saline may be used. The volume is determined by the number of milliequivalents calculated. For example, an 80-kg man whose serum sodium is 110 mEq/L would require 400 mEq to return serum sodium to 135 mEq/L. Half, or 200 mEq (about 400 mL of 3% sodium chloride), would be given rapidly, monitoring the neurologic, pulmonary, and cardiac status. The remainder would be given as needed, depending on a repeated serum measurement and clinical status. For patients who are less symptomatic and have a less severe hyponatremia, the administration of a potent diuretic and the infusion of normal saline solution may suffice.

Other Problems with Irrigants

If the area of instrumentation is infected, the irrigant may carry bacteria with it, resulting in bacteremia occasionally followed by sepsis. Other electrolyte abnormalities depend on the specific irrigant used. Currently, five types of isotonic fluids are in general use: sorbitol, 3.3%; glucose, 5.4%; glycine, 1.5%; mannitol, 3.0%; and urea, 1.8%. Water is also used; however, it is not isotonic.

Water

Because water is not isotonic, it can result in significant hemolysis of red blood cells when it enters the systemic circulation. This hemolysis results in an increased level of serum potassium and, during a typical TUR, elevated serum levels of free hemoglobin. However, it has been shown that hemoglobin is not toxic in levels up to 600 mg, provided it is not combined with abnormal serum proteins. In the latter case, it may in fact be nephrotoxic.

Sorbitol (3.3%)

Sorbitol is metabolized completely either to carbon dioxide and water or to dextrose. It also may be excreted by the kidneys. The use of this solution may result in an elevated level of serum glucose, which may be particularly severe in noncompensated diabetic patients. The same propensity to water intoxication occurs with this fluid as with any other urologic nonelectrolyte irrigant fluid. Rarely, sorbitol may result in an osmotic diuresis with dehydration and a hyperosmolar state. This solution should be used with caution in diabetic patients.

Glucose

Glucose solutions are no longer generally used because they are sticky and are not comfortably handled in the urologic suite. If used, however, they have the same complications as sorbitol.

Glycine (1.5%)

Ammonia intoxication has been reported after the use of glycine. Patients particularly prone to this complication are those with impaired hepatic function who presumably are unable to clear the ammonia generated from glycine metabolism. If the patient receives large doses of glycine, it may also cause salivation, nausea, and light-headedness.

Mannitol (5%)

The main side effect of mannitol is an osmotic diuresis that can result in dehydration and hyperosmolality. Occasionally, this solution may cause systemic acidosis.

Urea

Urea is no longer conventionally used because of its permeability to the intracellular and extracellular space. Its use results in elevated serum urea concentrations and also may cause an osmotic diuresis.

Volume Deficits

With significant loss of body fluids, dehydration, hyperosmolality, and neurologic disturbances occur. If allowed to persist, hypotension and death supervene. With a 4% loss of body weight caused by a water deficit, emergency rehydration is in order. These patients are generally symptomatic. A 6% loss of body weight caused by a water deficit results in shock and often death. Common urologic disorders that lead to dehydration include postobstructive diuresis, which results in a urine with a sodium content of 50 to 70 mEq/L and a potassium content of 10 to 40 mEq/L. These patients' urinary fluid losses may be replaced accurately with 0.5N saline solution. Prolonged vomiting or diarrhea also may result in significant dehydration. The former is replaced with 0.5N saline solution plus 40 mEq/L of potassium chloride if renal function is normal, and the latter is replaced with Ringer's lactate. Finally, diabetes insipidus may result in significant dehydration. This syndrome is discussed in detail in the section on polyuria. During replacement therapy and in the follow-up period, daily body weight, serum sodium, and serum osmolality are measured to determine the efficacy of therapy.

FLUID AND ELECTROLYTE ABNORMALITIES ASSOCIATED WITH URINARY INTESTINAL DIVERSION

Part of "10 - PERIOPERATIVE CARE "

Intestinal Conduits

The intestine's primary function is to selectively absorb electrolytes and nutrients. This function makes it less than an ideal structure as a urinary conduit or storage vehicle. Urine exposed to its surface is altered because some constituents are reabsorbed and others are diluted as a result of intestinal secretion. The extent to which the fluid is altered depends on the surface area to which it is exposed, the time of exposure, and the composition of the urine.

Electrolyte transport occurs throughout all segments of the bowel. In the jejunum, sodium absorption is coupled with glucose transport, whereas in the ileum and colon, sodium and chloride are actively absorbed. In these segments of bowel, there may be an exchange between sodium and hydrogen and chloride and bicarbonate. Thus with hydrogen absorption, sodium is secreted; with chloride absorption, bicarbonate is secreted. The movement of these ions depends on cyclic adenosine monophosphate (cAMP), and therefore blocking this enzyme alters transport properties (45).

Metabolic disorders of intestinal urine transport are treated by choosing specific drugs that block this enzyme system. Water moves according to its concentration gradient; thus hyperosmotic urine results in the movement of water into the conduit from the systemic circulation. Hypoosmotic urine, on the other hand, may result in a net movement of water into the extracellular space. The flux of water is particularly prominent in the jejunum, less so in the ileum, and least in the colon. Metabolic abnormalities brought about by intestinal alteration of urine are often compensated for by the kidney's ability to increase and alter its excretion rates of unwanted solutes. Severe metabolic disturbances often manifest themselves only when renal function is compromised, particularly when the serum creatinine concentration exceeds 2 mg/dL.

Syndrome of Hyperchloremic Metabolic Acidosis

The ingestion of acetazolamide (or acid), diarrhea, and intestinal fistulae can cause hyperchloremic acidosis; however, the most common cause in urologic practice is intestinal interposition. *This syndrome occurs in patients who have ileum or colon interposed in the urinary tract; is most common in patients in whom the urine remains in contact with the intestinal mucosa for extended periods, particularly those with ureterosigmoidostomies; and is most severe with compromised renal function*. The acidosis usually does not manifest an anion gap; however, recent evidence suggests that an anion gap may occur rarely in those patients with rectal bladders, continent diversions, and other bowel substitutes in which the urine remains in contact with the intestinal mucosa for extended periods. This anion gap is most likely caused by an increased absorption of phosphate, sulfate, and ammonium, resulting in decreased total body elimination of these anions.

Four hypotheses have been proposed to explain the acidosis: (a) renal tubule acidification defect, (b) intestinal absorption of ammonium, (c) intestinal bicarbonate secretion, and (d) active intestinal chloride transport. A renal tubule acidification defect seemed likely because many of these patients had ascending pyelonephritis. Pyelonephritis affects the distal tubule, and it was proposed that this interfered with the kidneys' ability to acidify (55). It is clear that a distal tubule acidification defect will make the acidosis worse, but it is unlikely that it is the primary mechanism because many patients with normal renal function also manifest the acidosis (87).

The second hypothesis proposed that the urea excreted in the urine is split to ammonium by intestinal bacteria, thereby increasing ammonium absorption, which accounts for the acidosis (7,80). Because ammonia derived from urea is not an acid (when hydrated with water, it is a base), this mechanism does not explain proton addition (hydrogen ion) to the systemic circulation. It may be, however, that ammonia serves as a proton acceptor from acid secreted in the urine and then is actively reabsorbed. Data from our laboratory suggest that ammonium is transported and results in significant proton loads to the patient.

The third mechanism proposed is bicarbonate secretion by the intestine. Clearly, the ileum and large bowel are capable of significant bicarbonate losses because patients with ileostomies and those with severe diarrhea can lose enough bicarbonate to become acidotic. Several experiments also have demonstrated bicarbonate loss in measurable quantities in patients with ureterosigmoidostomies (21). However, the amount of bicarbonate lost to the body in most cases of intestinal interposition seems insufficient to explain the severity of the acidosis. Experimental evidence in animals suggests that this plays only a minor role in most cases (52).

The final mechanism proposed is that active chloride transport is the primary cause of the acidosis (31). The hypothesis is that chloride is actively transported and then requires a cation to preserve electrical neutrality to diffuse across the membrane. The cation may be either hydrogen or ammonium, whichever is most available. Thus in effect hydrochloric acid and/or ammonium chloride enter the systemic circulation in sufficient quantities to account for the acidosis. The evidence to support this hypothesis comes from experiments that showed that when ion fluxes are measured across the intestinal segment exposed to urine, net hydrogen uptake is directly proportional to chloride transport. Moreover, chlorpromazine (Thorazine) and niacin, two drugs known to block chloride transport through their effect on cAMP, limit this acidosis (50,51).

From intestinal vesicle experiments it appears that the primary mechanism for the acidosis is the transport of ammonium across the intestinal epithelium in exchange for a proton. Chloride is absorbed to maintain electrical neutrality in exchange for bicarbonate. The net effect is absorption of ammonium chloride in exchange for carbon dioxide and water (60).

Other electrolyte abnormalities associated with hyperchloremic metabolic acidosis include hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia, and hypersulfatemia. Hypokalemia may be severe because the chronic acidosis falsely elevates the serum potassium and therefore obscures the severity of the total body potassium deficiency. On correction of the acidosis, these patients often require considerable replacement of potassium to replenish body content. The intestinal loss of potassium can be reduced by the administration of spironolactone.

The mechanism of hypocalcemia and hypomagnesemia is not clear. It has been suggested that chronic acidosis results in depletion of bicarbonate stores in the skeleton with release and loss of calcium initially through the urinary tract. The hypocalcemia is merely a reflection of total body depletion. Reports of rickets and growth retardation in some of these patients (8) suggest that abnormal calcium metabolism may be clinically significant. Large losses of

calcium in the urine with stimulation of calcium reabsorption by the tubule through the mechanism of parathormone would result in magnesium excretion by the binding of all available transport sites for calcium under maximum parathormone stimulation. Thus excessive magnesium loss through the urinary tract results in hypomagnesemia. Initial experiments in our laboratory suggest that the increased intestinal absorption of sulfate results in its blocking renal reabsorption of calcium and magnesium (62). Whatever the mechanism, it is clear that hypocalcemia and hypomagnesemia occur most commonly when renal function is significantly impaired. In patients with normal renal function, serum concentrations of these two ions are rarely more than slightly depressed.

Urea and creatinine also are reabsorbed by the bowel and may result in elevated serum levels that do not accurately reflect renal function. Because transport properties vary somewhat for various portions of the bowel, electrolyte abnormalities specific for each segment are described subsequently.

Jejunum

The jejunum is seldom used for intestinal diversion because of the severe fluid and electrolyte abnormalities that occur when it is used as a conduit or storage vehicle for urine. *These segments lose large quantities of sodium chloride and absorb significant amounts of potassium and urea.* With the extensive sodium and chloride loss into the lumen of the intestine, the osmotic gradient this creates necessitates the movement of water from the systemic circulation into the lumen of the intestine. This results in substantial fluid losses to the body. Some hydrogen absorption and bicarbonate loss also may occur. These patients become hyponatremic, hypochloremic, hypovolemic, hyperkalemic, and azotemic. They also may have a mild acidosis and an associated serum hyperosmolality (13,46). In response to these abnormalities, there is an increased secretion of aldosterone and renin, thus further reducing urine sodium concentration and thereby increasing the concentration gradient of sodium between serum and lumen, enhancing secretion by the jejunum. When short segments are employed for conduits and drainage is unimpeded, recent reports suggest that severe electrolyte abnormalities occur in fewer than 10% of patients (33).

Ileum

The ileum is perhaps the most commonly employed segment for urinary diversion. *Chloride is absorbed and bicarbonate secreted and ammonium absorbed in exchange for hydrogen ion by this segment.* Although rarely a clinical problem, these patients may develop hypokalemia associated with the hyperchloremic metabolic acidosis (19). The metabolic abnormality is more common in patients with compromised renal function. Although water does move into the conduit if urine flowing through it is hypertonic, because the ileum does not secrete large amounts of osmotically active agents such as sodium and chloride, the amount of fluid lost is not as extensive as for the jejunum.

Colon

The colon also transports chloride in exchange for bicarbonate, so patients with colon segments are prone to develop hyperchloremic metabolic acidosis. These patients are more likely to become hypokalemic, hypomagnesemic, and hypocalcemic than patients with ileal segments. However, they are less likely to become hypovolemic because fluid fluxes are less prominent in the colon than in ileal or jejunal segments. Indeed, patients with colon conduits can actually concentrate to about 400 mOsm/kg, as opposed to ileal segments in which the gradient generally does not exceed 350 mOsm/kg (61).

Treatment

The treatment of hyponatremic, hypochloremic, hyperkalemic, metabolic acidosis found in jejunal segment patients consists of oral sodium chloride, bicarbonate, and fluids. When severe, IV administration of saline solution in large volumes and the establishment of a diuresis correct both the hyponatremia and hyperkalemia, as well as the hypovolemia.

Hyperchloremic metabolic acidosis is treated by oral chloride restriction, bicarbonate replacement (either in the form of sodium bicarbonate or Polycitra), and drainage of the area of storage. In patients with a Koch pouch, rectal bladder, or ureterosigmoidostomy, this requires catheterization of the segment. Studies have shown that chlorpromazine and niacin may be effective. These drugs block active chloride transport in the intestine, thereby limiting the acidosis. This has been demonstrated in experimental animals and in patients (50). The advantage to these drugs is that a sodium or potassium load is not given as when bicarbonate or Polycitra is used. This may be particularly useful in patients who have congestive heart failure or those with severely compromised renal function in whom an excessive sodium or potassium load would be inappropriate. High dosages and prolonged use of chlorpromazine may result in the development of extrapyramidal symptoms including tardive dyskinesia. The side effects of niacin are usually minimal but may consist of agitation and flushing. Because of the CNS effects of chlorpromazine, we prefer to use niacin in children and chlorpromazine in adults.

BOWEL PREPARATION

Part of "10 - PERIOPERATIVE CARE "

Urologic operations in which bowel is used as a conduit or storage vehicle for urine are invariably elective; therefore

proper preparation of the bowel may be planned preoperatively. The major risks involved in operating on the bowel include wound infection, anastomotic breakdown, and peritoneal infections . *In unprepared bowel, the wound infection rate varies between 32% and 58%. This incidence may be reduced to 6% to 9% if mechanical and antibiotic bowel preparation are used* (14). Breakdown of the intestinal anastomosis is more common when performed on unprepared bowel. Antibiotics appear to have a protective effect on the anastomosis, particularly if the blood supply is compromised. In experimental animals, an unprepared bowel that is devascularized results in perforation and death, whereas an antibiotically prepared bowel that is devascularized heals. In a clinical study comparing colon anastomoses in prepared and unprepared bowel, the total number of complications and the number of anastomotic breakdowns were increased in the unprepared group. In this study, if the patients were steroid dependent, had peritonitis, received prior irradiation, or had diabetes mellitus or chronic renal failure, the chance of anastomotic breakdown was significantly increased (3). Finally, intraperitoneal abscesses are more common when unprepared bowel is operated on.

In mechanical preparation of the bowel, the enteric content is reduced, and in antibiotic preparation, the bacterial organisms are reduced. The mechanical bowel preparation reduces the amount of bacteria but not the number of bacteria per milliliter of feces. Spillage of enteric contents is less likely because there is less of it to spill; however, with a spill, the inoculum is the same as if the spill occurred in unprepared bowel. More recent evidence indicates that excessive mechanical bowel preparations are unnecessary. Two to four liters of polyethyleneglycol may be given orally the day before surgery, or 2 days before surgery, clear liquids are begun and 30 to 60 mL Phospho-Soda is given orally. On the day before the operation, 30 mL of Phospho-Soda is given (Table 10.7).

	Conventional		PEG + Electrolytes	
Preoperative Day	Diet	Cathartic	Diet	PEG
3	Low-residue plus supplements		Regular plus supplements	—
2	Clear liquids		Low-residue plus supplements	—
1	Clear liquids	30–60 mL Fleets Phospho-Soda	Clear liquids	2–4 L PEG + electrolytes

PEG, polyethylene glycol.

TABLE 10.7. MECHANICAL BOWEL PREPARATION

The mechanical preparation reduces the amount of enteric contents, not the number of bacteria in a single inoculum. Therefore the mechanical bowel preparation is supplemented with an antibiotic bowel preparation (Table 10.8). The risk of wound infection and other infectious complications is reduced from 30% to 6% when antibiotics are combined with the mechanical preparation. Antibiotics also protect vulnerable and ischemic bowel. The disadvantage to giving antibiotics in preparation for bowel surgery is that it increases the incidence of tumor implantation on the anastomosis, and it might play a role in the development of pseudomembranous enterocolitis (15). The former is generally of little consequence to the urologist; however, the latter can be a significantly morbid and sometimes fatal complication. It seems unlikely, however, that antibiotics are solely responsible for the development of the latter syndrome because there has been no change in its incidence in the preantibiotic and postantibiotic eras. It was originally

thought to be caused by a staphylococci but recently, *Clostridium difficile* and the endotoxin that it elaborates have been implicated. The most important factor in its initiation is intestinal ischemia. Other risk factors include bowel preparation, nasogastric tubes, gastrointestinal surgery, narcotics, advanced age, cancer chemotherapy, and renal disorders. The diagnosis is made by identifying the cytopathic toxin of *C. difficile* in the stool. Treatment is directed at repopulating the bowel surface with normal enteric flora and the administration of antibiotics to which the organism is sensitive: vancomycin, aminoglycosides, metronidazole, and ciprofloxacin.

Preoperative Day	Kanamycin	Neomycin + Erythromycin	Neomycin + Metronidazole	Tinidazole + Doxycycline
3	1 g kanamycin p.o. q.h. × 4, then q.i.d.	—	—	—
2	1 g kanamycin p.o. q.i.d.	—	1 g neomycin q.i.d. + 750 mg metronidazole q.i.d.	—
1	1 g kanamycin p.o. q.i.d.	1 g erythromycin + 1 g neomycin at 1, 2, and 11 PM	1 g neomycin q.i.d. + 750 mg metronidazole q.i.d.	2 hr preoperatively: 1,600 mg tinidazole + 400 mg doxycycline infused IV over 2 hr

TABLE 10.8. ANTIBIOTIC BOWEL PREPARATION

SHOCK

Part of "10 - PERIOPERATIVE CARE "

An all-encompassing definition of shock is impairment of cellular function caused by either a reduction in effective delivery of oxygen and nutrients to the cell or inability of the cell to use these substrates. Shock may be classified as hypovolemic, neurogenic, endocrine, anaphylactic, cardiogenic, and septic.

Hypovolemic Shock

When loss of blood, loss of fluid, or sequestration of fluid is etiologic, cardiac output and blood pressure fall while plasma renin and ADH levels rise. The sympathetic nervous system is stimulated, which results in the constriction of arterioles and major veins, an increase in heart rate and strength of contraction, a reduction in microcirculatory flow and sludging, and mobilization of glucose for energy production. If hypotension and peripheral vasoconstriction continue, a decrease in transmembrane potential occurs, membrane permeability increases, and fluid is sequestered, particularly in muscle cells. If the perfusion defect continues, cellular death supervenes.

Hypovolemic shock is generally divided into three phases. The first phase occurs with volume deficits between 0% and 10% and begins with a sequestration of fluid resulting in cellular edema. During this phase, the blood volume deficit is counteracted by stimulation of the sympathetic nervous system, which results in peripheral vasoconstriction and increased heart rate in an attempt to maintain blood pressure. ADH, renin, and aldosterone also contribute to the vasoconstriction and reduced urinary excretion in an attempt to restore extracellular fluid volume. The second stage occurs with a blood volume deficit of 15% to 20%. Cardiac output and arterial pressure are significantly reduced, despite the compensatory mechanisms previously described. The low blood pressure and the intense adrenergic discharge result in tachycardia, tachypnea, cutaneous vasoconstriction, pallor, diaphoresis, piloerection, apprehension, and restlessness. The third stage occurs when the deficit exceeds 25%. During this stage, tissue perfusion is inadequate, and if it persists for long periods, cellular death occurs. Vital organ function is severely impaired, capillary membrane integrity is lost, and disseminated intravascular coagulation may occur. It is at this point that irreversible shock follows.

Treatment

Hypovolemic shock caused by third-space fluid loss, as occurs in burns and retroperitoneal dissections, is treated with isotonic fluid replacement. Many advocate partial replacement with 5% albumin, suggesting that the total fluid requirement is less with a smaller amount extravasating into the third space and pulmonary interstitium. Other studies suggest that crystalloid is more likely to produce pulmonary edema than solutions of 5% albumin, hetastarch, or dextran. Others disagree, stating that colloid is unnecessary and that only crystalloid should be used in the initial phases of resuscitation. *When blood loss is the cause, whole blood is administered, which is appropriately typed and crossmatched.* Dextran may be used as a blood substitute for volume expansion; however, it carries the risk of creating clotting abnormalities through antigen–antibody reactions. Prolonged use of dextran also may engender renal failure. Hetastarch is a polysaccharide that is available in a 6% solution. It has replaced dextran as the drug of choice for volume expansion when blood and albumin are unavailable because renal and bleeding complications are less common. If after adequate volume resuscitation cardiac output is insufficient, ionotrophes and vasoconstrictors may be in order (see Cardiogenic Shock).

Attention also must be paid to the patient's ventilatory status. Hypoventilation with hypoxemia severely augments the deleterious effects of underperfusion.

In the successfully treated patient, there are three phases of fluid dynamics. The first phase follows the insult and is characterized by sequestration of fluid and cellular edema. This accounts for the major initial pathophysiologic problems encountered in hypovolemic shock. The sequestration generally ceases between 24 and 36 hours, provided the patient has been adequately resuscitated. In the ensuing 2 to 3 days, a homeostatic period occurs in which the sequestered fluid remains unavailable to the intravascular space. At approximately 4 to 7 days after the insult, the third phase is initiated in which the fluid is mobilized. It is during this phase that patients with limited cardiac reserve may develop congestive heart failure as the fluid is mobilized from the third space into the intravascular space. The judicious use of diuretics may be necessary to rapidly restore intravascular volume to normal.

Neurogenic, Endocrine, and Anaphylactic Shock

Neurogenic shock results from a sudden loss of vasomotor tone caused by a neural injury. This commonly occurs in traumatic injuries to the CNS.

Endocrine deficiencies resulting from a lack of function of the adrenal glands or pituitary result in circulatory failure. Uncontrollable diabetes may result in an osmotic diuresis with resultant hypotension.

Anaphylactic shock is the result of an acute systemic autoimmune reaction that causes a marked increase in vascular permeability with sequestration of edema fluid, bronchospasm, and laryngospasm. This sequestered fluid leaves the intravascular space, resulting in hypotension. Of patients who develop intraoperative anaphylaxis, 5% to 10% die (90). Agents that have been implicated in triggering the response include neuromuscular blocking agents, IV anesthetics, antibiotics, radiocontrast, blood products, protamine, and latex. Latex allergy may result in an anaphylactic-like reaction with symptoms as mild as nausea and flushing to angioedema, bronchospasm, and cardiovascular collapse. Three groups of patients appear to be at high risk: (a) myelodysplastic patients, (b) those with congenital urologic abnormalities, and (c) health care workers. In high-risk patients, consideration should be given to prophylactic administration of prednisone, diphenhydramine, and ranitidine (47).

Treatment

Neurogenic shock is treated with isotonic fluid administration until blood pressure returns to normal levels. Patients with adrenal insufficiency or pituitary insufficiency are treated with replacement corticosteroids and fluids that contain sodium. Anaphylactic shock is treated with epinephrine, fluids, antihistamines, and corticosteroids.

Cardiogenic Shock

Cardiogenic shock occurs when the heart fails to act effectively as a pump. This may be brought about by a myocardial infarction, cardiac arrhythmia, or depression of myocardial contractility resulting from a metabolic aberration. Rare causes include mechanical blockage that may occur in a tension pneumothorax, vena caval obstruction, and cardiac tamponade. The most common cause of the disorder is clearly myocardial infarction. Approximately 10% to 15% of patients with an acute myocardial infarction will develop cardiogenic shock. Mortality in this group is exceedingly high, approaching 75% (38). These patients present with cold, clammy skin; hypotension; tachycardia; anuria; and oliguria and are often confused and agitated. The pathophysiologic process includes a decreased cardiac output, decreased ejection fraction, normal or increased CVP, increased pulmonary capillary wedge pressure, and increased left ventricular end-diastolic pressure.

Treatment

Because hypotension results in decreased coronary artery perfusion with a propensity toward limiting the amount of oxygen delivered, one of the first hallmarks of therapy is to provide the patient with oxygen. Decreased oxygenation of the injured myocardium will result in progression of the infarction. Oxygen is administered by face mask, nasal prongs, or rebreathing bag. Patients with chronic pulmonary disease need to be monitored carefully if their respiratory drive is secondary to hypercapnia. These patients may require intubation. It is during the initial postmyocardial infarction period that life-threatening cardiac arrhythmias often occur. Therefore these patients need to be continuously monitored, and a large-bore IV line must be available to administer antiarrhythmogenic drugs. Often, these patients have a slight metabolic acidosis, which must be corrected with bicarbonate administration. The placement of a pulmonary artery catheter is generally indicated because the diagnosis can be conveniently made using this device, and treatment is often dictated by measurements performed. With the pulmonary artery catheter, cardiac output, preload, and afterload can be determined and will verify the diagnosis by revealing a decreased cardiac output. Preload is determined by pulmonary capillary wedge pressure measurement and afterload by peripheral resistance calculation. When the peripheral resistance is normal, an agent is chosen that will improve the cardiac output by increasing myocardial contractility. Dobutamine or isoproterenol is the drug of choice. When there is an increase in peripheral resistance, therapy is directed at increasing cardiac output and decreasing afterload. The afterload may be reduced with nitroprusside, and cardiac output can be increased with either dobutamine or isoproterenol. The dosage of nitroprusside must be monitored carefully because it may result in thiocyanate intoxication. When peripheral resistance and cardiac performance are decreased, the use of vasopressors, such as dopamine and epinephrine, is useful (44).

Septic Shock

Septic shock, unlike hypovolemic shock, does not necessarily result in a perfusion deficit to the tissues. Rather, it results in an inability of the body cell mass to effectively use substrate delivered to it. Septic shock is an important cause of morbidity and mortality among hospitalized patients. Approximately 25% to 40% of patients who sustain a bacteremia develop septic shock (72). In most cases, it originates from an infection with Gram-negative enteric bacilli. *Escherichia coli* is the most common pathogen followed by *Klebsiella, Enterobacter, Serratia,* and *Pseudomonas* species . Gram-positive organisms occasionally cause sepsis, and rarely, viruses, fungi, rickettsia, and protozoa, have been implicated. The genitourinary tract is the most common source, followed, in decreasing order of frequency, by the gastrointestinal tract, the respiratory tract, wound infections, infected IV catheters, and pelvic infections. Urosepsis in the critical care setting carries with it a 25% mortality (71). Patients at increased risk for the development of septic shock include those who have cirrhosis, diabetes mellitus,

and neoplastic diseases (67). Radiotherapy and/or chemotherapy particularly predispose the latter group of patients to sepsis. Mortality ranges between 40% and 90%.

Endotoxin, a lipopolysaccharide protein complex, which is part of the cell wall of Gram-negative bacteria, has been implicated as the initiating agent in the pathophysiologic process. Because other than Gram-negative organisms also cause the syndrome, it is clear that if endotoxin is an initiating agent, it is not the only one. The infecting organism activates proinflammatory cytokines. Prominent among these cytokines are tumor necrosis factor-α, interleukin-1 and interleukin-6, among others (10). Other cytokines that have been implicated include interleukin-6 and interleukin-8, a platelet-activating factor, interferon-γ, macrophage-derived proteins, and arachidonic acid metabolites. As a result of the production of these substances and the presence of bacteria, many biochemical and immunologic pathways are activated. The complement, kinin, and clotting systems are stimulated and activation of polymorphonuclear leukocytes occurs, and the release of the ß-endorphin histamine and prostaglandins is facilitated.

There are two phases of septic shock: the hyperdynamic and the hypodynamic. In the first phase, patients are hypotensive and have warm, dry skin. Arterial vasodilation, an increase in body temperature, hyperventilation with respiratory alkalosis, and an increase in pulse pressure and cardiac output occur. Although the absolute value of cardiac output in patients with septic shock is generally increased, it cannot achieve adequate perfusion of essential organs. These events may be heralded by a shaking chill, which is followed by a rapid rise in temperature. Lactic acidosis may supervene, indicating the cell's inability to utilize or obtain oxygen and substrate. However, the degree of lactic acidemia does not correlate with the lack of oxygenation in septic shock, nor is it of any prognostic significance (79). The vasoactive kinins, histamine, and prostaglandins result in vasodilation and perhaps some vasoconstriction in various vascular beds. ß-Endorphin produces cardiovascular depression, vasodilation, capillary leakage, and hypotension (43).

As sepsis continues, myocardial depression occurs, with a reduced ejection fraction and left ventricular dilation. The activation of the kinin system results in the release of bradykinin, an agent known to produce vasodilation of arterioles. Activation of the complement system results in depletion of the C3 and C5 components (72). The white blood cell count is elevated with a shift to the left; rarely, however, sepsis may result in a depressed count—a poor prognostic sign. Blood glucose is elevated as a result of the increased levels of glucagon, growth hormone, and catecholamines. Progression of the disease leads to leukocyte aggregation with development of disseminated intravascular coagulation, vascular endothelial damage producing capillary leak with interstitial edema, and depression of myocardial function. Platelet aggregation results in the release of vasoactive substances. Pulmonary platelet aggregation has been suggested as the initiating event in the adult respiratory distress syndrome (ARDS). Myocardial depression increases capillary permeability, and impaired cellular function leads to the second phase of septic shock, a hypodynamic state in which unresponsive hypotension and death occur.

Treatment

Treatment is directed at supporting the patient and defining the source of infection so that it can be eliminated. *Initially, blood, urine, sputum, and wound drainage, if present, are sent for culture. IV administration of bactericidal antibiotics is begun immediately.* The choice of antibiotics is dictated by the suspected source of the sepsis. An aminoglycoside at full dosage is administered initially. Dosage level subsequently is adjusted to the renal function. If an intraabdominal source is suspected, anaerobic coverage is added: clindamycin, chloramphenicol, or metronidazole. If a pulmonary source seems likely, a cephalosporin is added; if the urinary tract is suspect, ampicillin is given. *Blood pressure is supported with crystalloid and/or colloid infusions, the rate dictated by the blood pressure, CVP or right atrial filling pressure, and urine output. Crystalloid resuscitation is begun, but if it is inadequate to return filling pressure to normal, colloid is added.* It has been suggested that colloid infusion results in less capillary leakage with less subsequent interstitial edema formation. Corticosteroid administration is generally not recommended, except for specific circumstances of adrenal insufficiency. Recent studies show no benefit to their administration (73,81). Indeed, their administration may even be harmful.

The use of antiendotoxin antibodies has improved survival in some studies. Gram-negative bacilli share a common core lipopolysaccharide. In a series in which antiserum to this antigen from human volunteers was given to septic patients, mortality was reduced by 50% (97). Most subsequent studies have not confirmed these findings (81). In select cases, continuous intraperitoneal lavage also may be helpful. This therapy is particularly amenable to patients who are septic as a result of pelvic inflammation and abscesses. Dialysis catheters placed into the depths of the pelvis and irrigated with saline and antibiotic solutions are particularly helpful in these patients (69).

If hypotension occurs after adequate fluid resuscitation or if it persists, blood pressure may be supported with dopamine. In addition to its inotropic effect, the advantage of dopamine over other agents is that it increases renal blood flow. However, dopamine increases intrapulmonary shunting; therefore dobutamine may be preferable in patients with pulmonary complications. Although dobutamine does support blood pressure, it does not improve renal blood flow. In dopamine-resistant situations, norepinephrine (Levarterenol) may be particularly effective because of both its α- and ß-effects. However, neonates and young children have a diminished response to both dobutamine and dopamine and therefore epinephrine is more useful in the immediate resuscitative period (10). ß-Endorphins released in response to the stress of shock may be partially responsible for the

hypotension. It is clear that pituitary endorphins play a role in the pathophysiology of shock, but their exact role is somewhat controversial. The cardiodepressant effect of endorphins is mediated by opiate receptors in the CNS (29). Naloxone, an inhibitor of ß-endorphin binding, may result in significant improvement in the blood pressure and reversal of myocardial depression (75). Others have found that naloxone administration is not associated with an improvement in blood pressure or survival (24). Thyrotropin-releasing hormone also has been used effectively in patients with persistent hypotension. This drug apparently acts centrally, as does naloxone, and like naloxone, it requires an intact sympathoadrenal-medullary axis to be effective. Thyrotropin-releasing hormone and naloxone have an additive effect (24). The prostaglandins PGI and thromboxane A_2 may mediate some of the cardiovascular changes in shock but are not solely responsible for myocardial depression (11). They contribute locally to vasodilation, and it has been found experimentally that blocking the vasoconstrictor thromboxane A_2 in animals improves survival (17).

Antitumor necrosis factor antibodies, anti-interleukin-1 antibodies, and other inhibitors of cytokines have been used with mixed results. Some of the cytokines appear to be protective and thus indiscriminate blockade can be detrimental (81). Other forms of therapy directed at specific pathophysiologic mechanisms such as antiendothelium–leukocyte adhesion antibodies have been developed and may have promise. At this time their clinical role is undefined.

When afterload or ventricular wall tension is increased, cardiac output may be limited. Afterload can be reduced by selective use of vasodilators. Phentolamine (Regitine), an α-blocker, dilates both veins and arteries. It is particularly useful in patients with increased sympathetic tone. Nitroprusside is a short-acting vasodilator whose predominant effect is on the smooth muscle of the arteries. It is an excellent agent for titrating blood pressure in the short-term situation. Nitroglycerin is particularly useful in patients with an associated ischemic myocardium because it improves collateral flow to the heart while dilating the peripheral vasculature.

Sinus rhythm is the most effective rhythm for optimum cardiac output. When supraventricular and ventricular arrhythmias occur in association with a diminished cardiac output, restoration of normal sinus rhythm may be all that is required.

VENOUS THROMBOEMBOLISM

Part of "10 - PERIOPERATIVE CARE "

Pelvic operations have a high propensity for thromboembolic disease. Its prevention in the urologic patient is of particular importance because many operations are performed in the pelvic area. Urologic patients are often placed in lithotomy position, which impairs venous return. Because most thrombi develop in venous plexus along the calf and usually begin during the operation, it is easy to appreciate the significance of impaired venous return that is promoted by positioning.

Risk factors that increase the likelihood of thromboembolic disease may be grouped into three categories: stasis, intimal injury, and hypercoagulability. Stasis includes immobility, congestive heart failure, obesity, and varicose veins. Intimal injury is manifested in vascular disease, previous thrombosis, trauma, and surgery. Hypercoagulable states are associated with advanced age, postoperative state, malignancy, and myocardial infarction.

The prevention of thromboembolic disease has been a subject of considerable controversy. Elevation of the foot of the bed, avoidance of extremity compression, early ambulation, physical therapy, and leg wraps all have been used in an effort to prevent the sequelae of thromboembolic disease. Unfortunately, none of these devices has been shown to be of particular efficacy in the prevention of the disorder. More recently, the development of an alternating pressure cuff on the lower extremities, which facilitates venous return, has been shown to be effective (82). Intermittent compression boots have undergone many modifications, the most recent of which is asymmetric compression rather than circumferential, with the intention of being more effective prophylaxis (which is unproven). The role of excellent nursing care is emphasized when one considers the improvement in venous flow as a function of the various methods advocated. Moving the legs is as effective in promoting venous return as any of the aforementioned methods.

In several studies, the use of mini-dose heparin, that is, 5,000 units administered subcutaneously every 12 hours, has been suggested to decrease the incidence of pulmonary emboli. One study found a substantial reduction in pulmonary emboli as diagnosed by routine postoperative scans (54). Other studies have failed to show any significant difference with and without the use of mini-dose heparin. It is clear, however, that in patients undergoing pelvic lymphadenectomy, administration of preoperative and postoperative mini-dose heparin results in a greatly increased incidence of lymphocele formation (53). Therefore, in urologic practice, prophylactic mini-dose heparinization in the preoperative and postoperative periods has not been successful; consequently, it rarely has been used. Low-dose warfarin therapy also has been used for prophylaxis of deep venous thrombosis. In one study, it was as effective as alternate compression stockings; complications were minimal (34).

Pulmonary emboli may occur silently and be an incidental finding on a chest roentgenogram, or they may suggest their presence by causing dyspnea; chest pain; hemoptysis; and rarely, when massive, circulatory collapse. On physical examination, the pulmonic portion of the second heart sound may be increased, a parasternal heave may occur, on occasion a friction rub can be heard, and the ECG often shows right-sided heart strain as evidenced by right-axis deviation. The chest radiograph, when positive, reveals a lucent area that lacks vascular markings. Later a wedge-shaped

infiltrate develops. Pulmonary scans may be used to support the diagnosis, but the definitive study is a pulmonary angiogram or magnetic resonance angiogram (MRA). Therapy is directed at identifying the source and treating it while administering anticoagulants to the patient, initially with a continuous heparin infusion. If the pulmonary embolus is large or saddle-type and is causing circulatory collapse that is unresponsive to supportive measures, a pulmonary embolectomy is indicated. In select circumstances, the use of thrombolytic therapy is most effective in dissolving emboli. Urokinase, streptokinase, and recombinant tissue plasminogen activator (rtPA) have all been used. Although rtPA results in a more rapid thrombolysis than the other two drugs, it has not shown increased efficacy, because at 24 hours, the resolution is similar no matter what agent is used (43). It should be noted, however, that in postoperative patients, vascular suture lines and puncture sites are likely to bleed with the use of these drugs. Because thrombolytic therapy increases the risk of hemorrhage without significantly affecting long-term outcome, it is useful in very limited circumstances, such as in nonoperative patients with renal artery emboli or massive pulmonary emboli.

Patients who have had a pulmonary embolus documented by one of the aforementioned studies or those in whom the clinical suspicion is high should be treated preferably by anticoagulation. Patients who have pulmonary emboli and are not treated have a 50% chance of another embolus—half of whom die from the event (48). Thus treatment should be instituted without delay. Heparin is the initial drug of choice. Low-molecular-weight heparin is as safe and effective as unfractionated heparin in preventing pulmonary emboli (23). The advantage of the former is that it can be given twice daily subcutaneously (57). The activated partial thromboplastin time (aPTT) should be kept between 2.0 and 3.0 times control [International Normalized Ratio (INR)]. After stabilization, the patient may be given warfarin and the heparin tapered. Following heparin therapy, oral anticoagulants should be administered according to the risk of recurrent pulmonary emboli. In patients who have an initial episode and no ongoing risk factors, 4 weeks of therapy is required. For those with continuing risk factors, at least 3 months of therapy is required (58). Thrombolytic therapy for acute deep venous thrombosis has been used in an attempt to reduce recurrent deep venous thrombosis and the postthrombotic syndrome. Generally, urokinase is given in repeated boluses. However, its usefulness may be limited because it may be successful only if the agent is infused directly into the thrombus, making it difficult to administer (42).

Vena Cava Filters

Anticoagulants are occasionally contraindicated, in which case a vena cava filter inserted percutaneously should be considered. Complications include malposition, migration, arrhythmia, wound infection, recurrent pulmonary emboli, and recurrent deep venous thrombosis (83). Rarely, a massive saddle pulmonary embolus may require a pulmonary embolectomy when the aforementioned measures are unsuccessful in maintaining the patient's blood pressure.

The efficacy of vena cava filters in patients who have thrombophlebitis and are at risk for pulmonary emboli has been evaluated in a large multiinstitutional study. The use of heparin alone or heparin plus a filter was compared in these patients. Those who had filters had a decreased occurrence of symptomatic and asymptomatic pulmonary emboli. However, no effect was observed in immediate or long-term mortality. Moreover, the initial beneficial affect of filters was offset by a significant increase in deep vein thrombosis—related to thrombosis at the filter site (23).

RESPIRATORY DYSFUNCTION

Part of "10 - PERIOPERATIVE CARE "

Respiratory Insufficiency

Inadequate ventilation in the posttraumatic and postoperative periods results in hypercapnia, hypoxemia, or both. The primary goal of therapy is to provide the patient with the capability of maintaining an arterial oxygen partial pressure of at least 60 mm Hg on an inspired oxygen content as close to room air as possible. To achieve this goal, oxygen delivered by nasal prongs, rebreathing mask, a face mask, or an endotracheal tube with respiratory support may be required. However, there are constraints to the amount of oxygen that can be delivered. Limitation of the amount may be a consequence of the device used for delivery, but more commonly, the amount that can be safely delivered is limited by the fact that inhalation of high oxygen concentrations results in pulmonary toxicity. The hazards of high concentrations include suppression of the respiratory drive in patients with chronic pulmonary disease, retrolental fibroplasia (primarily a disease of the newborn but also described in adults), segmental atelectasis caused by the greater solubility of oxygen compared with nitrogen, impairment of respiratory ciliary function, a decrease in pulmonary surfactant, and direct injury to capillary endothelial cells.

The Pa CO_2, which is normally 40 mm Hg, is a primary indication of the adequacy of ventilation. Common causes of hypercapnia include obstructive pulmonary disease, ARDS, metabolic alkalosis, and respiratory depression resulting from sedation or CNS trauma. Hypocapnia may be a result of hypoxia, anxiety, pulmonary embolism, sepsis, and pulmonary insufficiency. Although an indicator of ventilatory adequacy, alteration of P CO_2 is rarely an indication for respiratory support. Of more importance is the partial pressure of oxygen (PO_2), which should be maintained above 60 mm Hg. A PO_2 less than 60 mm Hg requires a change in respiratory management. A normal PO_2 for a particular patient breathing room air before injury may be

estimated by subtracting half the individual's age from 100. If impending airway obstruction is not a problem, initial support of the PO_2 may be obtained by the use of nasal prongs or face masks. Humidified oxygen should be used when possible to prevent drying the nasotracheal mucosa. Oxygen delivered by nasal prongs generally cannot provide an inspired concentration much above 50%. Even though humidified, high-flows have a drying effect on the mucosa; Venturi masks provide constant flows of oxygen ranging between 24% and 40%, depending on the mask. Partial rebreathing masks can deliver in excess of 80% oxygen; however, humidity cannot be added to the system.

On occasion, posttraumatic patients require endotracheal intubation, preferably by the nasotracheal route with a prestretched low-pressure cuff and respiratory support (Table 10.9). Indications for intubation include (a) the facilitation of pulmonary toilet, (b) the prevention of upper airway occlusion, (c) protection against aspiration, and (d) the need for mechanical ventilation. The requirement for mechanical ventilation is assessed by vital capacity, inspiratory force, respiratory rate, arterial oxygen content, and work of breathing. Vital capacity, or the volume of a maximum inspiration after a maximum expiration, is normally 60 to 70 mL/kg body weight. If it is less than 15 mL/kg, ventilatory support is indicated. *The inspiratory force, or amount of pressure that the patient is able to generate against a closed airway, is normally -75 to -100 cm H_2O. Patients who can achieve no more than -25 cm H_2O require mechanical support.* The normal respiratory rate is 12 to 20 breaths per minute. A rate that exceeds 35 breaths per minute suggests the need for ventilatory assistance. The arterial oxygen partial pressure should exceed 60 mm Hg. If this cannot be accomplished by raising the oxygen content of inspired air through the use of face masks and nasal prongs, intubation should be performed. Severe intercostal retractions and a tracheal tug indicate an increased work of breathing and are forerunners of respiratory insufficiency. Initially, the respirator is adjusted to deliver 12 to 15 mL/kg of body weight at a frequency of 8 to 14 times per minute for the adult and 15 to 30 times per minute for the child. Inspired oxygen content (Fi O_2) should be the lowest needed to maintain the PO_2 above 60 mm Hg (an Fi O_2 of 40% is a good level to begin with, adjusting it as required). Not only must blood gas levels be monitored, adjusting the respirator accordingly, but also the circulatory status must be carefully followed, because occasionally institution of mechanical ventilation will cause a decrease in the cardiac output with lowering of the blood pressure.

Facilitation of pulmonary toilet
Prevention of upper airway occlusion
Protection against aspiration
Need for mechanical ventilation as determined by the following:
1. VC <15 mL/kg body weight
2. Inspiratory force <–25 cm H_2O
3. Respiratory rate >35 breaths/min
4. Po_2 <60 mm Hg despite high ambient O_2 concentration
5. Excessive, prolonged increase in the work of breathing

VC, vital capacity.

TABLE 10.9. INDICATIONS FOR ENDOTRACHEAL INTUBATION

When the PO_2 cannot be maintained by an acceptable Fi O_2 (less than 60%), the addition of positive end-expiratory pressure (PEEP) may be helpful. This technique maintains a specified pressure at the end of each respiration rather than allowing end-expiratory pressure to fall to zero. It is particularly useful in ARDS. Initially, 5 cm H_2O pressure is used. If the desired response is not achieved, it is increased in increments of 5 cm H_2O, carefully monitoring the blood pressure for signs of a significant reduction in cardiac output. Usually, no more than 15 cm H_2O is required. On rare occasions, however, as much as 25 cm H_2O pressure may be needed. With the use of PEEP, PO_2 can be maintained at acceptable levels with reduced Fi O_2. Other advantages include a decrease in pulmonary shunting and an increase in functional residual capacity. A proposed advantage is that it drives pulmonary edema fluid from the alveoli and the interstitium into the pulmonary capillaries. Its major disadvantages are a reduction in cardiac output and a diminished urine output. The latter effect is perhaps the result of an increased release of ADH.

One method of anticipating future respiratory difficulties and determining how the patient is progressing on the respirator is by sequentially determining the arterial oxygen gradient, P(A-a) O_2. This gradient is a sensitive indicator of early respiratory impairment. To calculate the P(A-a) O_2, the patient receives 100% oxygen for 20 to 30 minutes, arterial blood gases are drawn, and the barometric pressure is recorded. The calculation is as follows: barometric pressure minus water vapor pressure (47 mm Hg) minus the partial pressure of alveolar CO_2. Because alveolar CO_2 rapidly equilibrates with arterial CO_2, the P CO_2 obtained from the blood gas analysis may be substituted. This quantity minus the PO_2 is equal to the arterial alveolar oxygen gradient.

Acute posttraumatic pulmonary insufficiency occurs after major trauma, burns, hypoproteinemia, or inadequate fluid resuscitation during shock, severe sepsis, pancreatitis, or transplant rejection crisis (antigen–antibody reaction). The cause of ARDS is unclear. It appears that neutrophils contribute because the lungs of patients with ARDS are populated by large numbers of them. They release oxygen-free radicals and elastase, two substances that injure tissues. Macrophages release oxygen-free radicals, proteases, prostaglandins, leukotrienes, and cytokines and also have been implicated. Moreover, the cytokine tumor necrosis factor has been shown to play a role experimentally. Finally, defects in surfactant may be etiologic or merely perpetuate the disease (77).

After the initiating event, platelet microaggregates form in the pulmonary capillaries and injure the alveolar capillary endothelium. Vasoactive substances are released, resulting in increased capillary permeability (6). Peribronchiolar edema follows, which causes an increase in small airway resistance and a reduction in pulmonary compliance, making aeration of the lungs difficult. Pulmonary shunting also occurs. The PO_2 falls and the P CO_2 rises, often despite increases in the Fi O_2. Clinically, the patient becomes dyspneic, tachypneic, and hypoxemic. Functional residual capacity and lung compliance are reduced, and bilateral pulmonary infiltrates are often present on the chest film. The syndrome should be suspected in the septic or traumatized patient when the PO_2 falls despite efforts to increase the Fi O_2.

Treatment involves nasotracheal intubation and mechanical ventilation. PEEP is often necessary. If PEEP results in a reduced cardiac output, inotropic agents may be required to return blood pressure to acceptable levels. The use of colloid to increase intravascular oncotic pressure and thereby draw fluid from the pulmonary perivascular space into the capillaries is controversial, as is the use of steroids. Prophylactic antibiotics administered either by the parenteral route or by inhalation have little to recommend them. Infections are treated when they occur with the antibiotic to which the bacteria are sensitive. Unfortunately, none of the newer pharmacologic therapies has produced impressive results. Methylprednisolone, prostaglandin E, and *N*-acetylcysteine have not been shown convincingly to lessen mortality.

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11
RENAL AND URETERAL INJURIES

Contents

11A RENAL INJURIES

Jack W. McAninch

Richard A. Santucci

Part of "11 - RENAL AND URETERAL INJURIES "

J.W. McAninch and R.A. Santucci: Department of Urology, Wayne State University, Detroit, MI 48201.

Trauma is the leading cause of death for persons between 1 and 44 years of age. In addition, each year, millions of dollars are spent to rehabilitate trauma victims. The team approach to management provides the highest level of expertise in reducing morbidity and preventing mortality. The trauma surgeon relies on the urologic surgeon to deal with the complex injuries of the urogenital system. The urologic surgeon may not become involved in the initial resuscitation phases of trauma care because most injuries to the urogenital system are not life-threatening; however, he or she may become the most important member of the team 2 weeks later when urinary extravasation, abscess formation, and septic complications develop secondarily.

The kidney is the most commonly injured organ in the urogenital system (61), and renal injuries are still subject to controversy in diagnosis and management. Despite the current refined approach, many questions remain unanswered regarding when and for what patients a study should be done to evaluate a renal injury. Even when the diagnosis has been established, there is great controversy over operative versus nonoperative management. The urologic and surgical literature is replete with articles debating the merits of the respective approaches (18,22,80). No simple answers exist. One must review the literature critically and become familiar with the variety of approaches in renal trauma care to apply this information to an individual patient.

The following quotation from Erickson's 1860 *Textbook of Surgery* indicates the importance of careful clinical evaluation in patients with major renal injuries:

If the kidneys are injured, the patient will commonly experience a frequent desire to pass water, and this will be tinged

with blood, often to a considerable extent. The absence of blood in the urine must not, however, be taken as an indication that the kidney is not injured; it may be so disorganized as to be totally incapable of secreting, and subsequently no bloody urine finds its way into the bladder. A man was admitted into the hospital under my care for a buffer injury of the back; he passed water untinged with blood, but after death his right kidney was found completely smashed by the blow, with an extensive extravasation of blood in the celluloadipose tissue around it. Here it was evident that the disorganization was so sudden and complete that no bloody urine had found its way into the bladder.

This clinical picture continues to be reported today.

Approximately 8% to 10% of blunt and penetrating abdominal injuries involve the kidneys. In rural settings, blunt trauma accounts for the largest percentage of renal injuries (90% to 95%) (52); in urban settings, the percentage of penetrating renal injuries increases to 20% (85).

This chapter is intended to provide a logical diagnostic approach to the patient with renal injury and to establish a rationale for management that will ultimately preserve the largest amount of functioning renal tissue, while safely managing the patient's other injuries.

MODE OF INJURY AND PRESENTATION

The mechanism of injury to the kidney is broadly classified as blunt or penetrating. Blunt trauma is more common in most centers, accounting for 80% to 90% of injuries, and results from automobile accidents, auto–pedestrian accidents, falls, contact sports, and assaults (1,2,17,47,59). Gunshot and stab wounds cause 10% to 20% of renal injuries and represent the most common causes of penetrating injury. In 1968, Carlton and co-workers (12) reported associated intraabdominal injuries in 80% of their patients with penetrating renal injury. This observation was supported by Sagalowsky and colleagues (85): Of 122 patients with gunshot wounds, all had associated intraabdominal injury. Liver, small intestine, stomach, and colon were the most commonly injured organs. Stab wounds less frequently have associated intraabdominal injury, with reports ranging from 30% to 70% (42,85). This wide variation may be based on the location of the stab wound. Bernath and others (5) noted that stab wounds posterior to the anterior axillary line were associated with intraabdominal injury in fewer than 12% of cases.

Renal injuries from blunt trauma occur consequent to upper abdominal injury and rapid deceleration. Gross or microscopic hematuria is usually present (8,70). These patients often have profuse abdominal tenderness, lower rib fractures, vertebral body fractures, and flank contusions. A palpable abdominal mass with associated shock may be indicative of a rapidly developing retroperitoneal hematoma from a major renal parenchymal or renal vascular injury. Rapid-deceleration injuries usually involve multiple organ systems, and patients are often unconscious and in shock. Head-on automobile collisions and falls from great heights account for the majority of such injuries. Multiple bony fractures usually are present, as are injuries to the abdominal viscera, vascular system, chest, and head. The renal injury seen in such cases is often a renal pedicle avulsion or acute thrombosis of the main renal artery or one of the segmental arterial branches. Hematuria may not be present, and the diagnosis must be established by radiographic imaging prompted by a high index of suspicion (38,91).

Stab wounds to the kidneys generally have their entrance points in the lower thorax, flank area, or upper abdomen. The size of the entrance wound has little correlation with the extent of injury and the depth of penetration. Hematuria, most often gross, is usually present with major parenchymal injuries. The incidence of associated intraabdominal injuries varies greatly and may be related to the entrance site (5). Careful abdominal examination may reveal marked tenderness and generalized rigidity, indicating bowel perforation. Peritoneal lavage is useful for evaluating intraabdominal injury after stab wounds to the torso (27). Hemorrhagic shock is a common presenting sign, and reestablishment of circulatory volume is of prime importance in the initial treatment. Renal imaging should be done in all patients with stab wounds in the upper abdomen, flank, back, or lower chest, whether hematuria is present or not.

Patients with gunshot wounds to the torso that penetrate the kidney often are in a state of hemorrhagic shock with multiple organ injury. Rapid resuscitation is of prime importance, and immediate surgery may be required before diagnostic studies can be performed. The type of weapon—and of the bullet if known—should be ascertained, but the prevailing wisdom is to “treat the wound and not the weapon” (56). The damage that a missile can inflict is related to the kinetic energy expended, determined from the following formula:

$$KE = \frac{MV^2}{2}$$

where *KE* is kinetic energy, *M* is the mass of the missile, and *V* is the muzzle velocity of the weapon.

In general, the higher the muzzle velocity, the greater the tissue damage, although experimentally the actual wounding effect varies from MV1.5 to MV2.5 (56). Figure 11A.1 demonstrates the method by which bullets of high velocity cause extensive tissue damage: On entering the soft tissue of the body, the bullet creates a temporary pulsatile cavity that can be up to 40 times wider than the diameter of the bullet; a small permanent core of tissue is vaporized; and finally the bullet can tumble or fragment, further widening the area of tissue damage (21). [Many high-velocity

projectiles such as the M-16 yaw after penetrating some distance into tissue, causing an enlarged permanent cavity from bullet tumbling (33).] Temporary cavitation and vaporization can cause extensive damage (the "blast effect"), which may not be appreciated at operation. However, experts point out that the relationship between the volume of the temporary cavity and tissue damage is not absolute and that many so-called high-velocity wounds from assault weapons can leave a clean track with little devitalization (33). Intensive debridement may be required to remove the nonviable tissue created by such injuries, but some researchers have suggested that only a few millimeters of debridement may be required in cases of gunshot through muscle, whereas more extensive tissue excision may be needed in solid organs like the kidney and liver (56). This is borne out in analysis of gunshot wounds to the kidney: Injuries from high-velocity weapons require nephrectomy more often than those from low-velocity weapons (31).

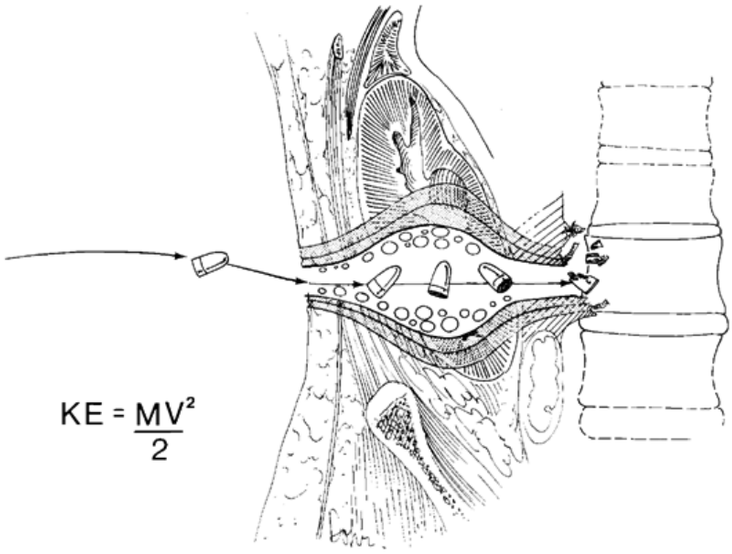

FIGURE 11A.1. Dynamics of missile soft tissue injury. (From McAninch JW. Renal injuries. In: McAninch JW, guest ed. *Urogenital trauma,* vol 2 of Blaisdell WF, Trunkey DD, series eds. *Trauma management*. New York: Thieme Stratton, 1985a:27–49, with permission.)

Most common handguns and many rifles are low-velocity weapons (muzzle velocity of less than 2,000 feet per second), and less extensive debridement may be needed. However, these weapons can cause extensive damage via a number of mechanisms, such as unintentional and intentional bullet fragmentation (34). Increasingly, specialty ammunition is available that is designed to maximize tissue damage after impact, by either intentional fragmentation (Dum-Dum, Devastator, exploding, and other "frangible" ammunition) or an increase in projectile diameter by flattening (hollow-point bullets). The effect of this specialty ammunition, in some cases, is that lower velocity missiles, as from a common handgun, can rival the tissue damage caused even by high-velocity rifles (93). Table 11A.1 lists muzzle velocities of common weapons.

TABLE 11A.1. MUZZLE VELOCITY OF COMMON WEAPONS

Weapon	Velocity (ft/sec)
0.22 short	1,045
0.22 magnum	2,000
0.38 caliber	1,330
0.45 caliber	1,320
AK-47	1,950
Carbine (0.30 caliber)	1,970
7.62 mm (M-14)	2,400–2,800
5.56 mm (M-16)	3,250

From McAninch JW. Renal injuries. In McAninch JW, guest ed. *Urogenital trauma,* vol 2 of Blaisdell WF, Trunkey DD, series eds. *Trauma management.* New York: Thieme Stratton, 1985:27–49, with permission.

HEMATURIA

The presence of blood in the urine is usually the first indicator of renal injury. In most reported series, more than 95% of patients had microscopic or gross hematuria (8,78,82,87,99). However, Bright and co-workers (8) first noted that the degree of hematuria does not correlate with the severity of injury. For example, a renal contusion is diagnosed in a patient with gross hematuria after blunt abdominal trauma, but results on excretory urography are normal. A patient with microscopic hematuria after a rapid-deceleration injury may demonstrate a major renal vascular injury. Guerriero and associates (38) noted gross hematuria in only 10 of 33 patients with renal vascular injuries, and Stables and colleagues (91) found no hematuria in 24% of patients with traumatic renal artery occlusion. In our recent series of 113 grade IV renal injuries, gross hematuria was noted in only 63%, and even microhematuria was absent in 4% (86). All series note the importance of hematuria as an indicator of injury but emphasize that it is a nonspecific finding and does not correlate with the seriousness of the renal damage.

The patient should be evaluated in the emergency room and urine should be obtained for study. Unconscious patients with serious injuries should be catheterized for dipstick urinalysis. If the results are positive, a finding of more than 5 red blood cells per high-power field (RBCs/HPF) would be expected (20). When time permits, microscopic urinary examination should be done.

Nicolaisen and colleagues (78) noted that adult patients sustaining blunt trauma had significant renal injury (defined as minor or major lacerations and vascular injuries) in the presence of gross hematuria or shock (systolic blood pressure less than 90 mm Hg) with microscopic hematuria. Mee and associates (70) subsequently reported a 10-year prospective study of patient selection for radiographic assessment after renal injury. The study included 1,146 patients (1,007 with blunt trauma and 139 with penetrating trauma). Significant injuries were found in 44 patients (4.4%) with blunt trauma, each of whom had either gross hematuria or microscopic hematuria associated with shock. Microscopic hematuria without shock was present in 812 patients with blunt trauma in whom there was no evidence of significant renal injury. Hardeman and associates (41) had similar findings.

Shock is defined as a systolic blood pressure less than 90 mm Hg, and any one measurement at or below this level from the time of evaluation by paramedics in the field satisfies this criterion. This requires careful inspection of paramedic and emergency room records before the determination is made that radiographic assessment is not indicated.

On the basis of available data, the following recommendations apply to the adult patient with blunt trauma: In the presence of gross hematuria or microscopic hematuria associated with shock, radiographic assessment should be done; patients with microscopic hematuria without shock do not require radiographic assessment. However, if physical examination or associated injuries prompt reasonable suspicion of a renal injury, renal imaging should be undertaken. This is especially true for patients with rapid-deceleration injuries, although in the studies of Mee and associates (70) and Hardeman and associates (41) vascular injuries were not missed when the preceding criteria were used.

Renal imaging is required in all patients with microscopic (more than 5 RBCs/HPF) or gross hematuria sustaining penetrating trauma or in pediatric patients. None of the previously mentioned studies found criteria to select patients for imaging who were in the pediatric age group or had penetrating injury.

CLASSIFICATION OF RENAL INJURIES

Categorizing renal injuries according to severity helps in selecting appropriate therapy and predicting results of treatment. Renal injuries can be classified according to the American Association for Surgery of Trauma (75) into five large groups: (a) renal contusions—bruises or subcapsular hematomas associated with an intact renal capsule and collecting system; (b) minor lacerations—superficial cortical disruptions less than 1.0 cm in depth that do not involve the deep renal medulla or collecting system; (c) parenchymal lacerations greater than 1.0 cm in depth without collecting system rupture or urinary extravasation; (d) parenchymal laceration extending through the renal cortex, medulla, and collecting system; or main renal artery or vein injury with contained hemorrhage; and (e) completely shattered kidney or avulsion of main renal artery or vein that devascularizes the kidney (Fig. 11A.2).

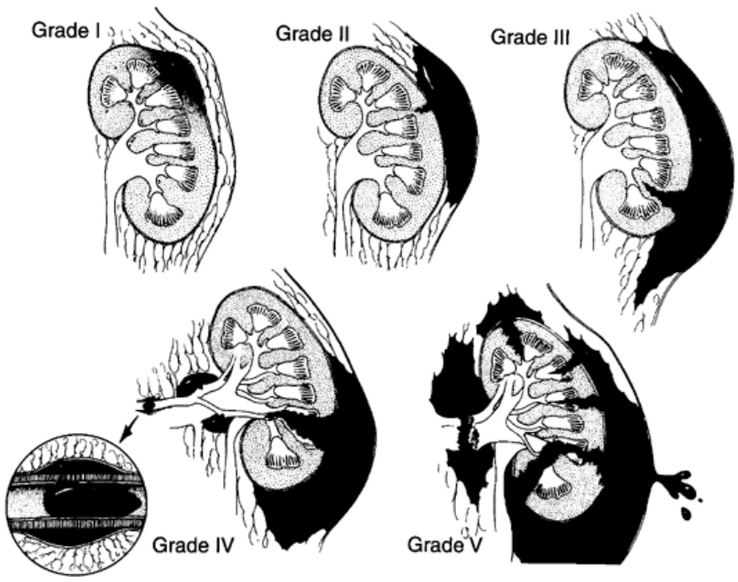

FIGURE 11A.2. Artist's rendition of the Renal Injury Severity Scale of the American Association for the Surgery of Trauma (AAST). Note that grade IV injuries represent parenchymal lacerations extending into the collecting system and injury to the main renal artery or vein with contained hemorrhage. These vascular injuries include traumatic renal artery thrombosis *(inset)*. (From Moore EE, et al. Organ injury scaling: spleen, liver, and kidney. *J Trauma* 1989;29:1664, with permission.)

Vascular injuries and major and minor lacerations constitute significant trauma. These patients should have complete radiographic assessment to determine the full extent of injury and select appropriate management. Categorization does not mandate operation, but it does aid the surgeon in directing the care of these patients. Review of more than 2,500 renal injuries indicates, for instance, that no grade I injuries require operative repair, while nearly 100% of grade V injuries require speedy nephrectomy or repair (87). Those in between (grades II to IV) require individualized therapy, with a general trend for more serious intervention (renorrhaphy or nephrectomy) as the grade increases (Fig. 11A.3).

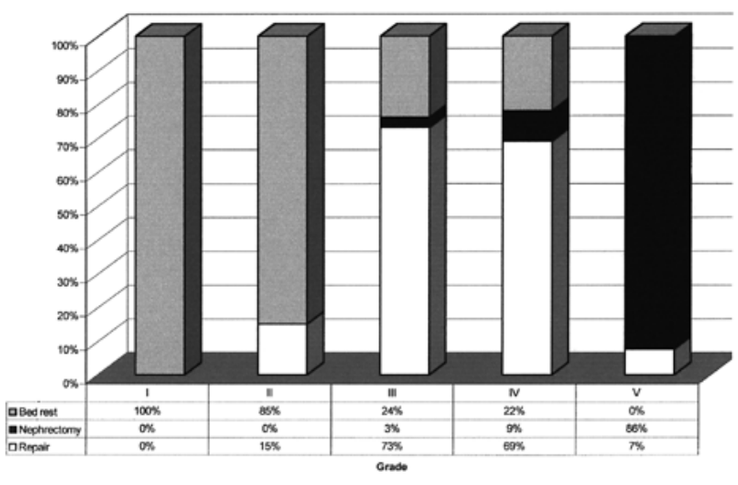

FIGURE 11A.3. Injury scale and treatment of renal injury in 2,500 patients with renal trauma. (From Santucci RA, Mario LA, Segal MR, et al. Classification trees are highly predictive of need for surgery in renal trauma patients. *J Urol* 2000;163[Suppl]:4, with permission.)

STAGING AND ASSESSMENT OF INJURY

Staging is the orderly process by which a renal injury is completely defined by history, physical examination, and radiographic or other imaging techniques. For instance, for

a patient with blunt trauma from an automobile accident who has gross hematuria, and in whom renal imaging shows the kidneys to be normal, the injury is categorized as a renal contusion, and no additional studies are necessary. However, if the results of renal imaging are indeterminate or abnormal, additional information will be needed to complete the staging and document the full extent of the injury. Increasing use of computed tomography (CT) scanning has allowed more accurate determination of injury severity than has been available in the past (7,66).

History, physical examination, and the determination of hematuria are the initial evaluative measures. The presence of gross or microscopic hematuria (more than 5 RBCs/HPF) continues to be the best indicator of injury. All patients sustaining penetrating trauma or pediatric patients with positive findings should have radiographic staging. Adult patients with blunt trauma can be selectively imaged. Figure 11A.4 shows a staging algorithm that is a useful systematic approach for renal trauma patients. Patients with gross hematuria or microscopic hematuria associated with shock (systolic blood pressure less than 90 mm Hg) should have radiographic staging studies. If physical examination or extensive associated injuries suggest renal injury, staging studies should be done.

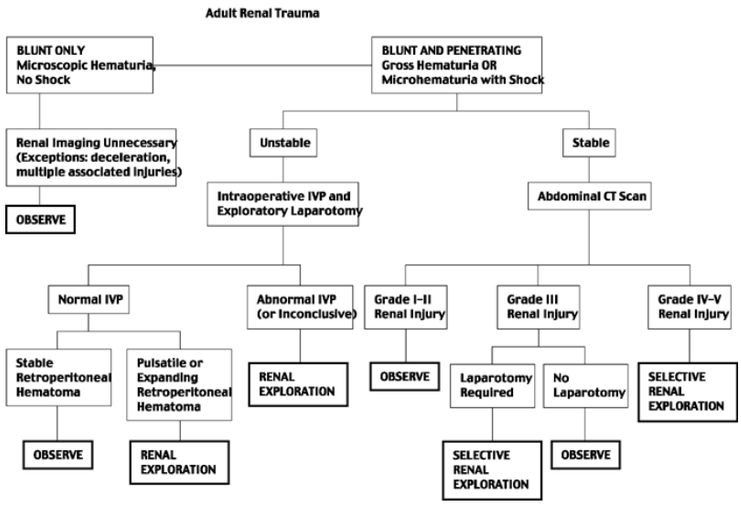

FIGURE 11A.4. Algorithm for the approach to the initial diagnosis and management of renal trauma. CT, computed tomography; IVP, intravenous pyelogram. (Modified from Meng MV, Brandes SB, McAninch JW. Renal trauma: indications and techniques for surgical exploration. *World J Urol* 1999;17:71, with permission.)

Computed Tomography

We aggressively pursue CT scanning in all patients stable enough to allow it (7). Because modern helical CT scanners can produce images before intravenous contrast is excreted in the urine, we obtain delayed scans (5 to 20 minutes after contrast injection) in all cases of suspected renal injury to allow contrast material to extravasate from the injured collecting system, renal pelvis, or ureter (10,49). For staging renal injuries, CT has several advantages: noninvasiveness, clear delineation of parenchymal lacerations, sensitive detection of urinary extravasation, outlining of nonviable tissue, definition of the extent and size of the surrounding hematoma, detection of associated injury, and provision of three-dimensional views of the kidney and retroperitoneum.

CT also has been useful in detecting arterial injury to the kidney (83,92).

In 85 patients in whom incomplete visualization on excretory urography or nephrotomography prompted suspicion of major renal injury (Table 11A.2), CT clearly differentiated major lacerations and detected extravasation more sensitively than excretory urography (Fig. 11A.5 and Fig. 11A.6) (7,32). As a result, CT enabled proper management in all instances. Fifty-two patients were managed nonoperatively, and thirty-three underwent surgery. The renal findings at operation confirmed the observations on CT in all surgical cases. In addition, CT detected major injuries to the liver, spleen, and bowel in seventeen patients.

TABLE 11A.2. COMPUTED TOMOGRAPHY IN 85 PATIENTS WITH SUSPECTED MAJOR RENAL TRAUMA

		Computed Tomography Findings				
	No. of Patients	Intrarenal Hematoma	Subcapsular Extravasation	Perirenal Hematoma	Parenchymal Disruption	Extracapsular Extravasation
Intravenous Pyelogram						
Subcapsular extravasation	1	0	1	1	0	1
Extracapsular extravasation	2	0	1	2	0	2
Filling defect	3	2	1	2	1	1
Displaced kidney	5	1	1	5	2	0
Irregular cortical margins	6	1	1	3	1	0
Delayed opacification	2	2	1	1	0	1
Diminished opacification	17	10	2	7	8	2
Nonfunction or nonvisualization	2	1	1	1	1	1
Angiography						
Subcapsular extravasation	1	1	1	1	1	1
Extracapsular extravasation	1	1	1	1	1	1
Parenchymal disruption	1	1	1	1	1	1
Vascular obstruction	2	0	0	1	0	0
Surgical Therapy						
Primary closure	4	1	1	4	2	2
Partial nephrectomy	4	1	3	4	4	2
Nephrectomy	3	0	0	3	1	0

From Bretan PN Jr, McAninch JW, Federle MP. Computed tomographic staging of renal trauma: 85 consecutive cases. *J Urol* 1986;136:561, with permission.

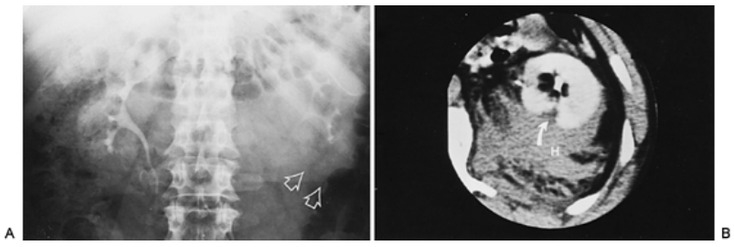

FIGURE 11A.5. Excretory urogram in a young man with abdominal pain and gross hematuria after blunt trauma reveals poor visualization of the lower pole of the left kidney and lateral deviation *(arrows).* **B:** Computed tomography scan shows retroperitoneal hematoma *(H)* and a minor laceration of the renal parenchyma *(arrow).* Nonoperative management was successful.

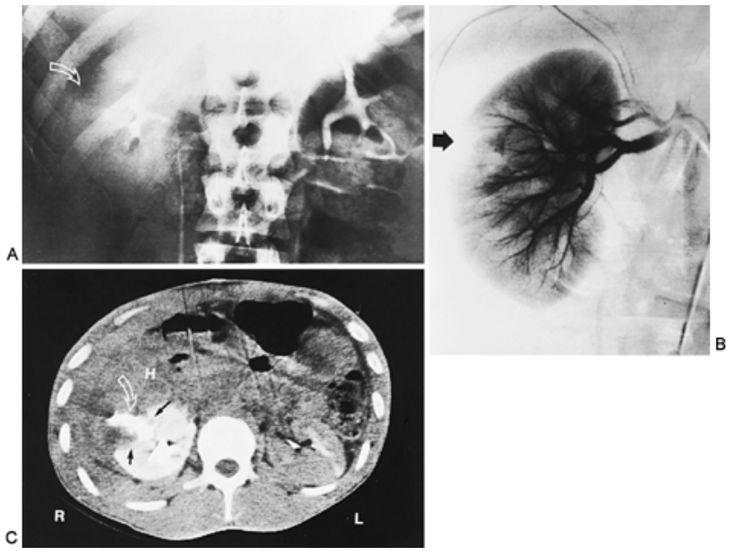

FIGURE 11A.6. Excretory urogram in a patient with a right flank stab wound and microscopic hematuria suggests a defect in the upper lateral border of the right renal parenchyma *(arrow).* **B**: Arteriography shows a minimum defect in the renal cortex *(arrow)* and no extravasation. **C:** Computed tomography scan reveals a large right renal laceration *(black arrows)* with extensive extravasation of opacified urine *(white arrow).* A large retroperitoneal hematoma is also noted *(H).* Operative repair resulted in renal salvage.

CT can indirectly detect major vascular injuries (79) and segmental artery injuries. In the patient shown in Fig. 11A.6, in whom excretory urography failed to visualize the kidney after a rapid-deceleration injury, CT demonstrated a nonenhancing soft tissue shadow of a normal-sized kidney on the involved side. One can use angiography to confirm the diagnosis. The major limitation of CT is the lack of detection of venous injuries to the main renal vein or its segmental branches.

Recent innovations in CT technology have shown potential for further improvement in diagnostic accuracy. Techniques such as calculating the volume of perirenal hematoma with CT, then roughly calculating the rate of renal blood loss, have improved the scan's accuracy in small studies (95). The feasibility of using three-dimensional CT reconstruction of renal injuries has also been demonstrated in a small number of patients (73). Although this appears to be a promising enhancement of standard CT, larger studies are required to determine whether it will improve the utility of standard CT imaging enough to enjoy wide use.

Intravenous Pyelography

In patients without a preoperative abdominal CT scan, an intraoperative “one-shot” intravenous pyelogram (IVP) is obtained. This requires 2 mg/kg of intravenous contrast (hypaque sodium 50% [Diatrizoate], Nycomed) given 10 minutes before a plain abdominal film is exposed (76). Standard IVP with multiple images, as would be done to evaluate nontraumatic upper tract disease, is not done. Intraoperative IVP can usually be performed with minimal disruption to the surgical team's efforts to stabilize the patient and is used not only to identify injuries, but also to confirm a functional renal unit on the uninjured side and to determine the presence of urinary extravasation, which can be difficult to detect intraoperatively. It also can exclude the need for renal surgery if findings are absolutely normal and there is only a nonpulsatile/nonexpanding hematoma (i.e., no absolute indication for exploration).

At our institution, intraoperative IVP has safely obviated renal exploration in 32% of patients (76). Although it can at times be insensitive for parenchymal injury, IVP is highly specific for urinary extravasation (14), and some reports have in fact shown it to be highly accurate in staging renal trauma (25,29,53).

Angiography

In the past, arteriography was the definitive study for staging major renal injuries. With the advent of CT, arteriography has been supplanted. However, it can still provide adequate information for management (54,102). It defines parenchymal lacerations and vascular injuries and is recommended when CT is unavailable. The most common indication for arteriography is nonvisualization of a kidney on excretory urography after major blunt abdominal trauma. Several causes for nonvisualization exist and should be considered: total avulsion of the renal artery and vein; renal artery thrombosis; absence of the kidney, either congenital or from surgical removal; and severe contusion causing major vascular spasm. Either digital subtraction arteriography or conventional arteriography may be used to evaluate vascular injuries. CT can detect vascular injuries (19), but arteriography gives more detailed information and defines the exact anatomic area of vascular injury.

When injuries to the segmental veins, main renal vein, and vena cava are suspected, venography can be used if the patient is stable enough (81). In these injuries, immediate operative intervention may be required to control bleeding and maintain the patient's hemodynamic stability.

Other Imaging Techniques

Although sonography has been used to evaluate and stage renal injuries (4,50,88), it provides less information than CT or arteriography and is unlikely ever to rival the near-100% accuracy of CT. Sonography can detect renal lacerations, but it cannot definitively assess their depth and extent and in one recent study performed very poorly: Experienced sonographers missed renal injuries 78% of the time (69). Furthermore, it cannot accurately detect vascular injuries. Sonographic techniques are improving, however, and it is possible that future use of newer ultrasound modes or contrast agents might improve diagnostic accuracy (44).

The use of radionuclide scanning has been limited. In 24 patients, Chopp and associates (23) combined this method with high-dose excretory urography and found that the number of arteriograms required for further staging was significantly reduced. This technique appears to provide less information than arteriography or CT (35,101).

Retrograde pyelography is of little benefit in evaluating renal injuries but is most useful in detecting associated ureteral or renal pelvic disruptions and perforations (71).

Although CT is still the imaging mode of choice, magnetic resonance imaging (MRI) may play a complementary role in the evaluation of renal trauma. MRI can be used in cases of severe CT contrast allergy, renal insufficiency when intravenous contrast cannot be given, and when CT scan is unavailable (55).

With an orderly approach to the staging of renal trauma, the full extent of the injury can be defined to allow intelligent and accurate management decisions. The ultimate goal of completed staging is to provide sufficient information for management that results in the preservation of renal parenchyma and the salvage of injured kidneys.

INDICATIONS FOR OPERATION

Blunt Trauma

The indications for operative intervention after renal injury vary greatly from one center to another. Blunt traumatic injuries create the most controversy. Contusions, corresponding to grade I injuries, represent 85% to 90% of blunt renal injuries, and in general, series results indicate that they can be managed nonoperatively. The remaining 10% to 15% of blunt injuries constitute minor and major lacerations and vascular injuries, which correspond to grades II to V. Most vascular injuries, when recognized early, call for operation and reconstruction when possible. Need for renorrhaphy or nephrectomy in our last 2,500 renal injury patients is documented in Fig. 11A.7 . Management of minor and major lacerations, however, is highly variable. Peterson (80) suggests avoiding renal operation unless bleeding is life-threatening; in most cases, when an operation is required, a nephrectomy should be performed. Cass (17) takes the opposite view and recommends immediate surgical management of major lacerations with or without extravasation. It is difficult to assess individual series because no group has directly compared operative and nonoperative management in a controlled fashion at one institution. The lack of a uniform classification system also makes comparison between series extremely difficult, although more uniform use of the AAST organ injury severity scale should obviate this problem.

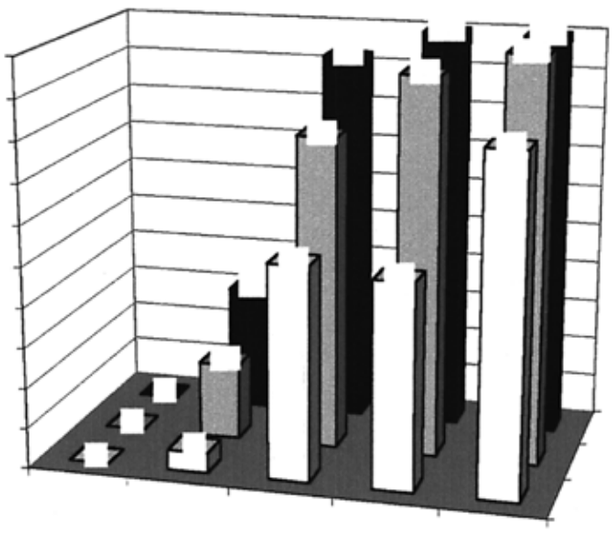

FIGURE 11A.7. The need for renal repair or nephrectomy classified by injury severity (AAST scale) and mechanism of injury (blunt trauma, stab wound, gunshot wound) for 2,500 renal injury patients.

Selecting the patient in whom complications are unlikely to develop with nonoperative management is difficult. Delayed bleeding, persistent extravasation with hematoma, and the potential for infection cause concern. Carlton (11) reported that, in his experience, 90% of the complications from expectant treatment occurred in the 10% to 15% of patients with blunt injuries more serious than contusions. Three studies in which nonoperative management was attempted for major renal injuries reported a threefold increase in complications over prompt operative management (46,53,100). Others have noted that when delayed operation is required to manage a complication, total nephrectomy commonly results (45,47).

We take an aggressive approach to staging the injury and thereby obtain adequate information to select the appropriate management, whether it is operative or nonoperative.

Indications for surgical exploration of the kidney can be categorized as absolute and relative. Absolute indications include expanding or uncontained hematoma and pulsatile hematoma, which might indicate the presence of grade V injury. Relative indications include urinary extravasation,

vascular injury, nonviable parenchyma, and incomplete staging. When the degree of urinary extravasation is minor, operation is not required, assuming that no other indication necessitates surgical intervention. Nonviable parenchyma secondary to segmental artery thrombosis without a parenchymal laceration can be followed expectantly with little risk of untoward problems. However, the patient with nonviable tissue involving 20% or more of the kidney in association with a deep parenchymal laceration should have renal exploration and repair to prevent delayed complications. The incompletely staged patient, perhaps already undergoing abdominal exploration for associated injuries, should have renal exploration and repair if necessary (64,68).

In a series of 1,193 patients with blunt renal trauma (68), the preceding indications mandated renal exploration in 31 (2.5%) (Table 11A.3). This experience indicates the high renal salvage rate (87%) that can be achieved in patients who require renal exploration after blunt trauma. With these indications and improved staging techniques, only approximately 2.5% of patients with blunt renal trauma now require renal exploration at our trauma center.

	No. of Operations		
Type of Injury	Repair	Nephrectomy	Total Operations
Blunt (1,193 patients)	27	4	31 (2.5%)
Stab wounds (106 patients)	45	4	49 (45%)
Gunshot wounds	46	7	53 (80%)

From McAninch JW, et al. Renal reconstruction after injury. *J Urol* 1991;145:932, with permission.

TABLE 11A.3. RENAL INJURIES AT SAN FRANCISCO GENERAL HOSPITAL

Penetrating Trauma

Most penetrating renal injuries require operative exploration. Only when preoperative staging clearly indicates that the extent of injury is minor can a nonoperative approach be used successfully. Approximately 70% of patients with penetrating renal injuries at San Francisco General Hospital require operative renal intervention (Table 11A.3). The indications for operative exploration are the same as those listed earlier when careful preoperative staging has been accomplished. Recently, Carroll and McAninch (14) reported that CT provided accurate preoperative assessment in 11 patients with penetrating renal injury and allowed nonoperative management in 8 patients. Associated intraabdominal injuries occur in 80% of patients with penetrating renal injury, and these patients often require immediate surgical intervention with no time allowed for careful preoperative staging (Table 11A.4). In such circumstances, bleeding and life-threatening conditions should be controlled in the operating room, and a “one-shot” excretory urogram should be obtained on the operating table to make certain that at least one normally functioning kidney is present and to gain information regarding the potentially injured kidney. If findings on excretory urography are abnormal, exploration of the ipsilateral kidney should be

performed. This careful, selective approach to penetrating renal injuries has not resulted in delayed renal operation at our institution.

TABLE 11A.4. ASSOCIATED ABDOMINAL INJURIES NOTED IN 109 OF 127 PATIENTS

Site of Injury	Number of Patients
Liver	36
Spleen	29
Small bowel	28
Colon	27
Mesentery	20
Stomach	20
Pancreas	19

From McAninch JW, et al. Renal reconstruction after injury. *J Urol* 1991;145:932, with permission.

Bernath and colleagues (5) and Heyns (42) advocate a nonoperative approach for stab wounds. From their data, it appears that when the entrance site is dorsal to the posterior axillary line, the incidence of associated abdominal injury requiring renal exploration is low.

Heyns and van Vollenhoven (43) have unsuccessfully shown that angiography with selective arterial embolization can control complications of delayed bleeding, which occurred in 15% of their patients initially managed expectantly.

Vascular Injury

Vascular injury of major renal vessels has been reported in 1% to 3% of patients with blunt renal injuries (38,58). Total avulsion of the renal artery and vein, seen after rapid deceleration, is the most serious injury because of acute hemorrhage. Acute renal artery thrombosis also is seen in rapid-deceleration injuries and is difficult to diagnose. The degree of hematuria, if present, is often insignificant (91). Many centers recommend that all patients known to be involved in rapid-deceleration accidents undergo excretory urography, whether hematuria is present or not. However, Mee and colleagues (70) noted that gross hematuria or microhematuria was present in all vascular injuries resulting from blunt trauma in their series, and they recommend selective imaging. When nonvisualization is found on excretory urography, immediate arteriography or CT is indicated.

The free movement of the kidneys in the retroperitoneum results in sudden stretch of the renal artery. The arterial intima, having little elasticity, tears, which produces thrombosis within the vessel lumen (Fig. 11A.8 and Fig. 11A.9). This quickly reduces blood flow to the kidney, which may then be viable for only a limited time. Rapid diagnosis and immediate operation are necessary to salvage the kidney (15,60).

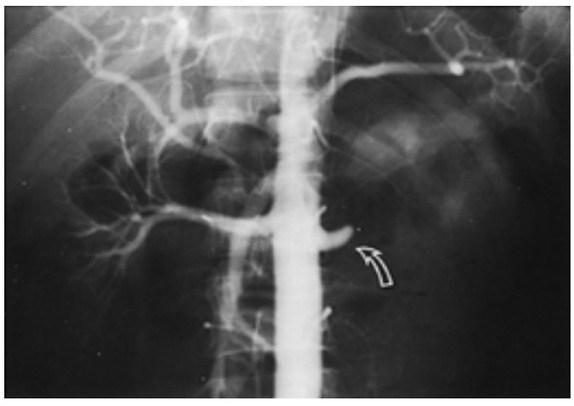

FIGURE 11A.8. In a 29-year-old man with blunt trauma, arteriography demonstrates acute left renal arterial thrombosis. (From McAninch JW. Renal injuries. In: McAninch JW, guest ed. *Urogenital trauma,* vol 2 of Blaisdell WF, Trunkey DD, series eds. *Trauma management*. New York: Thieme Stratton, 1985a:27–49, with permission.)

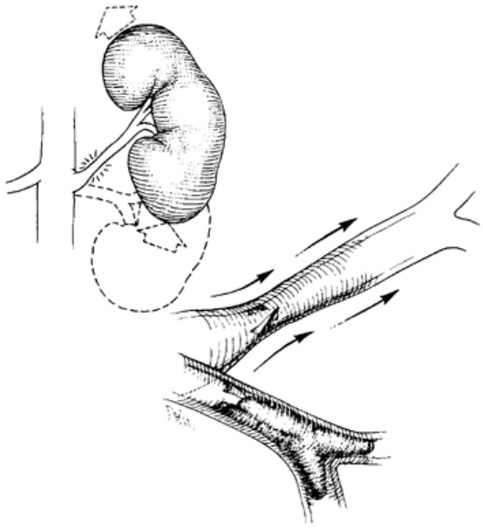

FIGURE 11A.9. Mechanism of arterial thrombosis from blunt trauma. (From McAninch JW. Renal injuries. In: McAninch JW, guest ed. *Urogenital trauma,* vol 2 of Blaisdell WF, Trunkey DD, series eds. *Trauma management*. New York: Thieme Stratton, 1985a:27–49, with permission.)

Venous injuries of the main renal vein or segmental renal branches constitute a serious, possibly lethal, condition. These injuries can result from blunt or penetrating trauma, and massive blood loss can be expected. Preoperative staging for an accurate diagnosis is difficult because excretory urography,

nephrotomography, CT, and arteriography do not adequately image venous injuries. Often, particularly on the right side, renal and vena caval injuries coexist (81), and resulting mortality can be as high as 50%.

RETROPERITONEAL HEMATOMA

The general surgeon is often confronted with the unexpected finding of a large retroperitoneal hematoma during exploration for an abdominal injury. Such a hematoma may be found in blunt or penetrating injuries. Historically, exploring the kidney that is surrounded by hematoma has been regarded as hazardous, and complete nephrectomy often has followed (94,99). The urologic surgeon who is called in for consultation should have a systematic approach to evaluating these hematomas. High-dose excretory urography should be performed on the operating room table to evaluate the status of the potentially injured kidney and to confirm the presence of a functioning contralateral renal unit. If the excretory urogram appears normal and no continued expansion of the hematoma is noted, surgical exploration can be avoided. However, when the excretory urogram is indeterminate or abnormal, surgical exploration of the hematoma should be performed. It is imperative to isolate the renal artery and vein before entering the hematoma to control the heavy bleeding that may develop during exploration. In cases of bilateral retroperitoneal hematomas requiring exploration, we choose to explore the kidney suspected of having the lesser injury first, assuming the patient's hemodynamic stability is maintained.

OPERATIVE EXPLORATION AND RENAL EXPOSURE

Once the decision for operative exploration is made, the preferred approach is a midline, transabdominal incision (12,64,89). This allows assessment of other intraabdominal visceral organs and major abdominal vessels. Repair of major vascular, spleen, liver, and bowel injuries should generally be performed before renal exploration and repair. However, if renal bleeding is massive and persistent, renal exploration takes precedence.

To control massive bleeding before renal exploration, it is important to isolate the renal artery and vein individually (Fig. 11A.10A) (9,13,68). The surgeon must be careful to

examine the anatomic relationships within the posterior abdomen and posterior parietal peritoneum before beginning vascular isolation. In many cases, the surgical landmarks are distorted by urinary extravasation and massive hematomas. The transverse colon is lifted from the abdomen and placed on the anterior chest. This allows the small bowel to be lifted free from the abdomen superiorly to the right to expose the small bowel mesentery and the posterior parietal peritoneum.

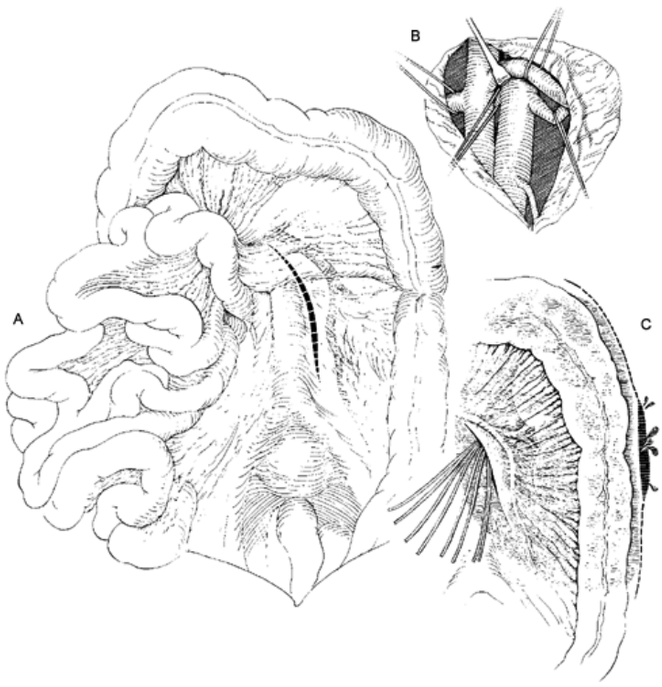

FIGURE 11A.10. Operative approach to renal vessels. **A:** Bowel is retracted superiorly to expose the retroperitoneum, where an incision is made medial to the inferior mesenteric vein over the aorta. **B:** Renal vessels are exposed, and vessel loops are placed. **C:** Hematoma is then entered from a lateral approach. (From McAninch JW, Carroll PR. Renal trauma: kidney preservation through improved vascular control—a refined approach. *J Trauma* 1982;22:285, with permission.)

Anatomic landmarks to be identified at this point are the inferior mesenteric vein and the aorta. If the aorta is covered by large hematoma, an incision can be made in the retroperitoneum just medial to the inferior mesenteric vein; by palpation through the hematoma, the aorta will be found. At this level, the aorta is free of major branches on its anterior surface and is usually easily and safely identified. The aorta is dissected superiorly on the anterior surface up to the area of the ligament of Treitz, where the left renal vein is found crossing anterior to the aorta. This is a major anatomic landmark because the left renal artery originates from the aorta just lateral and superior to the left renal vein, and the right renal artery lies medial and superior as it originates from the aorta (Fig. 11A.10B). Vessel loops of soft silicone can be placed around the individual vessels for retraction and occlusion. In most circumstances, it is unnecessary to occlude the vessels at the time of initial isolation. The right renal vein ordinarily can be isolated through the retroperitoneal incision; however, if it is difficult, mobilization of the second portion of the duodenum readily exposes the right renal vein and vena cava to make the vessel more accessible. Only vessels to the injured kidney need to be isolated.

Once vessel isolation is complete, an incision is made in the peritoneum just lateral to the colon, and the colon is reflected medially to expose the retroperitoneal hematoma in its entirety (Fig. 11A.10C). The kidney should then be totally exposed and mobilized for complete inspection. This can be done quickly and safely without concern for great blood loss because of the vascular control that has been obtained. If heavy bleeding is encountered, vascular clamps or vessel clamps can be used—in our experience, required in 12% of cases. In most circumstances, occlusion of the renal artery beyond 30 minutes is not required, and the kidney tolerates this amount of warm ischemia time well (16). If the time extends beyond this limit, renal cooling is advised during the continued reconstruction process.

Scott and Selzman (89) originally described this technique of early vascular control when exposing a traumatized kidney. Renal bleeding can be prevented and nephrectomy rates reduced. McAninch and Carroll (64) compared a series of patients in whom early vascular control was achieved with another group in whom vascular control was inconsistent (Table 11A.5). The nephrectomy rate in the former group was 18%, and all patients who required nephrectomy had sustained penetrating injuries. In the group with poor vascular control, the nephrectomy rate was 56%—a statistically significant difference. Clearly, when nephrectomy resulting from hemorrhage is prevented, as it can be by this technique, the renal salvage rate is greatly improved.

TABLE 11A.5. NEPHRECTOMY RATES IN PATIENT SERIES WITH AND WITHOUT EARLY VASCULAR CONTROL

Procedure	Early Vascular Control (Series II; 39 Patients), Number (%)	Poor Vascular Control (Series I; 34 Patients), Number (%)
Nephrectomy (n = 26)	7 (18)[a]	19 (56)[a]
Repair (n = 47)	32 (82)	15 (44)

[a] $p < .001$.
Data from McAninch JW, Carroll PR: Renal trauma: kidney preservation through improved vascular control—a refined approach. *J Trauma* 1982;22:285, with permission

Some authors do not advocate isolation of the renal vessels before exploration. Gonzalez and others (37) found no difference in the nephrectomy rate in 56 patients undergoing renal exploration with or without vessel isolation. However, the nephrectomy rate they report is notably higher than that of groups advocating isolation of renal vessels before opening Gerota's fascia. We believe the maneuver, which can be achieved in less than 15 minutes in most cases, is worthwhile and facilitates complex renal reconstruction.

OPERATIVE FINDINGS AND RENAL RECONSTRUCTION

Parenchymal Injuries

Complete renal exposure is of primary importance (Fig. 11A.11). The kidney is often surrounded by large hematoma, which should be completely swept away so that the entire surface area of the kidney and the hilar vessels is available for inspection. If massive bleeding is encountered from a vascular injury or a parenchymal laceration, temporary occlusion of the renal artery may be necessary to control hemorrhage. This is required in 12% of cases (13). Large intrarenal hematomas that reside in lacerations should be completely evaluated and the margins of the laceration inspected (68). All nonviable tissue should be completely removed. Hemostasis should be obtained on the laceration margins with 4-0 chromic sutures on a fine-tapered needle placed in a figure-of-eight over individual bleeding points (Fig. 11A.12). Chromic suture is preferred because its monofilament characteristics allow it to slide through the

tissue without tearing or cutting the renal parenchyma. Larger sutures often cause increasing amounts of tissue ischemia and are unnecessary.

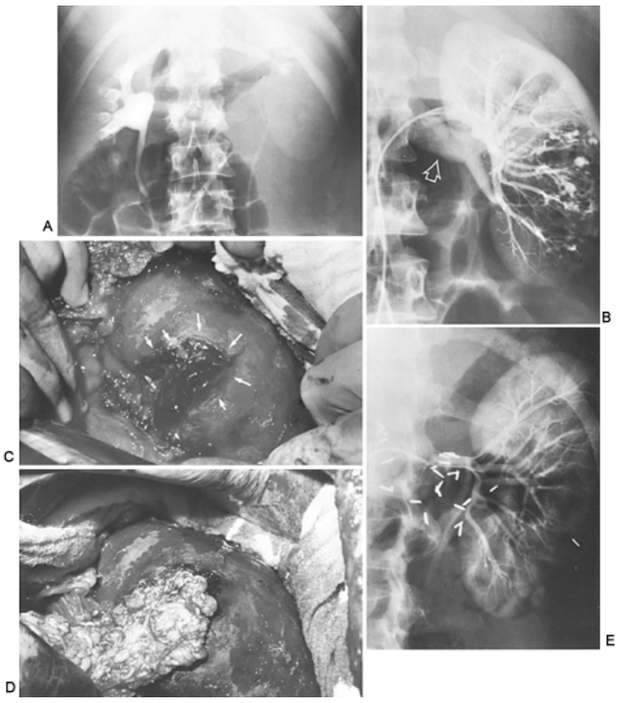

FIGURE 11A.11. A: Excretory urogram in a 19-year-old patient with blunt abdominal trauma and gross hematuria demonstrates poor visualization of the left kidney. **B:** Arteriogram shows numerous areas of vascular extravasation in the middle and lower left kidney. The prompt filling of the renal vein indicates massive arteriovenous shunting *(arrow).* **C:** At operation, a deep parenchymal laceration *(arrows)* was noted on the medial aspect of the kidney near the renal hilum. **D:** The laceration was debrided and the bleeding vessels suture ligated. The defect was covered with an omental pedicle flap. **E:** Selective left renal arteriography 6 months after injury demonstrates complete resolution of arteriovenous shunting and healing of the renal laceration. (From McAninch JW, Carroll PR. Renal trauma: kidney preservation through improved vascular control—a refined approach. *J Trauma* 1982;22:285, with permission.)

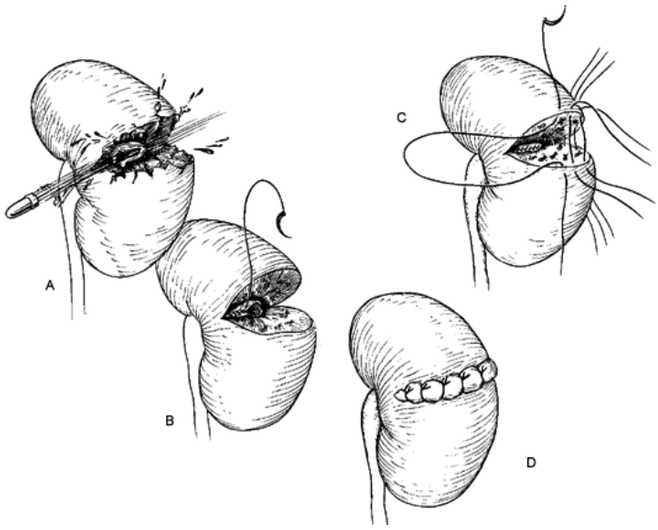

FIGURE 11A.12. Technique of renorrhaphy. **A:** Grade IV injury by gunshot. **B:** Closure of collecting system and ligation of individual bleeding parenchymal vessels. **C:** Closure of the renal defect with multiple interrupted sutures through the renal capsule over gelatin sponge bolster. **D:** Final appearance after repair.

As bleeding within the laceration comes under control, inspection should be directed to the collecting system in the depth of the renal laceration. It may be obvious that the collecting system is open; if so, interrupted sutures of 4-0 chromic or 4-0 polydioxanone should be used. Running sutures of the same material may be used to ensure a watertight closure if the collecting system is wide open. Closure of the renal parenchyma over the repaired collecting system provides another barrier to urinary leakage. Between the margins of the lacerated parenchyma, topical absorbable hemostat such as microfibrillar collagen hemostat is placed (Avitene; Bard). The capsule of the kidney is then closed with multiple 3-0 absorbable sutures such as Vicryl on a small taper needle (Fig. 11A.12C). The sutures are tied carefully over a bolster of absorbable gelatin sponge (Gelfoam; Pharmacia/Upjohn; Kalamazoo, Michigan), assisted by hand approximation of the kidney to achieve apposition (Fig. 11A.12D). This technique provides excellent hemostasis and is an aid in any delayed urinary extravasation or delayed bleeding (65). The gelatin sponge is absorbed within 3 weeks; the risk of future infection or calculus formation from its use is minimal (67). To identify the suture line on postoperative CT scans, we place titanium surgical clips (Autosuture Premium Surgiclip II; US Surgical; Norwalk, Connecticut) on the tied sutures. Ureteral stents are not routinely placed unless a renal pelvis injury is identified and repaired.

Often, the capsule will have been destroyed by the traumatic injury and is not available for use in closure. In such cases, we prefer a pedicle flap of omentum to cover the defect and to aid in hemostasis and prevention of urinary extravasation. The omentum has the advantage of being viable tissue, rich in lymphatic vessels and blood supply, which promotes healing of the injured area. When, as is often the case, omentum is not available and fragments of the capsule remain, a patch of perirenal fat or Vicryl mesh (polyglactin) can be placed over the defect and secured with interrupted sutures that catch the margins of the remaining capsule (without extending into the parenchyma), and these can be tied over an absorbable gelatin sponge bolster. In severe cases of renal injury without preservation of capsule, the entire kidney can be wrapped in a polyglycolic acid (Vicryl) mesh bag. This technique holds the injured kidney together until it heals (77).

Multiple lacerations may coexist, and each laceration can be reconstructed similarly. Occasionally after reconstruction and control of hemorrhage within each laceration, the entire

kidney can be wrapped in omentum to protect it against future problems and to promote wound healing.

Deep lacerations through the upper or lower pole of the kidney may devascularize a large segment of tissue, and a partial nephrectomy may be indicated (Fig. 11A.13A). The capsule should be preserved, and the segmental artery supplying the involved area may require ligation. In most cases, we have been able to spare the segmental vessel, which often supplies additional surrounding tissue, and remove only the nonviable area (Fig. 11A.13B). Hemostasis on the margins of the parenchyma should be achieved with the interrupted suture technique described previously, and the collecting system should be closed carefully (Fig. 11A.13C). To be certain that the closure is watertight, we often occlude the ureter and inject 2 to 3 mL of indigo carmine into the renal pelvis. Any extravasation becomes obvious. Coverage of the renal parenchyma after partial nephrectomy is important. We use any remaining capsule or, if this is unavailable, a pedicle flap of viable omentum (Fig. 11A.13D). If neither of these is available, a free peritoneal graft can be sutured into place over the defect.

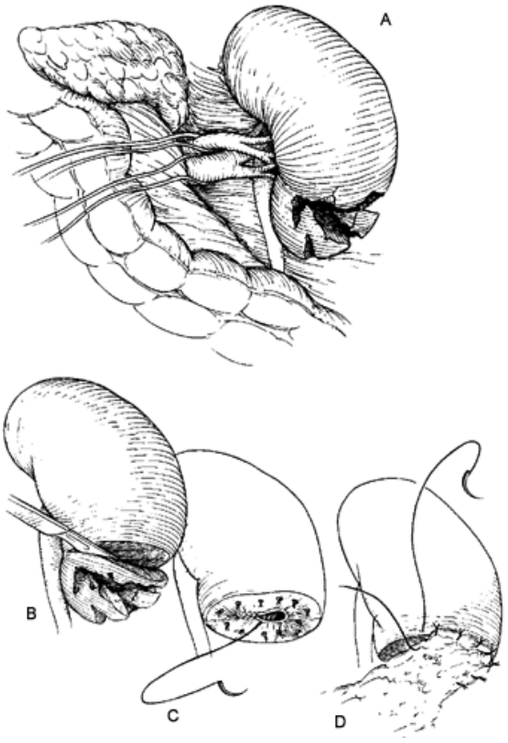

FIGURE 11A.13. Technique of polar nephrectomy for renal injury. **A:** Exposure of kidney with significant lower pole injury. **B:** Sharp amputation of the injured pole. **C:** Ligation of bleeding points with 4-0 chromic suture and watertight closure of the collecting system. **D:** Coverage of the renal defect with omental pedicle flap. (Modified from McAninch JW. Surgery for renal trauma. In: Novick AC, Streem SB, Pontes JE, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989:234–239, with permission.)

Retroperitoneal drains are left in place when there is a question of urinary leakage, but careful management is obligatory to prevent infection that may ascend along a drain tract. The drain is removed on postoperative day 3 if analysis of the drain fluid shows it is not urine. In situations in which urinary extravasation does not occur, drains are unnecessary. They should not be left in place in an attempt to drain retroperitoneal hematoma because they are not effective and only provide an avenue for potential infection. Cefazolin (Kefzol) or similarly appropriate prophylactic antimicrobial coverage is given while the drain is in.

Venous Injuries

Venous injuries cause massive bleeding, and repair on the right is complicated by the shortness of the renal vein and the frequent involvement of the vena cava. Complete occlusion of the vena cava above and below the area of injury temporarily controls bleeding until vascular clamps can be applied to the exact areas of damage. Good results can be expected in a majority of renal vein injuries requiring repair (96). Fine 5-0 vascular sutures should be used to close these defects. The severely injured left renal vein can be ligated if necessary because venous collaterals will adequately drain the kidney (9). Segmental renal vein injuries are best managed by ligation of the vessel. This does not cause ischemic damage because of the inner communication of the veins within the renal parenchyma.

Renal Artery Occlusion

Controversy surrounds the treatment of traumatic total renal artery occlusion. Some authors claim that acceptable success rates can be achieved by prompt revascularization (within 4 to 12 hours) (3,57). However, in multiple studies, the success of revascularization has been poor, approaching 0% (24,40,51,96). Current recommendations are to perform nephrectomy in most cases of traumatic renal artery occlusion, except in patients with solitary kidney or bilateral renal artery injury. Percutaneous placement of an endoluminal stent may be the best method of treatment (97).

Renal Artery Laceration

All patients with renal artery injuries must be treated individually in light of recent evidence that renal salvage is often not achieved in this population (51). Only those patients who can safely undergo several hours of operation in the periinjury period are candidates for renal artery repair. Patients with vascular injuries to the main renal artery occurring from blunt trauma who have delayed diagnosis

(more than 8 hours) or who are older (seven decades) have little chance of successful arterial reconstruction. In large series, renal lacerations have required nephrectomy in many cases (76%) (9); when vascular repair was attempted, it was successful in only 60%.

Renal branch injuries, on the other hand, are much less significant lesions that can be managed nonoperatively or, when they are discovered intraoperatively, treated by ligation (6). Angiographic embolization of branch artery injuries after stab wounds (30,36) or blunt trauma (28) also has been advocated.

Renal Pedicle Avulsion

Total renal pedicle avulsion, which involves complete laceration of the renal artery and vein from their attachments, requires immediate surgical intervention and does not allow time for diagnostic studies. Authors have suggested renal salvage in these patients only under extreme circumstances: A stable patient who can undergo lengthy operation, solitary kidney, and bilateral injury. If repair is attempted, autotransplantation appears to be the most successful approach (39).

POSTOPERATIVE CARE AND FOLLOW-UP

The postoperative care of the patient with renal trauma is similar to that for any major transabdominal surgical procedure, with nasogastric suction or gastrostomy as needed for bowel decompression and urethral catheter drainage until the patient is stable enough to void. Antibiotics should be given for bowel perforation or severely contaminated wounds. If the urine is infected, preoperative and postoperative antibiotics should be continued through a full 10-day course.

In most circumstances, the urine becomes free of clots within the first 12 to 24 hours and free of gross blood within 48 hours. Serial hematocrit readings should be obtained to make certain that continued bleeding does not occur. When drains are left in place, significant drainage is often noted, although this is commonly intraperitoneal fluid and not urine. One should check the creatinine content of the fluid, which will be many times the serum concentration if urine is present. Intravenous injection of methylene blue also may be used to evaluate possible urinary extravasation. Blood pressure should be followed closely in the early postoperative period as well as later on, for at least 1 year.

Patients can be discharged as soon as retroperitoneal drains are out and they are stable and eating. At the time of discharge, patients are allowed free ambulation without restriction and should be encouraged to return to normal physical activity as soon as the incisional pain subsides.

The patient should be seen in follow-up every 1 to 2 weeks for the first 6 weeks to monitor blood pressure and evaluate the urine for the presence of blood. Hypertension is uncommon, and microscopic hematuria should gradually subside. Approximately 3 weeks after injury, the patient should have a follow-up CT scan of the kidneys to evaluate the anatomic configuration of the kidney and to verify that no obstruction has resulted from perirenal scarring. Renal radionuclide scans are often helpful in evaluating the functional status of the injured kidney.

COMPLICATIONS

Early complications occur within the first 4 weeks of injury and include delayed bleeding, abscess, sepsis, urinary fistula, urinary extravasation and urinoma, and hypertension (48,90,98). Delayed bleeding can occur from the immediate postoperative period until several weeks later. The greatest risk of delayed heavy retroperitoneal bleeding occurs within the first 2 weeks of injury. Angioembolization is the primary treatment for delayed renal bleeding after trauma (43), but speedy nephrectomy may be required if bleeding is brisk. Abscess may develop in the perinephric space and in most circumstances is noted within the first 7 days. This may be associated with sepsis and is manifested by increasing temperature that may reach 41°C. Prompt surgical exploration and drainage are usually required; however, after appropriate diagnostic procedures, localized abscesses may be drained percutaneously. Symptoms of urinary extravasation in the first 4 weeks of injury may be manifested by a low-grade fever and continued pain in the area of the kidney. CT can aid in establishing the diagnosis and extent of extravasation. Retrograde ureterography should be performed if missed ureteral injury is a possibility. Percutaneous drainage has successfully managed extensive extravasation, but small amounts of urine in the retroperitoneal space appear to be of no particular consequence if they remain uninfected; these often resolve spontaneously without intervention. Hypertension in the postoperative period is uncommon; however, its presence and duration are extremely variable (98). In most circumstances, the hypertension does not require treatment; when indicated, medical therapy usually controls the problem. The hypertension appears to be renin mediated in most cases and is usually transient when it occurs in the early postinjury period.

Late complications include arteriovenous fistula, hydronephrosis, hypertension, calculus formation, and chronic pyelonephritis. Delayed hypertension has been noted by several authors. In a group of patients who had careful follow-up, Jakse and colleagues (48) noted the onset of hypertension some 15 years after renal trauma. Longstanding hypertension persists because of partial renal ischemia, resulting in a renin-mediated type of hypertension (90). Most cases can be managed medically, but surgical intervention may be necessary in unresponsive patients. Montgomery and others (74) have described a cohort of renal trauma

patients in whom initial evaluation (CT or IVP) was normal, yet who developed severe renovascular hypertension 2 weeks to 8 months after injury. Subsequent arteriography revealed unappreciated renal artery occlusion, arterial stenosis, segmental artery injuries, or extraparenchymal compression from scarring (Page kidney). Although all were young, these patients presented with complaints, including headaches, chest pain, nosebleeds and fatigue. Vigilance for hypertension is necessary in this population, even when severe renal injury is not expected. Arteriovenous fistulae are caused by both blunt and penetrating injuries but mainly by stab wounds (26). Delayed urinary bleeding is the usual presenting symptom, and many patients have associated hypertension. Angioembolization is the treatment of choice (84), but large fistulae require surgical correction and perhaps nephrectomy. Hydronephrosis can develop in the late postoperative period because of surrounding fibrosis and obstruction to the upper ureter or ureteropelvic junction. This condition may lead to calculus formation or recurrent pyelonephritis or both.

To detect many of these developing delayed complications, a CT scan is strongly recommended within 3 months of major renal injury. Additional follow-up should be done in these patients when persistent problems or suspicion of abnormalities exists.

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11B URETERAL INJURIES

Joseph N. Corriere Jr.

Part of "11 - RENAL AND URETERAL INJURIES "

J.N. Corriere, Jr.: Department of Surgery, Division of Urology, The University of Texas, Houston, TX 77030.

The sole function of the ureter is to transport urine from the kidney to the bladder. When the ureter is injured, it may become obstructed, creating hydroureteronephrosis and loss of renal function, or a fistula may occur, leading to urinary extravasation into the retroperitoneum or peritoneal cavity. If injury to another structure has occurred at the time of the ureteral injury, a fistula may develop. Most fistulae are to the vagina, skin, or bowel.

Extravasated urine can induce an intense inflammatory reaction, resulting in secondary fibrosis and ureteral obstruction. If the urine is infected, phlegmon and possibly life-threatening sepsis may develop, necessitating emergency surgical intervention.

In the past few years, the use of percutaneous and endourologic techniques has decreased the complications from ureteral injuries and prevented many patients from having to undergo open surgical procedures that once were standard therapy for these distressing problems.

ETIOLOGY

There are two major types of ureteral injuries: those caused by external violence, usually penetrating missiles, and the more common injuries resulting from surgical misadventure. The late complications of radiotherapy or migrating foreign bodies also can cause injury to the ureter. Table 11B.1 lists the various causes of ureteral injury.

TABLE 11B.1. CAUSES OF URETERAL INJURIES

External Violence
Penetrating Injuries
Gunshot wound
Knife wound
Impalement on spike
Blunt Injuries
Avulsion
Crushing injury
Surgical Injuries
Gynecologic Procedures
Abdominal hysterectomy
Vaginal hysterectomy
Salpingo-oophorectomy
Vesicovaginal fistula repair
Dilation and curettage
Excision of cervical stump
Cystocele repair
Colpocleisis
Endometrioma resection
Obstetric Procedures
Forceps delivery
Precipitous delivery
Cesarean section
Therapeutic abortion
Urinary Tract Procedures
Retrograde pyelogram
Ureteroscopy
Endopyelotomy
Ureterolithotomy
Renal pelvic surgery
Vesicourethral suspension
Vesicocolic fistula repair
Suprapubic excision of bladder tumor
Bladder diverticulectomy
Stone basket manipulation
Transurethral resection of a bladder tumor
Urinary Tract Procedures (continued)
Transurethral resection of the prostate
Radical prostatectomy
Vascular Surgery
Vena cava ligation
Aortic aneurysmectomy
Bypass procedures
Lumbar sympathectomy
Abdominal Procedures
Colectomy
Colostomy
Colostomy closure
Abdominoperineal resection
Appendectomy
Exploratory laparotomy
Enterolysis
Duodenal resection
Pancreatic surgery
Herniorrhaphy
Biliary surgery
Retroperitoneal Procedures
Retroperitoneal fibrosis surgery
Retroperitoneal lymphadenectomy
Retroperitoneal tumor resection
Laparoscopic Procedures
Neurosurgical Procedures
Laminectomy
Paravertebral nerve block
Radiation Injury
Migrating Foreign Bodies
Urinary calculi
Bullets
Swallowed objects

Injury Caused by External Violence

The most common cause of ureteral injury from external violence is gunshot wounds. These wounds account for more than 95% of the lesions (7,8,22,32,38,40,41 and 42,45,54). Knife wounds are the next most common agent, and very rarely, people fall and become impaled on a spike. Uncommonly, the wound from a crushing blow that damages bone involves the ureter. Finally, a well-described but rare injury occurs when the ureter is avulsed from the renal pelvis (Fig. 11B.1) (3,28). This injury is usually seen in a child who has a hyperextensible spinal column. The child is usually struck from behind, and the ureter tenses and snaps against the twelfth rib and transverse processes of the upper lumbar vertebrae. This injury as well as lower ureteral rupture secondary to blunt trauma can be seen in adults as well as children (13,24,26).

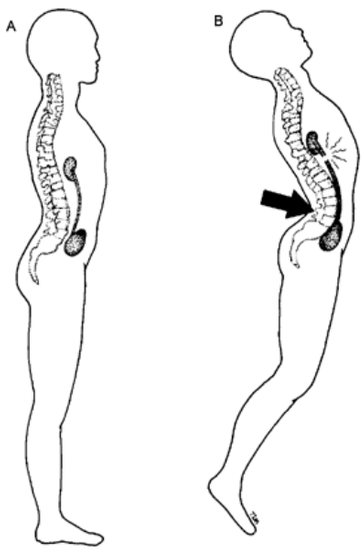

FIGURE 11B.1. A: Normal relation of urinary tract to spine in child. **B:** With a sudden blow to back, the ureter tenses against the hyperextended vertebral column and avulses at the ureteropelvic junction.

Surgical Injury

Ureteral injury may complicate 0.5% to 1.0% of all pelvic operations. Most of these are gynecologic procedures, but urinary tract procedures commonly account for 30%. The most common procedures are hysterectomy, salpingo-oophorectomy, vesicourethral suspension, ureteroscopy, endopyelotomy, and ureterolithotomy (5,9,14,15 and 16,34,47,51,52).

Surgical procedures on the great vessels and colon as well as retroperitoneal tumor excision are the next most common procedures leading to ureteral injury (4,6,31,46,48). As listed in Table 11B.1, many other procedures have been implicated infrequently (2,27). In the last few years, laparoscopic procedures have become a common cause of ureteral injuries (17,55,57).

Radiation Injury

Although radiation injury is often considered when a patient with a previously treated pelvic tumor is found to have ureteral obstruction, the incidence of radiation damage to the ureter is only 0.04%, whereas the incidence of ureteral obstruction caused by recurrent tumor in these patients is more than 95% (12,59).

Migratory Foreign Bodies

The most common migratory foreign bodies that perforate or obstruct the ureter are urinary calculi, bullets, and swallowed objects (18,43).

DIAGNOSIS

External Violence Injury

An excretory urogram or computed tomography (CT) scan with contrast must be performed when a patient has had a penetrating injury of the abdomen, retroperitoneum, or pelvis in the area of the urinary tract; a fracture of the eleventh or twelfth rib; or a transverse lumbar process or the bony pelvis is present. Such a test should also be performed if hematuria is present in a patient who has had significant abdominal or pelvic trauma.

The excretory urogram and CT scan with contrast are the best methods of diagnosing a ureteral injury. In the presence of such an injury, urinary extravasation will be seen on the study as well as some decrease in collecting system visualization (Fig. 11B.2). If a spiral CT scan is performed, the ureter must be seen in its entirety. If it is not, a delayed CT scan must be done or an injury may be missed because of the rapid time of the spiral study (37,50).

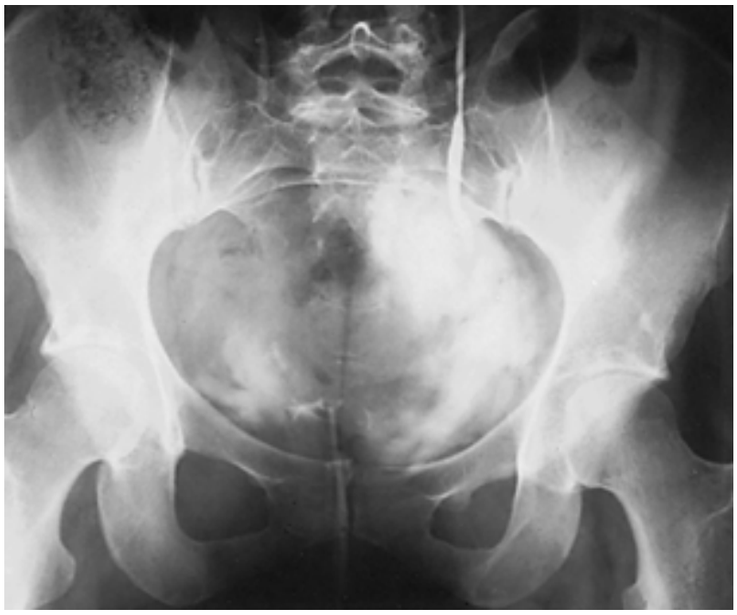

FIGURE 11B.2. Woman, aged 26 years, with lacerated left ureter secondary to stab wound of the abdomen. Intravenous pyelogram on the day of injury shows contrast extravasation in the left lower retroperitoneal area.

If the patient is to undergo surgical exploration, the ureter should be dissected from its bed and examined where it lies in proximity to the missile track. If whether an injury is present cannot be determined positively, one vial (5 mL) of indigo carmine should be injected intravenously (IV). Within 7 to 10 minutes, the dye should leak into the periureteral tissues if the ureter has been injured.

If the patient is not going to undergo exploration and the presence of an injury remains questionable, the most definitive study is a retrograde ureterogram. Often, this is not feasible in the trauma patient with multiple injuries. In such a case, ultrasound examination or, preferably, a CT scan may demonstrate the presence of extravasation (25,37).

Surgical Injury

If the urologist is confronted in the operating room with a possible ureteral injury, *the use of IV indigo carmine, as previously described, helps determine whether urinary extravasation is present.* Unfortunately, there is no good way to determine whether ureteral devascularization from the surgical procedure or the blast effect of a high-velocity missile has occurred other than by cutting the ureter and seeing whether it bleeds. Some surgeons advocate the use of IV fluorescein and a Wood's lamp. If there is fluorescence of the ureter, the vasculature is presumed to be intact. The presence of ureteral peristalsis is not helpful in the diagnosis because peristaltic movement may continue in the ureter for hours after it has been removed from the body.

The diagnosis of a ureteral injury generally is not made until many days after the injury has occurred. Table 11B.2 lists the most common signs and symptoms seen in these patients. If a ureteral injury is suspected, an excretory urogram or CT scan is mandatory. If the imaging study shows extravasation, delayed function, or hydroureteronephrosis, a retrograde ureterogram should be done to confirm the type of injury if it is not well delineated in the imaging study. This should be done just before institution of treatment to prevent sepsis from instrumenting a closed space.

Flank pain	1–21 days
Fever	>100°F
Anuria	Bilateral only
Ureterovaginal fistula	1–30 days
Ureterocutaneous fistula	1–30 days

TABLE 11B.2. SIGNS AND SYMPTOMS OF URETERAL INJURIES

In some patients, it may be determined that a percutaneous nephrostomy and possibly antegrade ureteral stent should be placed as therapy (i.e., an ileal diversion patient). In this instance, an antegrade rather than a retrograde ureterogram should be done.

The proper retrograde study is performed with a Braasch bulb or a cone-tipped catheter and contrast material injected at the level of the ureteral orifice. Passing a whistle-tip catheter into the renal pelvis does not rule out an obstructed ureter and is to be discouraged as a diagnostic study. As discussed later, this may, however, become part of the therapy.

CLASSIFICATION

A useful classification of ureteral injuries is presented in Table 11B.3 . An alternative system is that proposed by the American Association for the Surgery of Trauma (AAST) as presented in Table 11B.4 (36).

External Violence	**Surgical Injury (continued)**
Contusion	Transection
Partial laceration	Ligation
Complete laceration	Perforation
Crush	Devascularization
Avulsion	Fistula formation
Surgical Injury	**Radiation Injury**
Crush	
Avulsion	

TABLE 11B.3. CLASSIFICATION OF URETERAL INJURIES

Grade I	Hematoma: contusion or hematoma without devascularization
Grade II	Laceration: <50% transection
Grade III	Laceration: >50% transection
Grade IV	Laceration: complete transection with 2 cm of devascularization
Grade V	Laceration: avulsion with >2 cm of devascularization

TABLE 11B.4. AAST CLASSIFICATION OF URETERAL INJURIES

External Violence Injury

If a missile passes close to but does not penetrate the ureter, a contusion is present. If the ureter is penetrated, either a partial laceration or complete laceration is present. Rarely, a

ureter will be crushed, usually in association with a nearby bony injury of the same type, or avulsed from the ureteropelvic junction by a hyperextension injury.

Surgical Injury

A surgeon may crush a ureter with a clamp, avulse a ureter with a retractor, transect the ureter with a knife or scissors, or ligate the ureter inadvertently. A common endoscopic injury is ureteral perforation with a wire, ureteroscope, or other ureteroscopic tool (e.g., basket, laser). If the ureter is stripped of its adventitia and hence blood vessels, it becomes devascularized and necrosis usually occurs in approximately 10 to 14 days. This may lead to fistula formation, as can any of the other aforementioned injuries.

Radiation Injury

Uncommonly, ureteral injury occurs secondary to irradiation of the organ. These lesions may not be seen for months to years after therapy and usually result in ureteral obstruction.

THERAPY

External Violence Injury

Contusion

A contusion may be discovered during exploration in a patient who has had a missile pass close to the ureter, but the structure has remained intact. No therapy is necessary in these patients. If a high-velocity bullet (more than 2,500 feet per second) is implicated, there is always the danger of late necrosis of the ureter. In this instance, placement of an internal stent and drain in the area of the injury should be considered. This problem is seen more often in military conflicts than in civilian life (1,11,44,56).

Laceration

If a partial laceration is present and the ureter that is still in continuity is viable, placement of an indwelling double-J stent and closure of the wound with interrupted 4-0 or 5-0 absorbable sutures gives the best results (49,54,58).Some authors advocate running closure of the wound and elimination of all stents (9). Before the advent of the totally indwelling stent, this was clearly a better way to handle minor lesions because the placement of a transcutaneous stent and formal nephrostomy may increase the complication rate and extend the scope of the procedure (60). With the use of the indwelling stent, drainage is minimal and the patient can be discharged at an early date. All of the devitalized tissue must be debrided, with a Penrose drain placed at the site of the repair and brought out through a separate stab wound.

However, if the remaining intact ureter is of questionable viability or if there is a complete laceration of the ureter, all devitalized tissue must be excised before the decision on a repair is made.

Clearly, the procedure with the lowest complication rate is the ureteroneocystostomy (Fig. 11B.3). This repair can be performed only on a patient with an injury below the level of the iliac vessels. The kidney can usually be mobilized and lowered so that the gap between the ureter and bladder can be decreased a few centimeters. The use of a bladder flap also can help bring the bladder closer to the ureter (Fig. 11B.4) (10). Sometimes merely suturing the bladder to the psoas fascia (psoas hitch) can ensure that there will not be tension on the repair. A nonrefluxing reimplantation is most desirable but cannot always be performed. Because adults, especially women, usually have little trouble with vesicoureteral reflux, this should not result in major problems later in life.

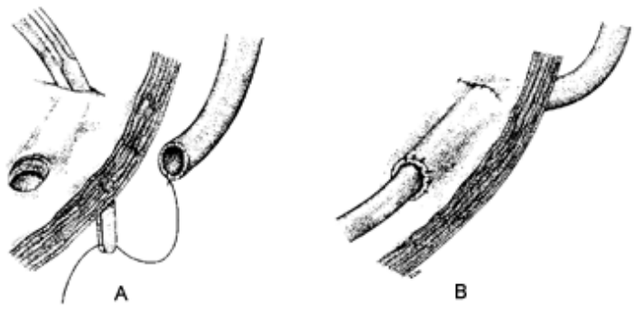

FIGURE 11B.3. Ureteroneocystostomy. **A:** Clamp through bladder wall from mucosa to serosa where ureter will enter bladder. Neo-orifice is created in mucosa of bladder. Submucosal tunnel is created from neo-orifice to entrance of ureter into bladder. **B:** Ureter enters bladder, runs into submucosal tunnel to neo-orifice, and is sewn in place. Stent is in ureter.

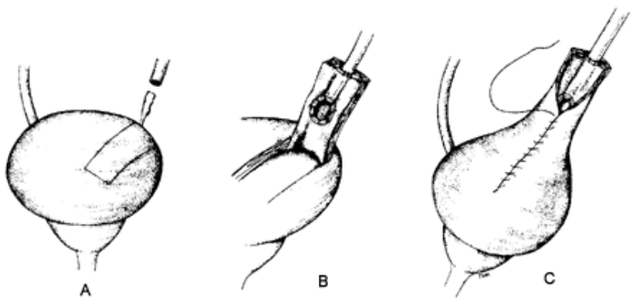

FIGURE 11B.4. A: Bladder flap to be created is outlined on bladder. **B:** Flap is created and ureter sewn in place by means of submucosal tunnel. **C:** Flap is sewn into tube to close bladder defect.

If the injury is too high for a ureteroneocystostomy to be performed, however, a ureteroureterostomy should be done (Fig. 11B.5). Traditionally, this was performed with a running suture of 4-0 or 5-0 absorbable material without stenting. The use of a stent and nephrostomy added major surgical time and complications to the procedure. If the wound was contaminated by bowel contents, stenting was mandatory.

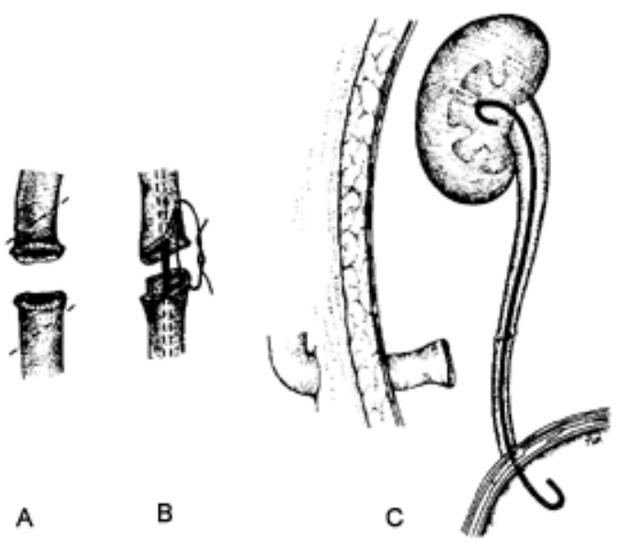

FIGURE 11B.5. A: Traumatized and severed ureter. *Dashed lines* show where spatulated edges will be trimmed. **B:** Ureter is spatulated and suturing begun, with stent in place. **C:** Anastomosis complete, double-J catheter in ureter, placement of Penrose drain by means of stab wound to area of anastomosis.

The use of an indwelling stent and interrupted sutures has become popular with the introduction of the double-J stent. The surgical time is shorter and the margin of

safety increased. No matter which technique is used, a Penrose drain should be placed as described previously. If a major length of ureter is lost, consideration should be given to a transureteroureterostomy or merely bringing the cut end of the ureter to the skin as a cutaneous ureterostomy for later definitive repair. Autotransplantation of the kidney to the hypogastric vessels plus ureteroneocystostomy also should be considered (1). This adds major operative time and increases risk to the patient, but in the patient with a solitary kidney it can be lifesaving. There are reports of using the appendix to replace lost segments of the ureter but not with long-term follow-up (33). If immediate reconstruction is impossible, consideration should be given to placement of a nephrostomy and delayed repair.

Crush Injury

When the ureter has been crushed along with other, adjacent tissues, debridement and usually ureteroureterostomy must be performed. All of the previously described techniques should be considered, and whichever seems appropriate should be used.

Avulsion Injury

Avulsion injury is essentially a complete laceration and requires debridement and definitive repair with stenting as described earlier.

Surgical Injury

Before a discussion of the types of repairs that should be used for a surgical injury of the ureter, some comments should be made about the prophylactic preoperative placement of ureteral catheters to identify the ureters at the time of exploration. Before performing a surgical procedure—especially when it is clear that the dissection will be difficult because of prior surgery, inflammation, or an inflammatory disease process such as endometriosis—many physicians place retrograde ureteral catheters into the ureters. It is difficult to verify that this technique actually decreases the incidence of ureteral injury in these patients. Perhaps the best that can be said is that it helps identify an injured ureter when the catheter is seen in the operative field.

Crush Injury

During a surgical procedure, a surgeon may inadvertently crush a ureter by placing a clamp on the structure or ligating it and then removing the clamp or ligature. In such a case, a decision must be made. Has the crushed ureteral segment been devascularized enough that it will eventually necrose and develop either a stricture or, more likely, a fistula? Unfortunately, there is no good intraoperative test to resolve this dilemma.

If there is good evidence that major injury has occurred, the ureteral segment should be excised and either a ureteroneocystostomy or ureteroureterostomy with internal stenting performed as described previously. If the surgeon chooses not to resect the segment, an indwelling stent placed either by opening the bladder or transurethrally at the end of

the procedure is a good safety measure. Placement of a drain in this instance is probably not mandatory.

Laceration Injury

When the ureter has been completely severed either by avulsion or transection and this is recognized intraoperatively, repair by any of the techniques outlined in the section on lacerations associated with external violence should be used. If a laceration is not recognized until after the surgery has been completed, however, various therapeutic decisions will have to be made. *Initially, retrograde ureteral catheterization should be attempted.* Unfortunately, most of the time the catheter cannot be negotiated past the laceration into the proximal ureter. Obviously, this technique is applicable only for a partial laceration. If it is successful, however, a double-J stent should be placed and the patient observed for resolution of the extravasated urine. At the first sign of deterioration, the patient should have a percutaneous or formally placed drain inserted to remove the extravasation.

If the retrograde catheterization is unsuccessful, a percutaneous nephrostomy should be placed and an antegrade stent passed into the bladder. After the extravasation resolves, a double-J stent can be placed for long-term drainage (15,30,39,53).

If drainage of the kidney cannot be established by the percutaneous route, surgical exploration must be performed (21,35). In the first few postoperative days, primary repair should be considered as discussed previously, but if the injury is discovered later in the postoperative period, nephrostomy tube placement and drainage of the extravasation should be done, with delayed repair planned for many months in the future. When large segments of the ureter have been lost, an ileal ureter can be used when primary repair is planned and not done in an emergency situation. Since autotransplantation has gained in popularity, however, this procedure has been used less. Often, in the seriously ill patient with a normal opposite renal unit, nephrectomy is the best choice.

Ligation Injury

When complete obstruction of the ureter is discovered, it is always tempting to return to the operating room and deligate the ureter. Except for ureters ligated at the time of vesicourethropexy, this may be a hazardous procedure and may lead to delayed necrosis and fistula formation. Probably the reason it works so well with vesicourethral suspension is that during this procedure large amounts of tissue are caught in the suture, so devascularization is less of a problem than is mechanical obstruction from angulation. Perhaps if the ureter is loosely ligated and a stent is placed after deligation, this procedure has some merit (19).

The more conservative approach is to place a percutaneous nephrostomy tube in the kidney and attempt to pass a stent antegrade past the obstruction (15,20,30,35,39,53). Retrograde stenting fails almost all of the time. If stenting is successful, balloon dilation, in an effort to disrupt the suture, may be tried but is unnecessary (23). If the ureter has been ligated with chromic suture material, the obstruction will usually resolve in 3 to 4 weeks (20). If it has been ligated with polyglycolic acid suture, it may take 6 to 8 weeks to resolve (Fig. 11B.6). If it has not resolved in 4 to 6 months, formal repair will be necessary by one of the previously described techniques. Once again, the patient who cannot withstand the complications associated with reconstructive procedures may best be handled by nephrectomy.

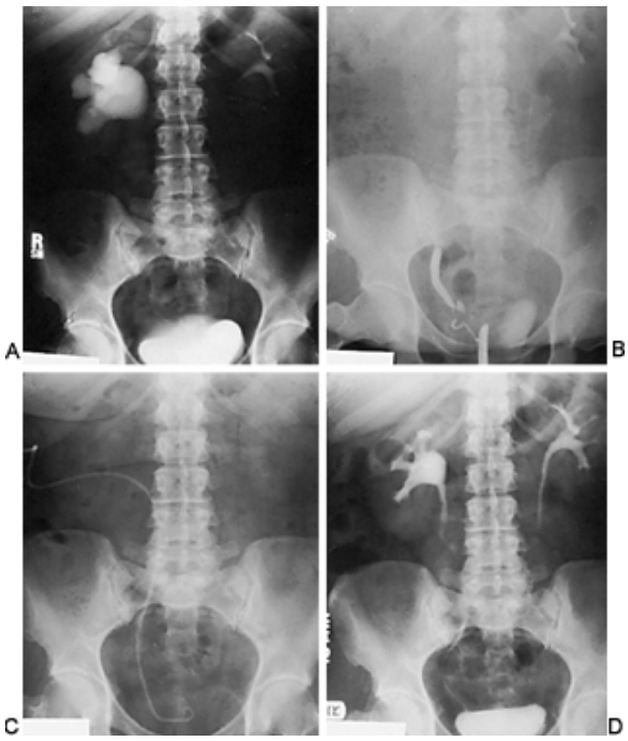

FIGURE 11B.6. Woman, aged 46 years, who developed a ureterovaginal fistula after an abdominal hysterectomy. **A:** Intravenous pyelography done on postoperative day 10 demonstrates obstruction of the right ureter. **B:** Retrograde ureterogram demonstrates the area of obstruction and some extravasation. **C:** An antegrade ureteral stent was placed beyond the fistula the following day and left in place 9 weeks. **D:** Intravenous pyelography done 6 months later demonstrates resolution of the hydronephrosis and a normal collecting system.

Fistula Formation

If necrosis occurs from any of the injuries listed in Table 11B.3 and the urine either collects in the retroperitoneum or abdomen or tracts to the skin, bowel, or vagina, a percutaneous nephrostomy and ureteral stent should be placed. As with ureteral lacerations, if the procedure is successful, in time the ureter will heal and the fistula will usually close. If a stent cannot be passed, the ureter will

usually stricture at the site of the fistula and formal repair will have to be performed 4 to 6 months after the injury with one of the previously described procedures (15,29,30).

Radiation Injury

Radiation injury, although uncommon, is usually discovered months to years after the therapy has been completed. Ureteral stricture formation is usually present. Repair is difficult because irradiated tissue heals poorly. Permanent internal stent diversion is one approach, as is nephrectomy or diversion of the urine into an isolated bowel conduit with both ureter and bowel outside the field of treatment. Occasionally, reconstructive procedures using irradiated tissue wrapped in omentum are successful (59).

POSTOPERATIVE CARE AND COMPLICATIONS

Indwelling ureteral stents can be left in place for up to 6 months without fear of complications. Although many have been in place for more than a year with little difficulty, after 2 months some of them develop calculi and may cause obstruction of the ureter (15). If a drain has been placed, it can usually be removed in a week, even if the stent is left for a longer period. Most patients can be promptly discharged from the hospital and have these items removed in the outpatient setting.

Patients with percutaneous nephrostomy tubes should be taught to irrigate the tubes and to change dressings. A nephrostogram should be done at 3-week intervals to see if the obstruction has been relieved. When the ureter is again draining, the tube can be removed on an outpatient basis.*Stents placed across fistulae should be left in place for at least 4 to 6 weeks and a pull-out ureterogram performed to ensure that the fistula has closed.* If the fistula site can be seen (skin or vagina), it should be inspected every 2 weeks until the site has sealed. The stent should not be removed until the opening is completely closed and the overlying skin or mucosa is intact.

Once all foreign materials have been removed, the patient should be treated with antibiotics to ensure that the urinary tract is sterile. Repeated cultures are recommended.

An excretory urogram or ultrasound should be performed 3 to 6 months after the repair and again a year later. Delayed obstruction is rare but can occur.

With formal surgical repairs, return to full activity takes 4 to 6 weeks. With the use of indwelling stents or percutaneous tubes, time to recovery is no longer than that usually seen with the primary surgical procedure.

The major complications from indwelling tubes, either totally indwelling or exiting from the kidney, are infection, tube obstruction, and calculus formation (15). If patients are instructed in how to irrigate the tubes at home, many trips to the emergency room or office can be avoided. Tubes may have to be changed if they obstruct, and pyelonephritis must be treated with appropriate antibiotics. Calculi must be handled at the time of tube removal.

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12

TRAUMA TO THE LOWER URINARY TRACT

Joseph N. Corriere Jr.

J.N. Corriere, Jr.: Department of Surgery, Division of Urology, The University of Texas, Houston, TX 77030.

Contents

BLADDER INJURIES

Part of "12 - TRAUMA TO THE LOWER URINARY TRACT "

In the child, the bladder is an abdominal organ and as such is vulnerable to external trauma. As the bony pelvis grows, the bladder becomes protected from injury, especially if it is empty of urine. The bladder is located extraperitoneally in the space of Retzius. Laterally, it is bound by the internal obturator muscles and the lateral umbilical ligaments. Its base is attached to the urogenital diaphragm, and Denonvilliers' fascia, or the rectovesical fascia, binds it loosely posteriorly. Unlike the rest of the organ, however, the dome of the bladder is mobile and distensible.

When the bladder is distended or the pelvis is fractured, the normal protective influence of the intact pelvic ring is lost, and in fact, the shearing force of a pelvic fracture commonly tears the bladder at its moorings. A spicule of bone may lacerate the organ, or it may rupture at the dome by a direct blow to the abdomen without bony injury. Conversely, missiles from an outside force, from internal migration, or in the hands of a well-meaning surgeon, may find the bladder despite its position.

Etiology

Penetrating Injuries

In usual civilian practice, the most common penetrating injuries of the bladder occur from surgical misadventure. Table 12.1 lists the types of procedures and instruments that have been associated with operative injury to the bladder (33,37,41,54,55,69,70,77,97,123,124). Trauma from external violence is most commonly caused by gunshot wounds (23,33,145).

Operative Injury	External Violence
Transurethral Procedures	Gunshot wound
Resectoscope	Knife wound
Lithotrite	Spike impalement
Cystoscope	**Internal Migration**
Urethral instrumentation	***Surgical Drains***
Gynecologic Procedures	Penrose
Abdominal hysterectomy	Saratoga sump
Vaginal hysterectomy	Foley catheter
Removal of cervical stump	***Intrauterine or Sterilization Devices***
Salpingo-oophorectomy	Lippes loop
Cesarean section	Dalkon Shield
Laparoscopy	Copper-7
Vesicourethral suture suspension	Copper-T
Dilation and curettage	Filshie clip
Suction curettage	***Hip Prosthesis***
Neovaginal construction	Pins
Abdominal Procedures	Trochanteric plate
Herniorrhaphy	***Penile Prosthesis***
Abdominoperineal resection	***Neurosurgical Shunts***
Anterior colon resection	***Swallowed Objects***
Neonatal umbilical artery catheterization	Pins
Laparoscopy	Toothpicks
Aortic bypass grafts	Knife blades
Tenckhoff catheter placement	Bones
Orthopedic Procedures	**Long-dwelling Foley Catheter**
Pelvic fracture manipulation	
Bone screw placement	

TABLE 12.1. CAUSE OF PENETRATING INJURIES OF THE BLADDER

Rarely, injury may occur from migration and erosion of internally placed foreign materials or swallowed objects, most commonly surgical drains, intrauterine or sterilization devices, hip prostheses, penile prosthesis, toothpicks, pins, knife blades, or bones (5,14,21,29,58,67,101,117,131,50). Finally, long-term Foley catheters have been known to erode through the bladder, usually at the dome, where it sits at the tip of the catheter (10).

Blunt Injuries

The most common cause of bladder injuries resulting from external violence is blunt trauma to the abdomen, mostly from motor vehicle accidents but also from falls, crushing injuries to the bony pelvis, or blows to the abdomen (Table 12.2).

The full bladder is especially vulnerable to a deceleration injury (23).

Motor vehicle accident	Crush of bony pelvis
Fall	Abdominal blow

TABLE 12.2. CAUSE OF BLUNT INJURIES OF THE BLADDER

In motor vehicle accidents, injuries are seen in passengers wearing seat belts when the force of the collision may focus on the abdomen and thus the full bladder, in the unrestrained child (or, less commonly, the adult) who is thrown by the impact against an unyielding object, or secondary to a pelvic fracture (129).

In our experience with 111 bladder injuries over a 7-year period, 86% were caused by blunt trauma and 90% of the blunt injuries were secondary to motor vehicle accidents (33). A total of 89% of the blunt injuries were associated with pelvic fractures. On the other hand, 9% of patients with pelvic fractures had a concomitant injury to the bladder.

Spontaneous Rupture

It is difficult to understand how a bladder can rupture “spontaneously” as is reported in most large series of these injuries. It is usually seen in the patient with preexisting bladder disease, usually in chronic retention, and is most likely associated with minor blunt trauma or unrecognized trauma in an obtunded patient (1,100).

Diagnosis

Signs and Symptoms

The signs and symptoms of rupture of the bladder are usually nonspecific. The patient may complain of suprapubic pain or relate that he attempted to urinate and could not. The discomfort of a concomitant fractured pelvis or other organ system injury often overshadows the pain from the damaged urinary tract.

Tenderness is present in the suprapubic area and bowel sounds absent, especially if it is an intraperitoneal rupture. Shock is rarely caused by an isolated bladder rupture. When it is present, another cause for the hypotension should be sought.

Bladder perforation during a transurethral surgical procedure with the patient under spinal anesthesia is commonly associated with acute symptoms on the operating table. Extraperitoneal injuries will cause lower abdominal pain, and the patient's blood pressure may begin to rise. Intraperitoneal injuries with extravasation of large quantities of fluid lead to abdominal distention and referred pain to the tip of the shoulder if the fluid irritates the diaphragm.

If recognition of an intraperitoneal injury is delayed, uroascites may develop and cause significant abdominal distention. This may cause respiratory distress and even lower limb venous occlusion, especially in the neonate (37). Peritoneal signs of tenderness and rebound will develop, and if the urine is infected, frank peritonitis may eventually be seen.

Hematuria is a hallmark finding with bladder injuries. In our experience and that of others, *gross hematuria occurs more than 95% of the time, with microscopic hematuria present in the remaining cases* (23,33).

Radiographic Examination

The static cystogram is the only study that will definitely diagnose a ruptured bladder (22,126).*If a urethral injury is suspected because of a pelvic fracture; the presence of blood at the urethral meatus; a high-riding prostate on rectal examination; or marked ecchymosis and edema of the perineum, scrotum, and/or penis, a retrograde urethrogram must be done before attempted urethral catheterization.*

If a ruptured urethra is found, urethral catheterization is usually contraindicated and a suprapubic cystotomy should be

performed. If the tube is placed percutaneously, a static cystogram must still be done to rule out a concomitant bladder injury. If the cystotomy tube is placed surgically, the bladder can be inspected at the time of the exploration and the cystogram eliminated.

It is best to perform this examination with fixed equipment in the radiology suite. A satisfactory study can be done in the emergency room with portable equipment and grid cassettes if absolutely necessary. A Foley catheter is placed in the bladder and the bladder emptied of urine. A 300-mL bottle of standard infusion contrast material (25% to 30%) and a similar amount of saline solution are attached to a Y connector and then to the catheter to obtain a 50-50 mixture.

A scout radiograph is taken and then 100 mL of the mixture infused. A second film is exposed to check for gross extravasation. If a bladder rupture is seen, the catheter is immediately placed to straight drainage. If extravasation is not seen, the remainder of the solution is instilled and films are obtained in the anteroposterior, oblique, and lateral projections.

The bladder is then drained of all contrast material and an additional film taken. This is especially important in patients in whom the oblique and lateral films may have been omitted because of concomitant injuries or the patient's clinical state. Small amounts of extravasation may be present behind a contrast-filled bladder and may only be seen on this view. The bladder should also be drained before proceeding with studies of the upper urinary tract. An excretory urogram or computed tomography (CT) scan with contrast should then be performed.

It cannot be overemphasized that *a normal cystogram on a urogram is not sufficient evidence to rule out bladder injury.* Often, a blood clot or omentum temporarily seals a small rent and the bladder will appear intact. Only the static cystogram with full vesical distention and a film taken after drainage can verify that a bladder rupture is not present. Similarly, the bladder image on a CT is limited because, like the cystogram on the urogram, it may not show a leak because it is not forcibly distended (51,57,87,108,128). On the other hand, the CT scanner can be used to image the bladder instead of the conventional radiograph in conjunction with a retrograde cystogram, and a proper diagnosis can be made. Ultrasound diagnosis is still not at the level of accuracy of retrograde contrast injection (40).

Classification

As can be seen in Table 12.3, bladder injuries secondary to blunt trauma are subclassified regarding the extent and location of the injury, whereas penetrating injuries are usually grouped together. However, as discussed in the section on therapy, when considering the treatment of iatrogenic penetrating injuries, extent and location become critical and must be differentiated. The American Association for the Surgery of Trauma (AAST) organ scoring system is presented in Table 12.4 (92).

Blunt Trauma
Contusion
Interstitial rupture
Intraperitoneal rupture
Extraperitoneal rupture
Intraperitoneal and extraperitoneal rupture
Penetrating Trauma

TABLE 12.3. CLASSIFICATION OF BLADDER INJURIES

Grade I	Hematoma: contusion, intramural hematoma Laceration: partial thickness
Grade II	Laceration: extraperitoneal bladder wall laceration <2 cm
Grade III	Laceration: extraperitoneal (>2 cm) or intraperitoneal (<2 cm) bladder wall lacerations
Grade IV	Laceration: intraperitoneal bladder wall laceration >2 cm
Grade V	Laceration: intraperitoneal or extraperitoneal bladder wall laceration extending into the bladder neck or ureteral orifice (trigone)

TABLE 12.4. AAST CLASSIFICATION OF BLADDER INJURIES

Bladder Contusion

A bladder contusion results from damage to the bladder mucosa or muscularis without loss of wall continuity. Extravasation is not seen on cystogram, but the bladder outline may be distorted (Fig. 12.1). The exact incidence of this injury is difficult to determine because often the diagnosis is made by exclusion in the patient with trauma to the lower abdomen and hematuria. The best overall estimate is that this injury accounts for approximately one-third of all bladder injuries.

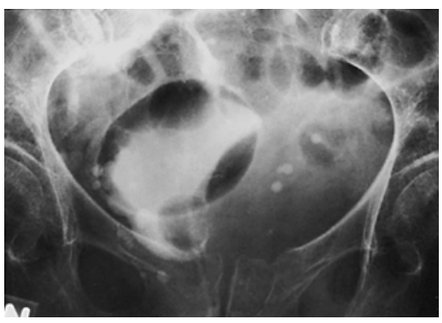

FIGURE 12.1. Bladder contusion secondary to a pelvic hematoma and pelvic fracture. (From Sandler CM, Phillips JM, Harris JD, et al. Radiology of the bladder and urethra in blunt pelvic trauma. *Radiol Clin North Am* 1981;19:195, with permission.)

Interstitial Rupture

Occasionally, an incomplete tear (non–full-thickness tear) of the bladder wall is seen secondary to blunt trauma. As with the bladder contusion, no extravasation is seen on the cystogram (Fig. 12.2). It is important to distinguish this injury from a bladder contusion because the therapy requires a longer period of catheterization because it may represent a full-thickness injury that has sealed with clots or

at least needs a longer time to heal as a result of the extent of the damage to the bladder wall.

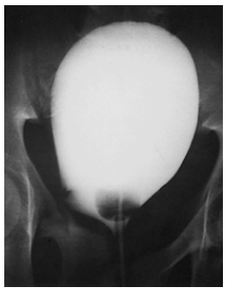

FIGURE 12.2. Interstitial bladder rupture secondary to a pelvic fracture.

Intraperitoneal Rupture

As mentioned, intraperitoneal rupture of the bladder occurs when there is a sudden rise in intravesicular pressure secondary to a blow to the pelvis or lower abdomen. This increased pressure results in rupture of the dome, the weakest and most mobile part of the bladder. Contrast material will fill the cul-de-sac, outline loops of bowel, and eventually extend into the paracolic gutter (Fig. 12.3). This injury is common in children because of the intraperitoneal position of the bladder. Intraperitoneal bladder ruptures probably account for one-third of all bladder injuries and are approximately equal in incidence to extraperitoneal ruptures.

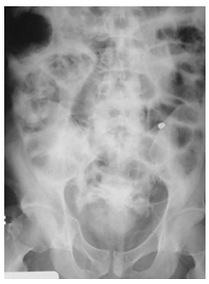

FIGURE 12.3. Intraperitoneal bladder rupture secondary to blunt abdominal trauma.

Extraperitoneal Rupture

Extraperitoneal bladder ruptures are seen almost exclusively with pelvic fractures. The bladder usually is sheared on the anterior lateral wall near the bladder base by the distortion of the pelvic ring disruption. Occasionally, the bladder is lacerated by a sharp, bony spicule. On cystography, flame-shaped areas of extravasation that are usually confined to the perivesical soft tissues are visualized (Fig. 12.4). If there is a large pelvic hematoma, the bladder will often be compressed into the “teardrop deformity.” Urinary extravasation may extend to the thigh by means of the obturator foramen to the scrotum by means of the inguinal canal, up the anterior abdominal wall, or retroperitoneally as high as the kidneys (Fig. 12.5). Sixty percent of the time a contracoup bursting rupture opposite the area of fracture is seen as well as an injury near the fracture site (23,33).

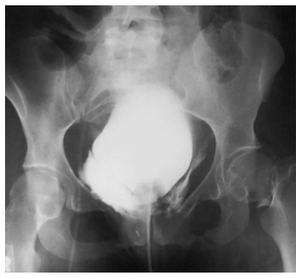

FIGURE 12.4. Extraperitoneal bladder rupture secondary to pelvic fracture.

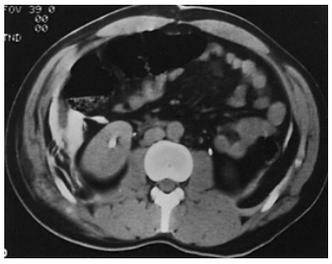

FIGURE 12.5. Computed tomography scan of patient with an extravesical bladder rupture.

Note extravasation as high as kidneys.

Intraperitoneal and Extraperitoneal Bladder Rupture

Occasionally, the bladder is ruptured both intraperitoneally and extraperitoneally. These injuries are caused by penetrating trauma or pelvic fractures. The radiologic findings

are a mixture of the previous descriptions of the single injuries.

Therapy

Penetrating Injuries from External Violence

All patients with penetrating injuries from external violence should undergo exploration of the abdomen and of the track the missile followed from its entrance wound to its exit wound. The peritoneal cavity should be opened through a midline incision, even if the injury is thought to be entirely extraperitoneal, and the intraabdominal viscera and major vasculature should be examined for damage. All devitalized tissue and debris (e.g., bullets, bone spicules, clothing) should be removed from the bladder and abdomen (23).

If the ureteral orifices are involved in the injury or there is concern about the integrity of the ureters, 5 mL of indigo carmine should be injected intravenously. In 7 to 10 minutes, the blue dye should appear in the bladder. A search for extravasation should be made and the ureters intubated with 5-Fr whistle-tip catheters if there is any concern that they have been damaged.

If a large pelvic hematoma is present, it is best left undisturbed if one can be sure by radiography (plain film, cystogram, urogram, and/or arteriogram) that there is no major disruption of the bladder neck, ureters, or vasculature. The bladder is then entered through its peritoneal surface at the dome and thoroughly inspected.

After debridement, the extraperitoneal vesical defect should be closed with a single-layer running 3-0 chromic or polyglycolic suture through the interior of the bladder. Extensive mobilization of the bladder to ensure a watertight closure or to place the knots on the outside of the bladder will usually only increase bleeding. If it is impossible to close the extraperitoneal defects, they should not be disturbed. With adequate bladder drainage, they will eventually heal without difficulty. Only injuries to the bladder neck must undergo reconstruction.

A suprapubic cystotomy tube may then be inserted in the bladder through a separate stab wound. At least a 24-Fr size should be used to ensure egress of blood clots. Either a Malecot or mushroom tube is recommended. The mushroom style has a firmer flange and is less likely to become dislodged, but the sideholes are small. If the tip of the catheter is excised before insertion, this drawback is overcome.

The tube should be sewn in place with an 0 chromic or polyglycolic purse-string suture, which is then used to fix the bladder to the wall at the site where it crosses the abdomen, again through a separate stab wound. This will ensure a controlled fistula if leakage occurs at the time of tube removal. The catheter should not be brought through the bladder wound because removal may disrupt the suture line, nor should it come through the abdominal incision because this increases the chance for wound infection. *The intraperitoneal bladder incision is closed with a double layer of 3-0 chromic or polyglycolic suture in a running watertight fashion. This is best done after the suprapubic tube is sewn into the bladder but before the tube is brought through and fixed to the abdominal wall.* If bleeding and clot formation are not excessive, a Foley catheter may be used instead of a suprapubic tube (139).

One-inch Penrose drains are placed near the suture lines and brought through separate stab wounds. The drains and suprapubic tubes are sutured to the skin with 3-0 nonabsorbable suture material. The wound is closed in a standard

fashion, and a sterile dressing is applied. If the orthopedic surgeon repairs a pelvic fracture at the same time using internal plates, drains and suprapubic tubes should not be used if at all possible to prevent infection near the foreign material.

Iatrogenic Penetrating Injuries

When the bladder is inadvertently injured during a surgical procedure, prompt repair with a double layer of 3-0 absorbable suture material and tube drainage with a Foley catheter or suprapubic tube usually ensures an excellent result. The most common mistake made is not thoroughly inspecting the entire bladder when the injury is discovered, thereby overlooking a second rent in the organ. This is especially disturbing during gynecologic surgery when a lesion of the dome is seen and repaired, but one at the base that also involves the vagina is missed.

Delayed recognition of operative injuries requires individualized attention. *If recognized in the first few days after surgery, immediate correction usually will be successful. Although some reports advocate repair of bladder injuries at the time of diagnosis despite the age of the injury, after 1 or 2 weeks, tissue edema impedes proper wound healing, increasing the failure rate of the repair. The success rate is improved by delaying repair for months. Only intraperitoneal injuries and uroascites demand prompt repair when they are discovered.*

Injury to the bladder by an endoscope (cystoscope, resectoscope, or laparoscope)—especially if the injury is extraperitoneal and properly recognized, the procedure immediately terminated, and the rent small—can be handled with large-caliber urethral catheter drainage and expectant therapy. These patients must be observed closely, and at the least sign of deterioration, abdominal exploration and repair of the bladder should be performed. If there is any evidence of uroascites or if the urine is infected, formal repair is mandatory.

Internal Migrating Objects

Internal migrating objects are rare injuries that necessitate removal of the foreign material and use of a urethral catheter or suprapubic tube drainage. Formal repair performed as exploration is usually necessary to remove most of these objects and must be done if the injury is intraperitoneal (29,101,131).

Bladder Contusions

Bladder contusions necessitate Foley catheter drainage for a few days or, if minor, no therapy at all. If there is a large pelvic hematoma and marked bladder neck distortion, the patient may have difficulty voiding. These patients may require prolonged catheter drainage. If there is a major injury to the sacrum and the patient cannot urinate, a cystometrogram should be performed to be sure there has not been damage to the sacral nerve roots that innervate the bladder. If no detrusor contraction is seen and the patient continues to be unable to void after multiple trials, intermittent self-catheterization should be instituted. Most of these problems are temporary unless accompanied by major neurologic deficit.

Interstitial Ruptures

As stated in the section on classification, interstitial ruptures are incomplete bladder wall ruptures, or they may represent a small full-thickness rupture that has sealed itself with clot or possibly omentum. They should probably be treated by 10 days of catheter drainage, just as the complete but unrepaired rupture, and followed up closely for a change in clinical status. A cystogram should be performed before catheter removal.

Intraperitoneal Ruptures

All intraperitoneal bladder ruptures caused by blunt abdominal trauma should undergo formal repair. The peritoneal cavity should be opened, all urine and blood evacuated, the viscera and vasculature inspected for injury, and appropriate therapy instituted. The bladder will usually have a large 5-cm or greater rent at the dome. If necessary, it should be widened thoroughly to inspect the interior of the organ. Any concomitant extraperitoneal rents should be closed with a single running 3-0 chromic or polyglycolic suture from inside the bladder. Devitalized tissue should be excised, and after a suprapubic tube has been placed as previously described, the dome wound should be closed with absorbable suture material. The suprapubic tube is brought through a separate stab wound, and a peritoneal drain is placed and brought out through a second stab wound. If the urine is relatively clear, a Foley catheter may be used instead of a suprapubic tube (139). The peritoneal cavity cannot and should not be drained. Closure of the abdomen is as previously described (23).

A few scattered reports indicate that intraperitoneal bladder injuries can be treated with simple Foley catheter drainage (99,121,122). When the literature is carefully reviewed, however, it is clear that most of these authors are discussing iatrogenic transurethral bladder perforations and not wounds caused by external violence. Most patients with intraperitoneal bladder ruptures caused by abdominal blows or a fractured pelvis have large gaping rents and marked uroascites when first seen. These patients must undergo prompt surgical repair because they rapidly deteriorate if not treated in a timely fashion (23). Finally, reports of laparoscopic repair are now appearing in the literature (9).

Extraperitoneal Ruptures

Isolated uncomplicated extraperitoneal bladder ruptures can be handled easily by 10 days of Foley catheter drainage (20,33,99,121,122). As some authors state, one cannot decide to treat only small extraperitoneal ruptures with catheter drainage and formally close large ruptures because it is difficult to relate the amount of contrast extravasation to the extent of the injury (20,23). Extravasation is related to the amount of contrast instilled and to the size of the injury. In our experience, however, extravasation into the pelvis, down the inguinal canal to the scrotum, and up the retroperitoneum as high as the kidneys can be successfully treated with catheter drainage. If the patient has uninfected urine and appropriate catheter care is used, the urine will quickly absorb and the bladder rent will heal.

However, it cannot be stressed enough that the nonoperative catheter drainage therapy is exactly that: No exploration for any reason is being performed, and the catheter is draining well, not poorly and intermittently, being obstructed with clots (76). *If the catheter will not drain easily and the urine does not clear properly, formal repair is best.*

If the patient with an extraperitoneal bladder rupture is to be explored for associated injuries and is not gravely ill, it is best to open the dome of the bladder, not disturb the pelvic hematoma, repair the rupture intravesically, close the bladder, and insert a suprapubic tube or Foley catheter as previously described. If the pelvic hematoma is opened for another reason, a drain should be placed. If it is not opened, no drain is necessary.

Intraperitoneal and Extraperitoneal Ruptures

Intraperitoneal and extraperitoneal ruptures need to be formally repaired as previously described. Most of these patients have major pelvic fractures and often have injured their urethra, bladder neck, or in the female, vagina as well. Prompt reconstruction, even in the face of a marked pelvic disruption, is usually necessary for a good long-term result. These cases all need to be individualized, especially those with major tissue destruction.

Postoperative Care and Follow-up

Postoperatively, if no other injuries are present, oral alimentation may be resumed when gastrointestinal peristalsis returns to normal, usually within 3 to 7 days of the injury. The bladder heals remarkably quickly, and if a good repair was achieved, the suprapubic tube or Foley catheter may be removed within a week. If there is any question about the closure, a cystogram should be performed before tube removal. If extravasation is present, the catheter should be left in place for further drainage and the cystogram repeated on the tenth postoperative day.

When the patient is voiding normally and there is no leakage of urine from the drainage site for 24 hours, the drain may be removed. Routine antibiotics are not necessary, but once the catheter has been removed, the urine should be cultured and appropriate antibiotics given if bacteriuria is present. If the urine is infected at the time of the injury and subsequent extravasation, antibiotics should be begun preoperatively and continued for at least a week. Frequent urine cultures should be obtained to avoid serious complications.

If the patient had an extraperitoneal injury that was treated with Foley catheter drainage alone, a cystogram should be done on the tenth postoperative day. In our experience, more than 85% of bladders are healed by that time, and the catheter can then be removed. Virtually all injuries treated in this manner are healed with less than 3 weeks of catheter drainage. In the rare male patient who has persistent extravasation, a punch suprapubic tube should be placed in the bladder to prevent urethral complications.

Full activity may be resumed within 3 to 4 weeks of surgery unless other injuries or complications dictate further therapy or rest. Other than urine cultures if indicated, no long-term follow-up is necessary.

Complications

The most serious complications for bladder ruptures are secondary to delay in diagnosis. When urine leaks into the peritoneal cavity, it equilibrates with serum, so peritoneal fluid analysis for creatinine and urea will not be helpful in diagnosis. If uroascites becomes marked, respiratory difficulty will develop, especially in infants. Emergency paracentesis may be lifesaving.

Sepsis from infected urine is a major threat. In the unrecognized intraperitoneal rupture, generalized peritonitis or loculated abscesses may develop. The bladder rent must be closed, the urine diverted, and all purulent collections drained surgically. Appropriate antibiotics must be given.

The mortality of patients with bladder ruptures is approximately 12% (23,33). The cause of death in these patients should never be secondary to the bladder wound if it is properly diagnosed and treated but will be caused by associated visceral or vascular injuries.

Injuries to the bladder neck, urethra, and vagina, if not promptly and properly repaired at the time of the injury, may result in incontinence, fistula, or stricture formation (88). In these cases, reconstruction will have to be delayed for months to allow edema, infection, and induration to disappear. In some patients, a neuropathic bladder may accompany the injury, and voiding may be impossible. Intermittent self-catheterization is a good way to overcome this problem.

URETHRAL INJURIES

Anatomically, the male urethra is traditionally divided into (a) the prostatic urethra; (b) the membranous urethra; (c) the bulbous urethra; and (d) the penile, or pendulous, urethra. When considering injuries to the male urethra, most surgeons use a classification that helps determine appropriate therapy such as (a) *posterior urethral injuries*–those of the prostatic and membranous urethra, above and including the urogenital diaphragm and (b) *anterior urethral injuries*–those of the bulbous and penile, or pendulous, urethra, below the urogenital diaphragm.

Because proper diagnosis is so critical to subsequent management and because both of these anatomic and mechanistic classifications can cause confusion, unified classifications have been developed that may help in the proper evaluation and therapy of these injuries [Table 12.5 (49) and Table 12.6 (92)]. These work best for blunt trauma but can be used for penetrating lesions as well.

Type I	Posterior urethra intact but stretched by pelvic hematoma
Type II	Partial or complete prostatomembranous urethral rupture above intact urogenital diaphragm
Type III	Partial or complete combined anterior/posterior urethral rupture with rupture of urogenital diaphragm
Type IV	Bladder neck injury with extension into posterior urethra
Type IVA	Base of bladder injury with periurethral extravasation (simulates type IV injury)
Type V	Partial or complete anterior urethral injury

TABLE 12.5. CLASSIFICATION OF URETHRAL INJURIES

Grade I	Contusion: blood at urethral meatus; urethrography normal
Grade II	Stretch injury: elongation of urethra without extravasation on urethrography
Grade III	Partial disruption: extravasation on urethrography, contrast at injury site with contrast visualization in the bladder
Grade IV	Complete disruption: extravasation on urethrography, contrast at injury site without visualization in the bladder; <2 cm of urethral separation
Grade V	Complete disruption: complete transection with >2 cm urethral separation, or extension into the prostate or vagina

TABLE 12.6. AAST CLASSIFICATION OF URETHRAL INJURIES

The female urethra is rarely injured (24,138). When it is damaged, however, it is usually accompanied by a severe bony pelvic disruption with concomitant injury to the bladder neck and vagina. It is usually more common in children than adults (2,56,73,88,113,134).

Etiology

Posterior Urethral Injuries

Almost all injuries of the posterior urethra in the male occur in conjunction with fracture of the bony pelvis (35,89,90,105). In modern civilian society, 90% of these injuries are caused by motor vehicle accidents involving automobiles, motorcycle riders, or pedestrians. Falls from a height, industrial crushing injuries, and sporting accidents make up the other 10% of the pelvic fracture patients (25).

This injury is most commonly caused by the shearing force of the bone disruption, with the prostate, attached by the puboprostatic ligaments, being pulled in one direction while the membranous urethra, attached to the urogenital diaphragm, is pulled in another direction.

Penetrating wounds of the posterior urethra from external violence are uncommon but do occur. Urethral instrumentation with perforation of the prostatic urethra, on the other hand, is more frequently seen (Table 12.7). There are two cases in the literature in which a lateral blow to the pelvis and thigh resulted in rupture of the posterior urethra at the junction of the prostatic and membranous urethra with probable concomitant rupture of the puboprostatic ligaments without fracture of the pelvis (34,119).

Posterior Urethral Injuries	***Straddle Injury (continued)***
Fracture of the Pelvis	Kick
Motor vehicle accidents	Bicycle
Fall, crush	***Penetrating Injury***
Sporting accidents	Gunshot
Penetrating Injuries	Machine injury
External Violence	Knife wound
Gunshot	***Urethral Instrumentation***
Stab	Catheters
Urethral Instrumentation	Cystoscope
Resectoscope	Sounds
Sounds	Filiforms, followers
Filiforms, followers	Self-instrumentation
Catheters	***Penile Surgery***
Lateral Pelvic Blow	Prosthesis placement, erosion
Anterior Urethral Injuries	Circumcision
Straddle Injury	***Sexual Intercourse***
Fall	Urethral laceration
Fence, ladder	Fracture of the penis

TABLE 12.7. CAUSE OF URETHRAL INJURIES

Anterior Urethral Injuries

Similarly, most injuries to the anterior urethra caused by external violence are the result of blunt trauma to the perineum (15,25,89,115). The bulbous urethra is usually crushed against the pelvic arch, generally when the patient falls astride an object. This may be while falling from a height, straddling a fence, or having a foot slip from the rung of a ladder. It is sometimes caused by a kick to the perineum or hitting a bump in the road while riding a bicycle and coming down hard on the seat or the crossbar.

Penetrating injuries of the anterior urethra caused by external objects are less common, but iatrogenic damage resulting from urethral instrumentation, especially inflation of a Foley catheter balloon in the bulbous urethra, occurs frequently (Table 12.7) (127). Surgery of the penis, most notably for penile prosthesis placement—or, later, prosthesis erosion—and circumcision can inadvertently damage the urethra.

Accidents secondary to sexual activity, either intercourse with urethral laceration or fracture of the penis, masturbation by urethral instrumentation, or genital mutilation by a mentally disturbed patient, also have been reported.

Diagnosis

Signs and Symptoms

Patients with a history of trauma to the perineum or who have a fracture of the bony pelvis should be suspected of having a urethral injury. If the patient has attempted to void, he may find he cannot or he may relate that he had the sensation of voiding but no urine came out of his urethra. This patient may have voided into his tissues.

Most patients with a ruptured urethra will have blood at the urethral meatus, and many of them will have swelling and ecchymosis of the penis, scrotum, and/or perineum. This is caused by urine and/or blood leaking into these structures. If the edema is only in the penis, it is probably contained within Buck's fascia. If it extends to the scrotum, perineum, or anterior abdominal wall, it will be contained by Colles' fascia.

In the patient with a fractured pelvis, rectal examination may reveal the prostate to be in a higher position than usual. This “high-riding prostate” is caused by disruption of the urethra with the prostate elevated from its normal position by a large pelvic hematoma, although the prostate also can be high-riding in the absence of a tear (type I injury, see later discussion). If the puboprostatic ligaments did not rupture, the prostate may have been lifted from its bed attached to a comminuted bone fragment. The soft, boggy hematoma will be felt where the prostate is normally found.

If the patient can urinate, he will usually have gross hematuria. It may be grossly bloody only at the beginning of the stream and/or at the end of the stream if the injury is a partial rupture.

Radiographic Examination

Any patient with a suspected urethral injury must have a retrograde urethrogram performed (32,126). Under no circumstances should an attempt be made to catheterize the urethra until this study delineates the anatomy and any damage done to that organ. Injudicious catheterization of the injured urethra carries the risk of converting a partial urethral rupture into a complete urethral rupture and possibly infecting a sterile periurethral or pelvic hematoma.

Trauma surgeons occasionally comment that placement of a urethral catheter is one of the first maneuvers that should be done in a multiple trauma patient, especially one who is hypotensive. They argue that urine output monitoring is critical in determining organ perfusion and proper fluid infusion rates. The urologic specialist should first counter with the point that blood pressure measurements also give the physician an idea of the level of organ perfusion. Second, the specialist should comment that virtually all multiple trauma patients will be sent to the radiology department to undergo appropriate studies within minutes of emergency room evaluation. At that time, a urethrogram can be performed along with other indicated x-ray films.

Some desperately ill patients who may have urethral injuries must be taken directly to the operating room for abdominal exploration before radiographic examination. At the time of surgery in these patients, a suprapubic tube should be inserted into the dome of the bladder for drainage. The lower tract may then be studied in the postoperative period and indicated therapy instituted. If the tube is not needed, it may be removed easily. As is discussed under complications of urethral ruptures, the long-term problems of incontinence, stricture formation, and erectile dysfunction, which seem unimportant at the time of injury, loom large in the postoperative period of these unfortunate men. The less urethral damage done, the more the patient will recover free of these complications.

Ideally, the urethrogram should be performed under fluoroscopic monitoring. If necessary, it may be obtained with fixed or even portable equipment in the emergency room. An easy technique that does not require special equipment is to insert a number 14- or 16-Fr Foley catheter into the urethra so that the balloon of the catheter is just 2 to 3 cm proximal to the meatus. One to two millimeters of saline solution is injected into the balloon to seat it in the fossa navicularis. No lubricant should be used or the catheter may slide out of the urethra.

The patient is then moved to a 25- to 30-degree oblique position, and approximately 25 mL of 25% to 30% contrast media is injected with a Toomey syringe into the urethra. An exposure is taken during the active injection of the

contrast medium to distend the urethra and produce a dynamic urethrogram (Fig. 12.6).

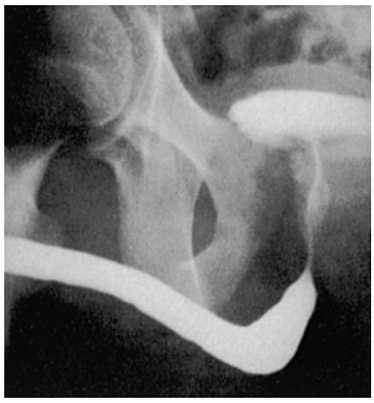

FIGURE 12.6. Normal retrograde urethrogram.

A penile clamp (i.e., Brodney or Knudson) also may be used but is cumbersome and may not always be available. Inserting the tip of the syringe directly into the urethra should not be done because the examiner's hand will be exposed to the x-ray beam.

The oblique position is best for demonstrating the entire anterior and posterior urethra. In the anteroposterior position, the bulbous urethra is foreshortened and the urethra, as well as areas of extravasation, will overlap, making the study uninterpretable.

If the urethra is normal, the balloon should be deflated, the catheter advanced into the bladder, the balloon reinflated, and a cystogram performed as previously discussed to rule out a bladder rupture. If a catheter has already been inserted into the bladder, it should not be removed. If a urethral injury is suspected, a urethrogram should be done around the indwelling catheter to rule out urethral damage. This can be done by inserting a 16-gauge Intracath alongside the Foley catheter and compressing the urethra while injecting contrast material.

Finally, an excretory urogram or CT scan should be performed to evaluate the kidneys and ureters. If a large pelvic hematoma is present, the bladder will have a “teardrop” appearance and ride high out of the pelvis (Fig. 12.7). This is commonly called a “pie-in-the-sky” bladder.

FIGURE 12.7. “Teardrop” or “pie-in-the-sky” bladder from a pelvic hematoma in a patient with a pelvic fracture.

POSTERIOR URETHRAL INJURIES

Part of "12 - TRAUMA TO THE LOWER URINARY TRACT "

Classification

As previously stated, virtually all posterior urethral injuries are secondary to fracture of the bony pelvis. Table 12.5 lists the classification of these injuries, which is helpful in planning their management (30,49,125).

Type I Injury

The posterior urethra and proximal bulbous urethra are stretched because the moorings of the prostate to the urogenital diaphragm have been ruptured and a hematoma has collected in the perivesical space (Fig. 12.8). Although stretched, the urethra is not ruptured. This injury accounts for 17% of posterior urethral ruptures.

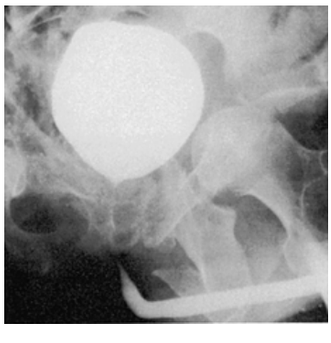

FIGURE 12.8. Type I urethral injury. Posterior urethra is compressed by hematoma. (From Sandler CM, Phillips JM, Harris JD, et al. Radiology of the bladder and urethra in blunt pelvic trauma. *Radiol Clin North Am* 1981;19:195, with permission.)

Type II Injury

Until recently, a type II injury was thought to be the most common type of posterior urethral injury. The classic description is rupture of the prostatomembranous urethra at the apex of the prostate above the urogenital diaphragm. Extravasation of contrast occurs superiorly into the pelvis but is limited inferiorly by an intact urogenital diaphragm (Fig. 12.9 and Fig. 12.10). The rupture may be complete or incomplete. Recent work has shown that this injury is present only 17% of the time.

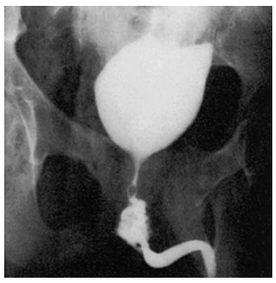

FIGURE 12.9. Type II partial urethral injury. All extravasation is in pelvis. Also note intraperitoneal rupture. (From Sandler CM, Harris JH Jr, Corriere JN Jr, et al. Posterior urethral injuries after pelvic fracture. *AJR Am J Roentgenol* 1981;137:1233, with permission.)

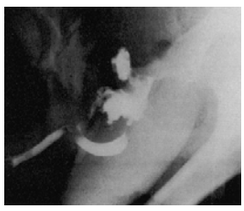

FIGURE 12.10. Type II complete urethral injury. All extravasation is in pelvis.

Type III Injury (Posterior/Anterior)

Type III is the most common injury seen; it is present 66% of the time. The prostatomembranous urethra is either partially or completely ruptured, and contrast extends into the pelvis. In this injury, however, the urogenital diaphragm and anterior or bulbous urethra also are injured, and contrast material will be seen extending into the perineum and into the bulbous urethra (Fig. 12.11).

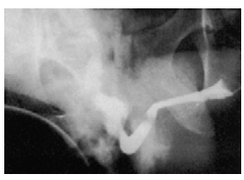

FIGURE 12.11. Type III complete urethral injury. Extravasation extends into perineum as urogenital diaphragm is ruptured. (From Sandler CM, Harris JH Jr, Corriere JN Jr, et al. Posterior urethral injuries after pelvic fracture. *AJR Am J Roentgenol* 1981;137:1233, with permission.)

Type IV Injury

Many times, an injury of the bladder neck will extend into the proximal urethra. As has been discussed under injuries of the bladder, these must have immediate repair to prevent incontinence and/or stricture formation (Fig. 12.12).

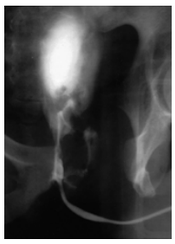

FIGURE 12.12. Type IV injury. Bladder neck injury with extension into the urethra.

Type IVA Injury

A confusing diagnostic problem occurs in patients with an injury near the bladder base. Contrast may extravasate around the urethra and what is really an extraperitoneal bladder injury can be confused with an injury of the proximal urethra. If the urethrogram is repeated under fluoroscopy, the true site of the injury can be determined (Fig. 12.13).

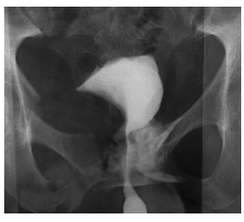

FIGURE 12.13. Type IVA injury. Extraperitoneal bladder rupture with periurethral extravasation simulating a true type IV urethral injury.

Penetrating Injuries

When the posterior urethra has been damaged by an external missile or intraurethral instrument, extravasation will follow the track of the injury. The extent and location of the injury are variable, and when caused by a gunshot wound, the bladder neck also is commonly damaged.

Therapy

Type I Injury

The patient with a pelvic hematoma compressing the urethra often will have difficulty voiding, so a urethral catheter should be left indwelling for a few days. However, once the patient has recovered sufficiently from the injuries to discontinue urine output monitoring and is alert enough to attempt to void, the catheter should be removed. Patients with a severe pelvic disruption, especially if the sacrum is damaged, may have some neurologic deficit and be unable to urinate. A cystometrogram should help determine the status of the bladder. If multiple trials of voiding fail, the patient should be taught clean intermittent self-catheterization while awaiting return of detrusor function. There are reports of delayed rupture of these injuries and some authors recommend suprapubic tube drainage instead of urethral catheter drainage (65).

Partial Urethral Rupture

The patient with minimum partial urethral rupture may be treated with urethral catheter drainage for 14 to 21 days, followed by a voiding cystourethrogram to ensure healing of the injury. If the catheter does not pass easily into the bladder or if the injury is extensive, urethral catheterization should not be done for fear that the partial rupture may be converted to a complete rupture. The patient should undergo suprapubic cystotomy by either the trochar technique or formal surgical placement. A cystogram must then be done in these patients to rule out a concomitant bladder rupture.

Clearly, the most conservative way to handle all of these injuries is to place a suprapubic cystotomy and not attempt urethral instrumentation. A voiding cystourethrogram through the cystotomy tube should be performed 14 to 21 days after the injury. If extravasation is no longer present and the urethra is of normal caliber or there is only a minimum stricture at the site of the injury, the tube should be removed and the patient allowed to void (32).

If there is a marked narrowing or total occlusion of the urethra at the area of previous extravasation, panendoscopy and a few days of urethral catheter drainage should be performed. The visual urethrotome should be available to incise any strictures that may be present.

If the strictured area cannot be successfully negotiated with the panendoscope, the patient should be left on suprapubic drainage for 6 months and delayed repair by one of the reconstructive procedures discussed later should be performed. Partial urethral ruptures account for approximately one-third of the posterior urethral ruptures.

Complete Urethral Rupture

There are three ways to treat a complete rupture of the posterior urethra: immediate surgical realignment, suprapubic cystotomy and delayed surgical repair, or endoscopic realignment. Immediate surgical realignment is the procedure of choice in the stable patient who (a) is going to have immediate pelvic exploration for a concomitant vascular or rectal injury, (b) has a severe prostatourethral dislocation with perhaps fixation of a "pie-in-the-sky" bladder and prostate to a displaced comminuted bone fragment by the puboprostatic ligaments, or (c) has major bladder neck lacerations or prostatic fragmentation (commonly seen in children) (4,44,47,81,111,135,147).

The procedure is performed through a lower abdominal midline incision. The hematoma is evacuated and a regular or fenestrated 16- or 18-Fr catheter is passed per the urethra

through the urogenital diaphragm into the prevesical space. The catheter is identified by sight or feel and brought into the surgical field. The anterior bladder wall is opened and the interior of the organ inspected. Lacerations are repaired with 3-0 absorbable suture. Another catheter is then passed out the bladder neck, through the prostatic urethra, and brought into the surgical field by sight. A single 0 nylon suture is used to tie the tips of the catheters together through their distal most eyes, and the bladder catheter is used to guide the urethral catheter into the bladder (Fig. 12.14A). The bladder catheter is removed, a second 0 nylon catheter is placed through the eye of the urethral catheter, and the suture eventually is brought out through the bladder and abdominal wall as a lock stitch to fix this catheter in place. Some authors have used interlocking sounds or magnetic catheters (116) to effect this alignment, but the high incidence of false passages with this technique has led to its virtual abandonment.

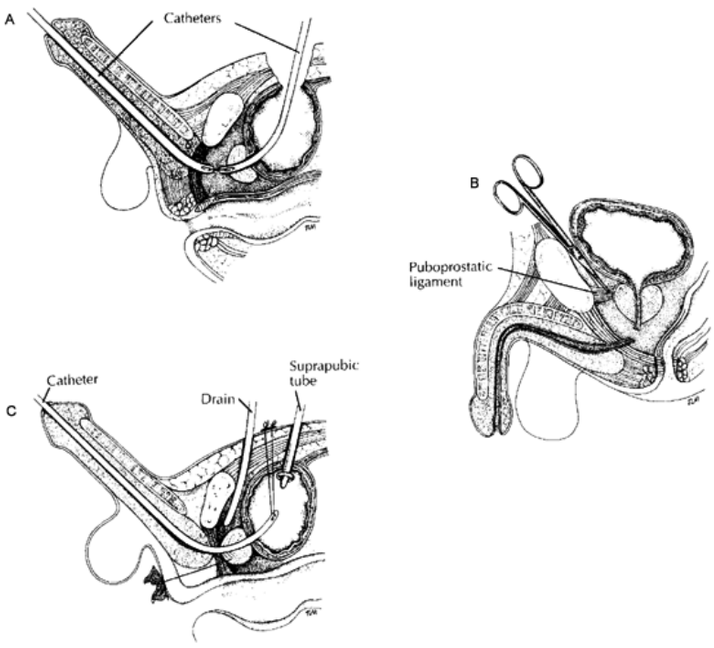

FIGURE 12.14. A: Catheter introduced into urethral meatus and by means of surgically opened bladder into bladder neck, then tied together in prevesical space. **B:** Unruptured puboprostatic ligament cut before repositioning of bladder and prostate. **C:** Urethral catheter lock-stitched to abdominal wall. Prostate kept in position against urogenital diaphragm by vest sutures.

It is now important to verify whether the puboprostatic ligaments have ruptured. If not, they must be transected, freeing the bladder and prostate from their bony attachments. If this is not done and there is severe distortion of the anterior pelvic arch, the bladder and prostate will never be able to be brought down to their normal position alongside the urogenital diaphragm (Fig. 12.14B).

One of the older techniques used to attempt realignment of the prostate was to insert a Foley catheter into the urethra and place it on traction. The idea was to pull the catheter's balloon snugly against the bladder neck and prostate to bring the organ into position. Unfortunately, to effect such a maneuver, if the prostate was still attached to the pubis, the Foley catheter would have to realign the pelvic bone as well. The procedure usually failed to accomplish this, and unfortunately, the force of the balloon on the base of the bladder often caused pressure necrosis of the bladder neck and an irreparable injury followed.

The prostate and bladder should now easily and without tension be repositioned against the urogenital diaphragm. Although some surgeons would attempt directly to anastomose the severed ends of the urethra, an easier and equally

effective repair can be effected by placing 0 nylon (Vest) traction sutures through the distal prostate, through the urogenital diaphragm, and onto the perineum, where they are tied snugly over a bolster (Fig. 12.14C). A suprapubic tube is placed in the bladder, a drain in the prevesical space, and the wounds closed.

The Vest sutures and drain can be removed in 14 days, but the urethral catheter should be left in place for 3 weeks. A retrograde urethrogram should then be done around the tube, and if there is no extravasation, it can be removed. A voiding cystourethrogram is then performed, and if the patient voids normally, the suprapubic tube is removed.

Delayed surgical repair is the procedure of choice if (a) the patient is medically unstable or (b) the surgeon is unskilled in performing major urethral reconstructive surgery. In the past few years, more and more urologists have made the delayed repair their procedure of choice for almost all patients with posterior urethral ruptures because the long-term results and complications of the various techniques have become available. As is later discussed, there is evidence that the incidence of stricture incontinence and erectile dysfunction may be lower with the delayed approach to the repair of this injury (59,95,98).

Once the diagnosis of a complete posterior urethral disruption has been made, a suprapubic tube is placed into the bladder either by trocar or formal cystotomy. A cystogram is then performed to ensure that there is no bladder rupture, and nothing more is done about the urethral injury at that time. A cystotomy tube is changed at monthly intervals and the patient has follow-up clinically until the pelvic hematoma has completely reabsorbed, all scar tissue has softened, the pelvic injury has healed, and the patient has been otherwise rehabilitated. This usually takes from 6 to 9 months after the accident.

Before the repair, a cystometrogram is performed to see whether the patient has normal bladder function, as is a combined cystogram and/or retrograde urethrogram x-ray film to determine the length of the urethral defect (Fig. 12.15). Most high-riding prostates and bladders spontaneously return to the pelvis during the delay, as the pelvic hematoma reabsorbs. With this information, a procedure for definitive repair can be made. Broadly the repairs that have been described are (a) a two-stage reconstruction, (b) a one-stage reconstruction, and (3) endoscopic reestablishment.

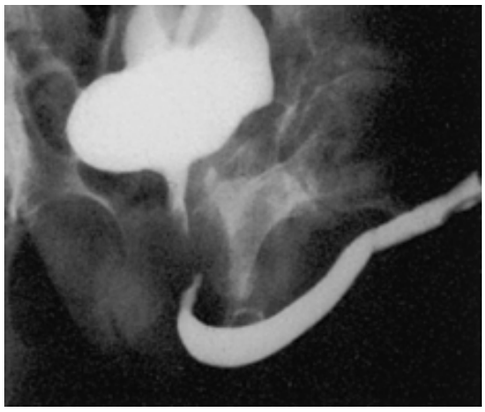

FIGURE 12.15. Combined cystogram and retrograde urethrogram in patient with a complete urethral rupture 6 months after injury.

The two-stage urethroplasty has been used since the early 1950s as a way to repair posterior urethral strictures (64,71,93,95,96). At the first stage, either through a perineal midline or pedicled flap incision, the urethra is incised ventrally through the entire stricture as proximal as the verumontanum. A scrotal or perineal skin inlay flap is then sutured to the cut edges of the urethra with interrupted absorbable suture material (Fig. 12.16). In essence, these techniques cause the strictured urethra to undergo marsupialization. A catheter is placed through the proximal ostium into the bladder, and a pressure dressing is applied to the wound. The previously placed suprapubic tube is removed on the day of surgery and the Foley catheter and dressing a few days later. The patient should void spontaneously.

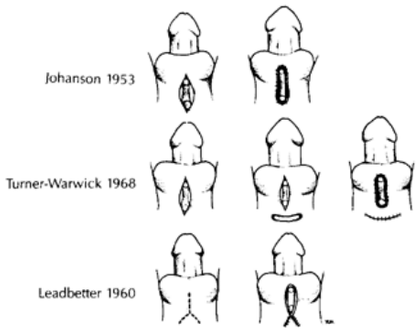

FIGURE 12.16. Various types of first-stage procedures of a two-stage urethroplasty.

Between the first and second stages the ostia, both proximally and distally, must be periodically calibrated. Once all the scar has softened and the wounds have healed, the second stage may be performed. The ostia must remain at least a 26-Fr size. It takes 4 to 6 months to be sure that the urethra is ready for closure.

During the second stage, the inlay is circumcised along with the underlying urethra to form an even tube of at least a 24-Fr caliber. The urethra is closed with interrupted or running absorbable sutures, as are the bulbocavernous muscles, subcutaneous tissues, and skin (Fig. 12.17). Some surgeons prefer nonabsorbable running pullout sutures for closure.

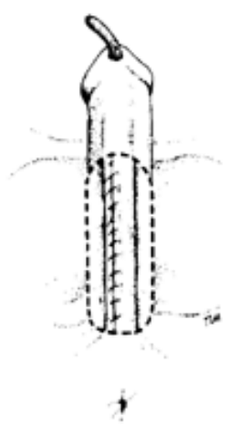

FIGURE 12.17. Second stage of a two-stage urethroplasty. Inlay circumcised *(dotted line)* and neourethra formed and closed. Bulbocavernosus muscles, skin, and subcutaneous tissue will then be closed in layers.

Urethral catheter and/or suprapubic tube drainage is used for 10 to 14 days, and a voiding cystourethrogram is

performed when the tube is removed. Catheter drainage should be continued for another week if extravasation is present.

There are basically three techniques described for one- stage reconstruction of posterior urethral strictures. *The original technique was an intussusception of the distal normal urethra into the proximal scarred urethra and prostate* (13,38,102,112). More recently, this procedure has been refined by performing a direct urethroprostatic anastomosis by either bypassing or excising the scarred area (6,31a,68,71,98,102,112,136,137,141,143,146,150). Resection of the symphysis pubis to attain access to the distal prostate is sometimes helpful (110,142).

With all of these procedures, a midline perineal incision is made and carried through the bulbocavernosus muscle to expose the urethra. The urethra with its corpus spongiosum is then dissected free in both directions to obtain adequate length. It is then divided just distal to the stricture, which means almost flush with the urogenital diaphragm.

If the intussusception technique is to be used, a curved sound is now passed by means of the suprapubic sinus tract, where the suprapubic tube has been in place, and guided into the internal urethral meatus. The tip of the sound is felt in the perineal wound at the site of the stricture. An incision is made with a scalpel onto the sound, which is then forced through into the wound. This tract is dilated to 30 Fr (13,102,112).

A small sound is now placed into the suprapubic sinus and out the distal tract and its tip is firmly invaginated into the open end of a 16-Fr red rubber catheter. The sound and catheter are drawn into the bladder and out the suprapubic sinus, and the free end of the catheter is inserted into the distal urethra for a distance of 5 to 8 cm (Fig. 12.18). The edges of the urethra are sewn to the catheter with 3-0 chromic catgut, and the catheter, with the urethra attached, is pulled through the opening in the prostate into the bladder (Fig. 12.19). The cut end of the urethra should be made to rest approximately 1 cm proximal to the verumontanum. A marking suture on the urethra before invagination is helpful to ensure this position. The outer wall of the urethra is now sewn with a few absorbable sutures to the area where it enters the tract.

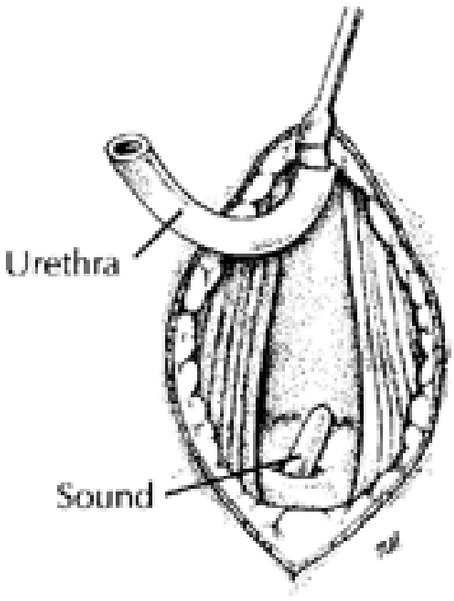

FIGURE 12.18. Urethra severed distal to stricture and retracted. Sound passed by means of bladder into bladder neck and prostatic urethra. Incision over tip of sound allows extrusion of sound into wound.

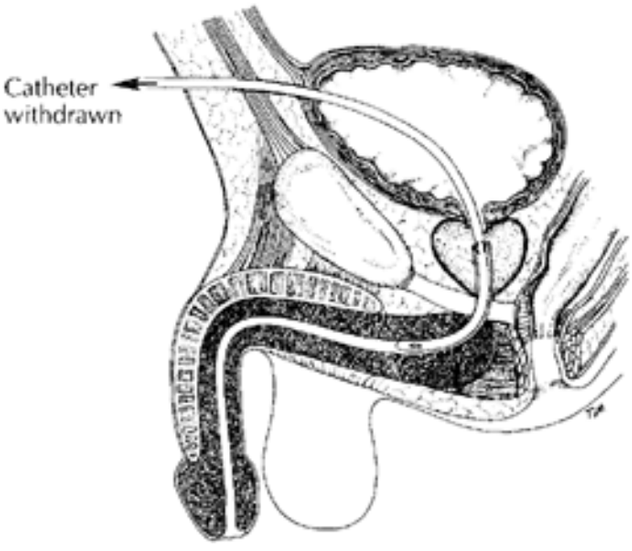

FIGURE 12.19. Catheter previously sewn to cut end of urethra drawn into bladder, intussuscepting bulbous urethra into prostatic urethra.

The catheter, which is now exiting the suprapubic sinus, is fixed with tension to the abdominal wall. A suprapubic tube is inserted into the bladder and placed to straight drainage. The bulbocavernous muscles, subcutaneous tissues, and skin are closed in layers, and a pressure dressing is applied to the wound.

The dressing is removed on the third day. The red rubber catheter will loosen and can be removed in approximately a week. A voiding cystourethrogram should be done on the fourteenth day and the patient allowed to void. A Foley catheter should be placed into the urethra if voiding is difficult and voiding trials should begin. The suprapubic tube can be removed. These patients may need periodic urethral dilation for a few months if voiding becomes difficult.

If an end-to-end prostatourethral anastomosis is to be performed after the urethra has been transected distal to the stricture, it should be spatulated (31a,68,71,98,102,112,135,136,146,150). A curved sound is now passed through the suprapubic sinus into the prostatic urethra. If negotiation of the internal urethral meatus is difficult, a panendoscope can be passed through the suprapubic sinus into the prostatic urethra. Palpation of the tip of the sound or panendoscope in the wound acts as a guide to identify the prostate. Similarly, the light in the panendoscope may shine through the tissues in the perineal wound and help identify the prostate by sight. Now the scar is excised with a scalpel and the prostate beveled from the verumontanum posteriorly to the midprostate anteriorly.

A 16-Fr fenestrated catheter is placed by means of the urethral meatus and drawn into the wound. A 0 nylon suture is tied to the distal eye of the catheter and the suture is drawn out the suprapubic sinus by the sound or panendoscope onto the abdominal wall. The catheter is now pulled into the bladder by the suture to be eventually anchored with the suture to the abdominal wall over a button. The spatulated end of the urethra is now sutured with four 3-0 absorbable quadrant sutures to the beveled-cut end of the prostate. The wound is closed in layers and a suprapubic tube is inserted and placed to straight drainage. A pressure dressing is applied to the wound (Fig. 12.20).

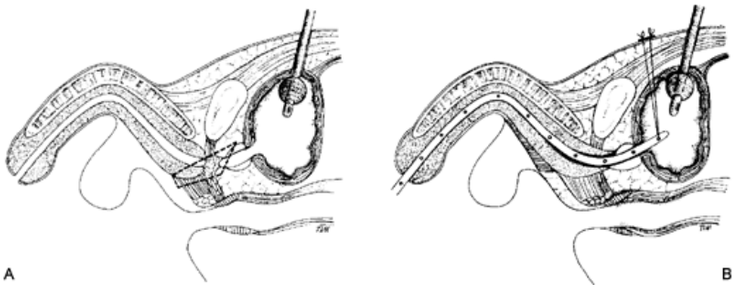

FIGURE 12.20. A: Preoperative status. Suprapubic tube in place. Area bounded by *dotted line* will be excised (includes scar). Prostate and urethra beveled. **B:** Urethra sewn to prostate end to end. Fenestrated urethral stent and suprapubic tube in place.

The dressing is removed on the third postoperative day. The urethral stent is removed in 3 weeks and a voiding cystourethrogram is performed. If the urethra is well healed, the suprapubic tube is removed. If extravasation is present, the patient is kept on suprapubic drainage for another week and the voiding cystourethrogram is repeated. By this time, the urethra should be healed, the patient should void normally, and the suprapubic catheter can be removed.

Occasionally, the prostate and bladder will not descend far enough to allow the anastomosis to be made perineally. If this occurs, a midline abdominal incision should be made and the bladder and prostate freed from above. Many times, gouges will have to be used to remove the underside of the pubis to obtain adequate mobilization. The anastomosis, stenting, and closure are still carried out as previously described in these cases, and a prevesical drain is placed. Because of the increased amount of dead space created when the prostate is dissected from above, the omentum should be freed, brought into the pelvis, and wrapped around the anastomosis to fill in this area. Postoperative management is similar to that described above, except the patient cannot be fed orally until his gastrointestinal tract recovers from the abdominal exploration. The drain can be removed in 1 week.

Transpubic urethroprostatic anastomosis without resection of the scarred area is performed through a lower midline abdominal incision (141,143). A Gigli saw is then passed beneath the pubis on either side of the midline and a trapezoidal piece of pubic bone is removed. This gives access to the anterior surface of the prostate, which is entered. The previously perineally mobilized and spatulated distal urethra is brought through the crura and anastomosed to the prostatic incision with 3-0 quadrant absorbable sutures over a 22-Fr Foley catheter. With this procedure, the prostate is not mobilized nor is the stricture excised. A suprapubic tube and prevesical drain are brought out through the abdomen. The wounds are closed as described previously (Fig. 12.20). The timing of urethral catheter, suprapubic tube, and drain removal is essentially identical to the end-to-end anastomosis procedure.

Some urologists have advocated merely reestablishing urethral continuity by *endoscopic realignment* (3,42,50,61,63,80,118,130). With this technique, a panendoscope is passed by means of the suprapubic sinus into the proximal urethra by one surgeon, and either a visual urethrotome or a resectoscope fitted with a Colling's knife is passed into the distal urethra by a second surgeon. With the light from the panendoscope as a guide, the distal operator cuts through the scar and into the prostatic urethra. A laser also has been used to create an opening (39). A 22-Fr urethral catheter is

then placed into the bladder, removed 1 week later, and the patient is allowed to void. Periodic dilations are usually necessary in these patients (7). Recently, the use of an indwelling metal stent also has been advocated (12,107).

ANTERIOR URETHRAL INJURIES

Part of "12 - TRAUMA TO THE LOWER URINARY TRACT "

Classification—Type V Injury

Most anterior urethral injuries caused by blunt trauma are secondary to straddle injuries (15,115). In these instances, the pelvis is usually not fractured and the overlying skin remains intact. Perhaps today there is a greater volume of iatrogenic injuries to the anterior urethra as a result of urethral instrumentation. The following subclassification of these injuries is useful when planning appropriate therapy.

Urethral Contusion

When a patient has undergone a straddle injury and has initial or terminal hematuria but has a normal urethrogram, a urethral contusion has occurred.

Partial Urethral Rupture

When a urethral injury is either caused by external blunt trauma or urethral instrumentation and a retrograde urethrogram demonstrates extravasation of contrast material but the urethra is in continuity and contrast material goes freely into the bladder, the patient is said to have a partial urethral rupture (Fig. 12.21).

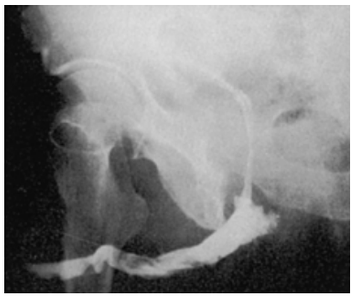

FIGURE 12.21. Partial anterior urethral rupture secondary to Foley catheter balloon blown up in bulbous urethra.

Complete Urethral Rupture

If after blunt trauma extravasation is demonstrated on a retrograde urethrogram and urethral continuity is lost, a complete urethral rupture is present (Fig. 12.22).

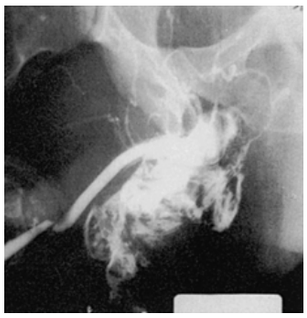

FIGURE 12.22. Complete anterior urethral rupture secondary to a straddle injury. Note the venous extravasation. (From Sandler CM, Phillips JM, Harris JD, et al. Radiology of the bladder and urethra in blunt pelvic trauma. *Radiol Clin North Am* 1981;19:195, with permission.)

Penetrating Urethral Injury

If the urethra has been injured by an external missile, urethral instrumentation, or migration of a penile prosthesis, a partial or complete disruption of the urethra may result. Only major lacerations or those associated with extensive tissue destruction are handled in a unique way from blunt injuries. Because of these therapeutic decisions, however, penetrating injuries are best placed into a separate category.

Therapy

Urethral Contusions

No special therapy is necessary for patients with anterior urethral contusions from blunt trauma. They usually are able to void normally, and their hematuria promptly clears. If necessary, a urethral catheter can be placed for a short period. In the absence of extravasation, there are probably no long-term sequelae of this injury.

Partial Urethral Rupture

If the extravasation on urethrogram is minimal, contained by Buck's fascia, and urethral continuity is good, patients with partial urethral rupture secondary to blunt trauma may be allowed to void or a urethral catheter can be placed into their bladder for a few days. If the injury is extensive and extends outside Buck's fascia, a suprapubic tube should be placed into the bladder and a voiding cystourethrogram repeated in 10 to 14 days. If the urethra is normal or there is only a large-caliber stricture, the

tube can be removed and the patient is allowed to void. Periodic urinary flow rates and urethrograms should be done to be sure a stricture does not develop at the site of the injury.

If a significant narrowing has developed, the patient should undergo panendoscopy and visual urethrotomy of the strictured area. A urethral catheter should be left in the urethra for 24 hours and the suprapubic tube removed. When the urethral catheter is removed, the patient should be allowed to void. Periodic urinary flow rates and urethrograms are critical follow-up measures in these patients (17).

Complete Urethral Rupture

Patients with complete urethral rupture from a blunt injury do not do well with primary repair and should have a suprapubic tube placed into their bladders. If extensive perineal extravasation of blood and urine is present, these patients will need close follow-up to determine whether these collections properly reabsorb or need surgical drainage. Occasionally, patients with extensive extravasation delay in presenting to the physician, and erythema, purulence, and frank necrosis may be present in the penis, scrotum, or perineum. These patients need subcutaneous drains placed, debridement and suprapubic urinary diversion performed, and antibiotics prescribed.

When the skin of the genitalia and perineum become normal and at least 14 days have elapsed from the injury, a voiding cystourethrogram and possibly a combined voiding cystourethrogram and retrograde urethrogram should be done to delineate the injury. A stricture of some magnitude will probably have developed. If urethral continuity is intact, panendoscopy and a visual urethrotomy may be all that is needed to incise the stricture (66,144). If this is successful, a urethral catheter should be placed for 24 hours and the suprapubic tube removed. These patients must have careful follow-up with voiding flow rates and retrograde urethrograms for recurrence of their stricture.

Most of these patients, however, will have developed complete occlusion of their urethra. If infection did not supervene on the extravasation of blood and urine, it will commonly be short. The patient should be left on suprapubic drainage until the perineum is well healed before reconstruction. This will usually take 4 to 6 months. A combined voiding cystourethrogram and retrograde urethrogram will delineate the extent of the stricture to be repaired, as was described in posterior urethral ruptures.

The two-stage urethroplasties previously discussed and illustrated in Fig. 12.16 and Fig. 12.17 have been used to repair strictures of the anterior and posterior urethra (64,78,132,133). Because the strictured area is usually at the penoscrotal junction, a simple midline incision rather than the scrotal or perineal inlay flaps is usually adequate for the first stage.

However, if a short stricture is present, a one-stage end-to-end urethroplasty plus or minus a ventral wall skin patch should be performed (36,84). In this procedure, a midline incision is made over the area of the stricture, which is identified with a urethral sound, and the urethra is mobilized in both directions. The strictured area is then excised and the dorsal wall of the urethra is reanastomosed. A full-thickness skin graft may be taken from the shaft of the penis, defatted, and used to widen the anastomosis. It is sutured in place with 4-0 absorbable sutures (Fig. 12.23). This needs to be done only if there is tension on the anastomosis or the lumen is compromised. A pedicle procedure as later described also can be used for this purpose.

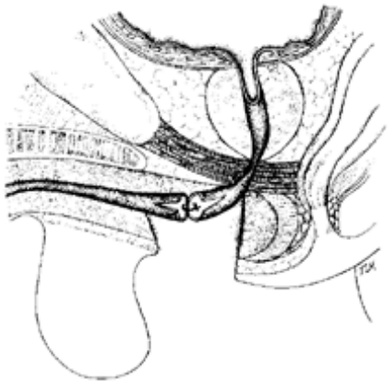

FIGURE 12.23. Strictured area was removed. Cut ends of urethra were spatulated ventrally. Dorsal walls were anastomosed. Ventral defect will be “patched open” with a full-thickness skin graft (see Fig. 12.24).

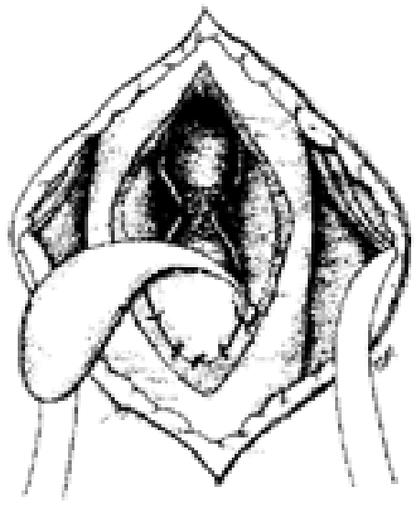

FIGURE 12.24. Free full-thickness skin graft sewn into incised urethra at area of stricture to widen stenotic section.

The bulbocavernous muscles, subcutaneous tissue, and skin are closed in layers. A urethral catheter is left in place for 3 to 5 days and the suprapubic tube continued on drainage for 14 days. A voiding cystourethrogram is performed at that time, and if no extravasation is seen, the suprapubic tube is removed. If extravasation is seen, suprapubic drainage is continued for another week and the study repeated.

If the stricture is long, a one-stage patch graft urethroplasty or pedicled urethroplasty can be performed (16,36,85,86,104). In these procedures, the stricture is identified as previously described for the end-to-end urethroplasty, but the urethra is not mobilized. Instead, the stricture is incised ventrally in the manner of a first-stage procedure of the two-stage technique, and then a free graft may be taken from the skin of the penis, defatted, and the entire incised urethra “patched” open (Fig. 12.24). Buccal mucosa also has been used in these repairs (43). In the pedicled technique, instead of a free graft, a suitable length of skin is freed next to the urethral incision but is left attached to its underlying blood supply. This pedicled graft is then inverted and sewn into the urethral defect (Fig. 12.25). A circular skin flap taken from the distal penis may have a

higher success rate than the use of local skin (86) (Fig. 12.26). Postoperative care is similar to that of the end-to-end technique with appropriate attention being given to the donor site.

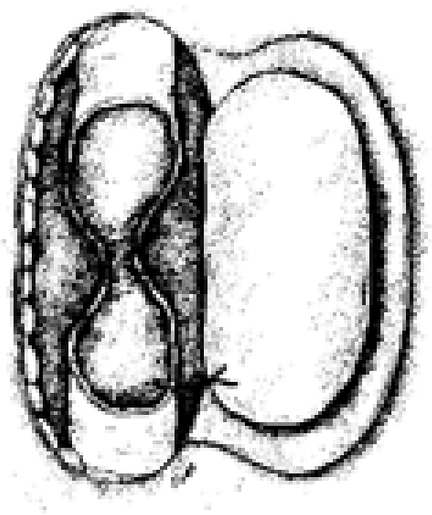

FIGURE 12.25. Pedicled skin graft sutured into area of stricture to widen stenotic section.

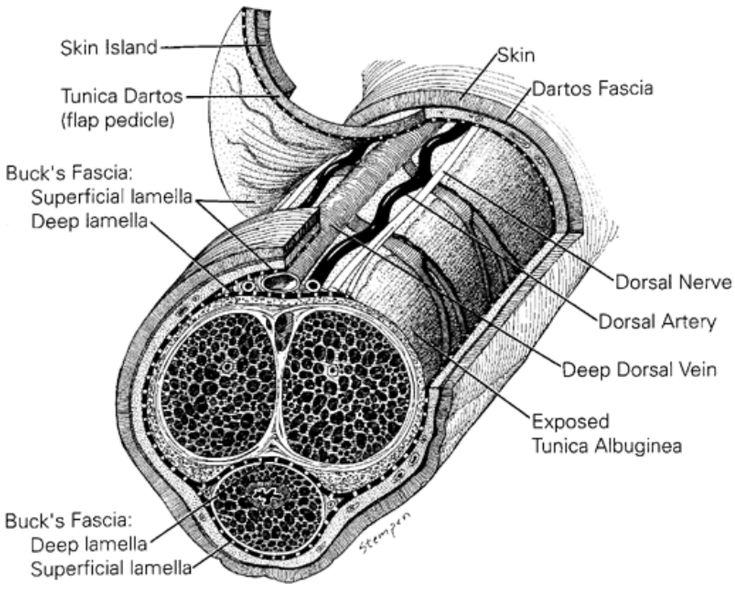

FIGURE 12.26. Flap pedicle with blood supply via tunica dartos. (From McAninch JW, Morey AF. Penile circular fasciocutaneous skin flap in 1-stage reconstruction of complex anterior urethral strictures. *J Urol* 1998;159:1209, with permission.)

Penetrating Urethral Injury

The most common penetrating injuries of the anterior urethra are secondary to urethral instrumentation. Most of these injuries are minor, and patients are usually allowed to void or a Foley catheter is placed in their bladder for a few days. Occasionally, a sound or filiform and follower is forced through the urethral wall and into the rectum. These patients need a suprapubic tube placed in their bladders for a few weeks, and their wounds will usually heal without sequelae. A retrograde urethrogram and/or voiding cystourethrogram should be done to ensure that the injury has healed before the patient is allowed to void.

During dilation of the corpus cavernosum for placement of a penile prosthesis, the urethra may be ruptured. If the prosthesis is not inserted and a Foley catheter is placed into the bladder for a few days, the perforation will heal. Sometimes, a prosthesis will spontaneously erode through the urethra, especially in patients with decreased sensation from neurologic disease, or if a Foley catheter is left in the urethra

for a long time in patients with penile prostheses. Merely removing the prosthesis will allow the urethral lacerations to heal. A Foley catheter may be placed for a few days to facilitate the process.

Penetrating injuries that need prompt surgical attention are those caused by external violence. Clean knife or bullet wounds merely need minimum debridement, closure of the defect with absorbable sutures, and suprapubic catheter drainage for 2 to 3 weeks (52). A voiding cystourethrogram and/or retrograde urethrogram should be done before removal of the suprapubic tube.

Dirty wounds with extensive tissue destruction and foreign material in the wound (e.g., metal pellets, oil, grease, hair, clothing) need to be cleansed thoroughly with antiseptic solutions and copious irrigation. Although debridement of devitalized tissue is important, it must be stressed that contused corpus spongiosum tissue is hemorrhagic and ecchymotic and may appear necrotic when it is only badly bruised. If debridement is vigorous, more urethra than is necessary may be removed and discarded, making eventual repair a formidable task. If a large section of urethra is lost, however, the ends of the urethra that are left should be sutured to the skin in the manner of a first-stage urethroplasty. Skin will have to be brought between the ostia to close the wound (Fig. 12.27).

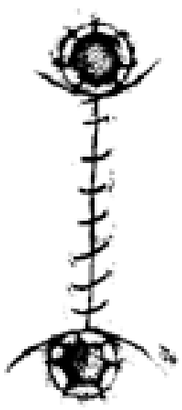

FIGURE 12.27. Damaged urethra has been discarded. Freshened edges of severed urethra sewn to skin. Normal skin brought between ostia to cover defect.

Suprapubic diversion should be done until the perineum has healed. This may take weeks to months. Radiographic studies will demonstrate residual stricture, which can be handled by one of the previously described urethroplasty techniques.

POSTOPERATIVE CARE AND FOLLOW-UP

Part of "12 - TRAUMA TO THE LOWER URINARY TRACT "

A discussion of when the stents, drains, and catheters should be removed is included with each of the previously discussed procedures. Antibiotics should be withheld in these patients until they have all tubes removed from their urinary tracts. At that time, they should receive appropriate antibiotics, and eventually urinalysis and urine cultures should be performed to ensure sterilization has been accomplished.

Periodic voiding flow rates should be done at 3-month intervals for at least a year. If flow decreases, a retrograde urethrogram should be performed. Patients with neurologic damage may not be able to void and may have to be taught intermittent self-catheterization. Those with bladder neck damage may be incontinent and need α-adrenergic drugs or collagen injections to become dry (60). Complete neurologic evaluation is imperative in these patients.

RESULTS AND COMPLICATIONS

Part of "12 - TRAUMA TO THE LOWER URINARY TRACT "

When the literature is reviewed for the results and complications of these various techniques, it is well established that *the primary realignment patients may have a higher long-term complication rate than do patients treated with delayed repair, despite the technique used* (11,32,44,72,75,83,98,150). The persistent restricture rate with primary repair is approximately 50% (38% to 53%), the erectile dysfunction rate is 36% (20% to 50%), and the major/moderate incontinence rate 14% (3.7% to 21%).

With the delayed procedures, it should be noted that although virtually all partial ruptures heal without stricture, almost all patients with complete ruptures initially develop strictures. After definitive repair, however, it is the rare patient who has a long-term stricture problem. However, the erectile dysfunction rate is similar at approximately 33% (17.6% to 62%) but the major to moderate incontinence rate is lower at 2% (1% to 4%) in well-reported series. It appears to be well worth the trade-off of wearing a suprapubic catheter for 6 or more months when compared with the long-term problems associated with early repair.

There is considerable concern that patients who undergo a transsphincteric urethroplasty and in essence have their internal urethral mechanism destroyed by the procedure, are later at risk for incontinence if a transurethral resection of the prostate is performed. This risk is certainly real. However, when one considers that these are usually young men with 40 to 50 years of life ahead of them and that only 10% of males will need a prostatectomy as they get older, the argument becomes thin for withholding the procedure.

However, when faced with an elderly patient with complete obstruction caused by a posterior urethral rupture who has previously had a transurethral prostatectomy and therefore has no bladder neck continence mechanism, the use of the intussusception procedure should be chosen. With this technique the stricture and sphincter (if it is still intact) are not resected but merely dilated. If the sphincter is intact and the stricture can be kept open with periodic dilations, the patient should be continent and able to void. If the sphincter has been irreparably damaged, the stricture, if not dilated, will recur.

The long-term results reported with endoscopic realignment are poor when compared to the open procedures (3,7,42,63,80,116,130). Although the incidence of erectile dysfunction

is approximately 30% (14% to 42%), which is comparable to the other techniques, it is now fairly well accepted that erectile dysfunction in patients with posterior urethral rupture is most likely caused by the injury and is not aggravated by the repair, no matter what procedure is used.

Similarly, the average major to moderate incontinence rate is 5.5% (0% to 12.5%), which is slightly higher than reported with the delayed repairs (2%) but lower than reported with primary realignment (14%).

The major objection to the endoscopic realignment is the persistent stricture rate of 54% (25% to 100%) and the need to continue with prolonged (possibly lifetime) urethral dilations in approximately 56% (25% to 100%) of the patients. Some authors even recommend leaving an indwelling catheter in the urethra after surgery for up to 3 months to keep the scar dilated and permit epithelization of the tract (3).

This high rate of restricture is because the mucosal edges of the disrupted urethra have been separated by scar and even if reepithelization of the tract does occur, the surrounding scar will persistently contract. Only a proper mucosa-to-mucosa anastomosis, with removal of all surrounding scar, can give the repair a high degree of long-term success without need for continued instrumentation.

INJURIES IN FEMALES

Part of "12 - TRAUMA TO THE LOWER URINARY TRACT "

There are few reports of rupture of the female urethra in the literature (2,24,56,88,138). Most of them are in children, and most of them also involve the bladder neck and vagina (88,109,134). These injuries need immediate reconstruction of the bladder neck and repair of all vaginal lacerations to ensure that the continence mechanism will be intact after injury as well as to prevent the formation of vesicovaginal fistulae. Retropubic repair over a stenting urethral catheter and use of a suprapubic tube usually produces a good result. Occasionally, a urethrovaginal fistula will develop and require secondary closure.

INJURIES IN CHILDREN

Part of "12 - TRAUMA TO THE LOWER URINARY TRACT "

As previously mentioned, most urethral injuries in females are in children and need immediate repair to prevent long-term complications (2,56,88,120,138). Males are treated by any of the previously described procedures but seem to do best when treated with the delayed technique (48,53,73,113). If the patient has an anterior stricture that can be incised with a visual urethrotome, this is preferable. If restricturing occurs, the child should be taught intermittent self-catheterization to keep the stricture dilated. Eventually, a formal urethroplasty should be performed (73,91,113,140). Transurethral resection of the scar with stenting also has been advocated (148).

FRACTURE OF THE BONY PELVIS

Part of "12 - TRAUMA TO THE LOWER URINARY TRACT "

Most patients that have fractures of the bony pelvis have multisystem injuries secondary to high-speed motor vehicle accidents (8,26,31,45,46,62,79,82,94,114). When an anterior arch fracture is present, the probability of a urinary tract injury is high. With a single break of the pelvic ring, 12.5% of patients will have an injury to the lower urinary tract, and with two breaks in the ring, 22% of patients will have such an injury (74,105).

Bladder ruptures, mostly extraperitoneal in nature, are seen 9% of the time, urethral injuries 3.5% of the time, and both a bladder and urethral injury 1% of the time. Aside from the urinary tract complications of stricture and incontinence, in the male, complete or relative erectile dysfunction can be seen in up to 65% of these patients (11,32,83). As previously discussed, there is a wide range of variation in the long-term complication rate depending on the initial care and the reconstructive procedure chosen for the repair of the injury. It must be stressed to emergency room and trauma team personnel that injudicious instrumentation of the urethra in the patient with a fractured pelvis and possible urethral injury may lead to a lifetime of chronic debilitation because of a momentary lapse in the proper management of this injury.

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13
THE ADRENALS

Andrew C. Novick

Stuart S. Howards
A.C. Novick: Urological Institute, The Cleveland Clinic, Cleveland, OH 44106.
S.S. Howards: Departments of Urology and Physiology, University of Virginia, Charlottesville, VA 22908.

Contents

ANATOMY

Part of "13 - THE ADRENALS "

The adrenal glands are a pair of retroperitoneal organs embedded in perirenal adipose tissue. They lie superior and medial to the upper poles of the kidneys within Gerota's fascia. Their lowest extent, particularly on the left, is close to the renal vessel; thus care must be taken to avoid injury to the renal blood supply during adrenalectomy. Computed tomography (CT) scanning has made it clear that the adrenal glands are anterior to the kidney. The cortex has a characteristic yellow color, which makes it easy to recognize during surgery. The medulla, which is usually not visualized, is brown or red. The glands are flattened with distinct edges and measure approximately 5 cm by 3 cm by 1 cm. The normal human gland weighs 4 to 5 g *in vivo* and 6 g in death (65). The terminal weight increase is caused by adrenocorticotropic hormone (ACTH) release during stress. The shape and size of the glands are variable.

The cortex has a mesodermal origin, arising in utero from the dorsal mesentery near the cranial pole of the mesonephros. The gland differentiates into an outer zone,

which will form the adult cortex, and a much larger inner fetal zone, which will be 80% of the gland at birth but rapidly degenerates while the outer portion grows (Fig. 13.1). The net result is that the gland at birth is twice as large as it is a few weeks later. The medulla arises from ectodermal neural crest tissue, which also generates sympathetic ganglion cells. Strands of this chromaffin tissue migrate to the adrenal cortex on its medial side and become centrally located in the gland.

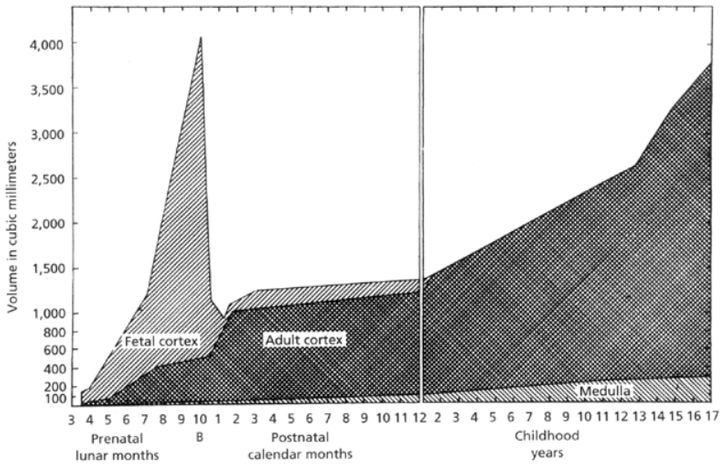

FIGURE 13.1. Growth of the adrenal cortex including the fetal cortex *in utero* and after birth. There is a striking decrease in the size of the fetal cortex after birth and a gradual increase in the adult cortex with aging. (From Bethune JE. *The adrenal cortex. A scope monograph.* Kalamazoo MI: Upjohn Co., 1974.)

Each adrenal gland is supplied with blood from three arteries that are branches of the aorta, renal, and inferior phrenic arteries (Fig. 13.2). These arteries form a plexus in the capsule that gives rise to cortical arteries, which in turn supply sinusoids surrounding the cords of cells in the cortex. There are no veins in the cortex. The medulla has a dual blood supply from major capsular arteries that pass directly through the cortex without branching and from the cortical sinusoids that connect to medullary capillaries. Thus the medullary cells are exposed to the cortical effluent with high concentrations of cortical steroids. The medulla and cortex drain into a large central medullary vein, the adrenal vein, which inserts directly into the vena cava on the right and into the renal vein on the left.

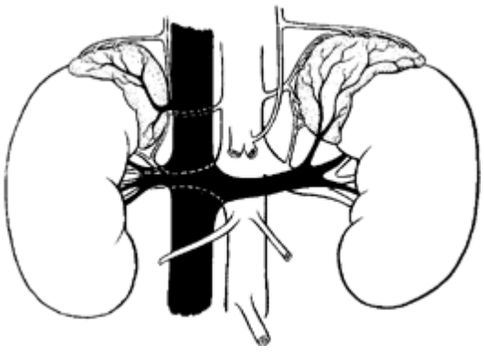

FIGURE 13.2. Blood supply to the adrenal gland. The gland is supplied by three major arteries, the superior, middle, and inferior adrenal arteries, which are branches of the inferior phrenic artery, the aorta, and renal artery. One major vein drains into the renal vein on the left and the vena cava on the right.

The cortical cells have sparse, possibly adrenergic innervation. The medullary cells are innervated by preganglionic sympathetic nerve fibers arising from the intermediolateral column of the lower thoracic spinal cord. These fibers travel with the splanchnic nerves and synapse with a group of medullary cells to form a functional unit. The medullary pheochromocytes are the equivalents of sympathetic ganglion cells.

The adrenal cortex contains three concentric zones: a thin outer zona glomerulosa, a thick zona fasciculata, and a thin zona reticularis (Fig. 13.3). The zona glomerulosa is composed of small (12 to 15 mm) columnar cells with sparse cytoplasm. The cells are packed in clusters and arcades. In humans, the zona glomerulosa may be absent in some areas of the cortex. Aldosterone synthesis occurs in steps in the smooth endoplasmic reticulum and mitochondria where the essential enzymes are located (48).

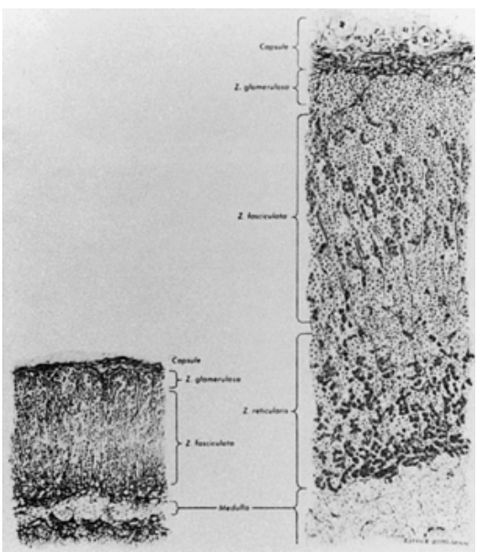

FIGURE 13.3. Histology of the adrenal gland. Note the cortex has three major components: the zona glomerulosis, zona fasciculata, and zona reticularis.

The zona fasciculata consists of polyhedral large (20 mm) cells arranged in straight cords one to two cells thick and filled with lipid droplets. The zona reticularis consists of smaller cells with few lipid droplets. The cells are arranged in now parallel anastomosing cords (Fig. 13.3).
The adrenal medullary consists of chromaffin cells generously supplied with cortex and blood vessels. They are polyhedral and arranged in cords with close association to the vascular spaces. Epinephrine- and norepinephrine-secreting cells are distinct; each contains a specific type of granule (48).
Ectopic adrenal tissue can be found in many locations, particularly near the adrenal glands, kidneys, celiac axis, or testis and spermatic cord. Unilateral congenital absence of an adrenal gland is a rare anomaly. When the kidney is absent, the adrenal is present in its normal position but is more disklike than triangular.

PHYSIOLOGY

Part of "13 - THE ADRENALS "

The adrenal cortex synthesizes cholesterol and also takes it from the circulation. The first and rate-limiting process in the synthesis of adrenal steroids is the conversion of cholesterol to pregnenolone (Fig. 13.4). The hormones critical to life that are produced by the cortex are (a) the glucocosteroids,

particularly cortisol, which affect carbohydrate and protein metabolism, and (b) a mineralocorticoid, aldosterone, which regulates sodium and potassium balance. These hormones must be replaced after bilateral adrenalectomy. The adrenal cortex also synthesizes androgens and estrogens, which in normal individuals are not as important in sexual development and function as their counterparts produced by the testis and ovaries. In certain disease states, these sex steroids have dramatic virilizing or feminizing effects.

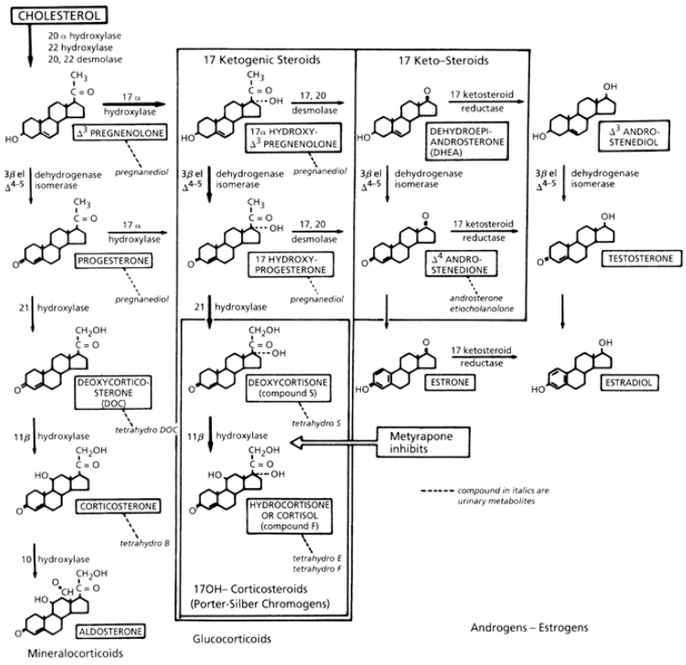

FIGURE 13.4. Biosynthetic pathways for the synthesis of adrenocortical steroids—also the site of metyrapone, urinary metabolites, and the Porter-Silber chromogens.

Steroidogenesis

All adrenal steroid hormones have the same steroid nucleus (Fig. 13.5). A ketone at the 3 position and hydroxyl groups at the 11 and 21 positions are required for potent glucocorticoid activity. An oxygenated carbon at the 18 position results in powerful mineralocorticoid activity. Elimination of the C_{20-21} side chain and incorporation of an oxygenated carbon at the 18 position create a potent androgen. Aromatization of the A ring generates an estrogen.

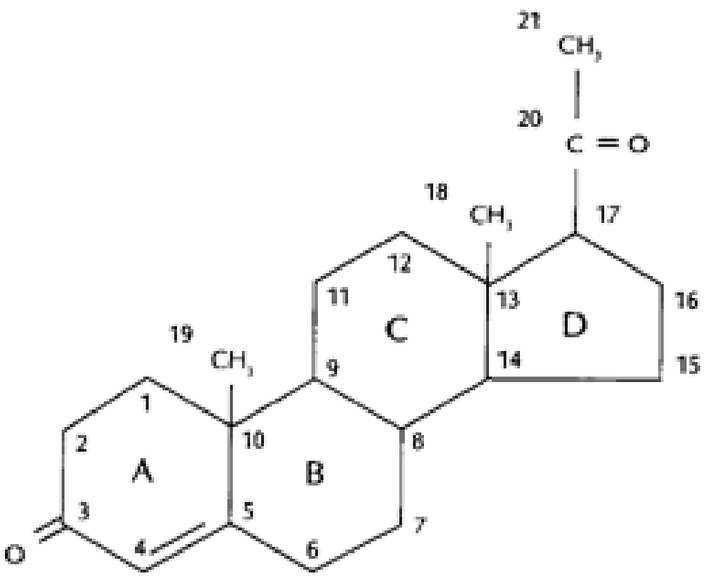

FIGURE 13.5. Common steroid nucleus.

The synthesis of glucocorticoids and sex steroids occurs primarily, although not exclusively, in the zona fasciculata and reticularis, respectively. Aldosterone is synthesized exclusively in the zona glomerulosa. The synthesis pathways for production of these hormones are presented in Fig. 13.4 . In certain situations, alternative pathways may become important; for example, if cortisol synthesis is specifically blocked, corticosterone synthesis may be increased to provide the necessary glucocorticoid.

Iatrogenic interruption of these pathways may be useful in diagnosis and treatment. Metyrapone decreases the conversion of cholesterol to pregnenolone. Thus, when the drug is used preoperatively, the levels of all adrenal steroids may be reduced. Metyrapone also inhibits 11-hydroxylation, the last step in cortisol synthesis (Fig. 13.4), resulting in an increase in ACTH and thus cortisol precursor production in the normal individual. Therefore metyrapone can be administered to test the hypothalamic-pituitary-ACTH axis and in the treatment of Cushing's syndrome, especially before surgical therapy. Aminoglutethimide inhibits the desmolase and the aromatase reactions, thus decreasing steroid synthesis. This property has been used in the treatment of hypersecretion of adrenal steroids, prostate cancer, and breast cancer.

Metabolism

Circulating cortisol is 75% to 80% bound to an α_2-globulin, transcortin; 15% is bound to albumin; and only 5% to 10% is unbound. The biologically active factor is the free hormone; thus alterations in the level of transcortin can have physiologic significance. The half-life of cortisol is approximately 70 minutes. Most of the hormone is metabolized in the liver, conjugated, and excreted as glucuronides in the urine. A small fraction of the cortisol (approximately 50 mg) is excreted unaltered in urine. Measurement of the urinary metabolites and free cortisol can be used to evaluate adrenal function.

Plasma aldosterone is weakly bound to a specific binding globulin and albumin. Ninety percent of the circulating aldosterone is cleared in one pass through the liver and then is reduced and excreted in the urine as the 3 and 18 glucuronides. Less than 1% of the aldosterone is excreted as the free hormone. Because of its rapid metabolism, the half-life of plasma aldosterone is only 20 minutes.

Adrenal androgens are excreted in the urine as dehydroepiandrosterone sulfate (DHEAS) and two reduced isomers, androsterone and etiocholanolone (Fig. 13.4). These compounds make most of the urinary 17-ketosteroids. Two-thirds of the 17-ketosteroids come from the adrenal and one-third from the gonad in normal individuals. Elevation of the urinary 17-ketosteroids generally indicates adrenal hyperfunction.

Regulation

ACTH is the regulator of glucocorticoid secretion and is also the primary determinant of the secretion of adrenal sex steroids. It is derived from a 31,000-Da glycoprotein, proopiomelanocortin, which is cleaved in corticotropic cells into ACTH, β-lipotropin, and a glycopeptide (87). ACTH is a single-chain polypeptide containing 39 amino acids. The active component of the molecule is the initial segment of 23 amino acids. The hormone is secreted in irregular bursts throughout the day, but the most active secretion occurs in the early morning, causing the diurnal secretion of cortisol. Cortisol secretion increases within minutes of an elevation in plasma ACTH levels. ACTH binds to an adrenal plasma membrane receptor and activates adenylate cyclase, which in turn raises tissue cyclic adenosine monophosphate (cAMP) levels. The cAMP activates critical protein kinases, which effect the phosphorylation of proteins that increase steroidogenesis.

The secretion of ACTH is controlled primarily by corticotropin-releasing factor (CRF), a protein with 41 amino acid residues, which is synthesized in the median eminence of the hypothalamus and travels to the pituitary by means of the portal-hypophyseal vessels (Fig. 13.6). Arginine vasopressin from the hypothalamus and several nonhypothalamic factors such as lymphokines (60) also can cause ACTH release (82). The peripheral plasma level of CRF in normal human subjects is 0.4 to 6.0 pmol/L (58). CRF secretion is regulated by four main factors: circadian rhythm, glucocorticoid feedback, ACTH feedback, and stress. Stress increases the secretion of CRF and ACTH, whereas there is a negative feedback relationship between plasma glucocorticoid levels and ACTH secretion. This inhibition of ACTH secretion is probably mediated at both the hypothalamus and the pituitary.

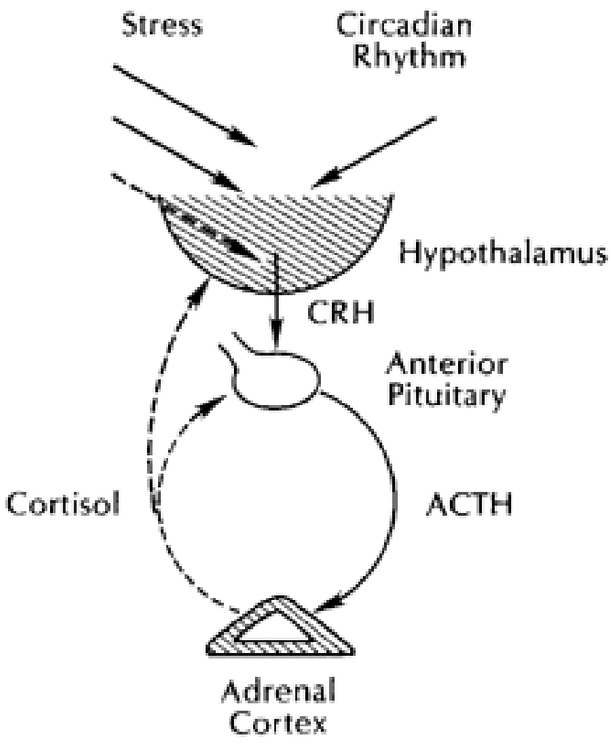

FIGURE 13.6. Hypothalamic pituitary adrenal axis including the long- and short-loop feedback circuits.

Three clinically relevant points related to ACTH secretion are as follows: (a) Some neoplasms secrete ACTH-like substances that can stimulate the adrenal gland to release glucocorticoids and thus cause Cushing's syndrome. (b) After treatment with large doses of exogenous glucocorticoids, not only is the adrenal gland unresponsive, but the hypothalamic-pituitary axis may be unable to secrete normal quantities of ACTH. (c) ACTH is not required for aldosterone synthesis and secretion, and therefore a patient with hypopituitarism does not require mineralocorticoid replacement.

Actions of Glucocorticoids

Glucocorticoids are essential for life. An adrenalectomized person will die even if provided with mineralocorticoids. Adrenal steroids and, indeed, all steroid hormones easily cross the cell membrane to bind with cytoplasmic receptor proteins that are present in target tissues. The steroid may be metabolized within the cell to a more or less active form. The steroid-receptor complex migrates to the cell nucleus, where it attaches to a specific group of genes. This causes the production of new ribonucleic acid, which in turn effects the synthesis of proteins that serve as structural building blocks of enzymes that regulate cellular function in various tissues.

Glucocorticoids are so named because they have major effects on carbohydrate metabolism, including the promotion of liver glycogen deposits and gluconeogenesis. In the starving patient, they allow survival by enhancing proteolysis, preventing death from hypoglycemia. They also have an antiinsulin effect. Thus they are diabetogenic, causing hyperglycemia during stress or when present in pharmacologic quantities.

Glucocorticoids have many permissive actions in that they facilitate processes that they do not initiate. Several additional effects of glucocorticoids are listed in Table 13.1 along with their clinical implications.

TABLE 13.1. EFFECTS AND IMPLICATIONS OF GLUCOCORTICOIDS

Effect	Clinical Implications
Enhance skeletal and cardiac muscle contraction	Absence results in weakness
Cause protein catabolism	Excess results in wastage and weakness
Inhibit bone formation	Excess decreases bone mass
Inhibit collagen synthesis	Excess causes thin skin and fragile capillaries
Increase vascular contractility and decrease permeability	Absence makes it difficult to maintain blood pressure
Have antiinflammatory activity	Exogenous steroid useful in treating inflammatory diseases
Have antiimmune system activity	Exogenous steroids useful in treating transplantation and various immune diseases
Maintain normal glomerular filtration	Absence reduces glomerular filtration

Actions of Adrenal Androgens and Estrogens

The mechanism of action of the major adrenal androgens DHEA, DHEAS, and androstenedione is similar to that described for the glucocorticoids. These compounds are weak androgens that have little effect in physiologic quantities. In disease states, however, they may virilize a female fetus (adrenogenital syndrome) (see Chapter 57), causing

pseudohermaphroditism, and virilize either prepubertal children or adult females with Cushing's syndrome. The effects of excess adrenal androgens are not clinically evident in the adult male, which delays the diagnosis of Cushing's syndrome in some men. Excess adrenal estrogens may cause breast enlargement in children and men.

Regulation of Glomerulosa Function

The primary regulator of aldosterone secretion is the renin-angiotensin system. Renin is an enzyme synthesized in the juxtaglomerular apparatus of the nephron. When released into the circulation, renin cleaves renin substrate, a globulin secreted from the liver, releasing the decapeptide angiotensin I. Angiotensin I is hydrolyzed to angiotensin II, an octapeptide, by converting enzyme, which is found primarily in the lung. Angiotensin II is a potent stimulator of aldosterone secretion. It is rapidly destroyed in the plasma by angiotensinases.

Renin secretion is regulated by a complex intrarenal mechanism (see Chapter 23). Decreased perfusion pressure in the renal artery and decreased chloride absorption at the macula densa cause increased renin release and thus ultimately increased circulating levels of aldosterone. Angiotensin II and aldosterone can inhibit renin secretion through short- and long-loop feedback systems, respectively. Catecholamines may increase renin release, but dopamine inhibits aldosterone secretion in sodium-depleted individuals. ACTH increases the sensitivity of the zona glomerulosa to angiotensin II and stimulates aldosterone secretion, but the latter effect is not long lasting. Potassium also causes an increase in aldosterone secretion. Thus aldosterone secretion is increased in the following clinical settings: (a) stress, (b) hemorrhage, (c) sodium depletion, (d) dehydration, (e) hyperkalemia, (f) congestive heart failure, (g) hepatic cirrhosis, (h) nephrotic syndrome, (i) estrogen administration, and (j) renal artery stenosis.

Effects of Mineralocorticoids

Mineralocorticoids are steroid hormones that effect ion transport in the epithelial cells of the kidney, gastrointestinal tract, sweat glands, and salivary glands, causing sodium absorption and loss of potassium. The target tissue specificity appears to be enzyme and not receptor mediated. Indeed, mineralocorticoid receptors are rather similar to glucocorticoid receptors and are saturated by glucocorticoids in most tissues because of the tenfold higher concentration of circulating glucocorticoids. The physiologic action of aldosterone is due to aldosterone synthetase and 11-ß-hydroxysteroid dehydrogenase in target tissues, which metabolizes glucocorticoids into receptor-inactive 11-keto congeners. The C-11 hydroxyl group in aldosterone is protected from this target tissue enzyme by its aldehyde at C-18 (30).

The mechanism of action is to increase production of an uncharacterized protein. Because protein synthesis requires time, the effect of mineralocorticoids is not seen until 1 or 2 hours after the tissue is exposed to the steroid. The most important physiologic effects of these compounds are to increase reabsorption of sodium and secretion of potassium and hydrogen ions in the distal tubule of the kidney. Mineralocorticoids do not cause excessive potassium excretion in sodium-depleted subjects. This fact is clinically important because sodium-depleted patients with hyperaldosteronism do not demonstrate a significant kaluresis. Excess aldosterone causes weight gain, increased blood pressure, hypokalemia, and mild metabolic alkalosis as a result of the physiologic effects described earlier. However, normal subjects “escape” the effects of excessive mineralocorticoids after approximately 14 days, and eventually blood volume returns to baseline levels. The mechanisms of the escape phenomenon, which has been studied intensely for years, remain uncertain. It appears that the rise in blood pressure may produce a pressure natriuresis, and also the arterial natriuretic factor may play a role. Mineralocorticoid deficiency results in sodium loss, and if uncorrected, death from hypovolemic shock. The naturally occurring mineralocorticoids are, in order of potency, aldosterone, deoxycorticosterone, 18-hydroxy-deoxycorticosterone, corticosterone, and cortisol. Table 13.2 lists the active mineralocorticoid and glucocorticoid activity of several naturally occurring and synthetic steroids.

Steroid	Glucocorticoid Activity	Mineralocorticoid Activity
Cortisol	1.0	1.0
Corticosterone	0.3	15.0
Aldosterone	0.3	3,000.0
Deoxycorticosterone	0.2	100.0
Cortisone	0.7	1.0
Prednisolone	4.0	0.8
9-α Fluorocortisol	10.0	125.0
Dexamethasone	25.0	0

TABLE 13.2. RELATIVE ACTIVITIES OF GLUCOCORTICOID AND MINERALOCORTICOID

Adrenal Medulla

The adrenal medulla secretes catecholamines into the circulation. The primary compound secreted by the medulla is epinephrine. Small quantities of norepinephrine and trace amounts of dopamine also are released from the gland. The adrenal medulla usually, but not invariably, acts in concert with the rest of the sympathetic nervous system. The hormones from the medulla are not essential for life.

Synthesis and Metabolism of Catecholamines

Catecholamines are synthesized from tyrosine in the adrenal medulla. The pathways of catecholamine synthesis are illustrated in Fig. 13.7 . In approximately 15% of the granules in the normal medulla, the last step in biosynthesis is the conversion of dopamine to norepinephrine (NE), accounting for the secretion of NE by the normal adrenal and by tumors of the gland. Most of the granules contain phenylethanolamine- *N*-methyltransferase, which converts NE to epinephrine (E), the major hormone of the adrenal medulla. In contrast, sympathetic nerves and other extraadrenal chromaffin tissue do not contain phenylethanolamine- *N*-methyltransferase and thus do not secrete E. This point is clinically useful in attempts to localize a catecholamine-secreting tumor.

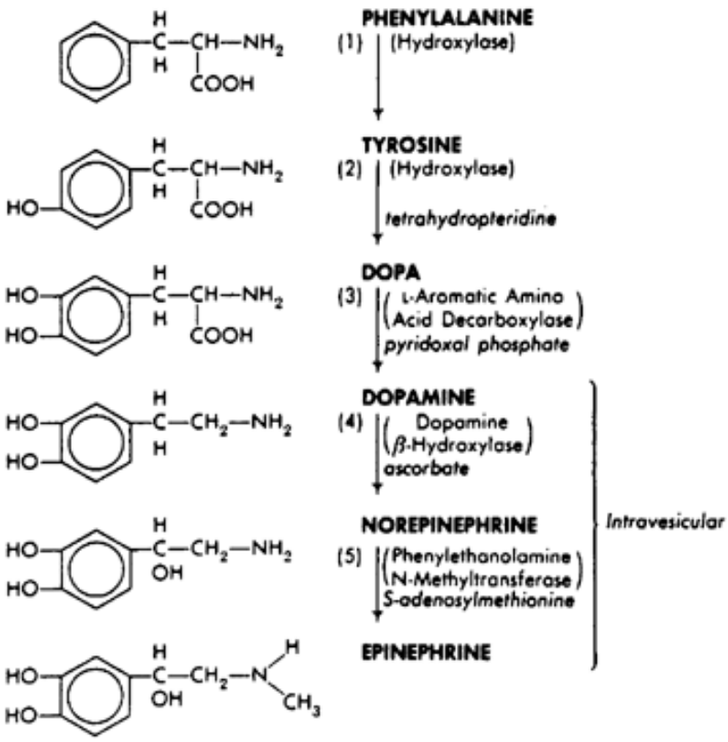

FIGURE 13.7. Biochemical pathways for the synthesis of norepinephrine and epinephrine.

NE and E have short half-lives in plasma, ranging from 1 to 3 minutes. They are degraded by two principal enzymes, catechol- *O*-methyl transferase and monoamine oxidase. Figure 13.8 illustrates the major metabolic pathways for circulating catecholamines. Catechol- *O*-methyl transferase converts NE and E, respectively, to normetanephrine (NMN) and metanephrine (MN). Determination of NMN or MN produces vanillylmandelic acid (VMA), a major metabolic product of catecholamine degradation. Less than 5% of the circulating NE and E are secreted intact in the urine. In a normal individual, NE from sympathetic nerve terminals makes up most of the intact urinary catecholamines, whereas E composes 20% of the total. The vast majority of the catecholamines are secreted in the urine as NMN, MN, VMA, and other metabolites shown in Fig. 13.6 . Measurement of these various products is important in the diagnosis of pheochromocytoma.

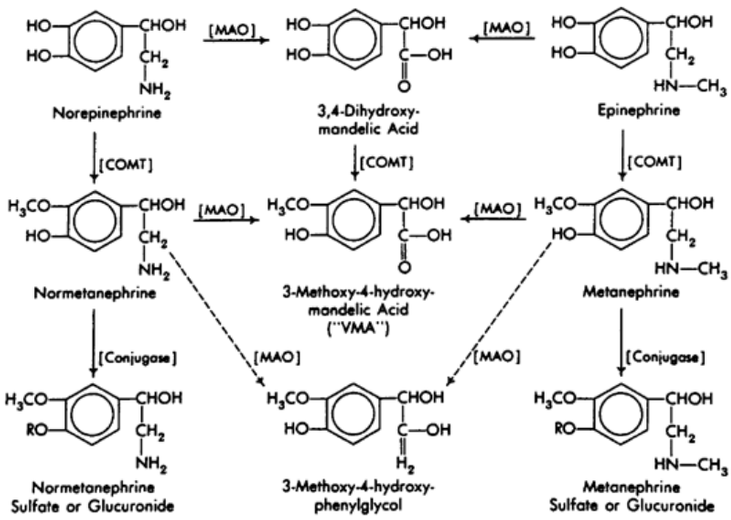

FIGURE 13.8. Metabolic pathways for the degradation of norepinephrine and epinephrine. The urinary metabolites are important in diagnostic evaluation of patients with suspected pheochromocytomas.

Regulation of Adrenal Medullary Catecholamine Synthesis and Secretion

Stimulation of the sympathetic nervous system during stress caused by stimuli such as fear, pain, or hemorrhage results in increased secretion of catecholamines from the adrenal medulla. Hypoglycemia is also a potent stimulator of adrenal catecholamine secretion. In most situations, the ratio of NE to E remains stable, although exceptions do occur. The basal plasma levels of E are 25 to 50 pg/mL. A total of approximately 150 mg is secreted daily. NE release at sympathetic nerve endings may spill over into the intracellular fluid or be retaken up by the tissues. The plasma level of NE is determined by a balance between the amount released into the circulation and the quantities metabolized and retaken up by the tissues.

Actions of Catecholamines

E and NE are potent hormones that activate α_1-, α_2-, β_1-, and β_2-plasma membrane receptors. E primarily stimulates β-receptors but also has some effect on α-receptors, particularly when the plasma levels of the hormone are high. Conversely, NE primarily affects α-receptors. Because these catecholamines can have α and β action, the effects of intravenously administered hormones vary quantitatively and qualitatively with the dose.

For example, at low dosages E causes vasodilation (a β-effect), which may result in hypotension, whereas at higher dosages there is a net increase in vascular resistance, causing hypertension with a larger increment in systolic than diastolic pressure, resulting in an increased pulse pressure. Both compounds have a positive inotropic effect on the heart and therefore increase cardiac output. Intravenously administered E causes tachycardia, whereas NE results in bradycardia because of the vagal reflex response to the increase in blood pressure.

Catecholamines help restore plasma glucose during exercise or stress by stimulating glycogenolysis in the liver, inhibiting insulin secretion, and increasing glucagon secretion. They also facilitate the reuse of lactate by exercising muscle and increase the release of free fatty acids into the circulation.

Excessive concentrations of catecholamines from exogenous sources or endogenous secretion in patients with pheochromocytoma may cause symptoms relating to the

previously described effects (see Pheochromocytomas). The symptoms in patients with pheochromocytoma are caused by E and NE. NE elevates the blood pressure and thus may cause headaches.

CUSHING'S SYNDROME

Part of "13 - THE ADRENALS "

Introduction

Cushing's syndrome is a complex of symptoms and signs caused by excess circulating glucocorticoids. The term is used to describe all patients with the clinical syndrome regardless of the cause. It is important to understand that Cushing's *disease* refers to the form of Cushing's *syndrome* caused by pituitary hypersecretion of ACTH. The most common cause of Cushing's syndrome is exogenously administered glucocorticoids. Twenty-five percent of endogenous Cushing's syndrome is caused by primary adrenal disease (i.e., adenoma or carcinomas). Seventy-five percent of the endogenous disease is excessive ACTH secretion, usually from the pituitary gland but occasionally from an ectopic source. Most patients with pituitary hypersecretion of ACTH (Cushing's disease) have microadenomas, although they may not be obvious during surgery. It is easier to understand the evaluation and treatment of patients with Cushing's syndrome if one keeps in mind that the *first* task of the clinician is to determine whether the patient has Cushing's syndrome. The *second* goal is to determine the cause of the syndrome, and the *final* assignment is to formulate a treatment plan.

Symptoms and Signs

Cushing's syndrome occurs in men, women, and children of all races but is most commonly diagnosed in women between the ages of 20 and 60 years. It is usually characterized by plethoric “moon” facies and central or “buffalo” obesity in the nuchal, truncal, and girdle areas (Fig. 13.9A and Fig. 13.9B). Protuberance of superclavicular fat pads is the cardinal physical finding that distinguishes Cushing's syndrome from obesity. Serial photographs of the patient are helpful in making the diagnosis because these pictures always document a shift in fat distribution, even if the patient is not obese. The protein wasting secondary to excess glucocorticoids causes easy bruising and thin skin, which results in pink or purple striae. Muscle wasting may cause severe weakness. The weakness is generally proximal and can be observed by asking the patient to do deep knee bends. Emotional symptoms and headaches are common. Adrenal androgens often cause hirsutism in women and prepubertal boys. Oligomenorrhea in women and acne also are common symptoms related to adrenal androgens. Fifteen percent of the patients have urinary stones caused by hypercalciuria. The full-fledged syndrome is easy to recognize, but the differential diagnosis may be difficult, particularly in men and also in women with hirsutism unrelated to Cushing's

syndrome. The most prevalent symptoms and signs of the syndrome are listed in Table 13.3 .

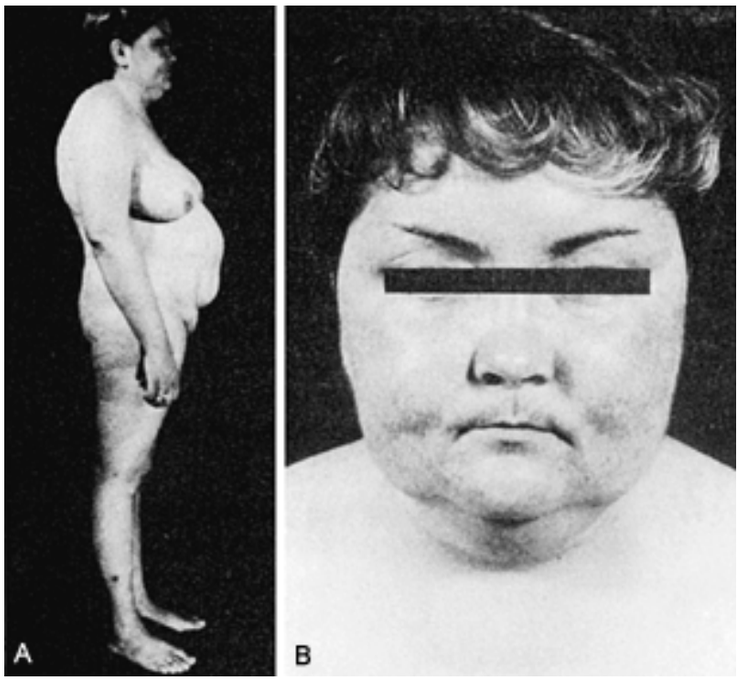

FIGURE 13.9. Typical appearance of a patient with Cushing's syndrome. **A:** Central obesity striae, buffalo hump, and moon facies. **B:** Protuberance of the subclavicular fat pads, hirsutism, facial pigmentation, and the fact that one cannot see the ears, which is typical of patients with Cushing's syndrome. There are also acne fold lesions on the skin.

TABLE 13.3. SYMPTOMS AND SIGNS OF CUSHING'S SYNDROME IN ORDER OF FREQUENCY

Symptoms	Signs
Central obesity	Central obesity
Hirsutism	Hypertension
Oligomenorrhea	Hirsutism
Purple striae	Purple striae
Plethoric facies	Plethoric facies
Easy bruisability	Acne
Personality change	Edema
Acne	Muscle weakness
Edema	
Muscle weakness	
Poor wound healing	
Backache	
Polyuria	
Polydipsia	
Impotence	
Growth arrest (children)	

Common physical findings in patients with Cushing's syndrome are hypertension and edema secondary to the mineralocorticoid activity of the adrenal steroids and, as mentioned previously, plethoric moon facies, central obesity, striae, acne, and hirsutism.

Differential Diagnosis

Cushing's syndrome is caused by the actions of glucocorticoids. Therefore anything that causes excess circulating levels of these hormones can evoke the syndrome. The most common cause is iatrogenic administration of glucocorticoids. Pituitary Cushing's syndrome or Cushing's disease accounts for the majority of the noniatrogenic cases. Approximately 95% of the patients with pituitary Cushing's syndrome have detectable pituitary tumors.

Evidence is mounting that the primary problem in these patients is hypersecretion of ACTH independently or CRF secretion (82). Ectopic secretion of ACTH or CRF (16) from tumors also can cause the syndrome. Finally, primary adrenal adenomas or carcinomas may secrete enough hormone to produce the syndrome. Adrenal tumors tend to be autonomous in their secretion of glucocorticoids, a characteristic that assists in the differential diagnosis of Cushing's syndrome. Most of these tumors are unilateral, but bilateral tumors do occur. Most children with Cushing's syndrome have adrenal neoplasms.

In patients younger than 15 years of age, adrenal carcinoma is the most common cause of Cushing's syndrome. Because most patients with adrenal cortical carcinoma have endocrine symptoms or a mass in the retroperitoneum, the syndrome is rarely suspected because of distant metastasis, although pulmonary and liver metastases are not uncommon and skeletal, brain, pleura, and mediastinal metastases do occur (45). Patients with ectopic or pituitary ACTH-dependent Cushing's syndrome may have hyperpigmentation. Galactorrhea occurs occasionally and only in individuals with pituitary hypersecretion of ACTH. Patients with adrenal carcinoma are characterized by hirsutism and virilism resulting from androgenic adrenal steroids, and individuals with ectopic ACTH tend to have severe manifestations of the syndrome attributable to the high levels of ACTH. The presence of a decreased serum potassium level in patients with this finding is highly suggestive of ectopic ACTH secretion, and the diagnosis should be pursued even if there is also suspicion of a pituitary cause.

The diagnosis of Cushing's syndrome is most frequently entertained when a physician is consulted by an overweight woman concerned about hirsutism. Most of these patients have excessive secretion of androgens from the ovary (50) rather than hyperadrenocorticism. Late-onset adrenal hyperplasia, however, has been reported in 24 of 400 women with hirsutism (54).

Laboratory Diagnosis of Cushing's Syndrome

There are two basic steps in the laboratory evaluation of individuals with suspected Cushing's syndrome: first, determining whether they have the syndrome, and second, identifying the cause.

Many tests have been recommended for diagnosis of Cushing's syndrome. We prefer to screen patients with a determination of the free cortisol in a 24-hour urine specimen. In our laboratory, the normal value is lower than 80 mg per 24 hours. Values vary with age and from laboratory to laboratory. Following are examples of such results (29).

A normal finding rules out Cushing's syndrome unless the clinical level of suspicion is high. If the urinary free cortisol is elevated, we then do a low-dose dexamethasone test. Dexamethasone is a biologically active glucocorticoid that suppresses the secretion of ACTH and thus endogenous adrenal glucocorticoids but does not affect the measurement of the endogenous hormones in the serum and their metabolism in the urine. The patient is given dexamethasone 0.5 mg orally every 6 hours four times daily. At 9 A.M. after the last 3 A.M. dosage, a blood sample is obtained. The normal individual will have a suppressed serum cortisol level of less than 2 to 5 mg/dL. Twenty-four-hour urine levels of free cortisol also should be depressed to less than 20 mg/L on the second and third days. Porter-Silber 17-OH corticoids and ketogenic steroids in the urine should be less than 2.0 and 5.0 mg/g of creatinine, respectively. The best criterion to use for the dexamethasone test is the value of 17-OH corticoids per gram of creatinine. The creatinine corrects for surface area. If the serum and urinary values are normal, the patient does not have Cushing's syndrome; if the values are elevated, Cushing's syndrome is likely. There are exceptions, however, including endogenous depression and alcoholic pseudo-Cushing's syndrome.

In other institutions the morning and afternoon serum cortisol levels and overnight dexamethasone test are used to make the diagnosis of Cushing's syndrome. In the normal individual, there is a diurnal rhythm in serum cortisol concentration, with a peak of 8 to 25 mg/dL at 6 to 9 A.M. and a nadir of less than 7 to 10 mg/dL in the afternoon (Fig. 13.10). Therefore the test is done by drawing blood samples at 8 A.M. and 4 P.M. Normal persons should conform to the stated values and display at least a 50% decrease between morning and afternoon determinations. This diurnal rhythm is not present in young patients (Fig. 13.10). Patients with Cushing's syndrome usually have elevated values, particularly in the afternoon, and also do not exhibit the normal diurnal rhythm. The overnight dexamethasone suppression test is done by giving the patient 1.0 mg of dexamethasone at 11 P.M. and obtaining a blood sample the next morning at 8 A.M. The normal individual will have a suppressed serum cortisol level less than 5.0 mg/dL, whereas the patient with Cushing's syndrome will have a serum cortisol level greater than 5.0 mg/dL (usually greater than 20 mg/dL).

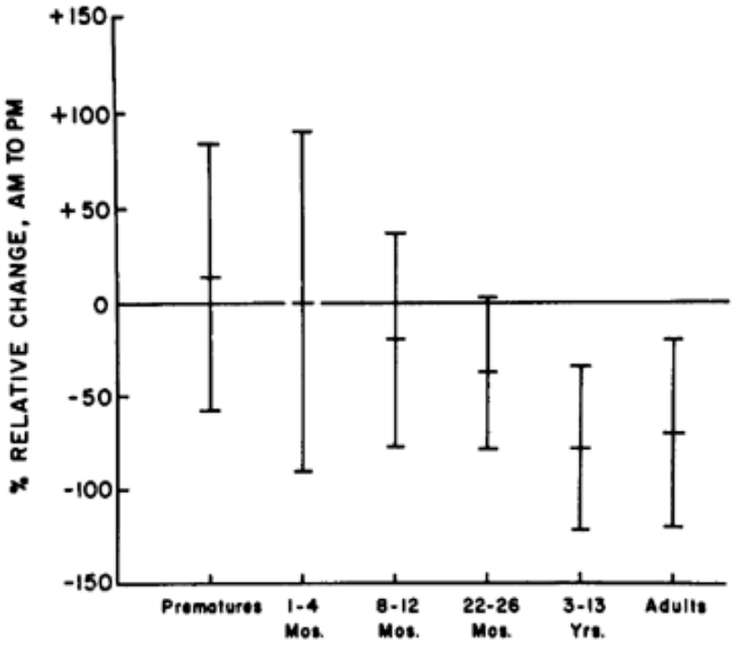

FIGURE 13.10. Diurnal rhythm in serum cortisol levels and its variation with age.

Laboratory Determinations of the Cause of Cushing's Syndrome

Many tests are available to facilitate the differential diagnosis of Cushing's syndrome. None of these tests is always correct, and the diagnosis can be difficult. Disagreement among test results is the rule rather than the exception. The diagnosis can be confused by the fact that pituitary Cushing's syndrome can cause autonomous adrenal hyperfunction when adrenal hyperplasia develops into a discrete adenoma (41). Among the many tests available, we prefer three: plasma ACTH, high-dose dexamethasone suppression, and the metyrapone test. The normal plasma ACTH level in an adult is 10 to 80 pg/mL in the morning and at least 50% in the evening (5,72). The morning plasma ACTH is suppressed to undetectable levels in patients with adrenal adenomas or carcinomas. In patients with ectopic secretion of ACTH, the value is elevated (200 to 1000 pg/mL), and in patients with Cushing's disease, it is normal or high (40 to 100 pg/mL) but elevated inappropriately for the level of cortisol. The high-dose dexamethasone test is done in the same manner as the low-dose test described earlier, except that each dose of the drug is 2.0 mg. Patients with ectopic ACTH secretion or adrenal tumors do not suppress, but those with Cushing's disease do.

Metyrapone inhibits the enzyme 11-ß-hydroxylase, thus preventing 11-ß-hydroxylation during steroidogenesis (Fig. 13.4). This eliminates the production of cortisol, which in turn increases the secretion of ACTH (because the negative feedback has been removed) and the secretion of adrenal steroids such as 11-deoxycortisol. In patients with ectopic ACTH secretion or adrenal tumors, metyrapone has no effect. Patients with Cushing's disease have an exaggerated response. There is a potential danger that metyrapone will cause adrenal insufficiency and adrenal crisis.

The administration of corticotropin-releasing hormone to patients with Cushing's syndrome caused by adrenocortical tumor usually results in little change in ACTH levels, whereas patients with pituitary microadenomas usually have

an exaggerated ACTH response. Nonetheless, because of large individual variations, corticotropin-releasing hormone testing is not recommended for routine use in the differential diagnosis of Cushing's syndrome (82). Oldfield and associates measured the levels of adrenocorticotropin in the peripheral blood and the plasma from both of the inferior petrosal sinuses in 281 patients with Cushing's syndrome. They found that an inferior petrosal sinus adrenocorticotropin level of twice the plasma concentration identified Cushing's disease in 205 of 215 patients (sensitivity 95%) with no false-positive results (specificity 100%). After CRF administration a measured ratio of greater than 3.0:1 was 100% accurate with no false-positive or false-negative results (68).

Localization of Adrenal Causes of Cushing's Syndrome

The techniques currently used to localize adrenal tumors are listed in Table 13.4 . Intravenous pyelography, arteriography, and adrenal vein venography are no longer recommended for localizing adrenal lesions in patients with Cushing's syndrome.

TABLE 13.4. LOCALIZATION TEST FOR CUSHING'S SYNDROME

Computed tomography or magnetic resonance imaging
Scintiscan: 6-β-iodomethyl norcholesterol (NP-59)
Ultrasonography

Most tumors of the adrenal that cause Cushing's syndrome are larger than 2 cm and therefore are easily visualized with CT or magnetic resonance imaging (MRI) (Fig. 13.11 and Fig. 13.12) (1,75). The adrenal gland on the affected side in patients with renal agenesis or inferior ectopy is a paraspinal disk-shaped organ that has a linear appearance on CT scan (49). Unilateral Cushing's adenomas are associated with contralateral adrenal atrophy. Adrenal hyperplasia is associated with diffuse thickening, occasionally with bilateral cortical nodularity in 10% to 20%. Adrenal carcinomas are usually larger in size (greater than 6 cm), irregular, with evidence of necrosis, calcification, or local invasion. Upon MRI, adenomas are generally isointense as compared with the liver on T_2-weighted images, whereas carcinomas are hyperintense and inhomogeneous. An intravenous pyelography, especially with tomography, also may reveal an adrenal mass, although it is less sensitive. Adrenal tumors typically displace the upper pole of the kidney laterally (Fig. 13.13), changing the axis of the kidney and the collecting system. They rarely displace the kidney caudally without shifting the axis. Sonography can be a useful screening technique, particularly for large tumors, and is useful in determining whether a retroperitoneal mass extends from or into the kidney or is separated from the kidney and/or the liver. If it is unclear whether a retroperitoneal mass is of adrenal or renal origin, arteriography may be useful because it is often pathognomonic of renal cell carcinoma and also may be useful in planning surgery. However, we do not routinely perform arteriograms in patients with suspected adrenal or renal tumors.

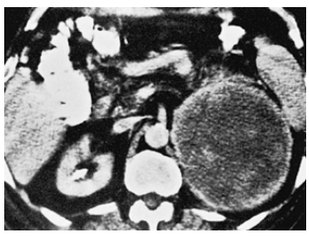

FIGURE 13.11. Computed tomography (CT) scan of a patient with a large adrenal hematoma. CT scans of patients with tumors causing Cushing's syndrome might be quite similar in configuration, although the intratumor density would vary.

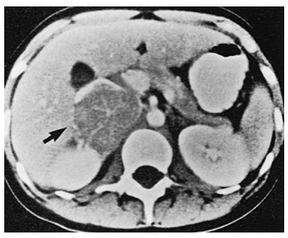

FIGURE 13.12. Computed tomography scan of a patient with pheochromocytoma *(arrow).*

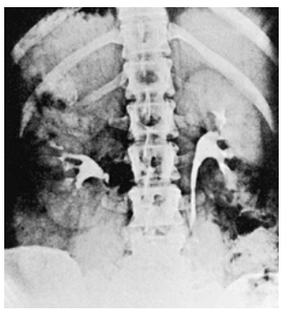

FIGURE 13.13. Intravenous pyelography of a patient with an adrenal mass. Note that the renal axis and the axis of the collecting system are deviated with the upper pole pushed outward. This is quite typical of an adrenal tumor. The tumors of the adrenal usually push the upper pole outward rather than pushing the kidney down.

Venography with catheterization of the adrenal veins is an extremely precise technique for diagnosing and localizing endocrinologically active adrenal tumors. However, it is difficult to catheterize the adrenal veins, particularly on the right, and even in experienced hands this method may fail. Also there is danger of damaging the adrenal gland if undue pressure is exerted in the adrenal vein. Adrenal masses also can be identified with scintillation scanning techniques using NP-59 (Fig. 13.14). We have found this technique useful in the evaluation of patients with Conn's syndrome.

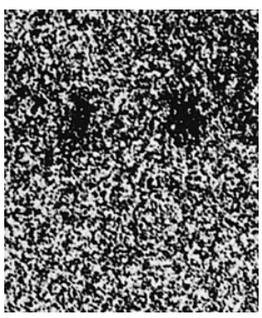

FIGURE 13.14. IP-59 scintillation scan of a patient with bilateral adrenal hyperplasia. Note that both adrenal glands are seen on this scan and are of approximately equal density. If the patient had an adrenal adenoma, the side with the adenoma would be highlighted, whereas the other side would not be visualized.

CUSHING'S DISEASE

Part of "13 - THE ADRENALS "

Transsphenoidal hypophysectomy, pituitary irradiation, bilateral adrenalectomy, and medical therapy are all used to treat Cushing's disease. The treatment of choice in most centers is transsphenoidal removal of the microadenoma (10,59,81). The current success rate is between 85% and 95%. This treatment is less morbid than bilateral adrenalectomy and avoids the complication of Nelson's syndrome. Pituitary irradiation (cobalt-60) with 4,000 to 5,000 rad has a reasonable success rate in children, approximately 80%, but only approximately a 20% cure rate in adults. Pituitary irradiation with a cyclotron (proton beam) may have a higher cure rate in adults, but this technique is available in only a few locations in the United States. We reserve bilateral adrenalectomy for patients who have failed pituitary surgery. Bilateral adrenalectomy may be complicated in 10% to 20% of cases by rapid postoperative growth of pituitary tumors and hyperpigmentation (Nelson's syndrome). Preoperative pituitary irradiation decreases the incidence of Nelson's syndrome.

Medical treatment with cyproheptadine 6 mg orally four times daily has been reported to cause remission in 60% to 65% of patients with Cushing's disease after 6 to 8 weeks. Mitotane, o,p-DDD, 6.0 g per day, or aminoglutethimide has also been used to treat patients with Cushing's disease, but because of significant side effects, we do not recommend these compounds except for inoperable cases. We prefer metyrapone 1.0 g per day. This drug has a short half-life and must be given every 4 hours. It is monitored by following serum and not urinary cortisol. Hypertension may result from accumulation of deoxycorticosterone. This can be treated with spironolactone. In general, in Cushing's disease medical therapy is used only when indicated to prepare patients for surgical treatment. The major use of medical treatment is in palliation of patients with Cushing's syndrome as a result of malignancies.

Adrenal Tumors

The distinction between a benign adenoma and a malignant adrenal cortical neoplasm is important because of the difference in long-term patient survival. Ultimately, the only method certain to establish the difference is pathologic analysis (86). Nonetheless, a reasonable assessment of the malignant potential can be made using clinical, biochemical, and radiographic information. A recent review of 40 patients (27 adenomas, 13 carcinomas) with ACTH-independent Cushing's syndrome was undertaken at our institution with the primary aim of establishing criteria for the preoperative delineation of adrenal adenomas from carcinomas (22).

The two demographic features that distinguished adenomas from carcinomas were age and tumor size. As compared with carcinoma patients, adenoma patients were significantly younger (39.6 versus 51.5 years) and their tumors were significantly smaller (3.3 versus 8.6 cm). Women constituted the majority of patients in both groups, and left-sided tumors accounted for 70% of cases in both groups. No specific physical finding differentiated adenomas from carcinomas.

All patients had elevated 24-hour urinary free cortisol values and low-normal ACTH levels. No specific biochemical abnormality identified either adenoma or carcinoma patients. Nevertheless, urinary free cortisol, 17-ketosteroid (17-KS), dehydroepiandrosterone sulfate (DHEAS-S), and lactate dehydrogenase (LDH) levels tended to be higher in carcinoma patients. A pure biochemical syndrome of glucocorticoid excess without elevation of 17-KS, DHEA-S, testosterone, or aldosterone was present in 68% of adenoma patients as opposed to only 8% of carcinoma patients.

Some groups have noted the presence of virilization/hirsutism as an important clinical clue suggesting the presence of carcinoma (69). This is based on the premise that carcinomas are less effective than adenomas at converting steroid precursors to glucocorticoids. In our recent review, this was not a discriminating feature (22). Whereas most carcinoma patients presented with a mixed endocrine syndrome (92%), adenoma patients commonly had virilization (93%), and 32% presented with a mixed endocrine syndrome as determined by biochemical analysis. There were a few noteworthy observations. Of the adenoma patients in whom DHEA-S was measured, 44% had subnormal values, and in the two patients with elevated levels the values were only mildly raised. In contrast, only one carcinoma patient had a subnormal level of DHEA-S, and 50% of the carcinoma patients had elevations that exceeded four times the normal value. Overall, the magnitude of the biochemical abnormalities were more severe for the carcinoma patients. These findings support the notion that adenomas in general are more efficient than carcinomas at converting steroid precursors to glucocorticoids; however, significant tumor-to-tumor variability remains. Although steadfast rules do not exist with regard to the preoperative hormonal profile capable of predicting the presence of adenoma versus that of carcinoma, it is likely that patients with ACTH-independent CS, normal 17-KS levels, and subnormal DHEA-S values have an adenoma, whereas those with greatly elevated 17-KS and DHEA-S levels have a carcinoma. Although steroid profiling may not dramatically enhance the management of patients with a small adrenal mass that is likely to be an adenoma, it is important for patients with suspected carcinoma because the steroid values can be helpful in the follow-up of these patients, serving as markers of recurrent disease.

The treatment of Cushing's syndrome secondary to adrenal tumors is surgical removal unless the tumor is unresectable. Preoperative preparation requires specific measures to correct metabolic abnormalities caused by Cushing's syndrome. These patients are prepared for surgery by treatment with metyrapone (250 to 500 mg orally every 4 hours) while awake. To the extent that these drugs reverse Cushing's syndrome, they decrease the operative morbidity and the mortality. Malignant adrenal tumors causing Cushing's syndrome in the adult do not have a good prognosis. The Cleveland Clinic series revealed a 44% 5-year survival in patients with localized disease who made up 49% of 82 patients, and a 13% and 6% 5-year survival in patients with regional and metastatic disease (9). In the M.D. Anderson series, 13 of 18 patients (72%) had recurrent disease (78). Of the 13, 8 patients had local recurrence. The prognosis is better in children.

Bilateral adrenalectomy is indicated for patients with Cushing's disease refractory to hypophysectomy. Postoperatively, these patients require replacement glucocorticoids and mineralocorticoids indefinitely. We usually give hydrocortisone sodium succinate (Solu-Cortef) 100 mg intravenously every 8 hours for the first few days and taper to an oral dose of 25 to 37.5 mg of cortisone acetate and 0.1 mg of fluorocortisone acetate (Florinef) daily.

PRIMARY HYPERALDOSTERONISM

Part of "13 - THE ADRENALS "

Deming and Luetscher (24) described a sodium-retaining substance in the urine in 1950. Three years later Simpson and associates chemically identified the compound as the 18-aldehyde of corticosterone, aldosterone. Within a year, aldosterone had been synthesized and, remarkably, Conn (19) described the clinical syndrome of primary hyperaldosteronism, or Conn's syndrome. Never before in the history of medicine had an important clinical advance followed so closely on the heels of a basic scientific discovery.

Conn's syndrome is defined as the adrenal hypersecretion of aldosterone in a hypertensive, nonedematous patient. The exact incidence of the disease is not known, but it accounts for approximately 1% of hypertensive patients. It should be pointed out that 1% of 35 million hypertensive patients in the United States is 350,000 people. Women outnumber men approximately 2.5 to 1, and 75% of the patients are between 30 and 50 years of age. Primary hyperaldosteronism should be suspected in any hypertensive patient with hypokalemia. The patients typically have hypertension, muscle weakness, polyuria, hypokalemia, and mild metabolic alkalosis. Table 13.5 gives the incidence of the common symptoms of primary hyperaldosteronism reported in Conn's original description of 103 cases.

Muscle weakness	73%
Polyuria (nocturia)	72%
Headache	51%
Polydipsia	46%
Paresthesia	24%
No symptoms	6%

TABLE 13.5. SYMPTOMS OF CONN'S SYNDROME

In recent years, the diagnosis of Conn's syndrome has been confirmed in many individuals with no obvious symptoms of hypokalemia. There are rare patients with primary

hyperaldosteronism who do not have unprovoked hypokalemia.

The headaches are caused by the hypertension, whereas the muscle weakness, polyuria, and paresthesias relate to the effect of hypokalemia on skeletal muscle, the renal concentrating mechanism, and peripheral nerves, respectively.

The major physical finding in patients with primary hyperaldosteronism is hypertension without edema. Mild retinopathy may be present. Routine laboratory evaluation reveals (a) a persistently dilute urine with a pH of 6.5 or higher, (b) a plasma potassium level below 3.5 to 4.0 mEq/L with the patient off all diuretic medication, and (c) mild metabolic alkalosis (elevated serum bicarbonate radical). The serum sodium concentration may be slightly elevated, and mild proteinuria is often present. The electrocardiogram often reveals premature ventricular contractions, depression of the ST segments, T waves, and the presence of U waves. When the diagnosis of primary hyperaldosteronism is entertained, three questions must be sequentially answered: (a) Does the patient have primary hyperaldosteronism? (b) If so, what is the cause? (c) If the disease is the result of an adenoma, what is the location of the tumor?

Does the Patient Have Primary Hyperaldosteronism?

By far the most common cause of hypertension and hypokalemia is essential hypertension treated with diuretics. Also, hypertension, hypokalemia, and hypersecretion of aldosterone are more often caused by secondary hyperaldosteronism than by primary hyperaldosteronism. Any stimulus that compromises renal blood flow may increase renin secretion and thus cause secondary hyperaldosteronism. Common clinical situations that evoke secondary hyperaldosteronism are listed in Table 13.6 .

Shock	Cardiac failure
Dehydration	Hepatic cirrhosis
Renal artery stenosis	Pregnancy

TABLE 13.6. CAUSES OF SECONDARY HYPERALDOSTERONISM

Rare causes of secondary hyperaldosteronism include renin-secreting renal tumors and Bartter's syndrome. Bartter's syndrome is characterized by elevations in plasma renin and aldosterone, hypokalemia, and hyperplasia of the juxtaglomerular cells in the kidney.

It is not always easy to determine whether a patient has primary hyperaldosteronism. Many different approaches to diagnosis have been recommended. One of the most difficult problems facing the clinician is which patients should be screened for primary hyperaldosteronism. Certainly, individuals with spontaneous hypokalemia (less than 4.0 mEq/L) and inappropriate kaluresis (greater than 3.0 mEq per day) may have primary hyperaldosteronism. To make the diagnosis we first perform a saline suppression test. With the patient in the supine position a serum sample is obtained for aldosterone, saline is infused at 500 mL per hour for 4 hours, and then another serum sample is drawn. A normal individual will suppress serum aldosterone to less than 10 ng/dL, whereas in patients with primary hyperaldosteronism, the serum aldosterone after saline infusion will be greater than 10 ng/dL. In addition, patients with the disease will have an increased plasma concentration and urinary secretion of aldosterone after potassium repletion to more than 3.5 mEq/L (12).

The captopril test is advocated by many investigators, but we find it less precise than the approach just outlined. The test is done by obtaining serum before and 2 hours after administration of 25 mg of captopril. In secondary hyperaldosteronism, the serum renin rises after the captopril, whereas in primary hyperaldosteronism it does not. Also, the aldosterone-to-renin ratio decreases in secondary hyperaldosteronism but not in primary.

What Is the Cause of Primary Hyperaldosteronism?

Primary hyperaldosteronism may be caused by an adrenal tumor (usually a unilateral adenoma), adrenal hyperplasia (“idiopathic”), deoxycorticosterone acetate-suppressible adrenal hyperplasia (indeterminate hyperplasia), or glucocorticoid-remediable family hyperplasia. The last two forms of the disease occur in adolescents and children, respectively, and are rare. Approximately two-thirds of patients with primary hyperaldosteronism have adrenal adenomas. The major differential diagnosis is between adenoma and hyperplasia. We make the diagnosis of adenoma if (a) there is an anomalous decrease in plasma aldosterone during ambulation, (b) the blood pressure is normalized on spironolactone (400 mg/L for 6 weeks), (c) the serum aldosterone-stimulating factor is *not* elevated (16), and (d) CT or MRI scanning shows a discrete adrenal mass. Biglieri and associates (7) also have noted that the plasma 18-hydrocorticosterone level after overnight recumbency is much higher (greater than 100 ng/dL) in patients with an adenoma than in individuals with hyperplasia. Despite these tests, the differential diagnosis may be difficult. Once the diagnosis of adenoma is made, we attempt to localize the tumor.

Where Is the Tumor?

Methods used to localize adrenal adenomas have included intravenous pyelography, aortography, phlebography, adrenal vein catheterization, radionuclide scan, CT, and nuclear resonance imaging. The NP-59 scan is a useful noninvasive technique. The patient is prepared for 3 days with Lugol's solution (5 drops twice daily) and oral dexamethasone

(0.5 mg every 6 hours). The Lugol's solution is continued for 2 weeks. Imaging is done after the 3-day preparation and again in 4 more days. CT scanning often identifies an adenoma (85), but false-negative results may occur because these adenomas are typically rather small. When CT scanning is used, thin-section CT techniques with section thicknesses of 1.5 to 3 mm should be used (37). The accuracy of CT scanning alone in patients with low-renin hyperaldosteronism has been estimated at 73% to 90% (90). This imprecision is due to the fact that CT scans may miss adenomas smaller than 1 cm. Ironically, with the increased sensitivity of CT scans, an additional, perhaps even prevalent, source of inaccuracy is the fact that modern CT scans overdiagnose adenomas because they find small nonfunctioning masses and confuse unilateral macronodular hyperplasia with adenomas (25).

MRI with and without gadolinium administration also can identify an adenoma-causing primary aldosteronism with the same efficacy as CT scanning. Adrenal vein catheterization with sampling and analysis of the effluent is perhaps the most precise way to localize a tumor, but, as pointed out in the discussion of Cushing's syndrome, it is technically difficult (33).

Treatment

The preferred management of primary hyperaldosteronism secondary to adrenal hyperplasia is medical treatment with spironolactone, which inhibits the action of aldosterone on the distal renal tubule. Reduction of plasma volume by diuretic therapy is an important aspect of treating hypertension in these patients. Administration of 200 mg of spironolactone per day (50 mg four times daily) normalizes serum potassium with relatively little effect on the pressure. The addition of hydrochlorothiazide (HCTZ) 50 mg per day (25 mg twice daily) rapidly reduces blood pressure while maintaining serum potassium concentrations within the normal range. Painful gynecomastia is a distressing side effect of spironolactone. Occasionally, agents that interfere with renal tubular ion transport, such as triamterene or amiloride, are also incorporated into a pharmacologic treatment program. Bilateral adrenalectomy has no place in the management of primary aldosteronism because complete adrenal insufficiency may be more difficult to treat than hypertension from aldosteronism.

The treatment of choice for an aldosterone-producing adrenal cortical adenoma is surgical adrenalectomy, which carries minimal morbidity and provides definitive therapy in most cases. Blumfeld and colleagues (8) demonstrated in 1994 that 35% of patients with a unilateral adenoma had normal blood pressure postoperatively without any concurrent antihypertensive medications. In an additional 56% of patients with residual hypertension postoperatively, addition of an antihypertensive agent decreased their blood pressure below 140/90 mm Hg. Thus more than 90% of patients with an adenoma had cure or significant improvement of hypertension following surgical excision. Medical therapy with spironolactone may be indicated for poor surgical risk patients with an adenoma. Occasionally, an adrenal gland removed for a suspected adenoma is found to contain one or more hyperplastic nodules. Although the results of adrenalectomy for hyperplasia are less satisfactory, some patients experience improvement of hypertension postoperatively (56). This therapeutic response is not completely understood and may result from a simple reduction in the amount of adrenal tissue.

Patients with primary hyperaldosteronism from an adrenal adenoma have a significant potassium deficit, which must be corrected preoperatively because hypokalemia increases the risk of cardiac arrhythmias during anesthesia. Supplemental oral potassium alone is not sufficient to overcome the kaluresis experienced by these patients. Preoperative treatment with spironolactone is also necessary both to correct hypokalemia and to facilitate blood pressure control. Some patients with a unilateral adenoma develop contralateral mineralocorticoid suppression, which may become manifest postoperatively as clinical hyperaldosteronism. This problem may also be prevented by preoperative spironolactone therapy because this allows reactivation of the renin-angiotensin-aldosterone system.

Because aldosterone-producing adenomas are invariably small and benign, laparoscopic adrenalectomy has now become the preferred surgical approach. Following adrenalectomy in such cases, there is usually a moderate urinary diuresis of sodium and retention of potassium. This requires appropriate volume replacement and close monitoring of serum electrolyte levels for the first week postoperatively. In some cases, hyponatremia and hyperkalemia develop in the immediate postoperative period secondary to suppression of the contralateral zona glomerulosa, with a resulting aldosterone deficiency. This phenomenon will necessitate mineralocorticoid replacement until the remaining adrenal gland recovers. In general, patients experience a rapid and uneventful postoperative recovery from adrenalectomy for hyperaldosteronism. Hypertension may take several weeks to resolve completely; however, ultimately 80% of patients are cured (56).

ADRENAL INSUFFICIENCY

Part of "13 - THE ADRENALS "

Adrenal insufficiency was described in 1855 by Thomas Addison—thus the eponym *Addison's disease.* Addison's disease is a rare entity, usually secondary to tuberculosis or autoimmune adrenocortical atrophy. Other causes include amyloidosis, histoplasmosis, blastomycosis, and metastatic carcinoma. Iatrogenic adrenal insufficiency secondary to high-dose adrenal steroid therapy or surgical adrenalectomy is more common. Urologists should be aware that ketoconazole

therapy for prostatic cancer may cause reversible adrenal insufficiency (83).

The symptoms of adrenal insufficiency include muscular weakness, fatigability, weight loss, hyperpigmentation, anorexia, nausea, vomiting, and diarrhea. Cardiac tamponade is a rare, often fatal complication of adrenal insufficiency. Hypotension is the cardinal sign. Hyponatremia and hyperkalemia are common. Plasma cortisol levels are low, as are levels of the various urinary metabolites of the endogenous adrenal steroids. The diagnosis can be confirmed by finding an elevated level of serum ACTH and a lack of significant response in serum cortisol after administration of ACTH (Fig. 13.15). Corticotropin-releasing hormone levels have been reported to be either elevated or normal in patients with Addison's disease (82).

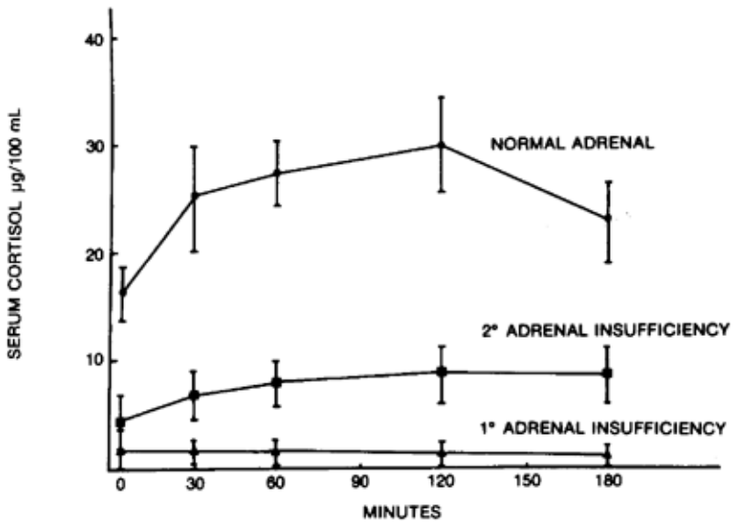

FIGURE 13.15. Serum cortisol response and response to adrenocorticotropin hormone infusion in normal persons and in patients with primary and secondary adrenal insufficiency.

The initial treatment is 100 mg of hydrocortisone every 8 hours. All patients maintained on adrenal steroid therapy should receive this dose for several days after any surgical procedure. The dose is tapered to a maintenance dose of 30 mg per day, given as 20 mg in the morning and 10 mg in the evening, to mimic the physiologic diurnal variations in serum levels. In patients with adrenal insufficiency secondary to pituitary disease, it is usually not necessary to provide mineralocorticoid replacement. In patients with no functioning adrenal tissue, fluorocortisol 0.05 to 1.0 mg per day will provide adequate mineralocorticoid replacement. The adequacy of the replacement therapy can be determined by monitoring blood pressure, serum electrolytes, renal function, and plasma ACTH and renin activity.

PHEOCHROMOCYTOMAS

Part of "13 - THE ADRENALS "

Pheochromocytomas are fascinating tumors that secrete catecholamines that cause a variety of symptoms, usually including hypertension. Most pheochromocytomas secrete NE and E. Occasional tumors release only NE, and rare lesions secrete dopa, dopamine, serotonin, somatostatin, ACTH, or E. The tumors are composed of chromaffin cells and may arise anywhere in the body where chromaffin tissue derived from primitive neuroectoderm is located. Approximately 95% of the tumors are located in the adrenal gland, but pheochromocytomas have been found in the bladder, Zuckerkandl's organ, and anywhere in the body that sympathetic nervous tissue is located. Three percent of pheochromocytomas are extraabdominal. Although only 0.1% to 0.2% of hypertensive patients have a pheochromocytoma, they should always be screened because the tumors are curable in 90% of the patients, and untreated pheochromocytomas frequently cause fatal complications such as cardiac arrhythmias, congestive heart failure, myocardial infarct, cerebral vascular accidents, and hemorrhage.

Pheochromocytomas may be familial. Patients with familial pheochromocytomas often have multiple tumors. These Sturge-Weber syndrome cases also are often associated with one of the variants of the multiple endocrine neoplasia syndrome, the most common of which is type 2A, characterized by carcinoma of the thyroid, hyperparathyroidism, and pheochromocytoma. DNA-polymorphism analysis facilitates identification of individuals at risk for this syndrome (80). Pheochromocytoma is also linked with von Recklinghausen's disease (café-au-lait spots) and von Hippel-Lindau disease (angiomatosis of the retina and hemangioblastoma of the cerebellum). Patients with von Hippel-Lindau disease also may have neurologic symptoms including seizures and mental retardation. Neumann and associates (64) reported that 19 of 82 (23%) unselected patients with pheochromocytoma were carriers of von Hippel-Lindau disease or had multiple endocrine neoplasia type 2. They recommended that all patients with pheochromocytoma should be screened for these abnormalities to reduce morbidity in the patients and their families.

Patients with a pheochromocytoma usually present with hypertension, although 15% to 20% are normotensive, and rare patients are hypotensive. Approximately 50% of the hypertensive patients have sustained elevations in blood pressure, and the remainder have characteristic paroxysmal hypertension. Hypertensive patients with sweating, tachycardia, and headaches have more than a 90% chance of having a pheochromocytoma, whereas individuals with none of these characteristics have less than a 1% incidence of pheochromocytomas (70). The common symptoms and signs are listed in Table 13.7 .

TABLE 13.7. SYMPTOMS AND SIGNS OF PHEOCHROMOCYTOMA

	Frequency (%)
Symptom	
Headache	80–85
Weakness	75–80
Diaphoresis	65–70
Palpitations	60–65
Orthostatic hypotension	50–60
Nausea and vomiting	35–60
Nervousness	35–40
Constipation	30–35
Sign	
Hypertension	80–85
Retinopathy	50–70
Decreased body weight	40–70
Fasting hyperglycemia	40–50

Adapted from Atuk NO. Pheochromocytomas: diagnosis, localization, and treatment. *Hosp Pract* 1983;18:187.

Patients, even those with sustained hypertension, often experience paroxysmal symptoms that may occur dramatically and suddenly. The frequency of these attacks is rather variable, and the duration is usually less than an hour. The attacks may be precipitated by emotional, physical, or pharmacologic stimuli. Neurocutaneous lesions, progressive diabetes associated with hypertension, and unexplained

intraoperative hypertension all should suggest the presence of pheochromocytoma.

The hypertension is caused by the release of catecholamines from the tumor *and* increased sympathetic neural tone. Bravo and associates (13) have shown that clonidine, a drug that decreases sympathetic tone, reduces blood pressure and heart rate in patients with pheochromocytoma without affecting plasma catecholamines or renin concentrations. Tumors that produce only NE are associated with fewer symptoms than those that release NE and E. The latter compound has a more pronounced affect on ß-receptors, causing symptoms such as diaphoresis and palpitations.

Laboratory Evaluation

The diagnosis of pheochromocytoma is made by documenting elevated levels of catecholamines in the blood or urine. The assays are rather precise, but false-positive results can occur secondary to drugs, stress, and other diseases that increase the concentrations of catecholamines (Table 13.8). Modest elevations in hematocrit levels are common as a result of a decreased plasma volume secondary to vasoconstriction.

Drugs	Diseases
Methyldopa	Guillain-Barré syndrome
Theophylline	Neuroblastoma
Ephedrine	Porphyria
Levodopa	Brain tumor
Tricyclic antidepressants	Carcinoid syndrome
Clonidine (withdrawal)	Intrahepatic cholelithiasis

TABLE 13.8. SOME CAUSES OF INCREASED CATECHOLAMINES

Patients can be screened for pheochromocytoma by analysis of a 24-hour urine sample for combined MN (normal 0.2 to 1.3 mg per 24 hours) and VMA. Normal values are shown in Table 13.9 . Urinary MN is the best single test. Urinary free catecholamines also can be useful; Duncan and associates (26) have shown that 24-hour urinary NE had a 100% sensitivity and a 98% specificity in a large group of hypertensive patients. An advantage of measuring urinary free catecholamines is that if E is present and NE is absent, the tumor is extremely likely to be located in an adrenal gland. These tests in combination are more than 95% accurate. The pattern most typical of malignant pheochromocytomas is elevated dopamine secretion, often with comparably high NE levels and low E secretions. This is because malignant pheochromocytomas often are deficient in dopamine ß-hydroxylase and phenylethanolamine N-methyltransferase.

	Adult (μg)	Infant and Child (Range μg/kg)
NE	80	0.4–1.6
E	25	0.02–1.6
VMA	8	83 ± 26
NMN	450	4.9–20.8
MN	300	3.1–15.6

[a]Catecholamine values for 24-hour urine collection.
E, epinephrine; MN, metanephrine; NE, norepinephrine; NMN, normetanephrine; VMA, vanilylmandelic acid.

TABLE 13.9. NORMAL VALUES FOR CATECHOLAMINES IN URINE[a]

Some authorities have recommended screening patients with an assay of plasma catecholamines. Bravo and Gifford (11) from The Cleveland Clinic have had excellent results with the plasma assay. The blood test also must be carefully done, with a supine and relaxed patient, and the laboratory must be experienced with the assay. In patients with equivocal values of plasma catecholamines, provocative testing may be necessary. Plasma catecholamines greater than 2,000 pg/mL are diagnostic of pheochromocytoma. If the catecholamine levels are between 1,000 and 2,000 pg/mL, clonidine suppression test (11) is performed. The principle behind this test is that in essential (neurogenic) hypertension, activation of the sympathetic nervous system results in an increase in plasma catecholamine. However, in patients with a pheochromocytoma, the increased catecholamines are due to the tumor itself, bypassing normal storage and release mechanisms. Therefore clonidine will not suppress catecholamine release in patients with a pheochromocytoma but will suppress catecholamine release in patients with essential (neurogenically mediated) hypertension. Following a 0.3-mg oral dose of clonidine, a 50% reduction in

plasma catecholamines and a catecholamine level less than 500 pg/mL is diagnostic of essential hypertension. However, postclonidine catecholamine levels greater than 500 pg/mL are indicative of pheochromocytoma. If resting plasma catecholamine levels are less than 1,000 pg/mL, a glucagon stimulation test is employed. Glucagon 2 mg is administered intravenously. One to three minutes later, a threefold increase in plasma catecholamine (greater than 2,000 pg/mL) is diagnostic of pheochromocytoma.

Localization of Pheochromocytomas

Once the diagnosis of pheochromocytoma has been made, it is necessary to localize the tumor for surgical planning. CT or MRI of the abdomen and pelvis are the best initial examinations (Fig. 13.12). These are performed because 97% of all tumors, including extraabdominal tumors, are located below the diaphragm. CT is widely available, is cost-effective, and can resolve masses as small as 1 cm. MRI is an alternative that requires no radiation exposure or intravenous contrast; however, it is more expensive. MRI has superior tissue characterization and, unlike benign adrenal adenomas, pheochromocytomas exhibit a high signal intensity on T_2-weighted images (37). MRI also avoids metallic clip artifact, which may be present on CT. Iodine-131-meta-iodobenzylguanidine scintigraphy is also an accurate method for anatomically and functionally characterizing pheochromocytomas (77,79) (Fig. 13.16). Its main advantage is the ability to image the whole body so that occult extraadrenal or metastatic disease may be identified. Its expense, limited availability, and diminished sensitivity restrict its utility. At present, it is a complementary study to CT or MRI in patients in whom there is a high suspicion of extraadrenal or metastatic disease.

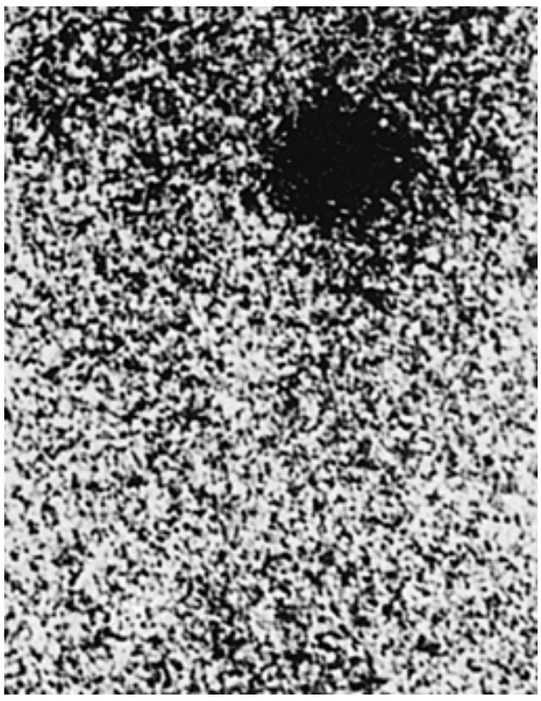

FIGURE 13.16. MIBG scan of a pheochromocytoma.

Treatment

The treatment of pheochromocytoma is surgical removal unless the operation is contraindicated. In the latter situations, medical therapy is indicated. In 10% of patients who have malignant pheochromocytomas, treatment should be governed by the basic principles of cancer management. The diagnosis is not frequently made preoperatively and may be difficult to confirm histologically. Tumors that invade adjacent structures or metastasize are considered malignant. Both α- and ß-adrenergic blocking agents and α-methyl-L-tyrosine (metyrosine, which blocks synthesis of NE by inhibiting tyrosine hydroxylase) all can be used to alleviate symptoms in patients with inoperable malignant pheochromocytomas.

The goal of perioperative medical management of the pheochromocytoma patient is to minimize cardiovascular morbidity. Preoperative α-blockade is indicated for 2 to 3 weeks to control the blood pressure and to facilitate intravascular volume expansion. Oral phenoxybenzamine is widely used, although some groups prefer a shorter-acting agent such as prazosin. Calcium channel blockers (verapamil SR, nifedipine XL) also are used. Advantages of calcium channel blockers include normalization of blood pressure without any of the side effects of chronic α-blockade. There is no orthostatic or “overshoot” hypotension. Furthermore, calcium channel blockers may prevent catecholamine-induced vasospasm and myocarditis. At The Cleveland Clinic, calcium channel blockers are the drug of choice for preoperative preparation of patients with pheochromocytoma. If additional control of hypertension is necessary, we add selective α_1-blockade with prazosin. ß-Blockade is indicated to treat cardiac arrhythmias or tachycardias, but only in patients with complete α-blockade. Propranolol should be avoided in patients with a history of bronchospastic disease because it causes bronchospasm. If a ß-blocker is indicated, low-dose metoprolol is more appropriate.

The other important aspect of preoperative preparation is volume repletion. Most patients with a pheochromocytoma are volume depleted due to catecholamine-induced vascular constriction. Whereas transfusion of whole blood was routine before 1985, it is now more appropriate to hydrate these patients aggressively with a combination of colloid and normal saline the night before surgery. Some groups also use adjunctive preoperative salt loading with a high-salt diet. These measures are integral to preventing hypotension following surgical removal of the tumor.

The surgical approach to pheochromocytoma is based on the size and anatomic location of the tumor. Large pheochromocytomas are removed through an anterior transperitoneal or a thoracoabdominal incision. With the availability of improved localization techniques, it is no longer necessary

to explore the abdomen routinely in patients with pheochromocytoma. Therefore, in select patients with a small adrenal tumor and no evidence of extraadrenal disease or multiple tumors, a unilateral extraperitoneal surgical approach may be used (21,46). Laparoscopic adrenalectomy is also currently being performed in some of these cases. Intensive intraoperative hemodynamic monitoring and the availability of rapidly acting vasoactive agents are essential to managing hypertension related to manipulation of the tumor. The anesthetic agent of choice is enflurane, which does not stimulate catecholamine secretion or increase catecholamine-induced cardiac variability. Intraoperatively, one may be faced with hypertensive crises before and during tumor removal, and hypotension following removal of tumor. To manage the hypertensive crisis, phentolamine or sodium nitroprusside may be employed. Bolus diffusion of esmolol, a ß-blocker, is especially helpful if phentolamine or sodium nitroprusside affords insufficient control. For hypotension, norepinephrine (4 to 8 mg in 500 mL normal saline) can be used judiciously.

After the tumor is removed, significant hypotension may occur as a result of arterial and venous dilation secondary to catecholamine withdrawal. This situation can be compounded by prior α-blockade or inadequate volume repletion. The primary treatment of choice is volume replacement with crystalloid; pressors should be administered only when volume expansion does not correct the hypotension. Hypoglycemia is another complication that can occur postoperatively and may manifest as hypotension resistant to volume repletion or vasopressors. The blood glucose level should routinely be checked in the postoperative period, and if hypoglycemia is identified, appropriate replacement therapy should be administered.

After removal of a pheochromocytoma, the blood pressure response depends on whether the patient's hypertension was sustained or paroxysmal. Only 75% of patients with sustained hypertension remain normotensive after surgery, whereas 95% of patients with paroxysmal hypertension remain normotensive. The presence of concomitant essential hypertension is the most common reason for treatment failure; however, the possibility of undiagnosed multicentric disease should be aggressively evaluated and ruled out. Long-term follow-up of all patients is important because recurrent or metastatic disease may develop many years postoperatively. Annual measurement of the blood pressure and plasma or urinary catecholamine levels should be used to follow these patients.

We recently reviewed the experience with surgical management, complications, and treatment outcome of histologically confirmed pheochromocytoma in 113 patients at The Cleveland Clinic (84). There were no surgical mortalities. Average length of stay in the intensive care unit was 1.2 days. There were only six major cardiovascular complications all of which occurred in patients who received preoperative medications, including five with α-blockade. Patients receiving no preoperative α-blockade required an average of 956 mL less in total intraoperative fluids, which approached statistical significance, and 479 mL less fluids on postoperative day 1, which was statistically significant. These findings suggest that preoperative α-adrenergic blockage is not essential in pheochromocytoma patients. In our experience, calcium channel blockers were just as effective and safer when used as the primary mode of antihypertensive therapy. These data also affirm that surgery for pheochromocytoma is safe in the modern era.

Malignant pheochromocytomas are difficult to diagnose histologically and often are resected incompletely because of metastases in the lung, liver, bone, or brain. There is no good chemotherapy. Streptozocin has limited antitumor activity. Treatment with cyclophosphamide, vincristine, and dacarbazine has resulted in some response (3). The metabolic effects of residual malignant pheochromocytoma can be ameliorated with phenoxybenzamine, propranolol, or α-methyl-L-tyrosine.

INCIDENTAL ADRENAL MASSES

Part of "13 - THE ADRENALS "

The incidental adrenal mass is a diagnostic and management dilemma created by the widespread availability of CT scanning (20). Such an “adrenaloma” or “incidentaloma” is a serendipitous finding in 0.3% to 5% of patients undergoing abdominal CT scanning. Most of these tumors (70% to 94%) are benign and biochemically inert (8,63). However, a small minority may be biochemically active or malignant. In this group, the most common abnormality is a Cushing's or pre-Cushing's syndrome in 0% to 18% of patients. Interestingly, in patients with a known extraadrenal malignancy, the autopsy incidence of adrenal metastases ranges from 8% to 38%.

Evaluation of an incidental adrenal mass should be limited and focused. A detailed history and physical examination, stool for occult blood, and a chest radiograph are mandatory. To look for occult malignancy, a mammogram may be performed in the female. Biochemical workup includes serum potassium, and 24-hour urine estimation for catecholamines, metanephrines, and urinary free cortisol. If there is any concern, a low-dose dexamethasone suppression may be performed. In hypertensive patients, a paired serum aldosterone level and an upright PRA should be obtained.

CT characteristics of adrenal masses that suggest malignancy include an irregular ill-defined margin, internal heterogeneity, and larger size. However, significant overlap and inconsistencies in these criteria have limited the diagnostic accuracy of CT scanning in the individual patient. In general, it is accurate to say that 90% of adrenal cortical carcinomas are larger than 6 cm in diameter, with adenomas rarely obtaining such large sizes (4,32,71,42).

However, size criteria per se, are weak and inconsistent discriminators between a benign and malignant adrenal

nodule. In Korobkin's (53) analysis of 135 adrenal masses, adenomas were smaller than nonadenomas (2.4 cm versus 4.5 cm); however, the authors emphasized that the considerable overlap between the two groups precluded identification of a highly specific threshold value. Kloos and colleagues (51) mentioned three patients with a 3- to 5-cm, biochemically inert adrenal mass, who were initially advised against an operation at an outside institution. Upon referral to the author's center 3 to 7 years later, these patients were found to have obviously progressed adrenal cortical carcinomas. Linos and Stylopoulos (57) reported three patients who were “incidentally found to have an adrenal cancer measuring 2.6 to 2.9 cm on CT.” An important factor to be considered when discussing adrenal mass size is the reported 20% to 40% CT scan underestimation of adrenal size when compared with their actual size on histopathology examination. CT densitometry has a higher sensitivity-to-specificity ratio. Using a threshold of 10 Hounsfield units, the sensitivity and specificity were 73% and 96%, respectively, for differentiating adenomas from nonadenomas (53).

Although, typically, MRI has been used to differentiate benign from malignant adrenal masses, one must be aware that an overlap of 20% to 30% exists. Compared with the liver or spleen, adenomas are usually isotense on T_1-weighted images and slightly hypertense or isotense on T_2-weighted images. Basically, adenomas change little in intensity from T_1- to T_2-weighted studies. In contrast, adrenal cancer is hypointense compared with liver-spleen on T_1-weighted and hyperintense on T_2-weighted images. Thus a mean signal intensity ratio between the adrenal mass and spleen of less than 0.8 indicates benign adenoma. However, hyperintensivity on MRI is not specific to adrenal carcinoma and can be seen with adrenal metastases, hemorrhage, neural tumors, or other retroperitoneal masses. More recently, chemical-shift MRI imaging was shown to detect a relative loss of signal intensity in 95% of adrenal adenomas compared with 0% of nonadenomas (62). It appears that future diagnostic algorithms may combine the accuracy of chemical-shift MRI and unenhanced CT densitometry for accurate nonoperative differentiation between adrenal adenomas and nonadenomas.

This critical decision when faced with an incidental adrenal mass is whether to perform surgical excision or continue with observation. Surgical excision is indicated for hormonally active masses, tumors 5 cm or larger, tumors with suspicious characteristics on CT or MRI, and masses that are documented to enlarge over time. Observation and periodic (every 6 to 12 months) radiographic follow-up are recommended for those who do not fall into one of the above categories.

Recently, several investigators have reported that a significant minority of patients with incidentally discovered adrenal masses have preclinical or subclinical functioning tumors with no clinical evidence of endocrinologic function, but they demonstrated autonomous cortisol production. Removal of these tumors results in improvement in hypertension, obesity, or diabetes in many of the patients (52,73).

The adrenal is also an extremely common site of metastatic lesions because of its intense vascular supply (6 to 7 mL/g per minute). In fact, adrenal metastatic lesions are more common than primary adrenal cancer. In the presence of a known extraadrenal malignancy, the chance that an adrenal mass is cancerous is approximately 8% to 38% (51). Fine-needle aspiration should be performed if a metastatic etiology is suspected. This can enable diagnosis of a metastatic adrenal lesion but is of limited value in delineating an adrenal adenoma from an adrenal cortical carcinoma (15). Surgical removal of the adrenal gland is indicated only if the adrenal represented the solitary site of metastatic disease.

ADRENOCORTICAL CARCINOMA

Part of "13 - THE ADRENALS "

Adrenocortical carcinoma is an uncommon disease, with only 80 to 130 cases per year in the United States (14). Approximately 50% of the tumors are endocrinologically functional. Cushing's syndrome, virilization, and feminization occur in 20%, 9%, and 3% of these patients, respectively, and primary hyperaldosteronism is present in less than 4% (39). Less than 30% of the tumors are localized to the adrenal gland at presentation. Surgical excision or debulking is the treatment of choice. Radiotherapy and chemotherapy have been disappointing, although approximately half of the patients will respond to mitotane for 10 to 12 months (61). Mean survival for localized disease is 5.0 years and for more extensive lesions is 2.3 years (9,18).

OPERATIVE APPROACHES TO THE ADRENAL GLANDS

Part of "13 - THE ADRENALS "

A wide spectrum of adrenal pathology may warrant surgical intervention. A variety of operative approaches are available for adrenal surgery. The optimal technique must be individualized according to the adrenal pathology, the patient's body habitus and surgical history, and the familiarity of the surgeon with each operative approach.

Posterior Approach

The posterior surgical approach to the adrenal gland was first described more than 50 years ago (89) and continues to find useful application in selected patients undergoing adrenalectomy. The advantages of this approach are that it is extraperitoneal and that adrenalectomy can be done with minimal disturbance of adjacent viscera. Anatomically, a posterior incision represents the most direct approach to the adrenal gland. Because no major muscles are transected, patient discomfort is generally minimal and early ambulation

is possible. If indicated, both adrenal glands can be exposed simultaneously through bilateral posterior incisions.

The major disadvantage of the posterior approach is the relatively small operative field, which restricts visualization and exposure of the great vessels. Therefore this approach should not be used to remove large adrenal lesions where wide exposure and early avascular control are necessary. This approach is also contraindicated in patients with a potentially malignant process, in whom an exploratory laparotomy must be done. Based on these limitations, the primary indication for posterior adrenalectomy is in patients with bilateral hyperplasia from Cushing's disease who have failed transsphenoidal hypophysectomy. This approach has also been used in the past to treat small benign adrenal lesions such as adrenal cortical adenomas causing hyperaldosteronism or Cushing's syndrome, and small adrenal pheochromocytomas; these small benign unilateral tumors are now being treated by laparoscopic adrenalectomy at many centers.

The posterior anatomic relation of the adrenal glands is illustrated in Fig. 13.17 . The pleural reflection extends below most of the eleventh rib and a variable portion of the medial aspect of the twelfth rib. The right adrenal gland lies more superiorly in the retroperitoneum than its counterpart on the left side. The left adrenal gland can usually be adequately approached posteriorly through the bed of the twelfth rib. The optimal incision for exposing the right adrenal gland is generally through the bed of the rib. In most cases, the location of the adrenal gland in relation to the ribs is known from preoperative imaging studies.

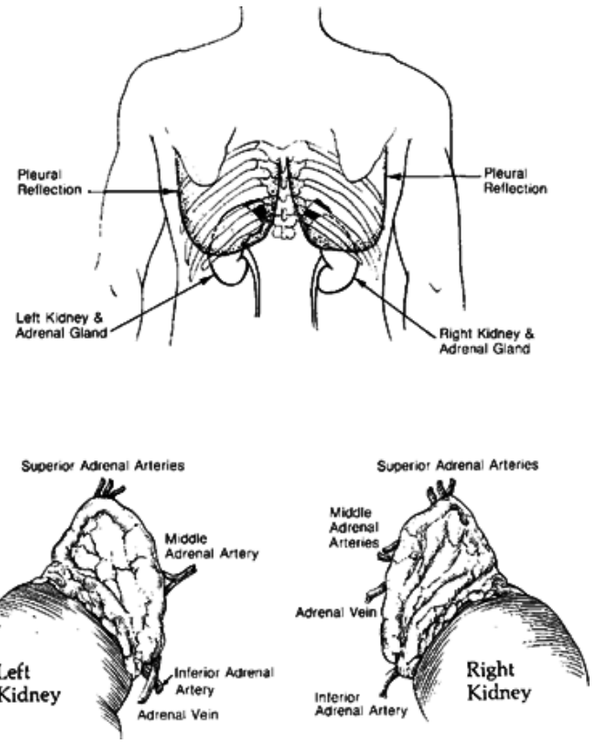

FIGURE 13.17. Sketch illustrating the posterior anatomic relations of the adrenal glands. (From Novic AC. Adrenal surgery. In: Novick AC, ed. *Stewart's operative urology,* 2nd ed. Baltimore: Williams & Wilkins, 1989, with permission.)

The patient is placed in the prone position on a laminectomy frame, which provides flexion at the hips and allows gentle dorsal curvature of the spine from the midthoracic to the lower lumbar levels. An oblique incision is made over the eleventh rib or twelfth rib and extended laterally almost to the midaxillary line (Fig. 13.18). The incision is developed to expose the entire length of the rib and the sacrospinalis muscle medially. The rib is resected subperiosteally, including as much of its medial aspect as possible to optimize exposure of the adrenal gland; such exposure also is facilitated by medial retraction of the sacrospinalis muscle. In operating through a twelfth rib incision, the diaphragm and pleura can readily be mobilized and retracted superiorly. However, in operating through an eleventh rib incision, attempting to mobilize the pleura superiorly may be tedious and can lead to one or more inadvertent pleural entries. In such cases, simply opening the pleural and diaphragmatic layers of the thoracic cavity in line with the incision can be done safely and provides excellent direct exposure of the adrenal gland (66,67). After the retroperitoneal space is entered, Gerota's fascia is incised

and the posterior surface of the kidney and adrenal gland is exposed.

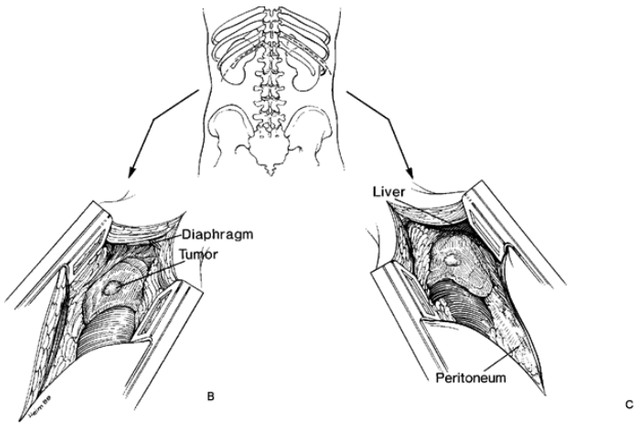

FIGURE 13.18. Sketch illustrating the posterior approach for adrenal surgery **(A),** through the eleventh rib on the right side **(C)** and through the twelfth rib on the left side **(B).** (From Novick AC. Surgery for primary hyperaldosteronism. *Urol Clin North Am* 1989;16:535, with permission.)

On the left side (Fig. 13.19), the attachment between the upper pole of the kidney and the inferior aspect of the adrenal gland is kept intact, so that gentle downward traction on the kidney can be done to enhance exposure. The apical vascular ligament is identified and transected between silver clips to deliver the gland more extensively into the operative field. The lateral borders of the gland are then freed, and the gland is retracted medially to expose its anterior surface. Care must be taken not to injure the pancreas, which lies just beneath the adrenal gland through this approach. The left adrenal vein is exposed as it courses downward just medial and anterior to the upper pole of the kidney to enter the left renal vein. The left adrenal vein is then ligated with 2-0 silk and divided. The upper stump of the vein can be left long and used as a handle for additional lateral traction on the gland. The inferior adrenal artery also is secured at this stage as it courses upward from the proximal aspect of the renal artery. Through use of lateral and upward traction, the left adrenalectomy is completed by securing and dividing the middle adrenal arteries as they course inward medially from the aorta.

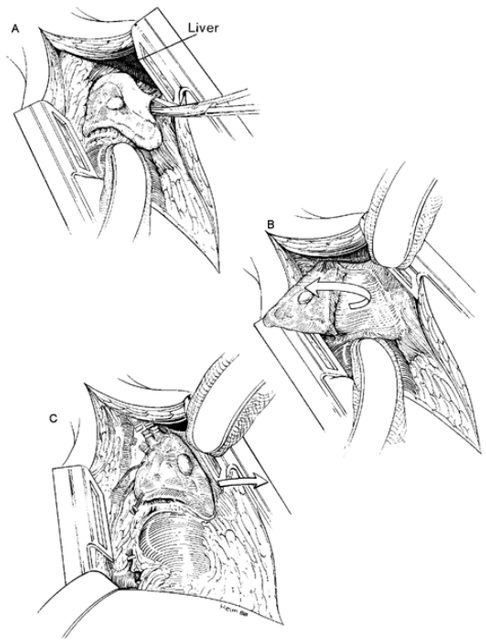

FIGURE 13.19. A–C: The technique of left adrenalectomy through a posterior incision. (From Novick AC. Surgery for primary hyperaldosteronism. *Urol Clin North Am* 1989;16:535, with permission.)

On the right side (Fig. 13.20), the kidney is retracted downward, and the liver is gently retracted upward to facilitate exposure of the adrenal gland. In some cases, the apex of the adrenal gland is adherent to the liver and must be carefully dissected free. The dissection is continued cephalad, and the apical vascular ligament is divided between silver clips. The lateral and inferior aspects of the gland are easily mobilized, and the dissection is carried around to expose the anterior surface medially to the level of the inferior vena cava. The gland is then returned to its normal anatomic position to expose the remaining inferior and medial vascular attachments. Gentle lateral traction on the gland is applied to facilitate identification, ligation, and division of the right adrenal vein. The remaining arterial supply is divided between silver clips to complete the removal of the right adrenal gland.

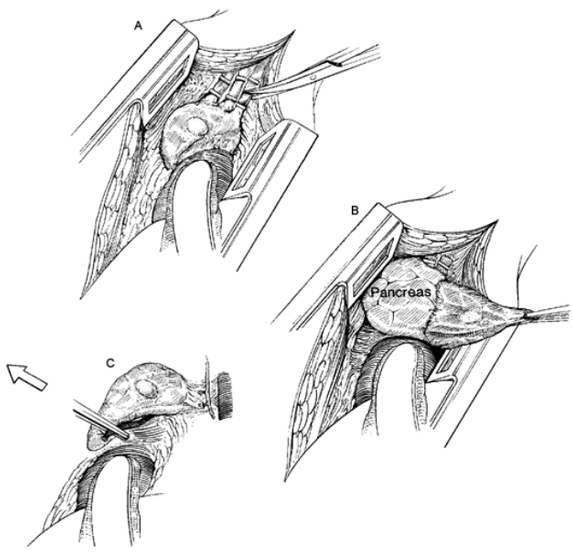

FIGURE 13.20. A–C: The technique of right adrenalectomy through a posterior incision. (From Novick AC. Surgery for primary hyperaldosteronism. *Urol Clin North Am* 1989;16:535, with permission.)

When adrenalectomy is completed, if a transthoracic incision has been used, the diaphragm is reapproximated with interrupted 2-0 silk mattress sutures. Airtight closure of the pleura is achieved using 3-0 silk or chromic sutures with the lung under positive-pressure expansion. Chest tube drainage is generally not necessary unless there has been difficulty in reapproximating the pleura. No surgical drains are used. A chest film is obtained several hours postoperatively in the recovery room to verify that the lung is fully expanded. Incisional discomfort with this approach

is mild, and ambulation is generally possible on the day after surgery.

Flank Approach

The extraperitoneal flank approach is an alternative to the posterior approach for removal of relatively small benign unilateral tumors. The flank approach has the advantage of relative simplicity and familiarity to the urologic surgeon. Also, in particularly obese patients, exposure of the adrenal gland through a posterior incision may be compromised; in such cases, the use of a generous extraperitoneal flank incision is preferable for performing adrenalectomy.

When an extraperitoneal flank adrenalectomy is performed, either the twelfth or the eleventh rib is resected to allow entrance to the retroperitoneal space. Alternatively, the retroperitoneum can be entered through an incision in the tenth or eleventh intercostal space. A classic subcostal flank incision is not recommended because of the difficulty in obtaining adequate superior exposure of the adrenal gland.

On the right side (Fig. 13.21), the colon and duodenum are reflected medially, and the liver is reflected upward to expose the kidney and adrenal gland. The kidney with its attached adrenal gland is retracted downward. The anterior, posterior, and apical aspects are mobilized by blunt dissection from the undersurface of the liver posteriorly and from the duodenum and hepatic flexure of the colon anteriorly. The apical attachments of the gland are then divided between silver clips. With the gland retracted laterally, small arterial branches entering the medial aspect of the gland are identified as they course beneath the vena cava. Branches of the inferior adrenal artery coursing upward from the proximal right renal artery are similarly identified. After these

vessels have been secured and transected, the right adrenal veinis located, secured, and divided. Residual apical vascular branches are then similarly secured and transected to complete the adrenalectomy.

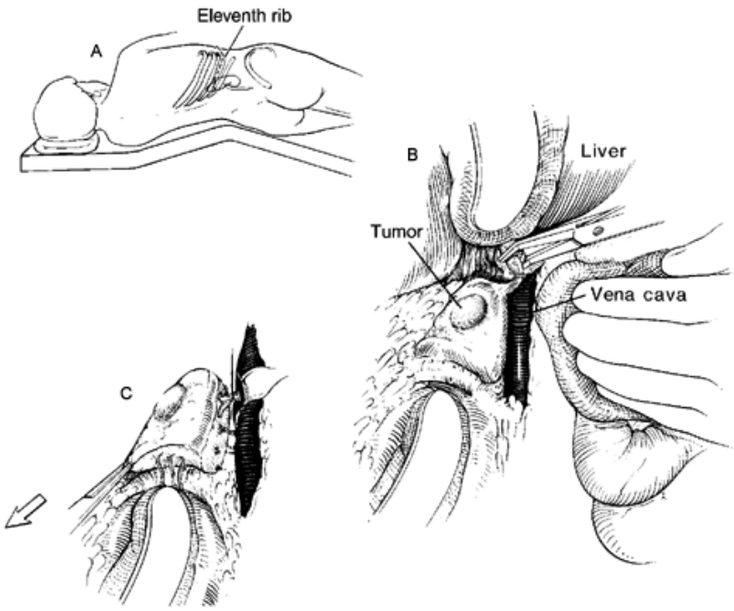

FIGURE 13.21. A–C: The technique of right adrenalectomy through an eleventh rib flank incision. (From Novick AC. Surgery for primary hyperaldosteronism. *Urol Clin North Am* 1989;16:535, with permission.)

Anterior Transabdominal Approach

The anterior transabdominal approach is indicated for adrenal lesions that are either large or potentially malignant. These include suspected or proven adrenal cortical carcinomas, large adrenal cortical adenomas, and large adrenal pheochromocytomas. In these cases, wide exposure is necessary, which cannot be achieved to the same extent through an extraperitoneal incision. With potentially malignant adrenal masses, intraabdominal inspection of other organs for metastatic disease is required. An anterior approach is also mandatory for adrenal malignancies that involve the inferior vena cava (74). The optimal anterior approach is through a bilateral subcostal or chevron incision, which provides much better exposure of the superior and lateral aspects of the adrenal gland than a midline incision. A unilateral extended subcostal incision can be used if the patient is thin and only one adrenal gland needs to be exposed. A vertical midline incision is used only if an extraadrenal pheochromocytoma is suspected in the retroperitoneum along the great vessels or in the pelvis.

The main advantage of the transabdominal approach is that it provides excellent exposure of both adrenal glands, the vascular pedicles, the abdominal organs, and the retroperitoneum. Its principal disadvantage is that the peritoneal cavity is entered. It is not the most direct avenue to the adrenal glands, and in an obese patient, exposure may be more difficult. Postoperative morbidity is higher than with extraperitoneal approaches because of an increased incidence of ileus, atelectasis, and incisional discomfort.

The patient is placed with a rolled sheet beneath the lumbar spine, and a unilateral extended subcostal or bilateral subcostal incision is made to enter the peritoneal cavity (Fig. 13.22). On the right side, the posterior peritoneum lateral to the ascending colon is incised, the colon and the duodenum are reflected medially, and the liver is retracted superiorly to expose the kidney and adrenal gland. The kidney is gently retracted downward to bring the anterior surface of the right adrenal gland into view. In most cases, it is necessary to release the upper margin of the gland from the liver with sharp dissection to obtain complete exposure. In cases of pheochromocytoma, it is important to secure the adrenal vein as soon as possible to interrupt catecholamine release from the tumor into the systemic circulation. If the vein lies far cephalad, as it often does, division of the arterial supply medially and inferiorly may be necessary before the vein can be exposed satisfactorily and safely. Surgical exposure is facilitated by medial retraction of the inferior vena cava. In cases of suspected malignancy, it is also best to isolate the medial blood supply first and to carry out the lateral dissection later. For tumors confined to the adrenal gland, after the blood supply has been secured, the remaining lateral and inferior attachments of the gland are mobilized and divided to complete the adrenalectomy.

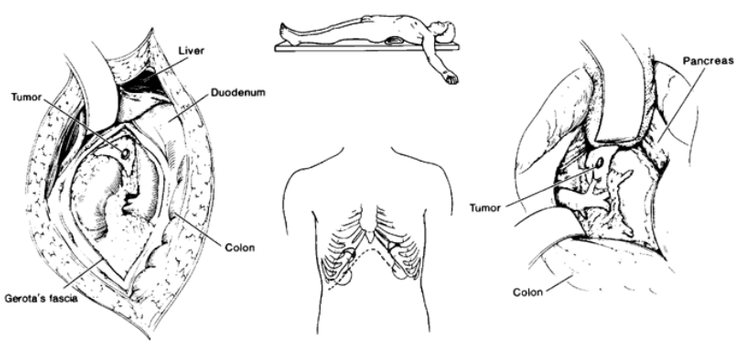

FIGURE 13.22. Anterior transabdominal approach to the adrenal glands. (From Guz B, Straffon R, Novick AC. Operative approaches to the adrenal gland. *Urol Clin North Am* 1989;16:527, with permission.)

On the left side, the adrenal gland is exposed by incising the posterior peritoneum lateral to the descending colon and dividing the ileorenal ligament with medial retraction of the colon and superior retraction of the spleen. The left adrenal vein is identified at its entry into the left renal vein

and is then ligated and divided. The inferior adrenal artery also is secured and divided at this time. The adrenal gland is mobilized posteriorly and laterally by blunt dissection. The gland is then retracted downward to expose the superior vascular attachments, which are secured and divided. The gland is then retracted laterally to expose the remaining medial arterial blood supply, which is secured and divided. Residual attachments of the gland to the upper pole of the kidney are divided into sharp dissection to complete the adrenalectomy.

In some cases, an adrenal malignancy may invade the upper pole of the kidney. In this event, radical en bloc removal of both the kidney and adrenal gland within Gerota's fascia is the indicated procedure (Fig. 13.23). The main renal artery and vein are secured and divided in sequence, as in a radical nephrectomy; the ureter also is secured and divided. A plane is then developed posteriorly along the psoas muscle, bluntly mobilizing both the kidney and adrenal mass from behind and laterally. With downward and lateral retraction on the kidney, the medial blood supply to the tumor mass can be better identified. This exposure is facilitated by medial retraction of the vena cava. The medial adrenal arteries are secured and transected. On the right side, as the dissection proceeds upward, the adrenal vein also is identified, secured, and divided. This vein is large and friable, often lies higher than the surgeon expects, and must be carefully dissected free from surrounding structures to prevent avulsion from the vena cava. Should such an avulsion occur, the caval entry is immediately secured with Allis clamps and the defect is oversewn with a continuous 5-0 arterial suture. After the blood supply is secured, the dissection is carried upward and laterally to completely remove the tumor mass and kidney en bloc within Gerota's fascia. A regional lymphadenectomy is then performed from the level of the inferior mesenteric artery to the crus of the diaphragm. Splanchnic nerves and celiac ganglia may be sacrificed if adjacent nodes appear involved by neoplasm.

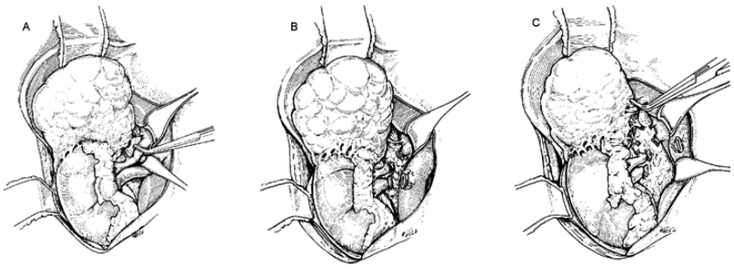

FIGURE 13.23. A–C: Technique of radical nephroadrenalectomy on the right side. (From Novic AC: Adrenal surgery. In Novick AC, ed. *Stewart's operative urology,* 2nd ed. Baltimore, Williams & Wilkins, 1989, with permission.)

Thoracoabdominal Approach

The thoracoabdominal approach to the adrenal gland is desirable for very large tumors that cannot be removed safely through an anterior transabdominal incision. It can be particularly advantageous for large right-sided adrenal masses, where the overlying liver and vena cava can limit exposure. There is less indication for this incision on the left side because the spleen and pancreas usually can be elevated away from the adrenal without difficulty. The thoracoabdominal incision provides excellent exposure of the suprarenal area (17,75); however, exposure of the contralateral adrenal is more difficult than with the anterior approach. Additional operative time is required to open and close a thoracoabdominal incision. Because the thoracic cavity is entered and the diaphragm divided, potential pulmonary morbidity is greater. For these reasons, the thoracoabdominal approach is reserved for patients in whom exposure beyond that provided by an anterior subcostal incision is considered important for complete and safe tumor removal.

The patient is placed in a semioblique position with a rolled sheet inserted longitudinally between the flank and hemithorax (Fig. 13.24). The incision is begun in the eighth or ninth intercostal space near the angle of the rib and is carried medially across the umbilicus. The intercostal muscles are divided to reveal the pleura and diaphragm; the diaphragm is divided circumferentially. On the right side, the hepatic flexure of the colon and duodenum are reflected medially and the liver is retracted upward to expose the adrenal tumor. On the left side, the descending colon is reflected medially with superior retraction of the pancreas

and spleen to expose the adrenal gland. The details of adrenalectomy or nephroadrenalectomy are the same as those described for the anterior transabdominal surgical approach.

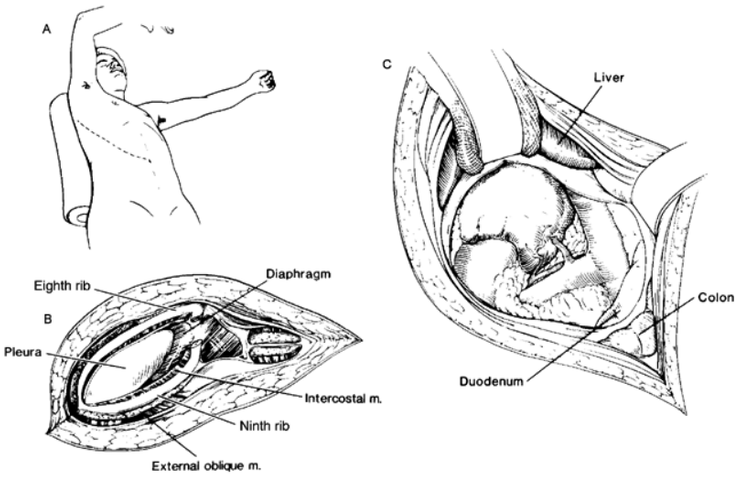

FIGURE 13.24. A–C: Thoracoabdominal approach to the adrenal gland. (From Guz B, Straffon R, Novick AC. Operative approaches to the adrenal gland. *Urol Clin North Am* 1989;16:527, with permission.)

Laparoscopic Adrenalectomy

Laparoscopic adrenalectomy was initially described by Gagner and colleagues in 1992. Since then, the rapid advances in minimally invasive surgery have led to laparoscopy becoming the technique of choice for many surgical adrenal disorders. Advantages of the laparoscopic approach include a shorter hospital stay, less postoperative pain, decreased patient morbidity, more rapid patient recovery, and a superior cosmetic result.

Several studies have confirmed the safety and efficacy of laparoscopic adrenalectomy for benign adrenal disorders such as (a) primary aldosteronism (36,38,88), (b) Cushing's disease or Cushing's syndrome due to an adrenal adenoma (27,38,55), or (c) other benign lesions such as a cyst or myelolipoma. Other indications have included small nonfunctioning adrenal masses with radiographic features suspicious for malignancy, small solitary adrenal metastases, and small adrenal pheochromocytomas (28,47). Laparoscopic adrenalectomy is currently contraindicated in large pheochromocytoma or clinical overt adrenal cortical carcinomas. As an extension of the latter, any radiographic evidence of local tumor invasion, venous extension, or lymphadenopathy would definitely contraindicate a laparoscopic approach.

Laparoscopic adrenalectomy can be performed by either a transperitoneal or lateral retroperitoneal approach. In a recent prospective, but as yet unpublished study, Gill compared these two approaches and found no advantage for the extraperitoneal approach in this setting. Most centers currently employ the transperitoneal approach for laparoscopic adrenalectomy. The availability of 2-mm instrumentation and camera technology has led to the emergence of needlescopic surgery. Data from our group (36) have shown that needlescopic adrenalectomy is feasible and does offer some advantages over conventional laparoscopic adrenalectomy. A description of the technique of needlescopic adrenalectomy follows.

The patient is secured in the flank (lateral decubitus) position with the table flexed and the kidney bridge elevated. With the use of the closed (puncture) technique, a needlescopic (2 mm) port, with *in situ* Veress needle introducer, is inserted into the abdomen just below the costal margin in the anterior axillary line (for a right adrenalectomy) or at the lateral border of the rectus muscle (for a left adrenalectomy). Proper intraperitoneal placement of the tip of the Veress needle is evaluated by the routine saline

suction-injection-suction technique. Carbon dioxide pneumoperitoneum is established (15 mm Hg). The 2-mm port assembly is advanced an additional 2 cm into the abdomen, and the Veress needle introducer is removed. A 1.9-mm needlescopic inserted through the 2-mm port visually confirms safe intraperitoneal access. Under needlescopic guidance, a 10/12-mm trocar sheath is placed into the peritoneal cavity at the superior crease of the umbilicus. The needlescope is removed and a 10-mm, 45-degree laparoscope is inserted through the umbilical port. Two additional secondary trocars, whose location varies depending on the side of the adrenalectomy, are inserted under visualization of the 10-mm laparoscope: (a) for a right adrenalectomy, a 2-mm port is located lateral to the xiphoid at the costal margin and a 5 mm port at the lateral border of the rectus muscle, 2 cm below the costal margin; (b) for a left adrenalectomy, a 2-mm port is located at the midaxillary line and a 5-mm port is located at the midclavicular line, both at the costal margin.

Right Needlescopic Adrenalectomy

The surgeon works through the lateral 2-mm port and the 5-mm port, whereas the assistant works through the medial 2-mm port (Fig. 13.25). The procedure is initiated under visualization by the 10-mm, 45-degree laparoscope placed through the umbilical port. The assistant retracts the liver cephalad with a 2-mm grasper placed through the medial 2-mm port; extreme care must be taken to avoid injury to the gall bladder and liver during this maneuver. With the use of 5-mm scissors, introduced through the 5-mm trocar, the triangular ligament of the liver is incised; this allows more secure cephalad retraction of the liver by the 2-mm grasper. The posterior parietal peritoneum is incised parallel to, and 1 cm below, the inferior edge of the liver. Located between the liver and the hepatic flexure of the colon, this horizontal peritoneal incision extends from the paracolic gutter laterally up to the inferior vena cava medially. With the use of a 2-mm grasper, inserted through the lateral 2-mm port, the incised edges of the peritoneum are retracted, and the adrenal gland is identified in the retroperitoneum.

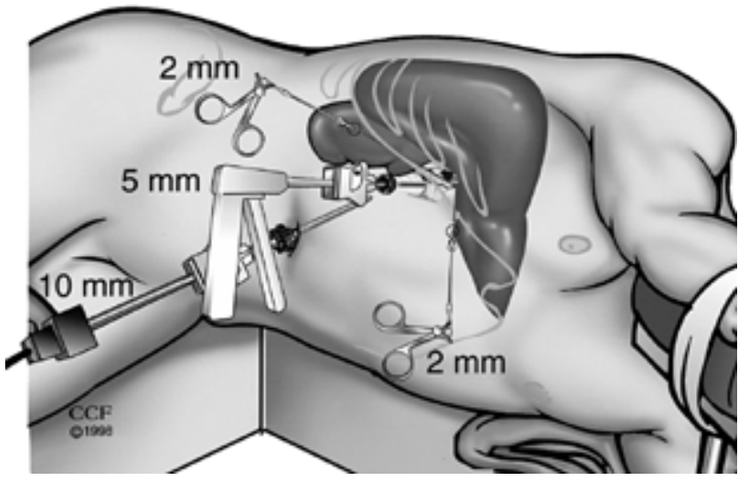

FIGURE 13.25. Needlescopic right adrenalectomy: port placement. Note that the 10-mm, 45-degree laparoscope is placed at the umbilicus. (From Gill IS, Soble JJ, Sung GT, et al. Needlescopic adrenalectomy—the initial series: comparison with conventional laparoscopic adrenalectomy. *Urology* 1998;52:180, with permission.)

Dissection is performed between the medial border of the adrenal gland and the inferior vena cava. This step is facilitated by lateral retraction of the adrenal gland and surrounding adipose tissue by the 2-mm grasper placed through the lateral 2-mm port (Fig. 13.26). Dissection along the right lateral edge of the inferior vena cava brings the main right adrenal vein into view. A 5-mm clip-applier, introduced through the 5-mm port, is used to secure the adrenal vein, which is then divided (Fig. 13.26). At this point in the dissection, the psoas muscle can be visualized through the laterally retracted adrenal gland and the inferior vena cava, signifying the posterior extent of the dissection.

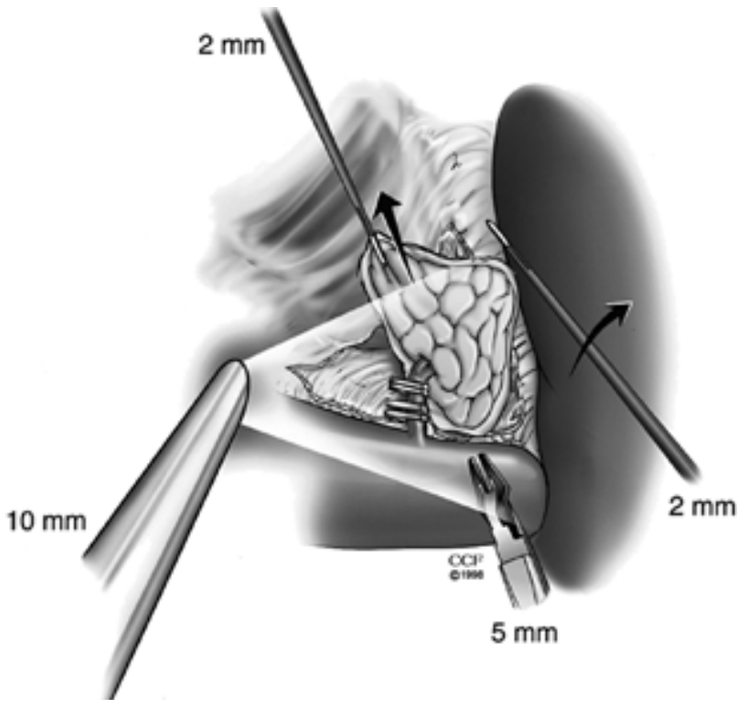

FIGURE 13.26. Needlescopic right adrenalectomy: dissection between the adrenal gland and the inferior vena cava brings the main adrenal vein into view. Care must be taken while retracting the liver cephalad with the 2-mm instrument. The main adrenal vein is clip-ligated by a 5-mm clip-applier inserted through the 5-mm subcostal port. Note that visualization is provided by the 10-mm, 45-degree laparoscope placed at the umbilicus. (From Gill IS, Soble JJ, Sung GT, et al. Needlescopic adrenalectomy—the initial series: comparison with conventional laparoscopic adrenalectomy. *Urology* 1998;52:180, with permission.)

Dissection proceeds along the superomedial border of the adrenal gland, where adrenal branches from the inferior phrenic vessels are clip-ligated and divided. After the superior edge of the adrenal gland is completely freed, the

adrenal gland is retracted anteromedially, placing its inframedially and inferior attachments on gentle retraction. With the use of a combination of hook-blade electrocautery and the 5-mm clip-applier, small adrenal branches from the renal artery and vein are secured, and the adrenal gland is mobilized meticulously from the superior aspect of the renal hilum. The avascular plane between the upper pole of the kidney and the adrenal is developed, thus mobilizing the inferior edge of the adrenal gland. The tail of the adrenal gland is freed, completely excising the specimen.

The 10-mm laparoscope is now removed, and the needlescope is introduced through the medial 2-mm port. A plastic bag is inserted through the umbilical port, and under needlescopic visualization, the specimen is entrapped and extracted intact from the umbilicus. After confirming hemostasis, fascial closure of the umbilical port is performed and all ports are removed under needlescopic visualization. The umbilical incision and the 5-mm port-site incision are closed with subcuticular sutures. Each 2-mm port-site puncture hole is closed with a single Steri-Strip.

Left Needlescopic Adrenalectomy

The surgeon works through the medial 2-mm port and the 5-mm port, whereas the assistant works through the lateral 2-mm port. The main differences in a left adrenalectomy include mobilization and medial retraction of the splenic flexure and descending colon, cephalad retraction of the spleen, and control of the left main adrenal vein. Although virtually no colonic mobilization is required during a right adrenalectomy, performance of a left adrenalectomy requires incision of the line of Toldt and formal mobilization of the splenic flexure and part of the descending colon. The splenocolic, splenorenal, and splenophrenic ligaments are incised to completely mobilize the spleen in a medial and cephalad direction. Occasionally, for a larger adrenal mass, the tail of the pancreas must be mobilized off the anterior surface of the adrenal gland.

Dissection along the superior border of the left renal vein identifies the left main renal vein (Fig. 13.27). Clip-ligation of the main adrenal vein is performed with 5-mm clip-appliers (Fig. 13.28). Many aortic branches to the adrenal vein are clip-occluded and divided to free the adrenal gland.

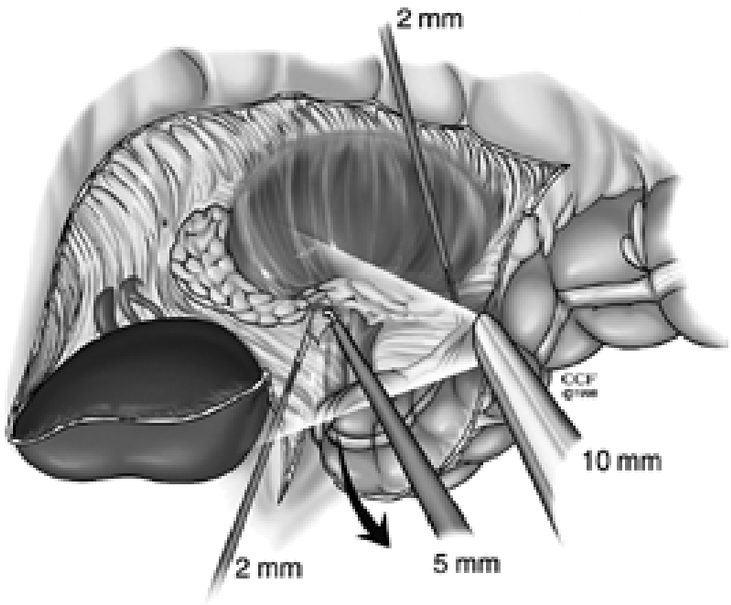

FIGURE 13.27. Needlescopic left adrenalectomy: identification of the left main adrenal vein. Note the T-incision along the line of Toldt. If adequate mobilization of the spleen is performed initially, the spleen stays retracted away from the operative site by gravity alone. Care must be taken while retracting the spleen and colon with 2-mm instruments. (From Gill IS, Soble JJ, Sung GT, et al. Needlescopic adrenalectomy—the initial series: comparison with conventional laparoscopic adrenalectomy. *Urology* 1998;52:180, with permission.)

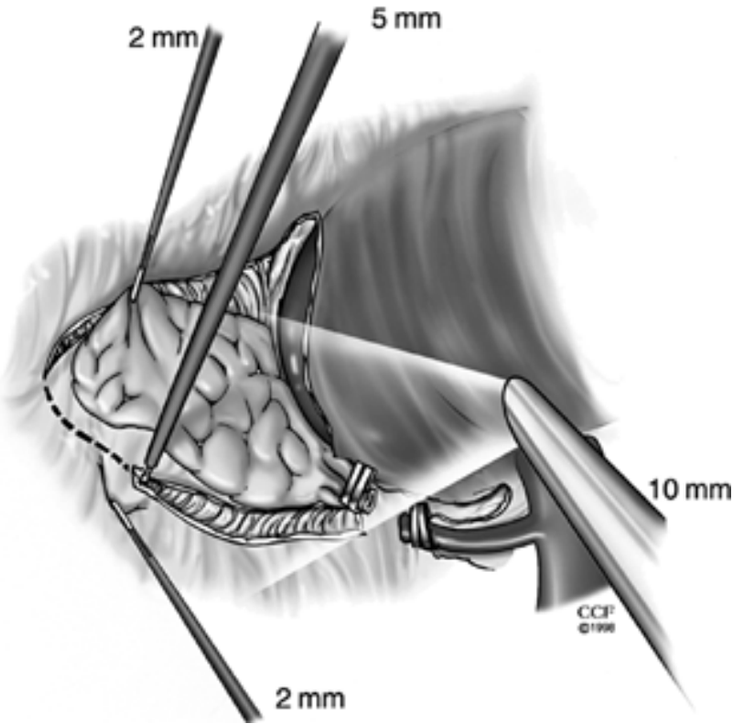

FIGURE 13.28. Needlescopic left adrenalectomy: clip-ligation of the main adrenal vein with 5-mm clip appliers. (From Gill IS, Soble JJ, Sung GT, et al. Needlescopic adrenalectomy—the initial series: comparison with conventional laparoscopic adrenalectomy. *Urology* 1998;52:180, with permission.)

During needlescopic adrenalectomy, visualization is provided by the 10-mm 45-degree laparoscope placed through an umbilical 10/12-mm trocar. From a cosmetic standpoint, the umbilicus is the optimal location to “hide” the mandatory 2- to 3-cm skin incision ultimately required for intact extraction of the excised adrenal gland. Our experience has shown that the diminished trauma of access by the needlescopic technique results in diminished port-site pain, and a superior cosmetic result (Fig. 13.29) (36). Currently, at our center, the needlescopic approach is the technique of choice when performing transperitoneal endoscopic adrenalectomy, except in patients with marked obesity or large

adrenal tumors. In the latter settings, a conventional laparoscopic technique is employed with four 10/12-mm trocar sheets placed along the costal margin. The primary port is placed by the closed (Veress needle) technique, and the three secondary ports are inserted under laparoscopic guidance. The technique of laparoscopic adrenalectomy is otherwise similar to the needlescopic technique.

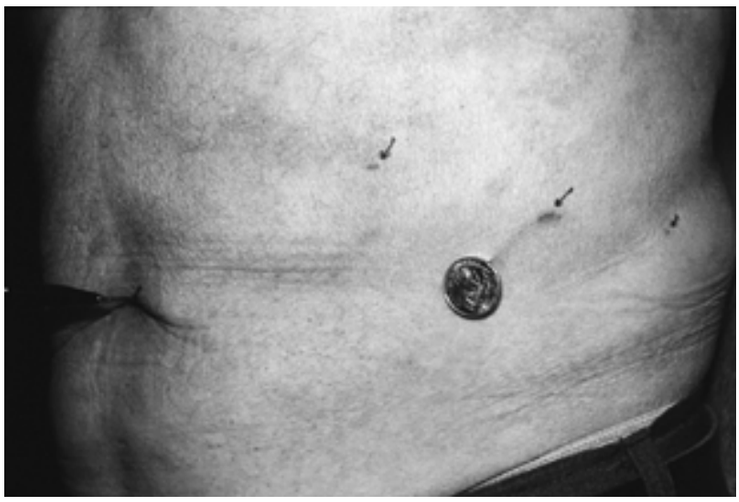

FIGURE 13.29. Patient photograph 2 weeks after needlescopic left adrenalectomy. The port-site skin incisions *(arrows)* are barely visible. (From Gill IS, Soble JJ, Sung GT, et al. Needlescopic adrenalectomy—the initial series: comparison with conventional laparoscopic adrenalectomy. *Urology* 1998;52:180, with permission.)

Recent studies also have shown that needlescopic adrenalectomy is less expensive than the open approach (43) and can be performed on an outpatient basis in select patients (34).

In a recent retrospective study, the results of laparoscopic/needlescopic adrenalectomy were compared with those of open adrenalectomy in 210 patients at The Cleveland Clinic Foundation (35). Laparoscopic/needlescopic adrenalectomy was performed in 110 patients from March 1996 through November 1998. Open adrenalectomy was performed in 100 patients from May 1987 through March 1996. Detailed data are outlined in Table 13.10 . There was no significant difference in operative time and the mean specimen weight was similar in the two groups. The laparoscopic/needlescopic approach was clearly advantageous with respect to less blood loss, reduced narcotic analgesic requirements, earlier postoperative oral intake, and a reduced hospital stay. Currently, needlescopic adrenalectomy is currently being performed as an outpatient procedure in many patients (34). Additional recent data from our group have demonstrated that needlescopic adrenalectomy has a reduced overall cost compared with open adrenalectomy (43). Based on data such as these, laparoscopic/needlescopic adrenalectomy is emerging as the standard of care for many patients with surgical adrenal disease.

TABLE 13.10. CLEVELAND CLINIC EXPERIENCE WITH LAPAROSCOPIC VERSUS OPEN SURGICAL ADRENALECTOMY

	Laparoscopic[a] (n = 110)	Open[a] (n = 100)	
Specimen weight (g)	29	28.6	
Surgical time (min)	188	218	
Blood loss (mL)	125	563	$p = .0001$
Narcotics (mg)	38	471	$p = .0001$
Oral intake (days)	1.0	3.2	$p = .0001$
Hospital stay (days)	1.9	7.6	$p = .0001$

[a]Mean values.
From Gill IS, Schweizer D, Nelson D, et al. Laparoscopic vs open adrenalectomy: Cleveland Clinic experience with 210 cases. *J Urol* 1999; 161:21.

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14

THE KIDNEY

W. Scott McDougal

W.S. McDougal: Department of Urology, Harvard Medical School; Massachusetts General Hospital, Boston, MA 02111.

Contents

RENAL ANATOMY

Part of "14 - THE KIDNEY "

The renal parenchyma is divided into an outer cortical zone and an inner medullary area. The medulla is subdivided into inner and outer portions, the former containing the 4 to 12 renal papillae. Each papilla is surrounded by transitional cell epithelium, the complex referred to as a *calyx.* It drains into an infundibulum, and the infundibula join one to another and then to the renal pelvis. A detailed knowledge of the calyceal anatomy is important, because endoscopic location of lesions within the kidney requires the ability to identify, on the two-dimensional roentgenogram, the location of the calyx in which the lesion is present and to correlate it with the gross anatomy of the kidney when visualizing the infundibula from the renal pelvis. The calyces located in the upper and lower poles often are compound and project directly to their respective poles. The remainder are arranged into an anterior and posterior row (Fig. 14.1). The anterior row of calyces forms an angle 70 degrees to the frontal plane; these are the calyces visualized laterally on an anteroposterior (AP) view of an intravenous (IV) urogram. The posterior calyces form a 20-degree angle with the frontal plane and are those visualized medially on the urogram (Fig. 14.2).

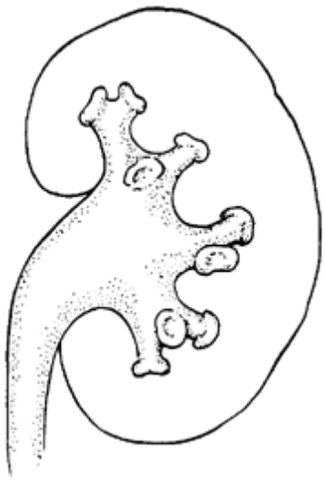

FIGURE 14.1. Calyceal anatomy. The polar calyces project to their respective poles while the middle calyces form an anterior and posterior row.

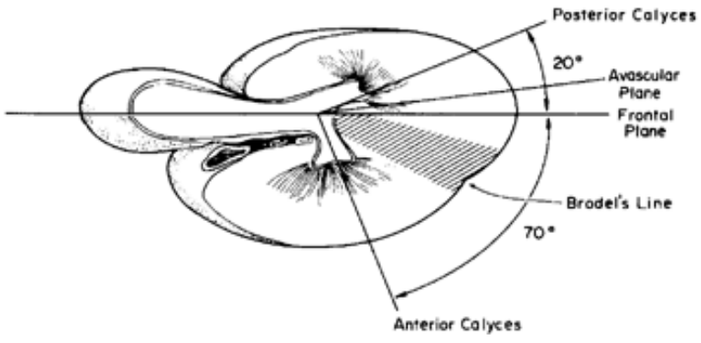

FIGURE 14.2. Location of anterior and posterior calyces. Notice that the anterior calyces form a 70-degree angle with the frontal plane and the posterior calyces a 20-degree angle with that plane. The avascular plane adjacent to Brödodel's line, through which the calyces may be entered without violating segmental vasculature, is depicted.

Segments of the cortex and medulla are served by end arteries, that is, arteries that do not anastomose with other arteries and therefore have little potential for the development of collateral vessels. The segments of the kidneys are the two polar, the anterosuperior, the anteroinferior, and the posterior (Fig. 14.3). The first main branch off the renal artery serving the renal parenchyma supplies the posterior segment. Thus location of this artery allows for identification of the subsegmental anatomy of the kidney. It allows identification of the avascular plane, adjacent to

Brödodel's line between the anterior and posterior segments, along which the kidney may be split and calyces entered through the parenchyma without violation of the blood supply to segments of the parenchyma (Fig. 14.2). The arteries branch from the main renal artery into, successively, the interlobar; arcuate; interlobular; and afferent, glomerular, and efferent arterioles. The efferent arterioles supply the proximal tubule from the glomerulus in the cortex from which it arose, and supply the proximal tubule and Henle's loop when it arises from a juxtamedullary glomerulus. The venous drainage follows the arterial supply; however, unlike the arteries, veins intercommunicate between the segments.

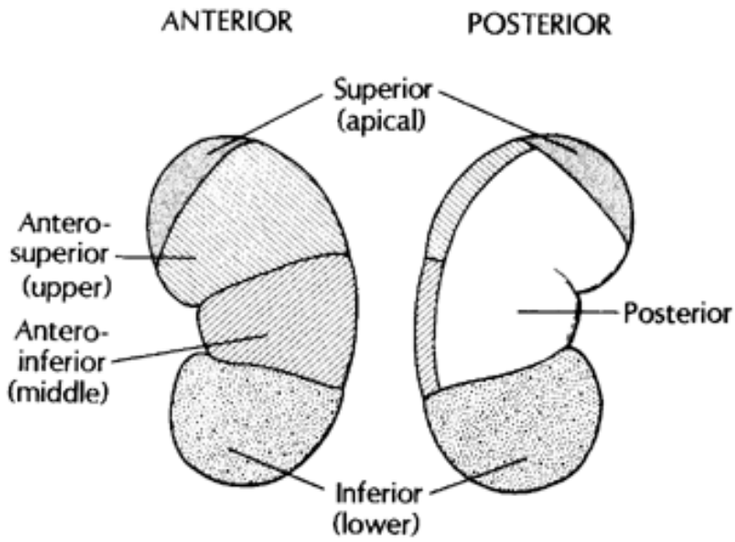

FIGURE 14.3. Segmental anatomy of the kidney. There are five segments: superior, inferior, posterior, anterosuperior, and anteroinferior.

There are two types of lymphatic networks in the kidney: a superficial system that drains the capsule and a deeper system that drains from the hilum (5). Lymphatic vessels in the kidney follow the arterial vessels from interlobular arteries proximally. The exact course of the lymphatic vessels distal to the interlobular arteries is not known. It has been suggested that the medulla contains few if any lymphatic vessels, whereas the cortex may be drained by regional areas from lymphatic vessels that actually do not penetrate deeply into the parenchyma (59). The renal capsule is supplied richly by lymphatic vessels. Capsule lymphatic vessels and parenchyma lymphatic vessels drain to the renal hilum and from there to the great vessel closest to the respective kidney.

The kidneys are supplied by sympathetic nerves from T4 to L4, which course to the celiac, superior, and inferior mesenteric and aorticorenal ganglia. The postganglionic fibers course to the renal hilum and then to the renal parenchyma. Once in the renal parenchyma, they travel with the vessels, eventually making contact with the juxtaglomerular apparatus and the basement membranes of the proximal and distal tubule cells. Innervation of the glomerulus is controversial. Stimulation of these nerves causes vasoconstriction and a short-term reduction in renal blood flow (RBF). Denervation of the kidney results in an increase in electrolyte excretion primarily caused by a diminished proximal tubule fractional reabsorption.

The hilum of the kidney contains the renal vessels, renal nerves, lymphatic vessels, lymph node tissue, and renal pelvis. The renal capsule extends to the renal sinus and incorporates it into the kidney proper.

There are two types of nephrons: cortical nephrons with short Henle's loops and juxtamedullary nephrons with long Henle's loops (Fig. 14.4). There are approximately 2 million nephrons per kidney, seven-eighths of which are cortical and one-eighth juxtamedullary. The arterial supply to the cortical nephrons differs from that of the juxtamedullary nephrons. In the former, the efferent arteriole courses along the proximal tubule belonging to the glomerulus from

which it came. This allows that arteriole to reabsorb filtrate that it left behind in the glomerulus. Because these nephrons have short Henle's loops, they play a lesser role in maximum urinary concentration than do the juxtamedullary nephrons with long Henle's loops. The efferent arterioles from the juxtamedullary nephrons course not only along the proximal tubule from the respective glomerulus but also dive deep into the medulla, coursing along their respective Henle's loops. The vessels that follow Henle's loops are called *vasa recta.*

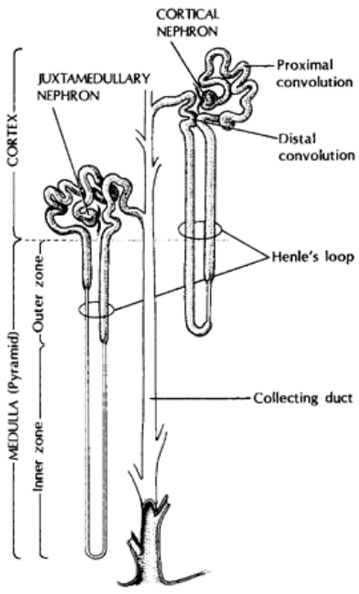

FIGURE 14.4. The renal parenchyma is divided into cortex and medulla and contains two types of nephrons: cortical and juxtamedullary.

The components of the nephron include the glomerulus, the proximal tubule, Henle's loop, the distal tubule, and the collecting duct. The glomerulus consists of an afferent arteriole, capillary and efferent arterioles, a juxtaglomerular apparatus, and Bowman's space and capsule (Fig. 14.5). The afferent arteriole, and to a lesser extent the efferent arteriole, are in intimate contact with the first portion of the distal tubule belonging to that glomerulus. This association is called the *juxtaglomerular apparatus* and consists of two parts: the macula densa, or the dark cells of the distal tubule, and the juxtaglomerular cells, or the endothelial cells of the afferent and efferent arterioles that contain renin granules. It has been postulated that this structure is responsible for the regulation of sodium conservation through the stimulation of aldosterone production and that it acts as a feedback mechanism for the intrarenal regulation of each nephron's blood flow and therefore glomerular filtration rate (GFR) (see the following discussion).

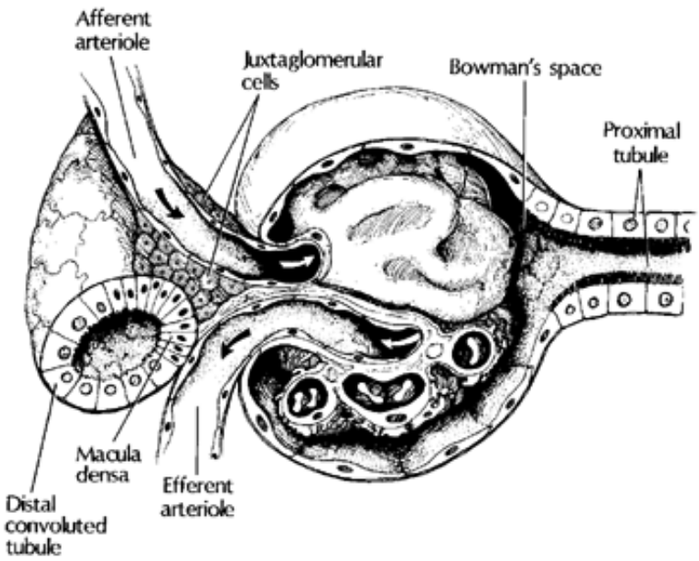

FIGURE 14.5. Glomerulus and juxtaglomerular apparatus.

The glomerular capillary network is the area through which plasma is filtered. The capillaries contain an endothelium, which lies on a basement membrane. On the other side of the basement membrane is Bowman's space. It is on this side of the basement membrane that the epithelial cells, or foot processes (podocytes), are found (Fig. 14.6A). Finally, mesangial cells that support the structures of the glomerulus are found within the glomerular tuft. These cells may play a role in causing arteriole constriction and in providing support for the aforementioned structures. Bowman's space empties into the convoluted proximal tubule. The cells of this portion of the nephron have a dense brush border on the luminal side (Fig. 14.6B) and are attached to each other by impermeable tight junctions. At the end of the proximal tubule, the nephron dives toward the medulla, where it attaches to the thin limb of Henle's loop. This portion of the proximal tubule is called the *pars recta.* Its brush border is less dense, and this area perhaps is less active in filtrate reabsorption than the other portion of the proximal tubule. The thin limb of Henle's loop descends and then turns back on itself and ascends toward its respective glomerulus. As it ascends, it changes to the thick limb of Henle's loop, which has notably different permeability and transport characteristics than the thin limb. The thick limb joins the first portion of the distal tubule whose cells are called the *macula densa*—a component of the juxtaglomerular apparatus. The distal convoluted tubule joins with many others to enter a collecting duct. The collecting duct traverses the parenchyma to the renal papilla (59).

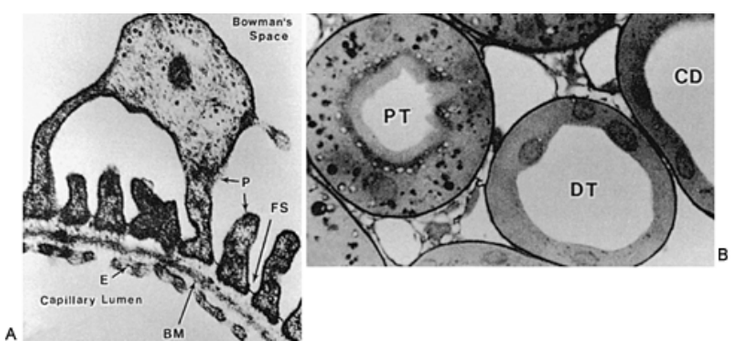

FIGURE 14.6. A: Electron photomicrograph of the glomerulus. BM, basement membrane; E, endothelial cell; FS, filtration slit; P, podocyte. **B:** Light photomicrograph of renal tubules. CD, collecting duct; DT, distal tubule; PT, proximal tubule (notice dense brush border). Notice the dense staining basement membrane surrounding each tubule.

RENAL PHYSIOLOGY

Glomerular Filtration

Plasma, water, and nonprotein crystalloids are separated from blood cells and protein within the glomerulus by a process called *ultrafiltration* (43). Nonchanged molecules with a molecular radius less than 20 Å are freely filtered (60). The forces involved in ultrafiltration are the hydrostatic pressure within the glomerular capillary, the permeability of the glomerular membrane called *hydraulic permeability,* the oncotic pressure of the plasma, and the hydrostatic pressure in Bowman's space. The hydrostatic pressure in the glomerular capillary remains relatively constant throughout its length, whereas the oncotic pressure rises along the course of the capillary as filtrate leaves. The net filtration pressure is the hydrostatic pressure minus the oncotic pressure minus the pressure in Bowman's space. Net filtration is determined by this pressure and the hydraulic permeability of the glomerular membrane. As blood courses along the length of the capillary, the net ultrafiltration pressure declines because oncotic pressure rises as a result of the increased protein concentration as fluid is removed from the capillary lumen (Fig. 14.7). This serves to keep the amount of filtrate constant despite capillary length and thus prevents loss of excessive fluid into Bowman's space. The permeability of the membrane is a function of the permeability of its component parts: the endothelium, the basement membrane, and the epithelial cells (podocytes or foot processes). The basement membrane and filtration slits account for 98% of the resistance, with the endothelium accounting for only 2% of the resistance (18). The podocytes are separated by filtration slits that contain pores having dimensions of 40 to 140 Å. Negatively charged glycoproteins are attached to the surfaces of the endothelial cells, basement membrane, and podocytes. Thus the membrane acts as a barrier by discriminating according to both the molecule's size and its electric charge (an electrostatic barrier).

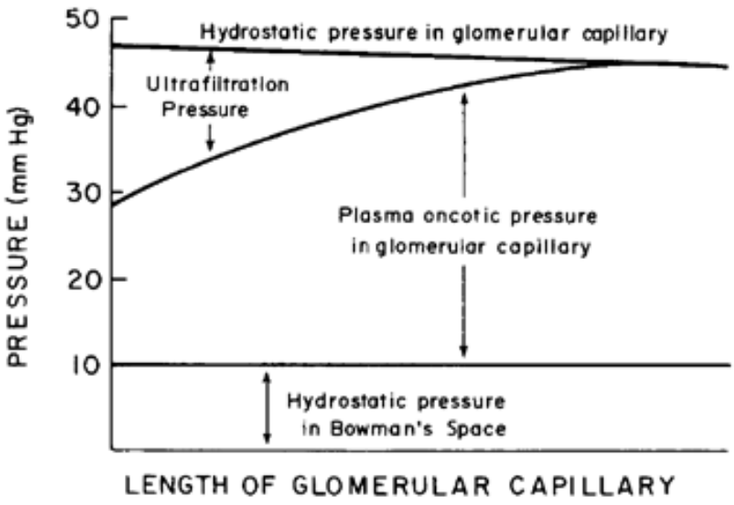

FIGURE 14.7. Forces of glomerular ultrafiltration. As fluid traverses the capillary and as some is filtered into Bowman's space, oncotic pressure within the capillary increases until it completely counteracts the hydrostatic pressure gradient. This limits the amount of fluid filtered into the proximal tubule.

The glomerular mesangium and renal vasculature are sensitive to a number of endogenous hormones. Angiotensin II, norepinephrine, the leukotrienes, platelet activating factor, adenosine triphosphate (ATP), endothelin, vasopressin, serotonin, and epidermal growth factor all may cause vasoconstriction.

The measurement of the quantity of plasma filtered by the glomeruli can be determined by a clearance technique. A clearance is defined as the volume of plasma from which the kidney removes a substance per unit of time. To measure the amount of fluid arriving in Bowman's space or the GFR, a substance is chosen that is freely filtered at the glomerulus

but is neither secreted nor reabsorbed by the tubule. Inulin, a starchlike polymer of fructose with a molecular weight of approximately 5,000, is such a substance, the standard against which other substances used to measure GFR are compared. Inulin clearance is independent of serum concentration and urine flow. The clearance is calculated from the following formula:

$$\frac{UV}{P}$$

where *U* is the urine concentration, *V* is the urine volume per unit of time, and *P* is the plasma concentration.

The amount of filtrate removed from the plasma remains relatively constant as a result of the forces previously described. The fraction of fluid in the glomerular capillary bed entering Bowman's space is called the *filtration fraction* and is approximately 20%; that is, 20% of the plasma arriving in the glomerulus leaves as filtrate into Bowman's space.

Tubule Reabsorption

Reabsorption by the tubule epithelium of substances essential to normal body function, such as water, sugars, amino acids, and electrolytes, is critical for homeostasis. Reabsorption of a substance may be determined by comparing its clearance with that of inulin: if the clearance of the filtered substance is less than that of inulin, it must be reabsorbed. Many substances that are reabsorbed are actively transported, thus having the potential to saturate the carrier mechanism, at which time a transport maximum (T_m) is achieved. T_m is the maximum amount of substance that can be actively transported when all carriers are saturated. Glucose, other sugars, sulfate, amino acids, phosphate, uric acid, and albumin have a T_m. The transport of a number of compounds can be facilitated by sodium transport. Glucose, uric acid, amino acids, and phosphate movement are enhanced in the presence of sodium, a process called *cotransport.*

Not all substances are reabsorbed by an active process. Passive reabsorption accounts for urea movement across the tubule. This type of transport is strongly affected by urine flow. At low flow rates, reabsorption of urea is increased, and at high flow rates urea is flushed from the tubule, thereby lessening its absorption. The flow of urea after filtration is not unidirectional. In certain portions of the tubule, urea is reabsorbed and in others it is secreted. Potassium and weak acids and bases (including drugs) also are secreted and reabsorbed in different portions of the nephron. The process is called *bidirectional transport.*

Tubule Secretion

Substances secreted are usually either weak acids or weak bases; they are foreign to the body and are either not metabolized or are metabolized slowly or incompletely. Secretion is confirmed when a filtered substance's clearance exceeds that of the inulin clearance. Examples of substances secreted include drugs (e.g., diuretics, antibiotics, salicylates), *para*-aminohippuric acid (PAH), and thiamine.

Renal Hemodynamics

Approximately 20% to 25% of the cardiac output flows to the kidneys, more than 90% of which perfuses the cortical region. Even though the medullary region gets only a small fraction of the total RBF, in absolute amounts it is perfused with approximately the same amount of blood as is resting muscle. The blood flow is sensitive to hemorrhage, the cortex being primarily affected. Antidiuretic hormone (ADH), the prostaglandins, renin, and sympathetic nerve stimulation affect RBF. ADH causes vasoconstriction and therefore prevents washout of osmotically active particles from the medulla. Prostaglandins are both vasodilatory and vasoconstrictive. Their vasodilatory action exerts a protective role in diseases causing vasoconstriction (20). Thromboxane, a potent prostaglandin vasoconstrictor, may play a role in altering RBF during obstructive uropathy (49). Others are not convinced that it alters renal hemodynamics. Renin, through the release of angiotensin, also causes vasoconstriction, and its release may be stimulated by an alteration of distal tubule sodium concentration, sympathetic nerve stimulation, and changes in intrarenal blood pressure. Angiotensin II exerts constrictive effects on both afferent and efferent arterioles, with an increased effect on the efferent arteriole. The subtype angiotensin II-2 receptor has been shown to have vasodilatory effects in selected circumstances. Angiotensin receptors also are located on mesangial cells, resulting in changes in glomerular surface area (12).

The renin-angiotensin system has been implicated in distribution of RBF; in regulation of GFR through its effects on afferent and efferent arterioles, on filtration coefficient, and on mesangial contraction; in sodium reabsorption by proximal and distal tubules; in renal concentrating mechanism; in potentiation of renal sympathetic activity; in interaction with prostaglandins; and as a renal growth factor (33). Stimulation of the sympathetic nerves supplying the kidney, through their innervation of the arterioles, causes vasoconstriction by stimulating contraction of endothelial muscle cells.

Finally, endothelin and endothelin-derived relaxing factor play a role in vasoconstriction and relaxation of the renal microcirculation. Under most conditions RBF remains relatively constant by a phenomenon known as *autoregulation.* Over a range of systolic blood pressures from 80 to 180 mm Hg, RBF and GFR remain constant. It has been suggested that the renin-angiotensin system, prostaglandins, the catecholamines, kinins, leukotrienes, ATP, serotonin, epidermal growth factor, platelet activating factor, and other substances regulate RBF by altering vascular resistance in the afferent and efferent arterioles by a complex set of interactions. Through this combined effect, intraglomerularhydrostatic

pressure is maintained relatively constant over wide variations in systemic pressure.

RBF usually is measured by a clearance technique (see the following). PAH is used, because it is filtered and secreted by the kidney. Thus the amount of plasma that delivers the amount of PAH found in the urine per unit of time is the amount of plasma that passed through the kidney, or the *renal plasma flow* (RPF) . The calculation is simple. However, from a practical point of view its determination is difficult, because both the renal vein and renal artery concentrations must be known to calculate the amount of plasma delivered to the kidney because the arteriovenous difference is the amount removed in one pass. The renal artery concentration is easily determined from a peripheral venous sample; however, an invasive technique must be used whereby a catheter is passed to sample the renal vein directly. This difficulty can be obviated if the renal vein concentration approaches zero. If the PAH concentration is kept low enough in the systemic circulation, essentially all PAH entering the renal artery is cleared in one pass. Thus the calculation simplifies to a clearance as follows: UV/P of PAH. Because approximately 10% of the arterial concentration remains in the renal vein at low systemic PAH concentrations and because this may vary by as much as 20% under differing experimental conditions, the calculation of RPF determined without actual measurement of renal venous concentration is termed *effective renal plasma flow* to indicate that it is not actual RPF but rather an approximation thereof, because renal vein concentration is assumed to be zero, which actually may not be the case. If the renal vein concentration were known, then actual RPF could be calculated by the clearance technique previously described. RBF may be calculated by dividing the plasma flow by the following quantity: (1 – hematocrit).

Sodium and Water Balance

Sodium is actively transported from the luminal contents to the interstitium. The bulk of energy expended by the kidney is involved in this active process. In the proximal tubule, approximately 60% to 70% of the filtered sodium and fluid is reabsorbed. Because water follows sodium passively and because the proximal tubule is freely permeable to water, the fluid in this portion of the tubule is reabsorbed isosmotically. A constant fraction of the filtered sodium is reabsorbed in the proximal tubule (i.e., glomerulotubular balance), normally approximately 70% despite variations in the GFR.

Glomerulotubular balance appears to be brought about by two processes. The first involves changes in filtration fraction, perhaps brought about by nervous or humoral factors. The second involves the process of cotransport. Because sodium reabsorption is linked to the reabsorption of various substances that are almost completely reabsorbed by the proximal tubule (e.g., glucose), when increases in the filtered load of the substance occur, an increase in sodium reabsorption is stimulated and vice versa.

In the thin limb of Henle's loop, water moves according to its concentration gradient. Thus in the proximal portion, water moves out, whereas in the distal portion it moves back in. Sodium follows passively. In the thick ascending limb, sodium and chloride are actively pumped from the lumen; however, this portion is impermeable to water, and thus the fluid becomes hypotonic. In the distal tubule, sodium is actively removed under the influence of aldosterone. Water moves according to the movement of sodium and its concentration gradient. In the collecting duct, sodium is reabsorbed, and water movement (collecting duct permeability to water) is influenced by the concentration of ADH.

Mechanisms responsible for sodium balance may be classified into three groups. The first factor responsible for sodium homeostasis is GFR, which alters sodium reabsorption through the mechanism of glomerular tubule balance. Occasionally, glomerular tubular balance may be disrupted under circumstances of excessive sodium loads.

The second group of factors include angiotensin and aldosterone. Angiotensin II exerts potent effects on sodium and bicarbonate transport in the proximal tubule (12). Aldosterone is released either as a direct action of hyperkalemia or angiotensin II on the adrenal gland or as a result of the release of renin or adrenocorticotropic hormone (ACTH) (23). Renin is released from the juxtaglomerular cells as either a consequence of a low afferent arteriolar pressure (secondary to hypotension) or decreased distal tubule sodium concentration. Stimulation of the sympathetic nervous system, various prostaglandins, and calcium channel blockers also stimulate renin production. Angiotensin II, vasopressin, endothelin, and adenosine inhibit renin release. Renin is produced in an inactive form and is activated by a serum proteinase. Activated renin acts on a protein substrate to cleave a decapeptide, angiotensin I. Angiotensin I is converted by a converting enzyme to a vasoactive octapeptide, angiotensin II (Fig. 14.8). Angiotensin II results in vasoconstriction and stimulation of the adrenal gland to release aldosterone (33).

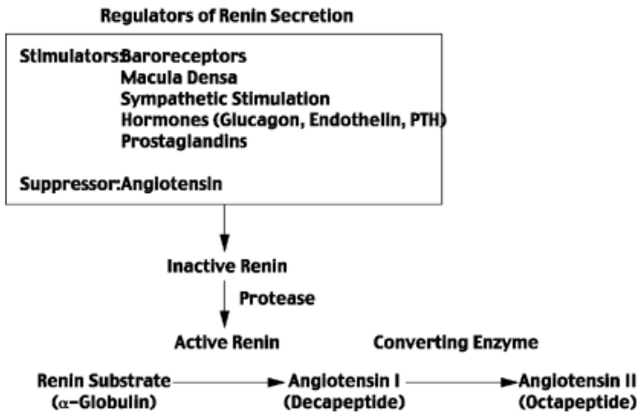

FIGURE 14.8. The renin-angiotensin system. PTH, parathyroid hormone.

Factors in the third group are nervous and/or humoral influences, which alter sodium transport. They are not well-defined; however, their effects are known. For example, volume expansion with sodium results in natriuresis that is caused by a decreased fractional reabsorption in the proximal tubule from 70% to 40% and a decreased sodium reabsorption in the distal tubule. This is not dependent on factors in either group one or two. A substance that may be responsible for some of these effects is *atrial natriuretic factor,* a 28-amino acid polypeptide that has been identified in the atrium. The 28-amino acid residue is the circulating form that is derived from a 126-residue precursor—the principal storage form. It has potent diuretic, natriuretic, and vasorelaxant properties. It also inhibits the release of ADH. The atria are the only established source of atrial

natriuretic factor. Its release is stimulated by stretch of the atrium, volume expansion, sodium concentration, osmolality, and certain vasopressor agents (69). Finally, prostaglandins play a minor role in the modulation of sodium and water excretion. Prostaglandins synthesized in the renal medulla act locally to enhance water and sodium excretion by (a) increasing RBF, (b) inhibiting sodium transport from the thick ascending limb of Henle's loop, (c) antagonizing the action of vasopressin on the collecting duct, and (d) inhibiting urea and sodium reabsorption from the collecting duct (19).

Concentration and Dilution

The ascending limb of Henle's loop is impermeable to water, and because sodium and chloride are actively reabsorbed, electrolyte transport occurs without water following. This establishes a hyperosmotic medullary interstitium, which is the primary determinant of the kidney's ability to concentrate. Henle's loop acts as a countercurrent multiplier increasing the concentration of solutes, whereas the vasa recta coursing along with Henle's loop preserve medullary tonicity by serving as countercurrent exchangers. This is particularly important, because plasma flow to the medulla is approximately ten times greater than tubule fluid flow. This unique relationship preserves medullary tonicity and thus concentration capabilities.

Urea recycling helps maintain osmolality in the medulla, both in the medullary interstitium and the tubule lumen. Urea concentration in Henle's loop increases as water leaves. Under the influence of ADH, urea reabsorption in the collecting duct is facilitated as water is reabsorbed. This maintains a high medullary tonicity. Thus during antidiuresis, urea provides 40% of the medullary osmotically active particles, whereas in diuretic states urea constitutes only 10% of the medullary solutes.

ADH adjusts the amount of water that is reabsorbed from the late distal tubule and collecting ducts. ADH increases tubule permeability, thus allowing water to travel according to its concentration gradient. In the collecting duct, where medullary tonicity is high, water is reabsorbed. ADH also causes vasoconstriction of the vasa recta, preventing the removal of solute from the medulla, thereby maintaining a high medullary tonicity. Prostaglandins also may play a role in this regulation by opposing the action of ADH. ADH is released as a result of stimuli from volume receptors or osmoreceptors. Osmoreceptors located in the hypothalamus, when exposed to increased osmolality, stimulate the posterior pituitary to release ADH. Similarly, volume receptors located in the left atrium or pulmonary veins also result in the release of ADH.

Acid–Base Balance

The daily production of 40 to 70 mmol of inorganic and organic acids (i.e., the fixed acids) and 13,000 mmol of carbon dioxide (CO_2), which momentarily generates hydrogen (the volatile acid), requires elimination by the body. This acid load requires buffering so that major pH shifts do not occur locally. The buffers include hemoglobin, protein, inorganic phosphate, organic phosphate, and bicarbonate. Organic phosphate is the major intracellular buffer, whereas the main extracellular buffer is the carbonic acid bicarbonate system. The latter is particularly effective, because the concentration of one component of the pair, CO_2 can be altered rapidly by the lungs.

Perhaps one of the most effective initial methods of buffering the volatile acid load is the reaction hydrogen has with hemoglobin. Oxygenated hemoglobin is more acidic than nonoxygenated hemoglobin. Thus when hemoglobin gives up its oxygen, it can take up a great deal of hydrogen without any overall change in local pH. CO_2 arising from

metabolism is hydrated to carbonic acid and dissociates into hydrogen and bicarbonate. The hydrogen is taken up by hemoglobin, and the CO_2 travels to the lungs as bicarbonate. The reverse reaction occurs in the lungs where hydrogen is given up, CO_2 is eliminated, and hemoglobin is oxygenated. Fixed acids initially are buffered by bicarbonate, phosphate, and proteins, thus lessening their effect on systemic pH. In the process of buffering, fixed acids consume bicarbonate. The volatile acid is excreted by the lungs and the fixed acids by the kidney, thus restoring buffer capacity.

The kidney reclaims bicarbonate by two mechanisms. Filtered bicarbonate is reclaimed in the proximal tubule, where 80% to 90% of that which is filtered is reabsorbed. This process occurs by (a) the secretion of hydrogen ion by the proximal tubule cell, (b) the combination of the hydrogen with filtered bicarbonate to form carbonic acid, (c) the dehydration of carbonic acid to CO_2 and water within the tubule lumen, (d) the diffusion of CO_2 into the proximal tubule cell, (e) the formation of carbonic acid, and (f) the removal of hydrogen to be secreted into the lumen thereby, in effect, reabsorbing bicarbonate. Filtered bicarbonate is reclaimed in this manner; however, bicarbonate consumed in the process of buffering fixed acid is restored and the hydrogen eliminated by hydrogen secretion in the cortical collecting tubule. The hydrogen arises from carbonic acid and thus results in bicarbonate generation within the tubule cell. The bicarbonate stores are thus replenished. The hydrogen ion secreted in the cortical collecting tubule by the Na-H antiport is fixed to phosphate, creatinine, and urate. These act as buffers and are excreted as weak acids. Hydrogen excreted in this manner is called *titratable acid* and, as such, lowers urinary pH. Because an intraluminal hydrogen concentration cannot exceed a concentration difference of more than 1,000:1, any amount excreted in excess of this back-diffuses into serum. The kidney is therefore incapable of lowering urinary pH values to less than a pH of 4.4. This mechanism limits the amount of hydrogen ion capable of being secreted. Fortunately, the ammonium system allows for further elimination of hydrogen ion without the need to lower urinary pH.

Ammonia is generated from glutamine in the proximal tubule. Ammonia diffuses across the membrane into the tubule lumen, flows to the distal tubule/cortical collecting duct, and combines with a hydrogen ion to form ammonium. Ammonium may be secreted by a number of transporters, NH4/H exchange being one. The quantitative role of this mechanism is not firmly established. Ammonium is trapped and combines with an available anion—usually chloride, sulfate, or phosphate—to form a neutral salt. The neutral salts do not influence pH and are excreted as such. Distal hydrogen secretion is promoted by increasing the severity of the acidosis, the presence of aldosterone, depletion of potassium, and increased delivery of sodium to the distal nephron. Factors that alter bicarbonate reabsorption in the proximal tubule include the serum concentrations of CO_2, potassium, chloride, phosphate, calcium, and parathormone, and the volume status of the patient. Increased bicarbonate reabsorption occurs with elevated CO_2, decreased potassium, diminished chloride, and elevated phosphate and decreased volume. Increased parathormone, hyperkalemia, and reduced CO_2 decrease bicarbonate reabsorption.

The final regulation of urinary acid excretion occurs in the collecting duct. Collecting duct acid–base balance is regulated by systemic acid–base states, potassium balance, sodium reabsorption, mineralocorticoids, and other peptide hormones (27).

Potassium

Only approximately 10% to 20% of the filtered load of potassium is excreted. It is reabsorbed in the proximal tubule and also may be reabsorbed in the distal tubule and collecting duct under certain experimental conditions. It is secreted in the distal tubule, and it is by this mechanism that most potassium is excreted in the urine. The rate of secretion is influenced by the presence of mineralocorticoids, urine flow, acid–base balance, and sodium intake. Mineralocorticoids stimulate the secretion of potassium, mainly in the cortical collecting duct. Their presence results in sodium reabsorption, but there is not a 1:1 ratio of sodium for potassium. Alkalosis results in increased potassium secretion, whereas acidosis results in hydrogen secretion at the expense of potassium secretion. Potassium and hydrogen ion transport are linked in some manner explaining this phenomenon. An increased flow rate keeps the concentration gradient high between tubule cell and lumen and therefore promotes secretion. Sodium, by increasing flow rates in the distal tubule or by its effect on the sodium-potassium cellular exchange pump, also increases potassium secretion.

Calcium

The bulk of filtered calcium is reabsorbed in the proximal tubule. However, the remainder is reabsorbed in the thick ascending limb of Henle's loop and the distal tubule. Its reabsorption depends on phosphate, magnesium, and parathormone. Hypophosphatemia decreases calcium reabsorption as does an increase in magnesium concentration. Parathormone increases calcium reabsorption and reduces phosphate reabsorption. Parathormone also stimulates the kidney to produce 1,25-dihydroxyvitamin D_3, which increases gut absorption and bone reabsorption for calcium. Magnesium, calcium, and sodium may share some of the same carriers, because if there is an excess of one, others tend to be excreted; that is, the common pump is saturated by the ion in excess.

Magnesium

Magnesium is reabsorbed in the proximal tubule, thick ascending limb, and distal tubule. Increased sodium, calcium, and mineralocorticoid reduce reabsorption. Osmotic agents, renal vasodilation, glucose, and hyperthyroidism increase excretion (68).

DETERMINATION OF RENAL FUNCTION

Part of "14 - THE KIDNEY "

Because of the complexity and wide range of functions the kidney performs, the assessment of renal function requires measurement of individual processes occurring in various portions of the nephron. It is not practical to measure each one; therefore, selected functions are determined and, unless otherwise indicated, it is assumed that these reflect the general function of the entire kidney. For convenience these studies are divided into five groups: (a) glomerular filtration, (b) RBF, (c) tubule electrolyte transport, (d) concentration and dilution, and (e) protein conservation.

Glomerular Filtration Rate

GFR is the amount of filtrate arriving in the proximal tubule per unit of time. It assesses the normalcy of RBF, glomerular integrity, and proximal tubule pressure. Its measurement is based on the concept of a clearance (see the following equation). The ideal substance for this measurement is freely filtered at the glomerulus and is not metabolized, secreted, or reabsorbed by the tubule. The material used to perform the clearance must be maintained at a constant concentration in the serum. For inulin this requires maintaining a constant IV infusion, because the substance is not endogenous to the body. Once a constant serum level is obtained, the amount of inulin excreted in the urine is measured per unit time (urine concentration, *U,* multiplied by the volume, *V,* of urine excreted: U × V). To find the amount of serum from which this amount of inulin was extracted, the product is divided by the serum concentration, *P.* Thus U × V/P gives the amount of serum completely cleared of the substance per unit time or the GFR.

A normal GFR (measured by inulin clearance) for a young adult is 130 mL per minute for males and 120 mL per minute for females per 1.73 m^2 of body surface area. Exercise lowers GFR, whereas pregnancy may increase it by as much as 50%. Hydration, either extreme overhydration or dehydration, also may affect filtration rate. In children older than the age of 1 year, when the GFR is corrected to 1.73 m^2 of body surface area, it is the same amount as for adults. In children younger than the age of 1 year, it is less—only approximately 50% of the corrected adult value in the neonatal period. Similarly, the GFR falls with age, until by the age of 60 years it is only 60% to 80% of the young adult value.

Several formulas have been developed to assess GFR from the measurement of serum creatinine alone without the need for a urine collection (30). Perhaps the most widely used formula is the following:

$$\frac{(140 - \text{age}) \times \text{Body weight (kg)}}{72 \times \text{Cr}_s}$$

where Cr_s is the serum creatinine concentration.

This gives the GFR for males; for females the value is multiplied by 0.85. This formula is useful for calculating GFR when the need to adjust drug doses arises. It is reasonably accurate when the GFR exceeds 40 mL per minute. This formula is inaccurate in patients with spinal cord injury (muscle wasting), in those with bowel interpositions in the urinary tract, and in those in whom one of the interfering substances is present (see previous discussion). It must be remembered that serum creatinine concentrations vary with muscle mass (more muscular individuals have a higher serum creatinine level), daily protein consumption, and metabolic state of the patient (13,52). Alterations in serum creatinine are a less accurate method of determining renal function.

Because of the inaccuracies of creatinine, other substances and methods have been developed in an attempt to measure GFR accurately without the difficulties encountered with the inulin clearance. Vitamin B_{12}, edetate (EDTA), sodium iothalamate, and sodium diatrizoate have been shown to have clearance rates similar to inulin. However, they appear to have no advantages over endogenous creatinine clearances except in selected circumstances.

Radiopharmaceuticals have enjoyed popularity as a less cumbersome method of determining renal function. The radiopharmaceutical technetium, labeled *pentetic acid* diethylenetriaminepentaacetic acid (DTPA)], is used for GFR measurements, and iodohippurate sodium ^{131}I (Hippuran) is used for RBF determination. Two methods are commonly used to determine GFR and RBF. The GFR or RBF can be calculated from an empiric formula that requires knowledge of the amount of isotope taken up by the kidneys over a 6-minute period (25). The second method involves injecting the isotope and withdrawing serial blood samples over several hours. The amount of isotope is determined in the blood samples, and a disappearance curve is plotted. GFR or RBF is calculated from the half-life of the disappearance curve (10). In patients with relatively normal renal function who are in good health, these methods correlate well with inulin clearances. However, they are inaccurate in patients with significant edema or ascites, in those with intestine interposed in the urinary tract, and in patients with poor renal function.

Renal Blood Flow

The kidneys receive approximately 20% of the cardiac output. Measurement of RBF allows an assessment of the

vascular integrity of the kidney and, to a lesser extent, the viability of the renal parenchyma. A clearance technique or isotope washout method is usually employed. Clinically, the clearance method is most convenient, because it requires no special instrumentation and is based on the Fick principle. The amount excreted in the urine (urine concentration, *U,* multiplied by urine volume, *V*) divided by the renal artery minus the renal vein concentration difference gives the amount of plasma required to deliver the substance. Because it is from renal plasma that the substance is extracted, RPF is determined as follows:

$$RPF = UV/A - RV$$

where *U* is urine concentration; *V,* urine volume per unit time; *A,* renal artery concentration; and *RV,* renal vein concentration. Because the determination of renal vein concentration is cumbersome, a substance that is completely extracted in one pass is chosen so that renal vein concentration is zero. Thus the calculation simplifies to UV/P. Because no known substance is extracted completely in one pass, the measurement is called *effective RPF.* PAH, iodopyracet (Diodrast), and Hippuran, when administered at low-dose levels, are removed almost completely and are the agents employed to measure RPF. The renal extraction is approximately 90%; thus there is approximately a 10% error rate. Moreover, not all blood to the kidney is exposed to functioning tubules and glomeruli, so this technique may be significantly inaccurate in disease. Normal values are 600 to 700 mL per minute per 1.73 m^2. RBF may be calculated from RPF by the following equation:

$$RBF = RPF/(1 - Hct)$$

where *Hct* is the patient's hematocrit level.

Washout methods involve injecting a bolus of isotope (xenon or krypton) in the renal artery and then measuring the speed with which the isotope leaves renal parenchyma by recording the rate at which radioactivity diminishes over the kidney by conventional scanning techniques. The concentration of isotope in the kidney as a function of time is plotted. The equation that describes the disappearance curve is of the fourth order or greater. By stripping the curve, that is, generating the equation for the curve, RBF to various segments (cortex and medulla) may be determined (58).

Finally, the disappearance of isotopically labeled Hippuran from the blood or timed accumulation by the kidney may be used as a gross estimate of RBF (see previous discussion).

Tubule Electrolyte Transport

Integrity of transport processes can be determined by assessing the transport of various electrolytes. This is important in certain disease entities, such as renal tubular acidosis (RTA) in which there is a defect in hydrogen ion secretion. That defect may be brought to light by stressing the kidney's hydrogen ion transport process. Other defects, such as distal tubule ammonium dysfunction, as occurs in certain patients who form uric acid stones, and salt-losing nephropathy, may be assessed similarly.

Sodium extraction rate may be used as a crude index of proximal and distal tubule function. The normal kidney under conditions of severe salt restriction should be able to excrete less than 0.1% of the filtered load of sodium in a urine concentration of less than 1 mEq/L.

Distal tubule function may be assessed by the administration of a mineralocorticoid and observation of a decrease in urine sodium concentration and a rise in urine potassium concentration. Distal tubule hydrogen secretion also may be assessed by administering hydrochloric acid, ammonium chloride, or one of the cationic amino acids (lysine, arginine, or histidine) and observing a decrease in the urine pH to less than 5 and/or a lack of ammonia generation.

Concentration and Dilution

Alterations in concentration and dilution indicate distal tubule and collecting duct dysfunction. Many entities affect these functions (Table 14.3), most often pyelonephritis and urinary obstruction. The normal kidney can dilute to an osmolality of 40 mOsm/kg and concentrate to 1,200 mOsm/kg. Concentrating ability is determined by either water deprivation or the administration of vasopressin. Diluting ability is determined by having the patient drink 1 L of water over a short time. The patient will excrete more than half the volume over 3 hours with a urine osmolality of 80 mOsm/kg or less.

Postrenal polyuria	Functional abnormalities
Obstruction	Nephrogenic diabetes insipidus
Intrarenal polyuria	Medullary washout
Anatomic disruption	
Sickle cell anemia	Prerenal polyuria
Pyelonephritis	Lack of ADH
Amyloidosis	Suppressed expanded extracellular fluid
Nephrocalcinosis	Diabetes insipidus
Metabolic abnormalities	Trauma
of ADH–collecting duct interaction	Diuretic agents (other than doxycycline or neuromuscular agents)
Hypercalcemia	
Hypokalemia	
Renal tubular acidosis	

ADH, antidiuretic hormone.

TABLE 14.3. DIFFERENTIAL DIAGNOSIS OF POLYURIA

DETERMINATION OF RENAL FUNCTION IN THE PRESENCE OF INTESTINAL SEGMENTS

Part of "14 - THE KIDNEY "

The assessment of renal function in patients in whom a segment of intestine is interposed in the urinary tract requires modifying the techniques normally employed to determine renal function in the intact collecting system. This is necessary because the intestine, which is used as a conduit, functions as a vehicle of urine transport and as an absorptive and secretory surface. Thus urine may be modified considerably after transversing intestine, making it difficult to determine whether the measured substance has been altered by bowel absorption or secretion. Many of the substances used to assess renal glomerular function or RBF are absorbed by the intestinal segment. Urea is perhaps the most permeable, but creatinine, inulin, and PAH also are significantly absorbed (36). Their absorption depends on their concentration and the amount of time they remain in contact with the intestine, which is a function of the surface area to which they are exposed and the urine flow rate.

Figure 14.9, Figure 14.10 and Figure 14.11 illustrate the dependency of urine flow rate on absorption of urea, creatinine, and inulin in patients with ileal and colon conduits. For clarity, the figures compare the percentage of maximum clearance achieved as a function of flow rate in normal collecting systems and ileal and colon interpositions. The illustrations demonstrate that when urine flow rates exceed 250 mL per hour, intestinal absorption for creatinine and inulin is negligible, and at these flow rates the substances more closely measure the true GFR and RPF (PAH shows a similar flow dependency). These curves were derived from a group of patients with ileal conduits, colon conduits, and intact urinary tracts. Because renal function varied from poor to normal, the patients were compared by factoring each measured clearance by the maximum clearance obtained for that patient. At high flow rates, patients with stomal stenosis tend to diminish their clearance, indicating that at these flows the intestine serves as a functional obstruction (45).

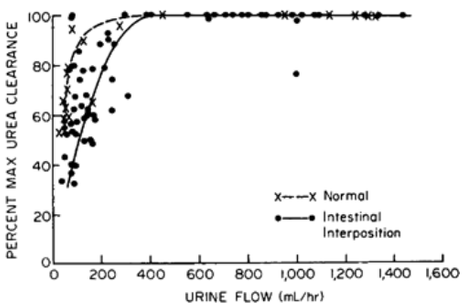

FIGURE 14.9. Flow dependency of urea clearance in patients with normal urinary tracts compared with those with ileal and colon interpositions.

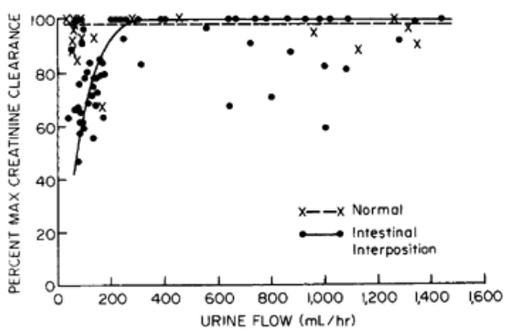

FIGURE 14.10. Flow dependency of creatinine clearance in patients with normal urinary tracts compared with those with ileal and colon interpositions.

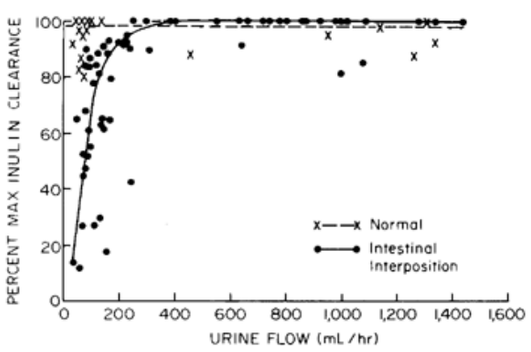

FIGURE 14.11. Flow dependency of inulin clearance in patients with normal urinary tracts compared with those with ileal and colon interpositions.

Measurement of Glomerular Filtration Rate

Because clearance is flow dependent, it is necessary to establish a diuresis in patients with ileal and colonic segments at urine flows between 300 and 700 mL per hour. These flows may be achieved by fluid administration alone. Rarely, a diuretic such as furosemide also may be required. The urine is collected over 1 hour. The volume is measured, and the substance used for the clearance is measured in the serum and urine. Creatinine is perfectly adequate in these patients, provided the serum does not contain excessive ketoacids, cephalosporins, cimetidine, trimethoprim-sulfamethoxazole, or propranolol (51). Because diuretic creatinine clearance parallels diuretic inulin clearance, the former is the clinically expedient method of determining the GFR. Creatinine clearance measured in this manner is approximately 20% less than inulin clearance at GFRs that exceed 20 mL per minute. If the GFR is less than 20 mL per minute, the creatinine clearance may overestimate the inulin clearance as a result of secretion by the renal tubule. At low GFRs (i.e., less than 10 mL per minute), the error rate may be as great as 50% (Fig. 14.12).

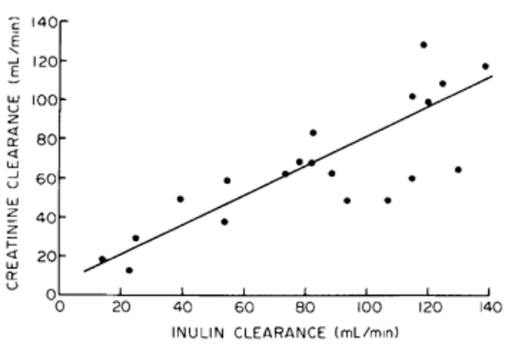

FIGURE 14.12. Diuretic inulin and creatinine clearances in patients with normal urinary tracts compared with those with ileal and colon interpositions. Notice the excellent correlation and that creatinine clearance is consistently 20% less than inulin clearance.

Renal isotope determination of GFRs in these patients is not useful, because there is little correlation between GFRs obtained by this method and those obtained by inulin clearance. This is true at all levels of renal function (45).

Because the bowel absorbs, secretes, and metabolizes creatinine, the calculation of the GFR from serum creatinine, age, weight, and gender by empiric formulas is totally unreliable and not useful in these patients (45).

Renal Blood Flow

PAH clearance obtained when urine flows range between 300 and 700 mL per hour accurately reflects effective RPF.

Isotope scans are not accurate in determining RBF in these patients.

Tubule Function

The determination of tubule function by the measurement of sodium excretion and hydrogen ion secretion under conditions of sodium deprivation or hydrogen loading (see previous discussion) cannot be accurately performed in these patients. Although some qualitative indication of the way electrolytes are handled can be obtained, the maximum capabilities of the kidneys with respect to electrolyte transport cannot be determined when urine is analyzed after it has traversed an intestinal segment.

Concentration and Dilution

Because the bowel cannot concentrate much more than 50 mOsm/kg greater than serum, urine traversing an intestinal segment, if more concentrated than serum, is diluted. Thus in patients with ileal and colon conduits, maximum urinary concentration usually does not exceed 400 mOsm/kg. The determination of maximum urinary concentrating ability of the kidney cannot be performed accurately in patients with intestinal segments (45). Although the kidney's ability to dilute can be assessed with the techniques described previously, maximum dilutional capabilities cannot be determined because of absorption by the intestine. Therefore statements about distal tubule and collecting duct function based on maximum concentrating ability in patients with colon or ileal segments are meaningless.

It is clear that patients who have colon or ileal conduits, those with intestine interposed in the urinary tract, and those in whom intestine is used as a urinary reservoir require special manipulations to measure renal function. GFR and RPF can be accurately assessed if, while they are being measured, urine flows range between 300 and 700 mL per hour. They must be measured by classic clearance techniques, not by either isotopic scans or empiric calculation from serum creatinine. Tubule function is most difficult to assess in these patients, and at present there is no good way of determining the kidney's maximum capacity for conserving sodium, excreting hydrogen, or reabsorbing water.

ACUTE RENAL FAILURE

Part of "14 - THE KIDNEY "

Acute renal failure (ARF) in surgical patients has numerous causes (Table 14.1). Whatever the primary cause, it is associated with significant morbidity and mortality and presents as a progressive rise in blood urea nitrogen (BUN) and creatinine levels, often with a decrease in urine output. ARF is said to be oliguric when the urine output is less than 400 mL per 24 hours and nonoliguric when the urine output exceeds this amount. The initial therapy and prognosis for ARF are determined not only by examining the serum chemistries and state of fluid balance but also depend on the expeditious assignment of patients to one of the three subdivisions of this disease: prerenal, intrarenal, or postrenal. Therefore it is necessary to begin diagnostic procedures

that will determine the type of ARF simultaneously with therapy directed at correcting fluid imbalance and electrolyte abnormalities.

Prerenal failure	Vasomotor nephropathy
Excessive nitrogen load	Shock
Myocardial pump failure	Sepsis
Hypovolemia	Transfusion reactions
Intrarenal failure	Crush injury
Occlusion of renal arteries or renal veins	Tubule toxins
Arteriolar damage	Drugs
Malignant hypertension	Myoglobin
Polyarteritis	Poisons
Hypersensitivity angiitis	Postrenal failure
Disseminated intravascular coagulation	Obstruction of the collecting system
Glomerulonephritis	Tumors
Lupus erythematosus	Calculi
Poststreptococcal glomerulonephritis	Infection and inflammatory lesions
Parenchymal damage	Fibrosis
Acute interstitial nephritis	Blood clots
Acute pyelonephritis	Renal papillae
Papillary necrosis	Increased intraabdominal pressure
Diabetes mellitus	Retroperitoneal hemorrhage
Nephrosclerosis	Osmolality, mOsm/L
Sickle cell anemia	Occasional hyaline
Analgesic medications	Occasional hyaline P cast
Cortical necrosis	Tubule epithelial casts
End-stage renal disease	Variable, initially low
Hepatorenal syndrome	
Hepatic artery ligation	

TABLE 14.1. CAUSES OF ACUTE RENAL FAILURE

Immediate Management of Acute Renal Failure

A careful history and physical examination often will suggest the type of ARF; however, the immediate management of this disease is dictated by the extent of serum chemical aberrations and fluid imbalance. Thus initial steps are directed at defining these abnormalities. An electrocardiogram (ECG), serum electrolytes, and urine for microscopic and chemical analysis are obtained. If the serum potassium is elevated, the ECG changes will indicate the rapidity with which the hyperkalemia must be corrected and will serve not only as a baseline against which the success of therapy may be measured but also as an immediate approximation of potassium concentration during the patient's course. Hyperkalemia results in progressive peaking of the T wave, prolongation of the QRS complex, and at high concentrations, absence of the P wave. When the serum potassium is greater than 7 mEq/L or when prominent alterations of the ECG occur (particularly when the P wave is absent), immediate reduction in serum potassium is accomplished by infusing hypertonic sodium bicarbonate and/or administration of insulin and glucose in a ratio of 1 unit per 5 g. Calcium is administered intravenously to stabilize myocardial conductivity. Acidosis and hyperkalemia may be partially corrected by giving bicarbonate, which results in a shift of potassium into the cell with preservation of electroneutrality by concomitant movement of hydrogen ion out of the cell. If some renal function is preserved, potassium secretion is increased in the distal tubule, because bicarbonate reduces the amount of hydrogen ion competing for the common hydrogen-potassium secretory mechanism, thus allowing it increased access to potassium. Glucose and insulin result in movement of potassium into the cell, either by binding it during glucose transport or during glycolytic phosphorylation. These mechanisms result in a transitory decrease in serum potassium, because it moves out of the cell in the former when acidosis recurs and in the latter when substrate has been metabolized. Therefore it is important to lower the total body serum potassium by simultaneously employing an ion exchange resin, such as polystyrene sulfonate (Kayexalate), 10 to 20 g orally or 50 g by enema, both given with sorbitol, or by peritoneal dialysis or hemodialysis. Usually 2 to 3 hours are required before ion exchange resins show an effect or before dialysis can be instituted. Most commonly, alkalization, ion exchange resins, and occasionally, dialysis are all that are required, with glucose and insulin being reserved only for those cases in which hyperkalemia is immediately life-threatening. The state of fluid balance is determined by analysis of intake and output, weight, venous or left atrial filling pressure, physical examination, and history. Inappropriate intake for the amount of output usually accounts for the imbalance; however, therapeutic maneuvers used to treat electrolyte abnormalities also may be contributory. Kayexalate, by exchanging sodium for potassium and sodium bicarbonate, can cause an excessive sodium load and fluid retention. When either overhydration or hypernatremia becomes an urgent problem, dialysis is most effective in correcting the disorder. Usually time is not of the essence, and sodium and fluid restriction will suffice. Low venous or pulmonary wedge pressure, clinical signs of dehydration, a history of blood loss, and hypotension indicate volume depletion and are treated by appropriate fluid replacement.

During the short-term treatment of hyperkalemia and fluid imbalance, an attempt should be made to define the type of ARF involved. A careful history and physical examination often can be diagnostic. The aseptic and atraumatic passage of a Foley catheter is helpful from both a diagnostic and, occasionally, a therapeutic point of view. If the patient is capable of voiding spontaneously and the residual is less than 30 mL, the catheter is withdrawn. If the diagnosis remains unclear after these simple maneuvers, a more sophisticated workup is in order and will include chemical analysis of the urine and serum for sodium, potassium, urea, creatinine, and osmolality; central venous or right atrial pressure determinations; and ultrasonograms of the kidneys. IV pyelography is rarely indicated. The degree of renal deterioration is usually of such an extent that visualization does not occur. Indeed, the contrast material may cause further deterioration of the severely compromised kidney; therefore indiscriminate use of contrast material is to be condemned. If the diagnosis is still in doubt, retrograde or antegrade pyelography or sonography is indicated. The characteristics and therapy for each type of ARF are described in detail in the following sections.

Prerenal Failure

Prerenal failure occurs when there is an excessive nitrogen load or reduced blood supply to the kidney. The former may result from increased muscle catabolism, blood breakdown within the gastrointestinal tract, or excessive protein alimentation. The latter appears in the presence of volume depletion, congestive heart failure, valvular heart disease, or any disease that causes myocardial pump failure.

Pathophysiology

In prerenal oliguria RBF is reduced. When the blood flow is reduced to a level such that the afferent arteriolar pressure falls below 60 mm Hg, reduced filtration pressure results in a decrease in the amount of filtrate delivered to the proximal tubule; glomerulotubular balance is disrupted; and sodium, water, and urea are reabsorbed in increased

amounts. A BUN-to-creatinine ratio of greater than 10:1 occurs because creatinine, when filtered, is not reabsorbed by the tubule, whereas urea is reabsorbed in increased amounts. The proportional excretion of BUN and creatinine, which occurs in health, is disrupted and the urea recirculates, thus resulting in the abnormally high BUN-to-creatinine ratio.

Diagnosis

Diagnostic indications of prerenal failure include a serum BUN-to-creatinine ratio that is greater than 10:1, and a central venous pressure (CVP) and right arterial pressure in volume depletion that are low, provided coexisting myocardial disease is not present. The small volume of urine excreted is highly concentrated with a low sodium content (less than 15 mEq/L). The urine urea concentration divided by the plasma urea concentration (U ÷ P urea) is greater than 20:1, and the U/P osmolality is greater than 1.5. The fractional excretion of sodium or the ratio of U/P sodium to U/P creatinine (U/P_{Na}-to-U/P_{Cr}) is less than 1%. The urine sediment may reveal hyaline casts but generally will be free of casts and red and white blood cells (Table 14.2).

Measurement	Normal	Prerenal	Intrarenal	Postrenal
Blood				
CVP, cm water	5–8	Low to normal	Normal to elevated	Normal to elevated
BUN-to-creatinine ratio	10:1	>10:1	10:1	10:1+
Urine				
Sodium, mEq/L	15–40	<15	>40	>40
Potassium, mEq/L	15–40	Variable	Variable	Variable
Osmolality, mOsm/L	400–600	>450	<300	<300
Volume, mL	800–1200	Low	Variable	Variable, initially low
Urine-to-blood ratio				
Urea	20:1	>20:1	<10:1	<5:1
Osmolality	1.5–2.0	>1.5:1	<1.2:1	<1.0:1
Creatinine	20:1	>40:1	<20:1	<20:1
Fractional sodium excretion, %	Variable	<1.0	>1.0	>1.0
Urine—microscopic analysis	0–1 RBC	Occasional hyaline P cast	Tubule epithelial casts	RBCs and WBCs
	0–1 WBC		RBCs, free heme, or myoglobin	Malignant cells
	Occasional hyaline P cast			Crystals
	No cellular casts			

BUN, blood urea nitrogen; CVP, central venous pressure; RBC, red blood cell; WBC, white blood cell.

TABLE 14.2. DIFFERENTIAL DIAGNOSIS OF PRERENAL, INTRARENAL, AND POSTRENAL FAILURE

Treatment

The treatment of prerenal oliguria is directed at the primary disease: (a) correction of the lesion that has caused the increased nitrogen load, (b) improvement of the failing myocardium, or (c) volume repletion.

Intrarenal Failure

Acute intrarenal failure may follow an ischemic or a nephrotoxic injury or interstitial or glomerular nephritis. Examples of ischemic injury include sepsis, hemorrhagic shock, aortic cross clamping, and surgical or obstetric misadventures; causes of nephrotoxic injury include drugs (aminoglycosides), crush injuries (myoglobin), and diagnostic agents (IV contrast), whereas the etiology of interstitial nephritis often includes drugs. One-half to two-thirds of the patients will be oliguric, whereas the remainder will have urine outputs exceeding 400 mL per 24 hours. Patients who present with nonoliguric ARF have higher sodium concentrations, greater fractional sodium excretions, shorter hospital stays, and a lower mortality and require fewer dialyses than do those who present with oliguria. Indeed, oliguric renal failure has a mortality of 50% to 70%, whereas mortality is approximately 25% in nonoliguric patients. The importance of the sodium excretion rate is emphasized by the finding that less frequently fatal, nonoliguric renal failure patients have higher sodium excretion rates than oliguric patients. Moreover, in the oliguric ARF patient, a persistent urine sodium concentration less than 40 mEq/L is associated with only a 37% survival, whereas those with a urinary concentration greater than 40 mEq/L have a survival rate of 56% (3). It has been suggested that a low fractional excretion for sodium indicates that the cause of the injury

involves tubular obstruction or alterations in renal hemodynamics rather than direct tubular nephrotoxicity (16). The recovery also somewhat depends on the cause of the ARF. Approximately 80% of patients with acute cortical necrosis and 66% of those with thrombotic thrombocytopenic purpura or the hemolytic uremic syndrome do not recover renal function adequate to support life. This is in contrast to patients with acute tubular necrosis and acute interstitial nephritis in whom 62% recover normal renal function. Thirty-one percent show a partial recovery, and only 6% have no recovery whatsoever (7). Another indication of recoverability is correlated with the length of time anuria occurs and the degree to which the kidney takes up nuclide on a renal scan. In one study, infants who remained anuric for at least 4 days after the acute insult and revealed no uptake of radionuclide on scan invariably died of their ARF, whereas infants with ischemic ARF who were nonoliguric and whose kidneys took up the nuclide had a more favorable prognosis (14).

Pathophysiology

A great deal of clinical and experimental data have been accumulated trying to define a pathophysiology for ARF. Unfortunately, most of the information comes from experimental animals, and correlation with the clinical situation often is contrived. A number of proposed mechanisms can be grouped into three areas: (a) vasomotor, increased nephron permeability, tubule obstruction, and decreased ultrafiltration (29); (b) injury to the cell resulting in necrosis or apoptosis; and (c) production of inflammatory mediators that cause injury often introduced by activated neutrophil infiltrations. Because the initiating events are multiple and varied, it is likely that in each case the ARF has been caused by a combination of some of these factors. It is important to understand each of the mechanisms because therapy of established ARF is based on these hypotheses.

The vasomotor theory proposes that there is not only a decrease in total RBF but also a redistribution of intrarenal blood flow. Xenon washout and microsphere injection studies have demonstrated a shift of blood flow away from the cortical nephrons toward the juxtamedullary nephrons (62). Some have suggested that this shift may be protective. Although under normal circumstances the whole kidney receives a blood flow resulting in oxygen delivery that far exceeds demand, the blood flow to the medulla is much less than to the cortex, resulting in limited oxygen reserves. It has been suggested that the medulla is most susceptible to ischemic injury and that the shift in blood flow to the medulla is an attempt to protect this segment (2). The renin-angiotensin system may play a role in the RBF shift. Moreover, prostaglandins also may be contributory. If the initial injury causes an increased release of renin, cortical afferent and efferent arteriolar constriction would result in reduction of cortical blood flow. Because stimulation of the autonomic nervous system releases renin, its role in the cause is unclear, but it may partially explain the occurrence of ARF in patients whose aortas have been cross-clamped. Further evidence for the importance of renin is demonstrated by depleting it in experimental models by either long-term salt loading or antirenin antibodies. A renin-depleted animal has not only a greater chance of recovery but also a more rapid return of function. Moreover, in many patients, renin activity is elevated early in the course of ARF (63). Unfortunately, specific antagonists of renin or angiotensin do not alter the course of these patients once the ARF is established.

Additional evidence for the significance of hormonal regulation of intrarenal blood flow during ARF comes from reports of indomethacin-induced ARF. Indomethacin blocks the synthesis of prostaglandins. PGE_2, a vasodilating prostaglandin, appears to play a significant role in maintaining RBF in the face of pathologic forces that tend to compromise it. Thus in the proper setting, eliminating PGE_2 results in the development or exacerbation of ARF (67). In addition to angiotensin II and prostaglandins, adenosine, increased cytosolic calcium, oxygen-free radicals, and endothelin have been implicated. Although renal vasoconstriction and low RBF may play key roles in the early stages of intrinsic renal failure, later spontaneous increases in RBF often occur without a concomitant increase in the GFR.

The hypothesis of increased tubule permeability proposes that although filtration pressure may or may not be reduced when the filtrate arrives in the proximal tubule, it leaks out, resulting in an effective reduction in filtration. Conflicting data supporting this theory have been reported. Some investigators have demonstrated leakage of labeled inulin and mannitol from the tubule. Moreover, the dye, lissamine green, has been observed to leak out of the tubule. However, others using micropuncture techniques have failed to show increased permeability in split-drop experiments.

Tubule blockade may play a major role in ARF after surgery. Myoglobin can precipitate in the tubule and cause mechanical blockage of the tubule lumen. In models of renal artery cross-clamping, up to 90% of the proximal tubules have been found to be occluded by swollen cells and desquamated proximal tubule microvilli; however, other experimental models that simulate medical causes of ARF are less convincing.

A decrease in ultrafiltration probably plays a major role in many causes of ARF. Numerous studies have demonstrated alterations in the glomerular basement membrane and supporting structures. These alterations result in a decrease in the membrane permeability by as much as 60%. This, coupled with decreased blood flow, results in a lessened hydrostatic pressure gradient and a marked decrease in the delivery of filtrate to the proximal tubule. Perhaps the changes that occur in glomerular membrane properties may

explain the dissociation between RBF and GFR, because a decreased glomerular capillary permeability would continue to cause a decreased GFR even with increased RBF (38).

The aforementioned theories fail to explain all aspects of ARF and, indeed, seem not to explain some circumstances of injury. Following severe injuries, cellular necrosis and the initiation of apoptosis occur—the latter resulting in progressive loss of renal tubule cells (31).

Finally, a variety of inflammatory mediators, including tumor necrosis factor, interleukin-1, interleukin 8, and macrophage chemoattractant protein, are produced by the injured kidney. Some of these may be provided by activated neutrophils, which infiltrate the interstitium of the injured kidney.

Diagnosis

The diagnosis of intrarenal failure is based on historic, chemical, and radiologic determinations. The BUN-to-creatinine ratio is 10:1, and the CVP or left arterial filling pressure is normal or elevated. The urinary sodium concentration exceeds 40 mEq/L with a variable potassium secretion—usually less than 20 mEq/L. The U/P osmolality is less than 1.2 and the U/P urea is less than 10. The fractional sodium excretion exceeds 1%. Tubule epithelial cells and tubule epithelial cell casts may be observed in the urine (Table 14.2). A radioimmunoassay of tubule antigens has been developed that successfully diagnoses 80% of patients with acute tubule necrosis (71). This test has not gained popularity because the diagnosis of intrarenal failure may be made with this degree of accuracy by conventional techniques.

Ultrasonography or roentgenographic studies of the abdomen without the administration of pyelographic contrast should be used in an effort to determine whether the acute problem is superimposed on prior renal disease. Preexisting renal disease may be demonstrated by unilateral or bilateral small kidneys indicative of a vascular or infectious cause. An enlarged renal outline may imply either acute renal vein thrombosis or an infiltrative lesion, such as myeloma or lymphoma, or postrenal failure when it is associated with dilated calyces. Radionuclide renal scans or magnetic resonance arteriography occasionally are helpful in cases of bilateral renal artery thrombosis and may suggest that therapy is needed.

The BUN rises between 10 and 20 mg/dL per day, whereas creatinine increases 0.5 to 1.0 mg/dL per day. Plasma potassium increases 0.5 mEq/L per day, and because 50 to 100 mEq of fixed acid is retained, the plasma bicarbonate decreases by 1 to 2 mEq/L per day. In the posttraumatic state, the hypercatabolic response may result in a more rapid rise in the BUN, potassium, and fixed-acid accumulation. A crush injury involving muscle necrosis and myoglobin nephropathy can result in rises in serum creatinine up to 2 mg/dL per day and rapid increases in serum potassium and uric acid. Hypocalcemia often is noted and may have significant cardiac consequences, particularly if the serum potassium is elevated.

Treatment

Careful fluid balance, the judicious use of ion-exchange resins, dialysis, and administration of a potent diuretic when oliguria occurs are the hallmarks of therapy (66). The use of furosemide in the treatment of acute oliguric intrarenal failure is controversial. Several studies have failed to demonstrate more rapid recovery, improved GFR, or reduction in the number of dialyses required, except when cardiac decompensation is present (11). On the other hand, converting oliguria to nonoliguria makes subsequent fluid management less cumbersome. If furosemide is given, a dose of 80 mg is tried; if unsuccessful, it is doubled. One of three responses occurs:

1. Oliguria persists. The patients are treated with replacement of net water requirements (insensible loss – water of metabolism = 10 to 15 mL/kg per 24 hours). If a return in urine output does not occur within 21 days, the chance of recovery of renal function is poor.
2. A diuresis ensues, GFR increases, and an immediate reversal in the rise of BUN and creatinine occurs. It is important to rehydrate the patient in this setting, because this response suggests prerenal oliguria. These patients recover, often obtaining normal renal function.
3. A diuresis occurs, GFR remains low, and BUN and creatinine continue to rise. These patients are treated with replacement of net water loss (10 mL/kg per 24 hours) plus urine output and gastrointestinal and tube losses.

Large sodium losses occur during this phase and require replacement. Potassium losses are small, although rarely they may be excessive and require replacement. Appropriate serum potassium concentrations are maintained by restriction of potassium and the use of ion exchange resins and dialysis.

Mannitol has been found to be useful in patients with ARF resulting from crush injury, but has not been shown to be particularly helpful in other types of renal injury.

Low-dosage dopamine (1 to 2 μg/kg per minute) has not altered the course of ARF; however, some evidence indicates that it is helpful in the hepatorenal syndrome and in preventing ARF if used during the early prodromal period (65). The administration of dopamine to these patients results in a significant increase in the diuresis and natriuresis and, when combined with furosemide, may improve renal function in at least some patients with ARF. Experimental evidence shows a synergistic protective effect with the combination of dopamine and furosemide in several models of ARF. Dopamine causes marked vasodilation of both afferent and efferent arterioles (26). Mannitol has been helpful in preventing ARF (if given before interrupting renal artery

flow) and in lessening the toxic effects of myoglobin. No study to date that has been properly performed has shown dopamine to be of any benefit in reducing morbidity or mortality.

ß-Blockers have produced variable results, and angiotensin and renin inhibitors have not proved useful. Alkalizing agents, by solubilizing organic acids (drugs) when they are causative, and diuresis, by diluting toxic substances (cisplatin and myoglobin), are helpful prophylactically. Finally, if given early in the course of the disease, calcium channel blockers may be helpful by reducing intracellular calcium in tubule cells that have suffered an ischemic injury and are deprived of ATP.

Atrial natriuretic peptide has been shown to convert some patients from oliguric renal failure to nonoliguric renal failure, but generally has not been found to be helpful in reducing mortality. Insulin-like growth factor has been shown to prevent the decline in GFR in patients with ARF in selected circumstances but also has not been helpful in changing morbidity or mortality.

Perhaps the one drug regimen that all agree is most helpful, particularly in severely malnourished surgical patients, is nutritional support. Hyperalimentation with essential L-amino acids has improved recovery and reduced the number of dialyses required (22).

Dialysis plays an important role in the management of these patients. If the BUN is greater than 100 mg/dL and the creatinine exceeds 12 mg/dL, dialysis is mandatory. Evidence suggests that if the BUN is kept below 70 mg/dL, the incidence of sepsis is reduced from 88% to 63%, bleeding from 60% to 36%, and mortality from 80% to 36% (15). Others have shown consistently that mortality is lowered, extrarenal complications are less frequent, and the clinical course is better in any type of ARF when dialysis is employed before the clinical signs of uremia occur, emphasizing the need to evaluate each patient rather than basing dialysis on some arbitrary number. Dialysis may be accomplished either peritoneally or hemically.

Recent evidence indicates that in the critically ill patient, dialysis under certain circumstances may in fact prolong ARF. This is particularly apparent in unstable patients who become hypotensive when placed on dialysis. In addition, the dialysis membrane may activate the inflammatory cascades, further compromising the recovery of the injured kidney.

Plasma exchange may be useful in treating patients whose renal failure is the result of nondialyzable substances, such as dextran. Slow continuous ultrafiltration with a filter placed between two limbs of a Scribner shunt has been useful in selected critically ill patients. Its advantages include hemodynamic stability, ability to remove large fluid volumes (thus making treatment modalities such as IV nutrition feasible), and no requirement for systemic anticoagulation. It has many disadvantages, among them electrolyte abnormalities, bleeding, clotting of the shunt filter, excessive drug removal, azotemia, hypotension, and bacteremia (57,64).

Mortality in this group is high; however, between 25% and 70% of patients surviving an acute tubule injury eventually recover sufficient renal function to support life without dialysis. Of those recovering, 20% to 40% will have a reduced GFR for 1 year or longer. Abnormalities of tubule function, including renal glucosuria and decreased concentrating ability, may persist indefinitely.

The most frequent cause of death is infection (61). It causes 36% of the deaths and is usually pulmonary in origin. The next most common cause of death is gastrointestinal hemorrhage. Delayed wound healing, poor generation of granulation tissue, anorexia, anemia, and bleeding abnormalities caused by platelet malfunction contribute to the high level of morbidity in this disease. Indeed, even mild ARF significantly affects morbidity, even in the absence of significant comorbid disease (41).

Because of the high mortality of ARF, perhaps the most effective treatment is prophylaxis. Adequate hydration and selective use of dopamine, mannitol, furosemide, and alkalization in patients undergoing surgery who are known to have a high risk for the development of postoperative ARF should lessen the incidence of the disease. Risk factors that carry with them an increased incidence of postoperative ARF include advanced age, cardiac or hepatic failure, sepsis, jaundice, rhabdomyolysis, and massive blood transfusions.

Myoglobin Nephrotoxicity

Rhabdomyolysis has been reported to be the cause of ARF in approximately 5% of all patients with acute renal insufficiency. The prognosis for recovery is excellent, provided rhabdomyolysis is recognized promptly and therapy is begun immediately. There are traumatic and nontraumatic causes of rhabdomyolysis (37). The former include crush injuries, electric burns, arterial occlusion, and surgery. Nontraumatic causes include increased muscle exertion, inflammatory muscle diseases, infection, toxic drugs, and metabolic abnormalities (particularly hypokalemia). In urologic patients, prolonged, exaggerated lithotomy position has been associated with rhabdomyolysis and ARF (24).

After the precipitating event the patient becomes acutely ill with fever, weakness, and pain. The urine is brownish and is dipstick-positive for heme. Because the molecular weight of myoglobin is much lower than that of hemoglobin, it is cleared rapidly from the serum. Thus a spun blood sample will reveal a clear serum in contradistinction to hemolysis, where the serum will be red as a result of retained hemoglobin. A high serum creatinine phosphokinase level establishes the diagnosis. Serum potassium and phosphate often are elevated, and hyperuricemia may be severe. The mechanism of ARF is unclear, but it probably is caused by a combination of events including low flow, prolonged contact of the tubule lumen with myoglobin, and high uric acid concentration.

Therapy is directed at establishing a diuresis with either a loop diuretic or by volume expansion, with saline solution combined with either mannitol or a loop diuretic. The diuresis dilutes the toxic myoglobin, removes it from the kidney, reduces the serum uric acid concentration, and modestly alkalizes the urine. Alkalization is advisable initially, because an acid medium promotes myoglobin dissociation into ferroprotoporphyrin and globin. The former is toxic (21).

Radiocontrast-induced Acute Renal Failure

The incidence of reduced renal function resulting from radiocontrast material has been reported to be as high as 12%. The incidence of contrast nephropathy in patients with normal renal function is lower than 2% after angiography and approximately 1.5% after IV urography. In contrast, among patients with diabetes and coexisting renal insufficiency, more than half develop substantial renal damage after IV urography (6). The occurrence of clinically significant ARF in the general population is exceedingly low; it is most commonly found after angiography or IV urography in patients with significant risk factors for the development of the disease. Almost all patients who develop clinically significant ARF have either previously existing renal disease with compromised renal function or diabetes with moderate renal impairment. However, adult-onset diabetic patients with normal renal function do not appear to be at increased risk for development of ARF. Patients with juvenile-onset diabetes are more likely to develop renal insufficiency even though they do not demonstrate significant renal impairment before the injection of contrast medium. Other factors that have been less well correlated with the development of renal insufficiency after the injection of radiocontrast include advanced age, dehydration, multiple contrast exposure within 24 hours, hyperuricemia, proteinuria, hypoalbuminemia, multiple myeloma, and impaired hepatic function. Dehydration per se does not appear to be a specific risk factor unless the patient has preexisting renal disease. Conversely, in patients with prior renal disease, establishing a diuresis after the injection of contrast medium appears to lessen the incidence of renal deterioration. In patients with multiple myeloma, there is no compelling evidence of any increased risk for contrast-induced renal failure unless there is preexisting renal insufficiency. However, contrast-induced renal failure in patients with multiple myeloma often has catastrophic implications because it is irreversible.

In summary, existing renal insufficiency is the single most important predisposing factor. Moreover, diabetes does not increase the risk of contrast-induced renal failure if renal function is normal and the patient is well hydrated and does not have juvenile-onset diabetes. When radiocontrast-induced renal failure does occur, 75% of patients are oliguric for the first 24 hours after contrast exposure. Prolonged oliguria results in only partial return of renal function. The serum creatinine generally peaks by the seventh postinsult day, and renal function returns to normal in 75% of the cases. Dialysis rarely is required, and almost all patients have an adequate return of function and do not require long-term dialysis (50). The pathogenesis of the disorder has been hypothesized to be the result of direct tubule toxicity, to renal ischemia caused by alterations in blood flow with shunting of blood from cortex to medulla, and to intratubular obstruction. Because contrast agents are uricosuric, tubule obstruction by crystals of uric acid has been proposed as the pathogenic mechanism. Finally, immunologic factors have been proposed, but the evidence is not compelling. It appears that the renal toxicity after contrast exposure is probably the result of direct tubule toxicity and renal ischemia (6).

Postrenal Failure

The causes of postrenal failure are divided into lower and upper urinary tract obstruction. The lower urinary tract is evaluated in the preliminary treatment, as previously indicated, by the passage of the Foley catheter. Obstruction of the upper urinary tract may be the result of ureteral calculi, blood clots, sloughed papillae, ureterovesical or ureteropelvic junction obstruction, ureteral tumors, ureteral stricture, extrinsic compression by retroperitoneal tumors, hemorrhage, fibrosis, tumor, or an inflammatory lesion. Recently, increased intraabdominal pressure has been reported as a cause of postrenal failure.

Pathophysiology

In the patient with postrenal failure, RBF is markedly reduced with a reduction in GFR to 10% of normal or less, causing a decline in filtration with decreased delivery of filtrate to the proximal tubule (47). This may be mediated through the renin-angiotensin system (46) and/or the prostaglandin system. Elevated concentrations of renin, the vasodilator PGE_2, and the vasoconstrictor thromboxane A_2 have been reported in obstructive uropathy (49). The significance of the prostaglandins in the pathophysiology of obstructive uropathy has been questioned recently. Specific inhibitors of thromboxane synthesis have failed to show any major effect on renal hemodynamics (42). Moreover, inhibition of prostaglandin synthesis during the obstructive phase has little influence on return of renal function, whereas inhibition of renin during this phase results in a major improvement in the return of renal function (44). Interstitial infiltration by lymphocytes and activated neutrophils result in cytokine release, which may explain some of the pathologic events. Moreover, apoptosis in the distal tubule and cortical collecting duct are initiated in animals with uretal obstruction. Even though complete obstruction

does occur, GFR does not cease but remains modest, and the fluid that is filtered is reabsorbed by the renal tubules, the peripelvic lymphatic vessels and veins, and the perirenal tissues when the urine extravasates around the fornices of the calyx. With the increased hydrostatic pressure within the ureter, destruction of tubule tight junctions occurs, causing increased tubule permeability (46). Permeability is increased throughout the entire nephron, proximal tubule, loop, distal tubule, and collecting duct; there is a reduction in the net sodium and water reabsorption with net addition of sodium by the collecting duct. Increased potassium secretion by the distal tubule occurs in the postobstructed phase, and during recovery, concentrating ability remains impaired for days (47). Although reduced, RBF persists and removes solute from the medulla. Thus after the relief of such obstructions, there is often an excessive volume output with large sodium losses and inability of the kidney to concentrate and excrete an acid load. The loss of medullary tonicity and the rapidity with which it is built up determines the degree and length of time urinary concentration is impaired. Rarely, concentrating ability may take as long as 6 to 9 months to return to normal. Should obstruction occur in the presence of infection or protein depletion and exist for prolonged periods, parenchymal destruction occurs. Under these circumstances complete return of renal function does not occur. The longest report of complete obstruction with the return of renal function to support life is 90 days.

Diagnosis

The diagnosis of upper tract obstruction is established by retrograde pyelography or occasionally by percutaneous puncture and antegrade pyelography. However, it should be remembered that indiscriminate manipulation of the urinary tract must be avoided, because sepsis, the most common cause of death in patients with intrarenal failure, all too often is a consequence of genitourinary manipulation. After lower urinary tract obstruction has been ruled out by the introduction of a Foley catheter, complete anuria demands retrograde or antegrade pyelography. In addition to obstruction, total anuria may be the result of bilateral renal artery thrombosis, aortic vascular catastrophes, acute glomerulonephritis, or cortical necrosis, and it may be present during the first 12 to 24 hours of acute tubular injury.

Abdominal roentgenograms, computed tomography scans, and renal ultrasonograms are useful. The diagnosis may be suggested by the presence of calcification in the course of the ureters; osteoblastic lesions of the bones implying carcinoma of the prostate, which may have invaded the bladder; or large pelves on ultrasonography, implying obstruction. Rarely, the ultrasonogram will show a nondilated system even in the presence of bilateral obstruction (56). Therefore if one's index of suspicion is high, retrograde or antegrade pyelography should be performed even though the ultrasonogram does not show hydronephrosis.

These patients are well hydrated; have normal or slightly elevated CVP; have a BUN-to-creatinine ratio of 10:1 or greater; and a urine microscopic examination may reveal red blood cells, white blood cells, crystals, or malignant cells. Urine sodium concentration is greater than 40 mEq/L, and potassium concentration is variable, usually ranging between 20 and 40 mEq/L. The renal concentrating ability is severely impaired, which is reflected by a U/P urea of less than 5 and a U/P osmolality of less than 1.0. The fractional sodium excretion is in excess of 1%.

Treatment

Therapy is directed at the site of obstruction, requiring a urethral catheter, a suprapubic cystotomy, a nephrostomy, a cutaneous ureterostomy, or indwelling ureteral catheters; double-J stents may be left temporarily until the metabolic status of the patient is stable enough to permit the appropriate surgical procedure. During the postobstructed period, large quantities of urine are excreted with a low osmolality and a high sodium concentration (50 to 70 mEq/L). These defects are unresponsive to ADH and mineral corticoid administration. Volume and sodium should be replaced as lost. D_5½NS is usually the appropriate infusion. Potassium losses are therapeutic initially, but if prolonged and excessive, replacement of potassium may be necessary later. Sodium and potassium conservation return to normal within 48 to 72 hours; however, the concentrating defect may persist for 7 to 12 days, making dehydration a potential danger should fluid be inappropriately restricted. Most of these patients, if they respond with a diuresis, will go on to recovery of renal function. If oliguria persists, the obstruction has caused destruction of parenchyma, and such patients are managed as described for intrarenal ARF.

Postrenal Polyuria

Postrenal polyuria occurs during partial chronic urinary obstruction or after the release of complete bilateral ureteral occlusion (postobstructive diuresis), provided that significant parenchymal damage has not occurred. As described previously, basic defects involve a washout of the medullary concentration gradient and increased tubule permeability. Such patients lose excessive volumes of fluid that generally contain 40 to 80 mEq/L of sodium and variable concentrations of potassium. They are incapable of both concentrating and acidifying their urine. Because there is no medullary osmotic gradient, ADH is ineffective. The management of these patients is as previously described and involves careful intake and output records, daily weights, frequent serum osmolalities, and careful physical examination to determine the presence of dehydration or edema.

Intrarenal Polyuria

Intrarenal polyuria results from an intrinsic impairment of the renal concentrating mechanism. It may be caused by anatomic disruption from disease, metabolic aberrations affecting the ADH–collecting duct interaction, or functional renal derangements (Table 14.3). A reduction in renal medullary tonicity may be caused by anatomic disruptions such as those found in sickle cell anemia. In such patients, portions of the renal medulla are infarcted as a result of low oxygen tonicity and sickling of the erythrocytes. Other diseases, such as medullary cystic disease, pyelonephritis, nephrocalcinosis, and amyloidosis, may similarly disrupt the medulla. Metabolic aberrations of the ADH–collecting duct interaction include hypercalcemia, prolonged hypokalemia, and RTA. These disorders are not uncommon in postsurgical and posttrauma patients.

Hypercalcemia initially interferes with the action of ADH on the collecting duct epithelium, and if it is corrected early, reversal of the concentrating defect is immediate. Prolonged hypercalcemia with calcium deposition in the thick ascending limb of Henle's loop, the distal tubule, and the collecting duct may result in permanent loss of renal concentrating ability. Prolonged hypokalemia may exert its effect by inhibition of the generation of adenyl cyclase, cyclic adenosine monophosphate (cAMP), or protein kinase and their interaction between ADH and the collecting duct. Restoration of the appropriate potassium level corrects the concentrating disorder. RTA also may cause a lack of concentrating ability. Because RTA often results in low serum potassium concentrations, it may be hypokalemia, not the RTA as such, that is responsible for the concentrating defect. In any event, restoration of normal serum acid–base and electrolyte balance corrects the problem, provided nephrocalcinosis has not complicated the disease.

Finally, other causes of polyuria include functional derangements, such as nephrogenic diabetes insipidus in which the collecting duct appears to be insensitive to circulating levels of ADH, and lack of medullary tonicity from persistent excessive urine output. The management of intrarenal polyuric states involves daily monitoring of body weight and serum osmolality and fluid replacement, volume for volume. Specific metabolic disorders, such as hypercalcemia, hypokalemia, and systemic acidosis, are corrected. Anatomic abnormalities, such as sickle cell disease, pyelonephritis, polycystic disease, myeloma, amyloidosis, and polyarteritis, are not amenable to any specific treatment with respect to polyuria, and therefore these patients are best treated in a supportive manner. Exogenous ADH is not effective in these disorders unless they have a metabolic cause and then only when the abnormality has been corrected.

Prerenal Polyuria

Prerenal polyuria is caused by insufficient ADH or by exogenous or endogenous diuretic agents. The intrinsic ability of the concentrating mechanism to function is maintained; however, if the polyuria is prolonged, it may result in washout of the medullary osmotic gradient, in which case an intrinsic renal defect would be superimposed on a prerenal defect (17). Insufficient ADH activity may result from suppression of ADH release in the pituitary, either as a normal consequence of volume overload or as a consequence of iatrogenic-induced reduction in serum osmolality. The common causes in volume expansion include over-administration of IV fluids, compulsive water drinking, and pathologic stimulation of the thirst center. Dilution of plasma osmolality occurs when sodium loss exceeds that replaced or when water is replaced in an electrolyte-poor fluid. Absence of or insufficient ADH production occurs in cerebral trauma and diabetes insipidus, which may be an inherited or acquired abnormality. Because the intrinsic concentrating mechanism is unaffected in these states, it is of paramount importance to determine the primary cause. If a lack of ADH is responsible, administration of this hormone is therapeutic. However, if volume abnormalities have caused this disorder, their correction will be curative.

Prolonged, persistent diuresis can cause dilation of the collecting system. After the prolonged diuresis, IV urography may reveal bilateral hydronephrosis. This hydronephrosis occurs on the basis of excessive diuresis and not on the basis of any mechanical obstruction. Because diuresis results in an increase in intraureteral pressure as bladder filling occurs, it is easy to understand why ureteral dilation occurs (see Physiology in Chapter 24).

CHRONIC RENAL FAILURE

Part of "14 - THE KIDNEY "

Chronic renal failure occurs most commonly as a result of glomerulonephritis caused by immunopathogenic mechanisms; diabetes, infection, toxins, obstruction, congenital

disorders, and hereditary nephropathies account for the majority of the remaining causes. The loss of renal function is usually insidious, not manifesting itself until late in the disease. The initial symptoms that herald a significant lack of renal function are protean and include fatigue, lassitude, and weakness. As the renal function continues to deteriorate, the patient may complain of a metallic taste, anorexia, nausea, vomiting, abdominal pain, hiccups, and diarrhea. With progression, there is an inability to concentrate, somnolence, twitching, bone pain, pericarditis, and hypertension (and its sequelae). All organ systems are affected at various stages in the disease. The detrimental effects of renal failure can be ameliorated by proper recognition and anticipation of the various complications with appropriate prophylactic therapy instituted before the abnormalities become clinically manifest.

Pathophysiology

As renal function decreases, those nephrons that continue to function increase in size, as do their respective glomeruli. This concept was originally suggested by Bricker and co-workers (9) and is known as the *intact nephron hypothesis.* Although this hypothesis has been questioned, because micropuncture data suggest a heterogeneity of tubule function in disease, it appears that within the constraints of biologic variability, the intact nephron hypothesis has the most evidence to support it and thus best explains the observed deterioration of renal function in chronic renal failure. GFR and RPF decrease, and functional mass decreases in parallel, whereas each individual nephron that continues to function increases its single-nephron filtration rate. Because fewer nephrons are functioning and those that are have increased their activity, if solute excretion is to be maintained, the fractional excretions for the respective solutes must increase. Sodium homeostasis is maintained until late in the disease by the mechanism of increasing single-nephron fractional excretion from less than 1% in health to 10% to 20% in disease. Late in the disease sodium excretion becomes fixed, and the nephron is incapable of varying its fractional excretion according to the needs of the patient, thus resulting in a salt-losing nephropathy. Salt restriction in such patients will result in substantial hyponatremia. This occurs late in the disease process. Similarly, water conservation and excretion are maintained until the GFR falls below 20 mL per minute, at which time the kidney is incapable of compensating for varying water loads or significant water deprivation. The kidney retains a remarkable ability to excrete potassium until late in the process. The increased flow rate obtained by the remaining functional nephrons facilitates potassium secretion. Acidosis, which is associated with increasing renal failure, also promotes potassium secretion. Mild hyperkalemia occurs when the GFR falls below 10 mL per minute. Significant hyperkalemia is uncommon until oliguria supervenes with a urine output less than 500 mL per 24 hours.

Acid–base balance is reasonably well maintained until the GFR falls below 20 mL per minute, then acid–base imbalance is a result of the failure of the distal tubule to maintain ammonia excretion (39). Even in advanced renal failure, not much alkali is excreted. Bicarbonate reabsorption is strongly influenced by the extracellular volume so that late in the disease, when the kidney is not capable of responding to fluid loads, excessive fluid intake often results in bicarbonate wasting.

The determination of renal function using creatinine presents certain difficulties in patients with chronic renal failure. Serum creatinine levels may be deceptively low because of increased metabolism by the gut and decreased muscle mass as a result of muscle wasting from the uremia. When the GFR is less than 15 mL per minute, the creatinine clearance will overestimate the true GFR (inulin clearance) as a result of tubule secretion of creatinine, often by as much as 50% to 100%.

Unfortunately, some aspects of renal function are maintained at the expense of others. Phosphate homeostasis is an excellent example of this “trade-off” phenomenon. As the need to excrete phosphate continues with decreased renal function, the intact nephrons are not capable of increasing their fractional excretion for phosphate. Serum phosphate rises, which results in a fall in serum calcium and the subsequent release of parathormone. Parathormone acts on tubules to increase phosphate excretion, thereby returning serum phosphate to normal levels. The other effect of parathormone on bone reabsorption also occurs, resulting in bone destruction. Bone destruction is the price, or trade-off, paid for maintaining a normal level of serum phosphate.

The increased filtration that each nephron must maintain appears to be responsible for its ultimate demise. It has been shown experimentally that increasing single-nephron GFR results in stripping off the glomerular endothelial cells, thus destroying the charge barrier that prevents deposition of circulating proteins in the glomerular basement membrane (55). The circulating serum proteins are then deposited and accumulate in the mesangium, resulting in the histologic appearance of glomerulosclerosis. Thus an initial insult that reduces renal mass, such as segmental injuries caused by obstruction, reflux, or dysplasia, may have occurred in the distant past, with renal failure occurring slowly over the ensuing years as a result of an increased workload of the remaining functional nephrons, with protein deposition causing their ultimate failure. In chronic renal failure patients in the Christchurch series, 12% of cases were the result of reflux nephropathy, few of which had been infected. These patients began dialysis at approximately 18 years of age, suggesting that the initial insult caused progressive renal deterioration as each remaining nephron was required to do more work (4).

The fact that protein is detrimental to renal function was suggested many years ago (1) and led to the development of the protein-restricted “renal failure diet.” When patients eat this diet, many of the symptoms of uremia are alleviated or

reduced. Administration of essential amino acids and their keto analogs have been successful in slowing the rise in BUN; however, the substances are not generally palatable. More recently it has been suggested that dietary protein may cause renal failure in patients who have sustained a renal insult (8). Thus dietary protein restriction may not only alleviate symptoms of uremia in patients with severely compromised renal function but may also prevent the progression of the disease in patients who have a modest decrease in renal function of insufficient degree to manifest signs or symptoms. Protein induces an acute increase in GFR through renal vasodilation and glomerular hyperperfusion. The elevated intracapillary pressures and transcapillary flux of ultrafiltrate eventually disrupt the integrity of the glomerular capillary membrane. Proteinuria ensues, and the increased flux of proteins exacerbates the glomerular capillary injury and causes progressive accumulation of mesangial deposits—the forerunner of focal glomerulosclerosis. Others have suggested that it may not be protein per se that causes the renal injury but rather the high phosphate intake from the protein. The phosphorus-induced renal injury is mediated through calcium-phosphate deposition in the kidney as a result of an increased filtered load of phosphate per nephron (28). Several prospective studies have shown that dietary restrictions of protein lessen the progression of renal deterioration in certain subgroups of patients, particularly those with advanced disease (54). Other studies have shown a nonsignificant slowing in the progression (34). In children, a multiinstitutional study has failed to show any effect of low-protein diets on slowing the progression of chronic renal failure (70). Proper control of blood pressure has been found to be one of the most important methods of slowing the progression of chronic renal failure.

Complications

Chronic renal failure is a systemic disease and, as such, affects every organ system in the body. The more common complications most relevant to the urologist include bladder and renal and/or perirenal infections, acquired renal cystic disease and renal carcinoma, infertility, impotence, and gynecomastia.

Renal, Perirenal, and Bladder Infections

Urinary tract infection is an important cause of morbidity and mortality in chronic renal failure and has been reported to be responsible for up to 20% of all deaths in patients with end-stage renal disease (ESRD) (35,48). As many as 10% of patients receiving hemodialysis have had, at any one time, a bacteremia secondary to an infection (53). Pyocystis, pyonephrosis, perinephric abscesses, and infected polycystic kidneys are not uncommon (40). The frequent absence of leukocytosis and fever coupled with a low index of suspicion (because a poorly functioning urinary tract is often dismissed) results in a delayed or missed diagnosis. A history of stone disease, congenital abnormalities of the collecting system, and pus from the urethra, coupled with urethral catheterization, renal ultrasonography, or computed tomography usually will lead to the diagnosis.

Acquired Renal Cystic Disease and Renal Cell Carcinoma

Patients on chronic dialysis for extended periods of time have a high propensity to develop cysts in their native kidneys. The incidence has been reported to vary between 35% and 80%. There is also a 100-fold increased risk of developing renal cell cancer in these cysts when compared with the general population (32). The acquired cysts make detection of renal cell cancers difficult. Patients who require periodic follow-up with ultrasound include those who have hematuria, flank pain, or other symptoms or signs that indicate a change in the kidneys.

Infertility

Both men and women who have ESRD are infertile. Even dialysis does not seem to restore their fertility. Serum hormone studies reveal an elevated level of luteinizing hormone and follicle-stimulating hormone and a depressed level of testosterone in the male patients. It appears that the failure occurs at the level of the testes.

Impotence

Gonadotropins are elevated, prolactin is elevated, and testosterone is depressed. Some patients respond to dialysis and others respond to androgen supplementation. A trial of bromocriptine to inhibit the elevated prolactin has been used with success in some patients, but the side effects of the drug usually prevent patients from continuing therapy.

Gynecomastia

Gynecomastia is not unusual, particularly early in dialysis. There is no satisfactory treatment; however, certain drugs aggravate the situation and should be discontinued if possible. The drugs include digitalis preparations, methyldopa (Aldomet), and spironolactone (Aldactone).

Gastrointestinal Tract

Mucosal ulcerations, ascites, pancreatitis, pruritus, and peptic ulceration are not uncommon. However, the symptoms of anorexia, nausea, vomiting, diarrhea, uremic breath, and metallic taste are more common.

Cardiovascular Disorders

Hypertension occurs in more than 80% of patients with ESRD. Three-quarters of these patients are hypertensive

because of volume overload. The patient must be overloaded by at least 5% of body weight for hypertension to occur. This can be completely corrected by dialysis and the selected use of potent diuretics. The other 25% of uremic hypertensive patients are volume independent. These patients are labile when dialyzed and often require potent antihypertensives for blood pressure control. Even so, some patients ultimately require nephrectomy for control of their hypertension. Congestive heart failure is not infrequent in these patients. Uremic pericarditis continues to be a frequent complication, even with dialysis. These patients often present with fever, chest pain, leukocytosis, and sometimes, a pericardial friction rub. Often they will respond to dialysis alone, but indomethacin or corticosteroid administration may be necessary. Rarely, cardiac tamponade occurs, signaled by an enlarging cardiac silhouette on chest x-ray films, an elevated venous pressure, and hypotension. Surgical drainage is the treatment of choice. Echocardiography has been used with great success to follow the size of pericardial effusions.

Neuromuscular System

Peripheral neuropathy is usually sensory, with patients complaining of burning sensation in the feet and legs, particularly at night. Its incidence has decreased with the advent of early dialysis. Left untreated, the neuropathy will progress to loss of sensation, muscle atrophy, and motor nerve involvement. Therapy consists of dialysis and replacement of nutritional deficits. Renal transplantation reverses the disorder. Central nervous system disorders include loss of attention, short memory, and disturbed sleep. Without treatment, agitation, seizures, and psychotic behavior with eventual coma supervene. Aluminum intoxication has been implicated, but its role remains controversial.

Hematologic Disorders

The major cause of anemia in uremic patients is the lack of bone marrow production. Other contributing factors include gastrointestinal bleeding; vitamin deficiency states, particularly folate, pyridoxine, and iron; and hemolysis. Therapy consists of dialysis, replacement of nutritional deficits, minimization of blood loss, and occasionally, the use of androgens. The recent introduction of recombinant erythropoietin has markedly changed the management of anemia of renal failure. Most patients can maintain a hematocrit level of approximately 35% if given erythropoietin. These patients report an improvement in their sense of well-being. Transfusion should be reserved for situations in which active bleeding occurs or in cases in which the anemia is severe and unresponsive to erythropoietin, that is, the hematocrit is less than 14%. These patients also have a bleeding diathesis, because platelet function appears to be disturbed. It is a qualitative rather than a quantitative defect. This abnormality will reverse with dialysis alone.

Skeletal System

Osteomalacia and hyperparathyroidism often are seen together in uremia. Renal osteodystrophy includes osteitis fibrosa cystica, osteoporosis, osteomalacia, and osteosclerosis. Hyperparathyroidism results in subperiosteal resorption of bone and, rarely, brown tumor formation. Growth retardation in children and deforming skeletal rickets also occur. Chronic acidosis leads to the osteopenia and depression of skeletal growth in children. The osteomalacia may be a result of aluminum intoxication. The complications are fractures, aseptic necrosis of the hips, bone pain, and deformities. Treatment involves correction of serum phosphorus, usually with antacids that do not contain aluminum, and the administration of calcium supplements and dihydroxyvitamin D_3. (Care must be taken not to give calcium or vitamin D until the serum phosphorus is normal, because metastatic calcification will occur and damage many organs.) Parathyroidectomy is indicated if roentgenographic changes of hyperparathyroidism or metastatic calcification occur.

Arthropathy or joint pain is usually secondary to gout when there is hyperuricemia or to pseudogout when serum uric acid is relatively normal but serum calcium and phosphorus are both high. Both disorders respond to correction of the met abolic disturbances.

Metabolic Disturbances

Metabolic acidosis occurs late in the disease. Hypercalcemia occasionally occurs, usually as a result of secondary hyperparathyroidism or excessive calcium or vitamin D supplementation. Hyperuricemia is extremely common and generally is not associated with gout. Hypermagnesemia is common in patients who are not receiving dialysis. This can be significantly aggravated by compounds that contain magnesium (e.g., antacids). It is important not to give drugs that contain magnesium to patients with ESRD, because these patients are prone to magnesium intoxication.

Treatment

Currently, treatment of ESRD involves four basic approaches. Early in the disease dietary manipulation with the use of selected drugs to maintain serum electrolytes is all that is necessary. As the GFR falls below 10 mL per minute, either peritoneal dialysis or hemodialysis generally will be required. Renal transplantation is the ultimate therapy for the disorder.

Drug Administration

The kidneys are the major route of drug metabolism and secretion. Renal failure necessitates altered handling of most drugs and giving them in the usual dosages to uremic patients will lead to elevated blood levels, toxic symptoms, and perhaps even death. Antibiotics, sedatives,

narcotics, and cardiovascular drugs often must be adjusted to an appropriate dosage level. Certain drugs should be totally avoided in uremic patients (Table 14.4). Drugs that commonly require altered dosage schedules are listed in Table 14.5 .

Antimicrobials	Antihypertensives
Methenamine mandelate	Methyldopa
Nalidixic acid	Guanethidine
Nitrofurantoin	Reserpine
Tetracyclines (other than doxycycline or minocycline)	Diuretics
Neomycin	Acetazolamide
	Mercurials
Analgesics—narcotics	Triamterene
Salicylates	Spironolactone
Acetaminophen	Thiazides
Phenacetin	
Phenazopyridine	Arthritis—gout
Meperidine	Gold salts
Morphine	Probenecid
	Phenylbutazone
Sedatives—tranquilizers	
Barbiturates	Antineoplastics
Glutethimide	Nitrosourea
Lithium	Cisplatin
Ethchlorvynol	
Methaqualone	Neuromuscular agents
Phenothiazines	Gallamine
	Pancuronium
Antacids—laxatives	Succinylcholine
With magnesium	
With phosphate	Antiarrhythmics
Mineral oil	Bretylium
	Others
	Terbutaline
	Acetohexamide
	Chlorpropamide

TABLE 14.4. DRUGS TO AVOID IN UREMIC PATIENTS

Antimicrobials	Cardiac glycosides
Aminoglycosides[a]	Digoxin
Cephalosporins[a]	Digitoxin
Penicillins[a]	
Polymyxins	Arthritis—gout
Vancomycin	Allopurinol
Flucytosine[a]	
Trimethoprim-sulfamethoxazole	Antineoplastics
Amantadine	Bleomycin
	Cyclophosphamide[a]
Analgesics—narcotics	Methotrexate
Salicylates[a]	Mithramycin
Meperidine	
Morphine	Neuromuscular agents
	Neostigmine
Antiarrhythmics	
Procainamide[a]	Miscellaneous
Quinidine[a]	Insulin
N-acetylprocainamide[a]	Cimetidine[a]
Antihypertensives	Clofibrate
Clonidine	Methimazole
Diazoxide[a]	Niacin
Nitroprusside[a]	Propylthiouracil

[a]Dialyzed significantly.

TABLE 14.5. DRUGS REQUIRING MAJOR DOSAGE REVISION IN UREMIC PATIENTS

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15

ALTERNATIVE MEDICAL THERAPIES FOR UROLOGIC DISEASES

Charles E. Myers Jr.

C.E. Myers, Jr.: Professor of Medicine and Urology, University of Virginia School of Medicine, Charlottesville, VA 22908.

Contents

DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994

Part of "15 - ALTERNATIVE MEDICAL THERAPIES FOR UROLOGIC DISEASES "

The past few years have witnessed a dramatic increase in the use of herbal products as well as other methods associated with alternative and complementary medicine. This has led to considerable attention on the part of the media, including a cover story in *Time* magazine. Estimates of the amount spent on supplements yearly generally are in excess of one billion dollars per year. Recent reports document that supplement use is common among prostate cancer patients. Unfortunately, these studies also show that patients often do not share this information with their physicians. During my initial visit with patients, I often find that patients spend more on supplements than they do on prescription medications.

What has fueled this shift toward herbal and nutritional supplements? Many patients view herbal products as offering a gentler, more natural form of therapy with fewer side effects. Although this may be true for some supplements, such as valerian, the side effects of many herbal products simply have not been publicized adequately. There is no question that it is much more convenient and pleasant to visit the local health food store than to make an appointment to see a physician, get a prescription, and have it filled. For many patients, this is then followed by a battle to have the cost reimbursed by an insurance company. The use of herbal products also puts the patient in control of his or her treatment.

As the American public turned their attention to natural healing products, the political and legal environment also began to change. One key event was the passage by Congress of a major new law governing the marketing and sale of these products. This law, called the *Dietary Supplement Health and Education Act of 1994,* severely restricted the ability of the U.S. Food and Drug Administration (FDA) to regulate supplements (9). This act represents the result of a struggle, dating back to the early 1960s, between the FDA and forces seeking to provide Americans with less restricted access to supplements. In this process, the FDA has managed to assemble a consistent pattern of failure in the courts and in Congress.

Two elements characterized the FDA strategy. Their stance was that supplements were either unapproved drugs or they were unapproved food additives. If they were drugs, then they had to pass the same review processes that a drug would. If they were to be used as a food additive, they had to pass through the strict review process that a new food additive would pass through. The supplement industry argued that it could not afford to take either path because of the limited profit potential involved. After all, at the end they would not have the exclusivity our system guarantees a new prescription drug.

The FDA sought to restrict the distribution of information on supplements in the form of books, articles, or pamphlets. In this effort, they attacked balanced and scientifically

sound as well as distorted and misleading material. The stance was that in any case these represented a marketing effort for unapproved food additives or drugs. In one case, the FDA objected to health food stores selling an herbal product and books on that same product. In the process, they managed to gain the opposition of free speech advocates, further complicating their political and legal difficulties.

The passage of the Dietary Supplement Health and Education Act of 1994 represented a clear repudiation of the FDA position. It is worthwhile to directly quote some of the text of this Act so that you can get a sense of the will of Congress.

Despite a voluminous scientific record indicating the potential health benefits of dietary supplements, the Food and Drug Administration has pursued a heavy-handed enforcement agenda against dietary supplements for over 30 years. The agency's approach has forced the Congress to intervene on two previous occasions, and yet again with the adoption of S.784.

Key aspects of the Act represent a clear statement of differing philosophy than the philosophy that dominated the FDA and much of establishment medicine.

1. “There is a link between the ingestion of certain nutrients or dietary supplements and the prevention of chronic diseases such as cancer, heart disease, and osteoporosis.”
2. “Healthful diets may mitigate the need for expensive medical procedures, such as coronary bypass surgery or angioplasty.”
3. “Preventive health measures, including education, good nutrition, and appropriate use of safe nutritional supplements will limit the incidence of chronic diseases, and reduce long-term health expenditures.”
4. “There is a growing need for emphasis on the dissemination of information linking nutrition and long-term health.”
5. “Consumers should be empowered to make choices about preventative health care programs based on data from scientific studies on health benefits related to particular dietary supplements.”
6. “Studies indicate that consumers are placing increasing reliance on the use of nontraditional health care providers to avoid the excessive costs of traditional medical services and to obtain more holistic considerations of their needs.”
7. “Dietary supplements are safe within a broad range of intake, and safety problems with supplements are relatively rare.”
8. “Legislative action that protects the right of access of consumers to safe dietary supplements is necessary in order to promote wellness.”

This Act countered FDA strategy in several ways. First, they declared dietary supplements were foods, not drugs. Instead, they created a new category of food by specifically defining dietary supplements to include dietary ingredients such as vitamins, minerals, herbs or other botanicals, amino acids, or other dietary supplements. A dietary supplement must be intended for ingestion, such as a tablet, capsule, powder, soft gel, gelcap, or liquid form. The Act also specifically states that customers can be provided with publications on supplements in connection with the sale of the dietary supplements. These publications must not be false or misleading, not promote a specific brand of supplement, and provide a balanced view of the available scientific literature. In the store, it must be physically separated from the supplement.

The Act allowed supplements to carry claims that they help preserve general well-being. In addition, they can claim that they help preserve the structure or function of parts of the body. However, they cannot state that the supplements are effective treatment of any disease, because this would be a drug claim. This section of the Act has been the subject of continual discussion and litigation between the FDA and representatives of the supplement industry. In retrospect, this aspect of the Act was not well thought out and was probably not enforceable.

The case of lovastatin is a good example of some of the difficulties involved in distinguishing a drug from a supplement. Lovastatin is an FDA-approved drug for the treatment of elevated cholesterol, marketed by Merck as Mevacor. However, lovastatin also can be found in a range of natural products such as oyster mushrooms and a form of red yeast used in China to season rice, and ingestion of these natural products will lower cholesterol levels. Extract of red yeast is now being marketed to people concerned about heart disease and information about its lovastatin content is widely available. As far as I can determine, there is no reason why, milligram for milligram, lovastatin in this red yeast extract is not as active as that in Mevacor. Yet, red yeast extract must be marketed as a supplement with an obscure structure-function claim about preserving the structure and function of the heart, whereas Mevacor is marketed specifically for its ability to lower cholesterol: once in the body, they act identically.

The end result of this Act has been mixed. There is no doubt that Americans now have much greater access to nutritional or herbal supplements. However, these supplements range radically in their value. Among these supplements are therapeutic agents with a strong scientific basis and proven clinical value. Most of these lack FDA approval because no company has been willing to take them through the expensive process the FDA mandates. In contrast, other herbal products have no scientific basis and no sound clinical trial documentation of efficacy, and even pose a health risk.

The Act specifically empowers the FDA to oversee quality control of supplements and they are given the power to remove unsafe supplements from the market. In practice, this process has not worked very well. The plain fact is that

the quality of supplements on the market is variable. Studies have shown that supplements from some manufacturers can contain 25% or less of the active ingredient than stated on the label. It also appears that supplements on the market are not adequately monitored for hazardous contaminants.

It would appear that there is a great need for increased regulatory supervision of the supplement industry. It would be best if Americans were ensured of the potency and safety of the supplements they purchase. While we wait for these changes, there are some promising trends. Several major pharmaceutical firms have purchased supplement companies and this promises improvement in quality control and standardization. In addition, several major supplement manufacturers are funding clinical trials that specifically document the value of their herbal extracts.

STRESS

Part of "15 - ALTERNATIVE MEDICAL THERAPIES FOR UROLOGIC DISEASES "

Time and again, patients relate how their prostate cancer appeared to develop following a period of stress. They then commonly ask if the stress was responsible for the fact that they now had cancer. Evidence from laboratory experiments do suggest that the stress hormones, epinephrine, norepinephrine, and cortisol, may play a role in the progression of prostate cancer. Patients often turn to alternative or complementary medicine for tools effective in the management of stress.

Problems with the Stress Response

It is important to realize that this stress response is very much designed to handle acute problems. When humans or other mammals are subjected to chronic stress, the continuous elevation of cortisol and catecholamines delays healing; suppresses the immune system; and contributes to high blood pressure, heart disease, and diabetes. Other diseases, such as duodenal ulcers, ulcerative colitis, rheumatoid arthritis, and psoriasis, also worsen during periods of stress. In essence, we are best designed by nature for a life where acute stress is followed by periods of peace and security.

Much of modern thinking about the biology of stress is based on the work of the Canadian scientist, Hans Selye (87). Through elegant laboratory experimentation and astute observation of human behavior, Selye developed a theoretic basis for analyzing the impact of stress that is still useful more than half a century after he first articulated these ideas. He pointed out that there were two distinct types of stress: distress and eustress. Distress would be loss of a job, death of a loved one, threat of debt, or similar events. Eustress would be the excitement associated with skiing down a mountain, reading an exciting novel, watching a football game, a new love, or other consuming passion. Although chronic distress obviously is not good, too much eustress also is a problem. Indeed, blood levels of catecholamines and cortisol elevate in response to both distress and eustress. The conclusion of this line of thinking is that it is important to keep a balance between periods of distress and eustress and periods of peace and quiet.

How can you judge the stress in a patient's life? I have found the stress scale developed by Miller and Rahe to be particularly useful (72). A sense of perspective is necessary in interpreting the results of this test. People differ in how well they tolerate stress. One person may become sick from stress-related illness even though his or her total score on this test may be relatively low. Others tolerate and even prefer a relatively high level of stress. In fact, some people appear to be addicted to catecholamines and only feel fully alive when they are under a high level of stress.

What are some of the symptoms that might tell you when your patients are under too much stress (Table 15.1)? They may find it difficult to concentrate or experience forgetfulness. They may awaken in the middle of the night with their minds churning over unresolved problems from the previous day. They may find that they have lost their appetite or suddenly find themselves overeating. They may become impatient or intolerant of others. They may find themselves losing their temper over minor issues. Their blood pressure may suddenly become higher or other stress-related diseases may worsen. It is important for you to become attuned to how your patients respond to stress and to develop a sense for when you need to advise them of the need to decrease life's stress. I think that having them take the Miller and Rahe stress test will help you recognize when stress has become too much.

▪ Forgetfulness	▪ Irritability
▪ Insomnia	▪ Substance abuse
▪ Altered eating habits	

TABLE 15.1. SIGNS OF STRESS

Epinephrine and Prostate Biology

The prostate gland is well supplied with sympathetic nerves. Activation of these sympathetic nerves plays a central role in ejaculation: without their activity, men experience a dry ejaculation. Obviously, this involves a sudden surge in sympathetic nerve activity. What about catecholamines from the adrenal medulla? Experiments in dogs indicate that ejaculation is fostered by a sudden increase in catecholamine release from the adrenal medulla plus action by the prostatic sympathetic nerves (Table 15.2).

▪ Important for ejaculation	▪ Blockade of α_1-adreno-receptors leads to apoptosis of prostatic epithelial cells and associated stroma
▪ Enhances response to testosterone and epidermal growth factor by normal and malignant prostatic epithelial cells	

TABLE 15.2. CATECHOLAMINES AND THE PROSTATE

What about chronic activation of the prostatic sympathetic nerves? Lee and his colleagues from Northwestern University in Chicago showed that if one cuts the sympathetic nerves to the prostate gland, it shrinks (70,71,98). If one cuts the sympathetic nerves to one side of the prostate

gland, that side will shrink. It appears that activity of the sympathetic nerves act in conjunction with testosterone to allow the prostate gland to reach its mature size.

These findings suggest that catecholamines stimulate the growth and/or survival of prostate cells. Direct evidence of this comes largely from the work of Kyprianou from the University of Maryland (22,60). When catecholamines interact with cells, they act through proteins found on the surface of these cells. These proteins, called *adrenoreceptors,* bind to the catecholamines and trigger the cell's response. A wide range of different adrenoreceptors are found in tissues throughout the body. Drug companies have made use of this fact to develop drugs that block the action of only one adrenoreceptor type at a time. Examples of this are the drugs Hytrin, Cardura, and Flomax. These drugs are selective for α_1-adrenoreceptors. Activation of the α_1-adrenoreceptors in the bladder and urethra blocks the flow of urine out of the bladder. Hytrin, Cardura, and Flomax block these α_1-adrenoreceptors, causing relaxation of the muscles in the urethra and bladder, making it easier for men to urinate.

These same α_1-adrenoreceptors also are found on the cells that line the ducts of the prostate gland and the fibroblasts that make up the support network for the gland. Kyprianou and others have shown that the α_1-adrenoreceptor–blocking drugs cause prostate lining cells and the fibroblasts to die. The same appears to be true, at least in the laboratory, for human prostate cancer cells.

How do catecholamines foster the growth and survival of human prostate cancer cells? The best insight into this issue comes from research done by Weber at the University of Virginia. All growth signals coming from cell surface receptors do so by activating an enzyme called *mitogen-activated protein* (MAP) kinase. Epidermal growth factor is one of the most important growth and survival factors for human prostate cancer cells. This growth factor acts by binding to a protein on the surface of these cells that is called the *epidermal growth factor receptor.* The resulting growth signal causes activation of MAP kinase, resulting in increased cancer cell growth. Catecholamines dramatically increase the ability of epidermal growth factor to activate MAP kinase (21).

Stress also has been shown to impair the function of the immune system. The function of natural killer cells appears to be consistently decreased following stress. This may be important for cancer patients because natural killer cells have the capacity to kill cancer cells. Natural killer cells have adrenoreceptors on their surface, and activation of these receptors by norepinephrine or epinephrine blocks the effectiveness of these immune cells. The adrenoreceptor in this case is a ß-receptor rather than the α-receptor involved in prostate biology. In the laboratory and in tissue culture, drugs that block the $ß_2$-receptor protect natural killer cells during periods of stress.

In summary, stress causes an increase in the release of epinephrine and norepinephrine from sympathetic nerve endings and from the adrenal medulla. These catecholamines stimulate the response of prostate cells, normal or malignant, to epidermal growth factor and testosterone. In addition, these catecholamines suppress the function of the immune system. If these factors are biologically important, it would be predicted that prostate cancer cells would spread preferentially to the adrenal gland. This is indeed the case. Recent detailed autopsy studies performed in men showed that the adrenal gland is the fourth most common site involved in metastatic prostate cancer (15).

Medical Approaches to Stress Reduction

The benzodiazepines are the most widely prescribed anxiety-relieving drugs. This drug class includes diazepam (Valium), chlordiazepoxide hydrochloride (Librium), and alprazolam (Xanax). The latter is now commonly used to relieve anxiety in cancer patients. There are several problems with the benzodiazepines. The most disturbing issue is that these drugs can be addicting (66). They also can impair coordination, leading to falls, accidents, and motor vehicle crashes. In addition, people treated chronically with these drugs can be troubled by loss of intellectual function. Both loss of coordination and impaired intellectual function are markedly increased if alcohol consumption follows ingestion of these drugs.

Buspirone and antidepressants, such as venlafaxine hydrochloride (Effexor), appear to circumvent many of these problems. Effexor may worsen high blood pressure, and in this situation, sertraline hydrochloride (Zoloft) has been found to be of value. These drugs are much less likely to impair coordination or intellectual function. In addition, they are safer to take in conjunction with recreational use of alcohol. Finally, their use is much less likely to result in addiction. However, as a note of caution, buspirone and the serotonin-reuptake inhibitor class of antidepressants can elevate circulating prolactin levels. Because prolactin promotes the growth and survival of prostatic epithelial cells, it is theoretically possible that these antianxiety drugs might adversely affect the outcome of treatment for prostate cancer.

A number of herbal products are reported to reduce stress. Valerian root is probably the best documented of

these (31,59). Valerian is mildly sedating, has no addiction potential, and seems quite safe. Its major limitation is that it appears to be less effective than Effexor or buspirone in lessening anxiety.

Drug-free Stress Reduction

Most communities of any size have programs where patients are taught stress reduction techniques. Often, these are associated with progressive community hospitals or other community-based health care delivery organizations. For many patients, these programs are of great value.

Most of these stress reduction programs are based on what is called the *relaxation response* (Table 15.3). During this response, pulse rate and blood pressure drop, the flow of blood to the hands and feet improves, and brain wave frequency slows (8,18,52). This occurs when a person places himself or herself in a quiet, pleasant environment and focuses his or her attention on something neutral and nonthreatening, such as a single candle flame or fish in an aquarium.

▪ Easy to elicit	▪ Increase in blood flow to hands and feet
▪ Decrease in pulse rate	▪ Decrease in blood catecholamine levels
▪ Decrease in blood pressure	

TABLE 15.3. RELAXATION RESPONSE

Many men are reluctant to engage in these techniques. Some of them are associated with religious or political connotations with which they may not agree. A relatively simple approach will give your patient a sense of what is involved.

First, find a comfortable chair in a quiet, pleasant place. After the patient has relaxed, take his blood pressure.

Have him pick some short word or syllable that he will repeat over and over again. In Hindu meditation, they use the word *om*, but the patient can just as easily use the word one, five, six, or ten. The key is that it should either have no emotional connotation or a pleasant one.

Next, have the patient close his eyes and repeat the chosen word or syllable. While he does this, have him purge his thoughts of any other concern. He also should try to ignore his surroundings and focus on the rhythm of the repeating word. He should continue this for 20 minutes. At the end of this period, his pulse and blood pressure should be remeasured; nearly always both will have declined significantly.

Patients should approach this with the idea that they are learning a new skill, like playing tennis or golf. They should expect that their comfort and skill will improve with practice. It is a common experience for people to think their initial attempts at meditation are failures. Even when they think they have not done well, it is very likely that engaging in this relaxation response will have had considerable impact on their stress level. If the patient plans to use the relaxation response optimally, he should plan to set aside 20 minutes at least once and, preferably, twice per day.

Will the relaxation response alter the progression of prostate cancer? There have been no clinical trials testing this idea. What we can say is that the relaxation response will lead to a decrease in blood epinephrine levels and a decrease in the activity of the sympathetic nervous system. As we have seen, there is a scientific basis for the hypothesis that blood epinephrine concentration and activation of the sympathetic nervous system might increase the growth of prostate cancer cells. At the very least, this technique may lessen the impact of stress on your patient's health and anxiety level.

ANTIOXIDANTS

Part of "15 - ALTERNATIVE MEDICAL THERAPIES FOR UROLOGIC DISEASES "

Antioxidants represent one of the most common supplement classes ingested by prostate cancer patients. Widely used examples include vitamin C; vitamin E; selenium; and plant polyphenols, such as those from green tea, grape seed, and pine bark. A growing body of scientific and clinical work supports the use of these compounds by patients with cancer and other diseases.

Antioxidant Defense Network

Many biochemical reactions essential for life carry with them the threat of oxidative damage to the tissues of the body. For example, the process by which mitochondria produce the adenosine triphosphate (ATP) that drives your muscles and other tissues creates side products such as hydrogen peroxide that can damage tissues by oxidation. Exposure to sunlight can enhance oxidative damage to skin cells. Chemicals that naturally occur in food can cause oxidative damage. We are able to safely eat these foods only because our bodies do such a great job defending us against oxidative damage; fava beans can cause severe injury if consumed by people who lack the normal defenses against oxidative damage.

It is now known that the body has a comprehensive antioxidant defense network in which each component part has a role to play (25,44). What are the components of this antioxidant defense network?

One group of enzymes function to destroy or detoxify common oxidants. For example, hydrogen peroxide is one oxidant commonly formed as a byproduct as the tissues in the body perform their daily tasks. Several enzymes are capable of detoxifying hydrogen peroxide. The enzyme catalase binds two hydrogen peroxide molecules together to form oxygen and water. A second family of enzymes,

called *glutathione peroxidases,* reduces hydrogen peroxide to water. Most of the known glutathione peroxidases require selenium.

A second group of components are vitamins that act as antioxidants. Vitamins C and E are prominent members of this group. Vitamin C is soluble in water and acts as an antioxidant in the water phase of the cell. Vitamin E is soluble in body fat and other lipids, but not in water. For this reason, vitamin E acts as an antioxidant for body lipids.

A third group of components is the dietary antioxidants. It is now apparent that most vegetables and grains contain antioxidants. Tomatoes contain the red pigment, lycopene. Green tea contains antioxidant polyphenols. Onions and garlic have large amounts of sulfur-containing chemicals that are strong antioxidants. Fruits such as blueberries, strawberries, and raspberries are another rich source of antioxidants. It now appears that these plant antioxidants act to bolster the effectiveness of other members of the antioxidant network.

The final component of the antioxidant defense network is a group of proteins that sequester iron and copper. This is important because free iron and copper can stimulate the conversion of peroxides into free radicals that rapidly react with and destroy normal tissues. Under normal conditions, this system is so effective that free iron and copper do not exist in body fluids or tissues. When sequestration of iron fails, it causes hemochromatosis and hemosiderosis. When sequestration of copper fails, it causes Wilson's disease.

When all four components of the antioxidant defense network are functioning optimally, the body can effectively handle attack by a wide range of oxidants without sustaining serious injury. Oxidative damage can include injury to DNA, the genetic material in a cell. This genetic damage can foster the development of cancer or promote the progression of cancer from a slow-growing local problem to one that grows and spreads rapidly. Thus a fully functioning antioxidant network can lower the risk that cancer will develop. However, this network operates so that various components overlap in their function, so that a deficiency in one component can be compensated by the others. For example, a low level of vitamin E may not be of great consequence if selenium, vitamin C, and dietary antioxidants are present at optimal levels. This is an important point to keep in mind when reading the results of clinical trials: any antioxidant can appear to have no impact if the subjects are taking in large amounts of other antioxidants and/or are not exposed to significant oxidant stress. Conversely, if the people in the trial are all subject to some oxidative stress, antioxidants may prove more effective than they would in normal subjects. For example, cigarette smoking subjects the body to increased oxidative stress and smokers may have a greater need for antioxidants than nonsmokers. This will prove important when we discuss some of the clinical trials involving antioxidants and prostate cancer.

Oxidants and the Development of Prostate Cancer

Why should antioxidants alter the risk of dying from prostate cancer? Wilding and his colleagues from the University of Wisconsin have published a series of papers that provide a possible answer to this question (83,84). They have shown that prostate cancer cells exposed to testosterone produce hydrogen peroxide and other oxidants. This led them to propose that testosterone exposure results in the production of oxidants that cause genetic damage. Genetic damage can play a role in the progression as well as the genesis of cancer. The implication of this line of research is that strengthening the antioxidant network may lessen the risk of developing prostate cancer. It may also slow the progression of this disease from a slow-growing cancer limited to the prostate gland to one that has spread throughout the body and become resistant to all therapies. Several antioxidants may alter the natural history of prostate cancer.

Selenium

Over the past few years, our knowledge about selenium and its effects on living organisms has increased dramatically. A search of the National Library of Medicine's online database, PubMed, shows more than 1,000 scientific articles published on selenium since January 1998.

One major factor behind this surge in interest about the health effects of selenium has been Clark and colleague's 1996 publication of a large, randomized, controlled clinical trial that demonstrated a marked reduction in cancer deaths associated with increased selenium intake (23,24). This trial was initiated in 1983 as a randomized controlled trial testing the impact of supplementation with 200 µg of selenium-yeast per day on the risk of skin cancer. This clinical trial enrolled 1,300 individuals residing in the Mid-Atlantic Coastal Plain from Virginia to South Carolina, an area long known to have low soil and water selenium levels. After 10 years, the overall cancer death rate was 50% lower in the subjects taking selenium as compared with the control group (Table 15.4). The cancers responsible for this difference were carcinomas of the prostate, colon, and lung: prostate cancer deaths were decreased by 64%, colon cancer by 40%, and lung cancer by 30%. The four major causes of cancer death are those of the lung, prostate, colon, and breast. Thus selenium dramatically reduced the death rate of

three of the four most common causes of cancer death in the United States. Furthermore, no cases of selenium toxicity were reported among the people in this trial who took selenium supplements for years.

▪ Deficiency exists where high rainfall and acid soils are present	▪ The 200-µg dose is recognized as safe and costs $0.10 per day
▪ 200 µg of selenium per day reduces prostate cancer deaths by 60%–70%	▪ Markedly enhances cytotoxic T-cell activity in cancer patients

TABLE 15.4. SELENIUM

Selenium and Prostate Cancer

Since the publication of Clark's paper, there has been one major study designed to test the validity of his findings. In his paper, Clark reported on the correlation between serum selenium levels and the risk of prostate cancer. One criticism of this approach is that serum selenium levels are just a "snap shot" of selenium levels at one point in time, whereas the development of prostate cancer takes many years and is more likely to be influenced by the average selenium level during that time period. Hair and nails are formed at the rate of approximately 1 mm per day, and thus hair or nail clippings are a better estimate of average selenium level. Giovannucci, from the Harvard School of Public Health, examined the selenium content of nail clippings from approximately 34,000 men and found that the risk of developing metastatic prostate cancer decreased as the selenium content of the nail clippings increased (103). When Giovannucci compared the men with the highest and lowest nail selenium content, he found a 65% reduction in the risk of metastatic prostate cancer.

What is the next step in this line of investigation? The National Cancer Institute (NCI) has just funded a large, randomized, controlled trial in which men will be randomized between control, vitamin E, selenium, and vitamin E plus selenium. Colteman, from the University of Texas, San Antonio, is the lead investigator on this clinical trial.

Selenium and the Immune System

A number of studies suggest adequate selenium levels are necessary for proper function of the immune system. The most convincing study is a randomized, controlled clinical trial in patients with head and neck cancer (56). Most patients with this cancer exhibit depression of the immune system. Cytotoxic T cells and natural killer cells are the most important parts of the immune system in terms of resistance to cancer. Natural killer cell function usually is profoundly depressed in head and neck cancer patients. Cytotoxic T-cell number and function also are commonly suppressed. Patients in this study all had untreated squamous carcinoma of the head and neck and were randomized to placebo or selenium at a dosage of 200 µg per day for 8 weeks. This trial was double blind, which means that neither the patients nor the doctors knew who was receiving placebo or selenium until the study was completed.

Plasma selenium levels were measured at the start and during the trial to ensure patients took the selenium as directed. During the 8 weeks, 88.3% of the patients took the assigned selenium dose. At the start of the trial, the average selenium levels in the two groups were 91.3 and 94.4 µg/L of blood plasma. After 8 weeks of selenium supplementation, the average selenium level increased from 91.3 to 105.3 µg/L.

Despite this minor increase in plasma selenium, there were major changes in the immune system. In the patients on placebo, cytotoxic T cells killed only 7% of the tumor cells. After 8 weeks of selenium supplementation, the T cells were able to kill 78% of the tumor cell targets. This is a rather remarkable shift given the short duration of treatment and small increase in selenium levels. To place these findings in perspective, in the Clark study, prolonged administration of the same dose of selenium, 200 µg per day, eventually increased the selenium levels to close to 200 µg/L, rather than the 105.3 µg/L after 8 weeks reported in this paper on head and neck cancer.

Other lines of evidence show the importance of the antioxidant defense network and selenium in protecting the immune system. HIV-1, the virus that causes AIDS, kills because it destroys T cells that are important in the immune response. HIV-1 increases oxidant stress in the T cells at the same time as it appears to weaken key elements of the antioxidant defense system. Selenium plays a major role in the ability of glutathione to act as an antioxidant. A selenium-containing protein, glutathione peroxidase, uses glutathione to convert hydrogen peroxide to water. Without selenium, glutathione peroxidase is unable to accomplish this task. Given this background, the fact that children and adults infected with HIV-1 live much longer if their selenium levels are adequate is not surprising (10,17).

In addition, one additional study examined restoration of normal immune function in the elderly by selenium combined with other nutrients. This study by Girodon, from the Scientific and Technical Institute for Foods and Nutrition, Conservatiore National des Arts et Metiers, Paris, involved a group of institutionalized elderly patients (40). It showed that 20 mg of zinc and 100 µg of selenium significantly increased antibody response to influenza vaccine and decreased the risk of upper respiratory infection.

Selenium and Viral Infections

In addition to its effects on the immune system, selenium can have a direct effect on the progress of viral infections (12). This is best studied in a virus called *coxsackie B.* Although not a household name, coxsackie B infections are common, and this virus can cause serious, life-threatening illness. Coxsackie virus infections typically start in the gastrointestinal (GI) tract, where they can cause nausea, vomiting, and diarrhea. From there, the virus can enter the blood stream and spread throughout the body. This virus can attack the nervous system, causing a disease that results in paralysis similar to that caused by polio. Coxsackie virus can enter muscles, where it can cause severe muscle damage and pain. For example, it can infect the muscles of the rib cage that are used to breathe and make it very painful to take a deep breath. When this virus enters the heart muscle, the

damage can be sufficient to require a heart transplant. In fact, coxsackie B virus infections are one of the leading reasons for heart transplant.

The link between selenium and coxsackie B virus starts in China. In the Keshan province of China, soil and water contain little selenium. Residents of this area can have daily intakes of selenium of less than 20 µg per day, compared with 200 µg per day in Clark's trial. Residents of Keshan can develop a form of fatal heart failure called *Keshan's disease.* However, this disease does not occur in residents of this area who manage to receive more than 20 µg of selenium per day. Subsequent studies showed that a disease similar to Keshan disease can be found in several parts of China, all of which are selenium deficient. In addition to being limited to geographic regions low in selenium, Keshan disease only appeared during certain seasons of the year: summer in Southern China and winter in Northern China. Seasonal patterns like this are characteristic of disease of infectious origin. This led the Chinese to isolate viruses from the hearts of people who had succumbed to Keshan's disease. Coxsackie B virus emerged as a common isolate. The Chinese scientists then showed that coxsackie B virus would infect mice and cause heart damage. Furthermore, the damage was much worse in mice on a low selenium diet compared with those on a high selenium diet.

This phenomenon was subsequently investigated by Beck from the University of North Carolina, Chapel Hill (12). Several strains of coxsackie B virus that are able to infect mice are available. These strains differ in the severity of the infection they cause in the mice, ranging from those causing mild disease to those that cause serious illness. Beck showed that the viral strains causing serious illness did much less damage to mice on high selenium diets compared with those on low selenium diets. Of even greater interest, when a viral strain that normally caused mild disease was allowed to infect a selenium-deficient mouse, the virus was permanently altered into a virus that would cause severe disease. Beck then showed that this change in viral virulence induced by selenium was always associated with the same genetic changes. In other words, passage of a mild virus in a selenium-deficient animal caused changes in the genetics of the virus, rendering it much more dangerous. This is currently the best explanation for why severe selenium deficiency can result in potentially fatal heart damage.

Vitamin E deficiency also worsens the impact of coxsackie B virus infection on the heart. In addition, when a mild form of the virus infects vitamin E–deficient mice, it becomes more virulent, just as it did in selenium-deficient mice. Again, the evidence shows that the antiviral activity is not specific for selenium, but reflects the fact that an optimally functioning antioxidant network suppresses the progression of coxsackie B virus.

Selenium and Heavy Metals

Metals such as arsenic, lead, mercury, cadmium, and thallium are all poisonous. Furthermore, industrial uses of these metals have led to large-scale environmental contamination. One of these metals, cadmium, has been specifically implicated as a cause of prostate cancer. Selenium alters the toxicity of heavy metal ions in several ways (99,105). It is important to note that selenium can bind these metal ions into complexes not soluble in water. To a certain extent, selenium can bind to these metal ions in the GI tract, diminishing the absorption of both selenium and the toxic metals. Once selenium has been absorbed, it can form complexes with these metal ions, lessening or delaying the toxicity of these metal ions. One of the side benefits of taking selenium supplements to decrease the risk of prostate cancer or to slow its progression is protection from the toxicity of these metal ions.

Selenium Dose

A daily selenium dose of 400 µg per day is now recognized as the maximum safe daily dose. This number may be increased as studies currently in progress are completed. In Clark's study, a dose of 200 µg of selenium-yeast was ingested for years without a single reported side effect, but with a major impact on cancer deaths. A number of additional studies, both short and long term, document the safety and effectiveness of this dose of selenium.

Forms of Selenium

Commercially available selenium supplements come in a wide range of chemical forms (Table 15.5). The most widely available form is as selenium-yeast, and 200 µg per day costs about 10 cents. This is also the form used in Clark's study.

▪ Selenium-yeast	▪ Selenomethionine
▪ Sodium selenate	▪ Selenocysteine
▪ Sodium selenite	▪ Selenodiglutathione

TABLE 15.5. DOSAGE FORMS OF SELENIUM

Unfortunately, some individuals are allergic to selenium-yeast. Selenomethionine also is widely available and appears safe. However, selenomethionine is not directly used by any of the selenium-requiring proteins in the body. Instead, it gets randomly taken up by all proteins in the body. After these proteins are broken down, the selenium gets recycled into biologically useful forms. Thus although it eventually acts to reverse selenium deficiency, it would not offer the rapid reversal most cancer patients might desire.

Sodium selenate and selenite are available and are rapidly reduced in the body to selenide. The latter is rapidly incorporated into the key selenoproteins in the body. The only disadvantage of these selenium salts is that their absorption from the GI tract is not consistent.

Selenocysteine is the form of selenium that is directly incorporated into the key selenoproteins in the body. Selenocysteine is commercially available and also is present in preparations such as selenoglutathione or selenodiglutathione.

Vitamin E

Vitamin E is soluble in lipids, but not in water. As a result, it largely acts to prevent oxidative damage to the lipids in a cell. In laboratory studies, vitamin E has been shown to act in concert with antioxidants present in the cytosol, such as vitamin C, glutathione, and selenium.

The first evidence that vitamin E might alter the progression of prostate cancer came as an unexpected result of a clinical trial designed to test the role of this vitamin in the prevention of lung cancer in smokers. In this trial, approximately 23,000 male cigarette smokers were randomized to placebo, beta-carotene, vitamin E, or beta-carotene plus vitamin E (48). At the point where men had been on the trial for 5 to 8 years, death rates from prostate cancer were 40% less in the men taking vitamin E alone compared with placebo. In contrast, the men taking beta-carotene experienced a 30% increase in mortality from this malignancy. The group taking beta-carotene plus vitamin E were not significantly different from the control group.

Vitamin E is not a single chemical substance, but a name given to a family of fat-soluble antioxidants (Table 15.6). These compounds differ in their content in foods as well as their ability to act as antioxidants. Although alpha-tocopherol is widely available and the form most commonly is used in laboratory and clinical studies, it is not the most active antioxidant. Recently, the work of two groups suggests that alpha-tocopherol may also not be the most active against cancer cells, including those of the prostate.

Alpha-tocopherol	Alpha-tocotrienol
Beta-tocopherol	Beta-tocotrienol
Gamma-tocopherol	Gamma-tocotrienol
Delta-tocopherol	Delta-tocotrienol

TABLE 15.6. VARIOUS TOCOPHEROL AND TOCOTRIENOLS

Moyad and Pienta, from the University of Michigan, have recently reported that gamma-tocopherol is more active against prostate cancer cells than is the alpha form of this vitamin (74). In contrast, other groups have found gamma-tocopherol no more active than alpha-tocopherol as an anticancer agent (42,53,69). Instead, they have found the most active tocopherol is the delta form. In addition, tocotrienols are considerably more active than the corresponding tocopherols, and the most active preparation currently available commercially is concentrated palm oil tocotrienols. Finally, vitamin E succinate appears to exert anticancer activity equal to or greater than any of the naturally occurring tocopherols or tocotrienols.

There is now evidence that vitamin E kills prostate cancer cells by a unique mechanism. All cells in the body have the capacity to commit “suicide.” This suicide can be triggered by several means. One means of accomplishing this is by activating certain proteins, called *death receptors,* on the surface of cells. These death receptor proteins are designed so that when they are activated, the cell bearing them rapidly destroys itself. One of the most common of these proteins is called *Fas.* When vitamin E–like chemicals kill prostate cancer cells, Fas rapidly appears on the surface of the prostate cancer cells and appears to undergo activation, leading to cell death. These findings suggest that vitamin E does more than prevent genetic damage caused by oxidants released as a result of testosterone exposure. In fact, it may well be that vitamin E–like molecules actually may be orally active chemotherapeutic agents with low toxicity. This concept has led at least one group to chemically synthesize analogs of vitamin E with the hope of increasing the anticancer activity of this family of compounds.

Plant Monophenols and Polyphenols

Plant phenols are one of the most potent groups of antioxidants. They can occur as monophenols or as clusters of monophenols, called *polyphenols.* Polyphenols are found in a wide range of plant products that have health benefits.

Green Tea

Green tea intake has been associated with a decreased risk of cancers of the prostate, colon, pancreas, skin, and other organs (2,62,93). It seems that green tea prevents the damage caused by a large number of cancer-causing chemicals and even excessive sun exposure.

It appears that green tea cannot only prevent cancer, but is able to stop the growth of or even kill human cancer cells. This ability was documented in human breast, lung, colon, pancreatic, and prostate cancers in tissue culture and in animal models. Growth arrest occurs at the G2/M interface, a portion of the cell cycle where tumor cells are most sensitive to radiation therapy. This is also the same portion of the cell cycle in which paclitaxel (Taxol) and docetaxel (Taxotere) act to block the cell cycle.

The major polyphenols from green tea are epigallocatechin-3-gallate (EGCG), epigallocatechin, and epicatechin-3 gallate. Together, these make up 30% to 40% of the solids extracted from green tea leaves during brewing. The contents of green tea have been examined carefully to determine the chemical in the tea responsible for the anticancer activity. The growing consensus is that most of the useful activity is caused by the polyphenol, EGCG. This compound caused the rapid shrinkage of human prostate cancers growing in mouse xenograft models. It should be pointed out that there is no known mechanism by which an antioxidant can cause cancer cells to stop growing or cause rapid shrinkage of a tumor mass. For this reason, it is likely that EGCG exerts its anticancer activity by a mechanism independent of its antioxidant activity.

EGCG and other green tea polyphenols are sensitive to light and air; they are most stable at a pH of less than 5.5 and when the tea is brewed at 180°F or less.

The amount of EGCG found in green tea appears to be effective as a cancer prevention agent. The amount needed to stop the growth of cancer cells or to cause the cancer to shrink rapidly in mice is much larger—projecting from the animal experiments, a dose equivalent to 10 or more cups per day would be necessary. Human clinical trials have progressed to phase 1, where a dose of green tea extract of 1,000 mg per day (equivalent to 10 to 12 cups per day) was well tolerated. At present, there are no published phase II or III clinical trials.

Proanthocyanidins

Proanthocyanidins are a large group of polyphenols that are widely marketed by the health food industry. Proanthocyanidins are very effective antioxidants, exceeding vitamins E and C in this regard. The proanthocyanidins are made up of the monophenols, catechin and procyandin, strung together like beads on a chain. There are a wide range of specific proanthocyanidins, each with a specific sequence of catechin and procyandins. When these compounds enter the stomach, the stomach acid breaks these chains into fragments composed of one individual catechin and procyandin units, each of which can act as a potent antioxidant. Some of the plant sources of proanthocyanidins can be found in Table 15.7 (45).

▪ Cocoa	▪ Cranberries
▪ Apples	▪ Red wine
▪ Grape seed	▪ Grape skins
▪ French Maritime Pine Bark (pycnogenol)	▪ Blueberries

TABLE 15.7. SOURCES RICH IN PROANTHOCYANADINS

The two richest sources of proanthocyanidins are cocoa and apples. Apples can vary widely in proanthocyanidin content: Red Delicious and Granny Smith have more than twice the concentration of McIntosh and Golden Delicious. Even McIntosh and Golden Delicious look impressive compared with other plant sources of proanthocyanidin. For comparison, red wine and cranberries have only one-third the concentration of these compounds as is found in Golden Delicious and less than one-sixth that found in cocoa.

Total proanthocyanidin content is not the whole story because some of these compounds have unique activities not related to their activity as antioxidants, which is likely based on specific combinations of catechin and procyandin units. For example, cranberries have a proanthocyanidin that blocks the ability of bacteria to adhere to the bladder lining, making cranberry juice a valuable adjunct in the treatment of bladder infections (33).

Cocoa.

Chocolate is made by combining cocoa butter with cocoa liquor. Cocoa powder is dried cocoa liquor. Alone or mixed with water, cocoa powder is dark brown, tastes quite bitter, and is marketed as cooking cocoa. Chocolate made only with cocoa powder, cocoa butter, and emulsifying agents is also dark and bitter and is marketed as cooking or baking chocolate. Sweet, dark chocolate that is free of milk or milk fat is marketed with up to 70% cocoa powder and can be quite tasty. It should be mentioned that the cocoa powder content sometimes is listed as “cocoa mass,” not cocoa powder. The antioxidant content of cocoa is very high and helps prevent chocolate from spoiling, making it very stable during prolonged storage.

After ingestion of chocolate rich in cocoa powder, the proanthocyanadins in the chocolate will break down, releasing epicatechins in large amounts. Within 2 hours of consuming 80 g of chocolate, blood levels of epicatechin increase by 1,200% (97). It takes approximately 6 hours for blood levels of this antioxidant to return to baseline. This sudden increase in epicatechin is so effective that it causes a 40% decline in oxidative damage to the fats in the blood.

This information about cocoa is relatively new and the full biologic impact of cocoa has not been fully investigated. In terms of total polyphenols and even epicatechins, cocoa is much richer than green tea. However, green tea has very specific epicatechins, such as EGCG, that act not only as antioxidants, but also act to kill cancer cells, including prostate cancer cells. In addition, extensive epidemiologic studies show a decrease in prostate cancer risk in men who chronically ingest green tea. Similar information is not available for cocoa powder.

Grape Seed Extract.

Grape seed extract is another rich, natural source of proanthocyanadins that is widely available and on which a number of papers have been published (85,89). The proanthocyanadins from grape seed extract have been shown to kill head and neck cancer cells without damaging normal cells. It also blocks the development of cancer in rodent skin exposed to chemical carcinogens. It will protect vitamin E in cells exposed to strong oxidants.

In animal models, grape seed extract exhibits potential beneficial effects that do not directly relate to the development or progression of cancer. When the blood supply to the heart is blocked temporarily and then restored, there is an intense wave of oxidative damage to the heart, called *reperfusion injury.* In animals subjected to this, administration of grape seed extract significantly lessens the damage. Finally, again in animals, application of grape seed extract to the skin was reported to increase hair growth by 230%.

Unfortunately, there are no useful clinical trials testing this preparation in humans. This is particularly striking in view of its widespread commercial availability and its popularity among cancer patients.

Pycnogenol.

Pycnogenol, a proanthocyanidin preparation, is an extract obtained from the bark of the French Maritime Pine and is widely available (50,65,78,95). As with grape

seed extract, a number of interesting papers have been published on this preparation. In laboratory experiments, pycnogenol protected the cells that line blood vessels from oxidative damage. In animal experiments, it reduced blood pressure by inhibiting angiotensin-converting enzyme. In aged mice, administration over 2 months increased the number of B and T cells, key members of the immune system. It also increased growth of bone marrow stem cells in tissue culture.

Like grape seed extract, the absence of useful clinical trials is striking in view of pycnogenol's wide commercial availability and popularity with patients.

Cranberries.

For *Escherichia coli* to successfully attack the bladder, it must be able to attach to the wall of the bladder so that it can avoid being flushed out with the passage of urine. The bacteria does this through the use of fimbria. Cranberries contain a proanthocyanadin that blocks the ability of *E. coli's* fimbria to attach to surfaces (3,33). Even more interesting, prolonged contact with cranberry proanthocyanadin changes the *E. coli* so that it loses the capacity to make fimbria.

There is currently a controversy regarding whether the consumption of cranberries, their juice, or their extract plays a role in the management of urinary tract infections. One comprehensive review of the literature has concluded that the evidence is too weak to support its use (55). Others support the opposite, concluding that cranberries do have a role to play in the treatment of urinary tract infections. The most impressive study was published in the *Journal of the American Medical Association* (JAMA) (6). In this study, women with urinary tract infections were randomized to receive 300 mL of cranberry juice a day or placebo. Those taking cranberry juice had a significant improvement in their recovery from the infection. Conversely, there is little evidence that cranberry juice intake prevents urinary tract infection and it did not help children with recurrent bladder infections (86).

The cranberry is a member of the *Vaccinum* genus, which also includes the blueberry, bilberry, and lignonberry. One paper examined the ability of proanthocyanadins from various members of this genus to block the action of chemicals that cause cancer. In laboratory tests, low-bush blueberry, cranberry, and lignonberry all showed significant activity (13). Blueberry extracts also have been shown to reverse the loss of coordination and the ability to solve maze problems in aged rodents. Unfortunately, there is no evidence that cranberries or other members of this genus prevent cancer or improve mental function in humans.

DIETARY FAT AND PROSTATE CANCER

Part of "15 - ALTERNATIVE MEDICAL THERAPIES FOR UROLOGIC DISEASES "

Enormous controversies exist regarding the link between diet and the risk of metastatic prostate cancer. The situation is so contentious that one can almost pick studies to support any conclusion he or she might favor. There are a number of reasons for this situation. Most studies use crude tools, such as requiring people to remember what they ate in the past or measuring the disappearance of certain foodstuffs from the economy of various countries. The determination of prostate cancer incidence also is difficult because different cultures vary in their willingness to accurately report prostate cancer as a cause of death. Given these problems, only the most robust associations between diet and prostate cancer will be reliable. One of these is the association between a diet rich in animal products, especially red meat, and prostate cancer, suggesting a strong link between a component of meat and the risk of prostate cancer.

Of course, not all studies of prostate cancer and diet are of equal quality. The best type of study would be a clinical trial in which patients were randomly assigned to diets high or low in specific fats. Trials that fit this description are currently in progress. Until they are complete, we have to fall back to our next best option. In this author's opinion, the best studies on diet and prostate cancer are those published by the investigators at the Harvard School of Public Health (34,38). These investigators conducted two trials, one involving physicians and a second involving other health care professionals. In both studies, information on diet was conducted prospectively and did not depend on people accurately recalling the composition of their diet in the distant past. The information from the two studies indicates that dietary fat did not influence the risk of localized prostate cancer, but did increase the risk of metastatic prostate cancer. When specific foods were examined, red meat, dairy fat, egg yolks, and creamy salad dressings emerged as significant risk factors.

Potential Dangers of Omega-3 Fatty Acids

One finding reported by Gann and associates (34) has elicited considerable controversy. These investigators reported that dietary intake of alpha-linolenic acid (ALA) was associated with a dramatic increase in the risk of developing metastatic prostate cancer. ALA is the major plant omega-3 fatty acid and increased intake of this lipid is thought to confer many health benefits. Extensive literature shows the ability of ALA and other omega-3 fatty acids to lower cholesterol, moderate high blood pressure, and suppress inflammation associated with rheumatoid arthritis and other diseases. Many dietitians and other health care professionals recommend that patients increase their intake of ALA to ensure a sufficient intake of omega-3 fatty acid. This fatty acid is present in large amounts in flax seed oil, where it comprises 50% of the total fatty acids present. Canola and soy bean oil are also rich in ALA. However, in addition to the Gann paper, a number of studies on the impact of ALA on prostate cancer have shown either no benefit or an adverse impact (4,27,41,47). These clinical studies have

been matched with laboratory research that also shows increased growth of prostate cancer cells exposed to ALA. For this reason, it probably is not prudent for prostate cancer patients to take dietary supplements rich in ALA, such as flax seed oil or essential fatty acid mixtures.

ALA is not the only omega-3 fatty acid. Two others, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found in the fat of ocean fish, such as wild salmon or haddock. Fish do not make EPA or DHA, but obtain it from the algae that they ingest. For this reason, the fat in farm-raised salmon will reflect the fact that they have been fed corn or soy meal rather than algae and may not differ significantly from cattle or pigs fed a similar diet. Oil obtained from wild fish appears to have all of the same health benefits of ALA but is not associated with an increased risk of prostate cancer. In fact, several studies suggest a decreased risk of prostate cancer in men who eat several servings of fish a week (77). For more than a century, industrialized countries have made the oceans the garbage dumps of last resort. A large amount of literature can be found on the toxic chemicals that concentrate in the flesh and oils of fish living in the ocean. These range from toxic heavy metals such as mercury, to chemicals such as dioxin. For this reason, fish or fish oil may not be the best source for EPA and DHA.

Fortunately, DHA that is free of ALA and from a source that is not likely to be contaminated by heavy metals or toxic chemicals can now be purchased. Algae that produce DHA are now grown commercially, and the DHA is extracted and sold as 100- or 200-mg capsules. This preparation appears to represent the best source for omega-3 fatty acids (49,57,91).

Animal Fat

Although dietary intake of red meat and animal fat consistently have been associated with increased risk of metastatic prostate cancer, the specific components of meat and animal fat responsible for this increased risk remain controversial.

One fatty acid, arachidonic acid, is present in much greater concentration in animal products. Vegans typically have arachidonic acid levels that are 10% to 30% of those found in meat eaters (81). This fatty acid is known to have a dramatic impact on the behavior of cancer cells, including cancer of the prostate. Arachidonic acid has been shown to enhance prostate cancer growth, to stimulate its spread, and to facilitate its ability to form new blood vessels. In addition, arachidonic acid products have been shown to kill cells of the immune system involved in the control of cancer.

Although a diet rich in meat can supply large amounts of arachidonic acid, most mammals can also produce their own. The “essential” fatty acid, linoleic acid, can be converted to arachidonic acid. Linoleic acid commonly is present in large amounts in many plant oils. In most animals used in diet experiments, such as rats and mice, this conversion is so efficient that a diet rich in plant oils will support high levels of arachidonic acid. This is not the case for humans, who are much less efficient in converting linoleic acid to arachidonic acid.

Dietary arachidonic acid does not cause any acute side effects. The typical American ingests approximately 100 mg of arachidonic acid each day. In clinical studies, people have tolerated five to ten times this amount for close to 2 months with no problems of any kind. It is only at doses of 7,000 mg a day that acute side effects have been seen in humans. The serious problems appear to develop only after chronic ingestion and in the context of preexisting disease, such as cancer (75).

Some investigators have argued that a diet rich in meat, and thus arachidonic acid, should not be of concern because humans evolved eating a diet rich in wild animal meat (67). Because humans survived hundreds of thousands of years on this diet, it is suggested that we must be well adapted to it. Although this idea is attractive superficially, the average life span of humans in primitive societies was typically less than 40 years. The diseases linked to high intake of animal fat, such as heart disease and cancer, are not common before the age of 50 years, long after the majority of people in primitive cultures would have died. Modern civilization has created an artificial situation, effectively doubling the life span of humans, thereby exposing us to diseases we are evolutionarily ill equipped to handle.

Arachidonic Acid and Prostate Cancer Biology

There is evidence that arachidonic acid is able to stimulate directly the growth of some cancer cells. This does not appear to be the case for prostate cancer cells. Arachidonic acid must be converted to one of several metabolites, called *eicosanoids.* For example, aspirin is able to relieve pain because it blocks the conversion of arachidonic acid to an eicosanoid, prostaglandin E_2 (PGE_2), which causes pain. Table 15.8 shows the major eicosanoids that can be made from arachidonic acid. Of these, 5-hydroxyeicosatetaraenoic acid (5-HETE), 12-HETE, and PGE_2 are known to be made by prostate cancer cells and to play a role in the growth and spread of this disease.

In men older than 50, lymphocytes are common throughout the normal prostate tissue. In radical prostatectomy specimens, it will be found that lymphocytes are

uncommon in prostate cancers of Gleason grades of 7 or higher. Arachidonic acid can be converted to a chemical PGE_2. Human prostate cancer cells have long been known to produce PGE_2 from arachidonic acid. In radical prostatectomy specimens, the cancer produced ten times as much PGE_2 as the surrounding normal prostate tissue (20). PGE_2 is toxic to both natural killer cells and cytotoxic T cells and is one potential mechanism by which prostate cancer evades the immune system.

Products of cyclooxygenase Prostaglandin E_2 and thromboxane A_2	Products of 12-Lipoxygenase 12-HETE and 5,12-HETE
Products of 5-Lipoxygenase 5-HETE and Leukotrienes	Products of 15-Lipoxygenase 15-HETE and 5,15-HETE

TABLE 15.8. SOME MAJOR EICOSANOIDS FORMED FROM ARACHIDONIC ACID

Arachidonic acid also markedly stimulates the ability of human prostate cancer cells to move and invade. This process requires the conversion of arachidonic acid to a substance called *12-HETE.* Inhibitors of 12-HETE formation are remarkably effective at arresting the movement of human prostate cancer cells (64).

Honn, from Wayne State Medical School in Detroit, has shown that conversion of arachidonic acid to 12-HETE by prostate cancer cells stimulates angiogenesis required for the growth of human prostate cancer (76). Honn and his colleagues first showed that simply adding 12-HETE to prostate cancer cells did not increase the growth rate of these cells. They then inserted additional copies of the gene controlling 12-HETE formation into these human prostate cancer cells. The original cancer cells and those engineered to make large amounts of 12-HETE were injected into mice. The cancers making increased amounts of 12-HETE grew much more rapidly and exhibit increased vascularity, suggesting increased angiogenesis.

In a separate study, Honn and colleagues examined radical prostatectomy specimens to see which cancers had the capacity to make 12-HETE and which did not (35). They found that patients with tumors able to make 12-HETE were much more likely to develop metastatic prostate cancer after radical prostatectomy. These findings are consistent with the capacity of 12-HETE to stimulate cancer cell invasiveness and angiogenesis in laboratory models.

Beginning in the mid-1980s, a series of investigators reported that the addition of arachidonic acid stimulated the growth of prostate cancer cells. None of these investigators was able to determine how arachidonic acid managed to increase the growth of these cancer cells. In a series of papers, it was confirmed that arachidonic acid stimulated the growth of both hormone-sensitive and hormone-independent human prostate cancer cells. It could then be shown that a specific metabolite of arachidonic acid, 5-HETE, was responsible for the growth stimulus provided by arachidonic acid. Furthermore, 5-HETE also acted as a potent survival factor for human prostate cancer cells (36,37).

The pathway by which arachidonic acid is converted to 5-HETE plays a major role in other diseases, including asthma, rheumatoid arthritis, and psoriasis. On the other hand, this pathway does not seem to be necessary for the health of humans or other mammals. Genetic engineering has been used to produce mice that make no 5-HETE. These mice bear offspring that are normal and that mature into normal adults. Therefore a drug that blocks the formation of 5-HETE might be effective against prostate cancer and have few side effects. In fact, several of the herbal products widely used to treat prostatic diseases, such as saw palmetto, block eicosanoid formation, including 5-HETE, in prostate cells (Table 15.9).

▪ Saw palmetto ▪ Pygeum africanum ▪ Stinging nettle	▪ Cernilton ▪ Boswellia

TABLE 15.9. HERBAL PRODUCTS THAT BLOCK EICOSANOID FORMATION

In summary, prostate cancer cells are known to metabolize arachidonic acid to eicosanoid products that stimulate the survival, growth, and invasiveness of these cancer cells (Table 15.10). Other arachidonic acid metabolites suppress immune function and facilitate tumor angiogenesis. Considered together, these findings provide a rationale for why a diet rich in animal fat might speed the progression of human prostate cancer. As presented in the following sections, a range of herbal products traditionally used to treat prostatic diseases are now known to inhibit the formation of PGE_2, 5-HETE, and various leukotrienes.

▪ Stimulates growth and survival ▪ Increases invasiveness ▪ Increases angiogenesis	▪ Contributes to immuno-suppression

TABLE 15.10. ARACHIDONIC ACID AND PROSTATE BIOLOGY

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) recently has appeared on the market as a nutritional supplement, and this was accompanied by a report of significant activity against human prostate cancer in a mouse xenograft model (19). As a result, this supplement is now widely used by prostate cancer patients.

When animals with a rumen, such as cows, goats, or sheep, are fed grass and not grain, they make a special fatty acid called *conjugated linoleic acid.* CLA is incorporated into the meat as well as the milk made by grass-fed animals. It reduces the amount of body fat in the animals and lessens the amount of fat in the milk they produce. This is one reason grain-fed beef has a higher fat content than animals raised on the range.

Originally, CLA was discovered as a component in diary fat that blocked the ability of chemical carcinogens to cause cancer. The benefits of this compound were quickly shown

to extend to other diseases in animal models (79). In animal models of diabetes mellitus, CLA was shown to make insulin's action more effective and reduced triglycerides. CLA acts to reduce inflammation in a manner similar to drugs such as aspirin or ibuprofen by blocking the conversion of arachidonic acid into PGE_2.

The initial observations that CLA would reduce the number of cancers in animals exposed to cancer-causing chemicals have been duplicated and appear to be quite impressive (51). In tissue culture, CLA slows or arrests the growth of a wide range of cancers, including human malignant melanoma, colorectal, breast, prostate, and lung cancer cell lines. The activity of CLA against breast cancer has been extended to experiments in mouse models of breast cancer. In these models, CLA slows or arrests the growth of the breast cancer masses. When these CLA-treated cancers are examined under the microscope, CLA is seen to cause an increase in apoptosis (a form of suicide), as well as slowing the rate at which the cancer cells duplicate.

There is currently only one paper on the activity of CLA against human prostate cancer (19). Cesano and colleagues used the most aggressive human prostate cancer cell line available, DU145. When DU145 is implanted in a mouse, it grows and spreads rapidly, killing the mouse in a short period of time. This cell line is hormone independent and is resistant to most cancer drugs. In fact, very few men have prostate cancers even remotely as aggressive as DU145. In this experiment, animals were given a food mixture that contained 1% CLA by weight. In the control mice, the cancer grew and spread rapidly to other tissues. In the mice on CLA, the cancer grew normally for a few weeks, gradually slowed and then stopped. After a few additional weeks, the cancers in approximately 30% of the CLA-fed mice began to turn black and fell off. In the control mice, the cancer had spread to the lungs in 80% of the mice, compared with only 10% in the CLA-fed mice. This dose of CLA caused no side effects in the mouse.

What mechanism best explains all of these effects? In one important study, the growth of human prostate cancers in a mouse model was markedly enhanced by feeding the mice corn oil, a fat rich in linoleic acid. CLA very effectively prevents the conversion of linoleic acid to arachidonic acid and can be expected to block the ability of arachidonic acid to foster the growth and spread of prostate cancer cells (7).

CLA has functions other than just blocking the conversion of linoleic acid to arachidonic acid. A group of proteins called peroxisome proliferator–activated receptors (PPAR) mediate the action of a group of cholesterol-lowering drugs, the most common of which is clofibrate. In addition to the ability to lower cholesterol, these drugs cause fat to accumulate in the liver and can lower the blood sugar. CLA has been shown to activate potently all three PPAR receptors (α, ß, and γ) (68,73). *In vivo,* CLA exhibits many of the effects one would anticipate from a PPAR agonist: improved glucose tolerance, lowered blood lipids, and increased liver lipids.

The interaction of CLA with the PPARs may play a role in the antitumor activity of these compounds. PPAR-γ agonists, such as troglitazone, have shown activity against human prostate cancer *in vitro* and *in vivo* (58). A clinical trial of troglitazone in men with prostate cancer showed slowing or arrest of tumor growth in a significant number of patients. However, no PPAR agonists have been reported to cause tumor necrosis such as that seen in the CLA-treated mice bearing DU145. For these reasons, it is suspected that the ability of CLA to block the growth and spread of prostate cancer cells may result from a combination of its ability to block synthesis of arachidonic acid and its ability to activate PPARs.

Despite these promising results, there are a number of problems with the widespread use of CLA by prostate cancer patients. First, all commercially available CLA preparations are complex mixtures of closely related isomers that differ in their biology and, presumably, their therapeutic effects. For example, one of the isomers appears to be the most active in altering the synthesis of milk fat; no one has identified the isomers most active against prostate cancer. It would be best to have a CLA preparation with a defined isomer composition, preferably limited to those with documented anticancer activity.

Second, no clinical trials have tested the effectiveness of any CLA preparation against cancer. In the mouse studies, the anticancer activity is apparent only after more than 1 month of continuous administration. The action of many drugs is ten times faster in mice than in humans, therefore an effect exhibited in mice after 1 month might take 10 months to be seen in humans. Based on this information, the most promising test of this compound would be in patients who could afford to wait close to a year for its therapeutic impact. On the other hand, humans and mice may differ in some way that allows CLA to act much more rapidly in humans. Without human studies, it is difficult to know if CLA is of benefit to patients with prostate cancer or even in which clinical situation this product will be of greatest value.

Saw Palmetto

Saw palmetto is a compound derived from the fruit extract of the American Dwarf palm tree that is native to the Atlantic Coastal Plain from North Carolina south through Northern Florida. The common herbal preparation of saw palmetto represents the extracted lipids and sterols.

All clinical trials testing saw palmetto in the treatment of benign prostatic hyperplasia (BPH) were reviewed in *JAMA* in 1998 (101). After critically evaluating the quality of the clinical trials and the consistency of the results, the authors concluded that saw palmetto was an effective treatment for BPH. This conclusion has been confirmed in two subsequent extensive literature reviews (14,100). Proscar currently is approved by the FDA as a treatment for BPH and

for male-pattern hair loss. In the clinical trials comparing finasteride (Proscar) with saw palmetto as treatment for BPH, finasteride was found to be less successful than saw palmetto.

One problem with these reviews is that they do not take into account the varying potency and quality of commercially available saw palmetto products. There are many different ways to extract these lipids and sterols, yielding products with differences in their biologic effects. In addition, the different brands and preparations are available with varying amount of extract per capsule. Consumer Labs, Inc., has tested 27 of the products on the market and found that only 17 contain an adequate amount of the specific fatty acids and sterols needed to produce a therapeutic effect. A list of the manufacturers that passed this test is available at their website, http://www.consumerlabs.com/

The only sure way of knowing whether a given saw palmetto extract is active is for the manufacturer to sponsor clinical trials that document its activity. Clinical trials are expensive and most herbal product companies have been reluctant to participate in such stringent tests of the value of their products. The economic justification was that the consumer did not demand this investment and the cost of such trials eroded the profitability of their business. A few companies have been foresighted enough to take part in clinical testing of their herbal extracts. In those few situations, we have solid evidence of the value of an herbal product as well as sound information about the effective dose and possible side effects.

The biochemical basis for the activity of saw palmetto against benign enlargement of the prostate almost certainly includes inhibition of the formation of dihydrotestosterone (DHT) within the prostate gland. Interestingly, although saw palmetto inhibits formation of DHT in the prostate gland, it does not inhibit formation in many other tissues and may not alter blood levels of this hormone (11,28). However, Proscar is effective at reducing prostatic DHT levels but is relatively ineffective in relieving the symptoms of BPH. The action of testosterone and DHT on the prostate gland is markedly stimulated by the hormone, prolactin. Saw palmetto is reported to block the response of prostate cells to prolactin (Table 15.11) (94).

▪ Decreases synthesis of dihydrotestosterone in the prostate gland
▪ Decreases responsiveness to prolactin
▪ Decreases formation of 5-HETE and leukotrienes

TABLE 15.11. SAW PALMETTO

Saw palmetto also has been reported to inhibit the enzyme 5-lipoxygenase, which converts arachidonic acid to the eicosanoid 5-HETE. This eicosanoid is known to stimulate the growth of prostate cells (80). Other products of 5-lipoxygenase, the leukotrienes, are potent mediators of inflammation.

In BPH, the increased size of the gland can arise from an increase in the number of cells lining the prostate ducts as well as an increase in the number of stromal cells in the space between the ducts. With this background, it is interesting to note that saw palmetto has been shown to cause the death of both the stromal cells and the cells lining the prostate ducts (82,92). This has been followed by one study showing that saw palmetto was able to slow the growth of prostate cancer cells and, at high enough concentrations, even kill these cancer cells. To date, there are no clinical trials testing saw palmetto in the treatment of prostate cancer, so it is difficult to know whether this observation is clinically relevant.

In summary, specific saw palmetto extracts appear to have useful activity in the treatment of BPH. This product appears to alter prostate biology through a number of mechanisms, some of which might also be relevant to the treatment of prostatitis and prostate cancer. Unfortunately, clinical trial documentation of the activity of saw palmetto extract is inadequate in the case of prostatitis and completely lacking in the case of prostate cancer.

Black Cohosh Root

The alcoholic extract of black cohosh root is widely used by women in Europe, and now in the United States, as a treatment for menopausal symptoms (46,63,96). Virtually all of the clinical studies have been performed with one preparation, Remifemin, which was originally developed in Europe and is now marketed in the United States. Many men with prostate cancer on hormonal therapy are using Remifemin or other black cohosh root preparations as treatment for their hot flashes and other symptoms of male menopause. In addition, some physicians caring for prostate cancer patients have been recommending it to their patients.

Black cohosh was one of the medicinal plants widely used by various Native Americans. It was also one of the first native herbal products adapted by early European settlers. Interestingly, the most common use for this herbal product by Native Americans and early European settlers appeared to be as a treatment for rheumatism. There is no convincing evidence that the Native Americans used it for menopausal symptoms. The use of black cohosh for this latter problem became widespread during the 1800s in both America and Europe. Its use in America subsided by 1900, but continued in Europe, especially in Germany. At present, virtually all significant clinical and laboratory investigations on black cohosh have been performed by European investigators.

Numerous clinical trials, including randomized controlled trials, have compared black cohosh root, almost always using Remifemin, with placebo and a variety of estrogen preparations commonly used as hormone replacement therapy for women. It is now well documented that this herbal preparation effectively reduces hot flashes in women. Remifemin also appears to be effective in countering the depression, insomnia, and other psychiatric complications

of female menopause. This black cohosh extract appears to prevent bone loss in animals after surgical removal of the ovaries, raising the possibility that it might also ameliorate the development of osteoporosis. This possibility has yet to be tested in humans. Remifemin also appears to act on the female genitalia, where it has been reported to cause estrogen-like effects on the vaginal mucosa.

The production of estrogen by the ovaries is stimulated by luteinizing hormone (LH). When the brain senses that sufficient estrogen is present, it decreases the production of LH, shutting down the production of additional estrogen (32). During menopause in women, LH production increases because the brain senses the absence of estrogen. The magnitude of this LH rise has been reported to correlate with the severity of menopausal symptoms. A majority of the studies indicate that a dose of Remifemin sufficient to reverse menopausal symptoms also blocks the release of LH.

As with most herbal preparations, Remifemin is composed of a mixture of different chemicals. Fractions have been identified that can bind to the estrogen receptor and appear to mimic the actions of estrogen. Another fraction can block LH release even though it has no estrogenic activity. These results suggest that it would be possible to prepare black cohosh extracts that selectively suppress the response of the brain to menopausal symptoms, such as hot flashes, depression, and insomnia, that lack any activity at the estrogen receptor.

The side effects of Remifemin appear to be mild. The most common side effect is transient gastric distress, which is seen in approximately 7% of women. In fact, it seems to be as well or better tolerated than the commonly used estrogenic medications. In particular, it appears to be much less likely to cause uterine bleeding. In standard test systems, it also does not cause mutations or stimulate the development of cancers. This is important because naturally occurring estrogens are known to promote the development of cancers of the breast and uterus.

In women with breast cancers that contain the estrogen receptor, there is concern that use of estrogen-based drugs might enhance the growth of the cancer. One of the concerns about soy phytoestrogens is that, at low concentrations, they enhance the growth of the estrogen-responsive human prostate cancer cell line, MCF-7 (30). It is only at higher concentrations that soy phytoestrogens retard the growth of this and other breast cancer cell lines. In contrast, several studies now show that Remifemin retards the growth of MCF-7 in tissue culture at all of the concentrations tested. This has led several commentators to suggest that this herbal product might be safe for postmenopausal women with breast cancer. However, it is dangerous to use such tissue culture data as proof of safety. The only valid study would be to directly test the impact of Remifemin in women with estrogen receptor–positive breast cancer. This testing has not been performed, and the author therefore hesitates to recommend Remifemin to women with established breast cancer or women at high risk for breast cancer because of family history.

How efficacious is the use of Remifemin and other black cohosh extracts in men? No clinical trials in which Remifemin or other black cohosh extracts were administered to men could be found. Black cohosh definitely should not be recommend to men who are not on hormonal therapy. The concern is that it might suppress LH production and this might lead to testicular atrophy. In men already on hormonal therapy, the estrogenic activity of this supplement may cause breast enlargement and other estrogen-dependent side effects. No information could be found about the impact of Remifemin and other black cohosh preparations on prostate cancer growth and spread, and it is impossible to predict its impact on this disease. Its use in men is questionable at best until there is a better understanding of its impact on the physiology of the human male and its effects on prostate cancer.

Lycopene

It has long been known that intake of fruits, vegetables, and grains are associated with a decrease in the risk of many cancers, but the specific components of these foods responsible for this reduced risk remain a matter of controversy. Lycopene is a member of a broad group of plant pigments, called *carotenoids,* that includes beta-carotene (orange color of carrots) and lutein (yellow color in many vegetables). Carotenoids, especially beta-carotene, have long been thought to play an important role in cancer prevention (93). Lycopene is the red pigment found in tomatoes, pink grapefruit, watermelon, and apricots and is related to beta-carotene and other carotinoids in structure (1). Evidence strongly indicates that intake of tomato products and lycopene offer protection against cancers of the stomach, lung, and prostate. Lycopene also appears to reduce the risk of cancers of the oral cavity, esophagus, breast, pancreas, cervix, and colon. What is more interesting is that none of the 72 studies reviewed in preparation of this chapter report a link between lycopene and an increase in the risk of any cancer. Furthermore, there are no reports of toxicity, regardless of dose.

In a recent review, Giovannucci discussed study after study in which the intake of lycopene, but not other carotenoids such as beta-carotene, correlates with protection from cancer (39). This is consistent with a recent randomized, controlled trial that found that supplemental beta-carotene actually increased the risk of death from prostate cancer. This is an important point, because many dietitians and alternative health practitioners are still recommending beta-carotene to men with prostate cancer. It is important to stress that there is no evidence to support this practice.

Lycopene is well absorbed from cooked tomato products such as tomato sauce or tomato paste, but not from fresh tomatoes. In addition, lycopene absorption is enhanced by

the addition of oil (61). The traditional practice around the Mediterranean of consuming cooked tomato products in combination with olive oil appears to have a strong rationale.

Why should lycopene reduce the risk of cancer? Carotenoids can act as antioxidants and as precursors to Vitamin A. Among the common carotenoids, lycopene is the most effective antioxidant and this property may be important given the activity of vitamin E and selenium against this cancer.

Several observations instill confidence in the importance of lycopene. First, the studies that report a reduced risk of cancer associated with lycopene involved the United States, Italy, the Netherlands, Spain, Sweden, Australia, Iran, China, and Japan, indicating the protective effect persists despite widely different dietary patterns, lifestyles, and ethnic background. Second, the protective effect extends to a wide range of human cancers, each of which has its own unique biology and is caused by different mechanisms. Third, in every country and with every cancer examined, lycopene intake never correlated with a significant increase in the risk of cancer.

What is lacking? Final proof of lycopene's importance will require a randomized, controlled clinical trial in which large numbers of people take a placebo or a defined amount of lycopene over a prolonged time period and the impact on cancer frequency and cancer deaths is measured. Because tomato products often are used in prepared foods in ways that are not obvious, this study will be difficult to conduct.

PC-SPES

PC-SPES is a combination of seven Chinese medicinal herbs with the addition of one North American herb, saw palmetto. This herbal product appeared a few years ago and is widely used by patients as a treatment for prostate cancer. The story of this herbal product illustrates the positive and negative aspects of the current regulatory environment with regard to supplements. This product did not proceed through the standard process by which prescription drugs are approved by the FDA. Shortly after this product was introduced, many in the medical field became aware that, in some patients, this product induced a significant decrease in tumor size. Physicians initially had no information about appropriate dosing, side effects, and antitumor activity of this preparation. Physicians specializing in prostate cancer have gathered experience with the use of this herbal product, largely because patients decided to try it on their own.

Reports about PC-SPES began to appear in medical literature. One noteworthy article by DiPaola and co-workers, of the Robert Wood Johnson School of Medicine, New Brunswick, New Jersey, appeared in the New England Journal of Medicine (29). The article showed that this preparation has estrogenic activity, but is distinct from known estrogenic drugs such as diethylstilbestrol (DES) and estradiol. They also found that PC-SPES caused a significant drop in blood levels of the male sex hormone, testosterone. It caused a greater than 50% drop in prostate-specific antigen (PSA) in 6 of 8 patients. The findings reported by DiPaola and co-workers suggest that the activity of PC-SPES in these patients represents a “hormonal” response equivalent to that caused by conventional estrogenic substances such as DES and estradiol.

A phase II clinical trial designed to establish the true effectiveness of PC-SPES was recently reported by Small of the University of California at San Francisco (90). In this study, essentially all of the patients who had not yet received hormonal treatment responded, consistent with the ability of PC-SPES to mimic the action of DES. Of even greater interest, almost half of the patients with hormone-refractory prostate cancer also responded. This response rate in hormone-refractory prostate cancer compares well with the most active cytotoxic chemotherapy regimens. Other groups also have documented the activity of this herbal preparation against human prostate cancer (26).

PC-SPES is not without significant side effects (Table 15.12). Virtually all men treated with this herbal product develop breast tenderness and gynecomastia. In addition, most men experience a loss in sex drive. GI toxicity in the form of diarrhea also can be a problem. Leg cramps are common and usually associated with a low serum magnesium level. Of greater concern, men with preexisting hypertension find its management more difficult. Shortly after the introduction of PC-SPES, a number of men were reported to develop thrombophlebitis and pulmonary embolism. For this reason, it became common practice to place patients on warfarin as prophylaxis against blood clots. However, in the large phase II trial conducted by Small, blood clots were no more common than one would anticipate from that normally seen in men with prostate cancer.

▪ Gynecomastia and gynecodynia	▪ Hypertension
▪ Loss of sex drive	▪ Thrombophlebitis
▪ Diarrhea	

TABLE 15.12. SIDE EFFECTS OF PC-SPES

Soy and Genistein

It has long been known that the risk of prostate cancer is low in populations where soy consumption is common. Soy contains isoflavones, such as genistein, that are thought to account for the health benefits of this legume. These compounds are alternatively referred to by their specific chemical name, such as genistein; as isoflavones; or as phytoestrogens. The latter term arises from the fact that these isoflavones mimic some of the biologic effects of the female sex hormone, estrogen.

In the laboratory, genistein has well-documented activity against prostate cancer (5,16,88,102,104). High concentrations of genistein and other soy isoflavones cause the death of prostate cancer cells. At somewhat lower concentrations, these isoflavones arrest the growth of prostate cancer and block tumor cell invasiveness. In addition, there are now several studies in which soy products or isolated soy isoflavones have been demonstrated to slow the growth of human prostate cancer cells in mouse xenograft models.

The mechanism by which soy isoflavones might slow the growth and/or spread of prostate cancer remains unclear. Genistein, at concentrations obtainable in humans, can block the action of both the epidermal growth factor and *Her-2/neu* receptors. This means that genistein can theoretically block one of the major mechanisms by which prostate cancer cells become hormone-refractory. Although these isoflavones act as estrogenic compounds in laboratory assays, men on soy-rich diets have only minor alterations in sex hormone levels. Finally, soy isoflavones appear to block tumor angiogenesis in laboratory models.

There is also considerable controversy about the best soy product to use to obtain high blood levels of genistein and other soy isoflavones. Genistein is absorbed much more effectively from fermented soy products such as miso, natto, and tempeh than it is from soy beans, tofu, or soy milk. In addition, soy phytoestrogen or genistein tablets or capsules currently on the market would easily permit the ingestion of several grams of soy isoflavones per day. An additional complication is that blood levels of genistein may underestimate the levels in the prostate. When genistein levels are measured in prostatic fluid, the concentration is five to ten times higher than in the blood.

Clinical use of soy isoflavones in the treatment or prevention of prostate cancer is made questionable by several problems. Although quite a few epidemiology studies show a correlation between high soy intake and a reduced risk of prostate cancer, a randomized, controlled clinical trial showing that these soy products prolong the life of men with this disease is still lacking (43,54). Clinical trials that show that soy products arrest or slow the growth of prostate cancer are even lacking. The dose and schedule for the administration of soy isoflavones most likely to affect human prostate cancer is not known. On the other hand, many health benefits appear to be associated with the use of soy protein as a substitute for animal proteins. The FDA recently has allowed firms marketing soy protein to claim that these products have a favorable impact on the course of coronary heart disease.

SUMMARY

Part of "15 - ALTERNATIVE MEDICAL THERAPIES FOR UROLOGIC DISEASES "

The Dietary Supplement Health and Education Act of 1994 guarantees Americans ready access to herbal products. Although selected herbal products have impressive therapeutic activity in tissue culture and animal models, with few exceptions, clinical trial documentation of activity is less than impressive. In fact, the common pattern is for initially promising laboratory findings to lead to widespread commercial availability without any intervening clinical investigation. An additional problem of great concern is that the commercially available herbal products vary widely in their quality.

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16

RENAL TUMORS

Chad W.M. Ritenour

Robert O. Northway

Fray F. Marshall

C.W.M. Ritenour, R.O. Northway, and F.F. Marshall: Department of Urology, Emory University, Atlanta, GA 30322.

Contents

Much of what is known today about renal tumors revolves around data from just the past century. Advances in both pathologic diagnosis and surgical technique have been steady since the first known nephrectomy approximately 140 years ago. Unfortunately, at this time, there is still no highly effective therapy, apart from surgery, for most malignant renal tumors. Nonetheless, continued research in this arena has yielded some important discoveries, and this challenge persists for future generations. As more is learned about the cellular characteristics, and specifically the molecular nature of these tumors, researchers will further target surgical and medical approaches to improve the prognosis of patients with advanced disease.

CLASSIFICATION

Part of "16 - RENAL TUMORS "

Although less common than benign renal cysts, solid tumors of the kidney are most often malignant in nature. The majority of these are adenocarcinomas, commonly called *renal cell carcinomas (RCCs).* However, numerous other lesions have been described in the kidney, and these have been found in all aspects of renal and perirenal tissue including epithelial tissue, vascular structures, neurogenic tissue, and mesenchymal derivatives. Childhood renaltumors [predominantly Wilms' tumor (nephroblastoma)], from embryonic tissue also are seen and are discussed elsewhere in this text.

Over the past decades, investigators have proposed several classification schemes for renal masses, although not one has been universally accepted as being both simple and comprehensive. Stratification has been based on tissue origin, behavior (malignant, benign, or inflammatory), and radiographic appearance. Histopathologic diagnosis, as related to molecular genetics, also has been examined in attempts to find common links between different tumors as well as to locate potential prognostic markers at the gene level (283).

With the advent of new molecular genetic data, specific morphologic and cytogenetic characteristics of the most common renal neoplasms, epithelial tumors, were recently integrated into a standard classification system. In 1997, at a consensus conference (the Diagnosis and Prognosis of Renal Cell Carcinoma) held by the World Health Organization (WHO) in combination with the Union Internationale Contre le Cancer (UICC) and the American Joint Committee of Cancer (AJCC), old categorization systems were modernized. An appreciation for the histologic diversity led investigators to reclassify on the basis of morphology and yet remain consistent with known genetic facts. The descriptive terms applied had historic reference, reflected salient morphologic features, and were unambiguous. The contemporary classification of adult renal epithelial neoplasia was generated as listed in Table 16.1 (239). Regardless of the classification scheme, the clinician must be aware of the behavioral characteristics of the mass once a diagnosis is made.

Benign Neoplasms	Malignant Neoplasms
Papillary adenoma	Conventional (clear cell) renal carcinoma
Renal oncocytoma	Papillary renal carcinoma
Metanephric adenoma	Chromophobe renal carcinoma Collecting duct carcinoma Renal cell carcinoma, unclassified

From Störkel S, Eble J, Adlakha K, et al. Classification of renal cell carcinoma. Workgroup No. 1. *Cancer* 1997;80(5):987, with permission.

TABLE 16.1. CLASSIFICATION OF RENAL EPITHELIAL TUMORS

BENIGN EPITHELIAL TUMORS

Part of "16 - RENAL TUMORS "

Papillary Adenoma

Several previous classifications of renal epithelial tumors have included adenoma as a distinct pathologic entity. However, significant controversy exists over the differentiation of adenomas from adenocarcinomas by histologic criteria (88). Distinction is important because adenomas generally are regarded as benign lesions, which do not progress to metastasis, whereas adenocarcinomas have known metastatic potential.

Asymptomatic papillary adenomas are the most common renal epithelial neoplasm. They are exclusive to the renal cortex and have been identified in 4% to 37% of autopsy specimens (88). Based on ultrastructural studies, papillary adenomas originate from a distal tubular cell (71). In addition, associated chromosomal changes (including trisomy 7, trisomy 17, and loss of the Y chromosome) similar to those seen with papillary RCC have been identified (125). Increased frequency of papillary adenomas has been found with smoking (279), end-stage renal disease with hemodialysis (107), and arteriosclerotic renal vascular disease (21).

On gross examination, papillary adenomas appear as very small yellow to pale gray spots in the renal cortex. Recently, Grignon and Eble (88) proposed a constellation of three histologic features to assist in identifying these lesions. First, the cellular architecture must be tubular, papillary, or tubulopapillary in character. Second, the diameter of the tumor should measure less than or equal to 5 mm. Although certain slightly larger lesions may be adenomas, the chance of malignancy is greater with increased sizes. Third, the cells should not histologically resemble clear cell, chromophobe, or collecting duct RCCs. If these criteria are satisfied, the diagnosis of papillary adenoma can be made with greater confidence.

Renal Oncocytoma

Renal oncocytomas are distinct pathologic lesions associated with benign clinical courses. Although earlier reports suggest metastatic potential of certain oncocytomas, these reports now are thought to have represented cases of chromophobe RCC, a similar but histologically different tumor not recognized at that time. Because chromophobe RCCs are known to metastasize, the distinction between oncocytomas and these carcinomas currently is important for therapeutic decisions and follow-up.

Oncocytoma and chromophobe RCC have many overlapping morphologic, histochemical, and ultrastructural features. Both are thought to arise from cells of the distal nephron (73,285). Some specific nuclear parameters such as binucleation or multinucleation or staining with an antimitochondrial antibody (113-1) can be valuable in distinguishing between the two tumors (252,253). Characteristically, the cytoplasm of oncocytoma cells is uniformly eosinophilic and granular, whereas that of chromophobe RCC is more variable. Both tumors exhibit chromosomal loss on chromosomes Y and 1, but recent research with oncocytomas has revealed a unique recurring chromosomal translocation about 11q13, in proximity to the BCL1 locus, that may serve as a marker for improved classification (167,224).

Oncocytomas are thought to account for 3% to 7% of solid renal tumors (136). They are approximately two times more common in males than in females. Most often, they are discovered as incidental findings on radiographic studies performed for other reasons. Occasionally, oncocytomas present with flank pain, hematuria, or an abdominal mass, but they usually are asymptomatic. The median age of patients at presentation is in the seventh decade, which is slightly older than for RCC.

On gross appearance, oncocytomas (Fig. 16.1) are a tan-brown color and are well circumscribed from surrounding renal parenchyma. Often, a central scar highlights the neoplasm. Necrosis and hemorrhage are not prominent. Although most oncocytomas are unilateral, approximately 4% to 6% are bilateral (46). Histologically, the cells show regular granular cytoplasm due to numerous mitochondria and uniform nuclei with few mitoses. Cases of oncocytosis with innumerable oncocytic nodules throughout the kidney and associated with one dominant tumor have been reported (254). Coexistence of oncocytoma with RCC also has been described in up to 10% of cases (46).

FIGURE 16.1. Oncocytoma with characteristic central scar and demarcation from surrounding renal tissue.

Radiographic studies rarely are diagnostic for oncocytoma because it often appears as any other solid renal tumor. Occasionally, a central scar is visualized on ultrasound studies or computed tomography (CT) scans, but this is nonspecific. Although angiography is now rarely performed for these tumors, a characteristic “spoke-wheel” appearance has been used to describe oncocytoma (273).

Due to lack of a pathognomonic radiographic sign, the diagnosis of oncocytoma rarely is made without an operation. The potential presence of concurrent malignant tumors within oncocytoma makes diagnosis by percutaneous needle biopsy risky. Partial nephrectomy with an adequate

margin is the surgical therapy of choice for small tumors, but large or multifocal tumors may require radical nephrectomy for complete excision.

Metanephric Adenoma

Metanephric adenoma is a recently recognized benign epithelial tumor. In a report of 50 cases, investigators concluded that it occurs most commonly in the fifth to sixth decades, with a 2:1 female predilection (44). Some of these tumors present with symptoms of polycythemia, flank pain, mass, or hematuria; however, approximately half are incidental findings on radiographic studies.

Metanephric adenomas characteristically range in size from 3 to 6 cm, with occasional reports of larger tumors (44). The tumors are well circumscribed with a gray, tan, or yellow color and occasional foci of hemorrhage and necrosis (115). Cysts may also be present. Calcifications, represented histologically by Psammoma bodies, are common. Cells are tightly packed and uniform with prominent nuclei and scant cytoplasm (88). Mitoses are rare or absent. Adherence to these histologic criteria will avoid having other, more common renal lesions misdiagnosed as metanephric adenomas (182).

Differentiation of metanephric adenomas from other renal tumors by ultrasound or CT scans is difficult (60). Although no known case has recurred following removal of the tumor, synchronous RCC has been found in several isolated specimens (45). Therefore all solid lesions of the kidney should be treated as malignant unless proven otherwise with tissue diagnosis.

A variant of metanephric adenoma has been termed *metanephric adenofibroma.* In one of the first descriptions, Hennigar and Beckwith (98) reported several tumor cases with an epithelial component identical to metanephric adenoma along with a spindle cell component similar to congenital mesoblastic nephroma. (They originally termed this new tumor a *nephrogenic adenofibroma,* but given its similarity to metanephric adenoma, the name was later modified to metanephric adenofibroma.) The combination of both histologic components is necessary for the diagnosis of metanephric adenofibroma, but careful sampling may be necessary to avoid missing small epithelial nodules (214). Patients with metanephric adenofibroma have ranged in age from 3.5 to 36 years, younger than most patients with metanephric adenomas, and appear to have a benign course.

MALIGNANT EPITHELIAL TUMORS

Part of "16 - RENAL TUMORS "

Renal Cell Carcinoma

Epidemiology

Malignant tumors of the kidney are estimated to represent approximately 2.5% of all new cancer cases in the United States each year. Statistical analysis showed that, for the year 2000, approximately 31,000 new cases and 12,000 deaths would occur (87). Most of these diagnoses are related to malignant renal epithelial tumors, or RCCs, which comprise approximately 85% of all renal neoplasms (161). Males show more than twice the incidence of females in studies of RCCs, with most patients presenting in the seventh and eighth decades of life. The highest rates occur in North America and Europe, especially Scandinavia (161).

Over the past several decades, both the incidence of diagnosis and numbers of related deaths for RCC have risen in the United States and other countries (34). This parallels higher numbers of incidentally discovered tumors found during radiographic screening studies performed for the diagnosis and management of other disorders. Routine ultrasonography, CT, and magnetic resonance imaging (MRI) now discover increased numbers of small lesions in the absence of symptoms (113,251). However, most epidemiologists do not believe that these incidental tumors fully explain the rising incidence of renal cancer (34).

Aside from the rise in small, early-stage kidney tumors, there has also been a smaller percentage increase in the number of higher-stage lesions found (33). This expanding discovery mirrors the overall rising mortality rates that have been observed in recent years. In the United States, these changes are most evident in the African American population, which shows greater increases in both incidence and

mortality for RCC when compared with Caucasians (34). The reasons for this racial difference are unclear.

Etiology

Based on information from case-control, genetic, and cohort studies, several risk factors have been associated with the development of RCC (Table 16.2). Most studies with sufficient sample size demonstrate a positive correlation between RCC and smoking cigarettes, which has been associated with up to a 35% increase in risk (282). The data suggest a dose-response relationship, with relative risk increasing with the numbers of cigarettes smoked, as well as a significant reduction in risk associated with cessation. Obesity also has shown positive associations with RCC (33). Greater risk exists for women with elevated weight than for their male counterparts, and the risk appears proportionate to the severity of obesity (161). With its increasing prevalence in the United States, obesity may contribute to the rising incidence of RCC.

Cigarette smoking	Occupational exposures (e.g., asbestos, petroleum, cadmium, lead)
Hypertension	
Elevated body weight	
Medications (e.g., diuretics)	Genetic predisposition (e.g., von Hippel–Lindau disease)
Acquired renal cystic disease	

TABLE 16.2. SELECTED RISK FACTORS ASSOCIATED WITH RENAL CELL CARCINOMA

Several epidemiologic studies link hypertension to elevated risks for RCC, with up to a threefold increase in risk reported (33). Diuretics, which often are used in the medical treatment of hypertension, have been particularly implicated (89,213). Acquired cystic disease, found in renal failure patients on hemodialysis, has been associated with higher rates of RCC (110,111). Occupational exposure to asbestos, petroleum, cadmium, and lead also has been reported to produce increased levels of risk (33).

Although relatively rare, familial cases of RCC have been linked to genetic causes. von Hippel–Lindau (VHL) disease, an autosomal-dominant genetic disorder, has long been associated with the development of RCC. The condition is characterized by hemangioblastomas of the retina and the central nervous system, especially the cerebellum, as well as cysts of the kidneys, liver, and pancreas. Pheochromocytomas also have been linked to the syndrome (69). Renal tumors in these patients tend to be small, multifocal, and bilateral.

Pathology and Molecular Genetics

Although collectively termed RCCs, malignant renal epithelial neoplasms are now subdivided under the new classification system, based on prominent morphologic features (239). However, in the past, pathologists long debated the varied histologic appearance of RCC. Of particular note, in the nineteenth century, Grawitz and others advanced the idea that these tumors were derived from malignant transformation of adrenal rest cells within the kidney. This belief led to later use of the term *hypernephroma,* first used to symbolize origin from cells above the kidney but now recognized as a misnomer to describe these tumors (116). Today, investigators know RCCs originate from renal tubular cells.

Although early study was limited to gross structural or numeric chromosomal alteration, investigators later discovered that discrete and specific loss of gene product from somatic cells could be linked to the origination and evolution of certain cancers (Table 16.3). Such thorough cytogenetic analysis of both sporadic and familial forms of RCC helped localize areas of suspect genetic alteration. In a particular major breakthrough, Seizinger and colleagues initially mapped the VHL gene to the short arm (3p25) of chromosome 3 (211).

Tumor	Affected Chromosomes
Conventional (clear cell) RCC	3p, 17
Papillary RCC	3q, 7, 12, 16, 17, 20, Y
Chromophobe RCC	1, 2, 6, 10, 13, 17, 21
Collecting duct carcinoma	1q, 6p, 8p, 13q, 21q

RCC, renal cell carcinoma.

TABLE 16.3. LOCATION OF POTENTIAL CHROMOSOMAL CHANGES IN RENAL CELL CARCINOMA

In one study, researchers noted VHL gene mutations in 57% of patients with sporadic RCC and confirmed its potential involvement with tumorigenesis of that entity (79). Further research has demonstrated that multiple mechanisms of VHL gene mutation, including methylation, deletion, insertion, transition, and transversion, are responsible for the phenotypic variability of the syndrome (79,99). Meanwhile, others have chosen to focus on the inhibitory function of the VHL gene. Current theory proposes that the VHL protein plays a role in tumor suppression by modulating a transcription elongation complex, elongin or SIII, and negatively regulating the accumulation of vascular endothelial growth factor (VEGF) (109,219).

Concurrent with the ongoing research of the VHL protein, there were multiple reports of chromosomal deletions in the same region (3p) with sporadic forms of RCC. Since the late 1980s, the loss of loci on the short arm of chromosome 3 has been the predominant mutation linked to clear cell carcinoma (Fig. 16.2), the most common subtype of RCC (67,284). Increasing focus on a cohort of sporadic tumors identified 86% of cytogenically examined specimens as having a detectable anomaly distal to band 3p11.2-p13 (124). Allelic loss of 3p now is thought to be an early event

in the pathogenesis of clear cell carcinoma, whereas others now consider additional allelic losses on chromosome 17 to be associated with the advanced disease.

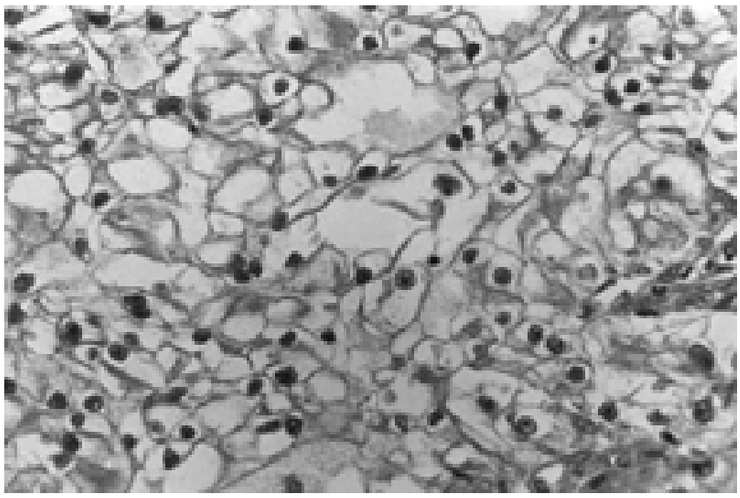

FIGURE 16.2. Histologic appearance of conventional (clear cell) renal cell carcinoma.

Among 60 nonpapillary RCCs studied at Memorial Sloan-Kettering Cancer Center, a significant correlation associating the deletion of chromosome 17p with tumor grade, pathologic stage, and nodal metastasis has been seen (188). Whether deletions of 3p occur in all renal cell cancers is under scrutiny, and many other chromosomal aberrations have been identified. Research to date shows that 3p genomic changes are conspicuously absent from the papillary variant of RCC and therefore reinforces the linkage between genes and representative histology.

Representing 10% to 15% of all renal cell cancers, the papillary carcinoma variant can be inheritable, multifocal, and bilateral, but generally suggests a more favorable prognosis. Long differentiated through immunohistochemistry, papillary RCC has distinct cytogenetic character, associated with loss of the Y chromosome along with trisomies of chromosomes 3q, 7, 12, 16, 17, and 20 (239). Recent research on those affected by hereditary papillary renal carcinoma implicates mutations, activating the MET protooncogene, to chromosome 7q31.1-34 (210). Investigators continue to propose that mutations in the MET protooncogene render the cells more susceptible to errors in chromosomal replication resulting in nonrandom duplication, a proliferative advantage, and the frequent occurrence of trisomy (286).

Chromophobe RCC accounts for approximately 5% of malignant renal epithelial tumors (239). Histologically, they are composed of two distinct cell types, those with granular eosinophilic cytoplasm and those with pale cytoplasm. Ultrastructural analysis shows numerous cytoplasmic microvesicles, and characteristic cytoplasm staining with Hale's colloidal iron is typical (42). Microscopic similarities exist between chromophobe RCC and oncocytoma, although distinctive nuclear features, including wrinkled “raisinoid” nuclei with frequent binucleation and perinuclear clearing are helpful in distinguishing between the two (253). A clinical analysis of patients with chromophobe carcinoma shows that the majority of tumors appear to be localized to the kidney at the time of diagnosis, but clinical behavior seems to be similar to respective stages of clear cell carcinoma (42). Large tumors and those with synchronous papillary carcinoma may be particularly prone to metastasis (192). DNA aneuploidy, especially hypodiploidy, is seen in the majority of cases with noted monosomy of different chromosomes (1,6,10,13,17,21,184) (239).

Collecting duct carcinomas represent a rare group of renal neoplasms. Unlike clear cell carcinoma, they arise from the distal portion of the nephron, commonly strike in a young population, and carry an unusually poor prognosis. Application of the aforementioned chromosomal inspection has discovered a frequent loss of heterozygosity at chromosome regions on 1q, 6p, 8p, 13q, and 21q (184). High density mapping of arm 1q in 13 collecting duct tumors shows an area of minimal deletion around the area located at 1q32.1-32.2 in 69% of the examined specimens (238). Considering these data together gives credence to the idea of a potentially unique set of molecular events in tumorigenesis, different from that of clear cell carcinoma.

RCC, unclassified, is a category reserved for malignant epithelial tumors that do not conform to any of the other subtypes. Of the total group of RCCs, they comprise approximately 4% to 5% (239). Specifically, composites of recognized subtypes, tumors with mucin production, and tumors with extensive sarcomatoid changes without recognizable epithelial elements are examples of this classification.

Pathologic grading of tumor cells has been shown to have prognostic value in cases of RCC (233). Several grading systems exist, although most pathologists rely on nuclear grading for renal lesions. The Fuhrman nuclear grading system is the most widely used in North America, and several studies confirm its relevance for prognosis (82). Nonetheless, all grading is subjective, and problems with standardization are recognized (154).

Clinical Presentation

Significant variability exists in the clinical presentation of RCC. However, a significant number of lesions are not discovered until reaching an advanced stage because small tumors isolated to the kidney are often asymptomatic. Aside from local symptoms produced by the tumor itself, a variety of systemic manifestations have been described. Therefore the clinician must be familiar with some of the extrarenal manifestations and must harbor a high suspicion for diagnosis. Although a classic triad of symptoms (pain, hematuria, and flank mass) has been associated with RCC, all three symptoms rarely are present together (150). Single symptoms occur much more frequently. Hematuria often is listed as the most common symptom, occurring in up to 60% of patients (161). Nonspecific symptoms such as fever, malaise, weight loss, and night sweats are also common.

Occasionally, a varicocele from compression or obstruction of the testicular vein is found.

Few other disease entities possess such a propensity for paraneoplastic syndromes as RCC (Table 16.4). Erythrocytosis, anemia, hypercalcemia, hypertension, acute hepatic dysfunction, and amyloidosis all have been associated with renal cancer (150) and sometimes have been the hallmark features at presentation. Questions remain regarding which signals, substances, or cytokines initiate the manifesting signs and whether these are markers for prognosis or recurrence.

Erythrocytosis	Acute hepatic dysfunction
Anemia	Amyloidosis
Hypercalcemia	Thrombocytosis
Hypertension	

TABLE 16.4. PARANEOPLASTIC SYNDROMES ASSOCIATED WITH RENAL CELL CARCINOMA

Several blood and serologic markers have been evaluated, and many have potential utility. Serum ferritin levels have been shown to be significantly elevated and higher than controls when looking at patients with RCC. In this group of patients, a statistically significant increase with advancing stage exists (57). Erythropoietin also can be elevated, presenting in as many as 63% of patients (242). More routine laboratory studies, including hematocrit and platelet levels, can likewise prove credible in regards to prognosis. In a series of stage IV tumors, patients with a normal platelet count had a mean increased survival of 59 months over those with thrombocytosis (platelet count more than 400,000) when controlling for pathologic stage, nuclear grade, and cell type (245). Others point to anemia and serum iron as useful tumor markers for initial evaluation and in follow-up (281). Anemia is the most common hematologic abnormality associated with RCC. Characteristically normocytic, normochromic anemia of chronic disease has been implicated. Following tumor resection, the anemia has usually resolved and some have shown that disease progression coincided with recurrent anemia (86,281).

Hypercalcemia has been associated with RCC and, like anemia, often resolves after removal of the primary tumor. Some elevation in serum calcium will be seen in 10% of patients. Experience shows that recurrent hypercalcemia can be an early sign of undetected skeletal metastasis or herald secondary sites that secrete an inciting humoral factor. Although parathyroid hormone–related protein (PTHrP) has been linked to the syndrome of humoral hypercalcemia of malignancy and has been detected in more than 95% of RCC, no significant correlation was identified when observing intensity of immunostaining of PTHrP and serum calcium levels (84).

Hypertension has been identified in many patients with RCC. A patient may be hypertensive as a consequence of hypercalcemia, but other factors such as polycythemia, arteriovenous fistulae, ureteral obstruction, or renin secretion may be responsible. Sufrin and colleagues noted that the elevated levels of renin were associated with high-stage renal tumors and hypertension (241). In fact, renin secretion is a known characteristic of RCC (103) but lacks specificity, because renin production has been reported with other cancers as well (55).

Acute elevation of liver enzymes (Stauffer's syndrome) has been described with certain cases of RCC (236). The majority of these cases show no evidence of hepatic metastasis from the tumor (19). Moreover, the enzymes often return to normal levels following removal of the renal lesion. Failure of liver function to return to normal has been significantly correlated with decreased survival (66). Recent work has shown that elevated liver enzymes, as well as other paraneoplastic syndromes, may be related to increased systemic levels of interleukin-6 (15,268).

Radiographic Diagnosis

The revolutionary improvements in radiographic diagnosis have radically changed the preoperative, intraoperative, and follow-up investigation of renal lesions. Standard historic, radiographic evaluation consisted of a chest x-ray film, intravenous (IV) pyelography, renal angiography, and possibly, bone scintigraphy. However, radiologists increasingly discover renal lesions incidentally through the newer modalities of ultrasonography, CT, or MRI while pursuing other suspected diagnoses. Although some may consider the plain film dated, one must recognize that 10% of RCCs will contain calcium and be detectable on abdominal plain films (112). Besides abdominal films, a chest radiograph has significant use and is a cost-effective tool for follow-up examination.

Intravenous Pyelography

Although there have been recent shifts away from excretory urography toward new imaging modalities, the intravenous pyelogram (IVP) remains a standard evaluation of the upper tracts for hematuria. On this study, renal masses may produce changes in the nephrogram and/or distortion of the collecting system. Occasionally, calcifications are present and also may be suggestive of a mass (133). The main limitation of IVP is its low sensitivity for small lesions compared with other studies (270). In addition, poor technique may lead to missed lesions altogether.

Angiography

Currently, angiography rarely is used in the initial diagnosis of renal masses, which historically show marked hypervascularity on angiogram. This study has been replaced almost

completely by less invasive modalities such as CT and MRI. Nonetheless, angiography still proves useful for surgical planning in certain cases of partial nephrectomy.

Ultrasound

Recent reviews show that in as many as two-thirds of patients with localized RCC, lesions are found fortuitously on ultrasound examination (4). Moreover, incidentally detected tumors are of a lower stage than the comparative symptomatic lesions and result in improved survival (122,187). Noninvasive and cost-effective, ultrasound has inherent advantages. Echogenic criteria are well described and categorized to differentiate simple lesions from complex lesions with malignant potential. The sensitivity of sonography exceeds that of IVP in detecting small renal lesions, but both fall short of CT in relation to lesions less than 2 cm (270). Although descriptive, echogenic features unreliably determine histology. Recent attempted modifications, such as digitization with measuring of the grayscale (221) and Doppler vascularity determinations (119), have provided little absolute data on differing histology.

Real-time dynamic imaging capability does allow for intraoperative sonographic assessment of deep parenchymal lesions (i.e., difficult to palpate), tumor extension into adjacent structures, and pathology with uncertain preoperative staging (185). With the expanding role of nephron-sparing surgery and partial nephrectomy, intraoperative ultrasonography helps determine the boundaries of resection, multicentricity, venous extension, and associated cysts that may not be appreciated with visual inspection or preoperative radiographic evaluation (28,146).

Transabdominal ultrasound has been used to assess the inferior vena cava (IVC) for tumor extension in those undergoing radical nephrectomy. Recently, intraoperative ultrasound has been used to help clarify preoperative findings at the time of surgery (96,138). Newer ultrasound studies including color-flow Doppler and transesophageal echocardiography (TEE) also have proved valuable for diagnosis. Even when a tumor extends beyond the proximal cava or renal vein, TEE facilitates the identification of tumor thrombus migration and air embolization, allowing for immediate intraoperative intervention (220). Color-flow Doppler has been used for cases of equivocal CT scans and has shown excellent accuracy for caval tumor (91,121,220,256).

An occasional diagnostic dilemma involves the identity of a renal cystic lesion by ultrasound. Bosniak developed a classification system for standardizing such lesions and identifying those with higher risk for malignancy (18). In a review comparing Bosniak classification with confirmed pathologic diagnosis, Seigel and colleagues found the incidence of malignancy with Bosniak I, II, III, and IV lesions to be 0%, 13%, 45%, and 90%, respectively (218a). One limitation of the Bosniak classification, which has been extended to cysts found by CT, is its subjectivity.

Computed Tomography

CT has distinct advantages over ultrasound and other modalities. Physicians can rapidly measure cyst densities, gain relational perspective between organs, and provide tumor staging with improving accuracy. New generation, multiphasic helical scanners enable greater detection of lesions, particularly small renal tumors, and foster a more thorough understanding of the capability. In contrast to conventional CT, helical scanning eliminates respiratory misregistration, and rapid acquisition allows for comparison of identical levels obtained before and after contrast. This is helpful in assessments of tumor extension into the renal vein (274). For maximum sensitivity, research shows that the differentiation of attenuation between a lesion and normal renal parenchyma is greatest during the nephrogenic phase, just before excretion of contrast into the collecting system, and not during the corticomedullary phase (39,246). Helical CT technology permits the production of detailed, high-quality three-dimensional (3D) reconstruction in a format remarkably similar to actual parenchymal, vascular, and adjacent structural anatomy. In one study, preoperative staging with 3D helical CT accurately depicted the pathologic character in 95 of 97 tumors; almost all of the renal arteries (96%) and renal veins (93%) were detected (40). Using these data obtained preoperatively readily simulates the surgical perspective and has proven a useful adjunct in nephron-sparing surgery (228,229).

For such reasons, CT has become the preferred method for staging of RCC (Fig. 16.3). Although the patient must ingest oral contrast and receive IV contrast, the procedure has less inherent risk than angiography and provides the surgeon with superior information (201). With CT, one can better define the regional extension of the mass through the renal capsule or into adjacent organs, such as the liver or

colon, and detect lymph node and distant visceral metastatic disease. Regarding venous involvement, Lang first reported the efficacy of CT scanning in evaluating extension into the renal vein and vena cava in comparison with angiography and sonography (131). CT has been criticized for its inability to identify the true cephalad extension of tumor thrombus, especially in the intrahepatic vena cava, but the advent of 3D reconstruction has added benefit in the detection of small accessory renal arteries and unusual venous branches (Fig. 16.4). Some suggest comparable vascular anatomic detail and even superior accuracy in relation to arteriography (40). Such data will only further reduce the indications for angiography in the evaluation of renal lesions.

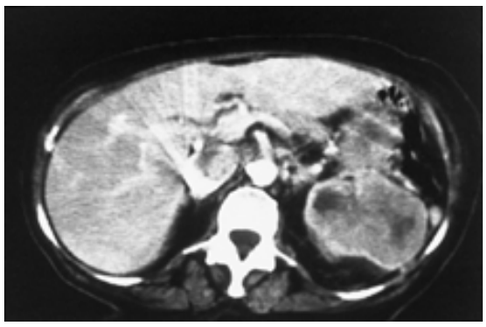

FIGURE 16.3. Axial view of computed tomography scan demonstrating large left renal mass. Also note contrast-filling defect in vena cava from associated tumor thrombus.

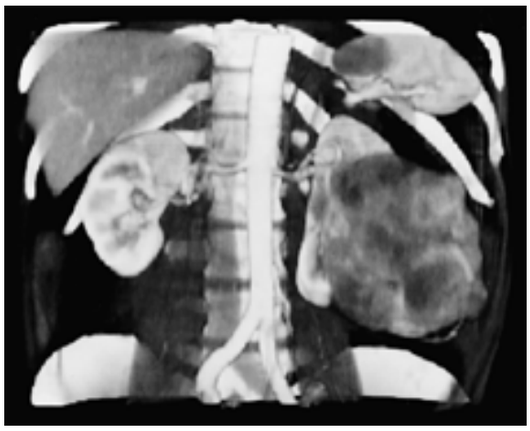

FIGURE 16.4. Three-dimensional computed tomography reconstruction view demonstrating excellent anatomic detail of left renal mass.

Magnetic Resonance Imaging

Currently, physicians use MRI in situations in which the patient has preexisting medical conditions such as renal insufficiency or a serious contrast allergy that preclude the administration of contrast material. MRI historically has held an advantage to CT in evaluating renal lesions because it depends less on technique and the first modality capable of multiplanar imagery. RCC appears heterogeneous on T_1-weighted images and then typically becomes hyperintense when compared with normal parenchyma on T_2-weighted images. Spin-echo sequences are used to assess venous involvement.

In particular, MRI has been extremely useful in assessing vascular invasion (Fig. 16.5) by RCC (80). Specifically, MRI is noted for its accuracy in assessing superior extent of tumor thrombus (240). It also delineates the tumor within the cava even when there is total caval occlusion. The modern addition of gradient-recalled echo (GRE) sequences enhances the detail, reducing flow and respiratory motion artifact, and facilitates precise localization and more confident detection of thrombus. In a 1992 study, caval thrombus was identified correctly in 13 of 13 (100%), renal vein thrombus in 23 of 26 (88%), and right atrial thrombus in 4 of 5 (80%) patients (200). In general, MRI remains the preferred study for caval assessment.

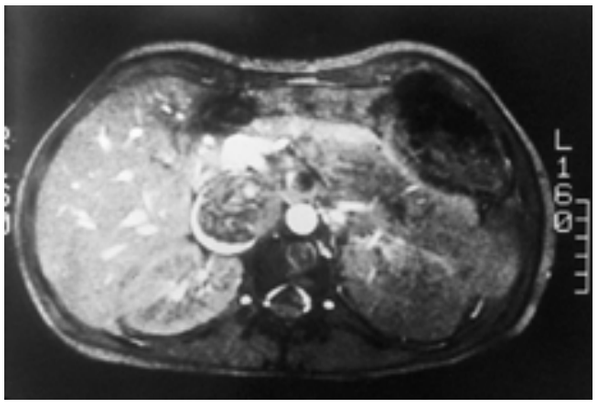

FIGURE 16.5. Axial magnetic resonance imaging view showing left renal mass with caval extension and surrounding contrast material.

Relatively long test time, high cost, obese body habitus that prohibits entry into the scanner, and ferro-magnetic prostheses or subcutaneous metallic foreign bodies are the current obstacles to MRI. Technology is advancing rapidly with open scanners and improving technical software. Much like CT angiography, researchers are using three-dimensional dual-phase MRI with gadolinium in the preoperative staging of renal carcinoma. Of the 18 patients enrolled in a prospective study, 30 of 31 (97%) surgically confirmed renal arteries were detected on preoperative scanning (35).

Positron Emission Tomography

Positron emission tomography (PET), like MRI, is another emerging noninvasive technology with potential applications to staging and detecting tumor recurrence. PET uses select endogenous substances with positron-emitting radioisotopes that accumulate in known sites of biologic activity. The most common radiotracer, 18-fluoro-2-deoxyglucose (FDG), resembles endogenous glucose and readily accumulates in the brain and myocardial tissue due to tissue demand. The renal tubules are unable to reabsorb FDG following filtration, and tracer detection consequently is prominent in the kidneys and bladder as well. In addition to these areas of resultant high uptake, malignant tumor foci generally possess a high rate of glycolysis and can be isolated on whole body imaging.

In one of the few studies that applied FDG PET scanning to RCC, Bachor and colleagues found that FDG PET detected 20 of 26 histologically confirmed renal tumors. Six cases failed to note the tumor focus, and three benign lesions were deemed falsely positive for malignancy (8). These data suggest some limitations with the modality. However, 10 of 10 patients with known progressive RCC in another study had their active metastasis identified with PET, whereas

conventional modalities noted only an increasing lesion in 7 of the 10 (102).

FDG allows for detection of small malignant nodes not meeting the pathologic size criteria of CT scanning. Moreover, PET also may prove superior to CT or MRI in situations where postsurgical anatomy or artifactual distortion due to surgical clips decrease the sensitivity and specificity of those examinations (264). Technical considerations such as bowel preparation, IV bolus hydration, bladder irrigation, furosemide washout, procedural length, and cost limit PET to select clinical and investigational situations.

Staging

Staging, like histologic classification, has undergone several modifications to better characterize renal tumors and to establish some prognostic information. In the 1960s, Robson (194) improved the earlier work of Flocks and Kadesky (66a), and his system formed the basis of staging in the following several decades (Fig. 16.6). However, this arrangement suffered prognostically by grouping tumors with renal vein involvement alone, with vena cava involvement, or with lymph node involvement all within the third stage. As a result, this classification basically has been replaced by the tumor, node, and metastasis (TNM) system proposed by the International Union Against Cancer in the 1990s (10).

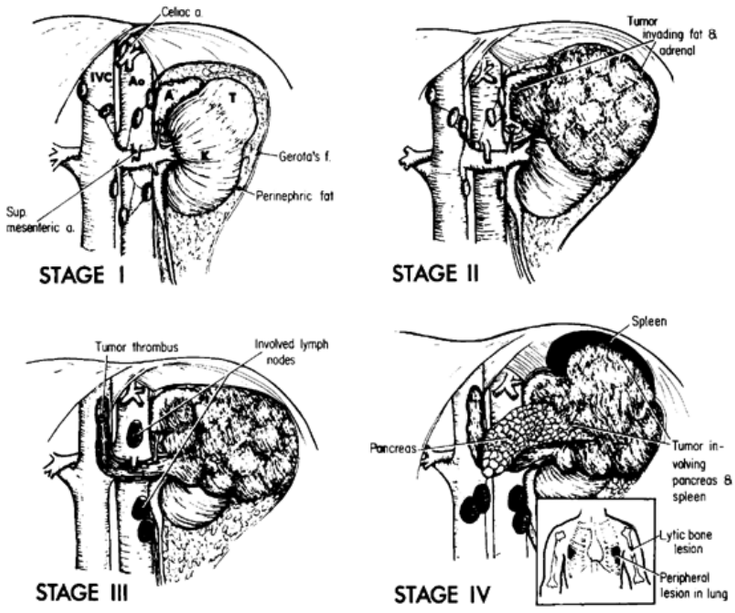

FIGURE 16.6. Robson staging classification of renal cell carcinoma.

In 1997, the TNM system was further revised, as listed in Table 16.5 (230). Analysis of the first classification of tumor stages revealed little difference in survival between T_1 and T_2 lesions when the distinction was tumor size reaching 2.5 cm (90,250). Therefore the discriminating size between T_1 and T_2 lesions was changed to 7.0 cm in the tumor's greatest dimension. Analysis of this change shows that the new system permits better stratification of cases according to survival, thereby increasing its clinical use (112,157).

T—Primary Tumor
- T_X Primary tumor cannot be assessed
- T_1 Tumor is ≤7.0 in greatest dimension and limited to kidney
- T_2 Tumor is >7.0 cm in greatest dimension and limited to kidney
- T_3 Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
  - T_{3a} Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
  - T_{3b} Tumor grossly extends into renal vein or vena cava below diaphragm
  - T_{3c} Tumor grossly extends into vena cava above diaphragm
- T_4 Tumor extends beyond Gerota's fascia

N—Regional Lymph Nodes
- N_X Regional lymph nodes cannot be assessed
- N_0 No regional lymph node metastasis
- N_1 Metastasis in a single regional lymph node
- N_2 Metastasis in more than one regional lymph node

M—Distant Metastasis
- M_X Distant metastasis cannot be assessed
- M_0 No distant metastasis
- M_1 Distant metastasis

From Sobin L, Wittekind C. *International Union Against Cancer (UICC): TNM classification of malignant tumors,* 5th ed. Philadelphia: Lippincott-Raven, 1997:180, with permission.

TABLE 16.5. TUMOR NODE METASTASIS CLASSIFICATION FOR RENAL CELL CARCINOMA (1997)

Therapy

The only consistently successful therapy for RCC to date has been surgical treatment for local, locally advanced, and minimally metastatic disease. Nonetheless, case reports of spontaneous tumor regression suggest that the malignancy may be susceptible to immune attack. This consideration, combined with new insights into molecular biology, has spawned significant research into potential immunotherapy for renal tumors. Unfortunately, although some regression has been seen in selected cases, complete response rates remain low. Likewise, both chemotherapy and radiotherapy demonstrate little success in treating this relatively resistant tumor. As the human genetic code is unraveled, clues into

the genetic abnormalities of patients with RCC will provide directions for new research that may yield new forms of treatment.

Radical Nephrectomy

The traditional gold standard therapy for patients with localized RCC and a normal contralateral kidney is the radical nephrectomy. This includes removal of the tumor-containing kidney and perirenal tissue within Gerota's fascia (Fig. 16.7). Theoretically, this encompasses the ipsilateral adrenal gland, although the issue of concomitant adrenalectomy often is debated. The question of whether to remove the lymph nodes draining the kidney at the time of nephrectomy is also controversial.

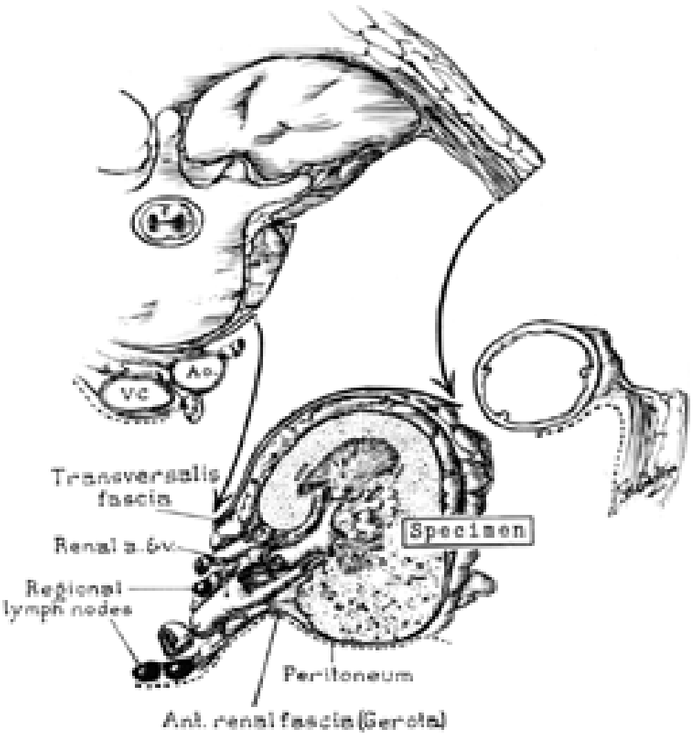

FIGURE 16.7. Radical nephrectomy specimen. Ao, aorta; VC, vena cava. (From Marshall FF. Radical nephrectomy: flank approaches. In: Marshall FF, ed. *Textbook of operative urology.* Philadelphia: WB Saunders, 1996:249, with permission.)

In 1869, the first elective nephrectomy was reportedly performed by Gustav Simon to treat a refractory ureterovaginal fistula (158). Removal of the tumorous kidney followed and the method was further developed in the twentieth century. Simple nephrectomy alone for cancer has fallen out of favor and currently is not recommended.

In 1963, Robson described a classic series in which he reported a 66% 10-year survival rate following radical nephrectomy for RCC (195). He attributed this excellent survival rate to early ligation of the renal pedicle and broader removal of the kidney with surrounding tissue, including perinephric fat and lymph nodes, from the crus of the diaphragm to the bifurcation of the aorta. Despite the small number of patients in this particular series, Robson continued to accrue patients for further reports (194) and can be credited with popularizing the concept of radical nephrectomy.

The kidney can be approached through several different incisions because of its location in the retroperitoneum. The urologic surgeon should be familiar with these different approaches and consequently tailor the operation to the individual patient while considering size of the tumor, location of the tumor within the kidney, and body habitus of the patient. Sometimes, the pleural and/or peritoneal cavities are entered as part of the nephrectomy procedure; often, neither of these spaces are violated. The choice of incision depends on the individual surgeon and hospital center, but currently, the most often used approach is the extraperitoneal flank incision. However, all approaches have two basic requirements: early ligation of the renal pedicle and adequate margins of tumor resection.

For the flank incision, the patient is placed in the lateral position with the operating table in the flexed position and the kidney rest elevated. The surgeon usually makes the incision over the eleventh or twelfth rib, and occasionally removes part of the rib to facilitate exposure. The goal is to stay in the extraperitoneal space and to avoid the potential complications of entering the peritoneum. Disadvantages include relatively more postoperative pain from incision of the flank muscles and the risk of pneumothorax from inadvertent entrance into the pleural cavity. Nonetheless, the flank approach provides excellent access to the renal fossa and is especially useful for small, localized tumors.

The transperitoneal approach has been used since the time of early nephrectomies. At that time, there were

significant complications of postoperative, often fatal, infections of the peritoneal space; however, these are rare with modern antibiotics. Today, the midline upper abdominal incision and the chevron incision are the most commonly used transperitoneal approaches. Advantages of these include easy identification of the renal pedicles and the ability to examine the abdominal organs. Moreover, the chevron incision permits much easier access to larger tumors. Disadvantages include poor exposure of the upper lateral quadrants with the midline incision and potential for ileus and intestinal adhesions.

The thoracoabdominal incision (Fig. 16.8), popularized by Chute, provides excellent exposure of upper pole tumors but involves entering the pleural space and, usually, the peritoneal cavity (37). With this approach, there is excellent exposure of the vena cava, so many surgeons prefer it for accessing tumors with caval thrombus. Entry into the chest cavity also allows for removal of any concomitant metastatic lung lesions, if necessary. A chest tube is required postoperatively.

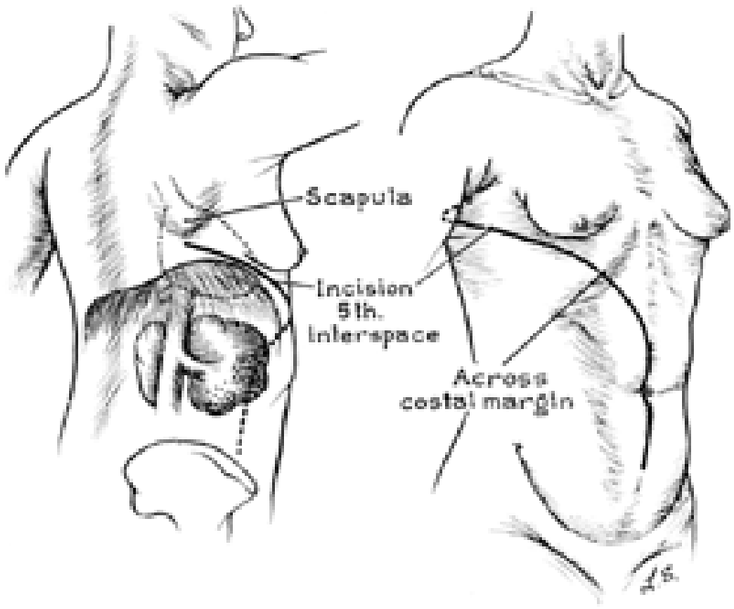

FIGURE 16.8. Thoracoabdominal incision. (From Marshall FF, Reitz BA. Radical nephrectomy with excision of vena caval tumor thrombus. In: Marshall FF, ed. *Textbook of operative urology.* Philadelphia: WB Saunders, 1996:265, with permission.)

Few surgeons use the subcostal incision for radical nephrectomy. Although this incision avoids the risk of unintentional entry into the pleural space, it generally provides relatively poor exposure of the kidney if the approach is kept extraperitoneal. Nonetheless, the benefit of examination of abdominal organs is possible if the incision is carried transperitoneally.

Lymphadenectomy

It has been established that RCC spreads through lymphatic routes. Studies have reported an approximate 20% to 25% average incidence of positive retroperitoneal lymph nodes when the nodes are sampled at the time of surgery (234). In 1935, Parker reported on the lymphatic drainage of the kidney. Based on his work, there are noted differences between lymphatics of the left and right kidneys (177). The left kidney most often drains to paraaortic nodes in the lumbar region, whereas the right kidney drains primarily to the interaortocaval and paracaval nodes (Fig. 16.9). These patterns have important implications when performing lymphadenectomy of nodes draining the kidney (147). One must also consider that anomalous vasculature and retroperitoneal processes, such as large tumors, ureteral obstruction, and caval extension, can alter these diagrammed routes.

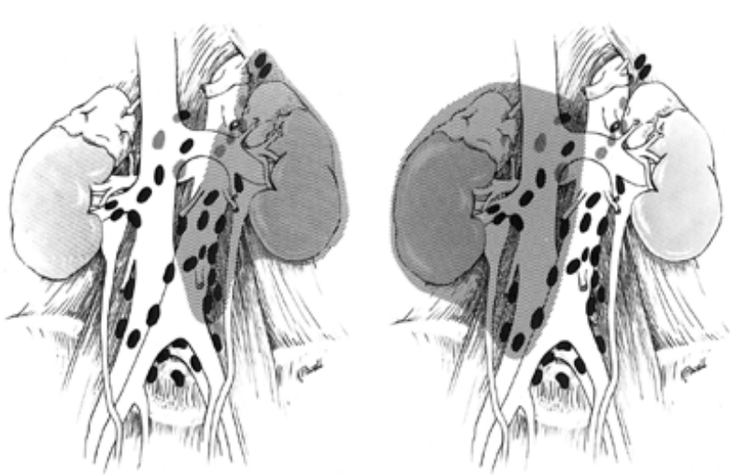

FIGURE 16.9. Lymphatic drainage patterns of the kidneys. (From Marshall FF, Powell K. Lymphadenectomy for renal cell carcinoma: anatomical and therapeutic considerations. *J Urol* 1982;128:677, with permission.)

In 1963, Robson suggested that extended lymphadenectomy at the time of surgery would be beneficial in terms of survival (195). Since that time, several others have advocated the removal of nodes found in the drainage pattern of the kidney as a means of preventing tumor spread. However,

the question of whether to remove nodes at the time of nephrectomy remains a controversial issue (181). In essence, all debate focuses on whether the benefits of the added procedure outweigh its risks. Currently, little data exist on patients prospectively randomized to receive nephrectomy with lymphadenectomy versus nephrectomy alone. Preliminary data from a randomized trial sponsored by the European Organization for Research on Treatment of Cancer (EORTC) showed little difference in disease progression between the aforementioned two groups (16,17).

Both proponents and opponents of lymphadenectomy make significant points. Those favoring lymphadenectomy in combination with nephrectomy argue that removal of nodes for pathologic examination will assist with true staging of the tumor and therefore may have prognostic implications. In addition, removing nodes may prove curative by excising metastatic spread along with the primary tumor and consequently improving survival rates. Those against lymphadenectomy argue that distant, often blood-borne metastases, for which lymph node excision provides no therapeutic benefit, occur commonly in advanced RCC (114). Moreover, considering the frequently aberrant distribution of lymph nodes draining the kidney, the removal of retroperitoneal nodes does not guarantee complete removal of lymphatic metastases. Studies that report increased survival with lymphadenectomy are limited by cohort size, lack of standardization, and retrospective analysis (234).

The extent of dissection when performing lymphadenectomy varies between individual surgeons. Limited regional dissection of the hilar nodes will have a much higher false-negative rate than will an extended retroperitoneal dissection. Until a prospective, randomized study with strict protocol regarding extent of node dissection is completed, the role of lymphadenectomy in RCC will be questioned.

Adrenalectomy

Available series report that the incidence of ipsilateral adrenal gland involvement in RCC ranges from 3.2% to 5.7% (202,206,212,257,266). Acknowledging this potential for adrenal involvement, Robson initially described ipsilateral adrenalectomy as part of the radical nephrectomy procedure (195). Recently, however, there has been considerable debate over the necessity of removing the adrenal gland at the time of nephrectomy (212,257,266). Reported benefits of avoiding adrenalectomy include lowered risk for adrenal insufficiency, preservation of adrenal tissue should the contralateral adrenal gland develop metastasis, decreased operative time, and decreased morbidity. Others point to studies showing that patients with adrenal involvement have a higher likelihood of positive lymph nodes or distant metastasis and therefore question the utility of excising the adrenal gland (202,212).

Research shows upper pole tumor location, left-sided tumors, and large tumors as risk factors for adrenal involvement in cases of RCC (202). Renal vein thrombosis also has been described as a risk factor (258). Most surgeons believe that extensive upper pole tumors, which have the propensity to spread to the ipsilateral adrenal gland by local extension, require adrenalectomy as part of the surgical procedure. However, tumors in the midpole and lower pole of the kidney also have shown adrenal gland metastasis, albeit in a much lower percentage; these tumors are thought to spread by hematogenous routes. Adrenalectomy also has been recommended when the adrenal gland contains a single metastatic lesion (212).

CT shows excellent sensitivity for adrenal lesions, and several investigators advocate its use to determine the need for adrenalectomy (75,193,206). Series report the negative predictive value of CT scans to be as high as 100% for adrenal abnormalities (257). Therefore a normal adrenal gland by CT scan makes the possibility of adrenal metastasis quite low. When abnormalities are detected, not all prove to be metastatic lesions because large tumors can cause displacement or poor visualization of the adrenal gland.

Overall, most studies report the yield of routine ipsilateral adrenalectomy at the time of nephrectomy to be quite low. As a result, many surgeons will avoid the adrenal gland in cases of small renal tumors not involving the upper pole. Certainly, those patients with risk factors for adrenal involvement can be identified preoperatively with radiographic studies, acknowledging that some with microscopic disease may be missed by this method. However, careful follow-up on these patients should identify the development of any other new lesions.

Nephron-sparing Surgery

In 1950, Vermooten was one of the first to suggest the idea of removing only part of a kidney affected by tumor (263). Nonetheless, the standard therapy for renal tumors soon thereafter became radical nephrectomy (145). Nephron-sparing surgery was later revisited, primarily for patients with marginal renal function, bilateral tumors, or a solitary kidney. Long-term studies of nephron-sparing surgery and outcomes now exhibit results comparable with radical nephrectomy in terms of tumor recurrence and survival. As a result, many urologists now advocate the use of partial nephrectomy for patients with a normal contralateral kidney. Overall, nephron-sparing renal surgery now has an increasingly expanded role in the management of even the most difficult localized renal tumors.

Enucleation.

Simple enucleation involves separating the pseudocapsule of a tumor from surrounding normal renal parenchyma and coring out the neoplastic tissue from the remainder of the kidney. The advantages of enucleation are its simplicity and minimal disturbance of the kidney, whereas its main disadvantage is the risk of leaving behind residual tumor. Approximately 20 years ago, two small series reported the success of enucleation with regards to renal tumors (30,85). Later investigation also showed enucleation

feasible and successful in certain cases of well-circumscribed tumors (149,169). However, CT scans cannot always predict which tumors would be good candidates for enucleation. At this time, most surgeons do not recommend enucleation as a primary treatment for the majority of tumors but rather suggest partial nephrectomy. Nonetheless, in cases of VHL syndrome, where salvage of as much functional parenchyma as possible is preferable, enucleation remains an acceptable procedure.

Partial Nephrectomy.

Standard partial nephrectomy differs from enucleation in that a normal rim of renal parenchyma is excised around the tumor specimen. While preserving renal tissue, partial nephrectomy also risks leaving tumor behind and therefore has risk of local recurrence. Studies report such recurrence to occur in approximately 4% to 8% of cases and attribute most instances to undetected multifocal tumors. Nonetheless, partial nephrectomy has proven to have disease-specific and overall survival rates comparable with radical nephrectomy.

The indications for partial nephrectomy have broadened over the years. Previous contraindications such as centrally located tumors (31) and tumors associated with normal contralateral kidneys (100) no longer prohibit consideration of nephron-sparing surgery. However, concerns regarding increased numbers of local recurrences with larger-sized tumors have led several investigators to suggest specific size limitations for the procedure. No consensus exists, but recent recommendations suggest elective partial nephrectomy only for tumors smaller than 2.5 cm (156) or tumors 4.0 cm or smaller (92).

The technique of partial nephrectomy (Fig. 16.10) most often involves the flank approach. Gerota's fascia and the overlying perinephric tissue are resected along with the tumor (186). In most instances, the renal vasculature is temporarily clamped to prevent significant bleeding during removal of the tumor. This requires cooling the kidney with ice slush to lessen chances of ischemic damage. Preoperative knowledge of the renal vasculature supplying the tumor allows for better surgical planning. Although this previously has been accomplished with angiography, newer, less invasive methods, such as 3D helical CT angiography, also are effective (228).

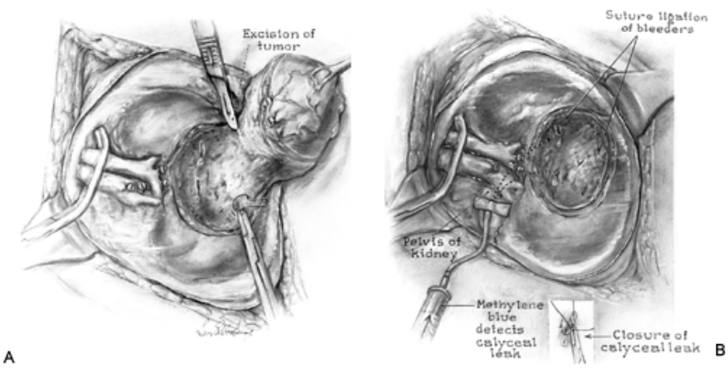

FIGURE 16.10. Technique of partial nephrectomy. **A:** Excision of the renal tumor after occlusion of the main renal vasculature. Vessels are ligated as encountered at the tumor base. **B:** Dye is injected into the collecting system to check for urinary leaks, which are then repaired. (From Marshall FF. Partial nephrectomy. In: Marshall FF, ed. *Textbook of operative urology.* Philadelphia: WB Saunders, 1996:274, with permission.)

Long-term follow-up of partial nephrectomy patients yields excellent survival rates. In a recent review of 485 patients at the Cleveland Clinic, overall and cancer-specific 5-year survival rates were 81% and 92%, respectively (92). Others also have shown excellent long-term tumor control with partial nephrectomy (261), and higher disease-free rates have been reported in patients with a normal contralateral kidney (100). Adequate selection of both individual patients and tumors appears to be the key to successful outcomes.

Cryotherapy.

Cryosurgical ablation of renal tumors has received attention over the past few years as an *in situ* form

of nephron-sparing surgery. The benefits of freezing tumors in other organs including liver, prostate, cervix, and skin have been described. Several small series have reported minimal complications with excellent local tumor control (14,197). Currently, no sufficient long-term data are available to compare cryosurgery with other modalities.

Cryotherapy may be performed through an open incision or laparoscopically. Typically, there are two phases, freezing and thawing, that cause cellular disruption and tissue ablation (197). In an examination of acute histologic changes of renal tissue after cryoablation, investigators reported extensive coagulative necrosis and hemorrhage beyond the boundaries of the tumor (56). Negative tumor margins apparently are obtained, but long-term pathologic changes are unknown.

High-intensity Focused Ultrasound.

Another attempt at nephron-sparing therapy for RCC includes high-intensity focused ultrasound (HIFU). HIFU involves ultrasound waves generated extracorporeally and then focused to a point inside the body, where they induce thermonecrosis of the tissue. Initial studies report HIFU therapy to be safe and efficacious (1,120), yet further investigation regarding long-term results of this new modality is needed for the future.

Laparoscopic Surgery

With the rapid development of minimally invasive surgery, urologists increasingly are using laparoscopy for the treatment of malignant renal tumors. The utility of the laparoscopic approach has been well documented (27,118,153,191), and the addition of hand-assisted techniques also further broadens its appeal, adding dexterity and tactile sensation (278). Retroperitoneoscopy, without violation of the peritoneal cavity, also has been described (76). Initial concerns about tumor implantation at trochar sites and recurrence in the renal fossa have not proven to be significant complications. In a multicenter review of 157 patients with a mean follow-up period of 19.3 months, no patient developed tumor implantation or recurrence in the fossa (27).

Inferior Vena Cava Extension

Studies of RCC show that vena caval extension occurs in approximately 4% to 10% of cases, with a strong male predominance (38,80,135,148,152). All levels of caval tumor thrombus, from the renal vein ostia to the right atrium of the heart, occur. Because there is no adequate medical regimen, surgery offers the only cure for caval extension of tumor. The difficulty of the surgical approach is related to the degree of cephalad extension by the tumor thrombus, and intracaval neoplastic extension may even necessitate cardiopulmonary bypass for a safe and complete excision.

A thorough preoperative history to evaluate intercurrent health problems is mandatory for all surgical candidates. Anesthesia, and sometimes medical, consultations are needed to optimize conditions and prepare patients for often long procedures with intense hemodynamic shifts. Particular attention should be applied to cardiovascular status, especially when cardiopulmonary bypass is considered. Patients with IVC invasion may also have unique presentations. Although rare, symptoms can include massive lower extremity edema from IVC occlusion, ascites from Budd-Chiari syndrome, severe congestive heart failure, intestinal malabsorption, varicocele, or engorgement of the abdominal wall veins. Embolization of a portion of the tumor thrombus also may produce signs consistent with pulmonary embolus.

A full radiographic evaluation of patients with RCC and vascular extension is required before any operative intervention. The purpose of this is twofold: to discover any metastatic disease and to establish the true cephalad extension of the intracaval tumor. This evaluation can be accomplished by a variety of studies including venacavography, ultrasound, CT, and MRI. Venacavography involves the direct injection of contrast dye into the vena cava. Intravascular tumor can be visualized as filling defects in the contrast-filled cava (Fig. 16.11). However, cavography sometimes requires both antegrade (femoral) and retrograde (basilic) injections to fully delineate tumor extent (Fig. 16.12) (80). Cavography has the obvious disadvantage of exposing remaining normal renal parenchyma to a potentially nephrotoxic contrast load. Because of its invasive nature, there is also a risk of dislodging intravascular tumor.

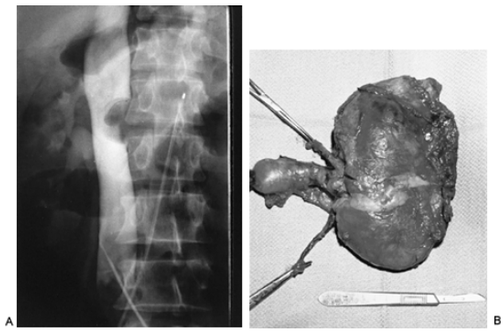

FIGURE 16.11. A: Venacavography demonstrates filling defect, suggesting extension of known left renal mass. **B:** Gross nephrectomy specimen in the same patient demonstrating distended renal vein from tumor thrombus.

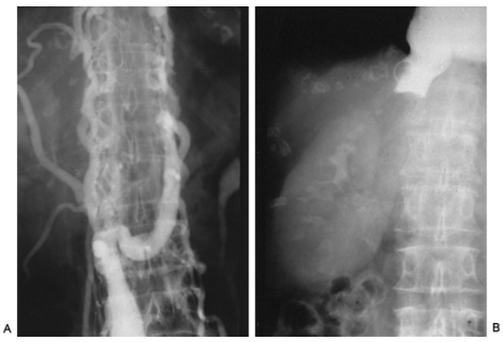

FIGURE 16.12. A: Antegrade venacavography with cutoff of contrast flow in the middle interior vena cava. **B:** Retrograde venacavography in the same patient demonstrating superior extent of tumor thrombus.

Approximately one-third of patients with IVC extension have at least one metastatic lesion (227). Multiple studies have shown that survival rates are poor with radical surgery in the setting of vascular extension and metastatic disease (243,244). Therefore a complete workup for metastatic disease is important before surgical intervention. Radiologic tests, including bone scans, play a valuable role in this setting. Routine serum chemistries and liver function tests also may provide clues to possible disease outside the kidney. Thorough knowledge of preoperative lesions will allow much better follow-up in the postoperative course.

Surgical approach in cases of renal neoplasms extending into the vena cava is dictated by the superior extent of the intracaval or intracardiac tumor. Involvement of intrahepatic and suprahepatic caval levels can create numerous potential technical problems, thereby lengthening operative time. When sections of vena cava must be resected, reconstruction to allow for adequate venous drainage poses new challenges. Furthermore, extension into the right atrium exposes one to the additional potential complications of cardiac surgery and cardiopulmonary bypass.

Exposure of the neoplastic kidney and associated tumor thrombus can be achieved through several operative approaches. Most cases of RCC with IVC involvement occur on the right side, but tumors in the left kidney require bilateral dissection. Regardless of laterality, full exposure is necessary to ensure complete resection of both tumor and

thrombus. The thoracoabdominal incision provides excellent exposure for renal tumors but more limited access to the aortic arch for cardiopulmonary bypass. The midline abdominal incision with extended sternotomy also allows for excellent visualization and has the added benefit of more direct access to the heart for cardiopulmonary bypass and hypothermia. However, this approach requires entry into the peritoneal cavity and therefore displacement of the bowel. The chevron incision with extended sternotomy may prove superior for exposure of large tumors in large patients. The most important goal of surgery for renal cell tumors with IVC extension is complete resection, including full removal of caval tumor and resection of any involved caval wall, if possible, because this has tremendous prognostic implications.

Following tumor excision, the vena cava can be reconstructed to allow for venous return from other structures including the contralateral kidney. Reconstitution of venous drainage after tumor removal depends on the extent of the cavotomy incision. Several studies report that at least 50% of the original IVC lumen diameter must be maintained with caval reconstruction to prevent blood thrombus formation and caval occlusion (151). Occasionally, synthetic graft material is used to construct new portions of the IVC (173,174), but harvested native pericardium for this purpose also has been described (151). In some situations, segmental cavectomy with ligation of proximal and distal ends has been used with satisfactory results (265).

Reconstruction of drainage for the contralateral kidney depends on the side of the lesion. For right-sided tumors, the left renal vein can be ligated, if necessary, because there is good collateral blood flow for venous drainage of the left kidney. Anatomic studies have shown this collateral flow to mainly depend on the left ascending lumbar vein, which receives a branch from the left renal vein and then joins the hemiazygous venous system to drain into the superior vena cava (38). The right ascending lumbar vein bypasses the right renal vein and therefore no collateral drainage for the right kidney exists. Because of this finding, the IVC must be reconstructed for left-sided tumors to allow venous return from the right renal unit.

Caval tumor extending into the retrohepatic and suprahepatic IVC requires extensive dissection (148). Significant bleeding can be encountered in posterior mobilization of the liver, particularly the caudate lobe. Some surgeons use division of the caudate lobe veins to allow for improved exposure of the vena cava and associated thrombus (Fig. 16.13). Even resection of the caudate lobe has been described (172).

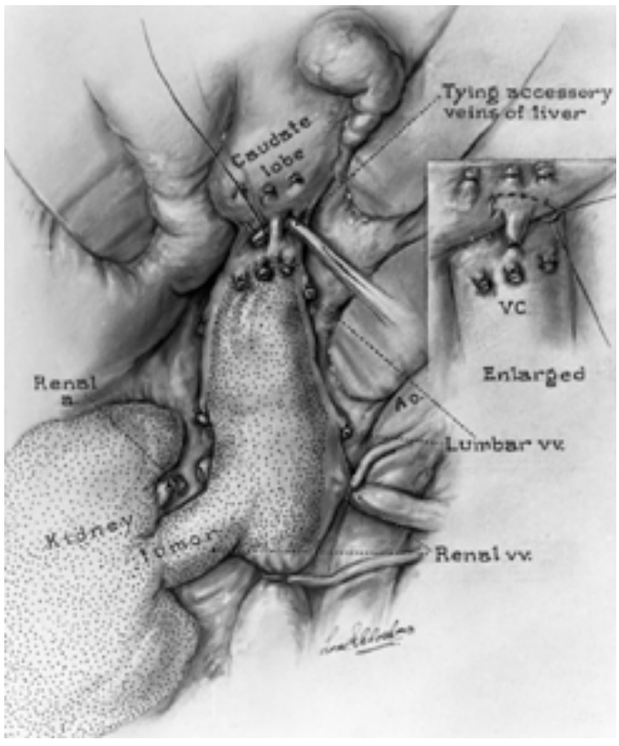

FIGURE 16.13. Removal of vena cava tumor thrombus often requires division of the veins from the caudate lobe of the liver. Ao, aorta VC, vena cava.

Perioperative morbidity and mortality have been well described with surgery involving tumor in the inferior vena cava. Pulmonary embolization of tumor thrombus is a well-recognized complication that sometimes can be avoided by preoperative or intraoperative placement of a vena caval (e.g., Greenfield) filter (20,68). However, a filter can complicate surgery and pose additional risks such as IVC occlusion or renal vein compromise (20). Operative blood loss can be massive, and significant hemorrhage can produce hemodynamic and cardiac effects. Coagulopathy can sometimes occur with prolonged cardiopulmonary bypass. If adequate venous drainage is not ensured for the contralateral kidney, renal failure can ensue.

A variety of studies have examined characteristics of RCCs with tumor thrombi to assess prognostic factors both preoperatively and postoperatively from pathologic diagnosis. However, many of these studies contradict others examining the same factors. Therefore several questions have not been completely answered, and confusion still exists. There is almost complete agreement that incomplete resection of tumor thrombus portends a much worse prognosis than total removal.

Whether tumor extension into the vena cava alone affects prognosis has been examined in several studies. In a retrospective analysis of 71 cases (median survival, 81 months), isolated caval extension offered little prognostic impact (32). However, a later European study reported a significant survival advantage for patients with tumors confined to the kidney versus those with venous extension (137). Most would agree that survival is affected more by associated tumor factors than venous extension alone. Microscopic invasion of the vein wall by tumor cells has been reported as the single most relevant prognostic factor in one study,

which showed a 45% chance of disease progression within 1 year of nephrectomy in this group of patients (262). A significant improvement in survival also was noted for patients with freely mobile tumor as compared with invading tumor (69% versus 26% 5-year survival, respectively). Of particular note, resection of the involved caval wall was associated with improved survival (97). Nonetheless, in one series of 26 patients, there was no survival difference between those patients with venous wall involvement and those without (137). Most studies have shown that the cranial extent of tumor thrombus alone has no bearing on prognosis in terms of survival (77,97,127,137). However, several studies report that higher-extending thrombi are associated with significantly decreased survival rates (159,232).

Spread to regional lymph nodes has repeatedly been shown to be a poor prognostic indicator for RCC (12,127). A significant decrease in life expectancy was found in this subgroup when compared with a full cohort of patients with tumors invading the vena cava (13 versus 32 months median survival; p <.001) (127). Investigators showed that 5-year survival in a group of 37 patients with IVC tumor extension was 0% for the subset with lymph node metastases (versus 33.6% overall). Multiple studies have also confirmed that the preoperative or intraoperative demonstration of distant metastatic disease combined with caval extension leads to a poor prognosis, even with radical nephrectomy (32,127,244). Such patients have much lower long-term survival rates, usually less than 15%, when compared with those without metastases (135,159,226,244).

For patients with caval thrombi from RCC, 5-year survival rates have ranged from approximately 30% to 60% following surgery, as in Table 16.6 (166). Again, these rates depend on the aforementioned factors. The presence of lymph node or distant metastases is associated with much shorter long-term survival, whereas the superior anatomic extent of the thrombus often does not appear to be as important. Excellent long-term survival has been achieved with complete surgical removal, so the preoperative evaluation to select suitable surgical candidates will have the greatest impact on survival rates.

Investigator (Year)	No. of Patients	Percentage of Patients Alive at 5 Years
Pritchett, et al. (1986)	25	28
Libertino, et al. (1987)	44	44
Hatcher, et al. (1991)	44	42
Swierzewski, et al. (1994)	100	54
Glazer and Novick (1996)	18	57
Nesbitt, et al. (1997)	37	34
Babu, et al. (1998)	15	55

TABLE 16.6. FIVE-YEAR SURVIVAL RATES IN STUDIES OF RENAL CELL CARCINOMA WITH CAVAL EXTENSION

Cardiopulmonary Bypass and Hypothermia.

The use of cardiopulmonary bypass and hypothermia has revolutionized surgery for IVC tumor thrombus extending into the right atrium. Bypass allows for an essentially bloodless field, which greatly assists in accessing and viewing pieces of caval and atrial tumor (Fig. 16.14). Moreover, this helps decrease the risk of tumor embolization during surgical manipulation (275). To date, use of cardiopulmonary bypass has not been shown to decrease survival in cases of renal tumors, but it does allow for full resection of the tumor. Perioperative mortality appears to be related to myocardial dysfunction, whereas short-term survival depends on lymph node and distant metastases (53). Length of bypass and arrest time also impacts survival. The surgeon places cannulas in the aorta and right atrium to allow for shunting of blood through the bypass machine. Systemic heparinization is used to prevent thrombosis. Once bypass has started, a cardioplegic solution is applied to the heart. To avoid subsequent permanent effects, optimal time for bypass is less than 45 minutes (148). Recently, a technique of minimally invasive (small incision) bypass has been described (64).

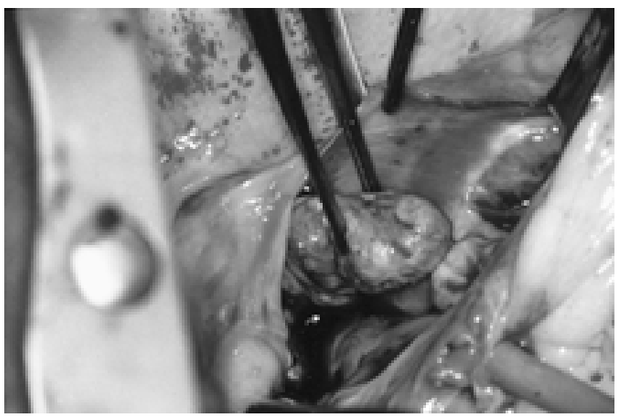

FIGURE 16.14. Removal of atrial tumor thrombus in the bloodless field allowed by cardiopulmonary bypass. Note the close vicinity of the tricuspid valve.

Metastatic Renal Cell Carcinoma

Years of intervention have done little to improve survival in patients with metastatic RCC. Regardless of the therapy used, results have been disappointing, and the search for effective treatment regimens remains a challenge for urologists and oncologists alike. Nonetheless, failure has fortunately bred an ever-expanding list of potential therapies, including chemotherapy and a multitude of immunomodulating options. Few sites in the body are safe from potential metastatic deposits with RCC; however, the most common

sites are the lungs, bones, lymph nodes, adrenal glands, and brain (203). At autopsy of patients with RCC, no significant difference in metastatic locations was seen in patients who had undergone previous nephrectomy versus those who had not had surgery (204).

Radiotherapy

RCC has been characteristically regarded as a radioresistant tumor. In the past, several studies have addressed the issue of adjunctive radiotherapy in the treatment of metastatic disease, but none have documented significantly increased survival in that group of patients. Today, radiotherapy most often is used for palliative treatment of symptomatic tumors or metastatic lesions (51,123). Several investigators have used brachytherapy for this purpose (129).

Specifically, radiation has proven effective under circumstances of osseous or brain metastasis by rendering palliation, possibly preventing progression, and improving quality of life. Stereotactically guided high-precision irradiation selectively destroys small intracranial lesions and preserves surrounding brain tissue (11,160). Externally applied radiation alleviates bone pain in up to 77% of treated sites (94). Future applications linking radiation and immunotherapy are under investigation. In an effort to improve tumor targeting, novel phase I trials are investigating both the accumulation and the therapeutic potential of radiolabeled (I-131) monoclonal antibodies (G250) in metastatic RCC (52,237). Early results are encouraging, but much research still is needed to prove efficacy.

Chemotherapy

Standard historic chemotherapeutic regimens have failed to impact disease progression, and ultimately survival, in the majority of patients. An extensive review of more than 83 published trials from 1983 to 1993 showed a 6% response rate in 4,093 adequately treated patients with advanced RCC. The most efficacious agents were continuously infused 5-fluorouracil and floxuridine, with remissions in 10% and 12%, respectively. Circadian infusion, meant to optimize drug metabolism, modestly improved the remission rate to 15% of the patients treated with floxuridine (280). A recent review confirms that chemotherapy options for treatment are limited and suggests use in advanced cases only (3).

Scientists attribute, in part, the unyielding multidrug resistance of RCC to a plasma membrane glycoprotein (P-glycoprotein) that promotes the efflux of therapeutic agent away from the targeted cell. Overexpression of P-glycoprotein has been shown in 80% of tumors, which is much higher than in normal proximal tubular cells (81). Several medications, including cyclosporine (196), tamoxifen (205), and calcium channel blockers (176), have been used in attempts to block the multidrug resistant activity and to enhance the effect of chemotherapeutic agents, but no additive responses beyond that of chemotherapy alone are documented.

Immunotherapy

Because of RCC's resistance to chemotherapy and radiotherapy, alternative approaches have been sought. Physicians long ago suspected an integral role for the immune system in cases of spontaneous regression, and immunotherapy has gathered increased consideration for systemic treatment of metastatic tumors. The first recorded case of spontaneous regression (from the Mayo Clinic in 1928) postulated that antibodies produced by the body were responsible for either rendering the tumor cells inert or destroying them (26). Admittedly rare, almost 100 cases of spontaneous regression exist in the literature (58), and 2 recent reports document partial, transient regression in 5% to 7% of patients with pulmonary nodules without the impact of therapy (144,175). Additional supportive data include modern immunohistochemical analysis demonstrating infiltration of T lymphocytes and macrophages (63) as well as observed clinical responses to infused cytokines, interferons, and interleukins. Approaches applying biologic response modifiers (cytokines), vaccination, and gene therapy are under current study.

Interferons.

Since its initial discovery in the 1950s, the family of homologous proteins known as *interferons* has expanded in both number and function. Interferons act on the cellular level, binding to a surface receptor and transducing important regulatory signals. The exact mechanism of antitumor activity is unknown, but research has shown interferons to impart, via signal transduction, potent antiviral, antiproliferative, and immunomodulatory function *in vivo* (106). Specifically, leukocytes produce interferon-α(IFN-α), which subsequently enhances natural killer cell function and induces major histocompatibility complex antigen expression.

Within the family of interferons, many individual proteins have been studied (126). Results from a well-constructed, randomized trial proved no difference, relative to placebo, in outcome of patients treated with interferon-γ (IFN-γ)-1b for metastatic RCC (78). IFN-α also has been thoroughly tested as a single agent, and promising initial data with this agent prompt further consideration of IFN-α as a therapeutic approach in patients with metastatic disease. An average of 3 to 4 months may transpire before the occurrence of an objective response from the initiation of therapy, but multiple studies show a reproducible response rate of 10% to 20% (24,61,163,260) and a complete response rate ranging as high as 5% (24). The patients most likely to respond are those who have undergone prior nephrectomy with good performance status, have a long disease-free interval, and have lung-predominant metastatic disease (143,208). Nonetheless, the duration of response rarely exceeds 2 years, with a mean time ranging from 5 to

15 months (276), and randomized trials have shown only a modest increase, 2 to 7 months, in survival time (231). In attempts to apply reports of *in vitro* synergy, randomized trials combining IFN-α with vinblastine failed to show improved survival over using interferon as the sole therapy and showed exacerbation of the subsequent interferon side effects, including leukopenia, nausea, vomiting, and neurotoxicity (165).

Interleukins.

Another of the biologic response modifiers, interleukin-2 (IL-2), was approved on the basis of safety and efficacy for the treatment of RCC by the U.S. Food and Drug Administration in 1992. Interleukins indirectly affect tumorigenesis by enhancing the proliferation and function of T lymphocytes, and clinical studies for renal tumors suggest an approximate 15% to 19% objective response rate with IV bolus administration (25,74,199). Moreover, the complete response rate registers as high as 9.3% and is durable. More than 75% of the complete responders remain disease free for 3 years, and some in excess of 10 years without evidence of recurrent RCC. Treatment favors those with good performance status, absence of prior immunotherapy, total dose administered, and maximal rebound lymphocytosis after cessation of IL-2 (199).

Toxicity of interleukins can be severe. Many patients suffer with relatively minor symptoms of fever, chills, nausea, vomiting, diarrhea, and general malaise, but high-dose IL-2 treatment also can spur significant hypotension, fluid retention, acute respiratory distress, confusion, and renal failure as a physiologic consequence of the resultant cytokine cascade (178). Intensive monitoring and, frequently, aggressive support that includes maintenance of blood pressure with volume and pharmacologic vasopressors is required with bolus infusion. Even though side effects generally subside with discontinuation of therapy, treatment-related mortality ranges as high as 4% yearly with early experience (74). More recent analysis from the National Cancer Institute accounting for all 1,241 individuals treated with high-dose bolus IL-2 reveals an overall mortality rate of 0.7% with no treatment-related deaths in the last consecutive 680 patients (199).

Attempts have been made to optimize results and diminish the significant and sometimes life-threatening side effects of IL-2. Modifying dosage may diminish the toxicity without changing efficacy in regards to partial or complete tumor regression (22,235). However, the data currently are inconclusive. An ongoing randomized trial specifically addressing the issue reports preliminary results showing the high-dose IV bolus regimen to be the most effective (162). Adding complementary products such as lymphokine-activated killer cells (132,198), tumor-infiltrating lymphocytes (23,62), or IFN-α (164) currently does not produce statistically significant improvement in regards to overall survival over IL-2 alone.

Gene Therapy

Another novel approach, gene therapy, has garnered much attention, and clinical trials of therapeutic gene transfer in the treatment of urologic cancer are underway. Fundamentally, all gene therapy is a procedure of molecular surgery, because physicians sterilely introduce therapeutic DNA into diseased cells by way of a vector. Successful chromosomal integration allows for replication with the remainder of the treated cell's genes. Through the introduction of normal or modified genetic code, the process of carcinogenesis may be reversed or prevented.

Two entirely different gene therapy strategies can be defined. The first is corrective gene therapy, which involves the replacement or inactivation of defective genetic material with genes that prevent, slow, or reverse the events that encompass tumorigenesis. Significant insight into the molecular mechanisms of carcinogenesis is emerging, and potential mutational targets such as the VHL gene are being identified. In fact, introduction of a normal chromosome 3p has been shown to modulate tumor growth rate in an RCC cell line *in vitro* as long as 10 years ago (218). Nonetheless, several impressive limitations, including targeting, efficacy, and efficiency of vector transfer, exist currently with respect to corrective therapy. The second strategy includes treatment with recombinant DNA that selectively enhances killing of malignant cells, directly or indirectly. This cytoreductive gene therapy is further along than corrective gene therapy in terms of clinical application. More than 80 clinical protocols have been approved worldwide (223).

Previous research involving multiple cytokine genes shows that granulocyte-macrophage colony-stimulating factor (GM-CSF) gene-transduced vaccines incite the most vigorous, durable, and specific tumor immunity (5,54). Additional study has found preliminary evidence that GM-CSF genetically transduced, irradiated tumor vaccines induce potent T-cell–mediated antitumor activity without toxicity (222). The action of GM-CSF after gene transfer involves local spread of the cytokine at high concentrations, triggering antigen-presenting cell ingress and activation. This paracrine physiology more closely mimics the natural biology of cytokine action compared with the systemic IV administration of recombinant cytokines. Similar to other immunotherapies, treatment parameters such as mode of delivery, the ideal concentration of stimulatory cytokine, and minimum number of tumor cells for antigen presentation have yet to be determined. The nascent frontier of gene therapy will continue to grow, along with the other novel immunologic approaches under study such as tumor-specific vaccination (105) and monoclonal antibody treatments (52).

Surgical Resection

The role of surgical resection in the setting of metastatic disease has been questioned (209). Specifically, with the

development of improved immunotherapy regimens, the benefits of adjuvant nephrectomy and/or resection of metastatic lesions have been addressed (248,267,277). Nephrectomy also has been performed for the palliation of severe symptoms, such as pain or hematuria. In addition, reasonable 5-year survival rates have been seen in cases of solitary metastatic lesions that have undergone metastasectomy. In all cases, the risks of surgical therapy must be weighed against the potential benefits of removing the malignant lesion. The lack of randomized studies in this area makes this a difficult comparison.

Controversy exists regarding whether to perform adjuvant cytoreductive surgery with immunotherapy and also regarding appropriate timing for the operation. Critics of surgery point to a meager rate of spontaneous regression (1% to 4.4%) with frequent recurrence (144), increased morbidity and operative mortality (13), and deferred subsequent cytokine therapy in some cases (190). On the other hand, proponents believe that excision of the primary tumor serves as an adjunct to systemic immunotherapy for purposes of tissue procurement and elimination of a suspected immunomodulator. Recently, adjuvant surgery for immunotherapy in metastatic RCC has been reported to have beneficial results in terms of survival, although studies are not conclusive (65). Previously, however, it was suggested that nephrectomy alone did not improve survival rates in patients with metastatic disease (47) or, at best, affected outcome in certain favorable patients only (83,168).

Patients with known metastatic disease who present with significant symptoms, including those from pain, hematuria, or paraneoplastic syndromes, may benefit from palliative surgery. Although occasional reports of spontaneous regression of metastatic lesions following nephrectomy have surfaced, palliative surgery has not been shown to have significant effects on overall survival. Nonetheless, palliation of symptoms may improve quality of life. Again, the risks of surgical intervention must be weighed against potential benefits of improved symptoms. A less invasive method of palliation for certain patients involves angioinfarction, in which blood flow to the kidney is blocked by use of an embolic material placed in the renal vasculature. Although theoretically appealing, angioinfarction conveys little prognostic benefit.

The percentage of RCC patients who present with a single detectable metastatic lesion ranges from approximately 1% to 3%, according to available studies (155,170,255). Evidence suggests that aggressive surgical therapy may have beneficial results in this select group of patients. The prototype metastatic lesion responding to surgical therapy is the pulmonary nodule. Moreover, improved survival has been associated with normal performance status, and a disease progression–free interval of more than 24 months from time of nephrectomy (142). Other types of metastatic lesions, including those to the central nervous system (179) and bone, also have shown effective long-term results.

The Future: Molecular Prognostic Markers

Recent evaluation reaffirmed the statistic significance of pathologic staging and nuclear grade in relation to survival (258). On a macroscopic level, metastasis can be qualified and generally portends a poor prognosis. However, the prognosis for patients with locally confined RCC is known to be variable. With ever finer focus, scientists are identifying morphologic character, proteins, antigens, and other prognostic markers that aid in both diagnosis and characterization of a particular lesion. Less specific prognostic signs and symptoms such as weight loss, anemia, hypercalcemia, and elevated liver function tests are giving way to clinicopathologic features discovered through application of immunohistochemistry, flow cytometry, polymerase chain reaction technology, and nucleic acid analysis. Already proven techniques have been expanded to generate better outcome data. For instance, distortion of nuclear shape has a long history in the histologic evaluation of tumors, but by using modern digital technology and mathematic equations for nuclear roundness and ellipticity, investigators found significantly improved prognostication (29).

Modern markers of proliferation such as Ki-67, silver- staining nucleolar organizer regions (AgNOR), and proliferating-cell nuclear antigen (PCNA) are present in cycling cells and therefore have potential utility in estimating the biologic aggressiveness of a given tumor. Several studies have identified the Ki-67 antigen and PCNA to be significant prognostic parameters in regards to survival and tumor recurrence, comparing favorably or even superior to grade and pathologic stage (48,101,249). In contrast to nuclear grading, the evaluation of positive staging is not only less subjective, but also reproducible and simple. In addition, AgNOR, Ki-67, and PCNA all have been shown to be independent predictors of survival and of greater prognostic value than histologic grade in multivariate analysis (48,93). Another measure of abnormal proliferation can be ascertained through detection of aneuploidy. Determinations of ploidy by flow cytometry are proving less reliable however, and in studies of locally confined tumors, conclusions regarding in its relationship to grade, stage, and prognosis are mixed (249).

Along with high proliferative indices, RCC has other inherent qualities ripe for prognostic analysis. Metastasis involves a complex series of events and depends on the cancer's ability to break from the primary location and implant in another area of the body. Two elements believed to be essential in this process are cell adhesion molecules and angiogenesis factors. Cadherins are a large family of transmembrane proteins responsible for mediating cell-to-cell adhesion, and when expression decreases, their inherent ability to modulate and preserve epithelial integrity diminishes. Lack of E-cadherin expression correlates with aggressiveness in several tumors, but only 20% of RCCs express the glycoprotein (117). E-cadherin appears to be localized to Bowman's capsule and other tubular segments rather than

to the proximal tubular epithelium. Such evidence brings to question whether E-cadherin plays an integral role in renal cell carcinogenesis.

As a result, more recent focus has shifted to cadherin-6. Shimazui showed this cadherin to be the major one in the proximal renal tubules and RCC itself. Investigating this relationship as related to prognosis, Shimazui's group found that aberrant expression of cadherin-6 connoted poor survival (216,217). These data have been reproduced in a series wherein the majority of renal cell cancers with histology-associated poor prognosis (e.g., high-grade clear cell cancers) showed aberrant expression. The tumors with a historically good prognosis (e.g., low-grade clear cell carcinomas and papillary cancers) exhibited normal cadherin-6 expression (180).

In a similar fashion, the degree of angiogenesis has been shown to correlate with the development of metastases in several cancers including melanoma (225), prostate (271), breast (272), and non–small-cell lung carcinoma (140). In one study, when investigating the relationship to malignant renal epithelial tumors, an immunohistochemical marker of angiogenesis, microvessel density, exhibited no correlation to clinical stage, pathologic stage, or tumor grade (141). However, another investigation showed that higher microvessel density was associated with longer patient survival in clear cell carcinoma; this relationship is contrary to that reported with other types of malignancies (49). RCC is a vascular tumor, but its direct relationship to angiogenesis has yet to be completely determined.

Proteins responsible for apoptosis, such as p53, have been extensively studied in many cancer models, including RCC. The p53 protein binds DNA and is believed to regulate transcription, acting as a “checkpoint” to induce cell cycle arrest (128). When mutated, this tumor suppressor gene inactivates the normal function of DNA damage surveillance. Aneuploid cells originate, carcinogenesis occurs, and tumor progression can ensue (104). Mutant p53 proteins have a prolonged half-life, and with accumulation are detectable with immunohistochemical analysis (130). Yet controversy exists in regards to the frequency of the mutation in RCC (ranging from 4% to 40% of specimens tested) and consequently, its resultant prognostic power. Uhlman found an 87% 10-year, disease-specific survival rate for patients with nonstaining Robson stage I tumors versus a 62% survival with p53 positive-staining tumors (p <.01). Moreover, p53 positivity was an independent predictor of survival, whereas tumor grade was not (259). More recently, others have demonstrated a significant correlation between p53 and nuclear grading and PCNA expression, and these researchers claim p53 to be an independent predictor of survival. Nonetheless, they also recognize the infrequency of staining and believe it to be a useful adjunct to the standard criteria of stage and grade (215). The clinical significance of p53 and other apoptotic markers has yet to be completely elucidated.

MISCELLANEOUS RENAL TUMORS

Part of "16 - RENAL TUMORS "

Renal Angiomyolipoma

Renal angiomyolipomas (Fig. 16.15) are generally benign tumors of the kidney that are named based on their three characteristic histologic components: blood vessels, smooth muscle, and mature adipocytes. Their extensive vascularity is associated with a significant propensity for hemorrhage, which can produce clinical symptoms. However, angiomyolipomas often may grow to large sizes before diagnosis. They can occur as a solitary lesion, in multiple sites within one kidney, or in both kidneys. Rare cases of malignant degeneration have been described (36,59,139), as well as coexistence with RCC (95).

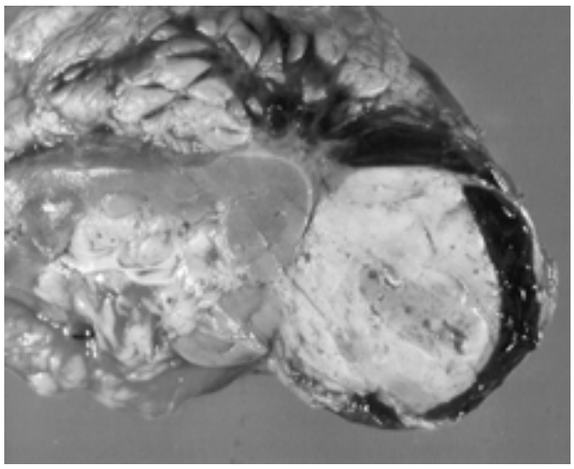

FIGURE 16.15. Gross view of angiomyolipoma.

Angiomyolipomas also are commonly associated with tuberous sclerosis, an inherited syndrome characterized by mental retardation, epilepsy, adenoma sebaceum, and hamartomas of multiple organs including retina, heart, bone, lung, and kidney (108). A significant number of patients with tuberous sclerosis will develop renal angiomyolipomas; therefore careful screening is required. In this group of patients, the tumors tend to occur at a younger age and to be multifocal and bilateral (238).

The size of the tumor appears to significantly affect its symptomatology. Steiner and associates (238) reported that tumors smaller than 4 cm produced no symptoms in their series of patients. However, tumors larger than 4 cm commonly produce symptoms (171,238). Flank pain is the most prevalent symptom at presentation, occurring in up to 70% of symptomatic patients (9). A palpable mass and hematuria, usually microscopic, also are seen. More rare presentations include hypertension and anemia. Rupture of the tumor with subsequent retroperitoneal hemorrhage also may produce significant hypotension, which can progress to hemorrhagic shock.

Often, radiographic imaging alone confirms the diagnosis of angiomyolipoma. The numerous fat–nonfat interfaces

with sonography produce an intensely echogenic lesion. Quantifying these echoes with computer assistance may aid in differentiation of angiomyolipomas from other renal tumors (221). CT scans can detect fat densities (–70 to –30 Hounsfield units) within the tumor, and the presence of fat is essentially pathognomonic for angiomyolipoma. The characteristic high signal intensity of fat on T_1-weighted images of MRI scans also can assist in the diagnosis. If fat cannot be detected in the lesion using radiographic studies, the tumor should be treated as malignant until a pathologic diagnosis confirms angiomyolipoma. Percutaneous needle sampling of the tumor for tissue analysis has been described (207).

The management of angiomyolipomas varies based on the individual patient. Once a diagnosis is made, the size of the tumor and the presence of symptoms determine the future course. The goal for therapy is renal preservation, when possible. Small, asymptomatic tumors may be followed with yearly ultrasounds, with no treatment necessary unless tumors become large or symptomatic. Tumors larger than 4 cm that are asymptomatic or mildly symptomatic also may be followed, but investigators recommend semiannual radiographic monitoring (171,238). Patients with extremely large tumors or those with severe symptoms should undergo therapy before the development of retroperitoneal hemorrhage. Embolization of angiomyolipomas often has been successful in control of bleeding and also can be therapeutic (171). Tumors that are poorly suited for angioinfarction or those with questionable diagnosis require surgical exploration for treatment. Nephron-sparing surgery with preservation of normal parenchyma is the preferred approach, when possible. Tumors that replace the entire kidney, multifocal lesions, and those with uncontrollable hemorrhage necessitate total nephrectomy.

Renal Medullary Carcinoma

Renal medullary carcinoma is a tumor found in patients with SC trait or hemoglobin sickle cell disease. It has been described mainly in African American adolescents and young adults, with a male predominance (6,41,43,45,70). This highly aggressive tumor quickly progresses to metastatic disease. Mean survival after diagnosis averages approximately 3 months (6,45), with only rare reports of survival past 1 year (41,183). Multiple failed chemotherapy regimens demonstrate the chemoresistance of this tumor (6,183).

Patients most often present with gross hematuria; therefore this symptom in a patient with sickle cell trait should prompt an appropriate workup (269). The tumor is concentrated in the medulla of the kidney, but satellite nodules in the renal cortex and renal sinus are often noted (45). Infiltrative growth is common (43), and venous and lymphatic invasion usually is present (45). Abnormalities on chromosome 3 and monosomy 11 have been identified in some patients (6). On radiographic studies of the kidney, contrast enhancement and echotexture are consistently heterogeneous (43). Hypovascularity also has been noted on renal angiogram (43,70).

Other Tumors

Aside from the more common tumors discussed previously, numerous other lesions have been described as occurring within the kidney (Table 16.7). In general, these are exceedingly rare tumors; many are derived from mesenchymal elements and are benign in nature (247). Metastatic deposits from other primary malignancies also are seen. Often, no symptoms are present and discovery of the lesion occurs as an incidental or autopsy finding.

Fibroma	Lymphangioma
Fibrosarcoma	Lymphoma
Fibrous histiocytoma	Mesoblastic nephroma
Hemangioma	Metastatic tumors
Hemangiopericytoma	Myxoma
Juxtaglomerular cell tumor	Neurogenic tumors
Leiomyoma	Osteogenic sarcomas
Leiomyosarcoma	Renomedullary interstitial cell tumors
Lipoma	
Liposarcoma	Rhabdomyosarcomas

TABLE 16.7. OTHER RENAL TUMORS

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17

UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT

Meidee Goh

James E. Montie

J. Stuart Wolf Jr.

M. Goh, J.E. Montie, and J.S. Wolf, Jr.: Department of Urology, University of Michigan, Ann Arbor, MI 48109.

Contents

EPIDEMIOLOGY AND ETIOLOGY

Part of "17 - UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT "

Incidence

Urothelial (transitional cell) carcinoma of the upper urinary tract is an uncommon disease, accounting for 4.5% to 9% of all renal tumors and 5% to 6% of all urothelial tumors (27,43,108,159,160). Renal pelvis urothelial tumors are two to four times more common than ureteral urothelial tumors (89,100,104,117). Upper urinary tract tumors rarely occur before age 40 years and have a peak incidence in the sixth and seventh decades of life, with a mean age at diagnosis of 65 years (7,54). Upper tract urothelial cancers are two to four times more common in men than in women and two times more common in Caucasians than in African Americans (7).

Risk Factors

Association with Balkan Nephropathy

In regions of Bulgaria, Greece, Romania, and Yugoslavia, the presence of an endemic form of nephropathy (termed *Balkan nephropathy*) has been associated with a high frequency of renal pelvic and ureteral tumors. Balkan nephropathy is a degenerative interstitial disease resulting in renal failure in its late stages. The upper tract tumors associated with this nephropathy tend to be low grade and slow growing, which encourages conservative management in these cases. Interestingly, there is no increase in the incidence of bladder urothelial cancer (118). These urothelial tumors occur bilaterally in 10% of these patients and account for 40% of all renal cancers in these geographic regions (125).

Occupational Risk Factors

Workers in the chemical, petrochemical, and plastics industries have been shown to be four times more likely to

develop renal pelvic and ureteral cancers compared with the population at large. In addition, workers who are exposed to coal, coke, asphalt, tar, and aniline dyes experience a similar increase in risk (122).

Smoking

Cigarette smoking is a major risk factor for urothelial cancer of the upper urinary tract, as well as the bladder. In a study by Jensen and colleagues (64), 56% of upper tract cancers in eastern Denmark were thought to be caused by cigarette smoking. The associated risk increased with lifetime amount of tobacco use and degree of inhalation. This study suggested that the association of tobacco use with upper tract urothelial cancer was even stronger than with bladder urothelial cancer. The addition of other types of tobacco increased the relative risk from 2.6 to 3.8. McLaughlin and associates (92) calculated that of upper tract urothelial tumors in three areas of the United States, 7 of 10 in men and 4 of 10 in women were attributable to smoking. Cigarette smoking appears to be the most significant acquired risk factor for upper tract urothelial cancer.

Analgesic Use

A number of case reports and epidemiologic studies have linked heavy use of analgesic mixtures with urothelial carcinoma of the renal pelvis. In particular, phenacetin, an aromatic amide with *N*- hydroxylated amines, has been linked in one study to 22% of patients with renal pelvis cancer and 11% of those with ureteral cancers (148). Other studies have been supportive of this association (91,99). The phenacetin metabolite *N*- hydroxyphenacetin, a potent liver carcinogen, may be responsible for the increased risk. The latency period can be as long as 25 years (45).

Prolonged use of nonsteroidal antiinflammatory drugs has been associated with the development of interstitial nephritis. This nephropathy is characterized by capillarosclerosis, a thickening of the basement membrane around the subepithelial capillaries, which is pathognomonic for analgesic abuse. Palvio and associates (114) noted capillarosclerosis in 15% of cases of upper tract urothelial cancer. Combination analgesics result in an even greater frequency of nephropathy, possibly as a result of synergy between aspirin, phenacetin, and other nonsteroidal agents. In a study by Jensen and associates (65), the relative risk for upper tract urothelial cancer attributed to analgesic abuse was greater for women than for men (4.2 versus 2.4).

Coffee Drinking and Artificial Sweeteners

There has been controversy over the association of upper tract urothelial cancer with coffee drinking or the use of saccharin. Although some have noted a slightly increased risk with the former (132), others have not (99). The preponderance of evidence suggests that saccharin is not associated with urothelial tumors (63,99).

Infectious Agents

Although there has been some evidence that human papillomavirus (HPV) may predispose to the development of bladder urothelial cancer, studies of HPV in upper tract urothelial cancer have not provided confirmation of a similar relationship (6,21,38,161). Chronic bacterial infections of the upper urinary tract have been linked to the development of squamous cell carcinoma, but the association with urothelial cancer is uncertain.

Cyclophosphamide

Cyclophosphamide is an alkylating chemotherapeutic agent widely used to treat lymphomas, leukemia, and other solid tumors. In addition, it has been used in the management of patients with autoimmune disorders such as rheumatoid arthritis, lupus erythematosus, and polyarteritis nodosa. One product of cyclophosphamide metabolism, acrolein, is toxic to the urothelium and thought to be responsible for injury to the mucosa. Cyclophosphamide exposure has been associated with an increased risk of both bladder and upper tract urothelial cancer (18,156).

Heredity

There have been several reported cases of familial urothelial carcinoma of the upper urinary tract. In particular, increased risk has been suggested among families with hereditary nonpolyposis colon cancer (47,84). Increased risk of urothelial carcinoma of the upper urinary tract has been associated with Muir-Torre syndrome, which is a rare autosomal-dominant disorder characterized by sebaceous tumors and at least one visceral malignancy (i.e., colon cancer) (48,73). There has been the suggestion of overlap with hereditary nonpolyposis colon cancer.

Chromosomal Abnormalities

Chromosomal abnormalities have been described in upper tract urothelial cancers. Reports describe gain of chromosome 7, complete or partial loss of chromosome 9, partial loss of chromosome 10, and partial loss of chromosome 21 (11,35,134,155). Some studies suggest that the changes seen are similar to those for bladder urothelial cancer.

Through mapping studies and examination of recurrent bladder tumors, there has been a suggestion that multifocal urothelial tumors arise from a monoclonal origin (83,144,157). In a molecular study of three patients, Sidransky and colleagues (144) showed that inactivation of the same X chromosome occurred in multiple tumor samples. A similar

clonal pattern was also seen in the allelic loss of chromosome 9q, a loss that is thought to occur early in tumorigenesis (151). Similarly, Van der Poel and colleagues (157) demonstrated that the same p53 mutation was present in multiple urothelial tumors present in one patient. While allelic loss of chromosome 9 is thought to be an early event, loss of chromosome 17p, containing the site for p53, is thought to be late event (52).

The chronology of genetic alterations in urothelial tumors might shed light on their development. Takahashi and colleagues (151) found that low-grade papillary urothelial tumors rarely acquire additional genetic alterations; genetic divergence and heterotopic spread appear to occur after alterations in chromosome 9. Their findings suggest that most multifocal low-grade superficial urothelial tumors are genetically stable and that alterations in chromosome 9 may be an early event in tumorigenesis.

Location and Distribution

Urothelial carcinoma is two to four times as common in the renal pelvis as in the ureter (89,100,104,117). In the ureter, lesions are more common in the distal portion (40). Zungri and colleagues (168) found that among patients with upper tract tumors, 78% had tumors in the distal ureter and 27% in the proximal ureter.

Upper tract urothelial carcinomas occur in a bilateral and synchronous fashion in 1.5% to 2%; 6% to 8% develop as bilateral metachronous lesions (103,160). Upper tract tumors occur in 2% to 4% of patients with previous bladder cancer. The mean interval between the diagnosis of bladder cancer and upper tract disease varies from 17 to 170 months (109). Carcinoma *in situ* (CIS) of the bladder increases the likelihood of upper tract urothelial cancer in patients with bladder cancer from 13.4% to 21%. The median time from diagnosis of bladder tumor to occurrence of upper tract tumor ranges from 62 to 88 months (25,95,138). Despite successful bacille Calmette-Guérin (BCG) treatment of CIS in the bladder, these individuals have a lifelong risk for developing upper tract tumors and thus should have continued evaluation of the upper tracts in addition to the bladder.

The risk of developing bladder tumors following the diagnosis of upper tract urothelial cancer is significantly higher. This incidence has been estimated at 20% to 48% (40,58,68,76,101,102,129). Although, as noted, some of these bladder tumors are found before or at the time of diagnosis of the upper tract tumor, most occur after the diagnosis of upper tract disease. In a series of 69 patients reported by Mukamel and colleagues (102), most of these bladder tumors occurred within the first year following nephroureterectomy, although late occurrences are noted as well (93). There has been some controversy as to the impact that the diagnosis of a bladder tumor has on survival of patients with upper tract urothelial cancer. In the two series compiled by Krogh and colleagues (76) and Charbit and associates (23), the additional diagnosis of a bladder tumor did not affect survival. However, the two series collected by Reitelman and colleagues (129) and Mukamel and associates (102) suggest that the additional diagnosis of a bladder tumor decreases survival significantly.

The higher rate of metachronous as compared with synchronous bladder tumors following the diagnosis of an upper tract tumor has led to speculation about the method by which urothelial carcinoma is disseminated in the urinary tract. These phenomena suggest that many of the tumors that recur do so as a result of direct seeding downstream or from longer exposure of the causative agent in the bladder.

Some investigators have pursued urothelial mapping as a method of determining the causal link between urothelial cancers in the bladder and the upper tract. Several studies indicate that there are widespread abnormalities in the urothelium of the renal pelvis and ureter in patients with upper tract urothelial carcinoma (68,82,85). Thus the entire urothelium is at risk for the precancerous and cancerous event. Furthermore, there appears to be a correlation between the grade of tumor seen and the degree of disturbance seen in the surrounding epithelium. McCarron and colleagues (90) evaluated 30 consecutive nephroureterectomy specimens and found that in most high-grade neoplasms, the remote urothelium expressed marked atypia or carcinoma. Conversely, the low-grade neoplasms were accompanied by the presence of only varying degrees of simple hyperplasia of the surrounding urothelium. These findings suggest that conservative approaches will be less effective in the setting of high-grade neoplasm because urothelium remains at risk. The incidence of subsequent ipsilateral upper tract urothelial cancer lesions has been reported to range from 14% to 30%, and the incidence of ipsilateral ureteral stump recurrence has been shown to range from 19% to 48% (76,89,150,164).

Others have theorized that tumors in the upper urinary tract occur as a consequence of seeding that occurs as a result of vesicoureteral reflux (164). This suggestion is supported by the findings reported by Babaian and Johnson (7) that 73% of ureteral cancers were in the distal ureter, 24% in the midureter, and 3% in the proximal ureter.

PATHOLOGY

Part of "17 - UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT "

Of upper tract collecting system tumors, 90% are urothelial carcinomas. These may occur as single or multifocal lesions. Grading for these lesions is similar to that for bladder cancer and is based on the worst grade seen. The current World Health Organization/International Society for Urological Pathology (WHO/ISUP) consensus classification of urothelial (transitional cell) lesions was developed in 1998 out of a need to have a universally accepted classification system (Table 17.1) (34,131). The term *urothelial* is preferred over the term *transitional cell.* Although investigators had all

agreed that grade was an important predictor of outcome, the use of multiple systems of grading had resulted in a lack of reproducibility. The goal of the WHO/ISUP 1998 classification was to define a classification continuum from normal tissue to invasive neoplasms (Table 17.1) (34,131). Comparison of this 1998 consensus grading system and previous three- and four-tiered grading system is shown in Table 17.2 .

TABLE 17.1. THE 1998 WHO/ISUP CONSENSUS CLASSIFICATION OF UROTHELIAL (TRANSITIONAL CELL) NEOPLASMS

Flat lesions with atypia
Reactive (inflammatory) atypia
Atypia of unknown significance
Dysplasia (low-grade intraurothelial neoplasia)
Carcinoma *in situ* (high-grade intraurothelial neoplasia)
Papillary neoplasms
Papilloma
Inverted papilloma
Papillary neoplasm of low malignant potential
Papillary carcinoma, low grade
Papillary carcinoma, high grade (option to add comment regarding presence of anaplasia)

Adapted from Reuter VR, Epstein JI, Amin MB, et al. A newly illustrated synopsis of the World Health Organization/International Society of Urological Pathology (WHO/ISUP) consensus classification of urothelial (transitional-cell) neoplasms of the urinary bladder. *J Urol Pathol* 1999;11:1.

TABLE 17.2. HISTOLOGIC GRADING CATEGORIES FOR PAPILLARY UROTHELIAL TUMORS

WHO 1998	WHO 1973	Murphy	Bergkvist
Papilloma	Papilloma	Papilloma	Papilloma
Papillary neoplasm of low malignant potential	Grade 1	Papilloma	Grade 1
Low-grade papillary carcinoma	Grade 2	Low-grade	Grade 2
High-grade papillary carcinoma	Grade 3	High-grade	Grade 3
			Grade 4

Adapted from Grignon DJ. Neoplasms of the urinary bladder. In: Bostwick DG, Eble JN, eds. *Urologic surgical pathology.* St. Louis: Mosby, 1997:246.

Carcinoma In Situ (High-grade Intraurothelial Neoplasia)

CIS (Fig. 17.1) has been characterized as a precursor lesion to invasive cancer. Cells with large, irregular hyperchromatic nuclei that compose a portion of or the entire urothelium define this high-grade lesion. Mitotic activity is commonly seen in the middle to upper urothelium. This designation encompasses lesions that used to be described as severe dysplasia or marked atypia.

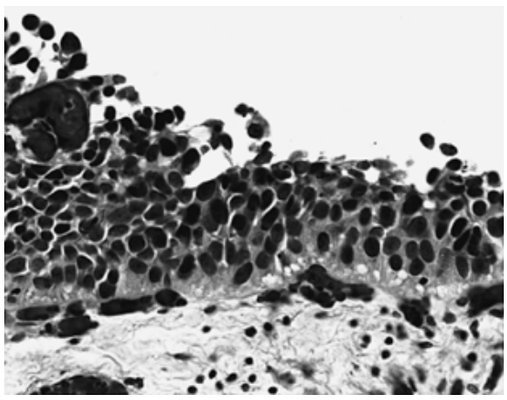

FIGURE 17.1. Urothelial carcinoma *in situ* with pleomorphic cells and hyperchromatic nuclei replacing the full thickness of the urothelium (×200 magnification). (Photo courtesy of Dr. Nader H. Bassily.)

Papillary Urothelial Neoplasms

Papilloma is a discrete papillary growth with a central fibrovascular core. The surface of the papilloma is covered by urothelium of normal thickness and cytology. Although they do not have the ability to invade or metastasize, papillomas do have a tendency to recur. This propensity for recurrence has been associated with subsequent development of carcinoma (17,34,131).

Papillary urothelial neoplasm of low malignant potential is the designation for a lesion in which there is an orderly polar arrangement of cells within papillae. The papillae exhibit minimal architectural abnormalities and minimal nuclear atypia. However, the nuclei are significantly enlarged or the urothelium has more layers than normal. Mitotic figures are infrequent. These lesions pose little risk for invasion or metastases.

Low-grade papillary urothelial carcinomas (Fig. 17.2) represent the next step in the continuum of urothelial change. Although the orderly appearance of the cell layers is preserved, there is now variation in the architectural or cytologic features. Despite the presence of cellular atypia, mitotic figures remain rare (34,131).

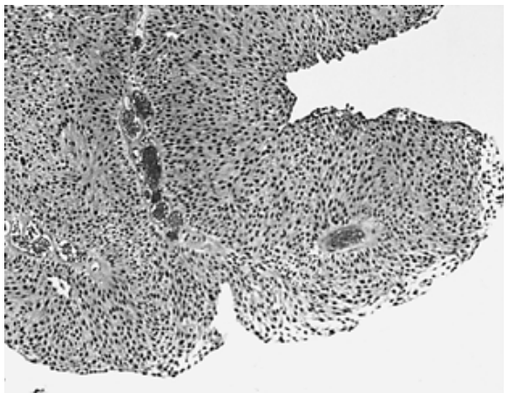

FIGURE 17.2. Low-grade papillary urothelial carcinoma with exophytic papillary fronds covered by thick urothelium. Note the mild nuclear atypia, intact basement membrane, and preservation of normal architecture (×40 magnification). (Photo courtesy of Dr. Nader H. Bassily.)

High-grade papillary urothelial carcinomas (Fig. 17.3) demonstrate disordered appearance even at low magnification. Both the architecture and cytologic features are involved. Marked to moderate cellular pleomorphism, clumped nuclear chromatin, prominent nucleoli, and mitotic figures all can be present. The pathologist may also add

an additional comment on the degree of anaplasia during grading (34,131).

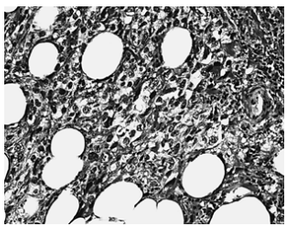

FIGURE 17.3. Invasive high-grade urothelial carcinoma growing in large solid sheet into periureteral fibrofatty tissue. Note the pleomorphic nuclei and disorganized pattern of growth (×200 magnification). (Photo courtesy of Dr. Nader H. Bassily.)

NATURAL HISTORY

Part of "17 - UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT "

Patterns of Spread

Urothelial carcinoma of the upper urinary tract can spread by (a) direct extensions through the wall of the collecting system into the renal parenchyma or surrounding structures, (b) lymphatic invasion, or (c) more rarely, vascular invasion. The paraaortic, paracaval, and pelvic lymph nodes are the most common sites for lymphatic invasion. Venous extension into the renal vein and the vena cava has been reported and is associated with poor prognosis (53,66,130). The most common metastatic sites for urothelial cancer of the upper tract are lung (31%), bone (22%), and liver (9%) (58).

Mucosal Spread

Global field changes present in the urothelium at the time of resection of the primary urothelial upper tract lesions may predispose the remainder of the upper tract to recurrence. Mahadevia and colleagues (85) demonstrated with urothelial mapping of nephroureterectomy specimens that widespread abnormalities of the entire urothelium are present concomitantly with the diagnosis of upper tract urothelial cancer. McCarron and colleagues (90) confirmed this finding. This group also demonstrated that the degree of urothelial disturbance parallels the grade of the principal lesion. The widespread nature of urothelial abnormalities may provide a plausible explanation for the high incidence (20% to 64%) of recurrent urothelial carcinoma in ureteral stumps (67,150).

Others have suggested that urothelial upper tract cancers are seeded from bladder tumors when malignant cells are washed into the upper tract through an incompetent ureteral orifice (113). Studies have suggested that patients with bladder cancer and vesicoureteral reflux are 16 to 22 times more likely to develop upper tract urothelial cancer than are bladder cancer patients without concomitant reflux (5,29).

TUMOR STAGE

Part of "17 - UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT "

Stage, along with grade, is an important prognostic indicator for upper tract urothelial carcinomas. Depth of tumor invasion is inversely correlated with survival. In a study of 103 subjects, patients with tumors of the renal pelvis or ureter without invasion beyond the midpoint of the muscularis experienced a 72% 5-year survival rate. Patients with tumors that had extended more deeply (Fig. 17.4) had a 5-year survival rate of only 32% (16).

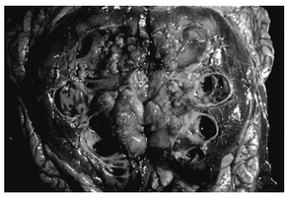

FIGURE 17.4. Gross specimen of stage T_3 urothelial carcinoma of the renal pelvis (extensive tumor, with focal invasion into peripelvic fat).

Renal pelvic and ureteral carcinomas are staged according to an assessment of the degree of tumor infiltration, nodal involvement, and presence of metastatic disease. The American Joint Committee on Cancer (AJCC) system (Table 17.3 and Table 17.4) uses combinations of tumor, node, metastasis (TNM) categories to form stage groupings.

TABLE 17.3. TUMOR, NODE, METASTASIS (TNM) STAGING FOR TUMORS OF THE RENAL PELVIS AND URETER

T	**Primary tumor**
T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma *in situ*
T_a	Papillary noninvasive carcinoma
T_1	Tumor invades subepithelial connective tissue
T_2	Tumor invades muscularis
T_3	Tumor invades beyond muscularis into periureteric or peripelvic fat or renal parenchyma but not adjacent organs
T_4	Tumor invades adjacent organs or through the kidney into perinephric fat
N	**Regional lymph nodes**
N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in a single lymph node, ≤2 cm in greatest dimension
N_2	Metastasis in a single lymph node, >2 cm but <5 cm in greatest dimension; or multiple lymph nodes, none >5 cm in greatest dimension
N_3	Metastasis in a lymph node(s) >5 cm in greatest dimension
M	**Distant metastasis**
M_X	Presence of distant metastasis cannot be assessed
M_0	No regional lymph node metastasis
M_1	Distant metastasis

Adapted from Fleming ID, Cooper JS, Henson DE, et al, eds. *AJCC cancer staging manual,* 5th ed. Philadelphia: Lippincott-Raven, 1998.

TABLE 17.4. STAGING OF URETERAL AND RENAL PELVIC TUMORS

Description	Stage	Tumor	Nodes	Metastases
Confined to the mucosa	Stage 0a	T_a	N_0	M_0
Carcinoma *in situ*	Stage 0is	T_{is}	N_0	M_0
Invasion into the lamina propria	Stage I	T_1	N_0	M_0
Invasion into the muscularis	Stage II	T_2	N_0	M_0
Extension through the muscularis into fat or renal parenchyma	Stage III	T_3	N_0	M_0
Spread to adjacent organs	Stage IV	T_4	N_0	M_0
Lymph node metastasis	Stage IV	Any T	N_1 to N_3	M_0
Distant metastasis	Stage IV	Any T	Any N	M_1

Adapted from Fleming ID, Cooper JS, Henson DE, et al, eds. *AJCC cancer staging manual,* 5th ed. Philadelphia: Lippincott-Raven, 1998.

SIGNS AND SYMPTOMS

Part of "17 - UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT "

Gross hematuria is the most common symptom of urothelial carcinoma of the upper urinary tract, present in 70% to

90% of patients. Flank pain may be present in 8% to 50% of patients and occurs as a result of ureteral obstruction by blood clots or tumor. Constitutional symptoms, such as weight loss, anorexia, and bone pain, are rarely present unless there is metastatic disease. A flank mass due to hydronephrosis or the actual tumor mass is noted in up to 10% to 20% of patients (39).

DIAGNOSIS

Part of "17 - UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT "

Excretory Urography

Upper urinary tract collecting system tumors may produce an intraluminal filling defect, unilateral nonvisualization of the collecting system, or hydronephrosis (4,10,162) on either excretory urography (IVP) or retrograde pyelography. The differential diagnosis primarily includes nonopaque calculi, blood clots, sloughed renal papillae, and fungus balls. Other considerations include fibroepithelial polyp (56), air bubble, granuloma, renal tuberculosis, and leiomyoma.

Although 50% to 75% of patients may exhibit a filling defect (Fig. 17.5), 10% to 30% of patients diagnosed with upper tract urothelial tumors demonstrate obstruction or nonvisualization of the collecting system, which limits the usefulness of excretory urography. Further evaluation of a nonvisualized collecting system usually requires retrograde pyelography.

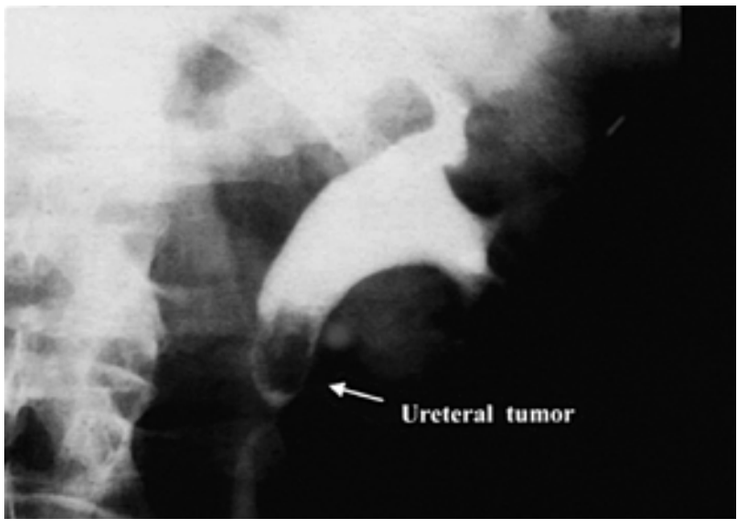

FIGURE 17.5. Intravenous urogram demonstrating a filling defect indicating a proximal ureteral tumor.

Retrograde Pyelography

Retrograde pyelography allows for excellent visualization of the collecting system and provides opportunity for direct collection of specimens for cytology. A bulb- or cone-tipped ureteral catheter is inserted through the ureteral orifice, and contrast is injected to visualize the collecting system under fluoroscopy. The contrast medium should be diluted to one-third or one-half its original concentration before use, which will allow better visualization of subtle filling defects. Care is taken to fill and view the entire renal pelvis and collecting system. Filling of the collecting system is performed with fluoroscopic monitoring in order to prevent overfilling, which may result in rupture of the renal fornices. Occasionally, dilation of the ureter distal to the ureteral tumor is noted, creating a “goblet” appearance. In this dilated region, a catheter passed distal to the tumor may form a coil; this radiologic appearance is called Bergman's sign (12).

When urine is being collected from the upper tracts for cytology, it is important to consider that the hyperosmotic contrast material injected for the retrograde pyelography may affect the interpretation of the cytology. Thus, once the ureteral catheter has been inserted, it might be advisable to first collect urine and saline barbotage for cytology before injection of contrast material.

Antegrade Pyelography

Puncture of the renal pelvis for either an antegrade study or a needle biopsy is not recommended. Although fine-needle

biopsy has been reported as a diagnostic technique for renal pelvis filling defects (107,135), seeding of the tumor along the needle tract has also been reported (145). Alternatives for evaluation of a nonvisualized collecting system, such as retrograde pyelography, ureteroscopy with or without biopsy, or computed tomography (CT) scanning, generally should be used first unless there are specific contraindications.

Computed Tomography

CT can be useful in differentiating between a radiolucent uric acid stone and an upper tract urothelial cancer as the source of the filling defect seen during IVP, as well as for staging of upper tract urothelial cancer. Following intravenous injection of contrast material, pelvic or ureteral urothelial tumors typically have an average radiodensity of between 60 and 80 Hounsfield units (HU). In contrast, uric acid stones have much higher radiodensity, usually greater than 200 HU. Other causes of filling defects have less distinctive radiodensities: papillary necrosis at 20 to 40 HU and blood clot at 40 to 80 HU (94). In a review of 343 published cases, 43% to 77% clinicopathologic correlation between upper tract urothelial cancer and CT scan imaging was accomplished, with 7% to 31% overstaging and 13% to 36% understaging (19,22,94,121). Some of the understaging occurred due to small tumor volume. The most common findings were hydronephrosis in the case of ureteral tumors and filling defects in the case of renal pelvis tumors.

Renal parenchymal invasion (Fig. 17.6) can be seen on CT as an alteration in renal contour. The invasive renal urothelial cancer appears as a centrally located mass that distorts the renal contour. Poorly defined margins of the tumor, obliteration of renal sinus fat, and obliteration or entrapment of the collecting system all may be signs of renal parenchymal involvement (37). The specificity of these finding ranges from 75% to 97%, and the sensitivity ranges from 64% to 78% (19,22,94,121).

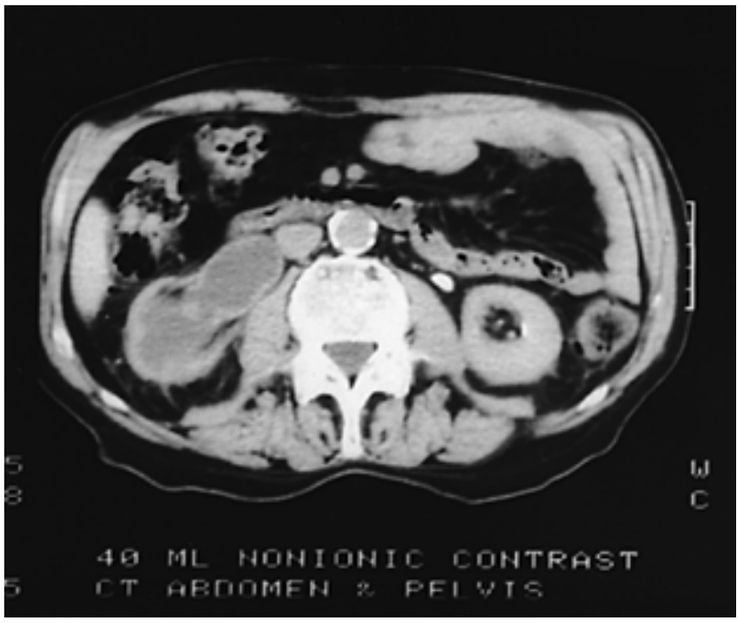

FIGURE 17.6. Computed tomography scan demonstrating a centrally located tumor with distortion of the renal contour.

In the case of ureteral tumors, determination of extension is less accurate, with a sensitivity of 67% and a specificity of 77% (94). Lymph node enlargement as a determinant of lymph node metastases has a sensitivity of 47% to 87.5% and a specificity of 94% to 100% (19,22,94,121).

CT urography is an evolving technique that attempts to duplicate and then improve on intravenous urography, taking advantage of the resolution and volumetric data acquisition of CT (149). The protocol varies from institution to institution, but generally it involves imaging during several phases of contrast excretion with three-dimensional reconstruction of images using a variety of algorithms. Although there are no large series yet describing the results of this new technique, it is likely that it will play an increasingly important role as an alternative to intravenous urography. Yet to be determined is the sensitivity of this technique for subtle tissue-density filling defects.

Ultrasonography

Surface ultrasonography provides a noninvasive method for evaluating the upper tracts that does not depend on the adequacy of renal function. In a series collected over a 9-year period (50), ultrasound identified the presence of hypoechoic

intraluminal tissue in 16 patients with ureteral tumors. All 10 IVPs and all 3 retrograde pyelograms performed in these patients were abnormal, but only 7 of 11 CT scans clearly demonstrated the tumor. The utility of ultrasonography may be limited if hydronephrosis is absent, or by large body habitus or interference from overlying bowel gas. Information regarding the depth of invasion is unavailable with this technique, and ultrasonography is extremely operator dependent.

To provide more useful information with ultrasonographic imaging, some investigators have employed endoluminal ultrasonography. A 12.5- or 20-MHz transducer is housed within a 6.2-Fr ureteral catheter that is passed in a retrograde fashion up the ureter under fluoroscopic guidance. Liu and colleagues (81) suggest that use of endoluminal ultrasonography can provide information regarding the size and location of the lesion, as well as some estimation of the depth of penetration. In addition to diagnosis of other nonneoplastic causes of filling defects (i.e., stones, air bubbles, and blood clots), this technique may allow for the determination of the location of adjacent vessels before endoscopic resection. The technique has not been widely accepted, however, because it requires an invasive procedure, and as such, it is usually performed at the time of the intended definitive procedure. In this setting, the ultimate utility of the information is uncertain.

Cystoscopy

Cystoscopic examination of the bladder is necessary to rule out the coexistence of a bladder urothelial cancer. As noted, patients with upper tract urothelial cancers are at 20% to 48% risk of having a bladder tumor, either synchronous or metachronous (40,58,68,76,101,102,129).

Cytopathology

Upper urinary tract urothelial cancers can be diagnosed by the examination of voided urine cytology. As with urine cytology in the bladder, the accuracy of diagnosis depends on the grade of the tumor. Accuracy of voided urine cytology ranges from 23% to 92% (30). Improvement in diagnostic accuracy (77% to 92%) can be achieved by obtaining the urine sample through ureteral catheterization. It is worth noting that in a study of retrograde catheterization for urine cytology done following transurethral resection of bladder tumors, 25% of patients with low-grade urothelial neoplasms and 32% of patients with high-grade urothelial neoplasms in the bladder had positive upper tract urinary cytology (133). All of these patients had negative IVP or retrograde pyelography. This suggests that the results from upper tract sampling in the face of concurrent bladder urothelial cancer should be viewed with caution.

The best yields of cytology occur when samples are obtained by saline barbotage of the ureter following catheterization: 87% sensitivity and 100% specificity have been reported with this technique (78). The saline barbotage may improve the accuracy by providing a shearing force to loosen cells from the urothelial lining. Minimo and associates (97) report that the addition of computed DNA measurements and assays for p53 expression can enhance the accuracy of material submitted for cytology in terms of correlation with final histologic grade.

Brush Biopsy

Brush biopsies of the upper urinary tract lesions are performed by passing a fine brush mounted on the end of a guidewire passed through a ureteral catheter into the collecting system up to the level of the filling defect (44). Under fluoroscopic guidance, the brush is gently moved back and forth over the filling defect. Confirmation of the location of the filling defect is obtained fluoroscopically with the injection of dilute contrast. The brush is then removed and the sample is sent for cytologic examination. In one study by Gill and colleagues (42), both sensitivity and accuracy approached 100%. In other series, accuracy has ranged from 78% to 92% (15,165). Accuracy was greater if the cytologic specimens were read as either positive or negative for tumor, rather than requiring accurate grading of the tumor.

Although complications are rare, hematuria and occasionally some flank pain can occur following the brush biopsy of the upper urinary tract. The hematuria is often self-limiting, although severe hemorrhage and perforation of the ureter have been reported (15). There is some concern that denuding the urothelium as a result of the brush biopsy

may provide an area for tumor implantation; however, in one retrospective study of 45 patients, there was no evidence of this (143).

Ureteroscopy

Flexible ureteroscopy was first reported in 1964 by Marshall (86), who passed a 9-Fr fiberscope into the ureter to visualize an impacted ureteral calculus. Since then, improvements in miniaturization, light-carrying capacity, fiber optics, and two-way active deflection have made flexible ureteroscopy an important part of the diagnostic armamentarium for upper tract urothelial cancer. Initially, Bagley and colleagues (9) had reported a 79% success rate in visualization of the whole intrarenal collecting system. However, with improvements in the equipment, one group was able to report in 1997 a 100% success rate (32). Ureteroscopy is an excellent modality to assist in the diagnosis of upper tract urothelial cancer when a filling defect of tissue density has been confirmed radiographically, but cytology is not positive for tumor. It is also useful for the evaluation of upper tract tumors to assist in treatment planning and, as described in a later section, the resection of selected tumors.

Use of flexible cup biopsy forceps or basket through the flexible ureteroscope has improved diagnostic accuracy for upper tract tumors. In the study by Keeley and colleagues (71) of 51 cases of upper tract urothelial cancer, 94% of the cases were diagnosed based on cytologic material collected. Grading of the ureteroscopic specimens was achieved in 82% of all cases (88% of diagnostic ones). The authors attributed their success to their sampling technique: ureteroscopic examination followed by aspiration, saline wash, biopsy of the lesions, and then another saline wash following the biopsy. In another study of 45 upper tract urothelial carcinomas, 40 (89%) were definitively diagnosed with ureteroscopic biopsy, and of these, the ureteroscopic biopsy grade matched the surgical pathology grade in 78% (49).

The possibility of pyelovenous or pyelolymphatic migration of malignant cells during ureteroscopy has raised some concerns. In one case report, tumor cells were noted in the submucosal lymphatic and vascular spaces when ureteropyeloscopy was performed immediately before nephroureterectomy (80). The authors suggested that the high-pressure irrigation required during ureteropyeloscopy played a role in forcing tumor cells into these spaces. A more recent study of 96 patients evaluating the long-term consequences of diagnostic ureteroscopy for upper tract urothelial carcinoma was unable to find any adverse effect on overall or disease-specific survival (55). Attempts to make definitive diagnoses of tumor stage with endoscopic biopsies of the upper tract collecting system risk perforation. Fortunately, deep biopsies are not required because in most cases the grade of the upper tract urothelial tumor is an adequate surrogate for stage, at least for the purposes of planning treatment (70,71).

Ureteral perforation following ureteroscopy has been reported with an incidence of 0% to 4.6% (1,13,46,51). Long-term complications of ureteroscopy, most notably ureteral strictures, have an incidence of 0.5% to 1.4% (1,13,46,51). It is important to note that the lower rates cited for ureteral perforations and strictures have come from more recent series using smaller-diameter (6.9- to 7.5-Fr) flexible ureteroscopes (46,51,154). With these instruments, formal dilation of the intramural ureter is not usually required and ureteral trauma is minimal. These small-diameter ureteroscopes make possible direct visual confirmation and sampling of almost any upper tract urothelial cancer, which should provide for more exact identification and assessment of lesions than was previously available with only radiography and ureteral catheterization.

TREATMENT

Part of "17 - UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT "

Prognosis

Tumor grade and stage are important determinants of long-term outcome in upper tract urothelial cancer. Low-grade and low-stage upper tract urothelial tumors have a good outcome regardless of whether a conservative or more radical surgical approach is taken. Patients with intermediate grade or multifocal disease ultimately have a better outcome with radical surgery. Unfortunately, patients with high-stage and high-grade disease often do poorly regardless of the approach.

In one study, patients with grade 1 tumors had a 100% 5-year survival rate, those with grade 2/4 had an 80% 5-year survival rate, and those with grade 3/4 had a 60% 5-year survival rate (33). Both patients with grade 4/4 cancer succumbed to their disease. In another report, 27% of patients with grade 2 and 73% of patients with grade 3 disease died of their disease (107). In contrast, Mufti and colleagues (101) found survival to be greater than 90% for patients with superficial well-differentiated tumors regardless of whether they were treated with nephroureterectomy or more conservative methods.

Some have found multiplicity of the tumors to be a negative prognostic indicator. In Mazeman's 1976 review (89), patients with multiple tumors in the upper urinary tract experienced a decreased 5-year survival rate (20% versus 37% in individuals with single tumors).

DNA ploidy has been evaluated as an independent prognostic indicator. DNA ploidy relies on flow cytometric measurement of DNA content. Al-Abadi and Nagel (3) were able to find a correlation between DNA ploidy and tumor grade or stage. Although they did not find ploidy to be an independent predictor of prognosis, they did demonstrate that patients with aneuploid tumors did poorly. The

poor response of aneuploid tumors was confirmed by Badalament and colleagues (8). In their series, patients with aneuploid tumors had a median disease-free survival of 19 months, and those with diploid tumors had a median disease-free survival of 59 months.

In an attempt to create a uniform management protocol for patients with upper tract urothelial cancer, the National Comprehensive Cancer Network guideline was created (136). Listed in the guideline are treatment algorithms using the latest information available on treatment outcomes. The guidelines incorporate the grade and stage in the management protocols.

Nephroureterectomy

Nephroureterectomy continues to be the preferred treatment for most upper tract urothelial carcinomas. The technique involves a simple nephrectomy and ipsilateral ureterectomy with the removal of a 2-cm cuff of urinary bladder. This procedure may be performed through a single midline incision or through two separate incisions such as a flank incision and a Pfannenstiel or lower midline incision to remove the distal ureter. Others have described endoscopic resection or mobilization of the intramural ureter followed by open en bloc resection of both the kidney and the ureter.

Johansson and Wahlqvist (67) advocate a transabdominal radical nephrectomy with adrenalectomy, in addition to a complete ureterectomy with bladder cuff. The 5-year survival rate of patients who had undergone the radical procedure was 84%, versus 51% for patients who had undergone more conventional resection. This difference was most marked in the high-stage patients (74% versus 37% 5-year survival). For small tumors, a simple nephrectomy with ureterectomy is probably sufficient, but in doubtful cases, or in the presence of a large tumor at high risk for invasion into the renal parenchyma, the inclusion of perinephric tissue as for radical nephrectomy (with or without adrenal gland, depending on tumor extent) is prudent. Komatsu and colleagues (75) also suggest that lymphadenectomy may provide some therapeutic benefit in selected patients. They found two long-term survivors whose nodes were located close to the original tumor. Other authors have not found a survival advantage to lymphadenectomy, reporting the likelihood of cancer death with uninvolved lymph nodes to be essentially the same as for those who had not undergone lymphadenectomy (23).

More recently, there has been the emergence of laparoscopic nephroureterectomy. This technique has been performed using both a transperitoneal and a retroperitoneal approach (41,90,127). Although requiring more specialized surgical skill and (usually) greater operative time, laparoscopic nephroureterectomy appears beneficial to the patient in terms of reduced blood loss, decreased postoperative narcotic use, and more rapid resumption of daily activities. In a series by Shalhav and colleagues (140), the disease-specific survival was identical for both laparoscopic nephroureterectomy and open nephroureterectomy (77%). Keeley and Tolley (72) reported similar success in 18 cases, in which only one patient with pT3 ureteral tumor developed a bladder and retroperitoneal recurrence.

Although laparoscopic nephroureterectomy appears to be a promising new minimally invasive technique, the technical demands and needs for specialized instrumentation make its widespread use unlikely at present. In addition, recent reports (2,111) of port site metastasis of urothelial carcinoma occurring following laparoscopic nephrectomy are worrisome, although in one of these cases (111) the urothelial carcinoma was unsuspected and the entrapment sac was torn during removal. Not only does urothelial carcinoma appear to have a propensity for wound seeding, but also intact specimen removal is desirable because the pathologic stage may have therapeutic implications. As such, when laparoscopic nephroureterectomy is performed for urothelial carcinoma, an incision large enough for extraction of the intact kidney is recommended. The addition of hand assistance to the laparoscopic technique, which allows the use of one hand within the operative field while maintaining pneumoperitoneum, takes advantage of this incision throughout the procedure rather than just at its conclusion. Hand assistance probably shortens operative time and appears to maintain the reduced morbidity of the laparoscopic procedure (163).

Renal-sparing Surgery

In the case of a pelvic tumor, a heminephrectomy or partial excision of the renal pelvis can be performed to remove the neoplasm with preservation of the kidney. Distal ureteral lesions can be managed by simple segmental resection and reimplantation; segmental resection of upper ureteral and midureteral tumors may require ileal interposition or autotransplantation. Conservative management may be indicated for patients with a solitary kidney, bilateral disease, or renal insufficiency. In patients with a functioning, disease-free, contralateral kidney, the indications for renal-sparing management (except for distal ureteral lesions) are less certain. The results of conservative management vary with the grade, stage, and multifocality of the neoplasm.

Open Surgical Approach

Localized surgical resection has been advocated for low-grade, low-stage distal ureteral tumors. Zungri and colleagues (168) demonstrated that survival for pTa disease was 100% regardless of whether the patient underwent more conservative or more radical surgery. In one series, Babaian and Johnson (7) reviewed the records of 44 patients with primary ureteral tumors and found that all of those with low-grade noninvasive disease confined to the distal third of

their ureter were disease free following ureterectomy at the time of last follow-up. Segmental resection for low-grade and low-stage ureteral tumors produces results similar to that for nephroureterectomy. Zoretic and Gonzales (167) found that following nephroureterectomy, the 5-year survival rate was 50%. In contrast, the 5-year survival rate following segmental resection for low-grade and low-stage lesions was 71.4%, with ureteral recurrence rate of 6%. Similarly, Mufti and colleagues (101) reported 100% survival for low-grade disease treated with conservative resection.

In the middle and upper ureter, there has been less success with local resection—partially due to the technical difficulties resulting from insufficient remaining ureteral length to allow for reimplantation. Ileal interposition and autotransplantation with direct pyelovesical anastomosis have been described in these situations. In one series of 50 patients who had tumors too proximal to allow for complete resection of the distal portion of ureter, the investigators reported a recurrence rate of 50% at 3 years (89). Similar results have been noted by Strong and Pearse (150), who found a 30% recurrence rate in the portion of the ureter distal to the tumor in patients treated with local resection.

Local resection of the renal pelvic or calyceal tumors has usually been associated with a less favorable outcome. During open surgical local resection of renal pelvic tumors, the luminal surface of the tumor being removed cannot be isolated as it can be for ureteral resection, and thus there is increased risk of tumor spillage into the surgical field. Open surgical resection of urothelial tumors in a renal calyx may require removal of renal parenchyma as well. Visualization of the calyces is limited, and multifocal disease that is not suspected radiographically might easily be overlooked. Open surgical resection of multifocal renal pelvic and calyceal tumors is technically difficult.

Mazeman (89) and Zincke and Neves (166) have reported recurrence rates as high as 45% to 65% following local resection of the renal pelvic tumors; the actual recurrence rates were dependent on grade. This is worrisome because Charbit and associates (23) noted that as many as 33% of patients had multifocal disease that was not recognized until histopathologic examination was complete, and that when recurrences occurred, 66% of these patients experienced an increase in grade or stage, or both. Mills and Vaughan (96) reported worse prognoses for invasive lesions in their series of 53 cases: patients with submucosal infiltration had an 80% 5-year survival rate, and those with periureteral fat invasion had only a 33% 5-year survival rate.

Findings suggest that the greater the length of the ureter remaining, the greater the chance for recurrence. Many investigators report that partial removal of the ureter results in a high ureteral stump recurrence rate. Recurrence rates range from 20% to as high as 58% (74,106,150) and may occur from 1 to 45 years after resection (102). Mazeman (89) showed that following subtotal nephroureterectomy, nephrectomy and partial ureterectomy, and simple nephrectomy, patients had recurrence rates of 24%, 32%, and 48%, respectively.

All these results taken together would suggest that elective open surgical renal-sparing management of upper tract urothelial cancers should be limited to distal ureteral tumors, or low-grade and low-stage lesions in the middle and upper ureter. Other tumors, such as those in the renal pelvis or higher-grade upper ureteral and midureteral cancers, are ideally treated with nephroureterectomy in the setting of a contralateral upper tract that is functioning and disease free. When open surgical renal-sparing management is chosen for such tumors because renal sparing is imperative (i.e., solitary kidney, bilateral disease, and renal insufficiency), it is technically difficult and carries a substantial risk of recurrence.

Endoscopic Approach

The first series describing ureteroscopic treatment of upper tract collecting system tumors involved the use of 12- to 13-Fr rigid ureteral resectoscopes. Size and rigidity limited the usefulness of these endoscopes. Endoscopic treatment for upper urinary tract disease has been simplified considerably by the development of small-diameter semirigid and flexible ureteroscopes. These have allowed clear visualization of tumors throughout the collecting system (Fig. 17.7). In addition, the application of the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser and the holmium:yttrium-aluminum-garnet (Ho:YAG) laser through small-diameter fibers has made the endoscopic treatment of larger tumors more feasible.

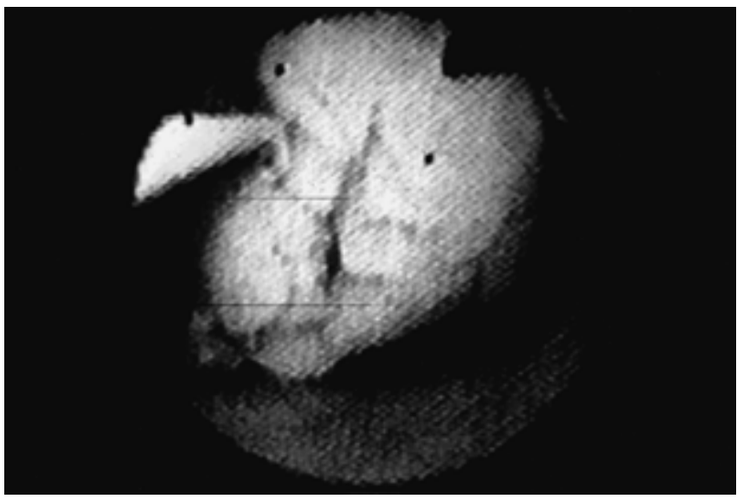

FIGURE 17.7. Endoscopic view of upper tract papillary urothelial carcinoma.

Simple fulguration with electrocautery can be used to treat small lesions or the base of a lesion following resection of the bulk of the tumor. However, fulguration of large portions of ureter may risk stricture formation. The depth of penetration (5 to 6 mm) of the Nd:YAG laser allows coagulation of full-thickness urothelium, but tissue ablation

is not optimal with this laser. The Ho:YAG laser produces more ablation than coagulation of tissue, although the process is slow through the small fibers that can be passed through ureteroscopes. Combinations of Nd:YAG and Ho:YAG lasers have been used, taking advantage of the coagulative power of the Nd:YAG laser and the ablative power of the Ho:YAG laser (153).

In one retrospective review of 92 patients treated ureteroscopically, 76% of patients with grade 1 and 2 disease were able to become tumor free (70). Tumor size (larger than 1.5 cm), greater tumor grade, and multifocality predicted poor outcome. Similar favorable outcomes in the endoscopic treatment of low-grade upper tract urothelial cancer were reported by Martinez-Pineiro and colleagues (87). They reported that patients with grade 1 disease had a much lower recurrence rate than patients with grade 2 disease, 27% and 40%, respectively.

Controversy surrounds whether location of the tumor may play a role in treatment outcomes. Ureteral cancers have a lower recurrence rate than renal pelvic tumors. Blute and colleagues (14) reported a 63% failure rate for patients with renal pelvic tumors. One possible explanation to account for this difference is the greater accessibility of the ureter for endoscopic treatment than the renal pelvis. In contrast, Martinez-Pineiro and colleagues (87) reported a higher failure rate for ureteral tumors (36.6% versus 10% for renal pelvic tumors). Tawfiek and Bagley (153) reported that local recurrence rate was essentially the same for renal pelvic tumors (33%) and ureteral tumors (31.2%).

Complications resulting from endourologic management include formation of ureteral strictures and ureteral perforation. The risk of stricture disease following ureteroscopic treatment may be related to need for dilation at the ureterovesical junction and the extent of cautery and ablation required for treatment of the lesion. The use of small-diameter flexible ureteroscopes has reduced the need for formal dilation of the intramural ureter. Although initial reports described stricture rates as high as 25% (137), more recent series have reported more modest rates of 5% to 13% (33,70,87).

Ureteral perforations occur as a result of deep resection and can be managed conservatively with stent placement. Elliot and colleagues (33) report successfully treating two cases of ureteral perforation during endoscopic resection with double-J stent placement. In addition, the theoretic risk of dissemination of malignant cells into the retroperitoneal space has been raised. A case report of extravasation and propagation of tumor cells beyond the collecting system and into the parenchyma following ureteroscopic examination supports this fear (80).

Percutaneous management, another alternative for the renal-sparing management of upper tract urothelial cancer, is more suited for large tumors in the intrarenal collecting system or proximal ureter (Fig. 17.8). Once percutaneous access has been obtained, the tract is dilated to allow placement of a sheath, through which an endoscope with resection loop or biopsy forceps can be used to remove the tumor. Ablation and fulguration with a flexible electrode, rollerball electrode, or laser (Nd:YAG or Ho:YAG) following biopsy of the tumor(s) is useful when disease is extensive or difficult to access (105,110).

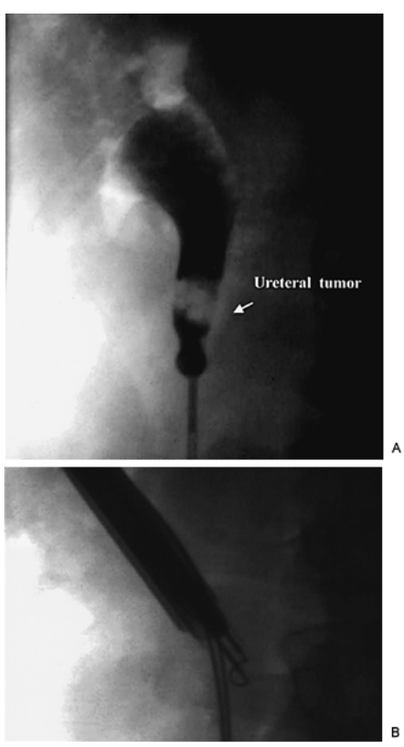

FIGURE 17.8. Percutaneous resection of large proximal ureteral tumor. **A:** Fluoroscopic view of lesion. **B:** Resectoscope in place for resection.

Similar to results obtained for ureteroscopic treatment, percutaneous resection or ablation of urothelial cancer has been most successful for low-grade and low-stage disease. In a series of 61 patients followed for a mean duration of four years, investigators reported 95% overall disease-specific

survival: 100% for pTa lesions and 80% for T_1 lesions (61). Recurrence rates correlate with grade and stage of disease (24,62,77,116). Jarrett and colleagues (62) reported an 18% recurrence rate for grade 1 disease and a 50% recurrence rate for grade 3 disease. They strongly advocated second- and third-look procedures performed approximately 1 week apart to ensure that complete resection had occurred. Similarly, Clark and colleagues (24) reported a 28% recurrence rate for patients with grade 1 or 2 disease and 50% recurrence for grade 3 disease. Patel and colleagues (116) found a 12.5% recurrence rate for T_a disease and 50% for T_{2b} disease. Other reported recurrence rates range from 11% to 45% (61,120). Orihuela and Smith (110) found lower recurrence rates if second-look nephroscopy was performed, if Nd:YAG laser had been used for ablation, and if BCG had been instilled following resection.

Most complications of percutaneous management of upper tract urothelial cancer are similar to those for percutaneous management of stone disease. The most common complications are bleeding and extravasation. In addition to the cancer-specific risk of forcing cells into the systemic circulation as a result of pyelovenous or pyelolymphatic backflow (as in ureteroscopy), a unique concern associated with percutaneous treatment is the risk of tumor cells seeding the nephrostomy tube tract. Reports of seeding of the nephrostomy tract are numerous (24,36,57,139,141). One group advocates iridium wire brachytherapy within the nephrostomy tube tract to prevent recurrences (116). With this technique, this group did not experience seeding in their series of 28 patients. Others suggest the use of single-stage percutaneous access, tract dilation, and tumor resection as methods to reduce the seeding risk (119). Additional suggestions to prevent pyelovenous or pyelolymphatic backflow include keeping the irrigation fluid bag less than 40 cm above the level of the kidney and making sure that there is a loose fit between the working sheath and the nephroscope. Some investigators have gone as far as to suggest use of sterile water as the working irrigant to take advantage of its cytolytic properties; however, this practice may be associated with dilutional hyponatremia. The long-term effect of percutaneous treatment on renal function is not known. Jarrett and colleagues (62) reported two cases of chronic renal insufficiency that developed following percutaneous treatment.

Adjuvant Therapy

Topical Agents

As in the case of superficial bladder cancer, many investigators have explored the use of topical therapy with BCG, mitomycin C, and thiotepa. Drug delivery into the collecting system has occurred in a variety of manners: retrograde installation using ureteral catheters, direct installation through a percutaneous nephrostomy tube, or resection of the ureteral orifice inducing reflux into the collecting system (56,126,142). Although these reports suggest some benefit from these agents, there have not been any randomized trials to unequivocally demonstrate survival benefit due to the rarity of their application for upper tract urothelial tumors.

Herr (56) described creation of a pyelovesicostomy to allow reflux of BCG into the collecting system. The patient remained tumor free at 13 months of follow-up. Orihuela and Smith (110) reported on six patients who received six weekly courses of BCG via nephrostomy tube following percutaneous resection. The BCG was well tolerated and no incidence of sepsis was reported. Although they had a small number of patients, they found a lower recurrence rate with the use of BCG (16.6% versus 80% without BCG). Patel and Fuchs (115) showed that BCG could be instilled in a retrograde fashion via a transvesical single-J ureteral stent. At 1 year of follow-up, 15 of 17 renal units treated were preserved. In addition, there has been report of reflux of BCG through a ureteroileal anastomosis used as a method to keep one patient recurrence free at 1 year of follow-up (126). The direct routes of administration offer more assured contact of BCG with the upper tract tissue.

Several investigators have reported use of mitomycin C. Smith and colleagues (146) reported the treatment of superficial papillary urothelial carcinoma in the distal ureter with mitomycin C. Despite leaving the primary lesions unresected, both patients became tumor free and remained so after more than 2 years of follow-up. Eastham and Huffman (31) reported on the delivery of mitomycin C via percutaneous nephrostomy tube (continuous infusion of 40 mg in 1,000 mL of saline infused continuously at 50 mL hour) or ureteral catheter (5 mg in 20 mL of saline instilled and held for 30 minutes). Five of their seven patients were disease free 1 to 12 months following treatment.

De Kock and Breytenbach (28) reported the use of six weekly courses of topical thiotepa via retrograde ureteral catheter following local excision of a renal pelvis tumor in a solitary kidney. The patient required two 6-week courses to become disease free and subsequently developed thrombocytopenia. Although there was no recurrence of her renal pelvic tumor, with 6.5 years of follow-up, the thrombocytopenia points out a potential risk of thiotepa. One unusual report of intraureteral use of thiotepa involves the use of a subcutaneously placed Ommaya reservoir in the treatment of bilateral primary urothelial carcinoma of the ureter (123). The patient received four courses of thiotepa injected through the reservoir and continued to receive maintenance treatment via a retrograde ureteral catheter following removal of the reservoir. At 8.5 years following his initial treatment, the patient remained recurrence free.

In the absence of comparative studies between BCG, mitomycin, and thiotepa for topical upper tract therapy, at our institution we prefer percutaneous administration of mitomycin for treatment of residual upper tract urothelial

neoplasms or prophylaxis following resection of high-grade disease, in patients who have imperative indications for renal sparing. Our protocol involves six weekly instillations of 30 mg of mitomycin in 60 mL of saline, instilled through a nephrostomy tube continuously for 2 hours at 30 mL hour. The nephrostomy tube is clamped between treatments, minimizing the inconvenience for the patient. Ureteroscopic reevaluation is performed 6 weeks after the last instillation, with repeat endoscopic fulguration or repeat topical therapy (possibly with BCG) in case of disease persistence, and removal of the nephrostomy tube if there is no evidence of disease.

Radiation Therapy

In an attempt to reduce local and regional failure rate, some investigators have explored the use of adjuvant radiotherapy. Cozad and colleagues (26) reported that adjuvant radiation decreased the 5-year local recurrence rate from 25% to 10%. This improvement in local control was also noted by Brookland and Richter (20), who noted an 11% local recurrence rate in patients with high-risk (stage III or grade 3) disease treated with radiation and a 45% local recurrence rate in patients who had not received adjuvant treatment. Although local control was possible, there was no improvement in the recurrence of distant metastasis and in overall survival. Maulard-Durdux and colleagues (88) reported that despite an improvement in local control, metastatic dissemination still occurred in 54% of patients. Ozahin and colleagues (112) also demonstrated this lack of improvement in overall survival in their review of 138 patients.

Chemotherapy

As in the treatment of advanced bladder urothelial cancer, cisplatinum-based chemotherapeutic regimens such as methotrexate, vinblastine, adriamycin, and cisplatinum (MVAC) have been used in both a neoadjuvant and an adjuvant setting (60,79,152). The effectiveness of cisplatinum-based chemotherapy regimens has been similar to that for bladder urothelial cancer. Lerner and colleagues (79), in a study of 28 patients with high-grade and advanced urothelial carcinoma of the upper tract, found a 54% overall response rate [18% complete response (CR) and 36% partial response (PR)] to platinum-based chemotherapy. However, 89% of these patients eventually succumbed to their disease. They suggested that their outcome might have been better if their patients had been able to tolerate a full course of treatment. Owing to renal insufficiency following their nephroureterectomy, all of these patients had required dose reduction. Similarly, Igawa and colleagues (59) found a 52.9% overall response rate for treatment of advanced renal pelvic and urothelial tumors. Although they were able to achieve durable CR, mean time to recurrence for patients with partial response was only 6.4 months.

More recently, investigators have reported success rates similar to that for MVAC using a combination of paclitaxel and carboplatin. Redman and colleagues (128) reported a 51.5% overall response rate (19% CR and 30.6% PR) in phase II trial. Similar results were also seen in a study of 32 patients at the University of Vienna, with a response rate of 71.9% (31.3% CR and 40.6% PR) (124). The toxicities associated with this combination, including myalgias, arthralgias, alopecia, and neutropenia, occur less often than with MVAC (124,128). Despite promising results, the mean time to progression after CR was reported at 7 months and after PR was only 5.9 months (124).

Others have reported additional success with a combination of gemcitabine and cisplatin. Gemcitabine, a cytosine analog, was shown to be active as a single-agent therapy in urothelial cancer (147). In combination with cisplatin, gemcitabine results in an overall response rate ranging from 41% to 52% (69,98,158). Toxicity associated with this combination was mainly hematologic. Median time to progression ranged from 5.5 months to 7.2 months, and median survival ranged from 12.5 to 14.3 months (69,98,158).

Although these new combinations present new therapeutic options in the management of advanced urothelial cancer, the long-term outlook for these patients remains poor.

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18

ADULT LAPAROSCOPIC UROLOGY

Jaime Landman

Elspeth M. McDougall

Indiber S. Gill

Ralph V. Clayman

J. Landman: Department of Surgery, Division of Urology, Washington University Medical Center, Barnes-Jewish Hospital, St. Louis, MO 63110.

E.M. McDougall: Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN 37232.

I.S. Gill: Section of Laparoscopic and Minimally Invasive Surgery, Cleveland Clinic Urological Institute, Cleveland Clinic Foundation, Cleveland, OH 44195.

R.V. Clayman: Division of Minimally Invasive Surgery, Department of Surgery and Radiology, Washington University, Barnes-Jewish Hospital, St. Louis, MO 63110.

Contents

HISTORY OF LAPAROSCOPY

Part of "18 - ADULT LAPAROSCOPIC UROLOGY "

Urologists have recently embraced laparoscopic surgery as another extension of their endourologic skills. Initially, this would appear to be a new era in urologic surgery. However, careful evaluation illustrates the extent to which we are the products of our past. The curiosity and adventurous thinking of past clinicians established a groundwork on which innovative modern surgeons have developed the potential of many basic concepts of laparoscopy. The first documented attempt to visualize a living human internal organ was by Philipp Bozzini in Frankfurt in 1806 (Table 18.1). He inspected the urethra with a double-lumen cannula; one lumen transmitted light from a candle and the other was for visualization (40). In 1877, Max Nitze in Germany first utilized a lens system for cystoscopy (147). This enabled him to view a magnified image of the urethra and bladder. Nitze, in collaboration with Joseph Leiter, refined his instrument to produce a practical endoscope, which consisted of a metal catheter with light provided from heated platinum wire loops sheathed in a goose quill and cooled by a continuous flow of water (147). Thomas Edison's invention of the incandescent light bulb in the United States in 1880 generated a new era of endoscopes (21).

1806	Bozzini uses a tube and a candle as a light source ("Lichtleiter") to visualize the human urethra.
1877	Nitze creates the prototype for the modern cystoscope.
1880	Edison invents the incandescent bulb.
1901	Kelling inserts a cystoscope into the inflated abdomen of a dog and describes "celioscopy."
1910	Jacobaeus performs laparoscopy in patients with ascites.
1929	Kalk introduces the foroblique (35-degree) lens and advocates a separate pneumoperitoneum needle and "dual trocar" technique.
1938	Veress develops a special needle to induce pneumothoraces to treat TB.
1952	Forrestier, Gladu, and Valmiere develop an endoscope with a proximal light source and a quartz rod system to transmit the light to the distal end of the scope.
1970s	Semm develops an automated insufflation device that monitors gas flow and intraabdominal pressure, and numerous instruments still used in modern laparoscopy.
1976	Cortesi uses the laparoscope for the first time in urology to localize a cryptorchid testis.
1987	Mouret performs the first laparoscopic cholecystectomy in a human.
1988	Mouret is denounced at Lycee Chirurgical de Francais.
1988	Dubois and Perissat in Europe and Reddick in the United States popularize laparoscopic cholecystectomy.
1989	Mouret is reinstated and given the Croix de Chirque, the highest honor of Lycee Chirurgical.
1990	Clayman and associates perform the first laparoscopic nephrectomy.

TABLE 18.1. HIGHLIGHTS IN THE HISTORY OF LAPAROSCOPIC SURGERY

The birth of laparoscopy can be attributed to Georg Kelling, a surgeon of Dresden, Germany. In 1901, he described "coelioscopy," a technique in which he filled the abdomen of a living dog with air and inserted a Nitze cystoscope to inspect the viscera. In the same year, D.O. Ott, a Russian gynecologist, published his "ventroscopic" technique in which he used a head mirror as a light source and inserted a speculum through a small abdominal or cul-de-sac incision to view the abdominal viscera (318).

Further work by H.C. Jacobaeus in Stockholm, Sweden, involved insertion of a trocar to create pneumoperitoneum in humans, and then insertion of a cystoscope to inspect the peritoneal or pleural space. In 1910, he reported on a series of patients in whom “laparoscopy” was performed, and he commented on cirrhotic changes in the liver, metastatic cancer, and tuberculous peritonitis (189). Bertram Bernheim, in 1911, performed the first diagnostic laparoscopy in the United States when he used a proctoscope and an ordinary light to examine the abdominal cavity (26). Subsequent to the pioneering work of these laparoscopists, new instruments and techniques were developed. Nordentoft used the Trendelenburg position to more easily view the pelvis of a cadaver (157). The sharp pyramidal-pointed trocar was developed by Orndoff in 1920 to facilitate trocar insertion (147).

The introduction of the oblique-viewing (35-degree) lens system by a German, H. Kalk, in 1929 allowed laparoscopy to become widely accepted as a diagnostic tool (205). Kalk also advocated the use of the pneumoperitoneum needle and the dual trocar to allow simultaneous visualization of and passage of instruments into the abdomen. He reported on more than 100 cases of laparoscopy using this technique and published the first color atlas of laparoscopy in 1935 (445). Ruddock, in the United States in 1934, performed peritoneoscopy with a device having integrated biopsy forceps (361). In 1938, Janos Veress of Hungary developed a special needle for inducing pneumothoraces to treat pre–antibiotic-era tuberculosis (429). This needle had a spring-loaded central blunt tip that protected the lung from injury after the needle passed through the pleura and currently is often used for the creation of pneumoperitoneum.

A major advance in the technology of laparoscopy occurred in France in 1952 when Forrestier, Gladu, and Valmiere used a quartz rod to efficiently transmit a proximal light source to the distal end of the endoscope (15). At the same time, in England, Hopkins and Kapany introduced early fiberoptic technology to endoscopy (157). These developments resulted in a wider acceptance of laparoscopy, particularly for gynecologic diagnostic purposes.

The concept of monitoring intraabdominal pressure during pneumoperitoneum was promoted initially by Raoul Palmer of Paris, as early as 1947 (320). Professor Kurt Semm of Kiel, Germany, a gynecologist and engineer, developed an automatic insufflation device to monitor intraabdominal pressure and gas flow (147). He was one of the innovative researchers and clinicians in the field of laparoscopy. Many of the instruments and techniques devised by Semm are still used today, including thermocoagulation during laparoscopic procedures, hooked scissors, tissue morcellators, the endoloop suture applicator, an irrigation and aspiration device, techniques for intracorporeal and extracorporeal knot tying, needle-holders, clip-appliers, atraumatic forceps, microscissors, and the “pelvic trainer,” designed to teach surgeons laparoscopic techniques (378). Semm expanded the indications for laparoscopy by advocating laparoscopic lysis of adhesions, bowel suturing, tumor biopsy, and incidental appendectomy.

The first case report of laparoscopy in the urologic literature appeared in 1976 when Cortesi and associates (66) used the laparoscope to successfully localize bilateral abdominal testicles in a cryptorchid adult patient. However, surgeons were generally slow to recognize laparoscopy as a valuable diagnostic tool, considering it to be a “blind” procedure, providing incomplete examination of the abdominal cavity. Laparoscopy lost further ground when computed tomography (CT) was developed for clinical use and ultrasonographically directed biopsies became generally available. Despite this turn of events, many pioneering surgeons continued to enthusiastically popularize laparoscopy as a valuable diagnostic and therapeutic modality with significant clinical benefits (135,136,159,180,320).

Therapeutic laparoscopy necessarily lagged behind diagnostic laparoscopy (137). Frimdberg, in Europe in 1978, performed laparoscopic cholecystectomy in pigs (105). In 1987, Philippe Mouret in Lyon, France, performed the first

laparoscopic cholecystectomy in a human (328). Interestingly, Mouret was denounced the following year at the Lycee Chirurgical de Francais for performing what was considered a surgical procedure with unwarranted risk for the patient. However, during 1988, Dubois and Perissat in Europe and Reddick in the United States popularized laparoscopic cholecystectomy (86,328,352). Within a matter of months, it became apparent that this minimally invasive approach to the gallbladder was going to revolutionize the practice of general surgery. Laparoscopic cholecystectomy has since become the standard of therapy for routine gallbladder removal. In 1989, Mouret not only was vindicated by reinstatement, but was awarded the Croix de Chirurgue, the highest honor of the Lycee Chirurgical.

Presently, laparoscopic surgery has pervaded not only gynecology and general surgery, but also thoracic surgery. The gynecologic procedures commonly performed are myriad: hysterectomy, ovariectomy, tubal ligation, and, more recently, tubal reconstruction. In general surgery, the three most commonly performed open procedures are all now in the realm of laparoscopy: herniorrhaphy, cholecystectomy, and appendectomy. In addition, other procedures are becoming more commonplace: adhesiolysis, bowel resection, choledocholithotomy, posterior truncal vagotomy, anterior seromyotomy, and Nissen fundoplication (71,81,208,330,377). With regard to thoracic surgery, the laparoscope has also made inroads in the treatment of emphysematous blebs and reflex sympathetic dystrophy and is also being used to perform lung biopsy and to drain loculated empyema. Similarly in cardiac surgery, single-vessel coronary artery bypass is now just beginning to be performed laparoscopically; the entire procedure is done in the closed chest on a beating heart.

The use of laparoscopic surgery in urology paralleled, to a large extent, the aforementioned developments in general surgery. Although Cortesi reported the first urologic laparoscopy to localize cryptorchid testes in adults in 1976, the initial pediatric laparoscopic localization of an undescended testicle was reported by Silber in 1980 (390). Since then, more than 350 laparoscopic procedures to identify an undescended testicle have been reported in the literature (260). The laparoscopic approach is more rapid, less morbid, and of equal accuracy compared with open surgical exploration for an undescended testicle. Over the past 15 years, laparoscopy has supplanted open surgical approaches to the localization of undescended testicles, management of intersex disorders, and the biopsy of pelvic gonadal organs.

However, it was not until the late 1980s, with the advent of interest in pelvic lymph node dissection, that laparoscopy made its entry into mainstream urology. Gynecologists were the first to advocate laparoscopic lymphadenectomy for staging of pelvic cancers (353). The first staging laparoscopic pelvic lymphadenectomy for prostate cancer was attempted by Hald in 1980. However, he found the extraperitoneal approach to be limited and unsatisfactory (150). It was the clinical work of Schuessler and Vancaillie in 1989 that demonstrated the feasibility of completing the staging of patients who had carcinoma of the prostate with the minimally invasive technique of transperitoneal, laparoscopic obturator node dissection (375). The reports of this work initiated a new era in urologic surgery, and soon laparoscopy was applied to a variety of urologic procedures previously approachable only by a flank or an abdominal incision.

The development of a surgical entrapment sack and a high-speed, 10-mm electrical tissue morcellator was integral to the concept of removing large, solid tissue specimens via a laparoscopic approach. In 1990, Clayman and colleagues (62) used this technology to perform the first laparoscopic nephrectomy. Since that time, unique laparoscopic techniques have been used in several medical centers to accomplish a variety of other urologic procedures, including nephroureterectomy, bladder neck suspension, pelvic lymphocelectomy, ureterolysis, and adrenalectomy (5,6,209,215,255,407). Anecdotal reports have included cystectomy, renal cyst decortication, renal exploration, partial nephrectomy, ureteroureterostomy, nephropexy, prostatectomy, and ileal conduit formation (225,265,300,301,322,372,426,441). Many recent applications of laparoscopy to urologic surgery have demonstrated the feasibility of these techniques to complete the intended diagnostic or therapeutic objective and provide the patient with a more comfortable and shorter recuperative period compared with more traditional open surgery. Continued laboratory and clinical research will expand the field of laparoscopic urologic surgery for both therapeutic and reconstructive techniques.

GENERAL LAPAROSCOPIC TECHNIQUE

Part of "18 - ADULT LAPAROSCOPIC UROLOGY "

Laparoscopy has been applied recently to myriad surgical procedures for the urologic patient. Despite this increasing diversity, there exists a set of basic concepts and principles associated with laparoscopic techniques in general.

Access with Gas

The basic principle of laparoscopy is to maximally distend the potential space of the peritoneal cavity, facilitate visualization of the viscera, and insert various instruments to complete the surgical procedure. Various gases have been used to create the working environment of the pneumoperitoneum, including filtered room air, nitrous oxide, carbon dioxide, argon, and helium.

Types of Insufflants

Nitrous oxide will support combustion if present in a high concentration (98). Therefore this gas is not acceptable as an insufflant for modern laparoscopy because of the increased use of laser and electrocautery techniques in most surgical

laparoscopic procedures. Indeed, nitrous oxide should not even be used as an anesthetic during any therapeutic laparoscopic procedures. It has been shown that during extended laparoscopic surgery, nitrous oxide may diffuse from the bowel into the peritoneal cavity in concentrations that could support combustion of bowel gas (298). There has been a report of a case of colonic explosion during colonic diathermy in a patient with rectal cancer (9). Thus it is advisable to avoid the use of nitrous oxide even as an anesthetic agent during long laparoscopic procedures.

Carbon dioxide is readily available in most operating rooms and is relatively inexpensive; thus it has become the most commonly used insufflant. Carbon dioxide absorption into the blood during laparoscopic surgery may lead to respiratory acidosis, increased ventilation requirements, and potentially serious cardiovascular compromise. In the clinical setting, the increased CO_2 load is not a problem if the patient is managed with controlled ventilation. As a result, most patients undergoing laparoscopic urologic procedures are managed with cuffed endotracheal general anesthesia and controlled ventilation. Mullet and colleagues (290) showed that CO_2 diffusion into the body, as measured by end-tidal CO_2, increases gradually and then plateaus approximately 10 minutes after insufflation; this observation is not influenced by the duration of intraperitoneal insufflation. During extraperitoneal pelvioscopy, CO_2 diffusion into the body is more marked and does not tend to plateau with the duration of insufflation. The anesthetic records of 62 patients undergoing laparoscopic renal surgery at Washington University were evaluated for hourly estimates of CO_2 expiration (Vco_2) during the preinsufflation period and the first 4 hours of insufflation (446). Vco_2 increased with time, although the increase over the previous interval was less pronounced every hour after the first. Most of the increase occurred during the first 2 hours of insufflation. Multifactorial analysis revealed that the extraperitoneal, as compared with the transperitoneal, approach and the presence of subcutaneous emphysema were strongly and independently associated with a greater increase in Vco_2. Pneumothorax and pneumomediastinum were significantly more common during extraperitoneal (37%) than transperitoneal (3%) laparoscopy. There were five postoperative cardiopulmonary complications, none of which was related to hypercapnia. Thus CO_2 absorption during laparoscopic renal surgery, which is greater than occurs during pelvic laparoscopy, was highest in patients approached through an extraperitoneal route and in those with subcutaneous emphysema. Nonetheless, with aggressive intraoperative mechanical ventilation, no sequelae of hypercapnia were noted in this series. Also, it must be noted that if one uses a cuffed Hasson cannula, the risk of hypercarbia with the retroperitoneal approaches appears to be eliminated. This type of cannula seals the port site, thereby effectively eliminating subcutaneous emphysema and the associated problems of hypercarbia (303).

Helium is biologically and chemically inert and therefore has been proposed as an alternative insufflating agent. Leighton and colleagues (234), in animal studies, showed that helium insufflated intraperitoneally did not cause hypercarbia, aciduria, or pulmonary hypertension when using the same insufflation conditions as for CO_2. These results support the concept that the transperitoneal absorption of CO_2, not increased dead space, is responsible for the respiratory acidosis observed during pneumoperitoneum.

Argon is an inexpensive inert gas that also has been used for intraabdominal insufflation. Animal studies at Washington University School of Medicine demonstrated that an argon pneumoperitoneum of 20-mm Hg pressure had the same hemodynamic and renal effects as 20 mm Hg of CO_2 (271). Argon is not absorbed as easily as CO_2; thus the degree of respiratory acidosis is less when using this agent as an insufflant. However, any of the inert gases, which are slow to reabsorb, may result in prolonged duration of subcutaneous emphysema that may occur during laparoscopy and also put the patient at a higher risk for problems should a gas embolus develop. There has been one report in the literature of an argon gas embolism during laparoscopic cholecystectomy when an argon beam coagulator was used for hemostasis of the liver bed (249). Gas embolism can occur whenever a large amount of any gas is administered directly into the vascular system; however, the poor solubility of the inert gases compared with CO_2 exacerbates the potential problems due to a gas embolism.

Method of Introduction

The pneumoperitoneum can be established using either a closed or an open technique. The Veress needle is used to penetrate the abdominal wall and deliver CO_2 gas into the abdomen for the closed technique of insufflation. This 14-gauge needle may be 12 or 15 cm in length and is either disposable or nondisposable. The 15-cm needle is useful in the very obese patient to facilitate successful access to the peritoneal cavity. The reusable needle is made entirely of metal and tends to be heavier than the disposable needle, which has a plastic hub; the needle point may become dull with repeated use and therefore must be sharpened regularly. Also, the reusable needle must be disassembled and all the parts cleaned after each use.

The Veress needle consists of an outer 14-gauge sheath with a sharp beveled tip and an inner spring-loaded, blunt tip. The blunt tip retracts back inside the outer sheath on meeting resistance of the fascia or peritoneum. This presents the sharp beveled tip to the fascia and peritoneum, allowing penetration (Fig. 18.1A). The inner blunt tip springs forward immediately on entry into the abdominal cavity and release of resistance (Fig. 18.1B). The hub of the Veress needle may have an indicator to show when the inner blunt tip is retracted or presented. The hub also has a Luer-Lok connector for attaching the aspirating-irrigating syringe of

saline and the CO_2 insufflating tubing. There may be a stopcock on this side arm to interrupt the flow of CO_2 into the abdomen.

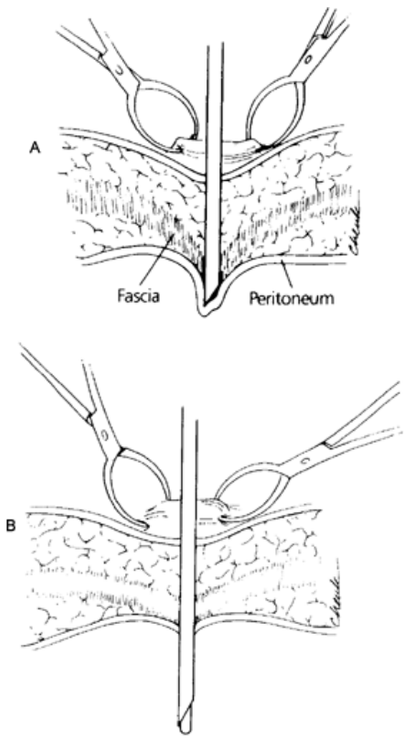

FIGURE 18.1. A: The Veress needle has a spring-loaded, blunt-tip obturator that is pushed back inside the sheath to expose the sharp tip of the sheath during penetration of the fascia and peritoneum. **B:** Immediately upon passing through the fascia and peritoneum, the inner blunt tip springs forward to protect the intraabdominal structures from the sharp needle tip. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

The Veress needle is most commonly inserted at the umbilicus because the peritoneum is closer to the skin at this point on the abdominal wall (Fig. 18.2). The properitoneal layer of fatty tissue, which lies between the linea alba and the peritoneum, is thinnest at the level of the umbilicus. The extremely obese or very thin patient may require special consideration during Veress needle and initial port insertion. Hurd and associates (181) studied the relationship of the umbilicus to the aortic bifurcation using magnetic resonance imaging (MRI) and CT. They assessed the effect obesity has on this relationship. In nonobese patients weighing less than 160 pounds (73 kg), the umbilicus is a mean distance of 0.4 cm caudal to the aortic bifurcation, with a skin-to-peritoneum distance of 2 cm. In obese patients weighing between 160 and 200 pounds (73 and 91 kg), the umbilicus is 2.4 cm caudal to the aortic bifurcation, with a skin-to-peritoneum distance of 2 cm. In obese patients weighing more than 200 pounds (91 kg), the umbilicus is located 2.9 cm caudal to the bifurcation of the aorta, with a skin-to-peritoneum median distance of 12 cm. The authors concluded that Veress needle insertion in the nonobese patient should be at a 45-degree angle from the horizontal (Fig. 18.3) to reduce the risk of major abdominal vascular

injury and properitoneal placement (182). Because of the increased distance to the peritoneum in the obese patient and the caudal displacement of the umbilicus in relationship to the aortic bifurcation, the Veress needle should be inserted at a 90-degree angle from horizontal to achieve intraperitoneal placement. In patients who have had previous abdominal surgery, alternative sites may be used for the Veress needle insertion to avoid adhesions.

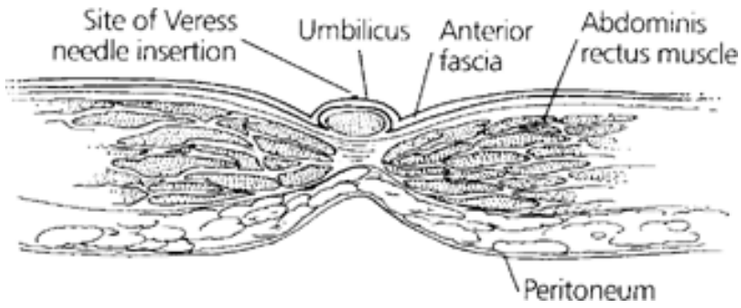

FIGURE 18.2. The properitoneal layer of fatty tissues is thinnest at the umbilicus, providing this site with the shortest distance between the skin and peritoneum. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

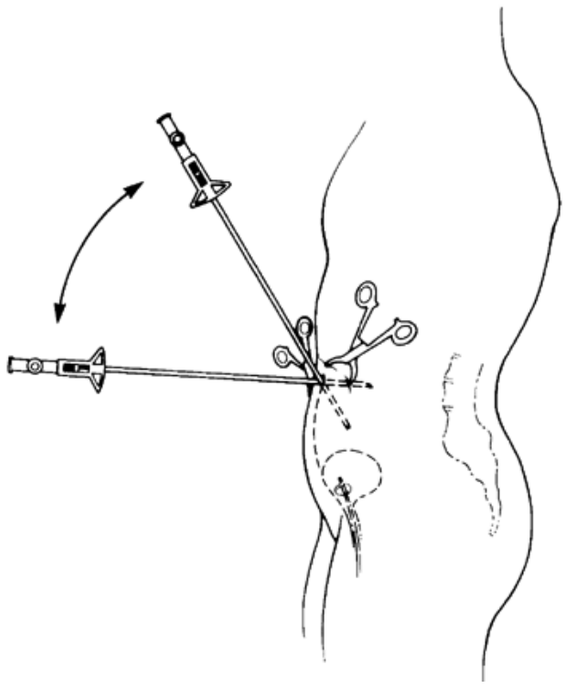

FIGURE 18.3. In the nonobese patient, the Veress needle should be inserted at a 45-degree angle from the horizontal to minimize the risk of injury to the retroperitoneal great vessels. In the obese patient, the increased fatty tissue space between the skin and the peritoneum dictates a Veress needle insertion at a 90-degree angle to the umbilicus to achieve intraperitoneal placement of the needle tip. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

A small skin incision is made with a no. 12 hook blade at the supraumbilical or infraumbilical crease. A sharp towel clip is placed on the skin edges, on either side of the incision, to stabilize the skin during needle insertion. The Veress needle is held like a dart in the dominant hand and passed into the wound. As the needle passes through the anterior abdominal fascia and then the peritoneum, resistance will be felt and also observed due to movement at the spring-loaded hub. A click may be heard as the blunt trocar springs forward into the peritoneal cavity.

The intraabdominal positioning of the Veress needle is confirmed by performing four test maneuvers. First, a 10-mL syringe with 5 mL of saline is attached to the hub of the needle. The syringe is aspirated to determine that no blood or bowel contents enter the barrel of the syringe. Second, the saline is injected through the needle; it should inject easily without any resistance. In the third step, the syringe is used to reaspirate the needle. With a true intraabdominal positioning of the needle, there should be no return of fluid into the syringe. As the syringe is removed from the needle, the small amount of saline remaining in the hub should flow easily into the abdomen. The final test is to advance the needle 1 to 2 cm into the abdomen; neither the tip indicator nor the hub should show any indication of encountering resistance. Only after all of these tests confirm satisfactory intraperitoneal positioning of the Veress needle should CO_2 insufflation begin.

The sterile insufflation tubing, which has been connected to the insufflator, is placed on the Luer-Lok of the Veress needle hub as the needle is held steady by the surgeon. CO_2 insufflation is commenced with a flow rate of 2 L minute or less, and the intraabdominal pressure limit is set at 10 mm Hg. The initial intraabdominal pressure should be less than 10 mm Hg. If the intraabdominal pressure is greater than 10 mm Hg, the needle should be rotated or withdrawn slightly. If the pressure remains high, the insufflation should be terminated and the Veress needle removed and reinserted; alternatively, an open technique for establishing the pneumoperitoneum can be used. The intraabdominal pressure usually remains less than or equal to 10 mm Hg until 500 to 1,000 mL of CO_2 have been insufflated. After 500 mL of gas is instilled into the peritoneal cavity, the abdomen will be slightly and symmetrically distended and tympanic on percussion. The insufflation flow rate can then be maximized and the desired pressure limit set for the primary trocar insertion.

Retroperitoneal Veress needle insufflation can also be performed in those patients in whom a retroperitoneoscopic approach is planned. The procedure is commenced by inserting a Veress needle through either the inferior posterior lumbar triangle (Petit's) in the posterior axillary line just above the iliac crest or the superior posterior lumbar triangle, just posterior to the tip of the twelfth rib. The retroperitoneum is inflated with approximately 2 to 3 L of CO_2, and then a 10- or 12-mm port is inserted at this site. Visualization of the retroperitoneal space with the laparoscope and blunt dissection with this instrument creates a small space within the retroperitoneum that will allow introduction of the dilating balloon catheter.

The dilating balloon catheter is created by cutting the middle finger off of a size 8 Triflex sterile latex surgeon's glove (Baxter Health Care Corp., Valencia, California). The finger of the glove is placed over the tip of a 16-Fr red rubber catheter and secured in place with two 0-silk ligatures so that the openings in the tip of the catheter lie within the finger of the glove. The balloon catheter is back-loaded through a 30-Fr Amplatz sheath until the balloon is retracted just inside the sheath. The assembled unit is inserted through the 10- or 12-mm primary trocar until the tip of the Amplatz sheath lies just at the port opening. The balloon catheter is advanced through the Amplatz sheath 3 to 4 cm into the perirenal space (outside Gerota's fascia), and then the balloon is filled with 1 L of normal saline. This provides an adequate working space and minimizes the risk of balloon rupture from overdistention. The fluid is aspirated from the balloon catheter, which is then withdrawn into the Amplatz sheath, and the balloon and Amplatz sheath are removed from the port. The pneumoperitoneum is established to a pressure of 10 to 15 mm Hg and the laparoscope is inserted.

For the neophyte laparoscopic surgeon, the open technique for obtaining a pneumoperitoneum is recommended. Indeed, some surgeons advocate this approach in all patients undergoing laparoscopic surgery to minimize the risk of vascular, bowel, or omental injury (204). One study has shown that the open technique for placement of the primary port, including establishment of the pneumoperitoneum, is faster, safer, and more cost-effective compared with the closed technique (16). However, this study used the closed technique in the initial 150 patients, changing to the open technique for the subsequent 150 patients (41). It is important to realize that complications can occur, albeit rarely, with the open technique for pneumoperitoneum (363).

The open technique should be used whenever intraperitoneal positioning of the Veress needle cannot be confirmed with confidence. Similarly, patients with multiple previous surgical procedures on the abdomen may have significant adhesions, obviating blind access to the peritoneal cavity.

The open technique of accessing the abdominal cavity involves a small (2- to 3-cm) laparotomy for insertion of a blunt-tip, Hasson cannula. The skin incision is usually made at or just below the umbilicus, unless there are preexisting abdominal scars, in which case a point lateral to the abdominus rectus muscle, farthest from the incisions, is

used. Through a transverse incision, the subcutaneous tissue is dissected and the anterior abdominal fascia is exposed and incised (2 cm) (Fig. 18.4A). The properitoneal fat is then bluntly swept off the peritoneum. The peritoneum is grasped, using small hemostats, and elevated (Fig. 18.4B). Scissors are used to incise the peritoneum to admit the surgeon's index finger. Satisfactory entry into the abdominal cavity is confirmed by digital palpation or visual inspection. A 0 Vicryl or silk suture is placed on either side of the fascial incision.

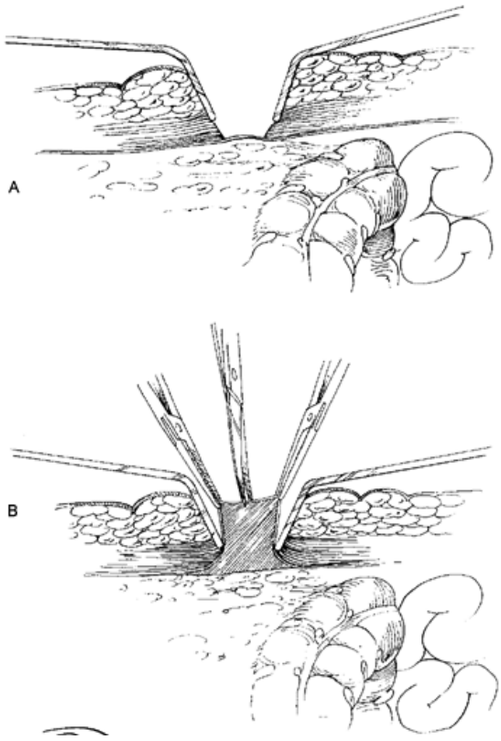

FIGURE 18.4. A: The open technique of port placement requires incision of the skin and fascia to accommodate the planned port and exposure of the peritoneum by bluntly retracting the peritoneal fat. **B:** The peritoneum is grasped and elevated by two small hemostats, and scissors incise the peritoneum to admit the surgeon's finger and then the blunt-tip port. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

The Hasson-type cannula used in the open approach consists of three components: a cone-shaped sleeve, a metal sheath with a trumpet valve to which two struts are affixed for tying the suture, and a blunt-tipped obturator. The metal sheath can be moved up and down through the cone-shaped sleeve to allow proper positioning before tightly affixing the sleeve to the sheath.

The blunt tip of the obturator within the Hasson cannula is inserted through the peritoneal incision, and the cone-shaped sleeve is slid down snugly against the fascia (Fig. 18.5). The two fascial sutures are secured to the struts on the sheath of the cannula, after the sleeve is secured to the sheath with the set screw. The fascial sutures fix the cannula in place. Sterile insufflation tubing is connected to the cannula and the blunt-tipped obturator is removed. The CO_2 insufflator is set at a high flow rate and the intraabdominal pressure is raised to 15 mm Hg. This port may now receive the laparoscope.

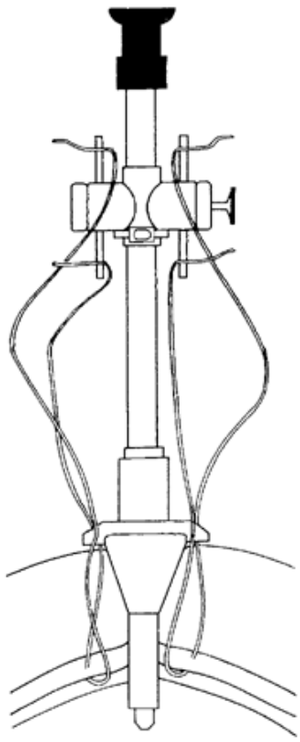

FIGURE 18.5. The blunt tip of the Hasson cannula is inserted through the peritoneotomy, and the cone-shaped sleeve is slid down snugly against the fascia. Two preplaced fascial sutures are secured to the struts on the sheath to hold the port in place. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

An open insertion can also be performed for retroperitoneoscopy. The Hasson cannula is usually placed at the superior posterior lumbar triangle. A 1.5-cm skin incision is made to accommodate the appropriate size of Hasson cannula chosen. A Kelly forceps is used to spread the subcutaneous fatty tissue and expose the fascia overlying the musculature. A 1.5-cm incision is made through the fascia with a no. 12 hook blade. The Kelly forceps are then used to spread the muscle layers into the retroperitoneal space. Next, blunt finger dissection can be performed confirming the retroperitoneal positioning of this incision; the surface of the psoas

muscle should be easily palpated with the tip of the surgeon's finger. The balloon catheter, back-loaded through a 30-Fr Amplatz sheath, can then be delivered directly into the retroperitoneal space. The Amplatz sheath is withdrawn, leaving the balloon catheter in position. The balloon is filled with 1 L of normal saline creating the retroperitoneal working space. The balloon is aspirated of the fluid and withdrawn. Alternatively, extensive blunt finger dissection of the retroperitoneal space can be performed in smaller patients in lieu of using the balloon.

The Hasson cannula is now positioned. Stay sutures placed on the fascia are used to secure the Hasson cannula in place. Alternatively, a Hasson with a balloon retention mechanism and an outer soft foam cuff device (Origin Medsystems, Inc., Menlo Park, California) can be used; with this device, no sutures need to be placed and the chances of subcutaneous emphysema appear to be decreased. The pneumoretroperitoneum is established to a pressure of 10 to 15 mm Hg.

Insufflator

The insufflator allows the laparoscopist to create and maintain the pneumoperitoneum. It consists of a valve mechanism, which can be adjusted and monitored, to allow the flow of pressurized gas from the tank into the patient's abdomen. The insufflator unit should consist of gauges that will (a) indicate the rate of flow (liters per minute) of CO_2 from the insufflator; (b) constantly display, on an analog or digital gauge, abdominal pressure (millimeters of mercury); and (c) indicate the total volume of CO_2 (in liters) that has been instilled into the abdomen. A separate indicator measures the line pressure of the gas tank, providing the surgeon with information regarding the amount of CO_2 remaining in the gas tank. The CO_2 is transported from the insufflator to the patient by flexible, inert tubing. The tubing may have an incorporated filter and a Luer-Lok fitting end to snugly attach to the Luer-Lok of the Veress needle or the side arm of one of the laparoscopic ports.

The CO_2 flow rate is adjustable to between 0 and 10 L per minute. A low flow rate of 1 to 2 L per minute is generally used at commencement of the insufflation process. After satisfactory instillation of 500 to 1,000 mL of CO_2, the flow rate is increased to a medium or high flow rate (6 to 10 L per minute) for the duration of the procedure. The insufflator should be placed just below the surgeon's monitor so that a continuous display of intraabdominal pressure is clearly visible to the surgeon throughout the operative procedure.

The insufflator can be preset for a specific intraabdominal pressure so that the flow of CO_2 gas will cease automatically if the preset pressure is exceeded and an alarm will sound to draw attention to the elevated pneumoperitoneum pressure. Intraabdominal pressures greater than 15 mm Hg are associated with decreased venous return due to vena caval compression, impaired ventilation as a result of pressure on the diaphragm, increased risk of CO_2 absorption causing systemic acidosis, and decreased urine output (269). For adult laparoscopic procedures, the intraabdominal pressure set point should be 10 to 15 mm Hg.

The insufflator should be tested for satisfactory functioning before each laparoscopic procedure. An additional reserve of CO_2 should always be available in the operating room.

Clinical studies at Washington University have shown that the volume of CO_2 insufflated and the insufflation pressure of the pneumoperitoneum during laparoscopy are directly related. However, this volume and pressure relationship is completely independent of patient weight, height, and body mass index (a measure of obesity) (267). Increasing the intraabdominal pressure from 15 to 30 mm Hg increases the volume of CO_2 insufflated by 50%. However, in animal studies, when the pneumoperitoneum pressure is compared with the estimated actual intraabdominal volume, the intraabdominal volume increases by only 5% to 6% when the intraabdominal pressure is increased from 15 to 30 mm Hg. These results suggest that increasing the pneumoperitoneum to 30 mm Hg does not significantly increase the actual intraabdominal volume, but the increased pressure may effect greater compression of the intraperitoneal viscera and put the peritoneum under more tension. Therefore increasing the intraabdominal pressure to 25 to 30 mm Hg for the primary port placement may facilitate this step of laparoscopy and minimize potential complications. Clinical studies at Washington University have shown that elevating the pneumoperitoneum pressure to 30 mm Hg for the primary port placement has no deleterious effect on the heart rate, blood pressure, cardiac output, or end-tidal CO_2 (284). Following placement of the initial port, which usually takes less than 10 minutes, the pneumoperitoneum is reduced to 15 mm Hg or less for the duration of the procedure.

Access Without Gas

Increased intraabdominal pressure is associated with significant changes in systemic vascular resistance, blood pressure, and cardiac return (207,235). Insufflation of gas into the peritoneal cavity results in an increase in intraabdominal pressure and vena caval compression with subsequent reduction in venous return to the heart. Insufflation to pneumoperitoneum pressures of 15 to 20 mm Hg is generally well tolerated; however, increases greater than 20 mm Hg often decrease cardiac output and arterial blood pressure.

The Trendelenburg position causes the weight of the abdominal contents to rest on the diaphragm. Insufflation of the abdomen exerts an additional force against the diaphragm. Together these factors restrict lung expansion and decrease pulmonary compliance, resulting in ventilation-perfusion mismatching (376). Absorption of insufflated

CO_2 into the vascular system combined with the ventilation-perfusion mismatching leads to significant hypercarbia during laparoscopic procedures (287). General anesthesia with controlled ventilation and close monitoring is able to minimize these effects (8).

Intraperitoneal pressures of 10 mm Hg or greater are associated with decreased renal vein flow and a concomitant decrease in urine output (269). Release of the pneumoperitoneum does result in a return of the renal vein flow and the urine output to preinsufflation values when the prolonged pneumoperitoneum has been at 10-mm Hg pressure. However, after prolonged pneumoperitoneum pressure of 15 or 20 mm Hg, the renal vein flow does not return to preinsufflation levels for up to 2 hours after desufflation.

Alterations in renal vein flow and urine output are seen also with insufflation of CO_2 into the retroperitoneum at a pressure of 20 mm Hg. Animal studies have demonstrated a significant increase in the end-tidal CO_2 following retroperitoneal insufflation. Accordingly, an increased ventilation rate was required to maintain the end-tidal CO_2 between 30 and 40 mm Hg. At necropsy in these study animals, diffuse bilateral distribution of gas throughout the retroperitoneum was noted, although the insufflation was performed through one port on one side of the retroperitoneum.

Wakizaka and colleagues (430) studied the effects of CO_2 insufflation during laparoscopic cholecystectomy on arterial blood gas analysis and urine output. Both the increase in $Paco_2$ and the decrease in pH was larger in the group of patients undergoing laparoscopy at an intraabdominal pressure of 15 cm H_2O, as compared with patients operated at an intraabdominal pressure of 10 mm Hg. At a pneumoperitoneum of 15 cm H_2O, the increase in $Paco_2$ was significantly higher if the operative time was more than 60 minutes, compared with patients with an operative time less than 60 minutes. This change in $Paco_2$ with respect to the operative time was not noted when the intraabdominal pressure was maintained at 10 cm H_2O. Also, obese patients (obesity index greater than 120) developed significantly higher levels of $Paco_2$ during CO_2 insufflation, compared with patients who were not obese.

In an attempt to avoid these complications of pneumoperitoneum, the Laparolift device (Origin Medsystems, Inc., Menlo Park, California) has been developed (299). The abdomen is accessed in a manner similar to the open technique. After the skin, fascia, and peritoneum are incised, a double-bladed lift device is inserted through the peritoneotomy with the blades closed. Once the blades are within the peritoneal cavity and resting against the undersurface of the anterior abdominal wall, they are opened to their maximum angle of 45 degrees. A hydraulic L-arm is secured to the operating table edge and directed over the patient. After endoscopically the positioning of the device's blunt blades are satisfactorily confirmed under the anterior abdominal wall, the lift device is connected to the hydraulic arm. The hydraulic arm then can be raised mechanically to apply between 0 and 15 kg of force on the abdominal wall. Animal studies at Washington University on the effect of pneumoperitoneum on renal function included evaluation of the Laparolift (269). As expected, unlike with a CO_2 pneumoperitoneum, the Laparolift did not have an associated increase in end-tidal CO_2 levels during its use. There was no associated decrease in urine output when applying the Laparolift at forces of 5, 10, or 15 kg. These devices have been used successfully to perform laparoscopic cholecystectomy and pelvic procedures (17,160). However, they are somewhat limiting during procedures, such as laparoscopic nephrectomy, in which the laparoscope and instruments are moved to different port sites during the operative procedure. The hydraulic arm positioned over the patient may limit easy access to some of the ports.

Other mechanical devices have been developed to elevate the anterior abdominal wall, thus creating an intraabdominal space for performing laparoscopic procedures. One of the original concepts used for elevating the abdominal wall was described by Kitano and colleagues (221a). After first obtaining a standard CO_2 pneumoperitoneum, they used a U-shaped trocar to traverse the peritoneal cavity and travel around the falciform ligament; the trocar then was lifted by a winch and framework located above the patient's anterior chest wall. Other groups have used long surgical wires placed in the subcutaneous tissue of the abdomen, or large-caliber suture material passed through the abdominal wall, to winch the abdominal wall anteriorly for exposure (17,160,293). The limited current clinical application of these devices suggests that they may be less than ideal for most laparoscopic surgical procedures.

Transperitoneal Approach: Pneumoperitoneum

Placement of the Primary Port

In the open technique, the primary port (Hasson cannula) is placed first, followed by establishment of the pneumoperitoneum. In the closed technique, the primary port is inserted after establishing an adequate pneumoperitoneum with the Veress needle. The pneumoperitoneum may be established between 15- and 30-mm Hg pressure before insertion of the port (267).

Before the Veress needle is removed, the skin incision is extended to accommodate the size of the planned port (usually 10 or 12 mm). The incision should approximate the diameter of the port as closely as possible to reduce gas leakage around the port during the procedure.

Trocars are available in a vast array of sizes and types and may be reusable or disposable. Trocars consist of two components: a sharp-pointed, removable obturator to facilitate insertion through the abdominal fascia and peritoneum, and an outer sheath through which the obturator passes. The sheath contains a valve or diaphragm through which

instruments may be passed without any loss of the CO_2 pneumoperitoneum. A side-arm stopcock on the port allows connection of the insufflating tubing. Laparoscopic trocars have a safety shield that retracts during insertion of the trocar through the fascia and peritoneum to allow exposure of the sharp pyramidal tip of the obturator. When the port tip enters the gas-filled peritoneal cavity, resistance from the fascial and peritoneal tissue is released and the spring-loaded shield moves forward and locks in place to cover the sharp tip of the obturator and reduce the risk of injury to the underlying viscera.

Corson and colleagues (65) studied the force required to insert nondisposable and disposable ports during a pneumoperitoneum of 11.57 mm Hg. Nondisposable trocars required twice the force used to pass through the anterior abdominal wall as compared with disposable trocars. In the animal laboratory, McDougall and colleagues (267) assessed the force required to insert four different types of 10-mm disposable trocars at 15- and 30-mm Hg pneumoperitoneum pressure. There was no significant difference in the force necessary for the insertion of each of the ports at 15- versus 30-mm Hg pressure. Also, there was no significant difference in force of insertion between the two trocar systems with a safety shield versus the nonshielded trocar. A trocar that used an electrocautery cutting current wire at the tip of the blunt obturator did require significantly less force by 1 to 2 kg during insertion when compared with the other three ports at both 15- and 30-mm Hg pressure. Therefore, after placement of the first port at an intraabdominal pressure of 30 mm Hg, it is reasonable to reduce the pneumoperitoneum to 15 mm Hg for all subsequent port placements.

In preparation for primary port placement, the patient is positioned slightly head-down, and the intraabdominal pressure may be increased transiently to 20 to 30 mm Hg. Following an adequate incision at the supraumbilical or infraumbilical crease, the subcutaneous tissues are spread with Kelly forceps in a cephalocaudal direction. This helps push small blood vessels from the path of insertion of the port and allows the incision to assume a more rounded configuration. The abdominal wall may be stabilized by grasping and raising it, beneath the umbilicus, in the surgeon's nondominant hand. Alternatively, a sharp towel clip may be placed just at the skin edge on either side of the incision; one towel clip is held and stabilized by the assistant, and the other is held by the surgeon's nondominant hand.

The surgeon holds the fully assembled trocar in the palm of the dominant hand with the hub of the trocar secured against the thenar eminence. The middle finger is extended along the shaft of the trocar to act as a brake and prevent too sudden or deep an advancement into the abdomen during insertion.

The trocar is inserted with a steady downward pressure and a twisting motion as the fascia is traversed. The pressure must be constant and maintained to prevent disengagement of the obturator from the sheath. If disengagement occurs, a click will be audible, which signifies that the safety shield has locked into position over the sharp obturator tip and further attempts to pass the trocar through the fascia will be futile. The trocar must then be removed and reset before proceeding with insertion.

Immediately upon entering the gas-filled abdominal cavity, the click of the secured safety shield will be heard, and the hissing of CO_2 gas escaping from the open side arm will confirm this position. The side arm is closed, the port is gently advanced 2 cm deeper into the peritoneal cavity, and the obturator is removed. The CO_2 insufflation tubing is connected to the side arm, which is then opened, and insufflation is commenced at a maximum flow rate with the maximum intraabdominal pressure set at between 10 and 15 mm Hg.

A nondisposable trocar may be used as a primary port, although it does not have the safety shield mechanism for the sharp pyramidal tip. Surgeons using nondisposable trocars may prefer to use the open technique for primary port placement to reduce the risk of intraabdominal injuries possibly associated with an unshielded trocar passed blindly into the peritoneal cavity. The Endotip port (Storz Endoscopy, Inc.) is a unique nondisposable trocar. It has a blunt leading tip and a screw configuration along the body of the cannula. This port is screwed through the abdominal wall until the hiss of CO_2 gas from the open sidearm confirms positioning in the abdominal cavity. The port minimizes trauma to the abdominal wall and reduces the risk of intraabdominal injury by providing a blunt leading tip.

Abdominal Inspection

Light Source

An efficient light source will optimize depth perception and image detail during laparoscopic surgery. Laparoscopic light sources are high intensity and use a xenon, mercury, or halogen vapor bulb with an output of 250 to 300 W. There should always be a reserve light bulb available in the operating room.

The intensity of the light output is manually adjustable. Some light-source units have an automatic light-level adjustment that varies according to the level of light reaching the camera; however, they should also have a manual control. Light is transmitted from the light source of the laparoscope by a flexible fiberoptic cable. These cables are light-source and laparoscope specific. It is essential that all the connections fit correctly and snugly to ensure no loss of light transmission to the surgical field. These cables are sterilized before each use and must be handled with care to avoid breakage of the individual fiberoptic fibers of the light cord. The integrity of the light cord can be reviewed before each procedure by connecting the cable to the light source

and observing for an even emission of light from the end of the cable; dark areas indicate broken fibers.

Camera

The camera system comprises the camera and a video monitor. The camera locks onto the eyepiece of the endoscope and magnifies the laparoscopic image to provide excellent visualization of fine anatomic details. The camera transmits the optical information from the laparoscope via a cable to the camera box. The camera box electronically reconstructs the image and transmits it to the video monitor where the optical information is displayed for viewing by all operating room personnel. Currently, most laparoscopic cameras are sterilized by soaking or by gas before each use, thereby precluding use of any plastic sterile camera wraps.

Recently, innovative digital technology has been put to use in endoscopic imaging equipment. Image enhancement is a digital-subtraction image processing system that works between the camera and the video monitor; the digital-subtraction process results in contrast enhancement, detail enhancement, edge enhancement, and edge correction of the endoscopic video images in real time. This allows the viewer to accentuate structures that are obscure or otherwise poorly visible to the naked eye. The increased detail recognition improves the potential video diagnostic capabilities and facilitates monitoring of technical operative procedures such as endoscopic suturing and dissection of fine structures.

Depth perception is the product of human binocular vision. Because the pupils of human eyes are separated by approximately 5 cm, each of the eyes sees an object from a slightly different perspective. The optic nerves relay the separate left and right views from the eyes to the brain. The two images are merged by the brain into a single, three-dimensional (3D) image that provides more information than either view separately. Developments in endoscopic video systems have attempted to replicate human binocular vision (367). These video systems consist of a camera system that acquires two separate endoscopic images; a signal processor that digitizes, accelerates, and synchronizes the two video signals; and a video display that alternately displays the two images at a rate of 120 frames per second so that the eyes and brain assemble the two images as if they were coincident. The resultant brain image is a single, three-dimensional image, as in normal binocular vision. The advantages of a 3D video system include restoration of depth perception to aid in definition of the relationship of anatomic structures, easier instrument placement and manipulation, and enhancement of the image, which facilitates more precise intracorporeal tasks such as suturing and knot tying. Some preliminary studies suggest that 3D video has the potential to make minimal-access surgery easier, quicker, less prone to error, and more applicable to advanced procedures (274,282). Work continues with these prototype 3D video systems to improve and refine this technology. At present, these systems are more expensive than the existing one-chip 2D video system and three-chip 2D video system. However, these costs may equalize in time.

The camera should be oriented so that the monitor image is in a “true,” upright position, which is the same as would be seen through an open abdominal incision. This is particularly important when using the 30-degree laparoscope. With this instrument, the camera must be held at all times in the true, upright position; the laparoscope can then be rotated through 360 degrees to provide visualization around and over intraabdominal structures, as well as up to the anterior abdominal wall. When a 0-degree laparoscope is used, the camera should be positioned in the true, upright position; then the laparoscope eyepiece can be locked onto the camera because rotation of the 0-degree endoscope will not change the straight-ahead field of vision as long as the camera is maintained in its true orientation.

Insertion of a cold or room temperature laparoscope into the warmer abdominal cavity may produce fogging of the lens and blurring of the monitor image. Accordingly, it is helpful to keep the laparoscope immersed in hot saline until insertion into the abdomen. Wiping the end of the lens with an antifog solution or povidone-iodine solution may also reduce condensation forming on the instrument. The insufflation of the cold CO_2 gas through the laparoscope port may also produce cooling and subsequent fogging of the laparoscope during the procedure. Therefore, following insertion of the second port, it is helpful to transfer the CO_2 insufflation tubing to the side arm of this port. It is important to maintain a watertight seal between the camera and the endoscope. Moisture collecting on the eyepiece or camera will produce blurring of the image and require disconnection of the two pieces and careful wiping to completely dry these surfaces before reconnection.

Video monitors are available from a variety of manufacturers in 13- or 19-inch sizes. The larger monitors provide a larger picture but poorer image resolution. Most monitors with higher resolution capabilities of 1,125 lines of resolution must be used with a camera system capable of providing the appropriate input.

Abdominal Inspection

The initial critical function of the first port inserted into the abdomen is to facilitate insertion of a 10-mm laparoscope to perform a complete inspection of the abdomen. The endoscope must be fully prepared for use before establishment of the pneumoperitoneum. The preparation of the endoscope involves several steps. The camera is locked onto the eyepiece of a 0- or 30-degree laparoscope. The 30-degree laparoscope allows more versatility in visualizing around or over intraabdominal structures, but this endoscope requires a conscientious camera operator to maintain proper orientation because the camera must remain true and stable while

the shaft of the endoscope is rotated to take full advantage of the 30-degree angulation of the lens. The light cable is connected to the light post of the laparoscope and the intensity of the light is turned up to the maximum setting. The laparoscope is then directed toward a white gauze pad and the image on the monitor is focused sharply on the monitor screen. While still focused on the white gauze pad, the camera “white balance” button is pressed until the indicator shows that white balancing has been completed. This ensures a naturally colored monitor image. As a final step it is helpful to prewarm the endoscope with warm saline and wipe the tip of the endoscope with an antifogging solution to reduce fogging of the endoscope on introduction into the warm abdominal cavity.

For primary ports of 10 mm or greater in size, a 10.5-mm reducer must be applied to the sheath before insertion of the laparoscope. These reducers may be detachable, or attached and flip on and off the sheath. With the sheath appropriately reduced, the 10-mm laparoscope is introduced into the abdominal cavity. The bowel immediately below the port should be examined for any evidence of bleeding or injury that may have occurred during the primary port placement. Blood dripping from the port may suggest a through-and-through bowel injury or abdominal wall vessel injury, which is better delineated after the second port has been placed, facilitating transfer of the laparoscope and examination of the primary port site. Blood dripping along the port may obscure the lens and make visualization difficult until the endoscope can be moved to an alternative port and the bleeding vessel controlled with electrocautery or a transcutaneous hemostatic suture.

With the laparoscope positioned satisfactorily in the peritoneal cavity, the surgeon proceeds with a systematic examination of the entire abdomen. The laparoscope is first directed caudally toward the pelvis, where the midline posterior wall of the bladder can be seen with the broad urachus (i.e., median umbilical ligament) extending up toward the umbilicus (Fig. 18.6). On either side of the bladder, the medial umbilical ligaments are usually quite prominent as they travel just lateral to the bladder; they also are umbilically directed. In very obese patients, the medial umbilical ligament may be difficult to identify. Lateral to the medial umbilical ligaments are the internal inguinal rings on either side of the pelvis. Extending from the internal inguinal ring, the vas deferens (male; Fig. 18.6A) or the round ligament (female; Fig. 18.6B) can be identified, passing medially to cross the free edge of the medial umbilical ligament before descending deeper into the pelvis. Also exiting from the internal inguinal ring are the gonadal vessels as they course cephalad just under the peritoneal membrane in the retroperitoneum. In female patients the midline uterus and laterally positioned ovaries are visualized. The laterally lying colon will also be visualized, and on the right side the cecum and appendix are apparent. There are often adhesions from the descending colon to the lateral pelvic wall. Coursing along the anterior abdominal wall are the inferior epigastric vessels, just medial to the internal inguinal ring and lateral to the medial umbilical ligament. These structures are more easily visualized using the 30-degree laparoscope.

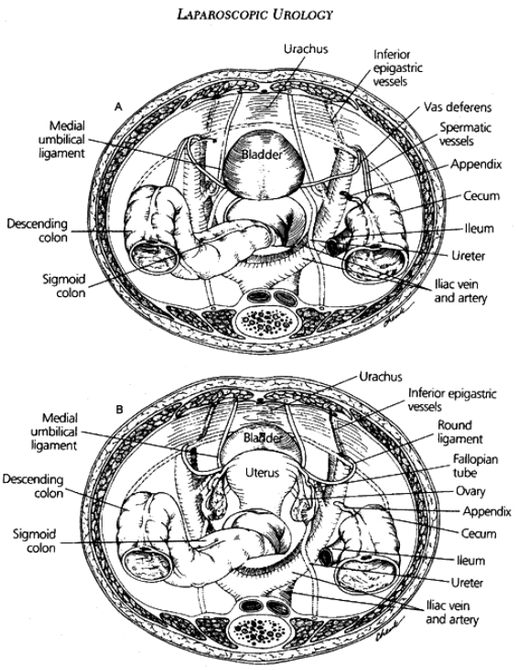

FIGURE 18.6. A: Laparoscopic examination of the male pelvis will include identification of the midline urachus and bladder, medial umbilical ligaments on either side of the bladder, bilateral internal inguinal rings, and spermatic vessels. The vas deferens may be seen just beneath the peritoneum, passing medially from the internal ring and crossing the medial umbilical ligament. **B:** Laparoscopic examination of the female pelvis will include identification of the midline urachus, bladder and uterus, medial umbilical ligaments on either side of the bladder, bilateral internal inguinal rings, and ovaries and fallopian tubes. The round ligament passes from the internal inguinal ring medially to cross the medial umbilical ligament. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

The laparoscope is then rotated to a cephalad orientation to view the upper abdomen. The liver, gallbladder, stomach, and spleen are examined. The omentum and small bowel should be assessed for any possible injury during Veress needle insertion or port placement. Also, there is usually an adhesion present from the splenic flexure of the colon to the abdominal sidewall.

Placement of Additional Trocars

After the abdominal examination has been completed, attention is directed to placement of additional ports to facilitate performance of the planned surgical procedure. The exact pattern of the port arrangement will depend on the type of procedure to be performed and the surgeon's preference. It is advisable to use a 10-mm trocar for the second port placement, allowing transfer of the 10-mm, 30-degree laparoscope for visualization of the primary port. This size endoscope is mandatory if omental, bowel, or abdominal wall vascular injury during primary port placement is suspected. Also, if one is planning to use any of the GIA-type laparoscopic staplers, a 12-mm port is necessary.

Secondary ports are positioned such that they are not too close to each other; if placed too close together, they will limit maneuverability because the sheaths interfere with each other on the abdominal surface, and the movement of instruments within the ports causes them to strike against one another and impede access to the surgical site (Fig. 18.7A).

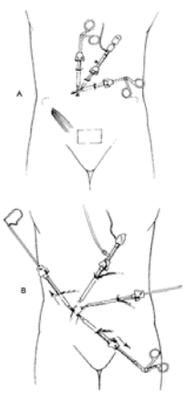

FIGURE 18.7. A: Ports placed too close together will limit the movement of the sheaths on the abdominal surface and cause the instruments to strike against one another and obstruct access to the surgical site. **B:** Optimal port placement allows the assistant to grasp tissue opposite the surgeon's grasper, thus creating traction and countertraction. The surgeon may then use a cutting device to incise the intervening exposed tissue. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

Pressure on the abdominal wall at the planned secondary port site and simultaneous laparoscopic visualization assist in determining the exact port site in relationship to the surgical field; the 30-degree laparoscope is most useful for this procedure. After selection of the port site, the room lights are dimmed and the area of the abdominal wall is transilluminated with the laparoscope inside the abdomen. The tip of the laparoscope is moved upward until it is just underneath the abdominal wall. Large superficial abdominal wall blood vessels can be identified and avoided using this technique. Trocars should not be placed through the abdominus rectus muscle. The inferior epigastric vessels can be visualized with the laparoscope; they are positioned just lateral to the medial umbilical ligament and caudal and medial to the internal inguinal ring. The 30-degree endoscope is useful for this maneuver to facilitate the secondary port placement immediately medial or lateral to the inferior epigastric vessels.

A transverse skin incision is made with the no. 12 hooked blade to precisely accommodate the size of the chosen port. Pressing the port, without the obturator, against the skin to

leave an imprint of the port circumference assists in determining the correct length of the skin incision. All secondary ports should be directed through the fascia and peritoneum in a direct line with the planned surgical site. If this principle is followed during port placement, the sheaths will naturally point toward the surgical fields. This minimizes the amount of torque applied to the port site during manipulation of the instruments and reduces tearing of the peritoneum, which may cause CO_2 leakage. It also improves the surgeon's limited tactile sensation during intraabdominal handling of the tissues with the instruments. Using continuous laparoscopic monitoring, the secondary port is advanced through the fascia and peritoneum with a constant pressure and a slow, twisting action. The tip of the obturator will be seen laparoscopically to enter the abdominal cavity, and the safety shield will snap forward over the sharp obturator tip. Insertion of the port is continued until the shaft of the sheath is seen to protrude 1 to 2 cm inside the peritoneum.

The resistance of the abdominal wall may not allow the obturator to pass through the fascia and peritoneum without placing the sharp obturator tip dangerously close to the underlying viscera. To counteract this situation, sharp towel clips may be placed on the skin edges of the port site to elevate the abdominal wall away from the viscera. Also, after the sharp obturator point has passed through the fascia and peritoneum, the port can be redirected toward the laparoscopic lens for the remainder of the sheath insertion, thereby directing the sharp obturator point way from the viscera.

It is important to secure the port to the insertion site so that it does not become dislodged during instrument manipulation.

Some ports consist of a self-retaining device, including (a) a Malecot flange system that will open on removal of the obturator or by opening a lever on the upper sheath; (b) inflation of a balloon at the distal end of the port sheath by injecting air through a side port; (c) a plastic retentive sleeve that is screwed down, over the sheath, through the fascia and peritoneum 1 to 2 cm, and tightened onto the shaft of the port; or (d) an integral screw edge on the outside of the port cannula. When using any of the retentive sleeves, it is essential to *never* use a plastic retentive sleeve in combination with a metal sheath because this can create a problem with electrosurgical capacitive coupling and subsequent bowel injury. Alternatively, the port may be sutured to the skin with a no. 2 Prolene suture; this technique has the advantage of allowing the port to be advanced farther into the abdomen, yet it cannot be inadvertently removed from the abdomen.

The first crucial function of the second inserted port is to facilitate examination and confirmation of accurate positioning of the primary port. Immediately following the securing of the second port, the laparoscope is transferred to the second port and the primary port is examined. This will ensure that no bowel or omental injury has occurred and that the port site has satisfactory hemostasis. The sheath of the initial port is then positioned so that 2 cm extends inside the abdominal cavity; a retentive device or suture may be used to secure this port in this position.

The laparoscope is then returned to the umbilical port position, and the remaining secondary ports for the surgical procedure are inserted. It is important to place these other ports to facilitate traction and countertraction of tissues held in grasping forceps by the surgeon and assistant, respectively. The surgeon's electrocautery scissors should enter the abdomen from the same side and in a similar trajectory to the laparoscope to allow the surgeon to work with a “true” monitor image and manipulate or cut the tissue held between the two grasping forceps (Fig. 18.7B).

Instrumentation

The selection of laparoscopic equipment has increased exponentially over the past 4 to 5 years, reflecting how much laparoscopic surgery relies on the associated technology. Many of the instruments are available as disposable or nondisposable products. The nondisposable instruments have the advantage of representing a single monetary expenditure for the hospital, but the disadvantage of becoming dull or less efficient with repeated use. The disposable instruments are more expensive, which is of increasing concern in our present era of health care cost awareness. Until recently, disposable instruments have provided more versatility and specific functions than the more traditional nondisposable instruments. Presently, some instruments are being developed as “reposable” units: They have components (e.g., the blades of the scissors or jaws of a forceps) that can be discarded or replaced and that are mounted on a nondisposable shaft; this combination makes their use less expensive than classic disposable units while providing the surgeon with optimal instrumentation for each procedure.

Laparoscopy remains limited by the loss of 3D and wide-field vision perspective and the reduction of tactile sensation. Many features of the instrumentation of laparoscopy attempt to accommodate or compensate for these limitations. It is important for the laparoscopist to be familiar with the equipment used in each laparoscopic case and to determine which additional instruments will better facilitate the performance of a specific planned procedure.

The intention of this review is not to provide an exhaustive list of available laparoscopic equipment, but rather to discuss the basic principles of the laparoscopic instrumentation available to surgeons and some of the more recent adaptations that may be useful in specific circumstances.

Grasping Instruments

Many grasping instruments are available for laparoscopy. These instruments vary in size from 3 to 12 mm and may be reusable or disposable. Grasping forceps are insulated, allowing them to be used for cauterization of the tissue they are grasping. The opening mechanism of grasping forceps may be single action, where only one jaw moves when the instrument is opened, or double action, with opening movement of both jaws. The double-action grasping forceps are usually preferable because they more closely approximate those used during open surgical dissection.

Grasping forceps may be locking or nonlocking. Two mechanisms have been developed to produce locking of the grasping forceps: the spring-loaded locking handle and the ratchet-style locking handle. The spring-loaded grasping forceps remains securely locked closed until the handle, which fits in the surgeon's hand, is firmly squeezed to open the jaws and release the held tissue. The ratchet-style locking grasper has a bar-type finger-activated ratchet that locks the jaws in the closed position with varying degrees of tension on the tissue. The jaws will not open until the ratchet lock is released.

The main difference between grasping forceps is the tip design. Grasping-forceps tips may be classified as traumatic or atraumatic. Atraumatic graspers have serrated grasping surfaces for gentle manipulation of tissues. The tip shape is variable and includes blunt, pointed (e.g., dolphin), straight (e.g., duck bill), curved, and right-angled. Traumatic graspers are designed to hold fibrous tissues securely and tightly and usually are toothed or clawed. The jaws of these instruments tend to be broader and longer. These instruments also include Allis, Babcock, and bowel clamps and may have tip-rotating and articulating functions to better access the operative site.

Cutting Instruments

Tissues can be transected using laparoscopic scissors, scalpels, electrosurgical probes, laser fibers neodymium:yttrium-aluminum-garnet (Nd:YAG) or potassium titanyl phosphate (KTP)], or high-speed ultrasonic instruments. Endoscopic scissors may be reusable or disposable and are available in a variety of shapes. Scissor blades may be straight or curved for dissection. Serrated tips are useful for cutting fascia, and a hooked tip facilitates transection of sutures. The scissors may be insulated to facilitate simultaneous electrocoagulation and transection of tissues. The ability to rotate or angulate the tips of the scissors, by turning a finger control knob, allows easier access to a variety of surgical sites. Scissors with angulating blades are useful for adhesiolysis between the bowel or omentum and the anterior abdominal wall. Curved electrosurgical scissors with rotating tip provide for excellent access to most surgical sites, rapid dissection of tissues, transection of tissues with mechanical (i.e., cold) cutting when near delicate structures such as the bowel, and electrical currents for incision and coagulation of tissues.

Laparoscopic scalpel blades are also available. These were initially developed for incising the common bile duct and have had limited applicability to laparoscopic urology. Recently, they have been used for incision of the urethra during a laparoscopic radical prostatectomy. Great care should be used when inserting, manipulating, or removing these instruments to avoid inadvertent intraabdominal injuries.

Electrosurgical currents may be applied to insulated instruments with needle-point, flat-spatula, or right-angled hook tips. A thin metal tip provides the greatest current density and the most efficient cutting. A needle electrode (i.e., Corson needle) creates a very fine incision of the peritoneum or tissues. A right-angle or hooked tip can be manipulated under tissues and used to draw the tissues away from underlying structures before electrical activation and incision of the tissue. The most common setting for cutting and coagulation currents on electrosurgical instruments is 25 to 50 W; the lowest setting necessary to achieve effective coagulation is recommended. It is imperative that the insulation material on the shaft of the instrument be completely intact to prevent inadvertent sparking of current between instruments or to adjacent tissues. Also, the entire active tip of the electrosurgical instrument should be visualized laparoscopically while being used, to avoid injury to adjacent structures (438). As previously noted, metal trocar sheaths should not be used in conjunction with plastic retention sleeves when electrocautery is being used. The plastic sleeve acts as an insulator and may allow electric charge to build up in the metal sheath. Inadvertent contact between the bowel and the metal sheath could result in a bowel injury or perforation.

The most effective electrocoagulation of small blood vessels is achieved by using an insulated grasper to grasp the tissue and oppose the walls of the vessel. Directly applying an electric current to the grasping forceps, or touching the tips of the forceps with an activated electrosurgical instrument in the coagulation mode, will coagulate the coapted vessel. Last, many electrosurgical instruments are combined with an aspirator-irrigator. This facilitates suctioning of the smoke generated during fulguration and cutting of tissues.

Monopolar electrosurgical instruments are most commonly used and require a remote ground so that the electric current applied to the tissues passes through the patient's body to the ground pad. Bipolar laparoscopic electrosurgical instruments are available. They incorporate both the live

and ground contacts in the tip of the instrument; no ground pad is used and the electric current passes only between the two contacts. Less energy is required for bipolar electrocautery, as compared with monopolar; thus inadvertent injury to surrounding structures is reduced.

Laser probes, including KTP (532 nm) and Nd:YAG (1,064 nm), also may be used for cutting and fulgurating tissues. The KTP laser facilitates noncontact cutting and noncontact fulguration. The Nd:YAG laser provides contact cutting and noncontact fulguration. A 600-micron fiber is usually passed through an aspirator-irrigator instrument for stabilization. Wavelength-specific protective eyeglasses must be worn by all operating room personnel whenever laser energy is being used. In addition, a special filter is necessary on the camera to prevent disturbance of the image during laser firing.

A recent development in tissue cutting and hemostasis is the harmonic knife. This instrument uses high-frequency ultrasound to create rapid vibration of the tip of the instrument. Using different frequencies and the edge or flat portion of the spatula tip, the surgeon can selectively cut or coagulate tissues.

Retractors

Retractors often are required to expose a surgical site by retracting liver, spleen, or bowel, or to facilitate dissection by retracting the kidney to place the hilar vessels on slight stretch. Although many retractors have been developed, the simplest remains a blunt-tip grasping forceps in either a 5- or 10-mm size, depending on the available port site. These instruments can be used to elevate the liver or spleen or medially retract the bowel. Instruments specifically designed to be retractors possess a feature that, when opened, increases the surface area against which they are placed. This allows dispersion of the force of retraction over a larger surface of the retracted structure, thereby reducing the risk of visceral injury. Also, better visualization results because a large amount of tissue can be retracted. Retractors include 5- and 10-mm instruments.

Fan retractors consist of three or four blunt-tip blades that can be opened after intraabdominal positioning. A variation of the fan retractor consists of two blades with an interposing V-hinge joint. When the V hinge is opened, the outer blades spread apart, creating a broad retracting surface. This retractor can be opened to the desired width and locked into position. Recently, the fan retractor has been modified by the addition of an inflatable balloon around the blades of the fan. After positioning the instrument into the abdominal cavity, the blades are opened. A syringe is attached to a side-arm connector, and the balloon covering the blades is inflated with 10 to 20 mL of air. This provides a larger surface area for retraction and thus better distributes the pressure applied to the tissues, potentially causing less ischemia and less chance of organ injury. Vein retractors are available in 5- or 10-mm diameter and consist of a broad, bluntly curved tip for gentle retraction of vascular structures. In addition, 14-gauge needle hook retractors are available; these are inserted separately into the abdomen, and the small hook end is advanced and secured on the peritoneal edge or tissue for retraction. A major advantage of this retractor is that it does not have to be passed through any of the ports.

There are several options for the surgeon to create his or her own retraction devices in the operating room. For example, a 24-inch length of umbilical tape, suture material, or vessel loop may be placed around the ureter or blood vessel for retraction purposes. The needle-pointed grasper of the Carter-Thomason device (see Exiting the Abdomen) can be used, through a small stab wound on the flank, to deliver and retrieve the ends of the tape, suture, or loop. A mosquito clamp on the abdominal wall side maintains tension on the retraction around the ureter or vessel, without using a port site for this purpose.

Sewing Instruments

Laparoscopic suturing and knot tying are two of the most challenging skills for the laparoscopic surgeon to acquire. Recent technologic developments have helped simplify some aspects of these techniques.

Laparoscopic ports used during suturing may vary from 5 to 12 mm in diameter. It is important to plan the surgical procedure and determine the most appropriate port size for each location according to the anticipated need for needle introducers, clip-appliers, or stapling devices. Reducer caps allow working instruments of smaller diameter (3.5 to 10.5 mm) to be used through larger laparoscopic ports (5 to 12 mm) without loss of the pneumoperitoneum. These reducers may be an integral part of the port or may be readily affixed to the top of the laparoscopic cannula.

Laparoscopic 5-mm needle-holders are used to grasp and manipulate needles during suturing of tissues. These devices may be single or double action. The single-action needle-holder has one fixed jaw and one moveable jaw, which is opened by squeezing the spring-loaded handle of the instrument. The double-action needle-holder more closely simulates the traditional needle-holder in that both jaws open when the ring handles are spread apart. The jaws may be serrated to provide a more secure grip on the needle. The hinge mechanism of the jaws should be flush with the shaft of the instrument when closed to facilitate intracorporeal knot tying; this design allows formed loops of suture to slide off the shaft easily without getting caught in the hinge mechanism.

Tissue graspers are usually 5 mm in diameter and should be atraumatic to facilitate grasping of the tissue to be sewn, to grasp the suture material without tearing it, and to assist in proper positioning of the needle within the needle-holder.

It is helpful to have a locking feature on this instrument to facilitate these functions.

The suture introducer is helpful to allow introduction of the needle and suture without entanglement on the flap valve system of the port. The needle-holder securing the needle and suture within the introducer are moved as a unit through the designated port, and the needle-holder and suture with needle are advanced into the abdomen. Alternatively, if one is working through a 12-mm port, the suture can be grasped just behind the needle by the needle-holder; the flap valve is then inactivated and the entire assembly is passed through the port.

Knot-pushers facilitate delivery of extracorporeally tied knots into the abdomen; they may be independent or an integral part of the suture material. The independent knot-pusher is used to slide (Clarke-Reich) or to slide and cinch (Gazayerli) the knot into place. The integral knot-pusher is attached to a preformed knotted loop in the suture. After the loop is passed over the tissues to be secured, the plastic knot-pusher is snapped free of its terminal plastic base and used to deliver and secure the preformed knot within the abdomen.

The most significant advancement in laparoscopic suturing technology is the development of the EndoStitch device (U.S. Surgical Corporation, Norwalk, Connecticut). This device consists of a double-sided needle (9 mm, straight) with the suture attached to the midshaft of the needle, a built-in needle-holder on both jaws of the instrument, and a toggle mechanism that allows the needle to be transferred from one jaw of the needle-holder to the other. With the loading unit provided, the needle with the attached suture is loaded into the laparoscopic needle-holder. The needle's position is fixed on the needle-holder, eliminating the need for repositioning the needle. Closing the handles passes the needle through the tissue. A switch of the toggle lever secures the needle in the opposite jaw of the needle-holder, thereby completing passage of the suture when the handles are relaxed and allowing the jaws of the EndoStitch to separate (Fig. 18.8). This instrumentation has greatly facilitated reconstructive laparoscopic urologic procedures such as the pyeloplasty (4).

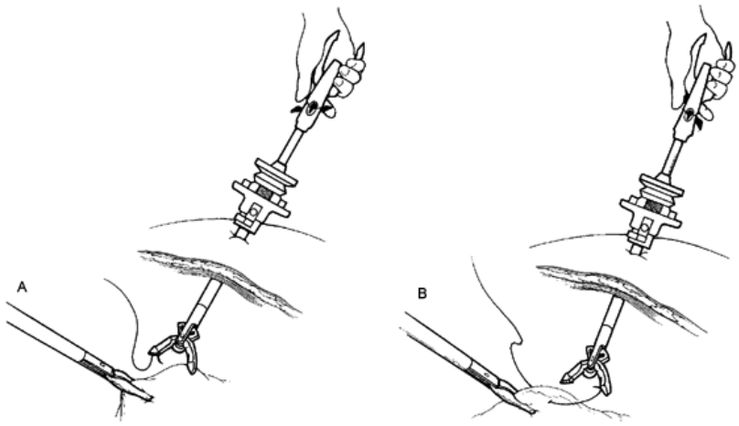

FIGURE 18.8. A: Automatic suturing device from U.S. Surgical Corp., Norwalk, Connecticut. The needle has a point on either end, and the suture is attached at midshaft. **B:** Either side of the jaws of the instrument alternately functions as the “needle-driver” to allow rapid back-and-forth passage of the needle, thereby providing the surgeon with a running suture. The same mechanism can be used to complete intracorporeal knotting of the ends of the suture.

Performing an intracorporeal knot is one of the more challenging skills for a laparoscopist to acquire. The vast array of techniques that have been described attests to the confusion and frustration that can be associated with learning this skill (256). Mechanical aids developed to facilitate or replace traditional surgical knots include, respectively, a polydioxanone (Vicryl) suture clip to secure a suture and metal clips or staples for occluding blood vessels, excising tissue, and reapproximating tissue edges (241).

The Lapra-Ty suture clip-applier (Ethicon EndoSurgery Inc., Cincinnati, Ohio) is a reusable device, and the Lapra-Ty (polydioxanone) suture clip is available in packets of six clips. The clips are individually loaded into the clip-applier and then positioned on a single strand of 0 Vicryl, 3-0 Vicryl, or 4-0 Vicryl. Tightly squeezing the handle of the clip-applier locks the suture clip onto the suture to act as a knot. Tensile-strength studies in the laboratory have shown that these suture clips, acutely, are as secure as a hand-tied surgeon's knot using the same suture

materials. These suture clips may be used to secure the ends of the suture material when performing interrupted or running suture techniques laparoscopically. Used in conjunction with the EndoStitch device, these clips have further simplified reconstructive laparoscopy.

Laparoscopic clipping instruments are available in two forms: (a) occlusive for occluding blood vessels and (b) tacking for approximating tissue edges or securing various foreign materials (e.g., cadaveric fascia, mesh) to tissues. Occlusive clips come in lengths of 6, 9, and 11 mm. The applier is passed into the abdomen via a 10-mm port. The clip-applier may be either a single-load reusable type or a multiload, disposable type, which comes with 15 to 30 clips already loaded in the applier; the latter device, especially if it comes with a semiautomatic feed system, is capable of firing clips in rapid succession. The tips of the clip are approximated by the jaws of the clip-applier before closure of the body of the clip, thereby allowing the surgeon to slide a clip up or down along a given vessel before securing it in place (Fig. 18.9). The 9-mm clips are as secure as a hand-tied surgeon's knot of 0 silk on the renal artery when pressure tested (216). The tacking clips close in either a rectangular or B configuration, and the applier is passed into the abdomen via an 11-mm port (Fig. 18.10). All clip-appliers have a rotating shaft, and some allow angulation of the working end, to help align the tip of the clip-applier with the structure to be clipped or tacked.

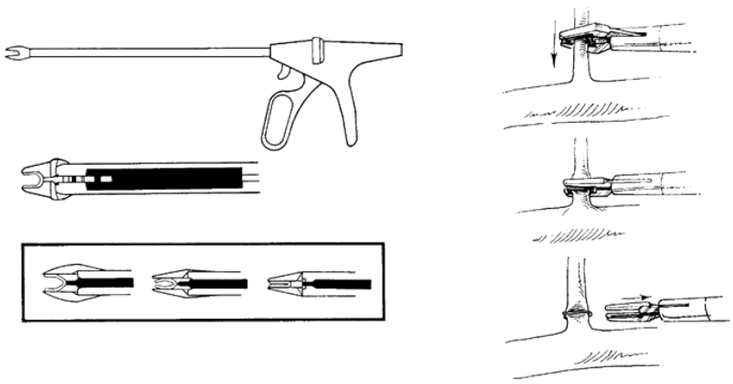

FIGURE 18.9. The clip-applier contains preloaded occlusive clips. After the jaws of a clip are placed around the suture to be clipped, the handle of the instrument is squeezed half-closed. This approximates the tips of the clip, which can be moved along the structure for precise placement. The handle is then fully closed, which securely closes the body of the clip on the structure. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

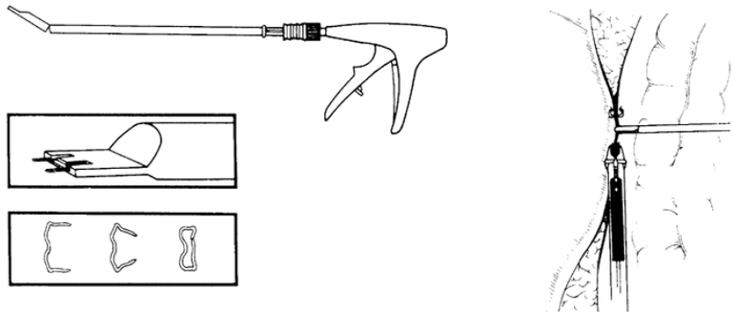

FIGURE 18.10. The tacking clips close in a rectangular or B configuration and are used to reapproximate tissue edges such as peritoneum to peritoneum or Marlex mesh to peritoneum. (Reprinted from Clayman RV, McDougall EM, eds. *Laparoscopic urology.* St. Louis: Quality Medical Publishing, 1993, with permission.)

Laparoscopic stapling devices are available only as disposable instruments and have rotating and articulating capabilities at the working end. Staple sizes range from 2.5 to 4.8 mm; smaller staples are used to occlude vascular structures, whereas larger staples are used to secure bulkier tissues. The length of each row of staples is 3 or 6 cm, and each cartridge delivers six separate rows of staples. As the staples are pushed into the tissues and closed, a knife simultaneously cuts the tissue between the third and fourth staple lines.

Developments in laparoscopic staplers (occlusive and reconstructive) have been most impressive. Indeed, bowel anastomoses can be readily performed laparoscopically using the same staple technology that was developed for open surgery. This technology has only begun to be transferred to urologic reconstructive surgery because of concerns over the potential of stone formation on the titanium staples that would be continuously exposed to urine within the reconstructed collecting system. However, in the bladder, titanium staples have apparently been well tolerated, and to date, there are no reports of stone formation on the staples used to secure a cuff of bladder during a nephroureterectomy (214,215).

Further advances in the realm of staple and clip technology will likely revolve around the development of extremely small absorbable clips. Already, absorbable clips have been developed for use in creating a right colon pouch for urinary

diversion (138,312). Presently, these staples are too large to be used for the delicate reconstruction of the ureter or renal pelvis.

The recent development of fibrin glue is further expanding the range of reconstructive laparoscopic urology. The first clinically effective use of tissue glue was in 1972 by Matras and colleagues (249a), who used a fibrin glue to join peripheral nerves. At present, there are two commercially available preparations: Tisseel and Beriplast (120). These systems consist of fibrinogen (70 to 100 mg/mL) in one part of a dual syringe, and a second solution in the opposite chamber of the syringe. The second solution contains thrombin, factor XIII, fibronectin, and ionized calcium with or without aprotinin, an antifibrinolytic agent. In theory, the fibrinogen determines the strength of the glue while the amount of thrombin directly determines the speed of reaction, which may vary from 5 seconds to several minutes. Aprotinin prolongs the presence of the glue at the anastomotic site for 2 to 4 weeks. The glue used in combination with cellulose has been used to perform hand-assisted laparoscopic partial nephrectomy for tumor (194). This technique provides excellent hemostasis of the transected renal parenchyma. The glue has also been used experimentally to aid in the creation of anastomoses, such as tubal reconstruction, vasovasostomy, or ureteroureterostomy (117,237,271,306).

Miscellaneous

Other instruments and devices are available that facilitate specific laparoscopic functions. The organ entrapment sack is made of either a durable double layer of impermeable nylon and plastic or a single layer of thick-walled plastic. The sacks vary in size from 2 by 5 inches to 10 by 8 inches. The sack is tightly rolled over an introducing device and inserted through a 10-mm port. Within the abdomen the sack is unrolled, and the neck of the sack is triangulated open with traumatic grasping forceps placed on the three equidistant tabs on the sack edge or by a metallic band that causes the mouth of the sack to spring open when inserted into the abdomen. The surgical specimen is deposited into the sack, the neck of the sack is closed, and the neck of the entire sack is pulled out by its drawstring through a 12-mm port site. If just the neck of the sack is delivered, the tissue is fragmented and removed from the sack using forceps; a 10-mm, high-speed electric tissue morcellator [note that this morcellator can only be used with a LapSac (Cook Urological Inc., Spencer, Indiana)]; or a jaw-system mechanical morcellator. The morcellation process is monitored laparoscopically to ensure that sack perforation or incorporation of bowel or omentum into a fold of the sack does not occur. Landman and colleagues (229) recently reported their evaluation of the various tissue morcellators in the animal model. They determined that all three presently available morcellators were feasible for renal morcellation. The Steiner morcellator (Karl Storz Inc., Culver City, California) resulted in more rapid morcellation, larger morcellation products, and comparable safety in their experimental model.

Aspiration devices are necessary during laparoscopy, and combined aspiration-irrigation devices are preferable. The aspirating channel may be attached directly to an operating

room vacuum and collection system. The aspirator consists of a 5- or 10-mm metal tube and trumpet valve. The irrigating channel is controlled with a one-way stopcock or trumpet valve. The irrigant must be pressurized to 250 to 700 mm Hg to allow adequate flushing of tissues and blood clots. The irrigation fluid most commonly used is saline and heparin (5,000 U/L); a broad-spectrum antibiotic (e.g., 500 mg of cephalosporin per liter) may be added to the irrigant. It is important for the aspirating tip of the instrument to have sideholes, in addition to the endhole, to maximize the suction ability of the instrument.

The development of laparoscopic ultrasound probes allows sonographic examination of tissues and Doppler detection of blood vessels during the surgical procedure. This may be useful in directing wedge resection of small renal lesions, identifying the testicular artery during laparoscopic varix ligation, or identifying the renal artery during a laparoscopic nephrectomy. The laparoscopic ultrasound probe is now articulating, which is helpful in performing intraoperative renal ultrasonography, especially during laparoscopic cryotherapy of renal lesions.

An argon beam coagulator may be used with 5- or 10-mm probes. This device uses argon gas (at a flow rate of 4 L per minute) to clear blood and fluid from the surgical field and deliver electrical current to a bleeding surface, thereby electrofulgurating the tissue. The surface temperature of the fulgurated tissue remains below 100°F, limiting the depth of injury to 1 to 2 mm (versus 5 mm, with standard electrocautery). This may be particularly helpful during wedge resection of the kidney or for a partial nephrectomy.

Another device, which recently completed clinical trials, is the pneumodissector. This instrument applies brief blasts of CO_2 gas at a pressure of 50 psi to facilitate dissection of connective tissues. Animal studies have confirmed that the pneumodissector will not cause laceration of the liver, kidney, aorta, or vena cava, even at a maximum pressure of 100 psi (63). After sharp incision of the peritoneum, the pneumodissector effectively assists in dissection of the fatty tissues and exposure of the renal hilar vessels. It has been shown, in clinical evaluation, to be a safe and efficacious technique for rapid blunt tissue dissection (327).

There has been recent interest in hand-assisted laparoscopy (HAL) as a method for inexperienced laparoscopists to acquire the skills necessary for performing laparoscopic renal surgery. It also has particular relevance to procedures that require an incision to remove the surgical specimen intact, such as laparoscopic nephroureterectomy for upper tract transitional cell carcinoma or live donor nephrectomy (212,295,393). It may also facilitate the successful performance of laparoscopic partial nephrectomy (2).

For placement of a hand-assist device, it is necessary to first obtain a Veress needle pneumoperitoneum and placement of a primary port in the midclavicular line. Under laparoscopic visualization, a skin, fascial, and peritoneal incision, of 6 to 8 cm in length, is performed at the midline. For a right-hand–dominant surgeon, this incision is made overlying and just above the umbilicus for left renal surgery, and overlying and just below the umbilicus for right renal surgery. Various HAL devices are available, but essentially they all provide an airtight seal of the abdominal wall and allow the surgeon to insert the nondominant hand, through a plastic sleeve, into the abdominal cavity to assist with tissue dissection and retraction while maintaining the pneumoperitoneum. The presently available devices include Pneumosleeve (Dexterity Inc., Blue Bell, Pennsylvania), Intromit (Applied Medical Resources, Laguna Hills, California), and Hand Port (Smith-Nephew, Worcester, Massachusetts).

Exiting the Abdomen

At the conclusion of the laparoscopic procedure, it is essential to exit the abdomen in an organized and systematic manner to minimize the risk of complications. Intraabdominal pressure should be reduced to 5 mm Hg because this will allow any venotomy previously tamponaded by the 15 mm Hg pneumoperitoneum to be recognized. The surgical sites and all the port sites should be examined closely for hemostasis. The abdominal cavity should be scanned from the pelvic region to the upper quadrants to rule out any injury to abdominal viscera.

After satisfactory examination of the abdomen, the 10-mm laparoscope is removed and replaced by a 5-mm laparoscope through one of the secondary 5-mm ports. The primary 10-mm (or larger) port is removed from the abdomen under laparoscopic visualization. The assistant places a finger over the port site to maintain the pneumoperitoneum. If hemostasis of the port site remains satisfactory, the fascia is closed using a figure-of-eight of 0 absorbable suture under continuous laparoscopic observation. A small S-curved or Sinn retractor is used to retract the skin and expose the fascia. The fascia is grasped with a Kocher clamp or toothed forceps. The suture is passed through the fascia, and laparoscopic visualization ensures that the bowel or omentum is not incorporated into the stitches. This procedure of port removal and fascial closure is repeated for all the remaining ports larger than 5 mm.

Identifying the fascia for placement of a figure-of-eight suture is often difficult, especially in an obese patient. Several companies have developed devices to simplify this final step in the laparoscopic procedure. The device that we have found consistently to be the most useful and least expensive is the Carter-Thomason closure device (47) (Fig. 18.11). This device consists of two parts: a metal cone with two through-and-through oblique channels drilled in it and a needle-tip 2-mm grasping forceps. The two channels in the cone part of the device serve to direct the sharp, needle-pointed suture-grasper through the fascia and peritoneum; this is always performed under laparoscopic visualization.

The suture chosen for closure should be a minimum of 12 inches in length. One end of the suture is grasped by the sharp, needle-pointed grasper. After removal of the port, the metal cone piece is placed into the port site; its tip is visualized by the laparoscope. The needle-point grasper is then inserted through one of the channels of the cone. Passage of the instrument through the fascia and peritoneum is monitored laparoscopically to avoid any intraperitoneal injury. When positioned well into the abdomen, the jaws of the needle-point grasper are opened to drop the suture. The jaws are then closed and the instrument is withdrawn from the working channel. The needle-pointed grasper is then inserted through the second channel, which directs the instrument through the fascia and peritoneum, 180 degrees from its initial insertion, on the opposite side of the peritoneotomy. After the needle-pointed grasper is positioned within the abdomen, the grasping jaws are used to secure the intraabdominal end of the suture and draw it out through the working channel. A 5-mm locking grasper can be used through another port to facilitate removal of the suture from the needle-grasper and for positioning the suture so that it can be easily grasped by the needle grasper on its second pass. The two ends of the suture should now lie on the abdominal wall, having passed through both sides of the fascia and peritoneum. The metal cone device is withdrawn from the port site and off the suture, which is tied down snugly to close the port site.

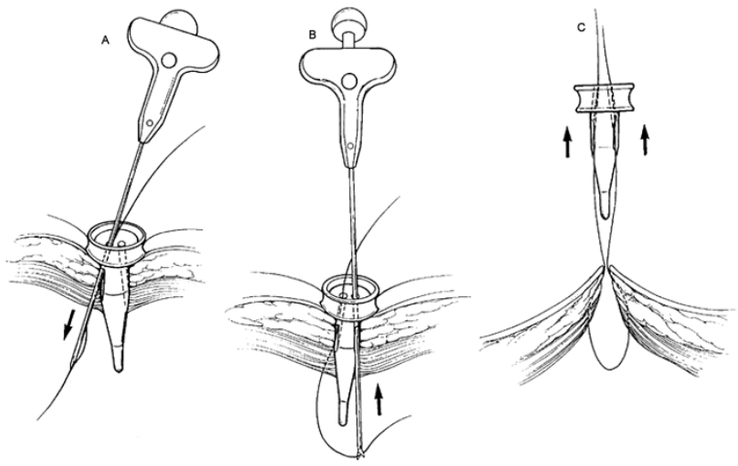

FIGURE 18.11. A: The Carter-Thomason laparoscopic wound closure device is inserted into the port site after removing the port. The suture end secured in the needle-pointed grasper is inserted through the channel, directing it through the fascia and peritoneum. **B:** The needle-pointed grasper is inserted through the second channel, is passed through the fascia and peritoneum opposite the initial suture insertion, and grasps the intraabdominal end of the suture. **C:** The two ends of the suture are tied down to complete the closure of the fascia and peritoneum.

After all of the sheaths larger than 5 mm have been removed and the fascia closed, all but the laparoscope-bearing 5-mm sheath are pulled from the abdomen under laparoscopic visualization. Fascial sutures are not necessary at these port sites if no bleeding is present from the sites; the only exception is in the child, in which case even the 5-mm ports require a fascial suture. If any bleeding is noted from a 5-mm port site, either electrocoagulation of the site or placement of a 0 absorbable suture is necessary.

The last sheath to be removed is the 5-mm sheath through which the 5-mm laparoscope has been passed. The pneumoperitoneum is maintained by having the assistant occlude the 5-mm port sites with a finger. The laparoscope is backed out until the tip is just protruding from the end of the port sheath. The last sheath and laparoscope are then

slowly backed out of the abdomen as a unit. As the 5-mm laparoscope is withdrawn, the site of the peritoneotomy and fasciotomy are examined to rule out bleeding. If bleeding is noted, the site may be coagulated through the sheath, or if this fails, one of the other 5-mm port sites should be replaced. The bleeding port site may then be sutured with a 0 absorbable suture.

The CO_2 is allowed to escape from the 5-mm port sites. The skin incisions of the port sites larger than 5 mm are closed in a subcuticular fashion using a 4-0 absorbable suture. The skin incisions of all the port sites are closed and secured with sterile adhesive strips. This method of exiting the abdomen should obviate bowel or omentum becoming entrapped by the fascial sutures and eliminate herniation through any of the port sites.

Retroperitoneal Approach

Following balloon dilation or blunt-finger dissection access to the retroperitoneum, a Hasson-type cannula or 10- to 12-mm trocar is inserted. The 10-mm, 30-degree laparoscope is inserted and the retroperitoneal space is inspected. On initial examination, the psoas muscle and genitofemoral nerve should be clearly seen. Gerota's fascia and the ureter are typically visible, although this may be difficult in the obese patient or in those patients with any degree of scarring or fibrosis in the retroperitoneal space. A small amount of venous blood overlying the tissues is normal, but there should be no active bleeding.

Insertion of additional working ports is performed under endoscopic guidance. A 10- or 12-mm port is placed at the inferior lumbar triangle; a 5-mm port is placed at the level of the twelfth rib on the anterior axillary or midclavicular line; and a 5-mm port is placed at the level of the twelfth rib on the posterior line. The placement of the ports should form a T shape.

When a retroperitoneal approach is used, only minimal dissection in the area of the ureter is needed to completely expose this structure. Likewise, pulsations from the renal artery are often visible early in the case as the surgeon moves the endoscope up along the medial border of the psoas muscle. Instrumentation for the laparoscopic retroperitoneoscopic procedure is similar to that for the transperitoneal approach.

As with the peritoneal approach to renal surgery, it is important to systematically exit the retroperitoneal space. Following completion of the surgical procedure, the CO_2 pressure in the retroperitoneum is reduced to 5 mm Hg and the operative and port sites are examined to ensure adequate hemostasis. With the retroperitoneal approach, the port sites do not require a fascial suture closure because there is minimal risk of hernia formation. Therefore the ports are removed under direct visualization. The port sites are irrigated with saline and the skin is closed with a subcuticular 4-0 nonabsorbable suture.

Physiology of CO_2 Insufflation

Cardiopulmonary Function

There are two very nonphysiologic situations that occur during laparoscopy. The first is insufflation of the abdominal cavity with gas, usually CO_2, and the second is the elevation of intraabdominal pressure. Studies comparing the effect of insufflants on hemodynamic and respiratory function indicate that the type of gas used does not significantly affect cardiac output.

However, CO_2 gas may increase the central venous pressure and the mean arterial pressure (MAP). Likewise, argon gas can markedly increase cardiac afterload by elevating arterial pressures and systemic vascular resistance, even more so than CO_2 gas. In addition, CO_2 has been demonstrated to have a negative effect on respiratory function, whereas argon and helium do not appear to have these limitations. Thus it appears that the best alternative to CO_2 as an insufflant is helium because of the limited effect on hemodynamic function and essentially no effect on respiratory function (203). Wolf and colleagues (447) reported that conversion to helium insufflation was able to successfully reverse a significant respiratory acidosis caused by a CO_2 pneumoperitoneum in a patient with severe chronic obstructive pulmonary disease during a laparoscopic radical nephrectomy.

Aside from the choice of gas used for insufflation, the increased intraabdominal pressure itself can lead to unfavorable hemodynamic changes, which are essentially pressure dependent. Cardiovascular, pulmonary, and renal effects of elevated intraabdominal pressure have been extensively studied in the laboratory and clinical setting.

An elevated intraabdominal pressure has been shown to increase atrial filling pressures, increase systemic vascular resistance, decrease venous return, decrease cardiac output, and reduce stroke volume (70,223,269). Peak inspiratory pressures have been shown to increase in conjunction with the elevated abdominal pressure. These effects are pressure dependent, usually not becoming evident until pressures reach 14 to 15 mm Hg (269,439). In animal studies concerning the effects of laparoscopic surgery on hemodynamic responses, it has been shown that the changes are minimal when intraabdominal insufflation is performed in healthy, well-hydrated, and hyperventilated animals (173). Similarly, for healthy patients in the clinical setting, these hemodynamic changes do not appear to have any significant adverse effect (132,284). Clinically, the respiratory effect of the elevated intraabdominal pressure is monitored using pulse oximetry and capnography. The pulse oximeter saturation should be maintained at greater than 93% and the end-tidal CO_2 should be maintained between 35 and 45 mm Hg, which usually ensures that the $Paco_2$ is less than 50 mm Hg. Increasing respiratory rate and tidal volume can usually control these levels satisfactorily. Even in the face of moderate pulmonary disease, despite an elevation of the

$Paco_2$ and respiratory acidosis, the impairment of pulmonary function usually causes no significant negative hemodynamic effect (85). However, in laboratory studies on septic animals, although laparoscopy could be performed, the hemodynamic compromise in the form of acidosis with cardiodepression was more apparent. Therefore the clinical application of laparoscopy in the septic patient should be approached with caution (141).

Renal Function

It is well recognized that a prolonged period of increased intraabdominal pressure is associated with decreased urine output, even to the point of anuria (269). This continues to be the most marked intraoperative renal effect observed from the pneumoperitoneum, and it is pressure dependent. In a human study, the use of a lower intraabdominal pressure (4 mm Hg), plus the aid of a retraction device, for performing the laparoscopic cholecystectomy led to no significant changes in urine output, effective renal plasma flow, or glomerular filtration rate (GFR) as opposed to the transient renal dysfunction that was noted with an intraabdominal pressure of 12 mm Hg (280). Although this transient renal dysfunction has been well documented, various mechanisms have been described to explain these changes: choice of insufflant, decreased cardiac output, ureteral obstruction, renal vein compression, renal parenchymal compression, and systemic hormonal effects (156,221). The choice of insufflant does not appear to have a direct affect on renal function (269). In animal studies comparing CO_2 to argon gas for pneumoperitoneum, no change in urine output was noted for intraabdominal pressures less than 15 mm Hg. For intraabdominal pressures of 15 mm Hg or greater, a similar impairment in urine output and GFR was seen for both types of gas.

The body of evidence also eliminates a decrease in cardiac output as a direct etiologic factor responsible for the renal dysfunction (221). Although cardiac output has been reported to decrease to as much as 37% of normal at 40 mm Hg, normalizing cardiac output with plasma expanders failed to improve the diminished renal blood flow and GFR (156).

In addition, ureteral obstruction resulting from extrinsic compression does not appear to play a role in oliguria (269). Placement of ureteral stents during pneumoperitoneum does not improve urine output. Likewise, intraoperative urograms in animals with decreased urine output during pneumoperitoneum confirm the absence of ureteral obstruction (221).

In contrast, changes in renal vein flow do appear to be linked to the oliguria associated with the pneumoperitoneum. To determine the etiology of oliguria, Kirsch and colleagues (221) subjected rats to intraabdominal pressures of 5 and 10 mm Hg. Urine output did not diminish until the pressure reached 10 mm Hg. At that level of pneumoperitoneum, vena caval blood flow decreased 92% and aortic blood flow decreased 46%, leading to the conclusion that the renal effect was due to renal vascular insufficiency from central venous compression. Similarly, McDougall and colleagues (269), using a porcine model, demonstrated a significant decrease in renal vein flow concomitant with a drop in urine output, but only at a pressure of 15 mm Hg or greater. Interestingly, renal vein flow and creatinine clearance remained diminished even after 2 hours of desufflation, although no long-term effects were noted (269). Subsequent animal studies, using MRI to provide a noninvasive evaluation of renal vessel blood flow and parenchymal perfusion, also demonstrated reduced cardiac output, reduced flow velocity in the renal vessels, decreased renal parenchymal perfusion, and a concomitant reduction in urine output. The changes seen in renal perfusion were similar in the cortex and medulla of the kidneys; these findings confirmed that a shunting phenomenon was *not* occurring in the renal parenchymal during the time of the elevated pneumoperitoneum pressure (258).

Although the renal vein compression hypothesis is supported to some extent by the foregoing studies, the most likely mechanism for oliguria during laparoscopy appears to be direct renal parenchymal compression, similar to that seen with a Page kidney. Razvi and associates (351) placed a pressure cuff around canine kidneys subjecting them to pressures of 15 mm Hg. This resulted in a decreased urine output of 63% in the treated kidney along with decreased GFR and reduced effective renal blood flow. As other investigators have observed, even after 2 hours of desufflation, renal blow flow did not return to baseline levels. The control kidney showed no significant changes in urine output or GFR.

From a hormonal standpoint, it is of note that aldosterone has been reported to be elevated during the oliguric period in the animal model, which correlates with the decreased urinary sodium and increased urinary potassium observed (56). It also supports the Page kidney effect as a significant component of the intraoperative oliguria observed during the pneumoperitoneum.

In healthy patients, this acute renal dysfunction appears to completely resolve postoperatively following desufflation; however, there is concern that in patients with preexisting renal disease, these transient changes may become clinically significant. To address this, Cisek and colleagues (59), in an animal model, performed renal reductive surgery to mimic chronic renal insufficiency. After being exposed to intraabdominal pressures of 20 mm Hg for 6 hours, simulating a complex laparoscopic procedure, a dramatic drop in urine output (80%), GFR (63%), and renal blood flow (20%) was noted, which did not return to baseline after 90 minutes of desufflation postprocedure. An increase in the urinary *N*- acetyl-ß-D-glucosaminidase (NAG) was observed, as was acute renal failure despite hydration and central venous pressure monitoring (59). However, at 1 week following the

insufflation tests, the GFR returned to the baseline, chronic renal failure level, indicating that no long-term effect on the renal function from the acute insufflation was identified, even in the face of preexisting renal insufficiency.

The observed blood flow changes have suggested the possibility of renal tubular damage secondary to ischemia, as a cause of the oliguria associated with pneumoperitoneum. NAG is present in renal tubular cells and is released into the urine in response to tubular cell injury. Micali and colleagues (277) measured preoperative and postoperative NAG levels in 31 patients undergoing laparoscopic surgery compared with 28 patients undergoing conventional open surgery. No differences in NAG were noted between the preoperative and postoperative levels in either of the groups or between the groups. They demonstrated that pneumoperitoneum was not associated with the change in the urinary concentration of NAG. Similarly, there was no correlation between urinary NAG levels and the total operative time. This observation suggests that significant ischemic renal injury is not associated with laparoscopic-related oliguria. This biochemical finding has been confirmed histologically in animal models. In a rat study, after a 5-hour pneumoperitoneum at a pressure of 15 mm Hg, acutely and chronically, no significant histologic differences could be identified when compared with control rat kidneys (232). McDougall and colleagues (269), in the porcine model, also confirmed a lack of histologic abnormality in kidneys rendered oliguric at pressures of 15 mm Hg.

Elevated intraabdominal pressures may also act via stimulation of a variety of systemic hormones, which contribute to the hemodynamic and renal effects. Independent of the type of gas used, excessive intraabdominal pressures (20 mm Hg or greater) are responsible for increasing serum catecholamines (279). Likewise, endothelin, a potent vasoconstrictor, has also been shown to increase in response to renal vein compression and during pneumoperitoneum in animal models. In fact, compression of a unilateral renal vein leads to a decrease in GFR and urine output in both kidneys and is associated with elevated renal vein endothelin concentrations, thus implicating it as a contributing factor to the oliguria observed during long laparoscopic cases (151). In other animal studies, the administration of a vasopressin antagonist improved renal function when compared with control animals, suggesting that the endogenous release of arginine vasopressin also contributes to the oliguria seen with increased abdominal pressures (84).

Methods to improve urine output during pneumoperitoneum, which have included the use of ureteral stents, fluid hydration, and intravenous dopamine infusion, have been unsuccessful in changing urine output. However, altering the temperature of the insufflated CO_2 has been found to partially counteract the hemodynamic and renal effects of increased intraabdominal pressure. A comparison of the use of warm (37°C) versus room temperature CO_2 during prolonged (greater than 90 minutes) laparoscopic surgery demonstrated a higher core temperature, urine output, and cardiac index with warm insufflation, suggesting that local vasodilation in the compressed kidney may restore enough blood flow to maintain GFR and urine output (14).

In conclusion, oliguria is a recognized component of the physiologic effect of increased intraabdominal or retroperitoneal pressure. The etiology is multifactorial, emanating from vascular and parenchymal compression and associated with systemic hormonal effects. Ureteral obstruction does not play a significant role. These changes are pressure dependent and are usually not apparent until pressures reach 15 mm Hg or greater. Likewise, this effect is not associated with any histologic pathology or evidence of renal tubular damage. Following the release of the pneumoperitoneum or pneumoretroperitoneum, the renal function and urine output return to normal with no long-term sequelae, even in patients with preexisting renal disease. It is important for the entire operative team to have an understanding of the physiologic effects of CO_2 insufflation. This will allow appropriate intraoperative monitoring and management and minimize intraoperative and postoperative complications.

Pneumoretroperitoneum

For the most part, gas insufflation into the retroperitoneal or extraperitoneal space has been associated with greater CO_2 absorption and hypercarbia as compared with intraperitoneal insufflation, especially in the presence of subcutaneous emphysema (133,269,448). This, however, is not entirely without controversy. Other animal and human studies have demonstrated the opposite results. In a canine model, Wolf and colleagues (446) noted a higher increase in $Paco_2$ and a greater drop in serum pH in the intraperitoneal insufflation group compared with the extraperitoneal insufflation group. Conversely, risk of thoracic dissection of gas was greater during extraperitoneal insufflation than during intraperitoneal insufflation. Wright and colleagues (453), in a human study, noted a more rapid increase in the $Paco_2$ in the transperitoneal group than the extraperitoneal group, although no significant difference in the overall magnitude of the rise was demonstrated. Nonetheless, regardless of the method of laparoscopy, appropriate ventilatory management, with hyperventilation, usually avoids any adverse sequelae of hypercarbia.

The renal and hemodynamic effects of pneumoretroperitoneum are similar to those seen with a pneumoperitoneum. A unilateral pneumoretroperitoneum leads to elevated systolic and diastolic aortic pressures, although the effect is less than that seen with the pneumoperitoneum (55). In contrast, at 15-mm Hg pressure, the decrease in renal vein flow is similar to that seen with the pneumoperitoneum (269). An elevated retroperitoneal pressure also leads to oliguria, and when maintained for 2 hours, it leads to a gradual

decrease in the contralateral kidney perfusion and a concomitant increase in the intraabdominal pressure (55). Likewise, this reduction in urine output is reversible after desufflation and leads to no identifiable pathologic renal abnormalities (269).

SPECIFIC LAPAROSCOPIC PROCEDURES

Part of "18 - ADULT LAPAROSCOPIC UROLOGY "

Laparoscopic access was initially applied within urologic surgery only for diagnostic purposes. Slowly, with advances in technology and skill, the indications for laparoscopic access have evolved such that diagnostic, ablative, and even complex reconstructive procedures are presently performed laparoscopically at academic centers throughout the world. The subsequent section is a comprehensive listing and description of the current state of the art of laparoscopic procedures in urology. The procedures have been stratified into diagnostic, ablative, and reconstructive designations and have been further subdivided into operations for either benign or malignant disease processes. For each procedure, a systematic review of the literature describing the indications, technique(s), efficacy, efficiency, equanimity, and economy is provided.

Benign Disease: Diagnostic Procedures

Renal Biopsy

Renal biopsy is often indispensable in the diagnostic evaluation of various kidney diseases. Since its original description by Iversen and Brun (188), the percutaneous approach has been the preferred procedure for sampling renal tissue for almost half a century. Percutaneous renal biopsy is indicated for patients with occult acute renal failure, nephrotic syndrome in an adult without signs of systemic disease, significant proteinuria, hematuria after urologic studies indicate no specific upper or lower tract causes, or systemic disease with suspected renal involvement (114,417). Valuable diagnostic and prognostic information can be obtained and treatment tailored to the patient based on biopsy results.

As a result of the efficacy and minimally invasive nature of percutaneous biopsy, biopsy under vision is reserved for patients for whom percutaneous biopsy is either unsuccessful or contraindicated. Percutaneous renal biopsy is sometimes difficult or impossible because of anatomic constraints such as mobility of the kidney, morbid obesity, positioning of the kidney high under the rib cage, spinal deformity, or the presence of impenetrable scar tissue or other organs around the kidney (e.g., a retrorenal colon). Absolute and relative contraindications for percutaneous renal biopsy vary among nephrologists. Reasons for referral for a renal biopsy under direct vision include failure of previous percutaneous biopsy attempts, inadequate tissue sample with the percutaneous biopsy, an uncooperative patient, marked obesity, a solitary functioning kidney, patients of the Jehovah's Witness faith, presence of renal artery aneurysm, calcific arteriosclerosis, or a coagulopathy (30,161,228,371).

Laparoscopic renal biopsy was initially described via a transperitoneal approach (396). Currently, however, the procedure is most commonly performed in a retroperitoneal fashion with the patient in the flank position under general anesthesia. Via a two-port approach, a pneumoretroperitoneum is obtained and the retroperitoneum is dissected bluntly. Renal biopsy is typically obtained with a single stroke of a laparoscopic cup forceps. Hemostasis of the biopsy site is then achieved with electrocautery or argon beam coagulation. The procedure has been described with mean operating room times ranging from 35 (115) to 90 minutes (131).

Diagnostic yield using this technique for laparoscopic renal biopsy has been high. Gaur and colleagues (115) described adequate tissue for diagnosis in 17 of 17 consecutive renal biopsies. Subsequently, other series have recorded 100% diagnostic yield in an additional combined total of 40 patients using either single or multiple biopsies under laparoscopic vision (53,131). These results are better than the reported diagnostic yield with percutaneous biopsy, which ranges from 80% to 95% (30,36,80,206,291).

Complications from laparoscopic renal biopsy have usually been minimal and self-limiting. Gaur and colleagues (115) reported 2 complications in 17 consecutive renal biopsies (12%). One patient required extension of a laparoscopic port site for hemostasis. The other patient had macroscopic hematuria, which resolved spontaneously after 2 days; this patient did not require a blood transfusion (116). In a series of 32 consecutive patients, Gimenez and co-workers (131) reported two complications (6%). An anticoagulated patient experienced postoperative pain, and evaluation revealed a perinephric hematoma. The hematoma resolved without intervention and the patient did not require transfusion. A single postoperative death was reported in this series. In this case, a female patient who underwent an uncomplicated biopsy and was found to have lupus nephritis was treated with high-dose steroids and experienced a perforated gastric ulcer. She was a Jehovah's Witness and refused blood transfusions, which ultimately resulted in her death. In a review of renal biopsy in eight morbidly obese patients, Chen and colleagues (53) reported no complications.

The overall frequency of complications after percutaneous needle biopsy of the kidney has been reported as 5% to 10% (114). In a comparison of percutaneous and open renal biopsies, Bolton and Vaughan (30) describe a 12% (20 of 171) complication rate for percutaneous biopsy and an 11% (11 of 100) complication rate for open renal biopsy. The severity of complications was similar, and transfusion requirements were equal at 3% for both the percutaneous and open renal biopsy group.

Convalescence from laparoscopic renal biopsy is rapid. Although Gimenez and colleagues (131) reported a mean hospital stay of 1.7 days (range 0 to 7 days), others have performed the procedure on an outpatient basis (53). Return to activity has been reported to be less than 2 weeks (116,131). Postoperative analgesic requirements are minimal, ranging from no parenteral medications (131) to an average of 3 mg of morphine (range of 0 to 8 mg) (53). Cost data on laparoscopic renal biopsy have not been published.

Evaluation of the Acute Abdomen: Posttraumatic and Postoperative

Exploratory laparotomy offers the greatest accuracy in the diagnosis of intraabdominal injury, but it is associated with significant morbidity. Laparoscopy may provide diagnostic capabilities equivalent to that of open exploration with less morbidity. Initial reports from the general surgery and gynecologic literature demonstrated the utility of laparoscopy in the diagnosis of the acute abdomen associated with trauma.

Laparoscopy was introduced as an alternative diagnostic modality for the evaluation of patients with abdominal injuries associated with trauma in the late 1970s (24,118). Since these reports, the diagnostic and therapeutic potentials of laparoscopy for the acute abdomen have expanded. Cuesta and colleagues (69) prospectively evaluated 65 patients with laparoscopic evaluation of their acute abdomen (excluding free-air and bowel obstruction) and were able to avoid exploratory laparotomy in 80%. In addition, these patients received smaller, more limited incisions for appropriate open surgical management of any laparoscopically defined problems. In a similar study, Chung and co-workers (58) prospectively evaluated 55 patients with an acute abdomen. They determined the accuracy of laparoscopic diagnosis to be the same as exploratory laparotomy. They managed 62% of patients laparoscopically, and these patients required significantly shorter hospitalization than matched controls treated by open operations. Morbidity was not increased by laparoscopy in patients who required conversion to open operation. The additional cost of the laparoscopic approach was not quantitated.

The urologic community is only beginning to explore the potential applications of laparoscopy in the setting of the acute abdomen. Bauer and colleagues (20) described the successful application of laparoscopic diagnosis and treatment of the acute abdomen in the urologic postoperative setting in three patients. In the first two patients, the laparoscopy revealed misplacement and malfunction of a suprapubic cystotomy tube and a gastrostomy tube, respectively. In the third patient, a large postoperative urinoma was managed by laparoscopic drainage and placement of a retroperitoneal drain and a suprapubic cystotomy tube.

Benign Disease: Ablative

Pelvis: Lymphocelectomy

The development of a lymphocele after surgical dissection was first documented by Mori in 1955 (286). The reported incidence of lymphoceles after pelvic lymphadenectomy for prostate cancer and renal transplant has ranged from 0.5% to 10% and 1% to 15%, respectively (304,310).

Small asymptomatic lymphoceles do not require treatment and may be followed with serial ultrasound evaluations. Spontaneous regression has been well documented, although absorption may take several months. Symptomatic or infected lymphoceles require intervention. Lymphoceles are most frequently symptomatic due to pressure exerted on one or more adjacent structures: the external iliac vein (edema of the lower extremity or venous thrombosis), lymphatics (lower extremity lymphedema), bladder (voiding symptoms), allograft ureter (renal dysfunction and obstruction of the collecting system), and anterior abdominal wall (pain and swelling).

The management of lymphoceles has evolved over the past two decades. Sterile lymphoceles have traditionally been managed by open transperitoneal marsupialization with or without omentoplasty. In 1983, Aronowitz and Kaplan (13) reported the first percutaneous drainage of a postoperative pelvic lymphocele. Lymphocele resolution was noted 3 weeks after insertion of a 9-Fr silastic pigtail catheter. More recently, the addition of sclerosing agents to percutaneous drainage has become increasingly popular. Tetracycline was initially used (270,387). Subsequently, successful management of lymphoceles with povidone-iodine has been described (38,130,413). In 1991, the first laparoscopic lymphocelectomy was performed by McCullough and colleagues (255).

Laparoscopic lymphocelectomy is accomplished via the transabdominal approach, and usually is performed with three trocar sites. After inspection of the abdominal cavity, the bluish-gray bulge of the lymphocele is identified in the pelvis (Fig. 18.12). If the lymphocele is readily identified, needle aspiration may be performed to further confirm the diagnosis. If the lymphocele is not readily apparent, decreasing the pressure of the pneumoperitoneum to 5 mm Hg may allow the lymphocele to appear more prominent. Alternatively, laparoscopic sonographic guidance can be used to identify the lymphocele. Failing this, transabdominal standard sonographic guidance can be used to allow for percutaneous puncture of the lymphocele, which can then be expanded with indigo carmine–stained saline. Occasionally, the location of the bladder relative to the lymphocele may be unclear. If this is the case, the bladder can be distended through the Foley catheter to help identify it relative to the lymphocele; the bladder should then be drained with an indwelling catheter.

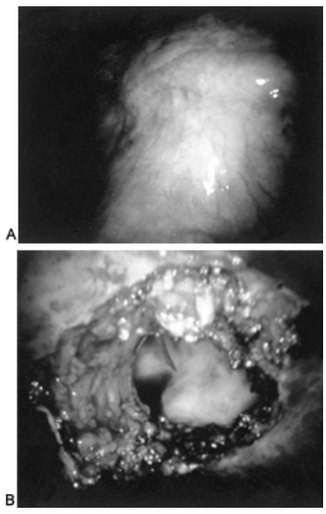

FIGURE 18.12. A: Laparoscopic inspection revealing the bluish-gray bulge of the lymphocele in the pelvis. **B:** Unroofed lymphocele with percutaneously placed needle visible within. See also Color Figure 18.12.

After confirmation of the lymphocele, using electrocautery scissors a 3- to 4-cm window is excised from the most translucent, thinnest portion of the lymphocele wall. Meticulous hemostasis about the edges of the peritoneal defect is obtained. The laparoscope is advanced into the lymphocele cavity, and intracystic loculations are disrupted by circular motions of the laparoscope. Complete decompression of the lymphocele can be further confirmed with intraoperative transabdominal or laparoscopic ultrasonography. If readily available, a pedicle of omentum may be advanced into the lymphocele cavity and anchored to the cut edge of the lymphocele with titanium clips.

Gill and co-workers (124) compared laparoscopic and open internal marsupialization of pelvic lymphoceles. This retrospective review compared three populations: 12 patients who underwent laparoscopic lymphocelectomy, 13 patients who had open surgery between 1990 and 1993, and 13 patients who had open surgery between 1980 and 1989. Baseline demographics were comparable among these three nonrandomized groups.

No patient managed laparoscopically experienced recurrence of a lymphocele. In contrast, 7 of the 26 patients (27%) managed with open surgery had recurrent lymphoceles. Although laparoscopic management required a longer operative time (177 versus 155 minutes), the patients who were managed laparoscopically had decreased blood loss (23 versus 68 mL), earlier resumption of oral food intake (0.9 versus 2.3 days), and an abbreviated convalescence (2.2 versus 5.6 weeks) (124).

Several other authors have addressed the issue of post–renal transplant lymphoceles and laparoscopic management. Bischof and colleagues (27) reported on 919 kidney transplants that were complicated by 63 (6.8%) symptomatic lymphoceles. Thirty-five of the 63 patients were drained percutaneously, with 47 aspirations (without associated sclerotherapy); 20 lymphoceles were drained by open surgery; and eight lymphoceles were drained laparoscopically. In both surgical groups, six patients each had previously been treated with percutaneous drainage, but reaccumulation of lymph fluid prompted more definitive management. The patients who underwent primary percutaneous drainage experienced local infection in 8 of 47 (17%) cases. One of these patients required open surgery after developing an abscess. Fourteen of 47 (30%) patients had recurrence. There was a single complication in the open surgery population: recurrence of a lymphocele that required a second open procedure. There were no complications and no recurrences in the population undergoing laparoscopic lymphocelectomy. Operative times were not reported. Similar excellent efficacy for laparoscopic lymphocelectomy has been reported by Melvin and co-workers (272) and by Shaver and colleagues (382), with eight and seven patients treated, respectively, without any recurrences.

However, not all reports have demonstrated superior efficacy with laparoscopic drainage. In a series reporting 59 lymphoceles associated with renal transplants, Gruessner and colleagues (142) reported recurrence rates of 48% (13 of 27), 22% (5 of 23), and 33% (3 of 9) for percutaneous, open, and laparoscopic drainage of lymphoceles, respectively. Patients drained laparoscopically had a shorter mean hospital stay than the patients treated with open surgery (3 versus 7 days). Operative time was not reported. Hospital costs for patients undergoing successful laparoscopic drainage were $8,300; for patients with primary open drainage, the costs were $15,680. In 36% (5 of 14), however, there was conversion from laparoscopic to open technique. Hospital cost for this population was $18,550. The only complication reported by the authors was intraoperative bleeding from the right inferior epigastric artery caused by a 5-mm trocar. The injury was repaired without conversion to open surgery (142). On the basis of this series, the authors concluded that posttransplant lymphoceles located lateroposterior and lateroinferior to the renal allograft were technically

difficult to access, and may be better managed by open drainage.

Laparoscopic lymphocelectomy has clearly become a viable option for the management of lymphoceles after both renal transplant and pelvic lymphadenectomy. In cases of multiloculated and recurrent lymphoceles, the laparoscopic lymphocelectomy is the procedure of choice, offering patients excellent efficacy, low morbidity, and an expeditious and more comfortable convalescence. Although limited data are available, it appears that laparoscopic management of lymphoceles may have the additional benefit of reduced overall cost.

Pelvis: Varicocelectomy

Normally manifesting in the adolescent period, varicoceles are found in 15% of the male population (369); however, they are described in up to 40% of men seeking treatment for infertility (64). Most men with varicoceles are asymptomatic, but in some cases, patients may have testicular pain or signs of testicular atrophy (140).

Before 1990, clinically significant varicoceles were treated with either surgical ligation or a percutaneous approach using an occlusive transvenous technique under fluoroscopic guidance (414). Surgical ligation of the spermatic veins has been accomplished by an inguinal (187), retroperitoneal (321), or subinguinal approach (248). The laparoscopic varicocelectomy was first described by Sanchez de Badajoz and co-workers (364) and subsequently was developed in the United States by Winfield and Donovan (440).

Laparoscopically, the varicocele is typically managed via a transperitoneal approach. The ipsilateral internal spermatic vessels are identified and the peritoneum is incised laterally. A T-shaped incision is made by incising toward the iliac vessels. Having gained access to the retroperitoneum, the packet of testicular vessels is dissected from the psoas muscle. Testicular traction may be intermittently applied to aid in the identification of the spermatic cord. Dissection of the testicular veins from the testicular artery is then performed. Identification of the testicular artery is aided by intraoperative laparoscopic Doppler sonography or the topical application of 1% lidocaine or papaverine to the spermatic cord. Spermatic veins are isolated, interrupted with clips, and transected. In contrast, other authors have greatly simplified the laparoscopic varicocelectomy by proceeding to secure and divide both the testicular veins and the testicular artery. Interestingly, the positive impact on fertility has been similar with either approach.

Several studies have compared the results of the different modalities for management of varicoceles. Trials comparing the results of sclerotherapy, open varicocelectomy, and laparoscopic varicocelectomy are presented in Table 18.2 . Abdulmaaboud and colleagues (3) retrospectively compared 301 patients with 417 varicoceles undergoing treatment with open surgery (131 cases), percutaneous retrograde sclerotherapy (163 cases), or laparoscopic varicocelectomy (123 cases). All three modalities were equally efficacious with regard to recurrence rate and improvement in semen parameters postoperatively. Specifically, the recurrence rates with open, percutaneous sclerotherapy, and laparoscopic treatment were 10.5%, 11.2%, and 9.1%, respectively. Comparison of semen parameters before and after treatment showed significant and equal increases in density and motility, as well as a significant reduction in abnormal forms in all groups. There was no significant difference in pregnancy rates with open surgery, sclerotherapy, and laparoscopy (37%, 41%, and 39%, respectively) (3).

Source	Indications	Technique	No.	Complications		OR Time (min)	Analgesics	Length of Stay	Full Recovery (days)	Cost	Failure Rate	Follow-up Period	Pregnancy Rate
				Minor	Major								
Abdulmaaboud et al. (3)	Infertility/pain	Open retroper	131	7.60%	None	22	NA	Outpatient	8	1X	11.20%	13 months	36.6%
		Sclerotherapy	163	6.70%	None	59	NA	Outpatient	1	0.2X	36.90%	12 months	41.4%
		Lap transper	123	4.90%	None	35	NA	Outpatient	3	2X	9.10%	12.5 months	39.1%
Winfield and Donovan (440)	Infertility	Lap transper	15	NA	NA	82.3	13.7 tab Tylenol No. 3	Outpatient	4.9	NA	0%	NA	NA
		Lap transper lift	7	NA	NA	170	22.5 tab Tylenol No. 3	Outpatient	6.6	NA	0%	NA	NA
		Open subinguinal	19	NA	NA	35.6	10.9 tab Tylenol No. 3	Outpatient	5.1	NA	0%	NA	NA
Mandressi et al. (247)	Infertility/pain	Open retroper	120	0.60%	None	21	26% required	3.2 days	11	$1,128	6.70%	NA	NA
		Lap transper	160	7.50%	None	32.1	6% required	2.1 days	5	$1,810	3.10%	NA	NA
Nickel et al. (305)	Infertility	Open subinguinal	27	NA	NA	38.8	9.2 tab Tylenol No. 3	Outpatient	4.2	NA	NA	NA	NA
		Open retroper	28	NA	NA	44.1	7.5 tab Tylenol No. 3	Outpatient	3.4	NA	NA	NA	NA
		Lap transper	14	NA	NA	118	8.4 tab Tylenol No. 3	Outpatient	3.4	NA	NA	NA	NA
Totals—laparoscopic			**319**	**6.40%**	**None**	**42.4 min**			**4.06**	**$1,810**	**5.70%**		
Totals—open			**325**	**4.20%**	**None**	**25.4 min**			**8.2**	**$1,128**	**9%**		
Totals—sclerotherapy			**163**	**6.70%**	**None**	**25.4 min**			**1**	**NA**	**36.90%**		

Note: "X" in the Cost column means that the author's institution does not permit publication of cost. Open surgery was therefore assigned an arbitrary value (X), and the other values are arbitrary.
All columns list mean values.
Lap, laparoscopic; NA, not available; retroper, retroperitoneal; transper, transperitoneal.

TABLE 18.2. VARICOCELECTOMY—COMPARATIVE TRIALS

However, the efficacy of percutaneous sclerotherapy is often overestimated; in the Adulmaaboud and colleagues (3) series, 26% of patients failed attempted percutaneous sclerotherapy due to technical difficulties. Problems resulting in failure of percutaneous management included perforation of the spermatic vein (4.3%), abnormal anatomy (10.4%), or spasm of the spermatic vein with failed catheterization (11.6%). If technical failures are included, the efficacy of percutaneous sclerotherapy decreases to 66%. This reported technical failure rate is consistent with most contemporary reports. In addition, although the overall success rate with left-sided varicoceles was 83%, the success rate with right-sided varicoceles was only 51% (3). Minor complications were associated with sclerotherapy; these included a groin hematoma, three femoral artery punctures, and minor contrast media reactions in seven patients. There were no operative complications reported in patients undergoing open or laparoscopic varicocele repair.

Sclerotherapy was carried out as an outpatient procedure performed under local anesthesia. Open surgery used a retroperitoneal approach and was performed with regional anesthesia in most cases, and laparoscopy was done under general anesthesia. Operative time for open surgery was significantly shorter than either sclerotherapy or laparoscopy. Open surgery required an average of only 22 minutes compared with 59 minutes and 35 minutes for management by sclerotherapy and laparoscopy, respectively. Patients undergoing sclerotherapy typically returned to normal activity within 1 day, significantly faster than the other management modalities. The open group experienced a significantly longer convalescence (8 days) than the laparoscopic group (3 days). Although not quantitated, the cost of sclerotherapy was reported to be one-fifth to one-fourth the cost of open surgery, and the cost of laparoscopy was approximately double that of open surgery (3).

In another large series, the relative merits of open and laparoscopic varicocele repair were prospectively evaluated by Mandressi and co-workers (247). Comparison of 120 patients managed by open surgery using Palomo's retroperitoneal technique with 160 patients who underwent laparoscopic repair revealed equal efficacy regarding both recurrence and improvement in semen parameters. Recurrence

rates of 6.7% (8 of 120) and 3.1% (5 of 160) were reported for the open and laparoscopic groups, respectively. Both populations manifested significant and equal improvement in postoperative semen parameters, including volume, sperm count, motility, and morphology. Pregnancy rates were not reported.

The mean total operative time for the laparoscopic group was 32 minutes, which was significantly longer than the open population, which had a mean operative time of 21 minutes. There were no intraoperative complications in either group. Minor postoperative complications occurred in 0.6% and 7.5% of the laparoscopic and open surgery groups, respectively. The only complication in the laparoscopic group was a case of shoulder pain that resolved spontaneously over 3 days. In the surgical group, two hydroceles (1.6%) and seven wound infections (5.8%) were recorded. The number of patients requiring postoperative analgesia was significantly higher in the surgical group. Only 6% of patients in the laparoscopic group required pain medications, whereas 26% of patients managed by open surgical venous ligation required pain medicines (247).

Hospital stay was significantly shorter for patients undergoing laparoscopic versus open varicocelectomy (2.1 days versus 3.2 days, respectively). On average, patients treated laparoscopically returned to normal preoperative activity within 5 days, whereas the patients treated surgically required 11 days. Overall costs were significantly more expensive for the laparoscopic than for the open procedure: $1,810 versus $1,130.

In contrast to a retroperitoneal open approach (i.e., Palomo technique), the subinguinal repair of a varicocele is thought to be less invasive and potentially less morbid. In this regard, Hirsch and colleagues (168) prospectively reported a comparison of open subinguinal and laparoscopic varicocele repair. Seventeen patients undergoing laparoscopic varicocele repair were compared with nineteen patients managed with the open subinguinal approach. Recurrence rates and changes in semen parameters were not reported. Average operating time was significantly longer for the laparoscopic group than for the open group (82 versus 36 minutes).

There were two reported complications in the open group: a minor wound infection and a subcutaneous hematoma. Both resolved promptly with conservative management. In the group treated laparoscopically, two patients failed laparoscopic management due to technical difficulties. In addition, two of the remaining 15 laparoscopically managed patients experienced complications that required overnight admission. One patient was observed after repair of laparoscopic trocar injury to the inferior epigastric vein. A second patient experienced nausea necessitating overnight observation (168).

All subinguinal cases were performed under local anesthesia with sedation; the laparoscopic group received general anesthesia. Postoperative analgesic requirements and convalescence were not significantly different for either management modality (168). Cost analysis was not performed in this study.

Nickel and colleagues (305) compared results of inguinal and subinguinal bilateral varicocele repairs with a published series of laparoscopic bilateral varicocele repairs. Twenty-seven patients underwent bilateral subinguinal repairs, and 28 patients underwent bilateral inguinal repairs. Results were compared with 14 patients undergoing laparoscopic bilateral varicocele repairs. Mean operative times for subinguinal, inguinal, and laparoscopic repairs were 39, 44, and 118 minutes, respectively. Pain medication was reported in number of pills of Tylenol with Codeine No. 3. Mean number of pills for subinguinal, inguinal, and laparoscopic bilateral repairs were 9.2, 7.5, and 8.4 pills, respectively. Mean time for return to work for the three groups was 4.2, 3.4, and 3.4 days, respectively. No advantage was noted for the laparoscopic approach.

To date, there does not exist a prospective, randomized trial comparing the efficacy of different modalities for varicocele repair regarding improvement in semen parameters or pregnancy rate. It seems clear, however, that percutaneous sclerotherapy provides an inexpensive, least invasive, and cost-effective first-line solution to the problem of a left varicocele. For those patients who do not respond to sclerotherapy, the next most reasonable option would appear to be a subinguinal open approach. Laparoscopic varicocelectomy, although feasible and safe, remains more costly and less efficient than either of the other two approaches; its use should be reserved for the rare patients in whom the percutaneous or subinguinal approach fails or when another laparoscopic procedure is to be accomplished concomitantly. Although only limited data are available, it appears that even when bilateral varicocele repair is required, laparoscopy should still not be the first line of therapy; indeed, in these patients, the subinguinal approach requires less operative time and results in equal postoperative discomfort and an equally expeditious convalescence.

Retroperitoneum: Adrenalectomy

Laparoscopic adrenalectomy was introduced by Gagner and colleagues (110) in 1992. Subsequent advances in minimally invasive surgery have allowed laparoscopy to become the technique of choice for management of the majority of surgical diseases of the adrenal gland. Indications for adrenalectomy include aldosteronoma, pheochromocytoma, adrenal cysts, adrenal myelolipoma, Cushing's disease, and Cushing's adenoma.

Although initially described as a transperitoneal approach, laparoscopic adrenalectomy can currently be performed using either a transperitoneal or retroperitoneal technique. The transperitoneal approach is performed with the patient in the flank position. Typically, for a right adrenal lesion, after achieving a pneumoperitoneum and

placing four subcostal ports, a transverse incision is made in the posterior parietal peritoneum (i.e., hepatic posterior coronary ligament) parallel to and just below the inferior edge of the liver. The incision extends from the line of Toldt, laterally, to the inferior vena cava, medially. Dissection begins between the medial border of the adrenal gland and the lateral border of the vena cava (Fig. 18.13); Gerota's fascia is incised and the main adrenal vein is identified and secured with three clips. The adrenal vein is then divided, leaving two clips on the caval side. Superiorly, the gland is dissected free from the diaphragm, where the diminutive inferior phrenic tributaries to the adrenal are encountered and secured with electrocautery. Next, the inferior portion of the dissection is completed, staying well away from the renal hilum. Last, the gland is freed laterally, following which it is placed in a laparoscopic sack and removed. For much of the periadrenal dissection through the perirenal fat, the harmonic scalpel can be helpful.

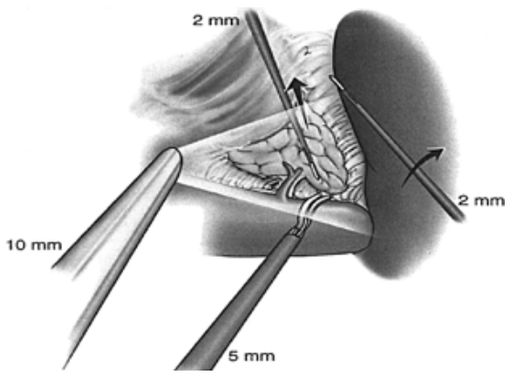

FIGURE 18.13. After incision of Gerota's fascia, the main adrenal vein is identified. (Reprinted from Spencer JR, O'Conor VJ Jr. Comparison of procedures for stress urinary incontinence. *AUA Update Series* 1987;18:259, with permission.)

Left transperitoneal adrenalectomy requires mobilization of the spleen and the splenic flexure of the descending colon; dissection of the latter also allows safe medial displacement of the tail of the pancreas. An incision in the peritoneum is made along the line of Toldt extending from the diaphragm caudal, past the splenic flexure of the descending colon; in doing this, any connections between the spleen and diaphragm are released (i.e., splenophrenic ligaments). A counterincision is then made perpendicular to the line of Toldt at the inferior border of the spleen; with this T-shaped incision, the splenic flexure of the colon is mobilized as the lienocolic ligament is secured and divided. Next, the kidney is further separated from the spleen by incising the lienorenal ligament. Occasionally, for a large adrenal mass, the tail of the pancreas must be identified and mobilized off the anterior surface of the adrenal gland.

At this time, the left renal vein may or may not be visible; if it is not, it may be necessary to trace the gonadal vein upward to identify its juncture with the left renal vein. In doing this, the anterior part of Gerota's fascia is incised. Dissection of the anterior and superior portions of the left renal vein allows identification of the left adrenal vein; it is secured with four vascular clips and divided. The medial dissection is then performed with any of the diminutive aortic branches to the adrenal gland being electrocoagulated. The gland is then freed laterally from the medial surface of the kidney. The specimen is placed into a laparoscopic entrapment sack for extraction.

Access for retroperitoneal laparoscopic adrenalectomy is gained via a 2-cm muscle-splitting incision in the midaxillary line just caudal to the tip of the twelfth rib. Balloon or blunt dilation is used to create a working space, and insufflation to 12 mm Hg is performed. A second trocar is placed on the vertebral side of the first trocar. The peritoneum is mobilized medially, allowing for placement of a third trocar on the medial side of the first trocar. Gerota's fascia is opened, exposing the adrenal gland. At times, a laparoscopic ultrasound unit is helpful to demarcate the location of the adrenal gland, especially in patients with Cushing's disease. The gland is dissected circumferentially. The adrenal vein is clipped and divided during the final phase of the dissection. The specimen is then placed in an entrapment sack and removed.

Although a prospective study comparing the merits of laparoscopic and open adrenalectomy has not been performed, a number of authors have retrospectively compared these modalities. Trials comparing the results of open and laparoscopic adrenalectomies are presented in Table 18.3 . In the following few paragraphs, studies have been selected in which transperitoneal open and laparoscopic, retroperitoneal open and laparoscopic, and transperitoneal laparoscopic versus open retroperitoneal approaches have been compared. In each comparison, the advantages of laparoscopy are apparent.

Source	Indications	Technique	Number	Complications		EBL (mL)	OR Time (hr)	Analgesics	Hospital Stay	Full Recovery	Cost
				Minor	Major						
Aldrighetti et al. (7)	Incidental	Open	12	2/12 (17%)	2/12 (17%)	NA	2.9	3 days	7.9 days	NA	NA
		Lap/transper	8	2/8 (25%)	0	NA	2.5	1.7 days	3.5 days	NA	NA
Bonjer et al. (31)	<7 cm	Open	30	8/30 (27%)	0	125	1	3.0 days	7.0 days	NA	NA
		Lap/retroper	42	3/42 (7%)	0	20	1.5	1.0 days	4.0 days	NA	NA
Brunt et al. (37)	All benign lesions, <8 cm	Open/transper	25	16/25 (64%)	3/25 (12%)	408	2.4	142 mg morphine	8.7 days	NA	$16,972
		Open/retroper	17	9/17 (53%)	0	366	2.3	54 mg morphine	6.2 days	NA	$12,266
		Lap/transper	24	4/24 (16.7%)	0	104	3.1	15.9 mg morphine	3.2 days	10.6 days	$13,184
Guazzoni et al. (143)	Benign hyperfunc-tioning	Open	20	7/20 (35%)	4/20 (20%)	450	2.4	320 mg ketoprofen	9 days	16 days	NA
		Lap/transper	20	0	1/20 (5%)	100	2.8	175 mg ketoprofen	3.4 days	9.7 days	NA
Jacobs et al. (190)	All benign lesions	Open	19	6/19 (32%)	0	263	2.5	NA	5.1 days	NA	$13,720
		Lap/transper	19	1/19 (5%)	0	109	2.7	NA	2.3 days	NA	$10,929
Linos et al. (240)	All lesions (<6 cm)	Open/transper	86	1/86 (1.2%)	4/86 (4.7%)	NA	2.6	3.4 days	8.0 days	NA	$2,724
		Open/retroper	61	5/61 (8.2%)	0	NA	1.8	2.3 days	4.5 days	NA	together
		Lap/transper	18	0	0	NA	1.9	1.1 days	2.3 days	NA	$2,920
MacGillivray et al. (246)	All lesions	Open	12	2/12 (16.7%)	3/12 (25%)	NA	2.8	NA	7.9 days	11.6 days	NA
		Lap/transper	14	3/14 (21.4%)	0	NA	4.3	NA	3.0 days	7.6 days	NA
Naito et al. (294)	<4 cm	Open	11	1/11 (9%)	0	150	2.8	11/11 (100%) needed	9.0 days	NA	NA
		Lap/transper	6	1/6 (16.7%)	1/6 (16.7%)	200	3.8	1/6 (16.7%) needed	9.0 days	NA	NA
Printz (341)	<10 cm	Open/tramper	11	NA	NA	391	2.9	1002 mg meperidine	6.4 days	NA	NA
		Open/retroper	13	NA	NA	288	2.3	801 mg meperidine	5.5 days	NA	NA
		Lap/transper	10	NA	NA	228 (ant. only)	3.5	93 mg meperidine	2.1 days	NA	NA
Shen et al. (384)	Hyperaldosteronism	Open	38	2/38 (5.3%)	2/38 (5.3%)	NA	NA	NA	NA	NA	NA
		Lap	42	0	0	NA	NA	NA	NA	NA	NA
Staren et al. (397)	All lesions	Open	20	NA	NA	NA	3	NA	6.1 days	NA	NA
		Lap/both	21	NA	NA	NA	3.4	NA	2.2 days	NA	NA
Thompson et al. (415)	All lesions	Open/retroper	50	5/50 (10%)	0	NA	2.8	48 mg morphine	5.7 days	7.0 wk	$6,000
		Lap/transper	54	17/54 (32%)	0	NA	2.1	28 mg morphine	3.1 days	3.8 wk	$7,000
Winfield et al. (444)	<6 cm and nonmalig-nant	Open	17	3/17 (17.6%)	0	266	2.3	28.8 mg morphine	6.2 days	6.5 wk	NA
		Lap/transper	20	9/20 (45%)	2/20 (10%)	183	3.7	14.8 mg morphine	2.7 days	3.1 wk	NA
Yoshimura et al. (457)	All lesions	Open	25	2/25 (8%)	0	345	2.2	3.4 doses	18.0 days	NA	NA
		Lap/both	28	8/28 (28.6%)	0	370	6.2	2.7 doses	12.0 days	NA	NA
Totals											
Laparoscopic			326	16%	1.40%	94 mL	3 hr		3.5 days	18.3 days	$8,301
Open			467	16%	4.20%	303 mL	2.4 hr		6.0 days	37.2 days	$6,152

All columns list mean values.
Both, transperitoneal and retroperitoneal approaches combined; EBL, estimated blood loss; lap, laparoscopic; NA, not available; retroper, retroperitoneal; transper, transperitoneal.

TABLE 18.3. ADRENALECTOMY—COMPARATIVE TRIALS

Guazzoni and co-workers (143) compared 20 transperitoneal laparoscopic and 20 open (both transperitoneal and retroperitoneal) adrenalectomies in the management of benign hyperfunctioning adrenal tumors. There were no conversions to open procedures. There was no significant difference in operative times noted, with laparoscopic and open adrenalectomies requiring 2.8 and 2.4 hours for completion, respectively (143). Estimated blood loss was significantly lower in the laparoscopic population at 100 versus 450 mL. Complications were encountered significantly more frequently in the open group (two patients experienced pneumothorax, two patients experienced wound infections, three patients required transfusion, two patients experienced postoperative ileus, and two patients had postoperative fevers greater than 38°C). In the laparoscopic group there was only one complication, a port site wound infection (143). Postoperatively, the patients

treated laparoscopically experienced significantly less pain: 175 mg of ketoprofen compared with 320 mg of ketoprofen. Length of hospital stay and convalescence were also significantly shorter for patients treated laparoscopically: 3.4 days versus 9 days and 9.7 days versus 16 days, respectively (143).

Thompson and colleagues (415) retrospectively compared 50 patients managed with open retroperitoneal adrenalectomy to 54 patients managed by transperitoneal laparoscopic technique. Seven patients in this series required conversion to open adrenalectomy. However, experience significantly affected the conversion rate; the conversion rate of 12% in the first 11 patients was reduced to 4.5% in the last 43 patients. Operative times were 40 minutes less for patients managed via the open approach: 2.1 versus 2.8 hours. Complications in the laparoscopic group occurred in 10% versus 18% in the open group. Most interestingly, these authors also sought to document the incidence of late complications. Late complications in the open group occurred in 54% of patients, including chronic pain at the wound site, severe laxity of the abdominal wall musculature, and bothersome flank numbness. In contrast, no late complications occurred in patients managed laparoscopically. The laparoscopic approach tended to be more expensive than the open approach: $7,000 versus $6,000.

Adrenal tumors less than 7 cm in diameter managed with either open retroperitoneal or laparoscopic retroperitoneal technique were retrospectively compared by Bonjer and colleagues (32). Forty-two laparoscopic adrenalectomies were compared with thirty open procedures. Two laparoscopic adrenalectomies required conversion to open surgery. Complications were significantly less in the laparoscopic population, 7% versus 27% (32). Mean operative times were 30 minutes longer for the laparoscopic group (1.5 versus 1.0 hours). However, the laparoscopic group experienced significantly less discomfort, requiring an average of only 1 day as opposed to 3 days of pain medication. Hospital stay for the laparoscopic group was also significantly shorter: 4 days versus 7 days (32).

Whereas most authors have sought to compare open to laparoscopic techniques, Takada and associates (410) compared the two types of laparoscopic approaches to each other: transperitoneal (27 cases) versus retroperitoneal (11 cases). In four cases (36%), laparoscopic retroperitoneal exploration was converted to transperitoneal adrenalectomy because of difficulty during the retroperitoneal exploration in three cases and secondary to a pancreatic injury in one case. In contrast, with the transperitoneal approach, there were no conversions. Mean operative time for retroperitoneal adrenalectomy was 4.1 hours, which was not significantly longer than the 3.9 hours required for transperitoneal laparoscopic adrenalectomy (410). Similarly, there was no difference in time to oral intake and time to ambulation. However, the complications and length of stay associated with each technique were not reported.

Overall, the laparoscopic transperitoneal approach is preferred by some authors for left adrenalectomy and the retroperitoneal approach is preferred for the right adrenal due to the posterior insertion of the right adrenal vein into the inferior vena cava. Also, some authors prefer a transperitoneal approach in cases of Cushing's syndrome due to the large amount of fatty tissue surrounding the adrenal gland that can greatly impede a retroperitoneal dissection.

Of all the indications for adrenalectomy, none is more challenging than pheochromocytoma given its potential to cause a hypertensive crisis and volume-related problems. A drawback to the laparoscopic approach is that it precludes thorough exploration of the para-aortic region and the contralateral adrenal gland. However, scintigraphy with ^{131}I-meta-iodobenzylguanidine, CT scanning, and MRI of the abdomen are capable of localizing pheochromocytomas very precisely, thereby, in many centers, precluding the need for additional surgical exploration. Bonjer and co-workers (32) reported successful laparoscopic management of eight pheochromocytomas. In this series, intraoperative systolic blood pressure did not exceed 180 mm Hg, heart rate remained below 140 beats per minute, and cardiac arrhythmias were not encountered. Similarly, Gagner and co-workers (109) reported on 17 patients who had 23 pheochromocytomas; 6 patients had bilateral tumors. All cases were completed laparoscopically. Unilateral adrenalectomy required an average of 3.8 hours and bilateral cases required 6.3 hours for completion. Hypertensive crises with systolic blood pressures greater than 200 mm Hg or diastolic pressure greater than 100 mm Hg occurred in nine patients, and all were well controlled pharmacologically. Hypotension, defined as systolic blood pressure less than 80 mm Hg, occurred at induction or after venous clamping in three bilateral and six unilateral cases and was corrected with volume expansion or pressor agents (109). These findings are consistent with recent recommendations from The Cleveland Clinic demonstrating good blood pressure control in patients with pheochromocytomas with hydration and calcium channel blockers, thus obviating the use of α-blockers for a prolonged period preoperatively (424). Only 4 of 17 patients (24%) required continued antihypertensive medications postoperatively. Complications were noted in 6% of patients.

When all of the series are reviewed it becomes apparent that the laparoscopic approach, whether retroperitoneal or transperitoneal, provides the following benefits: less blood loss, less need for analgesics, shorter hospital stay, and more rapid convalescence. When comparing the laparoscopic transperitoneal and retroperitoneal approaches for adrenalectomy, no significant differences have been reported. In sum, at this time, the laparoscopic adrenalectomy, like

cholecystectomy, has largely supplanted open surgery for adrenal disease.

Retroperitoneum: Renal Cyst Decortication—Simple Peripheral Cyst

Simple renal cysts are common incidental findings. They occur in at least 24% of all individuals older than 40 years of age and in 50% of individuals older than 50 years of age who are evaluated with abdominal CT scans performed for nonurologic indications (230). Simple cysts only rarely are discovered due to clinical manifestations. However, flank pain, abdominal pain, hematuria, recurrent infection, hypertension, and obstructive uropathy alone or in combination are the most common reasons that simple cysts require intervention (10).

Historically, open decortication was the treatment modality of choice for a symptomatic renal cyst. Although highly efficacious for eliminating cysts, one-third of patients undergoing open surgical management experienced perioperative complications, including wound infections, urinary retention, atelectasis, pneumonia, and venous thrombosis (227). Open surgical management is also associated with significant postoperative pain from the flank or abdominal wound and a postoperative convalescence of 1 month or more.

The advent of minimally invasive urologic technologies engendered less invasive techniques for the management of renal cysts. Alternative techniques for ablation of renal cysts include percutaneous cyst aspiration with sclerosis, retrograde endoscopic cyst incision with marsupialization, and percutaneous resection with fulguration (172,178,210). The least invasive of these options is cyst aspiration with sclerosis. This is an easily performed procedure done with local anesthesia on an outpatient basis with a low morbidity rate. Sclerosis of the cyst can be performed with a number of agents: bismuth phosphate, isophendylate, ethanol, and autologous blood. Reports of aspiration and sclerosis have demonstrated varying degrees of success.

Holmberg and Hietala (172), using sclerotherapy with bismuth phosphate, reported elimination of 10% of cysts and decrease in the size of another 36% at 3 years follow-up among 54 cysts. Complications included eight (15%) patients with postprocedure pain, two patients (4%) with perirenal hematomas not requiring transfusion, and five patients (9%) with fever for 1or 2 days (172). Liatsikos and colleagues (239) reported a series of 24 patients with large symptomatic renal cysts. Treatment consisted of aspiration under ultrasound guidance and sclerosis with alcohol and tetracycline. Two patients experienced mild pain with alcohol injection, but the procedure was successfully completed. One patient reported severe pain with tetracycline injection necessitating termination of the procedure. This patient underwent surgical unroofing of the cyst 3 weeks later. With a mean follow-up period of 20 months, all patients remained asymptomatic. Follow-up ultrasound evaluations revealed resolution in 11 of 24 (46%) and small residual cyst cavities in 12 of 24 (50%). There were no complications in this series.

Aspiration and sclerosis should be the primary form of intervention for symptomatic renal cysts. It should be noted, however, that cyst puncture cytology has been shown to be only 80% to 85% sensitive in diagnosing renal malignancy (359,416); however, in the face of a Bosniak 1–type cyst with the aspiration of clear fluid and a negative cytology, the cyst is invariably benign.

Laparoscopic renal cyst ablation has been described using both transperitoneal and retroperitoneal approaches; it has been used as both a primary and secondary modality for cyst therapy, but as previously stated, it should be most commonly used only when percutaneous aspiration and sclerosis fails in the treatment of a documented, symptomatic benign cyst. The transperitoneal approach is performed with the patient in the lateral decubitus position. If the cyst is in close proximity to the renal collecting system, a ureteral catheter may be placed before laparoscopy to facilitate identification of the ureter and renal pelvis. Typically the procedure can be performed with three trocar sites: umbilical, below the costal margin in the midclavicular line, and infraumbilical in the midclavicular line. The line of Toldt is incised and the colon reflected medially to expose the kidney. The cyst is typically readily identified as a bulge in Gerota's fascia. The fascia and perirenal fat are dissected off of the cyst. The outer cyst wall is then excised and sent for histopathology. The cyst base is then carefully inspected; any mural nodule or lesion is biopsied at this time and sent for frozen section. If the cyst is peripheral and not in close contact with the collecting system, the argon beam coagulator can then be used to fulgurate the base of the cyst.

The laparoscopic retroperitoneal approach is performed with the patient in the lateral decubitus position. Access just behind the tip of the twelfth rib is performed with either balloon dilation or digital dissection of the retroperitoneal space. Two additional trocars are placed: one anterior and slightly superior and one inferior and slightly posterior to the original access site. Incision of Gerota's fascia and blunt dissection of the perirenal fat are performed to expose the cyst. As with the transperitoneal approach, a segment of the cyst wall is excised and the base of the cyst is treated in the same manner.

Jahnsen and Solhaug (191) first described laparoscopic management of the symptomatic renal cyst. Rubenstein and colleagues (359) subsequently reported a series of ten patients with symptomatic renal cysts that were managed laparoscopically. Six patients had simple cysts, two patients had polycystic renal disease, and there was a single case each of a peripelvic cyst and multiple simple cysts. The indication for surgery in all ten patients was chronic pain; six patients had undergone prior needle aspiration of their cyst. Two patients, both of whom had undergone a negative preoperative

aspiration, were discovered to have renal malignancies at the time of surgery, and both underwent radical nephrectomy. The eight remaining patients were all asymptomatic without radiographic evidence of cyst recurrence at a mean follow-up of 10 months. Operative times ranged from 50 minutes to 4 hours (mean of 2 hours, 27 minutes), including one patient who underwent radical nephrectomy under the same anesthesia. There were no intraoperative complications and only two postoperative complications. Six patients did not require any postoperative parenteral narcotics. Median postoperative parenteral narcotic requirement was two tablets. Seven patients were discharged from the hospital on postoperative day 1, and overall mean hospital stay was 2.2 days. The mean interval to resumption of normal activity was 9 days. There were no long-term complications at a mean follow-up of 10 months (359).

Rassweiler and colleagues (347) reported experience with retroperitoneal management of 50 renal cysts. This report incorporated patients with septated or suspicious cysts, large simple cysts after failure of percutaneous aspiration and sclerotherapy, multiple renal cysts with deterioration of renal function, and simple hilar cysts that obstructed the collecting system. Operative time ranged from 30 to 130 minutes (mean of 80 minutes), and average hospital stay was 5.4 days. Mean opiate dose was 1.2 doses per patient. There were two (4%) complications, including one retroperitoneal hematoma requiring transfusion (347).

All of these studies suffer from the same problem: lack of long-term (i.e., longer than 1 year) objective follow-up and a uniform patient population. In this regard, because follow-up data are largely unavailable, no valid statements can be made regarding the need to fulgurate the base of the cyst, whether a transperitoneal or retroperitoneal approach is preferable, or whether it is necessary to place fat or omentum into the cyst cavity to prevent a recurrence.

Simple cysts are common and rarely have clinical manifestations. Although laparoscopic simple cyst decortication is feasible, safe, and effective, this type of intervention is rarely required. Initial management of symptomatic cysts should include aspiration and sclerosis for two reasons. First, this will largely preclude the unwelcome “surprise” of a renal cell cancer. Second, many simple cysts will respond well to sclerotherapy, thereby avoiding a more invasive, albeit laparoscopic procedure. As such, laparoscopic simple cyst decortication should be reserved for those patients who continue to suffer symptoms when percutaneous sclerotherapy fails.

Retroperitoneum: Simple Nephrectomy

Gustav Simon from the Medical School of Heidelberg University performed the first successful open nephrectomy in 1869. Despite technical modifications, this open surgical procedure remained essentially unchanged until the first laparoscopic total nephrectomy was performed by Clayman and colleagues in 1990 (61). The indications for simple laparoscopic nephrectomy parallel those of open nephrectomy and include any benign renal pathology resulting in sepsis, bleeding, pain, compression of surrounding structures, or hypertension that is difficult to control medically. Certain conditions, such as xanthogranulomatous pyelonephritis (XGP) or nephrectomy in patients with autosomal-dominant polycystic kidney disease (ADPKD), require special consideration (see sections on XGP and ADPKD).

Laparoscopic simple nephrectomy has been performed using either a transperitoneal or retroperitoneal technique (144). The transperitoneal procedure is performed in the lateral decubitus position. Twelve-millimeter trocars are placed at the umbilicus, in the midclavicular line under the costal margin, and 3 cm inferior to the umbilicus in the midclavicular line. Two additional 5-mm trocars are placed in the anterior axillary line at the tip of the twelfth rib and at the level of the umbilicus. Recent modifications have included elimination of one or both of the 5-mm trocars and reduction of one of the 12-mm trocars to 5 mm. At times, on the right side, an additional 5-mm trocar is placed just beneath the xiphoid process to aid in retraction of the liver during the hilar dissection.

Using monopolar electrosurgical scissors, the surgeon incises the line of Toldt from the hepatic or splenic flexure caudal across the iliac vessels until the ureter is identified. The ureter is dissected from surrounding tissues up to the level of the kidney. Gerota's fascia is entered and the dissection is continued on the renal capsule until the entire kidney has been freed from the perirenal fat (Fig. 18.14). The kidney can be retracted laterally and the renal hilum exposed. The renal vessels are carefully dissected. The renal artery is clipped five times and cut between the second and third clips (leaving two clips on the side of the specimen). Attention is then turned to the renal vein; it is secured with an Endo-GIA vascular stapler. The ureter is secured with four clips and divided; the kidney is then freed from any remaining retroperitoneal attachments. The specimen is then placed in an endoscopic sack and either morcellated with forceps or, after enlarging one of the port sites, the specimen can be removed intact.

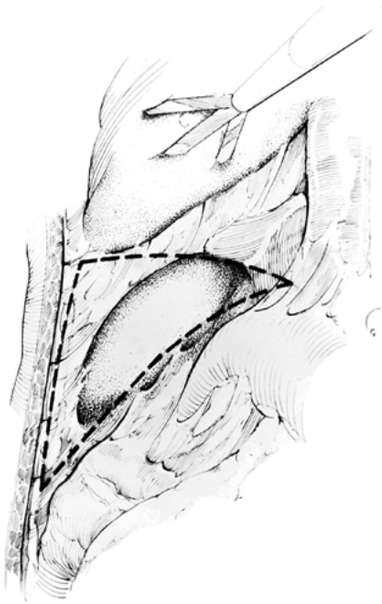

FIGURE 18.14. Dissection template for simple laparoscopic right transperitoneal nephrectomy.

Access for retroperitoneal simple nephrectomy is gained by a 2-cm incision just posterior to the tip of the twelfth rib. After balloon or blunt digital dissection of the retroperitoneum around Gerota's fascia, a Hasson cannula is placed. Three additional trocars are placed: a 5-mm posterior trocar, located at the angle of the twelfth rib and the erector spinae muscle; a 5- or 12-mm trocar in the midaxillary line, 2 cm cephalad to the iliac crest; and a 5-mm trocar subcostal in the anterior axillary line, thereby describing a T configuration for the four ports. Attention is first directed to the renal hilum, and the renal artery and vein are sequentially controlled with clip ligation and the vascular Endo-GIA stapler, respectively. Gerota's fascia is incised and the kidney is dissected from the perirenal fat. The ureter is dissected

from the surrounding tissues, clipped, and cut. The specimen may then be entrapped and morcellated.

Results of trials comparing open and laparoscopic simple nephrectomy are presented in Table 18.4 . Parra and co-workers (323) compared 12 patients undergoing laparoscopic transperitoneal nephrectomy for benign renal disease with 13 patients managed with a traditional flank incision. All laparoscopic procedures were performed via a transperitoneal approach. One patient in the laparoscopic group required conversion to open surgery after injury to a lower pole artery with minimal blood loss. A second patient in the laparoscopic group experienced a bowel injury that was repaired laparoscopically. Both patients had had previous open abdominal surgery. There were no intraoperative complications in the open group. Mean specimen weights were similar: 169 g in the open group and 157 g in the laparoscopic group. Operative times for the open and laparoscopic procedures were similar (157 minutes and 145 minutes, respectively). Mean blood loss in the open population was twice that of the group treated laparoscopically: 141 versus 295 mL.

Source	Indications	Technique	Number	Minor Complications	Major Complications	Extraction	OR Time	EBL (mL)	Analgesia	Length of Stay	Full Recovery	Cost
Kerbl et al. (218)	All benign	Lap-transper	20	15%	15%	Morcellated	355 min	200	54 mg morphine	3.7 days	1.8 mo	NA
		Open-retroper	23	None	None	Intact	165 min	332	23 mg morphine	7.4 days	9.85 mo	NA
Parra et al. (323)	All benign	Lap-transper	12	17%	None	8% morcellate	145 min	141	14 mg morphine	3.5 days	16 days	NA
		Open-retroper	13	15%	None	Intact	56.6 min	295	29 mg morphine	8.0 days	32.3 days	NA
Rassweiler et al. (346)	All benign	Lap-transper	18	22%	17%	Intact	06.5 min	NA	2 days	6.6 days	24 days	NA
		Lap-retroper	17	12%	18%	Intact	11.2 min	NA	1 day	6.3 days	21 days	NA
		Open-retroper	19	16%	11%	Intact	117 min	NA	4 days	0.1 day	40 days	NA
Totals												
Laparoscopic			**67**	**17%**	**14%**		**241 min**	**179**		**5.1 days**	**30.8 days**	
Open			**55**	**9%**	**4%**		**146 min**	**319**		**8.5 days**	**145 days**	

All columns list mean values.
EBL, estimated blood loss; Lap, laparoscopic; NA, not available; retroper, retroperitoneal; transper, transperitoneal.

TABLE 18.4. SIMPLE NEPHRECTOMY—COMPARATIVE TRIALS

All parameters of convalescence favored laparoscopic simple nephrectomy. Patients in the open group had eight times the morphine equivalents for pain relief: 130 versus 14 mg. Mean hospital stay was 8 days for open simple nephrectomy and 3.5 days when the procedure was performed laparoscopically. Similarly, return to full activity was more expeditious in the laparoscopic group (16 versus 32 days, respectively). Postoperative complications included a wound infection and a urinary tract infection in the open group. No postoperative complications were reported in the patients treated with laparoscopic simple nephrectomy.

Rassweiler and co-workers (346) reported results comparing the open and the transperitoneal laparoscopic approaches and the retroperitoneal laparoscopic approach for simple laparoscopic nephrectomy. Results from 18 transperitoneal and 17 retroperitoneal laparoscopic simple nephrectomies were compared with the results of 19 open simple nephrectomies. Two conversions to an open procedure were required in the transperitoneal group, and one conversion was required in the retroperitoneal group. Mean operative times for laparoscopic transperitoneal and retroperitoneal nephrectomies were similar, and significantly longer than times required for open simple nephrectomy: 207 minutes, 211 minutes, and 117 minutes, respectively. Transfusion rates were lowest in the retroperitoneal group: 5.9% versus 17% in the laparoscopic transperitoneal patients and 16% in the open group (346).

All parameters of convalescence favored the laparoscopic approaches. Mean time for analgesia requirement for the transperitoneal and retroperitoneal laparoscopic groups was 2 days and 1 day, respectively, significantly shorter than the 4 days of analgesic administration that patients undergoing open simple nephrectomy required. Hospital stay reflected a similar pattern with transperitoneal and retroperitoneal simple nephrectomy requiring mean hospital stays of 6.6 and 6.3 days, respectively, versus 10 days in the open group. Time to complete recuperation was again similar for transperitoneal and retroperitoneal simple nephrectomy (24 and 21 days, respectively); both results were significantly shorter than the mean 40 days of recuperation time for open simple nephrectomy (346).

Overall complication rates were similar for the three approaches. Complication rates for transperitoneal, retroperitoneal, and open simple nephrectomy were 39%, 29%, and 26%, respectively. In the transperitoneal laparoscopic group, three patients experienced bleeding during dissection; one patient required conversion to open surgery. The other two were well controlled and did not require blood transfusion. There was also a bowel injury that was managed by conversion to open surgery. In addition, there were two cases of subcutaneous emphysema and a subcutaneous abscess, both of which resolved with conservative management. In the retroperitoneal laparoscopic group, there was

also a conversion to open surgery as a result of intraoperative bleeding. One patient also required subsequent reexploration for a pancreatic fistula. As in the transperitoneal group, there was a single case of subcutaneous emphysema and a subcutaneous abscess, both of which resolved with conservative management. In the open population, two cases of intraoperative bleeding were reported that required blood transfusion. There was also a case of intercostal neuralgia that was managed with pain medications, a retroperitoneal hematoma that was successfully observed, and an incisional hernia that required surgical repair (346).

Eraky and colleagues (99) reported the largest experience with laparoscopic simple nephrectomy. In their report, 106 laparoscopic transperitoneal simple nephrectomies were performed for chronic pain (*n* = 73), recurrent urinary tract infection (*n* = 28), or hypertension (*n* = 5). All kidneys were entrapped in a LapSac and underwent manual morcellation with a blunt scissors and surgical clamps. Ninety-seven (92%) nephrectomies were successfully completed laparoscopically. Conversion was necessitated to overcome failure of entrapment in one patient, because of uncontrollable bleeding in three cases, and because of severe perirenal adhesions in five patients. Mean operative time was 186 minutes. When stratified by experience, however, the mean operative times were 217 minutes and 154 minutes, respectively, for the first 53 and second 53 cases. Twenty-four (23%) patients experienced minor complications consisting of low-grade fevers (less than 38 °C) and small asymptomatic hematomas. Four (3.8%) patients developed trocar site hernias. There were four (3.8%) major complications. These included a pulmonary embolism requiring anticoagulation, renal vein bleeding requiring reexploration, a colonic perforation requiring colostomy construction, and an infected hematoma that was drained percutaneously. Three of the four (75%) major complications and 17 of the 26 (65%) minor complications occurred in the first 53 cases. The mean hospital stay was 2.9 days, and mean follow-up period for the series was 14 months (range of 6 to 22 months). Analgesic requirements were not reported.

Laparoscopic simple nephrectomy accomplishes the objectives of its traditional open counterpart without exposing patients to additional risks or complications. The procedure offers the advantages of decreased pain, more rapid short- and long-term convalescence, and improved cosmesis.

Prospective, randomized comparison of the transperitoneal and retroperitoneal approaches for simple nephrectomy has not been performed; therefore there are no data demonstrating the superiority of either approach.

Retroperitoneum: Nephroureterectomy (Simple)

Laparoscopic simple nephroureterectomy was initially described in 1992 (92). Indications for simple nephroureterectomy include various benign diseases with concomitant renal and ureteral pathology that result in a kidney with poor renal function. Such clinical scenarios include vesicoureteral reflux in a single or duplicated system with recurrent episodes of pyelonephritis or pyoureteronephrosis.

Laparoscopic nephroureterectomy has been described using either a transperitoneal or retroperitoneal technique. The procedure is performed in the lateral decubitus position. In the transperitoneal approach the initial trocar is placed 2 cm superior and medial to the anterior superior iliac spine. Next, under endoscopic control three additional trocars are placed: just below the costal margin in the midclavicular line, several centimeters lateral and a few centimeters superior to the umbilicus, and in the midline approximately 2 to 3 cm above the pubis. A 5-mm trocar is placed in the midaxillary line subcostal. For operations on the right side, it is sometimes helpful to insert another 5-mm trocar subcostally near the xiphoid process to aid in retraction of the inferior border of the liver during the hilar dissection.

Using monopolar electrosurgical scissors, the surgeon incises the line of Toldt from the hepatic or splenic flexure caudal across the iliac vessels. The ureter is identified at the point where it crosses the iliac vessels. The ureter is dissected from surrounding tissues up to the level of the kidney. The renal hilum is exposed and the renal vessels carefully dissected. The renal artery is clipped five times and cut between the second and third clips (leaving only two clips on the side of the specimen). Attention is then turned to the renal vein, which is secured with an Endo-GIA vascular stapler. Gerota's fascia is incised and the kidney is dissected from the surrounding perirenal tissues. The ureter is then mobilized further caudally into the pelvis. In these patients it is sufficient to take the ureter at a point just below the iliac vessels, rather than attempting to secure a cuff of bladder; the ureter is divided between two pairs of clips. The specimen is then placed in an entrapment sack and morcellated; thereby completing the procedure without the need to enlarge any port site beyond its original 12-mm size.

Doehn and co-workers (83) described results with nephroureterectomy performed for benign disease. Sixteen patients who underwent transperitoneal laparoscopic nephroureterectomy were retrospectively compared with fifteen patients who underwent open retroperitoneal nephroureterectomy. All procedures were successfully accomplished laparoscopically. Operative time between the two groups was statistically similar: 100 minutes for the laparoscopic approach and 124 minutes for the open approach. Estimated blood loss for patients managed laparoscopically was significantly less (mean of 140 mL) than for open nephroureterectomy (470 mL) (83). Four (25%) minor complications were reported in the laparoscopic population. Three patients had a postoperative fever that was presumed to be from urinary tract infection. All three resolved within 2 to 5 days with antibiotic administration. One patient had back and shoulder pain for 3 days, which resolved with analgesics. There were three (20%) complications in the open population.

One patient had a pneumonia that resolved after 8 days of antibiotic treatment, and a second patient was successfully managed with antibiotics for a urinary tract infection. There was a single wound dehiscence that was managed conservatively on an outpatient basis (83). Oral intake in the laparoscopic population (11 hours) resumed significantly more quickly than in the open population (39 hours). Mean hospital stay was significantly shorter for patients managed laparoscopically: 6 versus 12.7 days. Similarly, patients in the laparoscopic group required significantly less analgesics in the form of morphine sulfate equivalents: 12 versus 40 mg. Patients undergoing laparoscopic simple nephroureterectomy returned to full activity almost twice as fast as patients undergoing open nephroureterectomy: 21 versus 39 days (83).

Prabhakaran and Lingaraj (339) reported on four pediatric patients who underwent simple nephroureterectomy for dysplastic kidneys. All four procedures were accomplished laparoscopically with a mean operative time of 176 minutes. Blood loss was minimal, and no intraoperative complications were noted. All patients resumed regular feeding on the first postoperative day, and mean hospital stay was less than 3 days (339). Similarly, Seibold and co-workers (379) reported on three children, 6 to 15 months of age, who underwent nephroureterectomy for nonfunctioning multicystic dysplastic kidneys and for reflux nephropathy. A single complication was documented: an incarcerated hernia through one of the 5-mm trocar sites.

Data regarding nephroureterectomy performed for benign disease are limited. However, these small series support the contention that laparoscopic simple nephroureterectomy is feasible, safe, efficacious, and accompanied by a rapid convalescence.

Benign Disease: Ablative—On the Horizon

Peripelvic Renal Cyst Decortication

Most peripelvic cysts are asymptomatic. However, they can occasionally enlarge and obstruct portions of the urinary collecting system. These cysts may rarely require surgical management.

One of the earliest reports of laparoscopic treatment of a peripelvic cyst was by Rubenstein and colleagues (359). They reported laparoscopic management of a symptomatic peripelvic cyst that was obstructing the upper pole renal collecting system (359). After transabdominal exposure, the cyst was unroofed, and a polytetrafluoroethylene wick was anchored within the cyst to maintain patency. Although the patient remained asymptomatic, a small cystic persistence (2 cm) was noted on follow-up at 10 months.

Hoenig and co-workers (169) reported on four patients with peripelvic cysts who were managed laparoscopically. Mean operative time was 338 minutes, and mean estimated blood loss was 90 mL. One intraoperative complication occurred: an injury to the renal pelvis that was sutured laparoscopically. Mean narcotic requirement was 385 mg of meperidine hydrochloride. Patients were discharged from the hospital at a mean of 2.8 days postoperatively and returned to normal activity at a mean of 3.3 weeks. Pain resolved in all four patients postoperatively but recurred 2 months after the procedure in the one patient who had been managed via a retroperitoneal approach. CT revealed recurrence of the peripelvic cyst, and the patient underwent open cyst marsupialization. With a mean follow-up of 13.5 months, the remaining three patients remained pain free. However, one of the three patients had radiographic evidence of a 2-cm, asymptomatic reaccumulation (169).

Laparoscopic management of peripelvic cysts is feasible and efficacious. The procedure is more technically challenging than management of simple peripheral renal cysts because of the proximity of the renal vessels and urinary collecting system. To date, only a few cases have been reported, and no long-term results are available.

Cystectomy

Laparoscopic simple cystectomy was first described by Parra and co-workers (322) in 1992. The procedure was performed in a 27-year-old female paraplegic with severe incontinence and urinary tract infections. She was initially managed with an ileocolonic reservoir with a continent stoma, but she subsequently developed multiple infections with purulent bladder drainage despite conservative management. A transperitoneal simple cystectomy was performed. Endo-GIA vascular staplers were used to ligate and divide the vascular pedicles and urethra and to separate the bladder from the vagina that was left intact. Operative time was 130 minutes, and estimated blood loss was 115 mL. The specimen weighed 22 g. Two 50-mg injections of meperidine hydrochloride and four tablets of acetaminophen with codeine were required for pain control. The patient was discharged home on postoperative day 5. Subsequently, Parra and co-workers (324) described a second laparoscopic simple cystectomy in a male paraplegic in 1995. The prostate was left *in situ.*

Laparoscopic cystectomy has been described in case reports and small series. Until further refinements of techniques and technology are available, the procedure remains investigational. Specifically, although the cystectomy itself seems to be rather straightforward, it is the bladder reconstruction or substitution that remains the key challenge to making laparoscopic simple cystectomy a viable clinical alternative.

Seminal Vesiculectomy

Isolated pathologic conditions of the seminal vesicles are uncommon. The advent of transrectal ultrasonography, CT, and MRI has made the discovery of isolated benign

lesions of the seminal vesicles more frequent. The decision to surgically manage seminal vesicle cysts depends on the degree of symptoms experienced by the patient. Surgical treatment is challenging due to the deep pelvic location of the seminal vesicles.

The initial report on a laparoscopic approach to the seminal vesicles was produced by Kavoussi and colleagues (211) in 1993. They reported their technique for bilateral seminal vesicle mobilization as part of radical perineal prostatectomy for carcinoma of the prostate. A 12-mm trocar is placed infraumbilically, and two 10-mm trocars are placed at the level of the umbilicus just lateral to the rectus muscles. Two additional 10-mm trocars are placed in each lower quadrant. A transverse incision is made through the anterior peritoneum overlying the rectovesical pouch. The ampullae and vasa deferentia are identified and dissected from surrounding tissue. Each ampulla is then separately isolated, clipped, and transected. The dissection is kept close to the seminal vesicles and prostate to avoid injury to the ureter, the rectum, or the adjacent neurovascular bundle of the prostate. Working medially to laterally, the surface of the seminal vesicle is defined by blunt dissection, and the artery to each seminal vesicle is isolated, ligated with clips, and divided. Gentle medial traction of the seminal vesicles allows for further lateral dissection, thereby freeing the seminal vesicle down to its base.

Successful seminal vesicle mobilization was performed in 15 of 16 (95%) patients. The solitary failure had extensive tumor involving the seminal vesicles. Mean operative time was not reported, but a range of 1 to 2.5 hours was described. Blood loss was minimal, and no short-term complications were reported. Long-term follow-up was not provided.

Carmignani and co-workers (46) reported laparoscopic unilateral seminal vesiculectomy in a symptomatic 19-year-old male patient. The patient complained of lower urinary tract symptoms and pain with ejaculation. Transrectal ultrasound demonstrated cystic dilation of the right seminal vesicle, and needle aspiration demonstrated immotile spermatozoa. Transabdominal laparoscopic cyst excision was performed. Total operative time was 180 minutes, and the patient was discharged home on the second postoperative day. There were no intraoperative or postoperative complications. At 6-month follow-up, the patient was asymptomatic and transrectal ultrasonography revealed a normal left and absent right seminal vesicles.

Ikari and colleagues (183) reported laparoscopic seminal vesiculectomy in two patients. The first case was a 24-year-old man complaining of left pelvic pain. Ultrasound and CT revealed a large left seminal vesicle cyst. A transperitoneal laparoscopic seminal vesiculectomy was performed. Operative time was 90 minutes, and the patient was discharged on the second postoperative day. There were no complications, and transrectal ultrasound 120 days postoperatively was remarkable only for absence of the left seminal vesicle. The second case presented was of a 10-month-old child with recurrent Gram-negative urinary tract infections. Ultrasonography revealed a 5-cm retrovesical cystic tumor. This was confirmed with MRI. Laparoscopic seminal vesiculectomy was performed in 120 minutes, and the patient was discharged on postoperative day 2. With 4-year follow-up, the child was asymptomatic and had not had recurrence of urinary tract infections (183).

Bilateral seminal vesicle mobilization to facilitate perineal prostatectomy is safe and feasible. However, due to the additional surgical time required for this portion of the procedure and given the now rare indications for a pelvic lymph node dissection, this approach is rarely used. In contrast, isolated pathology of the seminal vesicles, although unusual, is well resolved by a laparoscopic approach.

Partial Adrenalectomy

Partial adrenalectomy was first described by Janetschek and co-workers (193,198) for management of bilateral aldosterone-producing adenomas. Criteria for partial adrenalectomy continue to be defined; however, complete absence of adrenal function necessitates glucocorticoid and mineralocorticoid replacement therapy. This form of medical management is associated with a decreased quality of life (412). Accordingly, the preservation of any functioning adrenal tissue is preferable from the patient's standpoint.

For aldosterone-producing adenomas, Nekada and co-workers (297) demonstrated superior physiologic responses in patients undergoing open enucleation compared with open adrenalectomy. There were no cases of recurrent hyperaldosteronism in either group. Reported indications for partial adrenalectomy have included small functioning masses, renal masses with bilateral adrenal metastases, and syndromes associated with bilateral adrenal pathology.

Advances in the technology and quality of intraoperative ultrasonography have made laparoscopic partial adrenalectomy feasible (164,184,289). Presently available flexible 10-mm probes now afford the laparoscopic surgeon the ability to determine tumor characteristics and borders. Ultrasound can establish the presence of tumor, demonstrate that large tumors are without signs of malignancy, determine the degree of infiltration of the adrenal gland and surrounding structures, and help locate the adrenal vasculature (164). These criteria can be used to determine whether small adenomas are technically resectable via partial adrenalectomy. If a tumor is peripheral and the remnant after resection with an adequate margin is expected to be greater than 50% of the gland, partial adrenalectomy is feasible.

Janetschek and colleagues (194) reported results of four patients managed with six partial adrenalectomies (two bilateral). Laparoscopic partial adrenalectomies were performed in patients with inherited syndromes associated with von Hippel–Lindau disease or the multiple endocrine

neoplasia (MEN) 2b syndrome. Operative data specific for partial adrenalectomy were not separated from other laparoscopic adrenalectomies in this series. However, 2 of 6 (33%) patients undergoing partial adrenalectomy experienced complications. One patient experienced intraoperative bleeding that did not require transfusion, postoperative pneumonia, and lymphatic ascites in the postoperative period. Another patient developed a trocar site hernia. Patients undergoing partial adrenalectomy were able to return to full activity in 22 days and had complete recovery in a mean of 8 weeks.

Sasagawa and co-workers (366a) reported results of 15 laparoscopic retroperitoneal partial adrenalectomies for benign adrenal tumors. Adrenal transection was accomplished successfully in all cases using an endoscopic stapling device. Mean operative time was 162 minutes, and mean estimated blood loss was 12 mL. A single (7%) complication was reported; a pneumothorax was created due to intraoperative injury to the crus of the diaphragm. Postoperative parameters were not reported.

Most recently, Walther and colleagues (432) reported partial adrenalectomies performed on three patients with Von Hippel–Lindau disease. Mean operative time was 324 minutes, with an estimated blood loss of 100 mL. Postoperatively, the patients required a mean of 22 mg of morphine sulfate, and no patient required hormonal replacement. In two cases, partial adrenalectomy was unilateral, and in the last case bilateral partial adrenalectomy was performed. Mean hospital stay was 4 days, and patients returned to full activity in 12 days. No intraoperative or postoperative complications were reported. There was no evidence of tumor recurrence with follow-up of 3 years, 5 months, and 3 weeks reported for the three patients.

Laparoscopic partial adrenalectomy is feasible and, in properly selected patients, has demonstrated efficacy in controlling functioning adrenal tumors. Patients with bilateral adrenal disease may benefit from this management strategy because the morbidity and decreased quality of life associated with exogenous steroid replacement is thereby precluded.

Partial Nephrectomy and Wedge Excision

Partial nephrectomy is used therapeutically for various benign renal abnormalities. These maladies include vascular lesions, trauma, segmental obstruction or infection, and renal stone disease localized to either pole. Winfield and colleagues (441) performed the first laparoscopic partial nephrectomy for benign disease in 1992. The procedure was performed using a technique developed by McDougall and co-workers in a porcine model (265). In these animal studies, successful partial nephrectomies were performed using a plastic cable as a renal tourniquet and electrosurgical scissors for renal transection. Hemostasis was achieved with argon beam coagulation.

Numerous technologies have been studied for use in laparoscopic partial nephrectomy due to the suboptimal clinical results and technical difficulty of the procedure. Elashry and colleagues (97) compared the use of an electrosurgical snare and ultrasound dissection in a porcine model. Gill and co-workers (122) reported the first successful retroperitoneal laparoscopic partial nephrectomy in 1994. The procedure was performed using a double-loop sling used to secure the kidney and achieve circumferential hemostatic compression. Despite determined efforts, a safe, effective, and reproducible technique for a purely laparoscopic partial nephrectomy remains elusive.

Several series describe laparoscopic nephron-sparing surgery. Winfield and co-workers (443) described four successful laparoscopic partial nephrectomies in six attempts. All cases were performed without control of the renal vasculature using a 5-mm electrosurgical blade for parenchymal transection and argon beam coagulation for hemostasis. No attempts at closure of the collecting system were made. Two of their six attempts resulted in conversion to open surgery due to an inadequate specimen in one case and to hemorrhage in another patient.

In comparing their experience to open partial nephrectomy, although the blood loss was less in the laparoscopic group (525 versus 708 mL) and the analgesic requirements were lower (52 versus 118 mg of morphine sulfate equivalents), there were many drawbacks to the laparoscopic procedure. Mean operative time for the laparoscopic procedure (6.1 hours) was 2 hours longer than for the open procedures and the hospital stay was no different. Minor complications occurred in two of the laparoscopic patients (a residual stone and an obstructed drain). However, of note, full convalescence was 6 weeks shorter in the laparoscopic group (443).

McDougall and colleagues (266) described results from nephron-sparing surgery in 12 patients. This series included nine attempted polar partial nephrectomies, three of which required conversion to open surgery (i.e., dense fibrosis, hemorrhage, and inability to properly judge the point of incision). Of the nine polar nephrectomy patients, two had masses suspicious for malignancy, four had symptomatic calyceal dilation with or without stone disease, two had upper pole atrophy associated with a duplicated collecting system, and one patient had a nonfunctioning upper pole. Renal vessels were not controlled in any case, and parenchymal transection was performed with electrosurgical scissors in five cases, an electrosurgical snare in three cases, and an Endo-GIA stapling device in one case. Exposed parenchyma was then fulgurated with the argon beam coagulator. Intracorporeal suturing was used to close defects in the collecting system. Mean operative time for the successful partial nephrectomies was 6.5 hours, and mean estimated blood loss was 217 mL. A mean of 52 mg of morphine sulfate equivalent was required for postoperative pain management. Mean hospital stay was 5.3 days, and mean time to

complete convalescence was 4.2 weeks. There were three (50%) postoperative complications: nephrocutaneous fistula requiring placement of a percutaneous nephrostomy, retroperitoneal urinoma requiring drainage, and a 48-hour ileus (266).

Hoznek and colleagues (176) recently described a series of 13 patients who underwent a laparoscopic retroperitoneal approach to nephron-sparing surgery for benign disease. A complete partial nephrectomy was performed in only three cases, and in the other situations, a wedge-type excision was done (176). Surgery was performed for benign conditions in six (hydrocalyx with overlying atrophy in five and upper pole atrophy in one), equivocal solid masses in four, and indeterminate renal cysts in three patients. Intraoperative ultrasound was used to assess intrarenal anatomy in cases of borderline cysts and solid masses. Transection was performed with a rotating-tip electrosurgical scissors or a harmonic scalpel. In five patients, an atraumatic vascular clamp was placed on the renal vessels before transection. The transected raw parenchymal surface was covered with oxidized regenerated cellulose mesh impregnated with gelatin resorcinol formaldehyde glue (176). All procedures were successfully accomplished laparoscopically. Average operating time was 1.9 hours, and average intraoperative blood loss was 72 mL. There were only two postoperative complications, both urinomas. Mean hospital stay was 6.1 days. Analgesic requirements and time to full recovery were not reported.

Laparoscopic partial nephrectomy for benign disease in the adult is technically difficult and, even in the hands of experienced urologic laparoscopists, results in high conversion rates and significant complications. In contrast, reported results with wedge resection of benign renal lesions have been superior to those for partial nephrectomy. Many wedge resections are completed successfully with minimal bleeding and rapid postoperative convalescence.

Cyst Decortication in Autosomal-dominant Polycystic Kidney Disease

Autosomal-dominant polycystic kidney disease (ADPKD) is characterized by bilateral, multiple, nonfunctioning, and noncommunicating renal cysts. Typically, symptoms appear in the third and fourth decades of life and include hypertension, hematuria, and abdominal pain. Although the disease has protean manifestations, the most common presentation is abdominal pain; hypertension, pyelonephritis, hematuria, and palpable abdominal masses also are common. End-stage renal disease is the major late sequela of ADPKD and occurs in approximately 40% of patients.

It is widely believed that the progressive renal dysfunction seen in ADPKD patients is due to compression and distortion of adjacent noncystic renal parenchyma by the expanding cysts. However, cyst decortication has not been shown to result in improved renal function. As such, surgical treatment is indicated only for pain control after failure of medical management.

Minimally invasive methods have been used to treat these patients. Ultrasound- or fluoroscopically guided percutaneous cyst aspiration has been performed to drain a few large symptomatic renal cysts (23,112). However, this therapy has resulted in durable pain relief at 1.5 years in only 33% of patients (23). Likewise, percutaneous endourologic techniques have been used to treat one or several larger cysts; pain relief has usually been only transient. Better results have been obtained with open surgical extensive cyst decortication, but this is a major and often morbid procedure. However, Bennett and co-workers (23) reported that 81% of ADPKD patients treated with open decortication were still benefited at 1.5 years with regard to decreased discomfort.

Morgan and Rader (285) performed the first laparoscopic cyst decortication for a complex renal cyst in 1991. Subsequently, Barry and Lowe (18a) reported laparoscopic cyst marsupialization in patients with ADPKD. More recently, Brown and co-workers (35) reported results with 13 consecutive laparoscopic cyst decortications for patients with symptomatic ADPKD. Of the 13 patients, 6 (46%) had undergone prior cyst aspiration with or without attempted sclerosis. The procedure was technically successful in 12 of 13 (92%) patients. Estimated blood loss was less than 150 mL, and mean operative time was 2.7 hours. No intraoperative or postoperative complications were reported. Of 13 patients, 11 (85%) experienced immediate relief of symptoms. In two patients, a less than complete decortication of all large cysts was done; both failed to benefit. However, 3 of the 11 successful patients had recurrent pain at 7, 11, and 16 months postoperatively. The remaining eight (62%) had good pain relief (80% to 100%) with follow-up of 12 to 28 months.

Lifson and colleagues (238) reported results of cyst decortication in eight patients with ADPKD. All procedures were successfully accomplished laparoscopically. Mean estimated blood loss was 116 mL, and mean operative time was 137 minutes. There was one postoperative complication, a self-limited retroperitoneal hemorrhage that was managed with a 2-unit blood transfusion. Mean hospital stay was 2.3 days. During early follow-up, all patients had significant pain relief. A second procedure was performed in three patients with recurrent pain; it was successful in two of these patients. Overall, 71% were pain free at 6 months, and 57% were pain free at 2 years (238). Although this report did not include follow-up data on hypertension or renal function, an earlier report on these patients recorded late deterioration of renal function as manifested by progression of serum creatinine in 2 of 6 (33%) patients. Because there was no control group, it is unknown what effect the laparoscopic procedure had on the natural history of this patient population.

Laparoscopic cyst decortication for ADPKD is efficacious in resolving pain. Most patients experience resolution

of pain postoperatively, and approximately 60% have satisfactory pain control for up to 2 years. However, the effects of laparoscopic cyst decortication on renal function and hypertension remain undefined. Longer follow-up (i.e., 3 to 5 years) is necessary to delineate the long-term efficacy of the procedure for pain control and to carefully track the impact of this surgery on hypertension and renal function.

Donor Nephrectomy

Renal transplantation is the treatment of choice for end-stage renal failure. Live-donor renal transplantation offers advantages to the recipient when compared with cadaveric kidney transplantation. One-year patient and graft survivals for live-donor kidney transplants are 97% and 91%, respectively. In contrast, 1-year recipients of cadaveric renal transplants have patient and graft survivals of 93% and 81%, respectively (425). The incidence of delayed function and need for posttransplant dialysis are decreased with a live-donor kidney.

Despite the aforementioned advantages of live-donor transplantation, there has been reluctance on the part of prospective donors. In large part, this appears to be due to the anticipated 7- to 10-day hospital stay, 6-week convalescence period, significant postoperative pain, and large flank incision characteristic of open donor nephrectomy (77). The prolonged convalescence can lead to financial hardship, strains on the family unit, and job insecurity.

In 1994, the endourology group at Washington University reported the feasibility of laparoscopic donor nephrectomy in a porcine model. They described a series of laparoscopic donor nephrectomies with successful renal extraction associated with mean renal artery and vein length equivalent to open donor nephrectomy (121). Subsequently, in 1995, Ratner and colleagues (349) reported the first clinical laparoscopic donor nephrectomy. In this case, the allograft produced urine immediately, and the recipient's creatinine normalized by postoperative day 2. The donor experienced minimal postoperative pain and was discharged home on the first postoperative day. He returned to work as a welder 2 weeks after surgery.

Laparoscopic donor nephrectomy is performed with the patient in the lateral decubitus position; in most cases, the left kidney is selected. Trocar placement is similar to that described for laparoscopic radical nephrectomy. During the procedure, it is important to keep the patient volume expanded because vigorous hydration and low insufflation pressure combine to help maintain urine output (242). The administration of parenteral diuretics (12.5 g of mannitol and 40 mg of furosemide) is also beneficial.

The descending colon and splenic flexure are mobilized and reflected medially by incising the line of Toldt and dissecting the colon off of Gerota's fascia. Diaphragmatic attachments to the spleen are divided, allowing it to fall medially. Gerota's fascia is incised, and attention is directed to the renal hilum. The renal vein is freed from its adventitial attachments, and the gonadal, adrenal, and any associated lumbar veins are identified, clipped, and divided. The renal artery, usually behind the vein, is then identified and freed from surrounding tissue. Maximum length of the renal artery is achieved by dissecting it to its proximal origin at the aorta. The renal artery may be bathed with a topical solution of papaverine to prevent vasospasm. At this point, the patient is given mannitol and furosemide intravenously. Attention is turned to the ureteral dissection. The ureter is broadly dissected to the level of the iliac vessels, and it is taken en bloc along with the gonadal vein via an Endo-GIA stapler. The remaining attachments to the kidney are then divided.

An extraction incision is then made, leaving the underlying peritoneum intact to maintain insufflation. Right upper quadrant, midline, and Pfannenstiel incisions have been described; the last is cosmetically preferable. The incision should be generous enough for atraumatic extraction of the kidney. Before the surgeon divides the vascular pedicle, 3,000 units of heparin sulfate is administered intravenously. The Endo-GIA vascular stapler is then used to sequentially divide the renal artery and renal vein. An endoscopic extraction sack is then used to entrap the kidney, the peritoneum is opened, and the specimen is delivered. The incision should be lengthened as necessary to ensure atraumatic extraction. After injection of protamine sulfate to reverse the effects of the heparin, the fascia is closed and the pneumoperitoneum reestablished. The renal bed is inspected for bleeding. After adequate hemostasis is confirmed, all incision sites are closed.

Hand-assist techniques for laparoscopic donor nephrectomy have also been described. Access is achieved via the umbilicus, where a 12-mm trocar is placed. A second 12-mm trocar is placed in the midaxillary line midway between the iliac crest and the costal margin. The hand-assist device is placed in the midline above the umbilicus, and an incision equal in length in centimeters to the surgeon's glove size is created. The use of the surgeon's hand facilitates the procedure because it allows for manual blunt dissection, rapid renal exposure, and hand delivery of the kidney.

Philosophe and colleagues (331) from the University of Maryland have reported the largest single-center experience with laparoscopic donor nephrectomy. The records of 193 patients undergoing laparoscopic donor nephrectomy were compared with results from 168 open donor nephrectomies performed at the same institution before the advent of the laparoscopic technique. Mean warm ischemia times for laparoscopic donor nephrectomy was 158 seconds (307). Immunosuppression regimens were similar for both groups. Mean follow-up for the laparoscopic population was 10.7 months, and follow-up for the open population was 41.5 months. Donor characteristics were similar between the two groups.

The 2-year graft survival rates for laparoscopic and open donor nephrectomy were similar at 98% and 96%, respectively.

The 2-year patient survival rate was also similar, with laparoscopic and open donor nephrectomies resulting in survivals of 98% and 97%, respectively. Graft function, as assessed by serum creatinine levels at 3 months and 1 year, were similar between the two groups. Specifically, 3-month serum creatinine values for laparoscopic and open donor nephrectomies were both 1.6 mg/dL. At 1 year the serum creatinine values were 1.6 and 1.7 mg/dL, respectively. Philosophe and co-workers (331) reported delayed graft function to be similar for laparoscopic and open donor nephrectomy (6.2% and 5.1%, respectively).

Philosophe and colleagues (331) specifically addressed the incidence of ureteral complications, which had been reported as being as high as 11% in the initial series versus only 3% for the open donor nephrectomy group. There were 15 (7.7%) operations for ureteral complications in the laparoscopic group, compared with only 1 (0.6%) from kidneys procured using the open technique. Modifications to the laparoscopic surgical technique were made in October 1997 to try to decrease the rate of ureteral complications. Specifically, an Endo-GIA stapler was used to divide the ureter and a broad expanse of periureteral fat distally to include more periureteral tissue. Since the modification, the authors have had only a single ureteral complication in 62 consecutive patients; the complication was managed with a ureteral stent (331).

Data on complications were reported in an earlier article comparing laparoscopic and open donors from the University of Maryland (307). In the open population, there were two (2%) cases of delayed graft function due to acute tubular necrosis (ATN), three (3%) cases of early acute rejection, one (1%) ureteral complication, and two (2%) cases of sepsis resulting in allograft dysfunction. In the laparoscopic donor nephrectomy group, there were ten (7.6%) cases of ATN, three (2.3%) cases of early acute rejection, six (4.5%) cases of ureteral complications, two (1.5%) cases of pyelonephritis, one (0.8%) case of hemorrhage, one (0.8%) lymphocele, and two (1.5%) complications reported as “no records.”

Ratner and co-workers (350) described the Johns Hopkins University School of Medicine experience. Donors undergoing laparoscopic donor nephrectomy had significantly less intraoperative blood loss: 266 versus 393 mL. Postoperative analgesic requirements were significantly decreased in the laparoscopic group: 40 versus 124 mg of morphine equivalents. Similarly, oral intake was resumed more quickly in the laparoscopic group (0.8 versus 2.6 days). Hospital stay in the group of laparoscopic donors was 3.0 days versus 5.7 days required in the open population. Return to work was significantly faster in the laparoscopic population: 4 versus 6.4 weeks (350).

Results of 110 recipients of laparoscopically procured kidneys were compared with 48 patients receiving kidneys from open donors (350). Recipient serum creatinine in the laparoscopic group was significantly higher on postoperative days 2 and 3, but by day 4 there was no significant difference. There was no significant difference in creatinine clearance at 24 months: 75 versus 63 mL per minute. In addition, there was no significant difference in patient or graft survival, need for dialysis, or incidence or severity of rejection episodes. Recipients' complications were not significantly different when laparoscopic and open groups were compared. Ureteral complications occurred in ten (9.1%) of laparoscopically procured kidneys, compared with three (6.3%) of kidneys retrieved via the open approach. Vascular thrombosis occurred in three (2.7%) and two (4.2%) of laparoscopically procured and open donor kidneys, respectively.

Odland and colleagues (311) retrospectively compared 30 laparoscopic donor nephrectomies with 30 open donor nephrectomies. Of 30 procedures, 10 (87%) were successfully completed laparoscopically. The laparoscopic group had significantly longer operative times than the open group: 183 versus 148 minutes, respectively. Estimated blood loss and transfusion requirements were not significantly different between the two populations. Three laparoscopic donors (12%) required reexploration, two for bleeding and one for retrieval of a foreign body. All three explorations were successfully accomplished laparoscopically. No patient in the open donor nephrectomy group required reexploration. Persistent wound problems were significantly more common among open donors. Of patients in the open group, 55% experienced chronic wound problems, compared with 11% of laparoscopic donors.

Kidneys in the laparoscopic donor nephrectomy group had a significantly longer warm ischemia time when compared with the open donors (5.8 versus 1.7 minutes). There was no significant difference in serum creatinine at 2 weeks or 6 months. Similarly, there was no significant difference in delayed graft function between laparoscopic and open donor nephrectomy (12% and 3%, respectively). Acute graft rejection rates at 6 months were also similar between the laparoscopic and open donor groups: 27% and 37%, respectively. Graft survival rates for laparoscopic and open donor groups were 96% and 90%, respectively (311).

Total hospital costs were slightly higher for the laparoscopic than the open donor population: $11,123 versus $9,335, respectively. The shorter hospital stay associated with the laparoscopic approach was negated by the higher intraoperative costs for laparoscopy; mean operative procedure costs for the laparoscopic and open groups were $7,218 and $5,583, respectively.

Slakey and co-workers (393) reported results comparing 10 laparoscopic donor nephrectomies to 12 laparoscopic donor nephrectomies performed using the hand-assist device. When the hand-assist device was used, mean operative times were significantly reduced: 2.0 versus 3.1 hours with the pure laparoscopic technique. Similarly, warm ischemia times were significantly reduced with the hand-assist technique: 1.2 versus 3.9 minutes. Only one patient required

parenteral narcotics after leaving the recovery room, and all patients tolerated a regular diet when fully awake. There was a single complication in the series. One patient in the standard laparoscopy group experienced a deep venous thrombosis that was successfully managed with anticoagulation. All recipient kidneys functioned immediately, and all grafts had normal function with follow-up of 1 to 12 months (393). Comparative data on length of stay and convalescence were not presented.

Laparoscopic donor nephrectomy is clearly feasible and has removed some of the disincentives to live-donor kidneys. The operation provides donors the benefits characteristic of the laparoscopic approach to renal surgery in general, including decreased pain and more rapid recovery. Given these results, it is not surprising that Ratner and colleagues (350) have noted a greater than 100% increase in live donor transplants at their institution since the inception of the laparoscopic donor nephrectomy program. Although there is a “learning curve” that each surgeon must traverse, it would appear that the laparoscopic approach to donor nephrectomy has proven itself; in the larger series, the technique has equaled or surpassed the high standards achieved by open donor surgery for donor safety and graft function and survival. It appears that hand-assisted laparoscopic donor nephrectomy may help flatten the learning curve while improving the efficiency, without impairing the equanimity, of the laparoscopic approach.

Nephrectomy for Xanthogranulomatous Pyelonephritis

XGP is an atypical form of chronic renal infection characterized by destruction of the renal parenchyma and its replacement by masses of lipid-laden macrophages. XGP is usually associated with nephrolithiasis, obstructive uropathy, and an ongoing urinary tract infection. The treatment of choice is nephrectomy, which is challenging given the extent of the disease and the not uncommon involvement of the renal hilum and contiguous structures by the ongoing inflammatory process. Few authors have examined the role of laparoscopy in the setting of XGP.

Keeley and Tolley (213) described two cases of simple nephrectomy for XGP in a series of 100 nephrectomies. One of the two cases required conversion to open surgery. In the same year, Merrot and co-workers (275) reported a 13-year-old girl with XGP managed via a retroperitoneal laparoscopic approach. The procedure was successfully completed in 150 minutes, and the patient was discharged on postoperative day 4 without complication. Cadeddu and colleagues (43) reported results on three laparoscopic nephrectomies performed for XGP. Two cases (67%) required conversion to open surgery due to extensive perinephric scarring. No intraoperative or postoperative complications were reported (43).

Bercowsky and co-workers (25) compared the results of five patients who underwent laparoscopic nephrectomy for XGP with four patients managed with the open technique. Of note, in only 5 of the 9 patients (56%) was the diagnosis of XGP suspected preoperatively. Two cases were performed via the retroperitoneal approach. Laparoscopic nephrectomy was successful in 4 of 5 (80%) patients managed laparoscopically. Conversion to open surgery was necessary in one patient. In all patients, the dissection was considered very difficult because it was challenging to define lines of cleavage between the retroperitoneal structures and to dissect the renal hilum. Mean operative time was 6 hours in the laparoscopic group and 2.5 hours in the open population. Estimated blood loss was less in the laparoscopic group than in the open nephrectomy group: 260 versus 438 mL. Unlike most reports in which laparoscopy is compared with open surgery, among these patients, analgesic requirements and hospital stay were similar; however, time to normal activity (4.6 versus 9.3 weeks) and complete recovery (13.6 versus 16 weeks) were more rapid in the laparoscopic nephrectomy group (25). Complications occurred in three patients (60%) in the laparoscopic group: ileus in two patients and multiple complications in another patient (5-unit blood transfusion, retroperitoneal hematoma, pulmonary embolus, and a retroperitoneal abscess). No complications were reported in the open group.

Although simple nephrectomy for XGP is feasible, it is technically very challenging. The laparoscopic approach has been associated with a high conversion rate and has an increased risk of postoperative complications. In addition, the short-term benefits characteristic of laparoscopy are not as pronounced as in other laparoscopic procedures. As such, at most centers, a preoperative diagnosis of XGP remains a relative to absolute contraindication for laparoscopic nephrectomy.

Nephrectomy for Autosomal-dominant Polycystic Kidney Disease

The laparoscopic approach to these giant kidneys has only recently been described. These patients, despite being on dialysis or having undergone a successful renal transplant, continue to have symptoms and signs of their markedly enlarged kidneys: flank and abdominal pain, shortness of breath, gastrointestinal problems (early satiety, constipation), and renal-related hypertension.

Laparoscopic nephrectomy in these patients was initially reported by Elashry and colleagues (95) in 1996 at Washington University; this was performed in two patients with renal failure. The case time was 4.5 hours with a 3.5-day hospital stay. Patients returned to their baseline activity in 2 weeks. More recently, Dunn and colleagues (89) have updated the Washington University experience with nine ADPKD patients undergoing 11 nephrectomies for pain. In this group, the average operating time was 6.3 hours with an

average hospital stay of 3 days. Six significant complications occurred: blood transfusion, a vena cavotomy repaired laparoscopically, splenic cyanosis, pulmonary embolism, clotted arteriovenous fistula, and brachial plexus injury. Incisional hernias occurred in 2 of the 3 patients who underwent open intact removal. Patients returned to their baseline activities in 5 weeks. Relief of pain was achieved in all patients. In three patients, hypertension improved or resolved, whereas in three other patients, hypertension worsened postoperatively.

In these patients, the use of hand-assist laparoscopy would appear to offer a favorable compromise between a pure laparoscopic approach and intact removal. The hand-assist approach allows for rapid mobilization of these giant kidneys and provides a workable incision through which the cysts can be decompressed as the specimen is removed. In addition, because of the increased efficiency of hand-assisted laparoscopy, bilateral nephrectomy becomes a more feasible undertaking in these patients.

Benign Disease: Reconstructive

Pelvis: Bladder Neck Suspension

Stress urinary incontinence is the involuntary loss of urine from the urethra resulting from an increase in intraabdominal pressure and in the absence of a detrusor contraction. In 1996, the Agency for Health Care Policy and Research estimated that approximately 14 million Americans suffer from urinary incontinence, at an estimated annual cost of $46 billion (102). Factors involved in the normal continence mechanism in the female include an intrinsic coapting ability of the proximal urethra, a critical functional and anatomic urethral length, the ability of the pelvic floor to increase urethral pressure at the time of stress, and the proper anatomic location of the sphincter mechanism (398).

Multiple surgical procedures have been developed to suspend or support the bladder neck and thereby correct female stress incontinence. These include anterior colporrhaphy, anterior cystourethropexy, endoscopic needle suspensions, and sling procedures. Laparoscopic bladder neck suspension was first described as a transperitoneal approach by Vancaillie and Schuessler in 1991 (427).

At present, laparoscopic bladder neck suspension is usually performed in an extraperitoneal retropubic fashion. A 2-cm incision is created in the upper one-third of the distance between the symphysis pubis and the umbilicus. A dilating balloon is placed in the retropubic space and inflated with 1 L of saline. A laparoscopic trocar is placed and insufflation performed. Two additional trocars are placed just lateral to the lateral border of the rectus abdominus muscle. For a right-handed surgeon, one trocar is placed on the right side just opposite the initial trocar placement, and the other trocar is placed on the left side, several centimeters above the pubic ramus. Using intracorporeal suturing technique, sutures are placed on either side of the bladder neck, and are then passed through the midline cartilaginous notch of the posterior symphysis [modified Marshall-Marchetti-Krantz (MMK)] (Fig. 18.15A), through Cooper's ligament bilaterally (modified Burch) (Fig. 18.15B), or through the ileal pectinate line (modified

Richardson) (Fig. 18.15C). Sutures are tightened down to gently elevate the bladder neck and proximal urethra behind the pubic symphysis; the sutures are secured with an anchoring device (e.g., Lapra-Ty clip) or by intracorporeal or extracorporeal knotting techniques. A Foley catheter is placed in the bladder for 24 hours.

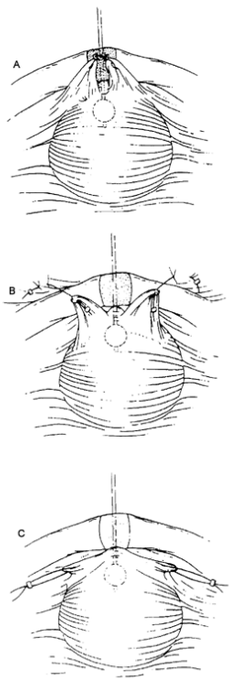

FIGURE 18.15. Laparoscopic bladder neck suspension. **A:** Modified Marshall-Marchetti-Krantz: Sutures are placed on either side of the bladder neck and are then passed through the midline cartilaginous notch of the posterior symphysis. **B:** Modified Burch: Sutures are passed through Cooper's ligament bilaterally. **C:** Modified Richardson: Sutures are passed through the ileal pectinate line.

Albala and co-workers (6) reported results of 22 bladder neck suspensions using transperitoneal MMK (*n* = 22) or Burch (*n* = 10) procedures. Twenty-nine (91%) procedures were successfully accomplished laparoscopically. Two conversions resulted from inability to place sutures, and one conversion was the result of bladder injury during dissection of the space of Retzius. All three of these patients were discharged on the third postoperative day without further complication. Mean operative times for the Burch and MMK procedures were 105 and 65 minutes, respectively. Estimated blood loss and analgesic requirements were not reported. Twenty-eight patients (88%) were discharged in less than 18 hours postoperatively. Nineteen (59%) patients were discharged home without a Foley catheter, and thirteen (41%) had catheters placed for 3 days. In the MMK group, all patients were cured of their incontinence more than 1 year after surgery. With a mean follow-up of only 7 months, all patients in the Burch group were also cured of their incontinence. Postoperative complications included urinary retention in two patients (6%) requiring cystotomy tube placement.

Ou and co-workers (319) reported results of 40 women with stress incontinence treated with a modified laparoscopic Birch procedure. A transperitoneal approach was used, and Proline hernia mesh was stapled to both the periurethral tissues and Cooper's ligament, thereby obviating intracorporeal suturing. Operative times and estimated blood loss were not reported. All 40 procedures were successfully accomplished laparoscopically. Average length of hospital stay was 1.2 days, and average duration of catheterization was less than 24 hours. Minor complications were reported in 6 of 40 (15%) patients: hematuria, low-grade fevers, urinary retention, and urinary tract infection. All complications were self-limiting and were successfully managed without intervention or transfusion. With a mean follow-up of 16 months, all patients had resolution or improvement of incontinence. Specific details regarding postoperative leakage of urine were not reported (319).

Although there was an initial rush toward performing laparoscopic bladder neck suspension, the success of the procedure began to unravel when it was reexamined in the light of longer follow-up (73). In this regard, Su and co-workers (403) reported a prospective comparison of laparoscopic and open bladder neck suspension. Forty-six women were randomized to extraperitoneal laparoscopic bladder neck suspension, and forty-six women were randomized to the open procedure. Operative times were not significantly different for laparoscopic and open procedures (66.5 and 72.8 minutes, respectively). However, mean estimated blood loss was significantly decreased in the laparoscopic population (53 versus 134 mL, respectively). Bladder drainage was significantly longer in the open group compared with the patients managed laparoscopically (6.8 versus 3.9 days, respectively). Analgesic requirements were not reported. With a minimum of 1 year of follow-up, postoperative urodynamic evaluation revealed both groups to have a significant and similar increase in leak point pressure. However, the continence rate was significantly better in the patient population managed with the open technique (96%) than with the laparoscopic technique (80%). In the laparoscopic group, there was a complication rate of 11%: two patients experienced outflow obstruction, two patients experienced *de novo* detrusor instability, and one patient developed a urinary tract infection. In the open group, there was a 17% complication rate: two patients with outflow obstruction, two patients with hematuria, three patients with detrusor instability, and one patient who developed a urinary tract infection.

Subsequent studies with even longer follow-up have shown further erosion of the success of laparoscopic bladder neck suspension. Specifically, McDougall and colleagues (268) compared results of 58 patients undergoing laparoscopic extraperitoneal bladder neck suspension with results of 42 patients managed by transvaginal Raz bladder neck suspension. Mean follow-up was the longest of any reports on this procedure: 45 months in the laparoscopy group and 59 months in the transvaginal group. Of 58 patients, 50 (86%) were available for follow-up in the laparoscopy group, and 29 of 42 (69%) of the transvaginal group were available for follow-up. Operative time was significantly longer in the population managed laparoscopically: 1.7 hours versus 45 minutes. Estimated blood loss was similar between patients managed with laparoscopic and vaginal technique (84 and 74 mL, respectively). Mean days of postoperative catheterization was 0.9 days for the laparoscopic bladder neck suspension group and 13.2 days for patients managed transvaginally.

Using the strict definition of absolutely no stress incontinence, 30% of patients in the laparoscopy group were completely dry and another 20% had occasional stress incontinence requiring no pads. This was not quite as sanguine an outcome as in the transvaginal group, among whom 34% were completely dry and 28% had occasional stress incontinence requiring no pads. In the remainder of the laparoscopy group, 46% of patients were using one to two pads daily and 4% required more than two pads per day. Of the 19 remaining patients in the transvaginal group, 31% were using one to two pads daily and 7% required more than two pads per day. Fourteen (28%) and eleven (38%) patients in the laparoscopy and transvaginal groups, respectively, experienced postoperative urge incontinence.

With any reconstructive procedure, it is important to determine that point in time when the “success” of the procedure becomes durable. For bladder neck suspension, it would appear that follow-up of less than 2 years is not sufficient. Indeed, in a review of the literature, Spencer and

O'Conor (395) established that failures occurred anywhere between 6 months and 23 years after surgery. They concluded that accurate determination of the efficacy of continence surgery should be established only after 5 years of follow-up. Although laparoscopic bladder neck suspension offers women with incontinence the advantages of minimally invasive surgery, the sparse long-term follow-up data to date suggest that the procedure, as it presently exists, probably does not offer women reasonable long-term continence. In addition, because recent information has shown that a significant population of women with type I and type II incontinence will also manifest some degree of intrinsic sphincter deficiency, many incontinence surgeons currently favor sling procedures that are efficacious in the management of both forms of stress urinary incontinence and have withstood the 5-year test of time (49).

Retroperitoneum: Pyeloplasty

Open pyeloplasty is the gold standard for correction of ureteropelvic junction (UPJ) obstruction in both pediatric and adult populations. Success rates following open pyeloplasty in contemporary series exceed 90%. However, because of the postoperative morbidity associated with open surgery, including significant pain and a prolonged convalescence period from the flank incision, several alternative, less invasive techniques to manage UPJ obstruction have been developed. Endoscopic or fluoroscopic retrograde and endoscopic percutaneous antegrade management strategies are both efficacious and decrease the convalescence period compared with open pyeloplasty; however, these techniques are associated with a lower success rate.

Laparoscopic pyeloplasty was first reported by Schuessler and co-workers in 1993 (372). The transperitoneal laparoscopic procedure attempts to duplicate the high success rate associated with open surgery while affording patients the advantages of minimally invasive management strategies.

Laparoscopic pyeloplasty can be performed in almost all patients with UPJ obstruction. Patients with a secondarily obstructed UPJ who have failed retrograde or antegrade percutaneous endopyelotomy are especially good candidates for this approach. The presence of ipsilateral renal calculi does not preclude laparoscopic pyeloplasty because flexible or rigid endoscopes can be used to access the renal collecting system during the laparoscopic procedure. Similarly, the laparoscopic approach is effective when there is a complex vascular arrangement around the renal pelvis. Only the presence of a small intrarenal pelvis is currently a contraindication to the procedure.

The procedure is performed via a transperitoneal approach using three or four trocars. After reflection of the colon, the ipsilateral ureter and renal pelvis are identified and fully mobilized. Dissection of an extensive length of ureter is avoided to prevent devascularization of this structure. If a crossing lower pole renal artery is present, it is preserved; all other vessels and peri-UPJ fibrotic tissue are divided. Next, a circumferential incision is made transecting the renal pelvis above the UPJ (Fig. 18.16A). The proximal ureter is spatulated through the level of the UPJ laterally (Fig. 18.16B). If anterior crossing vessels are present, the ureter and renal pelvis are transposed anterior to the vessels before performing the anastomosis. If the renal pelvis is markedly enlarged, pelvic reduction is performed. This is done using laparoscopic scissors and suturing techniques. The anastomosis is then completed using intracorporeal suturing with 4-0 absorbable suture (Fig. 18.16C and Fig. 18.16D). Suturing can be performed using a free needle and suture or with the assistance of a suturing device (e.g., EndoStitch, U.S. Surgical Inc., Norwalk, Connecticut). The anastomosis can be done either with interrupted or running sutures, depending on the surgeon's preference. An indwelling ureteral stent is placed along with a retroperitoneal drain; the stent is removed 2 to 3 weeks later, and the drain is usually removed before the patient's discharge from the hospital.

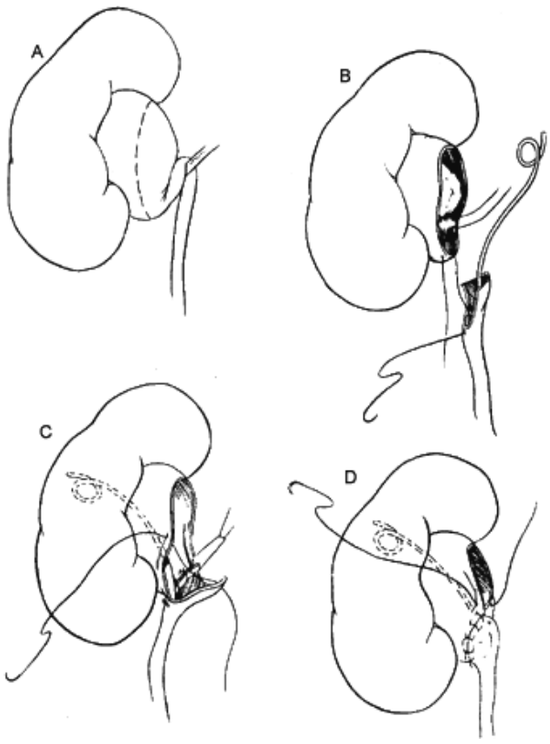

FIGURE 18.16. Laparoscopic dismembered pyeloplasty. **A:** Circumferential incision transecting the renal pelvis above the ureteropelvic junction (UPJ). **B:** The proximal ureter is spatulated through the level of the UPJ laterally. **C, D:** The anastomosis is then completed using intracorporeal suturing with 4-0 absorbable suture.

Initially, Schuessler and colleagues (372) reported results of four primary and one secondary UPJ obstruction managed

with laparoscopic dismembered pyeloplasty. All procedures were accomplished laparoscopically. Operative time ranged from 3 to 7 hours. Estimated blood loss was not reported. Mean hospital stay was 3 days, and all patients returned to normal activity within 1 week. No complications were reported. The procedure was immediately successful in 4 of the 5 cases; one patient, after removal of the stent, reported flank pain and was found to have a stricture distal to the UPJ. The patient underwent balloon dilation and was pain free with a patent ureter after 9 months of follow-up. All other patients remained symptom free and without radiologic signs of obstruction with follow-up ranging from 9 to 17 months (372).

Brooks and colleagues (34) retrospectively compared antegrade endopyelotomy, Acucise endopyelotomy, and laparoscopic pyeloplasty in the management of adult patients with a UPJ obstruction. There were 15 patients evaluated in each group. Mean operative times for antegrade endopyelotomy, Acucise endopyelotomy, laparoscopic pyeloplasty, and open pyeloplasty were 2.5 hours, 46 minutes, 6 hours, and 3.8 hours, respectively. Mean postoperative analgesic requirements for the different procedures varied widely. Analgesic requirements for antegrade endopyelotomy, Acucise endopyelotomy, laparoscopic pyeloplasty, and open pyeloplasty were 18, 1.2, 19, and 190 mg of morphine sulfate equivalents, respectively. Similarly, there was a wide variation in the mean hospital stay. Hospital stays for antegrade endopyelotomy, Acucise endopyelotomy, laparoscopic pyeloplasty, and open pyeloplasty were 3, 0.2, 3.1, and 7.3 days, respectively. A similar pattern was noted with time for full recovery: 4.7 weeks, 1 week, 2.3 weeks, and 10.3 weeks, respectively. Of 13 patients undergoing antegrade endopyelotomy, 3 (23%) required transfusion, as did 2 of 9 (22%) patients undergoing Acucise endopyelotomy. No patient in the laparoscopic pyeloplasty or open pyeloplasty groups required blood transfusion.

Complications were comparable among the four groups. One patient each from the antegrade and Acucise endopyelotomy groups experienced obstruction of their stents necessitating replacement. Two patients in the laparoscopic pyeloplasty group and one patient in the open pyeloplasty group experienced transient obstruction after stent removal. All three patients responded favorably to repeat stent placement. Other complications included a bulbar urethral stricture in the antegrade endopyelotomy group and a midureteral stricture in the laparoscopic pyeloplasty group. There was a single case of urosepsis related to a postoperative antegrade nephrostogram in the open pyeloplasty group (34). All 15 pyeloplasties in both the open and laparoscopic groups had successful outcomes. Success for the two incisional techniques, antegrade and Acucise endopyelotomy, were 77% and 78%, respectively.

Bauer and colleagues (19) retrospectively compared complications and outcomes of 42 patients undergoing laparoscopic pyeloplasty with 35 patients who underwent open pyeloplasty. All laparoscopic procedures were successfully accomplished. Operative time and hospital stay were not reported. There were five (12%) complications in the laparoscopy group: two cases of obstruction after stent removal requiring an additional month of stenting, one intraoperative colon injury that was repaired, one case of thrombophlebitis, and one case of pneumonia. In the open population, there were four (11%) complications: three cases of obstruction after stent removal necessitating stent or nephrostomy tube placement for more than 2 months and one patient with postoperative hemorrhage requiring transfusion.

There were no significant differences between preoperative and postoperative pain and activity scores between the procedures. Specifically, in the laparoscopic group, with a mean follow-up of 22 months, 62% of patients were pain free, 29% of patients had significant improvement in their pain, and 9% of patients experienced minimal or no change in symptoms. In the open surgery group, with a mean follow-up of 58 months, 60% of patients were pain free, 31% of patients reported improvement in their pain, and 3% of patients percent experienced minimal or no change. Objective success was based on the most recent radiographic follow-up (sonogram, intravenous pyelogram, or renal scan). Of the 42 patients in the laparoscopic group, with a mean follow-up of 15 months, 1 (2%) had a failure that was noted within 24 hours of stent removal. In the open group, two patients (6%) had postoperative obstruction with a mean follow-up of 30 months (19).

Laparoscopic pyeloplasty in the adult is a feasible but technically demanding procedure. In adults, the procedure matches the efficacy of open pyeloplasty while offering the benefits of a less invasive approach. However, laparoscopic pyeloplasty remains more morbid than the percutaneous or retrograde approaches to endopyelotomy. As such, although it is generally accepted as an excellent salvage procedure, its use as front-line therapy currently remains controversial.

Retroperitoneum: Nephropexy

Perhaps no urologic procedure has had as checkered a history as the surgical treatment of the patient with a ptotic kidney. Early in the twentieth century, renal ptosis was blamed for myriad symptoms and surgical therapy was applied to a large patient population who, despite fixation of their ptotic kidney, failed to benefit symptomatically (149). As such, nephropexy rightfully fell into disfavor. However, as with many controversial operations, the truth lies somewhere in the middle, and many urologists have come to realize that there is a certain, albeit small, number of patients whose lower quadrant abdominal discomfort is due to renal ptosis. This select group is almost invariably thin and female with the problem occurring almost uniformly on the right side. Classically, their pain is relieved with lying down, and

it is common for their right kidney, when in its ptotic position, to be readily palpable in the right lower quadrant. Lying and standing urograms and renal scans are helpful in the diagnosis; the latter may show evidence of decreased blood flow and reduced clearance when the kidney is ptotic. Myriad open procedures have been described to “pex” the kidney high in the retroperitoneum. Hence, it was only a natural progression of laparoscopic renal surgery that led Urban and colleagues (426) to report the first successful laparoscopic nephropexy in 1993.

Laparoscopic transperitoneal nephropexy is initiated by mobilization of the colon to expose Gerota's fascia. Gerota's fascia is then incised and the kidney is dissected along its anterior, posterior, and lateral aspects. Blunt dissection is performed to expose the fascia over the psoas muscle. The patient is then placed in a steep Trendelenburg position, and the kidney is fixed in place, high in the retroperitoneum. The kidney is anchored with four to five nonabsorbable interrupted intracorporeal sutures, placed between the lateral border of the kidney and the psoas or quadratus lumborum muscles (Fig. 18.17). In some cases, a second suture line is run between the anterior surface of the kidney and the upper edge of the incised posterior coronary hepatic ligament (94).

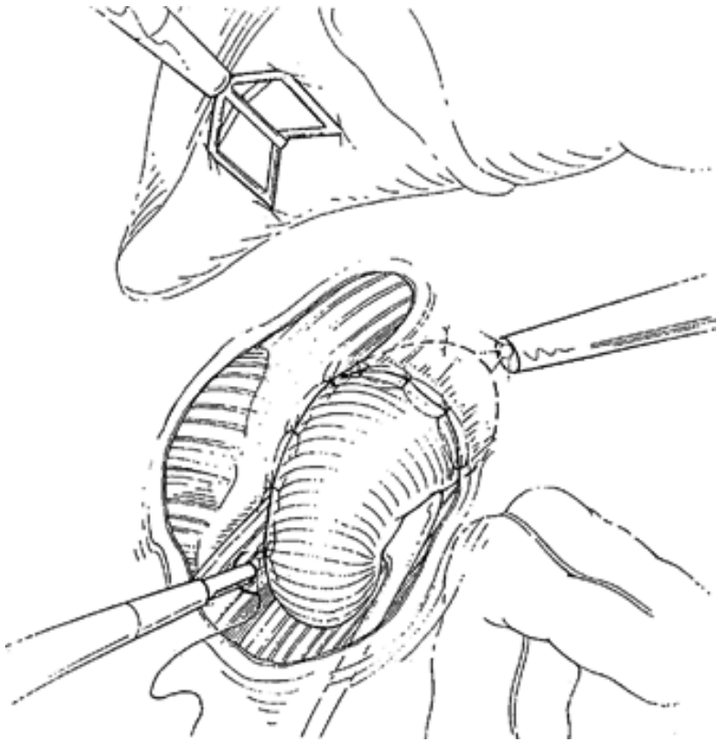

FIGURE 18.17. Laparoscopic nephropexy. Nonabsorbable interrupted intracorporeal sutures are placed between the lateral border of the kidney and the psoas and quadratus lumborum muscles.

Hubner and co-workers (177) described results of ten women treated for symptomatic nephroptosis who were managed with laparoscopic nephropexy. All ten patients had two nuclear renal scans that demonstrated a change in renal perfusion with alterations in posture. Operative time averaged 2.7 hours; there were no intraoperative complications. Patients required a mean of 10 mg of morphine sulfate for adequate pain control. Postoperatively, all patients underwent intravenous pyelography, which demonstrated no renal descent. With follow-up ranging from 6 to 42 weeks, all patients reported resolution of their symptoms.

Fornara and colleagues (106) compared results of 23 laparoscopic nephropexies with a historical control group of 12 patients who underwent open nephropexy. The laparoscopic group consisted of 1 man and 22 women, and all 12 patients in the open group were female. Of 23 patients, 22 (96%) in the laparoscopic group manifested pathology on the right side. In the laparoscopic group, pain scales were administered preoperatively and at follow-up. All laparoscopic procedures were successfully accomplished with a mean operative time of 61 minutes. Open nephropexies required a mean operative time of 49 minutes. Estimated blood loss was not reported. There were no intraoperative complications in either group.

Postoperative analgesic requirements were 15 and 38 mg of morphine equivalents for laparoscopic and open nephropexy, respectively. Mean hospital stay was 3.7 days in the laparoscopic group and 16 days in the patients managed with open surgery. Time to return to work was not available in the open group, but patients in the laparoscopic group returned to work in a mean time of 19 days. In the laparoscopic group, there were three (13%) minor complications: a urinary tract infection that resolved with antibiotic therapy and two retroperitoneal hematomas that were managed with observation only. In the open group, there was a single (8%) complication: a perirenal hematoma that required transfusion of 2 U of packed RBCs. Of the 21 patients in the laparoscopic group available for follow-up evaluation, all reported significant improvement in pain scores and none required regular analgesics for pain control. Three patients (25%) managed with open surgery had pain similar to what was experienced preoperatively (106).

McDougall and colleagues (257) reported long-term results of 14 women who had undergone laparoscopic nephropexy. The procedure was successfully accomplished in all 14 patients. Operative time was 4.1 hours, with an estimated blood loss of less than 50 mL in every case. The patients resumed oral intake in a mean time of 16.5 hours, and mean hospital stay was 2.6 days. Patients required an average of 37 mg of morphine sulfate for pain control in the postoperative period. There were no intraoperative complications, and there was a single postoperative complication. This patient experienced nausea and vomiting, which required a 5-day hospitalization for intravenous hydration. The symptoms resolved without intervention. Patients returned to their usual activities after a 6-week convalescence.

With a mean follow-up of 3.3 years, the patients experienced an average improvement of 80% on pain scales. Overall, 21% were considered cured, 71% were improved, and 7% failed. The one patient (7%) reported as a failure

still had more than 50% improvement in pain. All patients experienced radiographic resolution of nephroptosis; no patient manifested descent of the kidney of more than one vertebral body. Renal function as evaluated by serum creatinine was stable or improved in all patients (257).

Patients with symptomatic nephroptosis have excellent results with nephropexy. Laparoscopic nephropexy is feasible and effective in pain control in properly selected patients. Patients undergoing laparoscopic nephropexy have less postoperative discomfort and a more rapid convalescence than their open surgical counterparts.

Retroperitoneum: Ureterolithotomy and Pyelolithotomy

Until the 1980s, most upper ureteric and renal pelvic calculi that required treatment were managed by open surgery. With the development of extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, percutaneous renal surgery, and improved endourologic instrumentation, the need for open ureterolithotomy and pyelolithotomy has become minimal. Despite the rare indication for open stone surgery, several authors have taken even these few cases and proceeded to perform the necessary stone removal using laparoscopic techniques. The first laparoscopic ureterolithotomy and pyelolithotomy were performed via a retroperitoneal approach by Wickham (437) in 1979 and Gaur and colleagues (115) in 1992, respectively.

Laparoscopic ureterolithotomy has been described via the transperitoneal and retroperitoneal approaches. When done via the transperitoneal approach, the procedure is accomplished with a three-trocar technique. The primary trocar is typically placed infraumbilically in the midline, and two additional trocars are positioned in the midclavicular line, based on the location of the stone (i.e., one above and one below the stone's location). After mobilization of the colon, the ureter is identified and the stone located visually. The ureter is incised and the stone is extracted. The ureter is then closed with interrupted sutures, and a drain is left in the retroperitoneum.

Access for retroperitoneal laparoscopic ureterolithotomy is gained via an incision at the tip of the twelfth rib. The retroperitoneal space is created and two additional trocars are placed, usually one posterior to the initial trocar and a second directly inferior to the initial trocar and two fingerbreadths above the iliac crest. Additional trocar placement is dependent on stone location. The ureter is identified and the stone located visually. After incision of the ureter and stone extraction, one of several paths may be taken: (a) the ureter is closed with intracorporeal sutures, a stent is placed, and a drain is left in the retroperitoneum; (b) the ureter is not closed, but a stent is placed and a drain is left in the retroperitoneum; or (c) the ureter is not closed, a stent is not placed, but a drain is left in the retroperitoneum. Although laparoscopic suturing remains a challenging task, formal closure and stenting of the ureter along with placement of a retroperitoneal drain appears to be the surest way to preclude urinoma or other complications.

Transperitoneal pyelolithotomy is usually performed using three trocars. One trocar is placed at the umbilicus and the other two are placed in the midclavicular line (one subcostal and the other in the lower quadrant). The colon is reflected medially and the renal pelvis identified by following the proximal ureter in a cephalad direction. The renal pelvis is dissected from surrounding structures. A transverse pyelotomy is then made above the ureteropelvic junction. Renal stones are visualized and extracted by passing a flexible cystoscope through a 10- or 12-mm midclavicular cannula. Grasping forceps or a stone basket is used to extract calculi through the trocar. Stones too large to pass through a 10-mm trocar may be placed in a sack and extracted at the termination of the procedure. The pyelotomy is closed with a watertight running or interrupted 3 or 4-0 absorbable suture. A suction drain is left in the retroperitoneum, and an indwelling stent is left in the ureter.

Harewood and co-workers (155) reported results of nine ureterolithotomies. Patients all had large, longstanding, impacted, or obstructing calculi located in the upper or middle ureter. In six patients, a transperitoneal approach was used, and in three cases, the approach was retroperitoneal. The retroperitoneal approach was successful in one patient but required conversion to a transperitoneal approach in the other two patients. In all nine patients, the stones were successfully extracted with the laparoscopic approach. Ureterotomy incisions were closed after indwelling stent placements with two or three interrupted 3-0 chromic catgut sutures to achieve a watertight closure. These sutures were placed using an Ethicon semiautomatic suturing device (Johnson and Johnson Medical, Cincinnati, Ohio). Mean operative time was 158 minutes. Significant drainage occurred in the first five patients; this lasted from 1 to 3 days. Mean hospital stay was 5.2 days. Mean analgesic requirement was 27 mg of morphine sulfate. No intraoperative or postoperative complications were reported.

Turk and colleagues (422) reported results of 21 patients undergoing laparoscopic ureterolithotomy. The transperitoneal approach was used in 20 patients, and the retroperitoneal approach was applied in a single case. The procedure was successfully accomplished in 19 of 21 (90%) cases. Mean operative time was 90 minutes. In two patients, safe location of the calculus by laparoscopy was not possible and open surgery was performed. After indwelling ureteral stent placement, the ureterotomies were closed with running 4-0 PDS suture. Postoperative analgesic requirements were not specified. Patients were discharged between 2 and 7 days after surgery. In two patients, the ureteral stent was left in position for more than 4 weeks due to extravasation on radiographic evaluation. No other intraoperative or postoperative complications were reported.

Gaur and co-workers (115) reported results of eight attempted laparoscopic pyelolithotomies performed via a retroperitoneal approach. The procedure could not be performed in three (38%) patients. Two procedures were converted to open surgery because retroperitoneal access could not be adequately gained. In a third case, conversion to open surgery was necessitated by a tear in the peritoneum. Average operative time was 2 hours. Estimated blood loss was less than 250 mL in all cases. No attempt was made to close the pyelolithotomy incisions, and no indwelling stents were left in position. Average hospital stay was not stated. Drains were removed as outpatients within 7 to 15 days. Analgesic requirements were reported as minimal.

Micali and colleagues (276) presented results of 17 patients undergoing laparoscopic management of renal and ureteral calculi. Eleven patients were treated for renal calculi, and the remaining six patients had ureteral calculi. All procedures were performed using a transperitoneal approach. For renal stones a transverse pyelotomy was created, and stones were extracted using a flexible cystoscope. In 9 of 11 patients with renal calculi, a concomitant laparoscopic pyeloplasty was performed. A suction drain was placed in all 11 patients. A longitudinal ureterotomy was used in all ureteral cases. After stone extraction, ureterotomies were closed with one or two interrupted 4-0 absorbable sutures. Three (50%) patients undergoing ureterolithotomy had a suction drain placed.

Laparoscopic stone removal was successful in 15 (88%) cases. In one case, an investigational camera resulted in disorientation of the surgical team, requiring conversion to open surgery to locate the ureter. The second conversion resulted from inability to fragment a large stone that could not be removed intact. An incision was required to pass a lithotrite to crush the stone. Mean operative time including ancillary procedures was 4.9 hours. Mean estimated blood loss was 133 mL, and no patient required blood transfusion. Patients required 26 mg of morphine sulfate for pain control and had a mean hospital stay of 4.5 days. Return to full activity required 3 weeks. With a mean follow-up of 13.7 months, all patients were asymptomatic and stone free without obstruction on intravenous urography. There were three (18%) postoperative complications. One patient had a prolonged ileus and another patient experienced a *Clostridium difficile* infection, requiring hospital stays of 5 and 15 days, respectively. One patient experienced fever and abdominal pain 2 weeks after distal ureterolithotomy, and a retroperitoneal urinoma was identified and drained percutaneously. This patient did not have a drain placed after ureterolithotomy.

Laparoscopic ureterolithotomy and pyelolithotomy are feasible procedures. However, present-day technology, including ESWL, ureteroscopy, and percutaneous access techniques, offers patients a less invasive alternative for stone management. In general, laparoscopic management should be considered only when these modalities are unavailable or have been tried and failed or the patient is undergoing a concomitant laparoscopic procedure (e.g., pyeloplasty).

Retroperitoneum: Ureterolysis

Extrinsic compression and obstruction of the ureters is relatively uncommon and is often associated with significant patient discomfort and functional renal loss. Retroperitoneal fibrosis (RPF) and ovarian pathology are among the most common benign conditions associated with extrinsic obstruction of the ureter. Although ureterolysis for RPF is highly efficacious, it is associated with significant morbidity and occasional mortality. Laparoscopic ureterolysis has been described as a minimally invasive alternative to the open procedure. Laparoscopic ureterolysis was introduced by Kavoussi and co-workers (209) in 1992; Puppo and colleagues (343) subsequently reported the first bilateral procedure in 1994.

The technique is usually a four-port transperitoneal approach. In all cases, an external ureteral stent is placed immediately before the laparoscopy. After incising the line of Toldt and reflecting the colon, the surgeon circumferentially dissects the unaffected portions of the ureter proximal and distal to the fibrosis. Following this, the affected ureter is dissected out of the thick fibrotic tissue, being careful to remove it from the layers of periureteral fibrotic tissue without entering the ureteral lumen. Once freed, the ureter is brought into the peritoneal cavity, and the line of Toldt is then reestablished posterior to the ureter, using intracorporeal suturing or placement of apposing clips. An omental wrap of the ureter is usually not performed. At the end of the procedure, the external stent is exchanged for an internal ureteral stent; the ureteral stent is left in place for 4 to 6 weeks.

Elashry and colleagues (96) compared six patients undergoing unilateral laparoscopic ureterolysis for extrinsic ureteral obstruction with seven patients undergoing open unilateral ureterolysis for similar pathologic conditions. Laparoscopic unilateral ureterolysis was successfully accomplished in all six patients. Mean operative times for laparoscopic and open ureterolysis were similar (255 versus 232 minutes); however, in the open group, an omental wrap of the ureter was usually performed in addition to the ureterolysis. Estimated blood loss was decreased with the laparoscopic approach: 140 versus 373 mL. Hospital stay was shortened in the laparoscopic group: 2.8 versus 10.5 days. Similarly, return to full activity was expedited by the laparoscopic approach: 2.1 versus 7 weeks. There were no major or minor complications in the laparoscopically managed group. In the open group, there was one (14%) intraoperative complication and four (57%) postoperative complications. Intraoperatively, a ureter was avulsed during ureterolysis, requiring psoas hitch reimplantation. In addition, among the open surgery patients, two patients (29%) required postoperative blood transfusions, one patient (14%)

had a 6-day ileus, and one patient (14%) experienced wound cellulitis that resolved with intravenous antibiotic treatment. All patients in both groups were symptomatically improved or cured, and all had evidence of radiologic resolution of obstruction on follow-up evaluations (96).

Nezhat and colleagues (302) described laparoscopic ureterolysis in 28 women with severe urinary tract endometriosis. Twenty-one women in this series had partial or complete obstruction of the ureter. After ureteral catheter placement, the affected ureter was dissected free from surrounding tissues with hydrodissection and the CO_2 laser. Any evidence of ureteral endometriosis or fibrosis was vaporized using the laser. When the ureteral lumen was grossly entered, closure was performed with intracorporeal suturing. Pinpoint entries were not repaired. If the lumen was completely occluded and catheter placement was impossible, the affected segment was excised and primary laparoscopic anastomosis performed.

Seventeen women had extrinsic ureteral compression causing partial obstruction and four had full-thickness complete obstruction. Of the four with full-thickness involvement, three underwent primary repair and one was treated with ureteroneocystostomy. Mean postoperative hospital stay was 1.8 days. A single postoperative complication was reported. On postoperative day 1, a woman developed a pleural effusion requiring thoracocentesis and aspiration. On follow-up evaluation, 20 of 21 (95%) patients had patent ureters and functional kidneys. One woman (5%), who presented with unilateral complete ureteral obstruction, had a patent ureter postoperatively but only 10% to 20% function on the affected side; unfortunately, there was no preoperative functional evaluation in this patient (302).

Laparoscopic ureterolysis is feasible and effective. Benefits include rapid convalescence and minimal morbidity. Of interest is the success of laparoscopic ureterolysis as a singular procedure, devoid of using an omental wrap; elimination of this step from the ureterolysis procedure may well account for the reasonable operating room time and the markedly lower morbidity of the laparoscopic approach.

Abdominal: Peritoneal Dialysis Catheter Placement and Repair

Peritoneal dialysis (PD) was described by Ganter in 1923 (111). Despite offering several advantages over hemodialysis, complications related to the peritoneal catheter such as exit site infection, tunnel infection, incorrect positioning of the catheter within the abdomen, peritonitis, pericatheter hernia, pain, or mechanical dysfunction with related fluid drainage remain troublesome. Complications have limited catheter survival to only 51% to 60% at 18 months and 22% to 50% at 36 months (152,355).

The most common approach to PD catheter placement is the open surgical approach. Other methods for PD catheter placement, using guidewire techniques, have also been described. However, these methods have not gained widespread acceptance because of concerns over possible visceral injury.

Kimmelstiel and colleagues (220) first reported laparoscopic placement of peritoneal dialysis catheters in 1993. At present, the laparoscopic technique for PD catheter placement employs a 1.5-cm infraumbilical incision. After inspection of the abdomen for adhesions or other anatomic abnormalities that could hinder catheter flow, a second trocar is inserted in a lower paramedian position. The PD catheter is then positioned with its tip in the pouch of Douglas. After fascial closure, a subcutaneous tunnel is created for the PD catheter entry port. Intraabdominal position of the catheter is confirmed with a sterile saline flush before termination of the procedure.

Crabtree and Fishman (68) reported results of 29 patients undergoing laparoscopic PD catheter placement. All catheters were placed via two paramedian trocars placed at the level of the umbilicus. Twenty-nine attempted catheter placements were described with a single (3.4%) failure due to injury of an inferior epigastric artery. Operative times and estimated blood loss were not provided. Median follow-up was 4.4 months. Two patients experienced intraperitoneal bleeding that required transfusion in the postoperative period. All catheters were functional at the time of the report. Ten (36%) patients experienced delayed complications: six exit site infections, one exit site/tunnel tract infection, one case of peritonitis, one catheter leak, and one episode of outflow obstruction requiring laparoscopic manipulation for repair.

Wright and colleagues (454) performed a randomized prospective trial comparing 21 laparoscopic and 25 open PD catheter placements. Laparoscopic placement was accompanied by creation of a 2.5- to 3.0-cm lower midline incision for catheter placement. Complications were divided into an early group (occurring within 6 weeks of surgery) and a late group (occurring after 6 weeks). Four laparoscopic procedures required conversion to an open approach due to technical, nonhemorrhagic problems (i.e., unable to establish a pneumoperitoneum and obesity). Open surgery was faster than the laparoscopic approach: 14 versus 22 minutes. Estimated blood loss was not reported. There was no significant difference in the early or late complication rates between the laparoscopic and open groups: 48% versus 29% early problems and 48% versus 63% late complications. These problems, both early and late, were almost invariably due to exit site infections or peritonitis. The duration of hospital stay, pain scores, and analgesic requirements were not significantly different between the two groups. However, the laparoscopic group tended to have lower pain scores after the initial six postoperative hours. In sum, these authors found no significant benefit to the laparoscopic approach.

In contrast, Gadallah and co-workers (107) compared complications of 72 open surgical placements with 76 peritoneoscopic

PD catheter placements in a prospective randomized fashion. Peritoneal dialysis catheters were placed via a single 2-cm paramedian incision after laparoscopic visualization of the abdominal contents. Convalescence parameters and surgical data were not reported. Complications were considered early if they occurred within 2 weeks of PD catheter placement and late if they occurred more than 2 weeks after catheter placement. Early complications, commonly peritonitis or leakage, were significantly more common in the open group: 33% versus 13%. There was no significant difference in the frequency of late complications between open and peritoneoscopic approaches: 61% versus 58%, respectively. These complications included infection, catheter malfunction, and hernias (107).

Laparoscopic salvage of malfunctioning PD catheters has also been described. Amerling and co-workers (11) reported results of 25 patients with 28 episodes of PD catheter obstruction undergoing laparoscopic salvage procedures. In 23 (92%) cases, the catheter was successfully restored to function. In two cases, adhesions were so dense that the distal end of the catheter could not be identified. Obstruction was secondary to omental entrapment in 18 cases and to local adhesion formation in 10 cases. Operative time ranged from 40 to 120 minutes. When performed on low-risk patients, many could be discharged on the same day as the laparoscopic procedure. Only oral analgesics were required postoperatively.

Subsequently, the salvaged catheters remained patent for a mean of 9.2 months (range = 0 to 36 months). Overall, the procedural complication rate was 39%: catheter occlusion (one case), peritonitis (four cases), subcutaneous leakage (four cases), and trocar site hernia (two cases). The latter two problems were largely rectified with the routine use of a trocar site closure device (11).

Laparoscopic peritoneal dialysis catheter placement is a feasible procedure. A two-trocar site approach for access, placement, and manipulation of the PD catheter provides satisfactory results without the need for any incision larger than the port itself (i.e., 10 to 12 mm); likewise, fascial closure of all port sites is recommended to prevent subsequent leakage. The laparoscopically implanted PD catheters tend to have fewer early complications, perhaps because of better positioning and use of a smaller incision; however, the overall benefits of the laparoscopic approach appear to be minimal, and the operative time is longer. In contrast, salvage of nonfunctioning PD catheters is a feasible and perhaps more beneficial application of laparoscopy among these patients.

Benign Disease: Reconstructive On the Horizon

Sling Procedure

Pubovaginal sling, artificial sphincter placement, and periurethral injection therapies are the treatment options for intrinsic sphincter deficiency (type III) stress urinary incontinence. The pubovaginal sling has also become the primary modality for repair of type I and type II stress incontinence. The technique for performing a pubovaginal sling has been described for either a transvaginal or transabdominal approach. In an attempt to minimize postoperative pain and convalescence, the laparoscopic approach has been applied to the procedure.

Kreder and Winfield (226) described the initial laparoscopic sling placement for stress urinary incontinence via an extraperitoneal approach. Fascia lata was harvested from the patient's thigh in the usual fashion. Five trocar sites were placed in the lower abdomen, and a plane was created between the bladder neck and the vagina. The fascial sling was passed through the defect at the bladder neck and anchored to the rectus fascia 0.5 cm above the pubis with nonabsorbable sutures passed through two of the previously placed trocar sites. Two cases were described, one of which had to be converted to open due to an inadvertent urethrotomy. The successful laparoscopic case had an operative time of 6.5 hours with an estimated blood loss of less than 100 mL. The patient required 16 mg of intramuscular morphine postoperatively. Sluggish return of bowel function resulted in a 5-day hospital stay. At 3-week follow-up, the patient was doing well with a normal voiding cystourethrogram, and the catheter was removed. At 4-month follow-up, the patient was continent.

A laparoscopic pubovaginal sling procedures is technically feasible. However, with the evolution of a transvaginal approach in conjunction with synthetic or allograft materials for sling construction, the open procedure has become minimally invasive. Indeed, most of these patients are now treated on an outpatient basis. As such, it is unlikely there will be any advantage to patients in the application of laparoscopic technology for this purpose.

Sacral-colposuspension

Vaginal wall prolapse has been managed by abdominal sacral colpopexy or transvaginal sacrospinous ligament vaginal vault suspension. In an attempt to apply minimally invasive technology to vaginal wall prolapse, laparoscopic sacral-colposuspension has been described.

The procedure, as described by Ostrzenski (317), is performed via an extraperitoneal approach. The retropubic space is entered bilaterally between the urachus and the medial umbilical folds, and the space of Retzius is opened until the obturator foramen is visualized bilaterally. The vagina is digitally elevated to its normal position, and using 0-polydioxanone suture, the surgeon anchors it to the surrounding pelvic structures. Posteriorly, the vaginal apex is suspended to the deep layer of the uterosacral ligaments. The posterolateral vaginal cuff is suspended to the cardinal ligaments. Anteriorly, the vaginal vault is suspended to the pubocervical fascia. Finally, the pubocervical fascia and the anterolateral vaginal sulci are suspended to the fascia of

the obturator internus muscle and tendinous arch bilaterally. The peritoneum is closed after vaginal suspension has been accomplished.

Ostrzenski (317) reported the use of this technique in 27 patients with iatrogenic total vaginal prolapse after hysterectomy. The initial 17 patients underwent the procedure without suspension of the pubocervical fascia to the obturator internus and tendinous arches. The procedure was subsequently modified and the two groups compared. All procedures were successfully accomplished laparoscopically, and estimated blood loss was minimal. Mean operative time was 3.6 hours. Twenty-four (89%) patients were discharged on the day of surgery, with the remaining three (11%) discharged on postoperative day 1. No intraoperative complications were described. Two patients (7%) experienced postoperative urinary tract infections.

Of the initial 16 patients, 1 (6%) experienced complete vaginal prolapse within 6 months of the procedure. Eleven patients (69%) had no significant laxity of the vaginal apex or walls. Four patients (25%) displayed some degree of vaginal cuff descent postoperatively. After modification of the procedure, an additional 11 patients were evaluated. No patient experienced prolapse of the vaginal apex over a 42-month follow-up period. Ten patients (91%) displayed no laxity of the vaginal apex or walls. One patient (9%) demonstrated moderate vaginal wall descent.

There are limited data on laparoscopic sacral-colposuspension. However, the procedure appears to be safe and feasible. Preliminary results are promising, and patients may benefit from a more rapid convalescence with decreased pain. Data comparing open and laparoscopic techniques are required before a more definitive conclusion can be drawn.

Mitrofanoff Procedure

Clean intermittent catheterization is the preferred management option for the patient with a neurogenic bladder. When the urethra cannot be used, cutaneous appendicovesicostomy, as described by Mitrofanoff (283), offers a reliable alternative. The Mitrofanoff principle entails the use of a supple conduit, typically the appendix, brought to the skin as a catheterizable stoma with an antireflux connection to the urinary reservoir. Laparoscopic urinary diversion using the Mitrofanoff principle was initially described by Strand and colleagues (402).

Hedican and colleagues (162) reported their experience with a laparoscopic assisted Mitrofanoff procedure in eight patients ages 7 to 26 years. The laparoscopic technique was used to mobilize the cecum and harvest a gastric segment, thereby eliminating the need for an upper abdominal incision. The vermiform appendix was mobilized and a stapler fired across the base to isolate this segment. A laparoscopic suture was placed through the appendix to allow withdrawal through a trocar site. The remainder of the reconstruction was performed through a Pfannenstiel incision. The time for the laparoscopic portion of the procedures was not reported, and analgesic requirements were not quantitated. Median hospital stay was 8 days. One (12.5%) complication was reported: a patient required open reexploration for small bowel obstruction caused by a knuckle of ileum trapped between crossed mesenteries.

Lorenzo and co-workers (245) compared results of four open Mitrofanoff procedures with four laparoscopic Mitrofanoff procedures performed with the same basic technique in patients ages 17 to 58 years. Using four access trocars, the physician isolated the vermiform appendix with the vascular pedicle. Using a linear laparoscopic stapler, the physician transected the appendiceal base with a 3-mm cuff of cecum. The distal appendix was cut, and a direct anastomosis to the bladder was accomplished with four to six interrupted 4-0 Vicryl sutures. The proximal appendix, with the attached 3-mm cecal segment, was used to create the skin stoma. A 10-Fr Foley catheter was placed through the lumen of the appendicular lumen, and a skin stoma was created at the umbilicus. A Penrose drain was left in position.

All four procedures were successfully accomplished laparoscopically with a mean operative time of 2.45 hours versus 1.55 hours for the open procedures. Mean estimated blood loss was 200 mL in both groups. Mean hospital stay for the open and laparoscopic procedures was 5 and 3 days, respectively. The postoperative narcotic requirements of patients managed laparoscopically were reported to be significantly less than the requirements of patients managed with open surgery. The mean recovery time for the open procedure was 4 weeks; after the laparoscopic procedure it was 1.5 weeks. Postoperative laboratory tests demonstrated that all patients had sterile urine, and there was no laboratory or radiographic evidence of upper tract deterioration with a mean follow-up of 19.5 months (245). All eight patients remain continent both subjectively and by urodynamic assessment.

Laparoscopic urinary diversion applying the Mitrofanoff principle is feasible. Limited data are available; however, the procedure seems to afford patients the benefits of minimally invasive surgery while resulting in reliable urinary continence.

Ileal Conduit

Since its introduction by Bricker (33) in the 1950s, the ileal conduit has become a staple in the urologist's armamentarium. Indications for ileal conduit construction include the need for urinary diversion due to a diseased or otherwise nonfunctional bladder. Several groups have reported laparoscopic ileal conduit construction.

Kozminski and Partamian (225) described the first laparoscopic assisted ileal conduit. Bilateral ureteral dissection was performed. Bowel transection was performed by pulling the ileum through one of the trocar sites. A small mesenteric window was made at the edge of the bowel wall and a GIA

stapler was used to transect the bowel. After the ileal segment had been isolated, the free ends of the remaining transected bowel were pulled through a trocar site using previously placed suture tags. An extracorporeal antimesenteric side-to-side anastomosis was then performed using GIA and TA-55 staplers. The mesenteric window was then closed with Endoclips. Both ureters were anastomosed to the ileal loop in an end-to-side fashion. Each ureter was brought through a trocar site with the ileal conduit, and a standard hand-sewn anastomosis was performed on the abdominal wall. Operative time was 6.3 hours. The patient required no narcotic medications after the first 12 postoperative hours. He was started on a diet on postoperative day 5 and discharged home on postoperative day 7. He was able to resume normal activity 10 days after surgery. The patient had not experienced any complications at follow-up 3 months later (225).

Vara-Thorbeck and Sanchez-de-Bandajoz (428) reported laparoscopic assisted ileal conduit construction for a high-risk elderly patient with bladder cancer. The patient had a solitary kidney and known invasive bladder cancer with several episodes of urinary retention secondary to blood clots. Distal ureteral dissection was performed unilaterally. Sufficient ureteral length was dissected to allow an extracorporeal ureteroileal anastomosis to be performed. A 15-cm segment of ileum was isolated and bowel continuity reestablished with a side-to-side sutured anastomosis. A single-J stent was placed in the ureter before implantation in the ileal segment through an extended trocar site 4 cm in length. Operative time was 4 hours, and intestinal motility was noted on the first postoperative day. With a 4-month follow-up, the patient was symptom free and receiving radiation therapy.

Potter and colleagues (338) reported long-term follow-up of an ileal conduit constructed in 1995 with a completely intracorporeal technique. The ileal conduit was constructed in a 28-year-old man with a neurogenic bladder. The ileal segment was isolated with laparoscopic staplers, and ureteral anastomoses were performed using a “dunk” technique. After placement of 1 cm of distal ureter into the ileal conduit, four anchoring adventitial sutures were placed in the ureter. During 5 years of follow-up, the patient had no urinary tract infections and the skin stoma remained patent and viable. Intravenous urography performed 1, 2, 3, and 5 years after creation of the conduit revealed prompt, symmetric renal function and preservation of renal parenchyma without evidence of obstruction of the urinary tract. Retrograde contrast studies of the ileal conduit revealed no evidence of reflux, and the patient's serum creatinine remained stable at 0.8 mg/dL.

Laparoscopic assisted ileal conduit construction has been described and is feasible. The procedure is time-consuming, and the benefits of the laparoscopically assisted ileal conduit have not been clearly demonstrated due to the few number of procedures and the variations in technique. Comparison with traditional open techniques is lacking, and long-term follow-up data are just beginning to emerge, albeit in only a handful of patients.

Enteric Bladder Augmentation

Open enteroplasty is the most commonly used technique for augmentation of bladder capacity. Anastomosis of a well-vascularized patch of detubularized bowel can significantly and durably increase the storage capacity of the urinary bladder. Several investigators have described laparoscopic enterocystoplasty with different segments of the gastrointestinal tract.

Docimo and colleagues (82) described gastrocystoplasty in a young female patient with a neurogenic bladder. The patient had a small poorly compliant bladder with a capacity of 150 mL. Stomach was chosen as the source for augmentation because the authors believed it would be more technically straightforward. Using blunt and sharp dissection, the surgeon dissected the anterior bladder wall free of surrounding structures to the level of the urethra. Attention was turned to the stomach, where the greater omentum was divided distal to the gastroepiploic arcade and the transverse mesocolon was displaced posteriorly. The right gastroepiploic pedicle was dissected free of the right side of the greater curvature of the stomach to the level of the pylorus. After division of the omentum, a gastric wedge, 20 cm in length, was removed using five firings of a laparoscopic stapler. An EndoStitch suturing device was used to oversew the stomach. An EndoStitch device with 3-0 Vicryl suture was used to run the edges of the anastomosis of the gastric segment to the bladder. A 24-Fr Malecot suprapubic tube and a 20-Fr Foley urethral catheter were left to drain the bladder. The patient also underwent a needle bladder neck suspension. Total operative time was 10 hours, 55 minutes. The patient received a transfusion of 2 units of packed RBCs despite an estimated blood loss of 250 mL. Postoperatively, the patient received 247 mg of morphine via her patient-controlled analgesia device. Because of a transient urine leak, she was not discharged until postoperative day 13. Urodynamic evaluation 3 months after surgery revealed a bladder capacity of 315 mL. She remained dry on intermittent catheterization.

Gill and colleagues (127) reported results of laparoscopic assisted enterocystoplasty in three patients with reduced bladder capacity. Augmentation was performed with ileum in the first case and sigmoid colon in the second. The third patient underwent augmentation with cecum and right colon, and the terminal ileum was refashioned to create a continent conduit, which was brought out at the umbilicus as a catheterizable stoma. After selection of the appropriate bowel segment, 15 cm of bowel was delivered outside the abdomen via a 2-cm extension of the umbilical trocar site. Using open surgical techniques, each bowel segment with its mesenteric pedicle was isolated, bowel continuity reestablished, and the mesenteric window closed (Fig. 18.18A).

After detubularization, the bowel segments were anastomosed to the bladder with intracorporeal suturing (Fig. 18.18B). In the third patient, the terminal ileum was narrowed, the ileocecal junction was imbricated, and the ileum was brought out the umbilicus as a catheterizable stoma. Mean operative time was 6.8 hours. Mean estimated blood loss was 150 mL. The only intraoperative complication was a rectus sheath hematoma, which was controlled laparoscopically. Postoperative Jackson-Pratt drainage was minimal in all three cases, and drains were removed on postoperative days 3, 5, and 4, respectively. The first patient developed an ileus that delayed his discharge until postoperative day 7. The subsequent two patients were discharged on postoperative days 4 and 5. Analgesic requirements were 44, 55, and 229 mg of morphine. Follow-up bladder capacities and long-term patient outcomes were not reported.

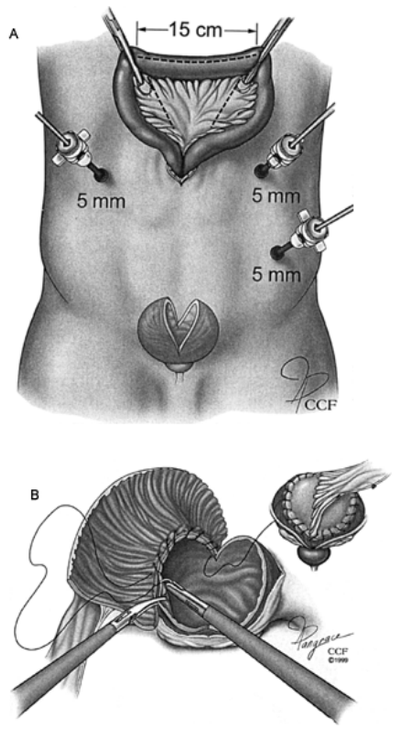

FIGURE 18.18. Laparoscopic bladder augmentation. **A:** Ileal segment is isolated and bowel continuity reestablished using open technique. **B:** After detubularization, the isolated ileal segment is anastomosed to the bladder with intracorporeal suturing.

Pure laparoscopic and laparoscopic assisted procedures for enterocystoplasty are feasible; however, in only one case has long-term data been provided as to the efficacy of the procedure. Further experience and eventual comparison with traditional open techniques are needed. At present, this laparoscopic approach remains under study.

Bladder Autoaugmentation

A consistent feature of the urologic approach to bladder augmentation has been the application of components of the alimentary tract as a vascularized source of graft material. Aside from the morbidity of harvesting the graft material, the use of bowel for urologic reconstruction is associated with significant late sequelae, including segment-specific metabolic disturbances arising from chronic contact with urine, pouch rupture, urolithiasis, and, rarely, carcinogenesis. Autoaugmentation (vesicomyotomy or vesicomyomectomy) represents an alternative approach to increasing the capacity of the urinary bladder while avoiding the incorporation of foreign epithelium. This technique entails the incision or excision of the detrusor layer of the bladder to create a large wide-mouthed diverticulum of urothelium. First described by Couvelaire and Agrandir (67) in 1955, the technique has undergone a significant evolution with variable results.

The technique of laparoscopic autoaugmentation was first described by Ehrlich and Gershman (91). Briefly, a transperitoneal pneumoperitoneum is established to 10 mm Hg. Four trocars are placed: umbilical, two midclavicular trocars on either side midway between the iliac crest and umbilicus, and a right lower quadrant trocar just lateral to the rectus sheath and inferior to the midclavicular right-sided trocar. The bladder is distended via a urethral catheter. Using curved laparoscopic scissors and low-power cutting current, the posterior wall of the bladder is incised until the urothelium is visualized. Using graspers, the surgeon teases the bladder muscle laterally, exposing additional amounts of urothelium. Any bleeding detrusor muscle is carefully coagulated with special care to avoid coagulation of the urothelium. The incision is extended posteriorly to the cul-de-sac and superiorly to the anterior fusion of the peritoneum and bladder. The bladder muscle is teased laterally for approximately one-third of the circumference of the bladder. A drain is left in the space of Retzius. The bladder is drained with a urethral catheter; a cystogram is performed 5 to 7 days postoperatively, and if there is no extravasation, the bladder catheter is removed.

In Ehrlich and Gershman's initial case report (91), an 8-year-old boy with a nonneurogenic neurogenic bladder

underwent a 1.2-hour laparoscopic autoaugmentation. The patient was discharged in less than 24 hours, and the drain was removed on postoperative day 2. On postoperative day 8, the patient's urethral catheter malfunctioned, resulting in a small bladder perforation that was treated with a percutaneous cystotomy tube. Voiding cystourethrogram at 2 weeks demonstrated no extravasation. One year postoperatively, the patient's persistent daytime and nighttime incontinence had markedly improved, with only minor leakage with strenuous athletic activity.

McDougall and colleagues (264) also reported their initial experience, albeit with an extraperitoneal laparoscopic autoaugmentation, in a 26-year-old woman with a traumatic spinal cord injury. Urodynamic evaluation revealed poor compliance, a decreased leak point pressure, and a bladder capacity of 85 mL. An extraperitoneal laparoscopic seromyotomy autoaugmentation was performed using a 3-Fr right-angle Greenwald electrode. The bilateral detrusor flaps were sutured to Cooper's ligament bilaterally with 1-0 polyglactin suture. Operative time was 6.5 hours, and estimated blood loss was 75 mL. The patient was discharged on postoperative day 2 with bladder drainage in place. Bladder drainage was continued for 1 month, at which time a cystogram revealed no extravasation. At 6-month follow-up, the patient had a normal cystogram, good compliance, a bladder capacity of 285 mL, and improved leak point pressure. The patient had daytime and nighttime continence, and she was catheter-free voiding by Valsalva with a residual of 30 mL.

Subsequently, Poppas and co-workers (337) reported two cases of laparoscopic seromyotomy autoaugmentation that were performed with KTP laser assistance. Two children with myelodysplasia and high-pressure neurogenic bladders unresponsive to conservative management underwent laparoscopic autoaugmentation. The detrusorotomy was performed with the KTP laser. A right-angle backstop device was used for the final portions of the detrusorotomy after initial access to the urothelium had been achieved. There were no reported complications. Initial results were promising, with improvement in symptoms, decreased peak detrusor pressures, and increased bladder capacity in both cases. However, at 5 months, both cases failed and went on enterocystoplasty.

Autoaugmentation is an attractive, minimally invasive method for the treatment of the contracted, high-pressure bladder. Although the technique is amenable to a laparoscopic approach, there is little experience and inconsistent results. Further detailed studies in the laboratory and clinical arena are needed to determine the appropriate application and best technique for autoaugmentation surgery.

Ureteroureterostomy

The need for ureteral reconstruction is usually due to an intrinsic stricture (e.g., trauma, infection, stone impaction) or extrinsic compression (e.g., endometriosis, retrocaval ureter). Whereas the former can often be managed by endoscopic techniques, the latter usually requires a formal ureteroureterostomy for therapy. Several authors have described laparoscopic ureteroureterostomy in the management of ureteral pathology.

Nezhat and colleagues (301) reported the use of laparoscopic ureteroureterostomy for the management of ureteral obstruction secondary to endometriosis. Using laparoscopic techniques, the surgeon excised the diseased segment of the ureter and performed a ureteroureterostomy using four evenly spaced full-thickness 4-0 PDS sutures. The sutures were tied intracorporeally. Operative time was 117 minutes, with an estimated blood loss of less than 100 mL. The patient was discharged on postoperative day 1. Two months postoperatively, the ureteral stent was removed and intravenous urography revealed a patent ureter. Twenty-one months postoperatively, the patient was asymptomatic with a normal ultrasound evaluation of the kidney.

Laparoscopic ureteroureterostomy for retrocaval ureter was initially described by Ishitoya and colleagues (186) and later by Matsuda and co-workers (250) in 1996. Polascik and Chen (332) also reported ureteroureterostomy in the management of an obstructed retrocaval ureter. Using three trocars, the surgeon identified and mobilized the affected portion of the ureter. The ureter was divided at the most visible portion of the dilated proximal segment. The distal segment was spatulated for approximately 2 cm. The ureter was repositioned to lie anterior to the vena cava, and a previously placed stent was advanced into the renal pelvis. Anastomosis was performed using several interrupted 4-0 polyglactin sutures with an EndoStitch device. A double-J stent was left in position at the end of the procedure. Operative time was 3.75 hours. The patient was discharged on postoperative day 2. Analgesics were not required after the first day, and the patient resumed full activity on postoperative day 4. Retrograde ureteropyelogram performed 4 months after surgery revealed a patent ureter (332).

Laparoscopic ureteroureterostomy is feasible and has demonstrated good results in the few reported cases. The procedure is technically demanding, but future advances in laparoscopic tissue apposition may result in simplification. In a porcine model, Maxwell and co-workers (251) reported successful laparoscopic ureteroureterostomy using vascular closure staple (VCS) clips to perform the anastomosis. Operative times to perform the ureteroureterostomy were reduced from 39.7 and 39.5 minutes with hand suturing and EndoStitch suturing, respectively, to 22 minutes using the VCS clips. The procedure resulted in patent ureters without stones or encrustation at subsequent evaluation 12 weeks later.

Calyceal Diverticulum

Most calyceal diverticula remain asymptomatic. The incidence of calculi within calyceal diverticula varies from 10%

to 50% (278). Options for management of these stones, when they become symptomatic, have included percutaneous extraction, ureteroscopic lithotripsy, and ESWL.

Gluckman and colleagues (134) reported the initial procedure of laparoscopic treatment of a stone-bearing, calyceal diverticulum. Subsequently, Ruckle and Segura (360) reported transperitoneal laparoscopic management of a stone-filled calyceal diverticulum. Later, Chen and colleagues (52) reported using a retroperitoneal approach for unroofing a calyceal diverticulum filled with milk of calcium.

Harewood and co-workers (154) described a series of three patients with calyceal diverticula that were managed by an extraperitoneal laparoscopic approach. All three patients had diverticula associated with calculi. All three cases were successfully completed laparoscopically with a mean operative time of 127 minutes. Blood loss was minimal in the first two patients, but hemorrhage was troublesome in the third patient, necessitating a transfusion of 3 units of packed RBCs. All calculi were eliminated, but there was a small recurrence of one (33%) of the diverticula. Patients received an average of six doses of meperidine and were discharged in 4 days. One patient experienced drainage from one of the trocar sites for 2 months that resolved without intervention. There were no other complications reported.

Hoznek and co-workers (175) reported results of retroperitoneal laparoscopic management of three patients with symptomatic calyceal diverticula. All procedures were successfully accomplished with a mean operative time of 80 minutes and minimal blood loss. The calyceal diverticular cavities were filled with surgical mesh impregnated with gelatin resorcinol formaldehyde glue. Average hospital stay was 6.7 days with patients requiring analgesics only during the first postoperative day. There were no complications reported. At 6 months, follow-up CT scan revealed no calculi or recurrence of the diverticula.

Laparoscopic calyceal diverticulectomy is a feasible procedure. However, for the most part, a laparoscopic approach is only considered first-line therapy by some endourologists for a large, anterior calyceal diverticulum, because all others can be expeditiously managed by percutaneous or ureteroscopic techniques.

Bladder Diverticulum

A urinary bladder diverticulum creates a separate, poorly contractile chamber and can lead to complications such as recurrent urinary tract infection, stone formation, ureteral obstruction, vesicoureteral reflux, and rarely, transitional cell carcinoma. Das (72) first described laparoscopic bladder diverticulectomy in 1992. Subsequently, there have been several reports regarding laparoscopic management of bladder diverticula.

Jarrett and colleagues (200) detailed their laparoscopic management of a large bladder diverticulum. After cystoscopic placement of a balloon catheter into the diverticulum, a transperitoneal approach was used to access the bladder. The peritoneum was reflected laterally and the diverticulum excised. The bladder was closed in a single layer with intracorporeal suturing expedited with Lapra-Ty clips. A cystotomy tube was left in position for bladder drainage, and Jackson-Pratt drains were left in position for drainage. Operative time was 6.5 hours. The retroperitoneal drain was removed on postoperative day 1. The patient was discharged on postoperative day 3. Analgesic requirement included 4 mg of morphine and 225 mg of intramuscular meperidine. On postoperative day 9, the patient had a cystogram that demonstrated no leakage and the Foley catheter was removed.

Iselin and co-workers (185) compared two laparoscopic urinary bladder diverticulectomies with four open cases. Patients in both groups underwent transurethral resection of the prostate followed by either laparoscopic or open urinary bladder diverticulectomy. Both laparoscopic diverticulectomies were performed successfully. Mean operative times for laparoscopic and open procedures were 4.2 and 1.7 hours, respectively. All cases had successful resolution of the bladder diverticula on follow-up. One complication occurred in the laparoscopy group: a pelvic hematoma was associated with a drop in hematocrit. The hematoma was observed and no blood transfusion was required. There were no significant complications in the open group. Hospital stay was 4.5 days in the laparoscopy group and 10.8 days in the open group. Mean time to full recovery was 2.5 weeks in the laparoscopic group and 8.7 weeks in the open population. The mean combined intraoperative and postoperative cost for the laparoscopic group was $9,800 versus $5,700 for the open group.

Laparoscopic bladder diverticulectomy is feasible, and the limited data available demonstrate that patients who undergo laparoscopic treatment of a bladder diverticulum have less pain and a more expeditious convalescence. Hospital costs are a major deterrent; however, the financial impact of the markedly shortened convalescence should also be considered.

Malignant Disease: Diagnostic

Pelvic Lymph Node Dissection

The staging of a malignancy is of paramount importance before treatment. No noninvasive imaging modality or technique has proven adequate for determining lymph node status. Accordingly, surgical pelvic lymphadenectomy has been accepted as the most precise method to assess nodal disease in the setting of prostate, penile, urethral, and cervical cancers. Laparoscopic pelvic lymph node dissection (LPLND) was first described by Schuessler and colleagues (375) in 1991. It was this procedure, more than any other, that introduced laparoscopy into mainstream adult urology. Since then, LPLND has been evaluated as a less invasive

alternative to the traditional open pelvic lymph node dissection at many centers.

Prostate cancer is the most common noncutaneous malignancy in men. The status of pelvic lymph nodes has a major impact on treatment and long-term prognosis in men with clinically localized prostate cancer. Clinical parameters including digital rectal examination, serum prostate-specific antigen (PSA) level, and Gleason's score can be used in conjunction with statistical tables to exclude the need for pelvic node sampling in patients with favorable characteristics (158,326). As such, the question arises as to which patients should be candidates for a lymph node dissection. We believe this is based on the potential therapy should the lymph node dissection reveal no metastatic disease. Specifically, when the risk of lymph node involvement is greater than 5% to 10%, staging pelvic lymphadenectomy is indicated if the treatment plan is for either perineal prostatectomy or radiation therapy. In contrast, among patients who are candidates for a radical retropubic prostatectomy, the threshold for performing LPLND is higher. These individuals should have upward of a 40% risk of nodal disease before proceeding with an LPLND because in this case, a positive LPLND will merely spare the patient a lower midline incision rather than avoiding needless extirpative perineal surgical or radiation therapy. Using these guidelines, fewer than 10% of patients with clinically localized prostate cancer are candidates for LPLND.

Transperitoneal LPLND is performed with the patient in the Trendelenburg position and rotated laterally. Peritoneal access and laparoscope insertion are through an incision at the umbilicus. Two additional trocars are placed bilaterally, lateral to the rectus abdominus muscle and approximately 2 cm inferior to the umbilicus. A fourth trocar is inserted in the midline above the symphysis pubis, thereby completing the “diamond” array of trocar placement. An incision is created in the parietal peritoneum just lateral to the medial umbilical ligament. The vas deferens is isolated and divided between clips or is electrocoagulated and cut. (In this regard, it is essential that each patient be told that following this procedure he will be infertile.) The external iliac artery is identified and dissected along its medial aspect; the external iliac vein is then identified and dissected anterior and medial along its length. The pubic ramus is identified medial to the external iliac vein and is dissected toward the midline. Next, the obturator space is carefully dissected, and the obturator nerve is identified and gently teased out of the nodal packet. The obturator vein can be divided if necessary, but the obturator artery should be preserved. The dissection is continued cephalad to the level of the bifurcation of the common iliac artery. All tissue bounded by the medial edge of the external iliac artery laterally, the pubis caudally, the obturator nerve and obturator vessels posteriorly, and the bifurcation of the common iliac artery cranially are removed. In those patients in whom there is a high suspicion for nodal disease, the dissection is “extended” by removing any nodal tissue along the common iliac artery up to the point where the ureter crosses the common iliac vessels; in addition, the nodal tissue in the presciatic (i.e., deep to the obturator nerve), presacral (i.e., medial to the hypogastric artery), and lateral/posterior to the upper portion of the external iliac artery areas may also be included in the dissection.

Another laparoscopic approach to LPLND, albeit less widely used, is extraperitoneal. This is performed by creating a 2-cm incision in the midline just below the umbilicus. After digital dissection, a balloon is used to expand the extraperitoneal space to 700 to 1,000 mL. Next, the balloon is deflated and removed; a Hasson-type trocar is placed into this incision. Three additional trocars are placed, in the same configuration as described for a transperitoneal pelvic lymph node dissection. The dissection proceeds laterally along the external iliac vein. Laparoscopic clips are used to control any lymphatics or venous branches visualized, in particular the inferior epigastric vein. All nodal tissue is taken from within the boundaries previously described.

Results of trials comparing open and laparoscopic LPLND are presented in Table 18.5 . Schuessler and colleagues (373) reported results of 147 consecutive patients with localized carcinoma of the prostate undergoing LPLND. Initially, the laparoscopic procedure was performed in a limited manner; however, the final 86 patients underwent an extended LPLND (hypogastric, external iliac, and obturator lymph node dissection). Mean operative time was 2.5 hours, and mean estimated blood loss was 100 mL. Mean postoperative hospital stay was 2 days. Only 20% of patients required analgesics at the time of discharge from the hospital, and 85% of patients returned to full activity within 2 weeks after surgery. The overall complication rate was 31%. The reoperation rate among all 147 patients was 7% (11 of 147). Of 11 patients, 7 were reexplored laparoscopically. Reexploration was performed in five patients (3%) for hemorrhage, one patient (0.6%) for a bowel laceration, one patient (0.6%) for a ureteral injury, and four patients (3%) for lymphoceles. The mean number of lymph nodes removed was the highest in any series: 45 (range of 13 to 86); the overall positive nodal involvement rate was 23%.

Source	Indications	Technique	Number	Minor Complication	Major Complications	OR Time	Estimated Blood Loss	Analgesia	Length of Stay	Full Recovery	Number of Nodes Taken	Cost
Parra et al. (322)	PreRRP	Lap-transper	12	None	None	3.1 hr	100 mL	NA	NA	NA	10.7	NA
		Open-retroper	12	NA	NA	NA	NA	NA	NA	NA	11	NA
Kerbl et al. (217)	PreCAPTx	Lap-transper	30	13.3%	16.6%	3.3 hr	100 mL	1.6 mg morphine	1.7 days	10.8 days	NA	NA
		Open-retroper	16	None	None	1.7 hr	12.5 mL	47 mg morphine	5.4 days	65.5 days	NA	NA
Troxel and Winfield (419)	PreCAPTx	Lap-transper	11	NA	NA	3.9 hr	NA	NA	1.6 days	7 days	NA	$10,068
		Open-retroper	50	NA	NA	2.7 hr	NA	NA	4.5 days	17 days	NA	$8,723
Perrotti et al. (329)	PreCAPTx	Lap-transper	20	None	25%	3.2 hr	NA	4.5 mg morphine	1.2 days	NA	NA	$4,245
		Open-retroper	7	NA	NA	1.5 hr	NA	NA	7 days	NA	NA	$4,262
		Minilap-retrope	13	None	15%	1.5 hr	NA	3.7 mg morphine	1.3 days	NA	NA	$2,516
Herrell et al. (165)	PreCAPTx	Lap-transper	19	None	None	3.5 hr	NA	NA	1.6 days	NA	8.5	NA
		Open-retroper	38	16%	5%	1.9 hr	NA	NA	5.6 days	NA	9.2	NA
		Minilap-retrope	11	None	None	1.7 hr	NA	NA	2.2 days	NA	8.8	NA
Totals												
Laparoscopic			**92**	**4.90%**	**12.30%**	**3.4 hr**	**100 mL**	**2.8 mg morphine**	**1.5 days**	**9.8 days**	**9.4**	**$6,311**
Open			**123**	**11.30%**	**3.50%**	**2.2 hr**	**215 mL**	**47 mg morphine**	**5.7 days**	**28.8 days**	**9.6**	**$8,175**
Minilaparotomy			**24**	**None**	**8.10%**	**1.6 hr**	**NA**	**3.7 mg morphine**	**1.7 days**	**NA**	**8.8**	**$2,516**

All columns list mean values.
Lap, laparoscopic; NA, not available; retroper, retroperitoneal; RRP, radical retropubic prostatectomy; transper, transperitoneal.

TABLE 18.5. PELVIC LYMPH NODE DISSECTION—COMPARATIVE TRIALS

Stone and co-workers (400) reported results of 130 LPLNDs performed for T_{1a} to T_{2a} carcinoma of the prostate. All LPLNDs were successfully performed laparoscopically. A median of five nodes per side was removed. Operative parameters were not reported. Five (3.8%) patients experienced major complications: two patients required transfusion of 1 unit of blood for injuries to an inferior epigastric vessel and an obturator vessel, respectively, one (0.7%) patient experienced a cerebrovascular accident, one (0.7%) patient experienced a bladder injury, and one (0.7%) patient required rehospitalization for intravenous antibiotics to treat an infected pelvic hematoma.

In a subsequent report, Stone and colleagues (401) compared standard, “limited” LPLND to extended LPLND for

detection of carcinoma of the prostate. Thirty-nine patients underwent an extended LPLND that included obturator, hypogastric, common, and external iliac nodes. These results were compared with patients undergoing LPLND that included only the obturator and hypogastric lymph nodes. A mean of 9.3 nodes was removed during modified LPLND, compared with 18 nodes removed during extended LPLND. Extended dissection was positive in the extended area in only one patient (2.6%). Even when patients were stratified into high-risk groups based on PSA greater than 20 ng/mL, Gleason score 7 or higher, or stage T_{2b} or T_{3a}, patients in the extended LPLND group did not have a significantly higher node positivity rates: 30% and 26.4% (p = .8), 27% and 19% (p = .4), and 25% and 15% (p = .17), respectively. Of note, the extended LPLND was associated with a significant increase in complications: 14 of 25 patients (36%) undergoing the extended dissection had complications, compared with only 3 of 147 patients (2%) in the standard group. Complications in the extended group included 11 (28%) cases of scrotal or penile edema, 4 (10%) cases of lower extremity edema, and 2 (5%) cases each of obturator nerve palsies, pelvic abscesses, and urinary retention (401).

Kerbl and colleagues (217) compared 30 patients undergoing a standard limited LPLND with 16 patients undergoing open pelvic lymph node dissection during the same period. All laparoscopic procedures were successfully completed. Mean operative time was significantly longer for the laparoscopic group: 3.3 hours compared with 1.7 hours for the open group. However, postoperative analgesic requirement was markedly less in patients undergoing LPLND: 1.6 mg of morphine sulfate equivalents versus 47 mg in the open group. Major and minor complications occurred in 13% and 17% of patients in the laparoscopic group, respectively. No complications were reported in the open group. A learning curve was noted in the laparoscopic group, with all major complications occurring in the first 12 patients. Major complications included a bladder perforation, a pelvic hematoma, a pelvic collection requiring drainage, and a delayed bowel fistula. Minor complications included subcutaneous emphysema in one patient, two instances of scrotal swelling, a scrotal hematoma, and one case of urinary retention. Hospital stay was 1.7 days in the laparoscopic group and 5.4 days in the open group. Similarly, return to full activity was expedited with the laparoscopic technique: 11 versus 66 days. Cost evaluation was also performed (217). Unilateral and bilateral LPLNDs cost $7,700 and $10,300, respectively. Open pelvic lymph node dissection was more cost-effective, with unilateral and bilateral procedures costing $6,600 and $8,200, respectively.

In 1994, Troxel and Winfield (419) performed a financial analysis comparing open and laparoscopic pelvic lymph node dissection. The total overall cost from hospital admission to discharge was $1,350 more for the laparoscopic approach. The same authors later performed a financial analysis comparing LPLND and open pelvic lymph node dissection during two separate time periods to evaluate the effect of the learning curve on overall cost (420). Cost analysis was performed comparing 50 men undergoing LPLND between 1990 and 1992 with 55 men undergoing LPLND between 1993 and 1994. Despite a decrease in preoperative and postoperative expenses (112% and 31%, respectively) in the laparoscopic group, the overall cost of the laparoscopic procedure remained unchanged because of increased operating room costs. Indeed, despite operative time decreasing by a mean of 19 minutes, the cost of surgical supplies increased $910 (104%), resulting in an increased overall absolute cost.

Ferzli and co-workers (104) compared 18 patients undergoing transperitoneal LPLND with 18 patients undergoing extraperitoneal LPLND in a nonrandomized, retrospective fashion. All prostate cancer patients received LPLND before brachytherapy or radical perineal prostatectomy. All laparoscopic procedures were successfully completed; one extraperitoneal procedure required open conversion due to dense adhesions from prior surgery. Mean operative time was similar between the two groups: 2.25 hours for transperitoneal laparoscopic LPLND versus 2.5 hours for the extraperitoneal LPLND. The mean number of lymph nodes removed was eight for both groups. Average length of stay was 3.2 days for the transperitoneal group and 2.7 days for the extraperitoneal LPLND group. The authors reported an increased complication rate in the transperitoneal laparoscopic group: 28% versus 0% in the extraperitoneal group. Complications included two patients (11%) requiring transfusions, one (5.5%) omental hernia, one (5.5%) prolonged postoperative ileus, and one (5.5%) infected lymphocele requiring percutaneous drainage. In the extraperitoneal population, there were no postoperative complications. However, one extraperitoneal procedure required conversion to open surgery and another procedure was converted to a transperitoneal laparoscopic approach when the peritoneum was entered during the dissection. Analgesic requirements and return to full activity were not reported (104).

Several groups have compared LPLND with mini-laparotomy incisions. Among these studies, two stand out. Both clearly favor the mini-laparotomy while also corroborating the benefits of LPLND as well as mini-laparotomy over a standard open surgical approach. Perrotti and co-workers (329) reported results comparing a standard open lower midline incision, a 6-cm mini-laparotomy incision, and LPLND. In their series, 7 patients underwent open lymphadenectomy, 13 patients underwent mini-laparotomy, and 20 patients underwent LPLND. Mean operative times for open and mini-laparotomy procedures were both 90 minutes. Mean operative time for LPLND was 190 minutes. Postoperative hospital stay for open, mini-laparotomy, and LPLND were 7, 1.3, and 1.2, respectively. Analgesic requirements were not reported for patients who underwent open pelvic lymph node dissection. However,

patients in the mini-laparotomy and LPLND groups required a mean of 3.7 and 4.5 mg of morphine sulfate equivalents, respectively.

One (5%) patient in the LPLND group required conversion to open surgery for control of hemorrhage. In addition, one (5%) patient in the LPLND group experienced mild left lower extremity discomfort that resolved without intervention, one (5%) patient experienced self-limited abdominal discomfort and bloating 1 week postoperatively, and two (10%) patients experienced scrotal swelling for 4 days postoperatively. In the mini-laparotomy group, no intraoperative complications occurred and only two postoperative complications were seen: one (8%) patient complained of vague abdominal pain, and one (8%) patient experienced a small area of skin separation at the wound site. Complications for the open group were not reported. Operative costs for both mini-laparotomy and open lymphadenectomy were $1,311, compared with $2,100 for LPLND. Total costs for open lymphadenectomy, mini-laparotomy, and LPLND were $4,300, $2,500, and $4,200, respectively (329).

Herrell and colleagues (165) similarly compared three techniques for pelvic lymphadenectomy. In their series, 38 patients underwent open lymphadenectomy, 11 patients underwent mini-laparotomy, and 19 patients underwent LPLND. The mean number of lymph nodes removed for open, mini-laparotomy, and LPLND were 9.2, 8.8, and 8.5, respectively. LPLND required significantly more operative time (3.5 hours) than either open lymphadenectomy (1.9 hours) or mini-laparotomy (1.7 hours). Hospital stay was significantly longer for open lymphadenectomy: 5.6 days compared with 2.2 days for the mini-laparotomy group and 1.6 days for the LPLND group. No complications occurred in either the mini-laparotomy or LPLND groups. In the open lymphadenectomy group, there were several complications (22%): three (8%) cases of ileus, two (5%) patients with urinary retention, and one (3%) case each of a lymphocele, a deep venous thrombosis, and a pelvic abscess.

One major criticism of LPLND has been the concern that this approach may result in seeding of cancer cells in patients with positive lymph nodes. Problems of this sort have been noted in patients with ovarian and other gynecologic cancers, but usually these cases were complicated by malignant ascites or direct violation of the tumor's borders during the dissection. Nonetheless, because of this hypothetical problem, Cadeddu and colleagues (44) evaluated the effect of LPLND on the natural history of carcinoma of the prostate in 52 men with node-positive LPLND. There were three (5.8%) deaths from prostate cancer at 3.0, 3.5, and 4.0 years, respectively, after LPLND; however, at a mean follow-up of 3.1 years, none of the patients developed trocar site tumor implantation. Adjuvant radiation therapy was administered in 12 (23%) men. Of 45 men treated with androgen ablation, 19 (42%) demonstrated biochemical progression during the study period. Among these men with node-positive prostate cancer, the 5-year actuarial biochemical progression-free rate was 45%, similar to the results with open surgery. As such, LPLND appears to neither alter the natural history of stage D_1 carcinoma of the prostate nor lead to trocar site implantation.

LPLND is feasible and is an adequate staging modality for carcinoma of the prostate. When performed by experienced laparoscopic surgeons, LPLND offers patients the comfort, low morbidity, and rapid convalescence characteristic of most laparoscopic procedures. However, it must be stressed that in skilled hands mini-laparotomy provides patients an equally comfortable and expeditious convalescence at less cost. The choice of which less invasive modality to use for pelvic lymph node sampling is dependent on the experience of the individual surgeon; however, it is equally clear that either method remains far superior to a standard open surgical node dissection.

Retroperitoneal Lymph Node Dissection

Patients with nonseminomatous germ cell tumors are at risk for retroperitoneal lymph node involvement. Although noninvasive staging techniques are somewhat accurate, 20% to 25% of patients with clinical stage I disease are understaged when only clinical nonsurgical staging modalities are used. Laparoscopic retroperitoneal lymph node dissection (LRPLND) was originally reported by Hulbert and Fraley in 1992 (179) and has subsequently been performed in patients with stage I disease after orchiectomy and, rarely, in patients with stage IIb disease after chemotherapy.

Gerber and co-workers (119) reported results of 20 laparoscopic retroperitoneal lymph node dissections performed in men with stage I nonseminomatous germ cell tumors. A modified unilateral retroperitoneal lymphadenectomy was performed in all patients. Anatomic boundaries for the dissection included the renal hilum superiorly, ureter laterally, medial aspect of the vena cava or aorta medially (right and left dissection, respectively) (i.e., the interaortocaval lymph nodes), and level of the origin of the inferior mesenteric artery inferiorly; the dissection was extended to the bifurcation of the common iliac vessels on the ipsilateral side, and the stump of the spermatic cord was excised. The retrocaval and retroaortic nodes were not removed.

Of 20 cases, 18 (90%) were successfully completed laparoscopically. In two cases, conversion to an open procedure was necessitated because of bleeding from gonadal vessels. One of these two cases required transfusion. Two additional patients required blood transfusion in the postoperative period [total transfusions = three (15%) patients]. Median operative time was 6 hours, and median estimated blood loss was 250 mL. A median of 14.5 nodes were removed per patient, with 3 of 18 (17%) manifesting disease in the lymph nodes. Most patients required intramuscular or intravenous narcotics for less than 1 day. Hospital stay was 3 days, and patients returned to full activity in 2 weeks.

Complications occurred in 6 of 20 patients (30%), including the 2 patients (10%) requiring conversion to open surgery. Other complications included two additional patients (10%) requiring transfusion in the postoperative period, one patient (5%) with myonecrosis that resolved with observation, and one patient (5%) with lymphocele. Of the 15 patients who successfully underwent retroperitoneal lymph node dissection and had no evidence of disease, none manifested retroperitoneal disease recurrence with a mean follow-up of 10 months. Of 15 patients, 1 (7%) presented with a lung nodule 4 months after retroperitoneal lymphadenectomy. CT scan demonstrated no evidence of retroperitoneal disease, and the patient received chemotherapy. There was no evidence of disease 9 months later. All 20 patients (100%) reported normal antegrade ejaculation.

Rassweiler and colleagues (348) reported results of 26 retroperitoneal lymph node dissections. Seventeen patients were managed for stage I disease, and the remaining nine patients underwent retroperitoneal lymph node dissection for stage II disease after chemotherapy. The procedure was successfully completed in 16 of 17 stage I patients (94%); however, it was successfully completed in only 2 of 9 stage II patients (22%). The stage I conversion resulted from bleeding that could not be controlled laparoscopically. Stage II conversions were all the result of difficult dissection attributed to the desmoplastic reaction associated with the disease process and chemotherapy. Mean operative time for stage I and stage II patients was 4.9 and 5.9 hours, respectively. Estimated blood loss was not reported. There were four (24%) postoperative complications in the stage I group. These consisted of a patient with a retroperitoneal hematoma who subsequently developed ureteral stenosis. This patient required ureterolysis 8 weeks later. Another patient developed a pulmonary embolism that was successfully managed with anticoagulation. In addition, there was a single case of retrograde ejaculation. There was one (11%) postoperative complication in the stage II group, a lymphocele. Patients managed for stage I disease had a mean follow-up of 27 months. No patient manifested a regional relapse, but two patients had pulmonary metastases that were treated successfully with three cycles of chemotherapy. Histopathology in all nine cases of stage II cases revealed necrotic material only, and no patient had evidence of disease with a median follow-up of 29 months.

Janetschek and co-workers (196) have done the most extensive work in the area of LRPLND. They reported results of 105 patients undergoing laparoscopic retroperitoneal lymphadenectomy either for stage I nonseminomatous germ cell tumors after radical orchiectomy or stage IIb nonseminomatous germ cell tumors after chemotherapy. The procedure was successfully accomplished laparoscopically in 103 of 105 (98%) patients. Two (2%) patients required conversion to an open procedure because of bleeding. Mean operative time was 6.3 hours; however, the authors reported a “long and steep learning curve.” Operative time for the first 14 patients was 8 hours; this progressively decreased such that operative time for patients 45 through 64 was reduced to 3.7 hours. Minor postoperative complications were not quantitated but included a small asymptomatic lymphocele, transient lower extremity edema, and transient chylous ascites. Chylous ascites was noted in 21% of patients undergoing retroperitoneal lymph node dissection after chemotherapy. In all patients, the ascites improved with conservative measures, including low-fat diet or medium-chain triglyceride diet. No major complications were reported. Of the 64 patients managed for stage I tumors, 47 (73%) were negative for malignant disease. With a mean follow-up period of 25 months, one patient (1.5%) developed a retroperitoneal recurrence outside the surgical field. Retrospective review of this patient's specimen revealed that a positive lymph node had been missed on the original pathologic evaluation. In contrast, among the patients who received chemotherapy, LRPLND yielded necrotic tissue in 61% of cases and mature teratoma in 37%; active tumor was found in only one patient (2%). With a mean follow-up of 27 months, no recurrences were reported.

In a subsequent report, Janetschek and co-workers (197) expanded their series of retroperitoneal node dissection for stage I nonseminomatous testicular cancer to 73 patients. The operative time continued to decrease; the last 13 patients had a mean operative time of 3.6 hours. Mean estimated blood loss in this group was 156 mL, including one of the two conversions with an estimated blood loss of 2,600 mL. Postoperatively, antegrade ejaculation was normal in all patients. There were no major complications, and a single (1.5%) minor complication was reported. One patient experienced transient irritation of the genitofemoral nerve. Only patients with a minimum follow-up of 6 months were reported; as such, the mean follow-up for this group was 43.3 months. There was only one recurrence, as previously described.

In 1996, Janetschek and co-workers (195) reported comparison between open retroperitoneal lymph node dissection and an earlier portion of their series. This report included the initial 29 patients treated for stage I nonseminomatous testicular tumors. To demonstrate the effects of the learning curve, data for the laparoscopic group were stratified into two groups. Group 1 represented the first 14 cases, and group 2 represented the latest 15 cases. Mean operative times for the open population, group 1, and group 2 were 4.2, 8, and 5.1 hours, respectively. Mean decrease in hemoglobin for the open group, group 1, and group 2 was 2.5, 3.6, and 1.8 g/dL, respectively. Patients managed laparoscopically had a significantly shorter hospital stay. Mean hospital stay for open, group 1, and group 2 patients was 10.6, 5.5, and 4.0 days, respectively. Analgesic requirements and time to full recovery were not reported.

Cost analysis revealed significantly higher operative costs in the laparoscopic group ($3,200 versus $2,500). In contrast,

the cost for hospital stay was less for the laparoscopic group. Overall, in Austria, laparoscopic retroperitoneal lymph node dissection was more cost-effective than open surgery ($4,000 versus $4,150). These calculations did not include cost of patient convalescence, which would have only added to the cost-saving benefits of the laparoscopic approach.

Laparoscopic retroperitoneal lymph node dissection is technically challenging but feasible, especially for staging of stage I nonseminomatous disease; for stage II postchemotherapy patients, a sanguine experience has been reported from only one center (197). The procedure offers these often very young patients the benefits of a minimally invasive approach, while accomplishing the goals of open retroperitoneal lymphadenectomy of effective lymphadenectomy and preservation of the sympathetic nerves responsible for ejaculation.

Malignant Disease: Ablative

Adrenalectomy

Laparoscopic adrenalectomy for malignant disease is highly controversial. Early reports have included removal of solitary adrenal metastases and smaller primary adrenocortical carcinomas. With small differences, the technique for laparoscopic adrenalectomy for malignant disease is essentially the same as previously described for benign adrenal pathology. However, in these cases, the dissection is more en bloc to include all of the periadrenal fatty tissue. On the right side, the borders of the dissection are the renal vein inferiorly, the line of Toldt and upper pole of kidney laterally, and the posterior coronary hepatic ligament superiorly. On the left side, the borders include the kidney laterally, the renal vein inferiorly, and the area of the lienorenal ligament superiorly. Gerota's fascia over the upper border of the adrenal is removed en bloc with the specimen.

Suzuki and co-workers (408) reported results of two patients who underwent laparoscopic adrenalectomy for malignant disease. The first patient underwent a transperitoneal laparoscopic adrenalectomy for what was thought to be a 5-cm cortisol-producing adenoma; however, the final pathology revealed an adrenocortical carcinoma. Despite removal of the tumor as an en bloc specimen, the patient presented with local recurrence and abdominal dissemination 19 months after surgery. The patient died 3 years after the initial procedure. In the second case, a patient with a 5.5-cm adrenal metastasis from poorly differentiated adenocarcinoma of the lung underwent a retroperitoneal laparoscopic adrenalectomy. The procedure required conversion to open surgery because of severe adhesions between the kidney and the adrenal tumor. The patient died of multiple metastases from lung cancer 8 months after surgery.

Elashry and colleagues (93) reported on two patients who underwent laparoscopic adrenalectomy for a solitary metachronous contralateral adrenal metastasis from renal cell carcinoma. The first patient presented 5 years after laparoscopic radical nephrectomy for T_2 disease; a 4-cm adrenal mass was detected during routine postoperative radiologic studies. The patient underwent an uncomplicated laparoscopic adrenalectomy. Operative time was 2.5 hours, with an estimated blood loss of 50 mL. Pathology of the specimen revealed metastatic clear cell renal cell carcinoma. The patient was without evidence of disease at 11-month follow-up. The second patient also presented 5 years after laparoscopic radical nephrectomy for T_2 disease; a 5-cm adrenal mass was detected during routine postoperative radiologic studies. CT-guided biopsy revealed malignant cells, and the patient underwent an uncomplicated adrenalectomy. Operative time was 4.3 hours and estimated blood loss was 75 mL. At 16-month follow-up, the patient remained free of disease. Both patients returned to full activity in 2 weeks.

Bendinelli and colleagues (22) reported results of six patients who underwent laparoscopic adrenalectomy for suspected solitary non–small cell carcinomas of the lung. The tumors ranged from 2.8 to 4.7 cm in diameter. In all cases, laparoscopic adrenalectomy was successfully performed without complication. There were no postoperative complications, and patients were discharged on postoperative day 2 or 3. Histology revealed metastatic disease in four cases and adrenal cortical adenoma in the remaining two patients. With a mean follow-up of 13.5 months, two patients were disease free. The remaining two patients with malignant disease died of other causes (myocardial infarct and trauma).

Because of the rarity of primary or resectable secondary adrenal cancer, to date, there are only a handful of reports of laparoscopic adrenalectomy for malignancy. The procedure is feasible and appears to be as effective as open surgery, but further evaluation is required before the long-term efficacy of laparoscopic adrenalectomy for malignant disease can be determined.

Radical Nephrectomy

Radical nephrectomy is the definitive surgical treatment for localized renal cell carcinoma as described by Robson and colleagues (354) in 1969. The procedure includes en bloc resection of the kidney and enveloping Gerota's fascia, along with the ipsilateral adrenal gland, proximal half of the ureter, and renal hilar lymph nodes. An important part of radical nephrectomy is early ligation of the renal artery followed by ligation of the renal vein. Recently, total nephrectomy rather than radical nephrectomy has been recommended for renal tumors occupying the middle or lower portions of the kidney, thereby sparing the ipsilateral adrenal gland (380,421).

Laparoscopic nephrectomy, as originally described by Clayman and co-workers (60) in 1991, was initially applied

to a tumor-bearing kidney (i.e., oncocytoma) and was a total nephrectomy in that the adrenal gland was spared. Initial application of the laparoscopic technique for radical nephrectomy, by the same urologists, was controversial. However, its role in the management of renal malignancies has evolved over the past decade, and the laparoscopic approach is presently accepted as a management strategy for selected renal masses.

Recommended size limitations for laparoscopic management of renal masses has been quite variable. Most series report results for localized tumors that are 7 cm in greatest diameter. However, recently, Walther and co-workers (433) reported a series of laparoscopic cytoreductive radical nephrectomies for renal masses up to 15 cm in greatest diameter, and in an early series, the Washington University group (262) reported successful removal of a stage T_{3b} lesion involving the renal vein. With experience, all renal tumors, short of those involving the inferior vena cava or larger than 15 cm, are currently considered at major centers for laparoscopic removal.

The surgical technique for laparoscopic radical nephrectomy was originally described via a transperitoneal approach. The transperitoneal procedure is performed with the patient in the lateral decubitus position. Three 12-mm trocars are placed: at the umbilicus, in the midclavicular line under the costal margin, and in the midclavicular line 3 cm inferior to the umbilicus. Two additional 5-mm trocars are placed: in the anterior axillary line off the tip of the twelfth rib and in the anterior axillary line at the level of the umbilicus. At times, on the right side, an additional 5-mm trocar is placed in the midline, just beneath the xiphoid, to aid in retraction of the liver, during the hilar dissection.

Templates for laparoscopic right- and left-sided radical nephrectomy are presented in Fig. 18.19 . Monopolar electrosurgical scissors are used to incise the line of Toldt from the hepatic or splenic flexure caudal to the iliac vessels and cephalad to the diaphragm. On the right side, this incision is continued cephalad to include division of the triangular ligament of the liver, whereas on the left side, the splenic attachments to the diaphragm are divided. Further dissection in the retroperitoneum on the right side takes the shape of a trapezoid: (a) the colon is dissected from the inferior surface of the kidney and the duodenum is dissected medially (i.e., Kocher maneuver) to reveal the surface of the inferior vena cava; (b) the posterior coronary hepatic ligament is incised from the line of Toldt, laterally, to the inferior vena cava, medially; and (c) the inferior vena cava is dissected from above the adrenal gland to the level of the insertion of the gonadal vein, and the gonadal vein is secured with two pairs of clips and divided. At this point, the hilar dissection can be accomplished by clipping and dividing the renal artery followed by stapling of the renal vein. The adrenal vein is then dissected, clipped, and divided. The ureter can then be dissected and divided, and the entire specimen can be moved onto the surface of the liver pending entrapment and morcellation or direct extraction by extension of one of the port sites or manually via a previously placed hand-assist device.

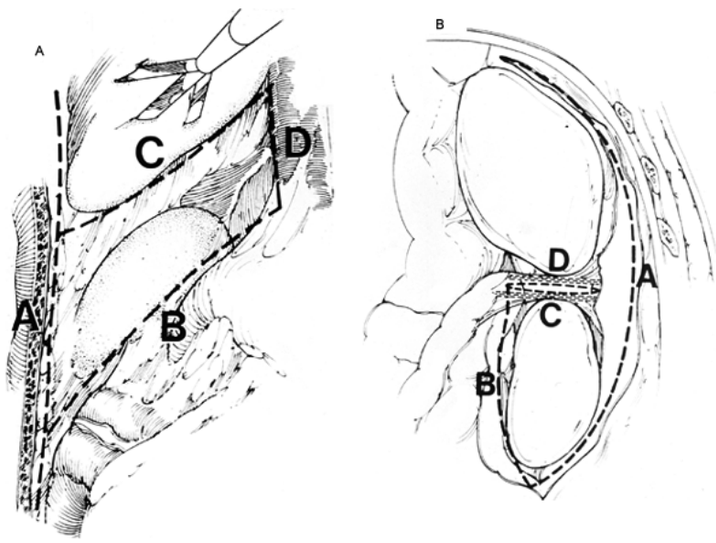

FIGURE 18.19. A: Trapezoid template for right-sided radical nephrectomy. *A,* The line of Toldt is incised from the hepatic flexure caudal to the iliac vessels and cephalad to the diaphragm. The incision is continued cephalad to include division of the triangular ligament of the liver. *B,* Reflection of colon and duodenum. *C,* Incision of posterior coronary hepatic ligament. *D,* Incision overlying the inferior vena cava from above the adrenal vein down to the insertion of the gonadal vein. **B:** Inverted cone template for left-sided radical nephrectomy. *A,* Incision of line of Toldt and medial through any splenophrenic attachments. *B,* Mobilization of the descending colonic mesentery off of Gerota's fascia. *C,* Incision of splenocolic ligament. *D,* Incision of splenorenal ligament.

On the left side, the dissection takes on the shape of an inverted cone: (a) the line of Toldt and splenophrenic attachments are divided; (b) the colon is dissected from the inferior surface of the kidney and Gerota's fascia and moved medially; and (c) the “opening” of the cone (defined as the splenocolic ligament) is divided anteriorly, and the splenorenal ligament, in the same plane, is divided posteriorly. The gonadal vein is then followed to its insertion into the renal vein where it is clipped and divided along with the ascending lumbar vein; the adrenal vein superiorly is likewise dissected, clipped, and divided. In this regard, the gonadal vein is the key to the entire subsequent dissection of the left renal hilum; tracing this vein cephalad reliably and safely leads the surgeon to the left renal vein. The renal artery is then dissected and divided followed by stapling and division of the renal vein. The ureter is then dissected, clipped, and divided. The entire specimen can be moved onto the surface of the spleen pending entrapment and morcellation or direct extraction by extension of one of the port sites or manually, through a previously placed hand-assist device.

Laparoscopic radical nephrectomy may also be performed via a retroperitoneal approach. Access to the retroperitoneum is gained with the Hasson technique through a 2-cm skin incision at the tip of the twelfth rib. After balloon or blunt dissection of the retroperitoneum outside Gerota's fascia, a second trocar (12 mm) is placed at the angle of the twelfth rib and the erector spinae muscle. Next, a third trocar (5 mm) is placed subcostally in the anterior axillary line and a fourth trocar (12 mm) is placed in the midaxillary line just cephalad to the iliac crest. Dissection is initiated around the renal hilum, with sequential control of the renal artery and vein with clip ligation and Endo-GIA stapling, respectively. Circumferential mobilization of the kidney within Gerota's fascia is performed. The adrenal gland may be spared depending on the size and location of the renal mass. The ureter is transected between clips. Next, off of one of the lower port sites, the incision may be extended horizontally to 8 to 10 cm, and the entire specimen retrieved intact; alternatively, an entrapment sack can be placed and the specimen can be secured in the sack. The latter approach often requires opening of the peritoneal cavity to provide sufficient space to maneuver the sack and the specimen. The specimen is then morcellated or removed intact depending on surgeon preference.

In an effort to simplify the technical aspects of laparoscopic surgery, hand-assisted techniques have been developed. This technique requires making a 7- to 8-cm transperitoneal incision over which one of a variety of wound-occlusive devices is affixed; the surgeon's hand and

forearm are inserted through the secured “airtight” device into the peritoneal cavity while maintaining a pneumoperitoneum. Wolf and co-workers (449) detailed their technique for hand-assisted laparoscopic nephrectomy. Peritoneal access is gained via a 12-mm incision at the lateral border of the rectus muscle inferior to the umbilicus. A second 12-mm trocar is placed in the midclavicular line 2 cm beneath the costal margin. An upper midline incision is made above the umbilicus with its length in centimeters equaling the surgeon's glove size. One of the commercially available occlusion devices is then applied to the incision, allowing the surgeon's hand to be inserted into the peritoneal cavity. For a right-sided nephrectomy, the surgeon's left arm is placed through the hand-assist incision; for a left-sided nephrectomy, the surgeon's right arm is placed in the incision. The laparoscopic instruments are placed in the subcostal trocar site. Alternatively, the hand-assist device may be placed periumbilically; a 12-mm port is then placed in the midline, midway between the xiphoid and umbilicus, and a second 12-mm port is placed in the midclavicular line, subcostal. The laparoscopic instruments are again passed via the subcostal port.

With the hand-assist approach, radical nephrectomy proceeds as previously described. Tissues are picked up with the surgeon's hand and managed using routine laparoscopic techniques. The renal hilum may be identified by palpation, and retroperitoneal dissection of the kidney is greatly facilitated by blunt finger dissection. For suture ties, a “one-handed” knot can be created by using the intraperitoneal hand and grasping the free end of the suture with a laparoscopic instrument. At the termination of the case, the specimen is extracted via the hand-assist incision.

Results of trials comparing open and laparoscopic radical nephrectomy are presented in Table 18.6 . To date, three large series have appeared in the literature, among which two directly compared laparoscopic and open radical or total nephrectomy techniques. In the largest published series, Barrett and co-workers (18) reported results from 72 attempted laparoscopic nephrectomies. Tumor size ranged from 1 to 9 cm (mean of 4.5 cm). The transabdominal approach and specimen morcellation were used in all patients. Eight patients underwent concomitant procedures, including six cholecystectomies, a tubal ligation, and a bowel resection.

Source	Indications	Technique	Number	Minor Complications	Major Complications	Extraction	OR Time	EBL (mL)	Analgesia	Length of Stay	Full Recovery	Follow-up	Recurrence	Cost
Dunn et al. (88)	<10-cm masses	Lap-both	61	34.40%	3.30%	65% morcellated	5.5 hr	172	28 mg morphine	3.4 days	3.6 wk	25 mo	8%	$15,816
		Open-NA	33	45%	9%	Intact	2.8 hr	451	78.3 mg morphine	5.2 days	8.1 wk	27.5 mo	9%	$13,672
Ono et al. (313)	<5-cm masses	Lap-both	60	8.30%	5%	57% morcellated	5.2 hr	255	30 mg pentazocine	NA	3.3 wk	24 mo	3.40%	NA
		Open-NA	40	2.50%	5%	Intact	3.3 hr	512	68 mg pentazocine	NA	8.1 wk	28.5 mo	2.50%	NA
Abbou et al. (1)	<9-cm masses	Lap-retroper	29	0%	6.90%	Intact	2.4 hr	100	1.8 mg morphine	4.8 days	NA	15 mo	3.40%	NA
		Open-NA	29	10%	17.20%	Intact	2.0 hr	285	2.3 mg morphine	9.7 days	NA	13 mo	3.40%	NA
Walther et al. (433)	Cytoreductive	Lap-transper	11	9%	9%	55% morcellated	7.5 hr	1409	283 mg morphine	7.3 days	NA	NA	NA	NA
		Open-NA	19	0%	18%	Intact	4.2 hr	1000	442 mg morphine	8.2 days	NA	NA	NA	NA
Totals														
Laparoscopic			**161**	**16.70%**	**5.00%**		**5 hr**	**274.5 mL**		**4.2 days**	**3.5 wk**	**22.4 mo**	**6.10%**	
Open			**121**	**15.50%**	**11.10%**		**3 hr**	**517.6 mL**		**7.5 days**	**8.1 wk**	**23.8 mo**	**4.90%**	

All columns list mean values.
Both, transperitoneal and retroperitoneal approaches combined; EBL, estimated blood loss; lap, laparoscopic; NA, not available; retroper, retroperitoneal; transper, transperitoneal.

TABLE 18.6. LAPAROSCOPIC RADICAL NEPHRECTOMY—COMPARATIVE TRIALS

Of the 72 patients, 6 (8%) required conversion to open radical nephrectomy. The six conversions were the result of unrecognized tumor-associated venous thrombus, large parasitic veins servicing a large renal tumor, adhesions to the spleen, scarring of the renal hilum from prior infection, hilar bleeding, and a case of sudden hypoxia and suspected gas embolus. Sixty-six patients underwent successful laparoscopic nephrectomy with morcellation. Mean operative time was 2.9 hours, including the eight concomitant nonrenal laparoscopic procedures. There was a single (1.4%) intraoperative mortality. In this case, the patient suddenly became hypoxemic during the morcellation of the entrapped specimen; immediate open exploration failed to reveal a source of hemorrhage or other life-threatening surgical problem. Resuscitation attempts failed. At autopsy, extensive miliary lung disease was identified; the precise cause of death could not be determined. A gas embolus was suspected, but never proven.

Two patients (3%) required blood transfusion. Three patients (4%) experienced bowel complications, including one trocar site hernia. The hernia occurred at the extraction site in a patient who had undergone concomitant bowel resection. There was a single case each of a wound infection and transient unstable angina. Hospital stay for the 66 patients undergoing successful laparoscopic radical nephrectomy was 4.4 days. Fifty-seven patients had the diagnosis of a renal malignancy. With a mean follow-up of 21 months, there were no port site recurrences, no intraabdominal or retroperitoneal recurrences, and no evidence of metastatic disease. Analgesic requirements and time to full convalescence were not reported (18). Longer follow-up by this group has revealed one patient who developed a port site recurrence along with distant metastatic disease; of note, the port site recurrence was not at the site through which the tumor was morcellated. This occurred in a patient with a T_2 lesion with sarcomatous elements. This is the first and, to date, only report of seeding following radical nephrectomy (17a).

Dunn and colleagues (88) described the Washington University experience with radical nephrectomy. Clinical data on 60 consecutive patients undergoing laparoscopic radical nephrectomy for renal tumors 10 cm in diameter or smaller were compared with 33 open radical nephrectomies performed for tumors 10 cm in diameter or smaller. The majority of the specimens were morcellated. Two patients (3%) in the laparoscopic group required conversion to open surgery: one received 2 units of packed red blood cells because of intraoperative bleeding, which at the time of open conversion was found to be due to back-bleeding from the 1,100-g specimen, and the other patient had an injury to the superior mesenteric artery requiring repair. The overall transfusion rate was 12%. In the open group, the overall transfusion rate was 15%. Mean estimated blood loss was significantly less for laparoscopic nephrectomy: 172 versus 451 mL. Operative time was significantly longer for patients managed with the laparoscopic technique: 5.5 versus 2.8 hours. There were fewer major and minor complications in the laparoscopic group than in the open group: 3% versus 9% and 34% versus 45%, respectively.

Major differences in recovery were noted. Patients managed laparoscopically required significantly less analgesics for adequate pain control: 28 versus 78 mg of morphine sulfate equivalents. Resumption of oral intake was significantly faster in the laparoscopic group: 18 versus 59 hours. Hospital stay was also significantly reduced with the laparoscopic technique: 3.4 versus 5.2 days. Full recovery was expedited by the laparoscopic approach: 8 versus 29 weeks. The average follow-up in the laparoscopic group was 25 months (range of 3 to 73 months) among 44 patients with documented localized renal cell cancer; 91% were disease free. Among the three patients who failed therapy, two patients developed metastatic disease in the liver, lung, bone, or a paracaval node. Both patients subsequently died: one 52 months postoperatively, presumably due to metastatic disease, and the other 2 years later from aspiration pneumonia. A local recurrence occurred in the third patient; this patient developed recurrent disease in the ipsilateral ureteral stump, which was subsequently excised at open surgery. In the open group, the average follow-up was 28 months; 90% remained disease free, similar to the laparoscopic group.

A cost evaluation was also performed. Mean total operating room cost for laparoscopic radical nephrectomy was $6,300. Operating room cost for open radical nephrectomy was $4,400. The large discrepancy in operating room expenditures was not offset by the decreased hospital stay, such that overall cost for the laparoscopic procedure was $15,800; the open procedure required $13,700.

Ono and co-workers (314) reported results of 60 laparoscopic radical nephrectomies

performed for renal masses less than 5 cm in diameter; the majority of specimens were morcellated. These results were compared with a contemporary series of 40 open radical nephrectomies. Forty-five patients (75%) underwent transperitoneal radical nephrectomy, and the remaining fifteen patients (25%) were managed via the retroperitoneal approach. Only one patient (2%) required conversion to an open procedure; this was prompted by uncontrollable bleeding from a left renal artery. Mean operative time for laparoscopic radical nephrectomies was significantly longer than open surgery: 5.2 versus 3.3 hours. Mean estimated blood loss, however, was significantly decreased in the laparoscopic population: 255 versus 513 mL. Patients undergoing laparoscopic radical nephrectomy required significantly less pain medication: 31 versus 68 mg of pentazocine. Hospital stay was not reported; however, mean time to full convalescence was significantly shorter in patients undergoing laparoscopic management: 3 versus 8 weeks (314). There was no significant difference in the complication rate between open and laparoscopic radical nephrectomy. Two patients (3%) in the laparoscopic group required intraoperative blood transfusions. There were five intraoperative complications, including the injury to the left renal artery. Other complications included a splenic injury, an adrenal injury, and bleeding from a periureteral artery. In addition, a duodenal injury was recognized on postoperative day 1; the patient was successfully managed by open duodenojejunostomy. In the postoperative period, there were two cases of paralytic ileus that resolved with conservative management and a pulmonary thrombosis that was managed by anticoagulation. There were only two intraoperative complications in the open population: an injury to the renal vein and a splenic injury. Postoperative complications in this population included a single case of paralytic ileus that resolved with conservative management. Three patients (8%) required blood transfusions.

All 60 patients in the laparoscopic group were alive with a median follow-up of 24 months. Of the 60 patients, 58 had no evidence of recurrence, metastatic disease, or trocar site seeding. The calculated 5-year survival was 95%. One patient had lung metastases discovered 3 months postoperatively by chest CT scan. The other patient had a right iliac bone metastasis, which was discovered 19 months postoperatively by CT scan and bone scintigraphy. Both patients were treated with α-interferon and were alive at the time of publication. Of the 40 patients managed by open radical nephrectomy, 39 (97.5%) were alive without evidence of metastasis or recurrence. There was no statistically significant difference in the calculated disease-free rates between the two techniques. One patient had both lung and bone metastases discovered 5 months postoperatively; α-interferon therapy was administered. The patient died of progressive disease after 11 months (314).

With regard to the retroperitoneal approach, Abbou and co-workers (1) reviewed 29 patients who underwent retroperitoneal laparoscopic radical nephrectomy and 29 patients who underwent open radical nephrectomy. A single laparoscopic procedure (3%) required conversion after a vascular staple was dislodged from the renal artery during specimen extraction. Mean operative time for the laparoscopic group was 2.5 hours, significantly longer than the 2 hours required for open radical nephrectomy. Mean hospital stay for patients managed laparoscopically was 4.8 days, significantly less than the 9.7-day hospital stay reported in patients undergoing open radical nephrectomy. There were two intraoperative complications in the laparoscopic group. The patient requiring conversion to open surgery was managed with transfusion of 2 units of packed red blood cells intraoperatively. Another patient experienced a colonic injury that was managed with a temporary colostomy. In the open population, eight complications (24%) in seven patients were reported: two cases of pneumonia, two cerebrovascular accidents, a case of phlebitis, a pulmonary embolus, a colonic injury, and an eventration. With a mean follow-up of 15 months, there was a single case of local recurrence and hepatic metastasis in the patient requiring conversion from laparoscopic to open technique. This patient had a 9-cm tumor with final pathology revealing a pT3b grade 2 renal cell carcinoma confined within the surgical specimen. The recurrence was noted 9 months postoperatively (1).

Ono and colleagues (314) compared transperitoneal and retroperitoneal laparoscopic techniques. Thirty-four transperitoneal laparoscopic nephrectomies with morcellation of the specimen were compared with 15 retroperitoneal laparoscopic radical nephrectomies. All but one transperitoneal (97%) and all (100%) retroperitoneal procedures were completed successfully using laparoscopic techniques. Mean operative times for the retroperitoneal and transperitoneal approaches were similar (4.9 and 5.1 hours, respectively). Estimated blood loss was also similar for the retroperitoneal and transperitoneal approaches (276 and 176 mL, respectively). Both procedures required the same amount of postoperative analgesia (29 mg of pentazocine), and the complication rate was similar.

With regard to the hand-assist approach, Wolf and colleagues (450) compared standard laparoscopic nephrectomy (8 cases) with laparoscopic nephrectomy performed with the hand-assist device (13 cases). The series consisted of 15 simple nephrectomies, 4 radical nephrectomies, and 2 nephroureterectomies. Mean operative times for hand-assist and standard laparoscopic nephrectomies were 4 and 5.4 hours, respectively ($p = .04$). Estimated blood loss for hand-assist and standard laparoscopic nephrectomies was 211 and 340 mL, respectively. There was no significant difference in hospital stay with hand-assist and standard laparoscopic nephrectomy patients: 3.1 and 3.0 days, respectively. Hand-assist patients required 57 mg of morphine sulfate in the postoperative period compared with 48 mg for the standard laparoscopic population ($p > .5$). The hand-assist patients returned to normal activity in 14 days, compared with 10 days for standard laparoscopic nephrectomy ($p > .1$). There was a single (8%) major complication in the hand-assist group, and there were three (38%) major complications in the standard laparoscopy group.

The most important aspect of laparoscopic total or radical nephrectomy for renal cell cancer has to do with the long-term efficacy of the procedure. In this regard, Cadeddu and colleagues (42) reported results of a multicenter study

encompassing 157 patients undergoing laparoscopic radical nephrectomy for pathologically proven renal cell carcinoma. Six patients (3.8%) required conversion to an open approach as a result of difficult dissection or hemorrhage. There were 16 (9.6%) perioperative complications in 15 patients and one intraoperative death. Mean follow-up was 19.2 months. There were no trocar site recurrences, and 151 patients (96%) had no evidence of disease recurrence at last follow-up. Four patients had progressive disease but were alive at the time of publication. All four patients had stage T_2 disease at the time of surgery. Three of four recurrences were at distant sites. One patient had a local recurrence in the ureteral stump 8 months postoperatively, as described in the Dunn series.

Another possible indication for laparoscopic nephrectomy has recently been examined by Walther and co-workers (433): cytoreductive surgery in patients with metastatic renal cell carcinoma before initiation of interleukin (IL)-2 immunotherapy. Patients with tumor thrombus, massive retroperitoneal lymphadenopathy, or liver invasion were excluded. Laparoscopically managed patients were stratified into two groups depending on whether the specimen was morcellated or removed intact. Results were compared with a contemporary group of open radical nephrectomies in similar patients. Open procedures were performed through a chevron incision extending from the midaxillary line of the ipsilateral side to the anterior axillary line of the contralateral side. After surgery, patients were randomized to treatment with either high- or low-dose IL-2.

Of the 11 patients, 3 (27%) in the laparoscopic groups were electively converted to open surgery because of tedious dissection. Transfusion requirements tended to be higher in the laparoscopic intact extraction group: 3.1 units (open group), 2.3 units (laparoscopic morcellated), and 5.2 units (laparoscopic intact extraction); of note, the estimated blood loss was greater in the laparoscopic intact extraction group (3,600 mL versus 1,300 to 1,600 mL in the other two groups). Patients in both laparoscopic groups had significantly longer operative times than patients undergoing open radical nephrectomy: 8.5 hours (laparoscopic morcellated) and 6.4 hours (laparoscopic intact) versus 4.2 hours for open removal. Postoperative complications occurred in four patients. In the laparoscopic group, a port site hernia and pressure necrosis of the skin occurred. In the open population, there was a pulmonary embolus and a small bowel obstruction. There was no significant difference in complications among the three groups.

Patients undergoing laparoscopic management of their tumors with morcellation were discharged from the hospital sooner (6.3 days) than patients undergoing open nephrectomy (8.2 days). Of note, patients with laparoscopic intact removal had a hospital stay similar to the open nephrectomy group: 9.2 days. Patients undergoing laparoscopic management with tumor morcellation had significantly less narcotic requirements (243 mg of morphine sulfate equivalents) than the laparoscopic intact removal group (332 mg of morphine sulfate equivalents) or the open surgery group (442 mg of morphine sulfate equivalents). Most important, the laparoscopic approach reduced time to treatment by almost 1 month; mean time to treatment with IL-2 for the open nephrectomy, laparoscopic intact, and laparoscopic morcellated groups was 11, 8, and 6 weeks, respectively. Time to full convalescence was not reported.

Overall, results comparing open and laparoscopic radical nephrectomy, by either a transperitoneal or retroperitoneal approach, are remarkably consistent. Patients treated laparoscopically undergo a procedure that respects the oncologic principles required for optimal management, while experiencing the benefits of a minimally invasive procedure. Specifically, patients managed by laparoscopic radical nephrectomy have significantly less pain, shorter hospital stays, and more rapid return to full activity when compared with patients undergoing an open procedure. These benefits are not associated with an increase in either intraoperative or postoperative morbidity. Tumor-free survival appears to be similar, in the short run (i.e., 2 years), between patients managed by open and laparoscopic approaches; 5- and 10-year data are needed. The expeditious convalescence associated with laparoscopic radical nephrectomy may be of value in patients with higher-stage malignancies. In this select group of patients, after a laparoscopic nephrectomy, adjuvant treatment can be initiated earlier.

Radical Nephroureterectomy

Laparoscopic radical nephroureterectomy for the treatment of upper tract transitional cell cancer was introduced by Clayman and colleagues in 1991 (62,261). Laparoscopic radical nephroureterectomy has been performed via both transabdominal and retroperitoneal techniques. Several techniques have been described for the management of the distal ureteral segment: transurethral resection (“pluck”), unroofing and stapled ureteral resection, intussusception, and needlescopic transvesical dissection. The usual recommendation for this procedure has been to proceed with any transurethral manipulation of the ureteral orifice and tunnel initially and then continue with the laparoscopic portion of the nephroureterectomy. However, because of concerns about possible local seeding of tumor cells, Clayman and colleagues (381) have recommended proceeding with the laparoscopic part of the procedure first, reserving any unroofing of the ureteral orifice and tunnel to the end of the procedure, thereby precluding any spillage of tumor cell–laden urine into the retroperitoneum.

Transurethral ureteral resection (“pluck” ureterectomy) is performed cystoscopically with the patient in a dorsal lithotomy position. The ureteral orifice, tunnel, and ureterovesical junction (UVJ) are transurethrally resected out to the perivesical fat. The ureter is thereby released from the bladder. Hemostasis is obtained and a urethral catheter is

placed. If done early in the procedure, as soon as the laparoscopic portion of the procedure is initiated, the ureter should be isolated and clipped to prevent further leakage of urine into the retroperitoneum. After laparoscopic dissection of the kidney, the surgeon can “pluck” the ureter cephalad, thereby precluding any pelvic dissection of the ureter. The major drawback of this approach is concern about leakage of malignant cell–laden urine into the retroperitoneum until the ureter is laparoscopically occluded. Instances of seeding after an open “pluck” procedure have been reported by several urologists (12,167,201).

Ureteral unroofing and stapling is performed with the patient in the dorsal lithotomy position. A guidewire is placed in the ureter, and a 7-Fr ureteral dilating balloon (5-mm diameter, 10-cm length) is inserted over the guidewire. An Orandi electrosurgical knife is used to unroof the intramural ureter at the 12 o'clock position. The dilating balloon is then removed, and a 7-Fr 11.5-mm occlusion balloon catheter is inserted, inflated in the renal pelvis, and snugged down at the ureteropelvic junction. A roller electrode is used to fulgurate the cut edges and interior of the opened ureteral tunnel. Later in the procedure, after the kidney has been completely dissected laparoscopically, the ureter is dissected caudally until the detrusor muscle fibers at the UVJ are identified. The retrograde 7-Fr occlusion balloon is deflated and removed. An Endo-GIA stapler is applied to the cuff of bladder at the UVJ, thereby simultaneously incising and securing the bladder cuff and the UVJ specimen. For this portion of the procedure, an angulating Endo-GIA stapler is most helpful because it allows a more direct approach to the UVJ, thereby securing an ample cuff of bladder. If there is concern about the contralateral ureteral orifice or tunnel, this portion of the procedure can be monitored intravesically by having the assistant pass a flexible cystoscope while the bladder cuff is being secured.

Application of a needlescopic technique for management of the distal ureter was described by Gill and colleagues in 1999 (128). The patient first undergoes cystoscopy to rule out a concomitant bladder tumor and to ensure adequate bladder capacity. Diminished bladder capacity (less than 200 mL) increases the technical difficulty due to limited working space. Cystoscopy is performed with the patient in a 30-degree Trendelenburg position. Two needlescopic trocars (2 mm) are inserted suprapubically into the bladder under cystoscopic vision. A 2-mm Endoloop is inserted through the needlescopic trocar. A 6-Fr ureteral catheter is passed through the loop and into the affected ureter with the assistance of a guidewire. A 24-Fr continuous-flow resectoscope is then passed into the bladder alongside the ureteral catheter. A Collings' knife is used to electrosurgically score the urothelium circumferentially around the intramural ureter such that a 2- to 3-cm cuff is outlined. With use of a 2-mm grasper, the ureteral orifice and hemitrigone are retracted anteriorly and a full-thickness incision is made with the Collings' knife. In this manner, approximately 3 to 4 cm of ureter may be dissected free from surrounding tissues. The previously placed Endoloop is then positioned over the ureter and closed tightly, occluding the lumen as the ureteral catheter is withdrawn. The tail of the Endoloop is then cut with 2-mm laparoscopic scissors. The bladder edges about the excised ureter are then coagulated. All instruments are removed from the bladder and a Foley catheter is left indwelling. The laparoscopic nephrectomy is then performed, and the ureter is pulled up with the specimen via a 7- to 10-cm incision (128).

The intussusception technique is only used when the patient has transitional cell cancer of the renal pelvis; it cannot be used in patients with ureteral transitional cell cancer. In this approach, the ureterectomy is done after the laparoscopic nephrectomy portion of the procedure. A stone basket is passed retrograde up to the middle ureter. The ureter is occluded just proximal to the stone basket and incised, thereby allowing the stone basket to exit the ureterotomy site. The ureter is then incised vertically for a distance of 1 to 2 cm, to create two or three flaps; the stone basket is opened and the flaps of ureter are passed through the wires of the basket. The basket is then closed and pulled caudal while the surgeon holds the sidewalls of the middle ureter stationary; this results in the ureter intussuscepting. The surgeon then releases the sidewalls as they too become intussuscepted; the ureter is thus pulled through the ureterovesical junction and into or out the urethra, in males and females, respectively. The surgeon can then either continue to pull the ureter out, thereby avulsing it at the level of the trigone, or introduce a resectoscope to release the ureter at the ureteral tunnel (76).

Laparoscopic nephroureterectomy has been performed using either a transperitoneal or retroperitoneal technique; the former is more commonly described. The trocar placement is identical to that for a radical nephrectomy, except that for the transperitoneal approach an additional 12-mm trocar is placed in the midline 2 to 3 cm above the symphysis pubis for passage of the Endo-GIA stapler to secure the bladder cuff. For a hand-assist approach, placement of the hand-assist device is in the lower midline so the surgeon's hand can be used to facilitate both the nephrectomy and ureterectomy portions of the procedure.

The nephrectomy portion, whether performed by a transperitoneal or a retroperitoneal route, is identical to that for a total nephrectomy. For the ureterectomy portion, if a pluck or needlescopic dissection was used, the ureter is simply pulled cephalad out of the pelvis; alternatively, if a ureteral unroofing approach is selected, the ureter is mobilized caudally into the pelvis, as described, and secured with the Endo-GIA stapler. The specimen is entrapped in an entrapment sack and removed intact.

Recently, Shalhav and colleagues (381) reported on 25 patients at Washington University who underwent transperitoneal laparoscopic nephroureterectomy; these patients were retrospectively evaluated, and the results were compared

with those of 17 patients who underwent open nephroureterectomy during a similar time period. Operative time was significantly longer for patients treated laparoscopically: 7.7 versus 3.9 hours. However, estimated blood loss was significantly less in the laparoscopic group: 199 versus 441 mL. All measures of patient comfort and convalescence favored the laparoscopic group. These patients resumed oral intake in a mean time of 1 day, compared with 4.8 days for the open group. The laparoscopic group averaged 37 mg of morphine sulfate equivalents versus 144 mg of morphine sulfate equivalents for pain relief in the open group. Hospital stay was also significantly shorter for patients undergoing laparoscopic nephroureterectomy: 3.6 versus 9.6 days. Resumption of full activity was facilitated by the laparoscopic approach: 2.8 versus 10 weeks. Major and minor complications occurred in 8% (postoperative bleeding, adult respiratory distress syndrome) and 40% of the laparoscopic group, respectively, and in 29% (e.g., pneumonia, myocardial infarction, acute renal failure) and 29% of the open group, respectively. There was one death in the laparoscopic group and none in the open group. At a mean follow-up of 2 years and 3.6 years for the laparoscopic and open groups, respectively, the bladder recurrence rate of transitional cell cancer was 23% and 54%, respectively. Of note, at 2 years in the open group, the bladder recurrence rate was similar to that in the laparoscopic group. Cancer-specific survival in the two groups was 77%, albeit with longer follow-up in the open cohort.

Of concern in the laparoscopic group was the identification of two retroperitoneal recurrences in the pelvis; this occurred despite neither patient having had any identifiable gross extravasation of urine at the time of the procedure. Because of these two cases, the authors have changed their protocol such that the integrity of the bladder and the ipsilateral ureter and kidney are absolutely maintained throughout the procedure. Accordingly, transurethral unroofing of the ureter is now done at the end of the procedure, following dissection, entrapment, and removal of the entire specimen (i.e., kidney, ureter down to the ureterovesical junction, and periureteral cuff of bladder). At that time, using the resectoscope equipped with an Orandi knife, the ipsilateral ureteral orifice and tunnel are unroofed until the staple line is visualized; then the roller electrode is used to electrocoagulate the interior of the opened ureteral tunnel from the level of the incised orifice out to the staple line.

Recently, there has been increasing experience with the hand-assist approach to laparoscopic nephroureterectomy. The largest series to date is from Stifelman and associates (399), who presented 22 cases of hand-assisted laparoscopic nephroureterectomy for upper tract transitional cell cancer. The average operative time was 4.5 hours, with an estimated blood loss of 180 mL. Of note, there were no intraoperative complications. Mean narcotic requirements were 55 mg of morphine sulfate equivalents; the average hospital stay was 4.1 days with a convalescence of 2.7 weeks. At 13-month follow-up, bladder recurrences were noted in 18% and metastatic disease had developed in 9%. Compared with a pure laparoscopic nephroureterectomy, this approach markedly decreases the operative time with only a slight increase in the amount of pain medications required and a minimal increase in hospital stay. Data on the cost-effectiveness of the hand-assisted nephroureterectomy have yet to be compiled.

Laparoscopic radical nephroureterectomy is a viable option for the management of upper tract transitional cell carcinoma. The procedure respects the oncologic principles of the open procedure and does not appear to increase morbidity. Of note, the characteristic advantages of laparoscopy, including decreased pain and expedited convalescence, are particularly evident. The hand-assist approach appears to greatly facilitate laparoscopic nephroureterectomy while providing nearly similar benefits. However, concerns over retroperitoneal recurrence have discouraged the more widespread use of this approach. More long-term data are needed to realistically address these misgivings. Likewise, data are needed with regard to the best way of managing the distal ureter to minimize the risk of an extravesical recurrence. To this end, meticulous follow-up with pelvic CT scans is essential among these patients.

Malignant Disease: Ablative On the Horizon

Partial Nephrectomy and Renal Wedge Excision for Renal Tumors

Recently, several papers have revealed the excellent survival achievable with partial nephrectomy or, to a lesser extent, wedge excision among patients with small renal tumors (4 cm or smaller). The technical success rates and long-term patient survival with nephron-sparing surgery have been shown to equal results with radical or total nephrectomy for the management of stage I renal malignancies (103,148,259,309,442). Laparoscopically, renal wedge excision is technically much easier to accomplish than a formal partial nephrectomy. As such, it is not surprising that the initial experience with laparoscopic wedge excision was reported in 1993, but the initial successful laparoscopic partial nephrectomy for renal cancer was not reported until 1997 (97,263).

In general, only lesions of 2 cm or smaller that are predominantly exophytic are candidates for laparoscopic wedge excision. The basic method is to use a transperitoneal approach for anterior lesions and a retroperitoneal approach for posterior lesions. After renal mobilization, the lesion is identified either endoscopically or with an intracorporeal ultrasonographic probe. For the latter purpose, a flexible ultrasonic probe is most useful. Dissection around the lesion proceeds down to the renal capsule, being careful to keep the perinephric fat over the lesion undisturbed. If the fat overlying

the tumor is displaced, it should be sent as a separate specimen for staging purposes.

After the lesion is well delineated, excision of the lesion with a margin of normal tissue is performed. Ultrasonic hook, ultrasonic shears, monopolar scissors, bipolar instruments, and other modalities have all been used for the wedge excision. To date, no transection modality has provided consistently reliable hemostasis. In this regard, a 5-mm argon beam coagulator is extremely useful to control small and medium-sized vessels and to stop parenchymal bleeding. Other hemostatic techniques include application of fibrin glue, gelatin formaldehyde resorcinol glue, bovine collagen, Surgicel (oxidized regenerated cellulose, Johnson and Johnson, Somerville, New Jersey), and Gelfoam (absorbable gelatin sponge, Pharmacia and Upjohn Co., Kalamazoo, Michigan). If the collecting system has not been violated, no drain is left.

Several techniques for laparoscopic partial nephrectomy have been described; however, these have largely been limited to single or several case reports. In general, these lesions are in the 2- to 4-cm size range. The approach is similar to the wedge excision with regard to locating the affected area of the kidney. No indwelling stent is placed. To try to prevent hemorrhage, a variety of devices have been employed: cable tie, double loop sling, and Endoloop suture occlusion (380a). More recently, hand-assist techniques have enabled the surgeon to use hand compression, thereby facilitating the transection of the affected area. The incision through the parenchyma is accomplished with any of the aforementioned modalities used for the wedge excision. Clayman and colleagues (97) have attempted to do this with an electrosurgical snare; however, their sanguine animal experience did not transfer into the clinical realm. Once the affected area is excised, the underlying incised parenchyma and collecting system can be most easily closed using a combination of fibrin glue and a hemostatic fabric. Alternatively, the collecting system can be sutured closed and parenchymal hemostasis can be obtained using a combination of the argon beam coagulator and the application of bovine collagen. By giving the patient an intravenous dose of furosemide (Lasix) and indigo carmine, the surgeon can make a final check to rule out any urine leak. A drain is left in the retroperitoneum.

McDougall and colleagues (266) reported results of nine partial nephrectomies and three wedge resections. The partial nephrectomies were for benign disease and have been previously reviewed. All three wedge resections were for small renal masses and were successfully completed laparoscopically. Mean operative time for these three cases was 3.5 hours. Mean estimated blood loss was 92 mL. Patients had a mean hospital stay of 2.7 days and required an average of 21 mg of morphine sulfate for pain control. Mean time for complete convalescence was 4 weeks, and there were no intraoperative or postoperative complications. Pathology revealed a renal cell carcinoma, an oncocytoma, and an old infarction. At 46 months, there was no recurrence of tumor in the one kidney with renal cell cancer (266).

Janetschek and co-workers (194) reported results of seven patients undergoing laparoscopic wedge resection for renal tumors up to 2 cm in diameter. Final pathology revealed five lesions to be renal cell carcinoma; the remaining two were multilocular cysts. All procedures were successfully completed laparoscopically. Mean operative time was 3.7 hours, and mean estimated blood loss was 311 mL. There was a single intraoperative complication: high abdominal pressures from the argon beam coagulator resulted in pneumothorax that resolved without the need to place a chest tube. No patient required analgesia after the second postoperative day. Mean hospital stay was 4.6 days, and patients returned to full activity between 7 and 21 days postoperatively. Long-term follow-up data were not available.

The initial laparoscopic partial nephrectomy for a renal cell cancer was reported in 1997 by Elashry and colleagues (97). This initial case required 5 hours; an electrosurgical snare was used to incise the renal parenchyma. The snare failed to provide satisfactory hemostasis; the argon beam coagulator proved effective in this regard. The collecting system was closed using intracorporeal suturing. The procedure was complicated by a urinoma requiring percutaneous nephrostomy tube drainage; the patient was in the hospital for 5 days. Total analgesic requirement consisted of 60 mg of ketorolac. Long-term follow-up was not available in this case report.

Wolf and colleagues (451) reported results of ten laparoscopic nephron-sparing procedures performed in nine patients; eight of these procedures were completed using hand assistance. They compared their results with 11 open procedures. Of 11 tumors, 8 (73%) were malignant. There was no significant difference in operative time between the laparoscopic and open approaches (3.3 versus 2.7 hours). Estimated blood loss for the laparoscopic and open groups was 460 and 210 mL, respectively. This included a laparoscopic wedge resection complicated by a 1,860-mL blood loss. There were three complications in each group. Laparoscopic complications included a patient requiring a transfusion of 4 units of packed red blood cells and transient urinary retention in two patients. Complications in the open group included two transfusions of 4 units of packed red blood cells and an arteriovenous fistula requiring embolization. Patients managed laparoscopically required less analgesic medications (40 versus 105 mg of morphine sulfate equivalents). Hospital stay was 2.0 days for the laparoscopic group and 3.5 days for the open group. Return to normal activity was also more expeditious in the laparoscopic group (8 versus 23 weeks). Long-term follow-up data were not available.

Division of the laparoscopic procedures into polar nephrectomy, wedge resection, and enucleation revealed that the operative time and estimated blood loss are higher with a partial

nephrectomy (445a). The operative times for laparoscopic partial nephrectomies, wedge resections, and enucleations were 4.2, 3.3, and 2.4 hours, respectively. Estimated blood loss for uncomplicated laparoscopic partial nephrectomy, wedge resection, and enucleation was 550, 300, and 300 mL, respectively. Mean length of stay for all three procedures was similar at 2 days.

Results for laparoscopic partial nephrectomy and laparoscopic wedge resection are frequently difficult to distinguish in the literature. Both procedures, although technically challenging with present technology, are feasible. Laparoscopic wedge resection has been described with results demonstrating the procedure to be effective, in the short run, and safe. Laparoscopic partial nephrectomy remains challenging, with the optimal technique yet to be developed. Both procedures suffer from a lack of cases and an absence of any long-term follow-up data.

Renal Cryoablation for Renal Tumors

The management of small renal masses continues to evolve with the progression from open radical nephrectomy, to open partial nephrectomy, to laparoscopic nephrectomy, and most recently to laparoscopic nephron-sparing surgery. Presently, the next step in minimally invasive therapy is just beginning to be explored: needle ablative therapy. Recently, cryotherapy has been used in the clinical management of small renal masses (Fig. 18.20). The ability of intraoperative laparoscopic ultrasound probes to accurately monitor the progression of the resulting ice ball has further stimulated interest in this modality. Other renal ablative modalities just beginning to be explored in the laboratory include wet and dry radiofrequency, photon irradiation, thermal rods, ethanol gel, and microwave therapy (Fig. 18.21).

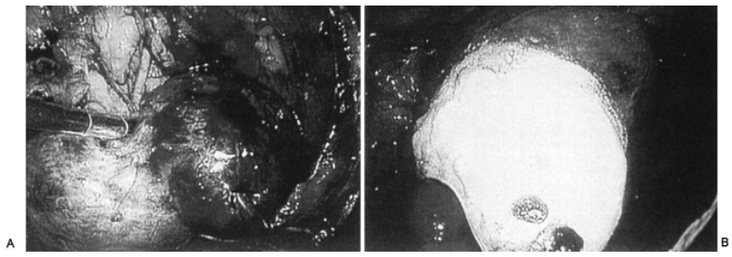

FIGURE 18.20. Renal cryotherapy. **A:** Mobilized kidney with cryoprobe inserted in renal mass. **B:** Ice ball engulfing renal mass. (Reprinted from Elsevier Science, with permission.)

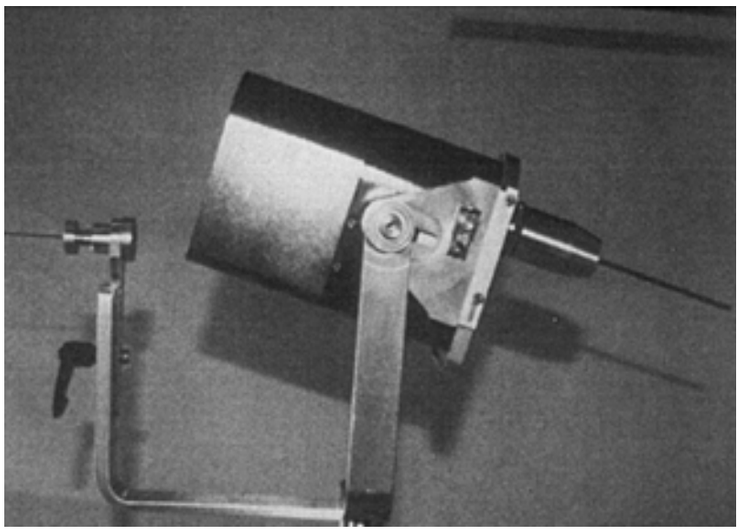

FIGURE 18.21. Photo beam irradiation source. (Reprinted from Mary Ann Liebert Co., with permission.)

Zegal and co-workers (458) performed cryotherapy in six patients with renal masses less than 4 cm in greatest diameter. The kidneys were accessed via open laparotomy incisions, and one to three cryoprobes were inserted into the renal masses under ultrasonographic guidance. Two cycles of cryoablation were applied to each tumor with a 1.5- to 2.0-cm ice ball margin created around each mass. All patients were successfully treated. During a follow-up period of 3 to 22 months, all patients were followed with CT scan, MRI, or both. There was no evidence of tumor recurrence during this relatively brief follow-up period.

Bishoff and co-workers (28) reported results of eight patients with T_1 renal tumors managed with laparoscopic-guided cryosurgical ablation. Mean tumor size was 2 cm. A transperitoneal laparoscopic approach

was used to access anterior or medial tumors, and a retroperitoneal approach was used to access posterior and lateral tumors. A cryoprobe, 4.8 mm in diameter, was used for tumor ablation, and a double freeze cycle of 5 minutes with a single thaw cycle of 15 minutes was applied. Renal biopsies at the time of surgery revealed renal cell carcinoma in six patients and were indeterminate in two patients. There were no intraoperative or postoperative complications reported. Mean operative time was 3.7 hours, and the mean estimated blood loss was 87 mL. Hospital stay was 3 days. With a mean follow-up of 7.7 months, no patient had radiographic evidence of tumor recurrence.

Gill and colleagues (126) reported laparoscopic cryoablation of 11 exophytic renal tumors ranging in size from 1.5 to 3.0 cm. A 4.8-mm conical-tipped cryoprobe was used (Fig. 18.20A). All procedures were successfully completed via a retroperitoneal approach. Laparoscopic ultrasound guidance was used for probe placement and to monitor the ice ball (Fig. 18.20B). Mean surgical time was 2.4 hours, and estimated blood loss was 75 mL. Hemostasis was achieved using the argon beam coagulator and Surgicel (oxidized regenerated cellulose, Johnson and Johnson, Somerville, New Jersey). Mean postoperative analgesic requirements consisted of 21 mg of morphine sulfate equivalents. Nine of ten patients were discharged within 23 hours. One patient tolerated the procedure well but required an 8-day hospital stay for stabilization of his cardiac status and systemic anticoagulation therapy. Intraoperatively, there was a single complication (a small liver laceration that was coagulated). Postoperatively, the only complication was a perirenal hematoma. Mean follow-up was 5.5 months and consisted of CT scan and MRI radiologic evaluation. All lesions continued to decrease in size during the follow-up period. Three patients underwent follow-up CT-guided biopsy of the cryoablation site. There was no evidence of tumor on any of the three biopsies.

Follow-up data from The Cleveland Clinic series was subsequently presented by Levin and co-workers (236) in a patient group now expanded to 22 patients. Needle biopsies were performed in all patients 3 and 6 months after cryotherapy. No patient had recurrent disease on these biopsies. However, one patient with a negative biopsy at 6 months had a local recurrence at 12 months; laparoscopic radical nephrectomy was performed and revealed a 1.3-cm focus of renal cell carcinoma.

Laparoscopic cryoablation of small renal masses (less than 3 cm) under ultrasonic guidance is feasible. In small series of highly selected patients, the procedure has so far been safe and resulted in a rapid convalescence. However, follow-up has been relatively brief, and one case of oncologic failure has already been reported at less than 2 years postprocedure. Accordingly, at this point in time, renal cryosurgery for smallrenal masses remains a largely investigational technique pending further long-term (i.e., 3- to 5-year) follow-up.

The next decade will be of great interest as each of the forms of needle ablative therapy comes under clinical investigation. By the year 2010, effective needle ablative therapy may well become the norm for renal lesions in the 1- to 4-cm size range. With advances in this arena, nephron-sparing surgery, as we currently know it, may well begin to fade from the scene.

Radical Prostatectomy

Radical prostatectomy was performed for the first time by Proust (342) in 1901 via a transperineal incision. Developments in this form of surgery occurred slowly; indeed, it took more than 40 years before Millin (281) proposed a retropubic approach. Likewise, it took almost another 40 years for another major change to occur in this operation; in 1983, Walsh and co-workers (431) modified the retropubic approach to make it “nerve-sparing,” thereby preserving potency.

Laparoscopic transperitoneal radical prostatectomy was introduced by Schuessler and colleagues (374) in 1997. The technique has been subsequently modified and its application greatly expanded by Guillonneau and Vallancien (145). Recently, an extraperitoneal approach to laparoscopic radical prostatectomy has also been described by Savad and Ferzli (368).

Guillonneau and Vallancien (146) reported results of 120 consecutive patients undergoing laparoscopic transperitoneal radical prostatectomy. Mean operative time was 4.0 hours. The authors used a five-port array. The prostatectomy was done in the following order: infravesical mobilization of the seminal vesicles and division of the vasa, anterior dissection of the bladder, entry into the endopelvic fascia, suture ligation of the dorsal venous complex, incision of the bladder neck, take-down of the pedicles with bipolar electrosurgical coagulation, urethral dissection and incision, take-down of the rectourethralis, and entrapment of the specimen. The urethrovesical anastomosis was completed using completely intracorporeal sutures; six to eight individual sutures were placed and tied. When patients were stratified by thirds, operative times for the first, second, and third groups were 4.8, 4.1, and 3.9 hours, respectively. Mean estimated blood loss for all patients was 402 mL. When stratified by sequential experience, estimated blood loss was 534, 517, and 277 mL for the three groups, respectively. Conversion to an open procedure occurred in 7 (5.8%) patients, all of whom were among the initial 80 patients. Conversion resulted from bleeding in three cases and from difficult dissection in four cases. Twelve patients (10%) required transfusion; however, the transfusion rates decreased with experience: 15%, 12.5%, and 2.5% for the first, second, and third group of 40 cases, respectively.

There were three (2.5%) intraoperative complications: an epigastric vessel injury that was repaired laparoscopically, an obturator nerve palsy that resolved with conservative management, and a rectal injury that was repaired laparoscopically. Postoperative complications included two patients

(1.7%) with a 5-day ileus and nine patients (7.5%) with leakage from the urethrovesical anastomosis. In seven of these nine patients, the leakage resolved spontaneously by postoperative day 5 with suction drainage alone. In one case, percutaneous aspiration of a urinoma was required, and one patient required anastomotic repair that was performed laparoscopically. One patient required open exploration for bleeding from an injured epigastric artery that was not appreciated intraoperatively. In addition, 14 patients (10%) experienced urinary tract infections, and three patients (1.5%) had transient urinary retention. Morphine sulfate was requested by only 9% of patients by postoperative day 1 and by only 2% of patients by postoperative day 2.

Definitive histologic examination revealed prostatic intraepithelial neoplasia in 2 patients (1.7%), stage pT2a disease in 37 patients (30.8%), pT2b in 68 patients (56.7%), stage pT3a in 7 patients (5.8%), and stage pT3b in 6 patients (5%). The overall positive surgical margin rate was 15%. With a mean follow-up of only 2.2 months, PSA levels were 0.1 ng/mL or less in 95% of the 94 patients studied. No instances of port site seeding were noted.

Mean postoperative catheterization time was 6.6 days. Catheterization times for the first, second, and third groups of patients were 7.9, 7.3, and 5.7 days, respectively. The 120 patients had a mean functional follow-up of 1.7 months. Eighty-five patients (71%) were completely continent (no pads), with 58% of patients regaining continence within 30 days. No patient had experienced a postoperative bladder neck contraction. Of the 60 patients with at least 6 months of follow-up, the continence rate was 73%.

Preservation of the neurovascular bundles was routinely performed only in the final 40 patients. Twenty of these patients (50%) were potent and sexually active before surgery. In 9 of these 20 (45%), spontaneous erections were reported postoperatively; however, only one patient (5%) reported rigidity sufficient for sexual intercourse. Of interest, the authors noted that the overall cost of laparoscopic radical prostatectomy in France was $1,237 less than that for an open retropubic radical prostatectomy (146).

The work of Abbou and co-workers (2) has been contemporaneous with that of Guillonneau and Vallancien (145,146). Laparoscopic transperitoneal radical prostatectomy was performed in 43 men. The approach was similar to that described by Guillonneau and Vallancien except that running sutures were used to effect the urethrovesical anastomosis. The median operative time for the first ten patients was 7 hours (n = 5) without lymphadenectomy and 8.6 hours (n = 50) with lymphadenectomy. After the first ten patients, the operative time for laparoscopic radical prostatectomy dropped to 4.3 hours in 21 patients without lymphadenectomy and 5.1 hours in patients with lymphadenectomy. Estimated blood loss was not reported.

Complications included two (4.7%) cases of prolonged lymphatic drainage, one (2.3%) rectal injury managed with open suture repair and colonic diversion, and four (9.3%) vesicoureteral anastomotic leakages that were managed by open surgery in three cases and laparoscopically in one case. One month after surgery, 36 patients (84%) were continent. Of the remaining seven patients (16%), five had only minor and occasional leakage during extreme stress; this population did not require use of pads. The remaining two patients wore only one pad daily for minor stress incontinence. With a mean follow-up of 6.3 months, all 43 patients had a serum PSA of less than 0.1 mg/dL. Positive surgical margins were identified in 12 (28%) specimens.

Laparoscopic radical prostatectomy is feasible. Subsequent modifications have made the procedure more expeditious, and initial results for both cancer control and patient morbidity are promising. At present, the procedure remains technically challenging as demonstrated by lengthy learning curves even in the hands of experienced laparoscopic surgeons. Long-term comparative data with open radical retropubic prostatectomy and with open perineal prostatectomy are needed to determine the role of the laparoscopic approach.

Radical Cystectomy

The first laparoscopic radical cystectomy and urinary diversion was reported by Sanchez de Badajoz and colleagues (365) in 1993. Denewer and co-workers (78) subsequently reported a series of ten patients who underwent laparoscopic radical cystectomy and continent pouch construction performed through a limited incision. Seven of the ten patients (70%) had received radiation therapy 1 to 4 months before laparoscopic cystectomy. Bilateral pelvic lymphadenectomy was performed. The rectovesicle pouch was sharply entered, and dissection of Denonvilliers' fascia was performed to mobilize the posterior portion of the bladder. Both bladder pedicles were secured with the laparoscopic stapler. A stapler or electrosurgical scissors dissection was used to separate the urethra at the pelvic floor. An 8-cm subumbilical midline incision was then used to create a sigmoid pouch with an intussusception antireflux valve. Individual ureteral anastomoses were also performed in an open fashion via the same 8-cm incision. In this series, the mean operative time was 160 minutes for cystectomy, and an additional 55 minutes was required for pouch construction. Mean intraoperative blood transfusion rate was 2.2 units of packed red blood cells per patient. Hospital stay was 10 to 13 days. A single intraoperative complication was reported: the external iliac artery was divided in one patient. The vessel was successfully repaired during the open portion of the procedure. Postoperative complications occurred in four patients (40%). These included a case of urinary leakage that resolved without any need for stenting or reoperation, a deep venous thrombosis, and a pelvic collection that required percutaneous drainage. One patient died postoperatively; this individual developed postoperative hemorrhage. Reexploration was

followed by disseminated intravascular coagulation, multisystem organ failure, and death (78).

Puppo and associates (344) reported results of five laparoscopically assisted transvaginal radical cystectomies in women with invasive bladder cancer. A bilateral cutaneous ureterostomy was performed in the first case. In the remaining four cases, an ileal conduit was accomplished through a mini-laparotomy at the stoma site. The specimen was removed transvaginally in four cases. In one case, vaginal atrophy necessitated removal through a midline laparotomy.

All procedures were successfully accomplished laparoscopically. Mean operative time was 7.1 hours, and although estimated blood loss was not reported, three patients (60%) required transfusion (mean of 3 units of packed red blood cells). Analgesic requirements were not reported. Hospital stay was 10.6 days. No major complications occurred intraoperatively. Two patients had significant lymphatic drainage for 1 week that resolved without intervention. All patients were reported to be alive with a mean follow-up of 10.8 months, but their disease status was not reported.

Gill and co-workers (123) reported results of two laparoscopic radical cystoprostatectomies with ileal conduits performed for invasive transitional cell carcinoma. In both cases, for the first time, the cystoprostatectomies and ileal conduits were constructed completely intracorporeally. Mean operative time was 11 hours, and mean estimated blood loss was 1,100 mL. Both patients resumed ambulation on postoperative day 2. Oral intake was resumed on postoperative day 4, and the patients were discharged on postoperative day 6. The two patients required 108 and 17 mg of morphine sulfate equivalents for analgesia, respectively. No intraoperative or postoperative complications were reported. Time to full convalescence was not reported. Long-term follow-up data were not available.

Laparoscopic cystectomy and diversion appears to be feasible. However, its application has been limited to very few institutions, and to date, there have been no large series and no direct comparisons with open cystectomy and diversion. Follow-up is too brief to comment on the long-term efficacy of this approach or to address concerns regarding possible seeding.

NEWER TECHNOLOGY

Part of "18 - ADULT LAPAROSCOPIC UROLOGY "

As the era of industrialization wanes, the age of computer-based information technology has become ascendant. Medical application of these advanced technologies will lead to major diagnostic and therapeutic advances. In this section, the impact of these newer technologies on laparoscopic surgery is presented. In this regard, the following areas are addressed: needle ablative therapy for renal tumor ablation, robotics, virtual reality as applied to laparoscopy, improvements in optics, newer laparoscopic tissue approximation techniques, and newer tissue dissection techniques.

Needle-invasive Ablation of Renal Tissue

Nephron-sparing surgery for renal tumors has become an established practice in select patients with a compromised global nephron mass and in patients with small tumors (less than 4 cm) (308). Within the past decade, minimally invasive techniques have been increasingly implemented for renal surgery. In keeping with these trends, various alternative energy sources for tumor ablation have also been developed. In urology, the majority of alternative treatments for solid organ tumors were originally investigated for treatment of benign and cancerous pathologies of the prostate. These treatments have now been adapted for renal surgery as well. The anatomic location and laparoscopic accessibility of the kidneys, as well as advances in imaging, have permitted accurate localization and ablation of renal tumors using these newer techniques. The various alternative energy sources described herein include cryoablation, radiofrequency ablation, microwave thermotherapy, high-intensity focused ultrasound (HIFU), and interstitial photon radiation energy.

Cryoablation

Uchida and colleagues (423) pioneered clinical renal cryoablation in 1995, using the percutaneous technique. Delworth and colleagues (76a) first reported open renal cryoablation, and Gill and colleagues (125) published the initial experience with laparoscopic renal cryoablation in 1996. At present, cryoablation is the most widely investigated and clinically used energy source for renal tumor ablation.

During renal cryoablation, tissue destruction is achieved by alternate cycles of freezing and thawing (108). Alternate freeze–thaw cycles are responsible for cell injury as a result of progressive metabolic failure secondary to extracellular and intracellular ice formation. As tissue temperatures approach the freezing zone, extracellular fluid is transformed into ice. Increased extracellular osmotic pressure relative to the intracellular compartment results, which draws water out of the cells. The ensuing increased intracellular solute concentration is detrimental to cell survival (254). Subsequently, intracellular ice formation occurs as a result of extension of extracellular ice directly, or as a result of continued rapid tissue cooling. The incorporation of minute blood vessels within the growing ice ball results in regional vascular occlusion that further accentuates tissue destruction. Profound tissue hypothermia inhibits tissue metabolism, adversely affecting cellular repair and survival following the cryotherapy insult.

During the thaw cycle, the osmotic effect is reversed. Extracellular ice melts, causing hypotonicity and thereby shifting water into the intact cells, causing cell swelling and disruption of cellular membranes. Thawing causes vasodilation and increased vascular permeability, tissue congestion, and edema. Platelet aggregation and microthrombi formation occur as a result of endothelial damage. Several small blood vessels are occluded following the thaw cycle. The microcirculatory failure and vascular stasis that result from cryoablation further augment the cytocidal effect of intracellular freezing. The resultant tissue anoxia is the basis of delayed cryoinjury. Repetition of the freeze–thaw cycle further potentiates tissue destruction (292). Sindelar and colleagues (392) proposed that an enhanced host cryoimmunologic response to the cryoablated tissue may be an additional mechanism of tissue destruction.

At the advancing edge of the ice ball, a 1- to 2-mm transition zone separates the zone of lethal destruction from the nontargeted normal renal parenchyma (296). This zone typically demonstrates a less pronounced and variable degree of cellular destruction.

Early to intermediate changes occurring a few weeks after cryosurgery include coagulative necrosis, which reduces the tubular cell remnants into proteinaceous aggregates, and variable amounts of chronic inflammation (273). The tubular basement membrane and collagenous network remain intact and form the framework for the subsequent deposition of fibrin. Late changes, occurring 3 months after surgery, include tissue destruction and autoabsorption within the lethal zone. Fibrin is laid down as part of the reparative process.

Chosy and colleagues (57) studied the lethal temperature required for renal cell destruction in the porcine model. Using thermosensors, a temperature of -19.4°C was found to be necessary for uniform cell death. This lethal temperature was achieved up to 3.1 mm inside the edge of the ice ball. Temperatures achieved at the tip of the cryoprobe are typically in the range of -140° to -180°C. Clinically, to ensure complete tumor destruction the freeze zone is extended approximately 1 cm beyond the edge of the tumor. To maximize the cold effect on tissues, concurrent renal artery clamping during the procedure has been suggested as a possible method for prevention of temperature conduction (the heat sink effect). However, Campbell and colleagues (45) demonstrated no significant advantage associated with this maneuver in the porcine model.

It is critical at all times to ensure that the ice ball is not in contact with any surrounding organ structure. Porcine studies have demonstrated deleterious effects such as small bowel obstruction and pelviureteral obstruction due to inadvertent injury caused by direct contact of these structures with the ice ball (45,125). However, Sung and colleagues (406) have recently demonstrated spontaneous watertight urothelial regeneration following intentional cryoinjury to the renal collecting system, thereby potentially paving the way for the cryotreatment of more centrally located tumors.

Percutaneous interventional MRI-guided cryoablation in 17 patients was recently reported by Shingleton and colleagues (386). The technique represents a less invasive form of renal cryoablation than the laparoscopic technique. Cryoprobes as small as 1.8 mm can be used. Short-term follow-up appeared promising.

Radiofrequency Interstitial Tumor Ablation

The role of hyperthermia in tumor destruction was noted initially by Busch (39) as early as 1866, in a patient with a sarcoma. Radiofrequency waves are low-frequency electromagnetic waves (frequency ranging from 0.5 to 1.0 MHz) that have the potential to alter the molecular kinetics of the tissues that they traverse. Radiofrequency waves cause ionic and molecular agitation, which results in a rise in kinetic energy. The resulting heat is the basis for thermotherapy (404). These low-frequency electromagnetic waves have greater tissue penetration than microwaves.

Clinical utility of radiofrequency ablation was established for the destruction of accessory cardiac conduction pathways responsible for arrhythmias (366). Radiofrequency ablation has also been employed for the treatment of hepatocellular cancer and osteoid osteomas and for performing neurotomy (75,244,357). In urology, transurethral needle ablation (TUNA) and transperineal radiofrequency interstitial tumor ablation (RITA) have been used for the treatment of benign prostatic hyperplasia and cancer of the prostate, respectively. Zlotta and colleagues (460) initially described RITA of a renal tumor in 1997. Their study included renal tumor radioablation before ipsilateral radical nephrectomy.

The size of the radiolesion depends on the length of the probe, the duration of contact, and the power used. Electrodes may be monopolar or bipolar. RITA induces vaporization and tissue charring in the immediate vicinity of the electrode tip. As a result, tissue impedance rises, thus limiting the size of the radiolesion. To overcome this problem, saline-infused RITA has recently been described using a probe through which hypertonic saline can also be infused (333). Radiofrequency waves spread along the interstitial saline infusion, minimizing tissue charring, thus resulting in larger radiolesions in an extremely short period of time; indeed, with this approach, tissue impedance is reduced by upward of 66% at 1 minute. Hoey and colleagues (170) demonstrated lesions ranging from 2.5 to 22.8 cm^3 (mean of 8.5 cm^3) using this technique, compared with lesions of only 0.06 to 0.93 cm^3 (mean of 0.34 cm^3) when using the dry radiofrequency probe. Polascik and colleagues (333) produced lesions involving 25% to 50% of the rabbit kidney (i.e., up to 2- by 1.3- by 1-cm lesions) with a 30- to

45-second treatment with “wet” RITA at 50 W. Clinical trials using wet RITA for the treatment of renal tumors are yet awaited.

Microwave Thermotherapy

Microwaves are electromagnetic waves with high frequencies, ranging from 300 to 3,000 MHz. In 1979, Tabuse (409) initially reported using microwaves for tissue during hepatic surgery. Its initial application as a method of thermotherapy was described by Yerushalmi and colleagues (455) in 1982 for the treatment of prostate cancer. Transrectal and transurethral heat applicators have been described for treatment of patients with prostate cancer and benign prostatic hyperplasia, respectively.

Laparoscopic microwave thermotherapy has been described for the experimental destruction of rabbit VX-2 renal tumors (219). The needle electrode was 1 mm in diameter and 8 mm in length with a 5-mm coaxial cable. Microwaves (2,450 MHz) were generated at a maximum output of 110 W. Coagulative necrosis was achieved over a 5- to 6-mm radius around the probe. During microwave thermotherapy, temperatures of 84° ± 3.3°C were achieved at a distance of 5 mm from the electrode, and temperatures of 55° ± 1.6°C were achieved at a distance of 10 mm from the electrode. The procedure is rapid, with desired effects being seen within 30 seconds. An advantage of the coagulative effect of microwaves is that tissue hemostasis is achieved simultaneously. However, lesions of a limited size are produced, which may necessitate the placement of multiple probes. Furthermore, a considerable amount of steam may be generated during treatment, which may interfere with laparoscopic visualization. Clinical trials using microwave therapy for the treatment of renal tumors are pending.

High-intensity Focused Ultrasound

Several studies have investigated the effects of HIFU for treatment of prostate cancer. Tissue temperatures of 85°C and lesions 18 mm in size have been reported within a few seconds of initiating treatment. HIFU is performed with a 1- to 2.25-MHz ultrasound transducer. Low-intensity exposure (less than 500 W/cm^2) for longer than 1 second is typically associated with thermal coagulative damage of the targeted tissue, whereas higher-intensity exposure (greater than 3,000 W/cm^2) causes tissue cavitation resulting in punched-out lesions (87). Cavitation is induced by conversion of tissue water into vapor. The vapor bubbles absorb energy from the ultrasound waves and grow larger. Once the bubbles reach their resonance they collapse, releasing high pressure and temperature, which induces tissue destruction. Pressure and temperature as high as 28,000 bars and 10,000 K, respectively, may be generated. Ultrasound waves of intermediate intensities tend to produce changes, which include cavitation surrounded by an area of coagulative necrosis. However, the ultrasound waves must be accurately focused on targeted tissues. Misfiring or inaccurate focusing may result in destruction of nontargeted neighboring tissues.

Chapelon and colleagues (51) studied the effects of HIFU on renal tissues of rats and dogs. Subsequent human trials resulted in incomplete tumor destruction and production of superficial burns (436). Although studies to determine the true efficacy and safety of this developmental treatment modality are yet necessary, it has the potential to be a completely noninvasive ablative modality for destruction of renal tumors.

Interstitial Photon Radiation

The role of interstitial photon therapy for stereotactic ablation of brain tumors is well established. Radiosurgery has also been used for the treatment of brain metastasis from metastatic renal cell cancer. Chan and colleagues (50) studied the feasibility of using intracavitary photon radiation for renal ablation in dogs. A 3.2-mm-diameter probe was inserted into the renal parenchyma, and local radiation of 15 Gy was delivered. An average lesion of 2.5 cm was produced. The animals maintained normal renal function over a 6-month survival period. The exposed tissues demonstrated changes suggestive of coagulative necrosis with a sharply demarcated rim, signifying unaffected surrounding renal parenchyma.

Compared with the high intensity and high energy of external beam radiation and the low intensity and low energy of brachytherapy, interstitial radiation is associated with high intensity and low energy. Hence, it does not produce the excessive tissue destruction seen with external beam radiation, nor does it require the prolonged treatment time necessary with brachytherapy. Furthermore, interstitial photon radiation may be delivered percutaneously. The potential of this form of treatment has not yet been explored at the level of clinical urology.

Robotics

Advances in robotics in the fields of industrial and aerospace-related technology have led to the simultaneous growth of medical robotics (153). A robot is a programmable automated task performance system controlled by microprocessors. Telerobotic devices synergistically integrate machine and real-time remote human interactions via electronic interfaces. Surgical procedures performed in such a manner are referred to as telepresence robotic surgery.

Robotic surgery has triggered advances in microsurgery (including vascular surgery) and laparoscopy. For totally robotic procedures, the surgeon is seated at a control station from where the robotic arms can be telemanipulated (one arm holds the laparoscope, and two arms hold laparoscopic instruments)

using two robotic ergonomically designed handles. A dedicated computer and coaxial cables link the two systems. For laparoscopic procedures, the robotic arms operate specially designed laparoscopic instruments that are inserted through standard laparoscopic ports.

AESOP (Automated Endoscope System for Optimal Positioning, Computer Motion, Goleta, California) is an example of a single robotic arm for control of the laparoscope (362) (Fig. 18.22). It was the first robotic system approved by the U.S. Food and Drug Administration (FDA) for laparoscopic intervention. The system obeys the surgeon's voice based on a preprogrammed voice card and voice recognition software. A safety feature incorporated into the AESOP arm is a mechanism that automatically releases the laparoscope from its clasp when any pressure in excess of 5 pounds is applied. A technical drawback of the current system is the inability to control telescopic zoom and angular rotation of forward-oblique laparoscopes.

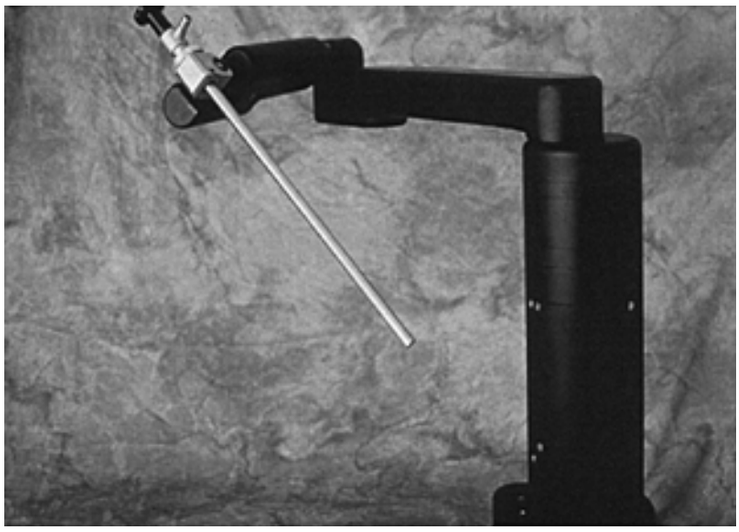

FIGURE 18.22. AESOP robotic arm.

The Green Telemanipulator Surgical System (SRI International, Menlo Park, California) was originally designed as a remote operational system that could perform surgical tasks in the battlefield (139). The system consisted of robotic arms with four degrees of freedom. The da Vinci Surgical System (Intuitive Surgical, Inc., Mountain View, California) is a sophisticated robotic system developed from the Green prototype with 3D image capability (385). A feature unique to this system is the Endo-wrist technology of the robotic arms. The arms have six degrees of freedom of motion, and a seventh degree of motion is provided by distally located computer-enhanced joints designed to further accentuate surgical dexterity. The ARTEMIS (Advanced Robotic Telemanipulator for Minimally Invasive Surgery) and the Zeus Microsurgical Robotic System (Computer Motion, Goleta, California) are other robotic systems designed for minimally invasive surgery. The Zeus system may be used in conjunction with the AESOP laparoscopic manipulator and consists of robotic arms with six degrees of freedom. Newer robotic systems have been designed to provide force and tactile feedback to the operator. Currently, however, these haptic interfaces are still largely developmental.

Initially, clinical applications in urology included transurethral resection of the prostate and prostatic biopsy (74,358). Kavoussi and colleagues, in a comparison between human versus AESOP robotic laparoscopic control (eight laparoscopic pelvic lymphadenectomies and three laparoscopic Burch colposuspensions), concluded that the robotic system was more effective and accurate than human laparoscopic control (209a). In another study, Partin and colleagues (325) successfully performed 82% of 17 cases using one or two AESOP robotic arms with a single surgeon. Human intervention was warranted in the event of any intraoperative complications such as significant hemorrhage. At The Cleveland Clinic, experimental robotic-assisted laparoscopic pyeloplasty (405) and the initial study on completely robotic laparoscopic nephrectomy and adrenalectomy in the porcine model have been performed.

The Future of Robotics

During laparoscopy, a fulcrum is created on the shaft of the instrument at the site of entry into the body (the trocar). As a result, the surgeon's movements are inverted before being transmitted to the distal instrument tip. To eliminate this inversion, the Human Interface Technology Laboratory at the University of Washington is developing an immersive robotic interface (315). This futuristic system proposes to give the surgeon the perspective of being shrunk and immersed into the patient's body for direct control of the distal tips of the laparoscopic instruments. This would involve the use of robotics and virtual reality images and would eliminate the inversion effect produced during routine laparoscopy. Furthermore, this may improve precision while shortening the learning curve associated with laparoscopy. Current robotic surgery is based on a “master-slave” interaction in a telerobotic manner. The rapid developments in information technology and neural networks may well pave the way for completely automated robotic surgery performed independently. Using computer algorithms and artificial intelligence with sensory inputs from the environment, future robotic systems may be able to perform complex preprogrammed tasks without the need for any interference from the human “master.”

Remote Robotic Surgery

Advanced telecommunication technology has incredibly hastened the speed of data transfer over the past few years. Using high-bandwidth telecommunications, a surgeon can remotely control a surgical procedure being performed transcontinentally. Lee and colleagues (231) at Johns Hopkins University in Baltimore reported telementoring of a

laparoscopic adrenalectomy performed in Innsbruck, Austria, 5,083 miles away, and telementoring of a laparoscopic varicocelectomy in Bangkok, Thailand, 10,880 miles away, in 1998. With further development of telecommunications and optics for data transfer, long-distance remote robotic surgery may become part of standard clinical teaching and practice.

Virtual Reality

Similar to flight simulators, which are designed to train pilots, virtual reality systems are being developed as a potential method for surgical training. Virtual reality systems seek to simulate real-patient situations by means of a series of synthetic computer-generated animations. Besides its potential use to train surgical residents, it will also enable more experienced surgeons to rehearse steps of a procedure before the actual operation. By entering patient-specific sophisticated imaging data into the simulator, a surgeon will be navigated through the area of interest. Such “enhanced” reality systems seek to augment reality with patient-specific images.

A laparoscopic virtual reality simulator comprises a manikin in which the laparoscopic instruments are manipulated. The surgeon wears a head-mounted display or alternatively uses a 3D video monitor. The system is equipped with a stereolaparoscope and auditory and haptic feedback (174). In addition, head, hand, and instrument-tracking technology is incorporated (435). A series of computer-generated images are relayed, consisting of representations of various anatomically correct cartoons. The images respond to movements of the surgeon by producing tissue deformation effects, bleeding, and other real-life physical situations (54). A state-of-the-art graphics computer with texture mapping capabilities is essential to generate these images. Alternatively, instead of the use of a manikin, systems are being developed that incorporate the use of a “dataglove.” The MIST-VR (Minimally Invasive Surgery Trainer—Virtual Reality) is an example of a developmental virtual reality system for laparoscopic training (171).

Optics

Image clarity and optimal visualization are key to the success of any laparoscopic procedure. Analog images are being replaced by higher-resolution digital images. Charge-coupled devices (CCDs) form the core of all digital and electronic cameras. A CCD chip is a light-sensitive solid-state silicon chip containing a series of pixels. Pixels are electronic sensors that discharge an electric charge when struck by light. When a photon strikes the CCD, an electrical potential is generated, creating a digital image. These images can be relayed, printed, or stored for future reference in computers or using optic computer disks. Current laparoscopic cameras may contain one to three CCD chips with 25,000 to 50,000 pixels. Higher-resolution triple-chip cameras function in a manner such that each chip is dedicated to one of the three primary colors: red, green, and blue (RGB). Images are transmitted employing RGB video channels. Advances in digital technology have enabled the production of cameras with several megapixels of image resolution. When clinically available for laparoscopic applications, these cameras will provide unparalleled visualization and definition.

In its present design, the laparoscopic camera is typically mounted to the proximal end of the laparoscope. An air interface exists between the laparoscope and the camera, which hampers image quality. Eliminating this air interface by directly mounting the CCD on the distal tip of the laparoscope would provide for clearer images.

Newer high-definition television monitors provide better sharpness and definition of displayed images. These monitors display up to 1,125 lines of resolution compared with 525 lines of resolution displayed by the ordinary television monitor. High-definition head-mounted displays incorporating liquid crystal on silicon microdisplays are available (OptiVu, Optimize, Los Gatos, California). Video images archived in the digital format are permanent, are easily retrievable, and can be stored on desktop computers that can be used for multimedia presentations. Digital video disc (DVD) technology with improved Moving Pictures Expert Group (MPEG-2)–quality images has resulted in crisp image storage and playback. Desktop and notebook computers with DVD cards and optimal memory capacity can store and display these high-quality movie images. Video imaging is a rapidly advancing field. Currently, MPEG-4 through MPEG-7 image qualities are being developed. In the years to come, these images will provide far superior resolution than current technology.

Stereoscopic Laparoscopy

Standard current laparoscopy involves 2D image technology. A disadvantage is the lack of depth perception. With increased operator experience, laparoscopic procedures are becoming more technically complex, necessitating superior visualization. Stereoscopic images have the potential to provide precise high-quality images with depth perception.

To produce 3D images, a video system must convey differing offset images to each eye. Stereoscopic images are obtained by using a stereolaparoscope, which consists of a laparoscope with two optical lenses. The laparoscope is equipped with a stereo camera containing two CCD chips. The surgeon wears a head-mounted device (HMD) with a liquid crystal display and active shutter glasses. Images are alternately cycled at 120 Hz to each eye (282). The right eye exclusively views the right image and the left eye the left image. While an image is provided to one eye, the shutter covers the opposite eye. Images cycled at less than 120 Hz cause perceptible flickering. Currently available

HMDs are rather heavy and somewhat uncomfortable when worn for prolonged periods. Alternatively, a 3D monitor with lenticular lenses in front of the screen or passive-polarized glasses may be used. The left eye image is selectively displayed to the left eye and the right eye image to the right eye.

Widespread use of 3D technology in its current form has not gained popularity. In its current form, stereoscopic laparoscopy does not yet provide optimal depth perception. Moreover, trained laparoscopic surgeons attain a sense of depth perception over time, and hence may not feel the need for this expensive technology (166). Learned 3D vision is akin to watching 2D television or movies and yet being able to perceive depth efficiently. Nevertheless, advances in the field of optics such as the use of high-definition video displays with improved clarity and improvements in stereoscopic technology may render stereoscopic laparoscopy more useful.

Optics for Ergonomic Comfort

Laparoscopic surgery involves peering into a television monitor positioned straight ahead on a vertical rack for hours at end. Thus the surgeon's line of vision is away from the actual operative field. This dissociation of the surgeon's vision from the line of work may be associated with significant physical strain. This problem can be rectified by using an image projector and a sterile screen, which can be intraoperatively manipulated by the surgeon to provide a direct line of view of the surgical field at the patient's skin level, thereby eliminating the need to look up at the television monitor during the procedure (ViewSite, Karl Storz Inc., Culver City, California; and Inside View, LSI Solutions, Rochester, New York). The advent of flat screen technology will similarly enable the surgeon to view the laparoscopic field comfortably.

Techniques for Laparoscopic Tissue Approximation

Fibrin Glue

Fibrin glue is produced by mixing appropriate quantities of fibrinogen with thrombin. The latter cleaves fibrinogen into fibrin monomers, which crosslink with one another to produce a sealant (388). The initial use of fibrin glue was directed toward achieving tissue hemostasis. Currently, it is employed for tissue approximation as well. The ability to obtain fibrinogen concentrates in the 1970s led to the high-level production of fibrin glue; however, the risk of transmission of blood-borne viral diseases such as hepatitis and HIV led the FDA to withhold its use (120). Recently, autologous fibrin glue has been prepared using cryocentrifugation, cryofiltration, and ethanol precipitation methods, making it safer for commercial use (456). In addition, with recombinant DNA technology large quantities of safe blood products are becoming available.

Fibrin glue is commercially available in a double-barreled syringe containing fibrinogen and aprotinin in one barrel and thrombin admixed with calcium chloride in the other barrel. The fibrinogen content determines the strength of the glue, and the thrombin content determines the rate at which glue stabilizes. The addition of aprotinin protects against rapid resorption of the glue. Fibrin glue has been used for several reconstructive procedures, such as vasovasostomies, and for sealing splenic injuries (391,418). In laparoscopic urologic surgery it has been used to perform pyeloplasties and ureteral reanastomosis. McKay and colleagues (271) demonstrated the feasibility of performing laparoscopic ureteral reanastomosis with fibrin glue in pigs. Compared with the animals that underwent open ureteral reanastomosis, animals treated with fibrin glue had more pronounced inflammation and fibrosis. In another porcine animal study conducted by Wolf and colleagues (452), ureteral repair with fibrin glue was associated with better flow characteristics and histology than laparoscopic suturing. Eden and colleagues (90) reported the clinical use of fibrin glue for laparoscopic dismembered pyeloplasty.

Cyanoacrylate Glue

Cyanoacrylate glue, or superglue as it is known, is a heavy-duty adhesive. It has powerful hemostatic and adhesive qualities. It rapidly polymerizes on contact with any ionic medium, including blood or saline. Indeed, polymerization can be so rapid that iophendylate or glacial acid may need to be added to slow the reaction (48). It has been clinically used as a hemostatic agent in interventional radiology and as a skin sealant. Experimentally, it has been associated with some degree of fibroblast and human tendon cell cytotoxicity, and it has also been associated with a marked inflammatory response and fibrosis (100,202). Cyanoacrylate is nonabsorbable, and its effect on mucosal approximation must be studied in detail before its utilization for tissue approximation in urology.

Laser Welding

The use of lasers in urology for tissue ablation and for hemostasis is well established. The initial successful laser weld for achieving vascular anastomosis was performed by Jain and colleagues (192). The concept was derived from the use of electrocautery for closure of venotomies, described by Sigel and Acevido (389). The basis of tissue welding is the photothermic effect of lasers on tissue proteins. At approximately 60°C, collagen fibrils tend to uncoil and then crosslink (370). The ideal tissue-welding laser should have optimal tissue penetration and should be associated with a strong weld while limiting the thermal damage and lateral spread of heat. Advances in the field of laser welding include

the use of laser solders, thermal feedback, and chromophore enhancement. In 1988, Poppas and colleagues (336) developed tissue solders for improving the strength of the weld and for limiting the lateral spread of heat by acting as a heat sink. The protein solder is effectively incorporated into the weld, thereby strengthening the tissue approximation (434). Albumin in concentrations of 40% to 50% is the most commonly used solder. The endpoint of laser welding may be determined by studying the color of the lased tissue. This is a rather inaccurate method that can lead to overheating of the tissues. The use of infrared thermal sensors (222) and chromophore enhancement with substances such as indocyanate and fluorescein may provide more accurate real-time thermal feedback and thereby prevent tissue damage. Nd:YAG lasers with a penetration of 3 to 5 mm and KTP lasers that penetrate up to 1 mm have been used for tissue approximation (335). Also, the use of the 1.9-µm diode laser for gastrocystoplasty in the canine model has been associated with good results; Bleustein and colleagues (29) demonstrated better results and less thermal damage with the use of the diode than Nd:YAG. The tensile strengths achieved with the diode lasers were comparable with that attained during tissue suturing (29). Laser welding appears to be an impressive and effective way of achieving sutureless tissue approximation.

Alternative Tissue Dissection Techniques

Alternative energy sources for laparoscopic tissue dissection include the use of ultrasound energy, pneumodissection, and hydrodissection. The harmonic scalpel (UltraCision) is driven by ultrasound vibrations. The power box is attached to forceps or a blade and vibrates at 55,500 cycles per second. The rapid vibration is associated with release of thermal energy, which facilitates simultaneous tissue coagulation. However, there is minimal risk of lateral spread of tissue coagulation (233).

Gardner and colleagues (113) reported the feasibility of high-pressure CO_2 for laparoscopic tissue dissection. Pneumodissection at 50 psi could be safely performed in the porcine model with a 5-mm pneumodissector. Short bursts of high-pressure CO_2 were used as a blunt dissector. The use of higher pressures (greater than 60 psi) was associated with splenic trauma when the pneumodissector was fired directly on the spleen. The same group presented their experience with the use of this technique in 20 patients (327). Acid–base imbalances were documented, although they were not statistically significantly different from the level of hypercarbia noted in patients undergoing a CO_2 pneumoperitoneum without use of pneumodissection. In their studies, gas embolism did not occur in either the animal or clinical cases.

Another tissue dissection technique involves the use of water under pressure. Hydro-jet dissection was employed to perform laparoscopic partial nephrectomy in the porcine model by Shekarriz and colleagues (383). An ultracoherent stream of normal saline, with a pressure of up to 30 atm, was used for dissection of the renal parenchyma during a partial nephrectomy. An average of 195 mL of saline was used per case. The saline stream effectively cut through the parenchymal tissue, preserving the intrarenal vasculature and collecting system.

Microlaparoscopic and Needlescopic Instruments

Instruments of smaller caliber than regular laparoscopic instruments have been developed to further decrease the morbidity and improve the cosmetic result associated with laparoscopic procedures. Needlescopic instruments are introduced through 2-mm (i.e., 14-gauge) trocars. A minute skin puncture results that needs no more than a single Steri-Strip for closure (129).

However, currently available mini-laparoscopic instruments are inferior in performance to larger 5-mm instruments. A 2-mm laparoscope does not provide the image clarity seen with a 10-mm laparoscope. Moreover, 2-mm clip applicators are not available and adequate suctioning cannot be performed. A judicious combination of conventional laparoscopic and mini-laparoscopic instruments is currently the best use of this technology. Significant advantages such as decreased pain and better cosmesis are noted when the 2-mm access is substituted for 5- or 10-mm ports. With further technologic development and improvement of instruments, it is possible that reconstructive procedures will be performed entirely via 2-mm ports.

CONCLUSION

Part of "18 - ADULT LAPAROSCOPIC UROLOGY "

With the incorporation of newer technologies, laparoscopic procedures of greater technical difficulty will be addressed in the future. More complex reconstructions and challenging ablations will be performed laparoscopically, with increasing confidence. Progressive technologic development is directed toward achieving increased efficiency, precision, and cost-effectiveness.

Computers in the 1950s were room-sized machines and had the storage capability equivalent to a few silicon chips of today's computers. Newer machines and instruments are smaller and yet vastly more powerful. We are presently in a transition from bulk technology to molecular technology. The future will witness progress in the fields of artificial intelligence and nanotechnology. A nanometer is one-billionth of a meter, and nanotechnology is the anticipated technology involving the use of molecular-sized devices. It has been envisaged that these micromachines will be able to perform a range of diagnostic and therapeutic procedures intracorporeally. When injected into the circulation, they will be able to find their way in a preprogrammed manner

into the area of interest and intelligently execute the task for which they were programmed. Molecular-scale surgery and cell repair machines involving nanorobotics may be possible in the future. In the years to come, the role of the master surgeon may well be reduced to that of today's house officer: to just “put in a line.”

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19

ENDOUROLOGY OF THE UPPER URINARY TRACT: NONCALCULOUS APPLICATIONS

Elspeth M. McDougall

Ralph V. Clayman

R. Sherburne Figenshau

R.V. Clayman and R.S. Figenshau: Department of Surgery (Urology) and Radiology, Washington University, Barnes-Jewish Hospital, St. Louis, MO 63110.

E.M. McDougall: Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN 37232.

Contents

Although initially limited to calculous disease, today the span of endourology encompasses almost all types of maladies affecting the upper urinary tract. This is due to significant advances in the endoscopic and auxiliary instrumentation available to the urologic surgeon. Presently, rigid working endoscopes have become as small as 6 Fr, and their flexible counterparts are only 7.5 Fr. Despite the small size of these endoscopes, a working channel of 3 Fr or larger is available for the passage of myriad instruments, ranging from biopsy forceps to electrosurgical and laser probes.

As a result of these developments, diagnostic and therapeutic procedures, previously possible only through a large incision, now can be performed effectively endoscopically. From a diagnostic standpoint, a minimally invasive approach has been most beneficial in the upper urinary tract in the areas of lateralizing hematuria, filling defects, renal masses, and obstruction. Likewise, the therapeutic approach to many upper urinary tract disease entities has progressed from an open to an endourologic treatment. In the ureter, endourologic approaches have been used for treating strictures, transitional cell cancer, and ureterovesical fistulae. In the kidney, a minimally invasive approach has been used to deal with ureteropelvic junction (UPJ) and infundibular obstruction, calyceal diverticula, and transitional cell cancer. In addition, benign renal masses, including cysts and abscesses, have been treated successfully endourologically. Most recently, these same techniques have been used to resolve similar problems affecting a renal transplant. In these patients, both stricture and fistula problems have been managed successfully endoscopically. The endourologic approach also has been applied to perirenal processes, such as abscesses, urinomas, and lymphoceles.

DIAGNOSTIC RENAL AND URETERAL APPLICATIONS

Part of "19 - ENDOUROLOGY OF THE UPPER URINARY TRACT: NONCALCULOUS APPLICATIONS "

Lateralizing Hematuria

In the diagnosis of lateralizing hematuria, an endourologic approach has become the final and definitive step in the diagnostic regimen (200). Among patients with macroscopic hematuria, the laboratory evaluation usually includes urine for cytology, urinalysis to rule out proteinuria associated with medical renal disease, coagulation studies, and when appropriate, a sickle cell preparation.

Aside from these basic studies, much has been written about examination of the morphology of the red blood cells in the urine in order to differentiate bleeding attributable to a glomerular problem (i.e., dysmorphic red blood cells) from bleeding caused by an anatomic lesion (i.e., normal-shaped red blood cells). Using interference microscopy, Tomita and associates (358) have identified five different red blood cell shapes indicative of a glomerular or nonglomerular (i.e., anatomic) site of bleeding. In patients with 15% glomerular red blood cells, the sensitivity and specificity of the test for glomerular bleeding was 90% and 98%, respectively. The accuracy of this study is further enhanced if the urine has a pH of less than 6.4 or is highly concentrated (osmolality greater than 400 mOsm/kg H_2O); likewise, identification of one subtype of the glomerular red blood cells (a doughnut cell) further increased the certainty of glomerular bleeding (196). Other reports have been less encouraging, with a sensitivity and specificity of 73% and 60%, respectively; however, these values were substantially improved when obvious causes of hematuria, such as urinary tract infection or urolithiasis, were eliminated from the data pool. Accordingly, in the patient with no obvious cause for lateralizing hematuria (i.e., negative radiologic studies), the appearance of deformed red blood cells on phase contrast microscopy or on a Coulter counter can be more than 90% accurate in diagnosing the presence of a glomerular, nonsurgical problem (4,270,311).

Also of interest are recent reports on detailed protein analysis of the urine among patients with hematuria of undetermined etiology. A nonglomerular source of hematuria is associated with an increase in high-molecular-weight proteins. Specifically, when the urine albumin exceeds 100 mg/L, the measurement of α_2-macroglobulin in the second voided morning specimen is recommended; if it is also elevated (i.e., α_2-macroglobulin-to-albumin ratio greater than 2.0×10^{-2}), a nonglomerular, postrenal site of bleeding is likely (127).

After the aforementioned studies, the next tests are usually radiologic and endoscopic: an intravenous urogram and cystoscopy. The intravenous urogram should clearly show the examiner all of the calyces and the entire length of the ureter; this might require additional radiographs and repositioning the patient to fill the entire ureter. Failure to image all of the calyces or the entire ureter necessitates completion of a retrograde ureterogram. If intravenous urography (IVU) fails to reveal an obvious cause for the hematuria (i.e., no filling defects, stones, or apparent renal masses) and cystoscopy reveals blood emanating from the right or left ureteral orifice, the next procedure is usually a computed tomogram or ultrasound (US) examination to rule out an occult renal mass that might have been missed on the IVU (227). If this study is unremarkable, there is some support for proceeding to a renal arteriogram to rule out an arteriovenous malformation or other large vascular anomaly; if discovered, the vascular abnormality can be embolized during the same angiographic session (Fig. 19.1).

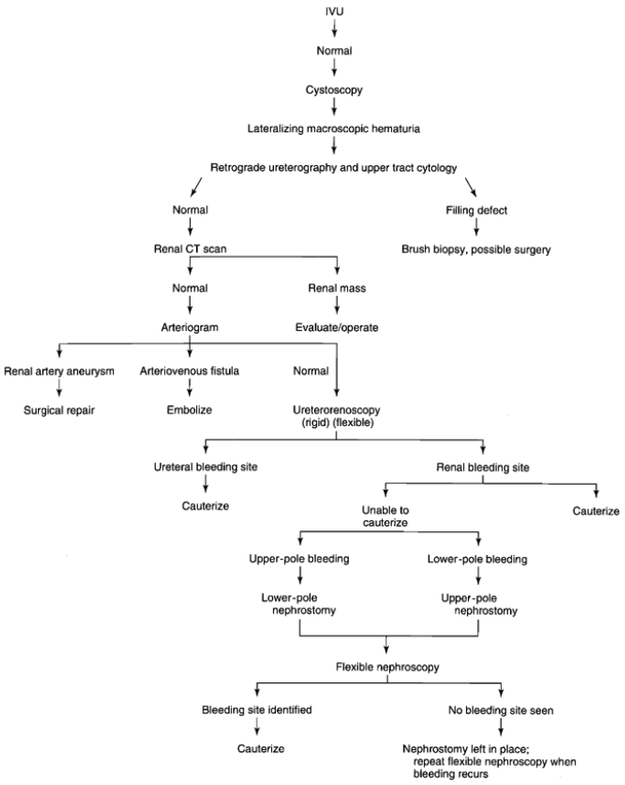

FIGURE 19.1. Lateralizing essential hematuria: evaluation. CT, computed tomography; IVU, intravenous urography. (From McMurtry JM, Clayman RV, Perminger GM. Endourologic diagnosis and treatment of essential hematuria. *J Endourol* 1987;1:145, with permission.)

When radiographic studies have failed to identify an obvious cause for lateralizing hematuria, it is necessary to proceed with ureteroscopic evaluation of the ipsilateral urinary tract. The role of percutaneous nephroscopy in these patients is limited; indeed, this approach would be considered only in the rare event that ureteroscopic examination was not possible (e.g., patient with a cross-trigonal reimplantation) or was unsatisfactory (i.e., inability to closely examine the lower-pole calyces in the face of an otherwise negative examination).

Technique

Diagnostic ureteroscopy is performed routinely under intravenous sedation, thereby eliminating the more morbid effects and prolonged recovery time incurred by general or spinal anesthesia (368). The patient's urine culture must be sterile. In examining the upper urinary tract in a patient with lateralizing hematuria, it is essential that the examiner visualize each area of the ureter and renal collecting system *before it is traumatized by a guidewire or other blindly passed instrument.* Accordingly, the procedure is begun by examining the distal ureter with a short, rigid, less than 7-Fr ureteroscope. This endoscope is introduced directly into the affected ureteral orifice and slowly advanced up the distal ureter, being certain to visualize the full circumference of the ureteral lumen. The irrigant pressure is kept at or below 40 cm H_2O. At this point, no guidewire has been passed into the ureter. (In rare cases, it may be necessary to extend a 2- to 3-cm length of guidewire from the end of the ureteroscope to help open the ureteral orifice and to serve as a guide for the passage of the ureteroscope. However, this is done under direct endoscopic, not fluoroscopic, monitoring. Again, the goal is to see each area of the ureter before it is manipulated.)

The rigid endoscope is passed as far up the ureter as possible. However, if passage of the endoscope becomes difficult, a guidewire is introduced. The guidewire is passed only to the most proximal point of ureteroscopic examination. Under fluoroscopic control, the rigid ureteroscope is withdrawn; during this time, the examiner's eyes should be focused on the tip of the guidewire to make certain that while withdrawing the ureteroscope the guidewire is not inadvertently advanced up the ureter. A less than 10-Fr, or

preferably less than 8-Fr, flexible ureteroscope is introduced over the solitary guidewire; the flexible ureteroscope is passed up to the point where the rigid ureteroscopic evaluation of the ureter ended (121). The guidewire is removed and the proximal portion of the ureter is examined carefully with the flexible ureteroscope up to the ureteropelvic junction.

Now the previously obtained IVU is examined carefully and each calyx is numbered. The endoscopist then proceeds to examine the renal pelvis, upper-pole calyces, middle calyces, and lower-pole calyces in sequence (Fig. 19.2A, Fig. 19.2B and Fig. 19.2C). Adhering to this sequence precludes the creation of iatrogenic lesions (i.e., bruising) along the os of the upper-pole infundibulum during flexion of the endoscope into the lower pole. As each calyx is entered, a small amount of dilute contrast is injected through the endoscope to determine the exact location of the endoscope; the assigned number of the entered calyx is then checked off. It is important to use minimum pressure on the irrigant flow during the ureterorenoscopic procedure (less than 40 mm Hg). Also, aspirating the upper collecting system through the flexible ureteroscope will reduce the volume of fluid and pressure within the upper collecting system and may help identify an area of venous bleeding. Any obvious lesion, such as a hemangioma, is treated directly with either neodymium:yttrium-aluminum-garnet (Nd:YAG) laser or electrocautery (via a 2-Fr electrode) (Fig. 19.2D); similarly, if a small tumor is noted, it is biopsied and then fulgurated.

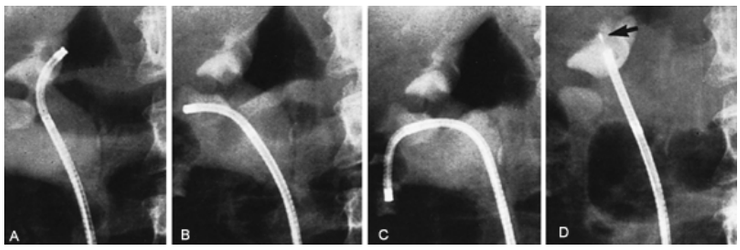

FIGURE 19.2. A–C: Flexible uteroscope examining collecting system of adult female patient with essential hematuria. **D:** Vascular lesion was identified and fulgurated with a 3-Fr electrosurgery probe *(arrow).*

After completely examining the collecting system, a guidewire is passed through the ureteroscope, and the ureteroscope is withdrawn. A 5- to 7-Fr indwelling ureteral stent is then placed, and the bladder is drained. The patient usually can be discharged on the same day (376). The stent is removed 3 days later in the office. Oral antibiotic coverage is given preoperatively and for 4 days after the procedure.

Results

Successful examination of the entire collecting system with the previously described approach is high. Bagley (12) noted that with a small (8.5-Fr), flexible ureteroscope, equipped with both primary and secondary deflection, the intrarenal collecting system could be examined satisfactorily in 92% of patients. The most difficult area to examine was invariably the lower-pole calyces.

Among patients coming to ureteroscopy for lateralizing hematuria of undetermined origin, approximately 50% are found to have a discrete vascular lesion that can be fulgurated. These vascular lesions (i.e., hemangioma or arteriovenous malformation) appear to be equally distributed throughout the kidney. Coagulation of the lesion results in an immediate successful outcome in more than 90% of patients; however, follow-up data at only 7 months reveals rebleeding in 12% of “successfully” treated individuals. This is not overly surprising given the finding that 12% of renal hemangiomas are multiple, thus implying that although the hemangioma that was bleeding may have been treated at the initial ureteroscopic session, a smaller, nonbleeding lesion may have been missed only to bleed at a later date (181). Nakada and colleagues (259) reported an average 58-month follow-up in 17 patients undergoing flexible ureteroscopy and intrarenal ureteroscopic therapy for lateralizing essential hematuria. Among 11 patients with a discrete lesion, only 18% subsequently rebled; however, for patients in whom no pathology or multiple bleeding sites were noted, the recurrence of hematuria was high (83%) (Table 19.1).

			Unilateral Diagnosis							
Authors	No. of Patients	Method of Nephrostomy	Ureteroscopy	Discrete Vascular Abnormality	Diffuse Vascular Abnormality	Stone	Tumor	No Diagnosis	Treatment	Rebleeding	Average Mean Follow-up Range (mo)
Gittes and Varady (115)	12	Operative (12)	None	5	7	0	0	0	Nephrectomy (1) Partial nephrectomy (11)	None	—
Patterson et al. (285)	4	Percutaneous (3)	Rigid (4)	1	3	0	0	0	Fulguration (4) Nephroscope (3) Ureteroscope (1)	None	5 (2–10)
McMurtry et al. (241)	8	Percutaneous (7)	Right (2) Flexible (1)	4	3	1	0	0	Fulguration (8) Nephroscope (7) Ureteroscope (1)	25% (4–6 mo)	6 (2–41)
Kavoussi et al. (181)	8	None	Flexible (6)	Not specified		0	0	0	Fulguration (6) Ureteroscope (6)	12% (7 mo)	11 (7–18)
Bagley and Allen (13)	32	None	Flexible (30)	14	9	1	1	5	Fulguration (16) Nephroureterectomy (1) Stone removal (1)	Discrete: 8% (1 of 12) Diffuse: 100% (4 of 4)	—
Kumon et al. (210)	12	None	Flexible (12)	9	1	0	0	2	Fulguration (9)	None	10.3 (6–21)
Nakada et al. (259)	17	None	Flexible (17)	10	2	1	1	3	Fulguration (11)	Discrete: 18% (2 of 11) Diffuse: 83% (5 of 6)	58 (24–103)
Tawfiek and Bagley (353)	23	None	Flexible (23)	11	2	2	3	5	Nephroureterectomy (1) Fulguration (16) Stone removal (1)	Discrete: 0 Diffuse: 20% (1 of 5)	8 (4–18)
Summary	**116**			**47%**	**23%**	**4%**	**4%**	**13%**		**Discrete: 12% Diffuse: 40%**	

TABLE 19.1. ESSENTIAL HEMATURIA: DIAGNOSIS AND TREATMENT

In 5% to 10% of patients, despite a completely negative cytology and unremarkable radiologic evaluation, a renal calculus or small, upper tract transitional cell cancer will be detected. This usually can be treated at the same time as the diagnostic ureteroscopy, using ureteroscopic lithotripsy or electrical or laser lithotripsy, respectively (12,13,189,210,259,353) (Table 19.1).

In the remaining patients, multiple, putative sites of bleeding are noted; in these patients, the success rate of *in situ* endoscopic electrocoagulation is less effective. As an alternative, intrarenal instillation or systemic therapy may be attempted. Bahnson (17) reported instilling 10 mL of

1% silver nitrate into the renal pelvis via a retrograde ureteral catheter in three patients with lateralizing hematuria caused by sickle cell hemoglobinopathy; in all three patients, the bleeding ceased after one or two instillations. During an average follow-up of 13 months, no rebleeding was reported. Likewise, Stefanini and associates (342) noted that oral epsilon aminocaproic acid at a daily dose of 150 mg/kg divided into four 6-hour intervals, given for up to 3 weeks, appeared to control hematuria in the short term in four patients with upper tract hematuria caused by tumor or trauma.

Renal Mass

An endoscopic approach to a renal mass is rarely necessary. Modern imaging modalities, including US, computed tomography (CT), and magnetic resonance imaging (MRI), largely have supplanted the need to obtain a confirmatory tissue diagnosis.

All renal masses can be separated into three broad categories: cystic, solid, and indeterminant. The vast majority of renal masses are simple cysts. Renal US can definitively diagnose a renal cyst provided the lesion fulfills the diagnostic criteria of being anechoic at high and low gain and has a strong posterior wall. Similarly, CT criteria for a cyst are likewise reliable: a thin-walled lesion with a homogenous interior of low density [i.e., 0 Hounsfield units (HU)] is invariably a simple renal cyst (Fig. 19.3). If these criteria are not met, the lesion is considered indeterminant and further diagnostic studies are indicated.

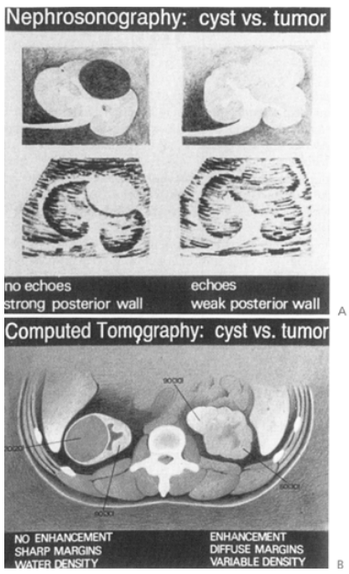

FIGURE 19.3. A: Characteristics of cystic *(left side)* and solid tumorous *(right side)* renal mass as each would appear on a renal ultrasound study. **B:** Characteristics of a cystic *(left side)* and tumor-bearing *(right side)* kidney as each would appear on a computed tomogram study. Numbers refer to Hounsfield units with and without *(in parentheses)* intravenous contrast administration.

For solid, noncystic lesions, the CT or MRI study is essential. One advantage of MRI is in the patient with renal insufficiency or a contrast allergy; in these patients the gadolinium-enhanced scan is of particular value (204,325). For the diagnosis of a solid lesion, the key point is to determine whether there is any fat within the lesion. If fat is found within the lesion, an angiomyolipoma is probably present; a solid lesion without any fat is more likely a renal cell cancer. The former, if smaller than 3.5 to 4 cm and asymptomatic, can be followed, whereas the diagnosis of a renal cell cancer leads to surgical ablation (269,363) (Fig. 19.4).

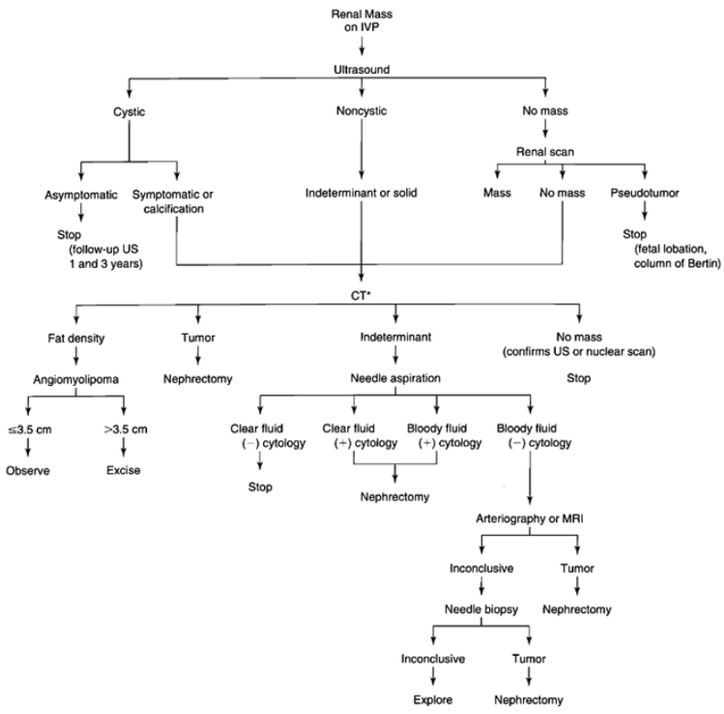

FIGURE 19.4. Diagnosis of renal cell cancer. CT, computed tomography; IVP, intravenous pyelogram; MRI, magnetic resonance imaging; US, ultrasound. (*If contrast allergy or renal insufficiency, substitute MRI for CT scan.)

Technique

Only in the case of an indeterminant lesion or a solid lesion in a patient with a known cancer (i.e., differential diagnosis of primary renal cancer versus a metastatic lesion) does it behoove the urologist to seek a more definitive diagnosis. In this regard, a US- or CT-guided puncture or biopsy of the lesion is indicated. If the contents are fluid, cytology, culture, and electrolytes can be obtained on the specimen; however, if the lesion has a solid component, an aspiration or needle biopsy can be obtained.

Needle biopsy of a renal lesion may be done either percutaneously or via a transrenal approach. The percutaneous approach to renal biopsy is by far the better-known procedure, having been used since 1950. The Vim Silverman needle and Tru-Cut needle have been the mainstays of percutaneous renal biopsy; however, recent advances in biopsy guns have provided the physician with much smaller 18-gauge, spring-loaded systems, which can be accurately guided to the lesion under US or CT imaging.

Leal (219) has described a transurethral, transrenal approach to renal biopsy. Using a torque control guidewire and 5- and 8-Fr catheters, the calyx closest to the parenchymal

mass is accessed. The guidewire is pushed into the mass and the 8-Fr catheter is then advanced into the mass. The guidewire and 5-Fr catheters are removed, and aspiration is applied to the end of the 8-Fr catheter during fluoroscopic imaging. The 8-Fr catheter is then removed and the plug of tissue is flushed out and sent for histologic evaluation; an indwelling ureteral stent is placed.

If all of these methods fail to yield a definitive diagnosis, a retroperitoneal laparoscopic or open approach may be necessary, at which time both a diagnostic biopsy and definitive therapy can be accomplished (Fig. 19.4) (53).

Results

Overall, the vast majority of incidentally discovered renal masses are cysts. A simple renal cyst is identified during abdominal CT in 25% to 33% of patients more than 50 years of age. In contrast, Tosaka and colleagues (359) noted

that among 46,000 adults undergoing US screening for renal masses, a mass was noted in only 1%. Among these masses, two-thirds proved to be a normal renal variant; cystic lesions (23%) greatly outnumbered renal cancers (5.4%). However, when the patient has a renal mass in association with macroscopic hematuria, flank pain, or a palpable flank mass, the chance of a renal cell cancer being present exceeds 50% (53). Other renal masses, specifically angiomyolipoma, renal pelvic tumors, and other benign lesions, are all relatively uncommon, accounting for approximately 5% of all renal masses among asymptomatic patients (359,363).

Complications from percutaneous renal biopsy with the larger 14-gauge needles occurred in 2% to 11% of patients; however, most of these problems were of a minor nature. The nephrectomy rate from renal biopsy is 0.06%, with a mortality rate of 0.08%. However, the advent of 18-gauge biopsy needles has resulted in the apparent elimination of major complications such as death or nephrectomies in some series; minor complications occur in only 5% (predominantly symptomatic perirenal hematoma or hematuria). The improved safety margin of this approach now has made it feasible to pursue a percutaneous biopsy even in the case of a solitary kidney (79,81,320).

Concerns about possible postbiopsy seeding of the needle tract are not sufficient to alter the course from percutaneous biopsy to renal exploration. Reported cases of seeding of the needle tract are few and are usually associated with unusual circumstances, such as multiple biopsies of a lesion over time, the use of large needles, or other extenuating circumstances (112,222,369).

Although the intrarenal biopsy method is of interest, it has been used successfully in only three patients, according to Leal's original report. Subsequent information has yet to be published. There is no information regarding complications from this approach. Overall, it remains significantly more invasive than currently available percutaneous biopsy techniques and thus would be of greatest value in those few patients in whom a percutaneous approach was unsuccessful or not feasible (e.g., massive obesity).

Diagnosis of Filling Defects Within the Upper Urinary Tract

As with the evaluation of a renal mass, the workup of the patient with a filling defect in the upper urinary tract should proceed in an orderly fashion from less invasive to more invasive studies. The patient's prior history and a fresh urinalysis with urine cytology and urine culture can help steer the clinician toward the correct diagnosis from the outset (Fig. 19.5). As such, patients with a history of stone disease or transitional cell cancer of the bladder are immediately suspect for similar upper tract conditions. Likewise, individuals with a history of diabetes, recurrent upper tract infections, analgesic abuse, or sickle cell disease may have papillary necrosis or an associated blood clot. Patients with a history of inflammatory bowel disease are at risk for developing a filling defect because of the presence of air in the collecting system from a ureteroenteric fistula. In addition, a long-term history of *Escherichia coli* urinary tract infection can be associated with malakoplakia or, in the diabetic patient, with emphysematous pyelonephritis. Pneumaturia may similarly indicate a fistulous bowel communication with the upper or, more commonly, lower urinary tract.

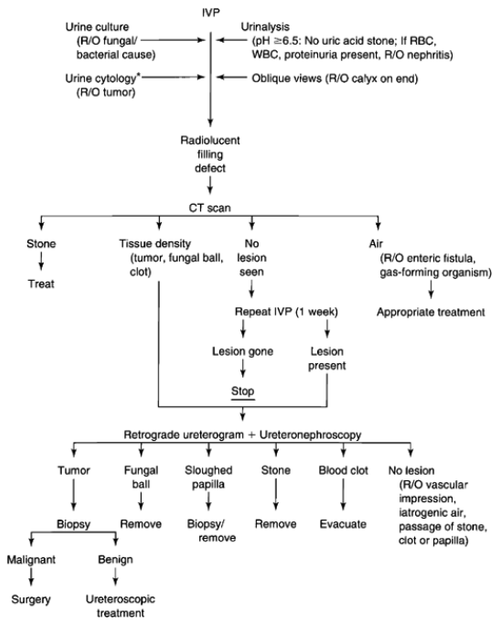

FIGURE 19.5. Radiolucent filling defect in the upper urinary tract: evaluation. CT, computed tomography; IVP, intravenous pyelogram; RBC, red blood cell; R/O, rule out; WBC, white blood cell. (*With a positive urine cytology, sterile urine, and a soft-tissue filling defect, a surgical procedure—that is, ureteroscopic confirmation versus surgical ablation—for suspected transitional cell carcinoma is reasonable.) (Modified from Resnick MI. Radiolucent filling defects. In: Resnick ME et al, eds. *Decision making in urology.* St Louis: Mosby, 1985:18, with permission.)

A complete urinalysis, performed by the urologist, is essential (Fig. 19.5). If the urine pH is above 6.5, the likelihood of a uric acid stone becomes remote. The presence of a significant amount of hematuria may indicate that the filling defect is secondary to a blood clot. A urine sample sent for cytology can be helpful if it is positive for malignant cells; however, the accuracy of this test is highly dependent on the skill of the cytologist. In one report, a false-positive cytology was noted in 17% of patients, and false-negative cytologies ranged from 10% to 80%, depending on the grade of the tumor (16,71,242,310,322). The urine culture also is helpful; the presence of fungi may indicate a fungal ball, whereas the presence of mixed aerobic and anaerobic bacteria would indicate a ureteroenteric fistula.

The next step in the diagnostic evaluation of a filling defect discovered on intravenous urography is either US or CT (Fig. 19.5) (301). US is safe, is relatively inexpensive, and has the ability to clearly show a larger stone because of its characteristic acoustic shadowing; however, the resolution of US is not as reliable as CT scanning (74). In Bagley's series, US evaluation of 14 patients with an upper tract filling defect failed to image 5 of 6 tumors and 4 of 4 stones. In contrast, CT imaged 57% of the stones (4 of 7) and 36% (5 of 14) of the transitional cell tumors (16).

When a stone is definitively identified, urinary alkalinization, high fluid intake, and if hyperuricemia is present, the use of a xanthine oxidase inhibitor are indicated (74). This should result in dissolution of the presumably uric acid stone within weeks to months. If, on subsequent radiographic studies, the stone persists unchanged in size, extracorporeal shock wave lithotripsy (ESWL) can be undertaken. Failing ESWL, a ureteroscopic or percutaneous approach is the next step.

When despite these studies the lesion remains indeterminant, retrograde ureterography and ureteroscopy are the next steps (Fig. 19.6). Even in the face of a positive cytology, given the 17% false-positive cytology rate in Bagley's series, a strong case can still be made for proceeding with diagnostic ureteroscopy and biopsy (16).

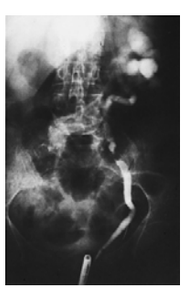

FIGURE 19.6. Retrograde uterogram reveals a midureteral filling defect with associated obstruction. The patient had macroscopic hematuria. Subsequent uteroscopy and biopsy established the diagnosis of a high-grade transitional cell cancer of the ureter.

Technique

In the past decade, the diameter of the rigid ureteroscope has decreased rapidly from 12.5 Fr to only 6 to 7 Fr; these diminutive endoscopes still contain working channels in the 3- to 4-Fr range. Their small size enables the urologist to

perform ureteroscopy without the need to dilate the distal ureter. However, although these semirigid endoscopes can usually traverse the entire length of the ureter in the female, manipulation over the iliac vessels in the male may be difficult. As such, for upper ureteral lesions in the male or for lesions located in the renal collecting system, flexible ureteroscopy is necessary.

Like their rigid counterpart, the flexible endoscopes have undergone a significant decrease in size over the last 10 years, from 13 to 7.5 Fr. The latter endoscope still has a 3.6-Fr channel; thus it can usually be passed up the ureter without ureteral dilation and yet allows the urologist the ability to use a full range of instruments, including biopsy forceps, electrosurgical probes, and laser fibers. In addition, these endoscopes have an actively deflectable tip mobility of 170 degrees and passive secondary deflection, thereby facilitating their introduction into the lower-pole calyces (121). Also of interest are reports of even more diminutive, 2-Fr diagnostic passive flexible videoureteronephroscopes that can be passed through a 6-Fr guide tube to provide both vision and a 3-Fr working channel (380). However, experience with these endoscopes is limited.

Unlike in the case of lateralizing essential hematuria, the patient with a filling defect in the collecting system provides the endoscopist with an identifiable target. The endoscopist can approach the site of interest directly; however, in patients with suspected transitional cell cancer or stone, a systematic examination of the entire collecting system is still indicated to rule out other sites of stone or tumor growth. The normal saline irrigating fluid is kept at 75 mm Hg or

less to prevent pyelovenous or pyelosinous backflow. Only when the biopsy forceps or a stone basket is in the endoscope's channel is the irrigant pressure increased to maintain flow (i.e., 150 mm Hg). As soon as the instrument is withdrawn, the irrigant pressure is lowered to 75 mm Hg.

After the ureter and renal collecting system are fully examined, the lesion can be addressed directly. If it is a stone, intracorporeal lithotripsy with a holmium:yttrium-aluminum-garnet (Ho:YAG) laser or a 1.9-Fr electrohydraulic lithotripsy probe through the flexible ureteroscope, or laser, electrohydraulic, ultrasonic, or pneumatic lithotripsy via the rigid ureteroscope, can be accomplished. If a cystic lesion is found, a biopsy can be obtained and the lesion unroofed and fulgurated (Fig. 19.7). If a tumor is discovered and a flexible ureteroscope is being used, the ureteroscope can be removed and an 8-Fr catheter and 10-Fr sheath can be introduced into the ureter. After withdrawing the 8-Fr catheter, a second guidewire is placed in the upper urinary tract. The 10-Fr sheath can then be replaced with a ureteral access sheath. This is passed over one of the guidewires, the dilator is removed, and the 12- or 14-Fr sheath is left in place. As such, when the ureteroscope is withdrawn during the biopsy process, the sheath maintains access to the ureter so the ureteroscope can be returned easily to the site of the lesion. If a rigid ureteroscope is being used, an access sheath is usually not placed.

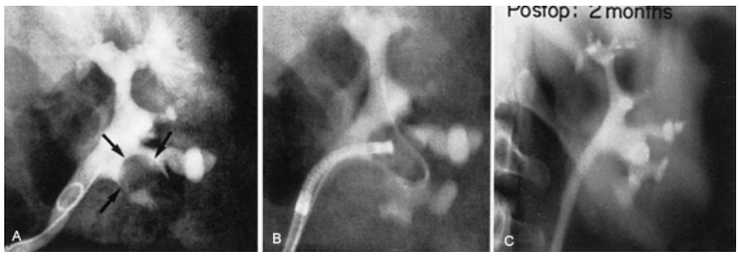

FIGURE 19.7. A: Filling defect *(arrows)* previously identified on an intravenous urogram is clearly delineated on this retrograde ureterogram. A guidewire has been passed up the ureter in preparation for introduction of the flexible ureteroscope. **B:** Via the flexible ureteroscope, a biopsy of the lesion was taken. It was found to be a benign cyst; accordingly, an electrosurgical probe was passed through the ureteroscope and the interior of the cyst was fulgurated. **C:** Two months later a follow-up intravenous urogram reveals no recurrence of the cyst.

When a suspected transitional cell tumor is viewed ureteroscopically, cytology samples are obtained immediately before any biopsies and just after the biopsy procedure via a saline irrigation directly in front of the lesion (186). Next, at least four to five biopsies are obtained. To do this, a 3-Fr biopsy forceps or a diminutive stone basket is passed. In the former instance, the opened biopsy jaws are advanced deep into the lesion; the jaws are then closed and withdrawn from the lesion by pulling the entire endoscope caudal (Fig. 19.8). Thus a larger piece of tissue may be obtained than if the closed biopsy forceps were pulled into the working channel, thereby shearing off the specimen. Alternatively, a stone basket may be opened at the site of the lesion and

twirled into the lesion, thus entrapping a large amount of tissue; as the basket is twisted amidst the papillary fronds, tissue is detached and trapped on the wires of the basket. The partially closed basket and endoscope are then withdrawn as a unit, again to preclude shearing tissue from the basket. In Bagley's experience, the use of a biopsy forceps or stone basket produced equivalent results with regard to obtaining a definitive diagnosis, 68% to 76% (186).

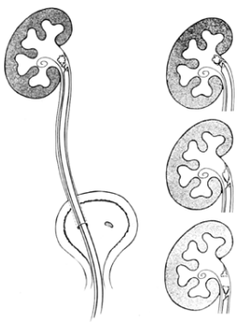

FIGURE 19.8. A 3-Fr biopsy forceps has been passed through the flexible ureteroscope in preparation for biopsying a papillary tumor. Once the jaws have been secured on the tumor, the entire endoscope with the biopsy forceps extended is pulled out of the ureter and urethra, thereby removing a large piece of the tumor. Note that a safety guidewire remains in the ureter. If the forceps is pulled into the endoscope, pieces of the tumor may be sheared off, thereby rendering the specimen too small for diagnostic purposes. Alternatively, a stone basket can be used to trap and avulse the tumor, thereby providing a large specimen for histologic analysis. (From Clayman RV, Kavousi LR. Endosurgical techniques for noncalculous disease. In: Walsh PC et al, eds. *Campbell's urology,* ed 6. Philadelphia: Saunders, 1992:2254, with permission.)

Two of the biopsies can be sent for cytologic analysis, and the remaining biopsies are sent for routine histologic analysis. It is also helpful to have the pathologist come to the operating room so that the pathologist can appreciate the intact appearance of the lesion; this can be invaluable during the pathologist's subsequent histologic assessment of the diminutive biopsy specimens.

Following the procedure, an indwelling ureteral stent usually is placed; the stent is removed in the office 3 days later. Most of these procedures are completed on an outpatient basis under intravenous sedation. Antibiotic coverage may be given immediately before the procedure and continued orally for 4 days after the procedure.

With regard to antegrade nephroscopy via a percutaneous tract, this is a less desirable means for accessing the upper urinary tract, especially in the patient with a suspected transitional cell cancer. It is far more invasive and morbid than ureteroscopy and does not provide any more information than a ureteroscopic examination (282). As such, antegrade nephroscopy would be used only in the rare instance in which an upper tract lesion could not be visualized adequately, biopsied, or treated through the ureteroscope. In this regard, the nephrostomy tract is positioned as far from the lesion as possible while still remaining on a fairly direct line with the lesion. Accordingly, if the lesion is in the ureter, an upper-pole or middle-posterior-calyceal approach is chosen; however, if the lesion is in the kidney, a remote calyx is selected as long as the surgeon will still be provided with a sufficiently direct route to the tumor such that rigid endoscopic equipment can be used. In addition, concerns over seeding the nephrostomy tract from an unsuspected transitional cell cancer remain a valid albeit unlikely consideration. There has been only one report of such an occurrence (147).

Results

For the most part, the actively deflectable ureteroscopes are preferred to their passive cousins because they allow reliable access to most lesions and permit the examiner to perform a more complete examination of the entire collecting system. Endoscopes smaller than 7.5 Fr have been used usually for diagnostic purposes; these diminutive passive endoscopes are as small as 2 Fr. However, considerably more skill and patience are necessary. Nonetheless, Yoshida and colleagues (380) were able to obtain diagnostic information in 87% of their patients using a 2-Fr passive endoscope, positioned through a 6-Fr guide tube.

Among patients coming to ureteroscopy, a transitional cell cancer is diagnosed in 16% to 40%, and a stone is noted in 18% to 44% (121,181,295). The other common finding is that of a vascular impression or essentially normal urothelium in 16% to 24% (16,181). Less common diagnoses are blood clot, papillary necrosis, fibroepithelial polyp, inverted papilloma, intrarenal cyst, pyelitis cystica, “eccentric” papilla, fungal ball, submucosal hemorrhage, air, and malakoplakia (Table 19.2). In addition, on rare occasions, a renal cell cancer may produce a filling defect in the collecting system without a significant accompanying mass effect in the renal parenchyma (123).

	Diagnosis
Common Entities	
Tumor	Transitional cell carcinoma
Urolithiasis	Uric acid calculi
Blood clot	Trauma/tumor
Air	Iatrogenic (retrograde ureterogram)
Infection/ inflammation	Papillary necrosis Fungal ball
Uncommon Causes	
Tumors	Leukemic infiltrate Angiomyolipoma Multiple myeloma Lymphoma Wilms' tumors Renal cell carcinoma Cysts Fibroepithelial polyp Squamous cell carcinoma Adenocarcinoma Leukoplakia Amyloid Sarcoma Connective-tissue tumors Metastatic tumors
Urolithiasis	Matrix Xanthine Indinavir
Blood clot	Coagulopathy Nephritis Anticoagulants
Air	Enteric fistula Gas-forming organism
Congenital	Vessel crossing Ectopic papilla End-on-calyx
Vascular	Renal artery aneurysm Vascular impression (vessel crossing renal pelvis/upper pole infundibulum, lower pole vessel, ovarian vein) Arteriovenous fistula
Infection/ inflammation	Pyelitis cystica Ureteritis cystica Tuberculosis Malacoplakia Helminths Fistula
Foreign body	Iatrogenic

From Clayman RV, Lange PH, Fraley EE. Transitional cell cancer of the upper urinary tract. In: Javadpour N, ed. *Principles and management of urologic cancer,* ed 2. Baltimore: Williams & Wilkins, 1983, with permission.

TABLE 19.2. RADIOLUCENT FILLING DEFECTS IN THE UPPER URINARY TRACT: DIFFERENTIAL DIAGNOSIS

Obstruction of the Upper Urinary Tract

In evaluating the patient with upper urinary tract obstruction, the urologist needs to determine both the functional significance and the cause of the obstruction.

The diagnosis of functional obstruction is of primary importance because this, along with the patient's symptoms, helps determine whether the obstruction requires therapeutic intervention. In general, abnormal dilation of the upper urinary tract is initially diagnosed by renal US or intravenous urography. However, the presence of dilation does not mean that there is obstruction (e.g., congenital megacalycosis). Likewise, the presence of dilation may occur in the face of either functionally insignificant narrowing or longstanding obstruction to which the kidney has accommodated, such that the renal pelvis pressure is low and the threat to renal function is nil. Radiographic studies, such as retrograde ureterography or antegrade nephrostogram, provide only anatomic, not functional, information.

As such, once hydronephrosis is noted, the next and most important step is to determine if there is any functional impact. Today, urologists have three studies available to define the significance of narrowing in the upper urinary tract: duplex Doppler renal US, Lasix washout renal nuclear scan, and the antegrade pressure-flow study (i.e., Whitaker test). Of these, the simplest study is duplex Doppler renal US. In this study, an external Doppler US probe is used to determine peak systolic and end-diastolic velocity over the renal interlobar and arcuate arteries. The *resistive index* (RI) is defined as peak systolic velocity minus end-diastolic velocity, divided by the peak systolic velocity. In the face of functionally significant obstruction, the peak systolic velocity is blunted, and thus the RI rises. In general, a RI above 0.75 and a difference in resistive indices of 0.10 or more between the two kidneys is believed to be consistent with functionally significant obstruction. Values between 0.70 and 0.75 with a differential that is greater than 0.05 are equivocal (i.e., gray zone) (275,303,354). In these indeterminate cases, the administration of a diuretic followed by repeat determination of the resistive indices may help classify more accurately the nature of the obstruction (275). Resistive indexes less than 0.70 with a differential of less than 0.05 are normal. Using these parameters, Gilbert and co-workers (113) noted that the results with duplex Doppler renal US were similar to diuretic renography. Similarly, Rodgers and associates (303) noted that among 20 adults with acute renal colic caused by a ureteric calculus, the RI was elevated in 93%. However, other investigators have shown that renal RI measurements may not be valuable in detecting acute urinary tract obstruction. Older and colleagues (272) demonstrated, in 54 patients evaluated by renal RI, that although the mean RIs of the obstructed and nonobstructed patients were statistically different, the wide overlap of the values for each group precluded clinical usefulness for the individual patient. The sensitivity of RI was only 42%, with 11 false-negative results; specificity of RI for obstruction was 79%.

Diuresis renography is the major study used to determine the presence or absence of functionally significant obstruction; however, the test must be administered properly and a

standard protocol must be followed in order to obtain meaningful data. Significant variables include the state of renal function, degree of patient hydration, fullness of the bladder at the time of the study, the amount of diuretic given, the type of radiopharmaceutical used, and the point in the examination when the diuretic is administered (235). In the adult, the diuresis renogram is accomplished using intravenous ^{131}I Hippuran (*o*-iodohippurate), ^{123}I Hippuran, or technetium-99m diethylenetriamine pentaacetic acid (DTPA). Renal imaging is done at 2, 5, 10, 15, and 20 minutes after giving the radionuclide with the patient in a supine position. At the 20-minute point, if it appears that the adult kidney may be obstructed, furosemide (40 mg) is given intravenously. In the normal unobstructed, two-kidney situation, half of the radionuclide tracer should drain from the kidney within 12 minutes. If it takes longer than 20 minutes, the kidney is considered obstructed (Fig. 19.9); results between 12 and 20 minutes are considered to be in a gray zone, and the test is deemed inconclusive. The presence of medical renal disease, renal artery disease, or massive hydronephrosis may blunt the response of the kidney to furosemide or alter the dilution of the excreted radionuclide, thereby resulting in a false-positive study; this occurs in 9% to 30% of diuretic scans. On the other hand, a false-negative diuretic scan is rare; hence, if a normal curve is obtained, the system is probably not obstructed. An equivocal result or suspicion of a false-positive result should lead to performance of a Whitaker perfusion test (vide infra) (231,277,278,349).

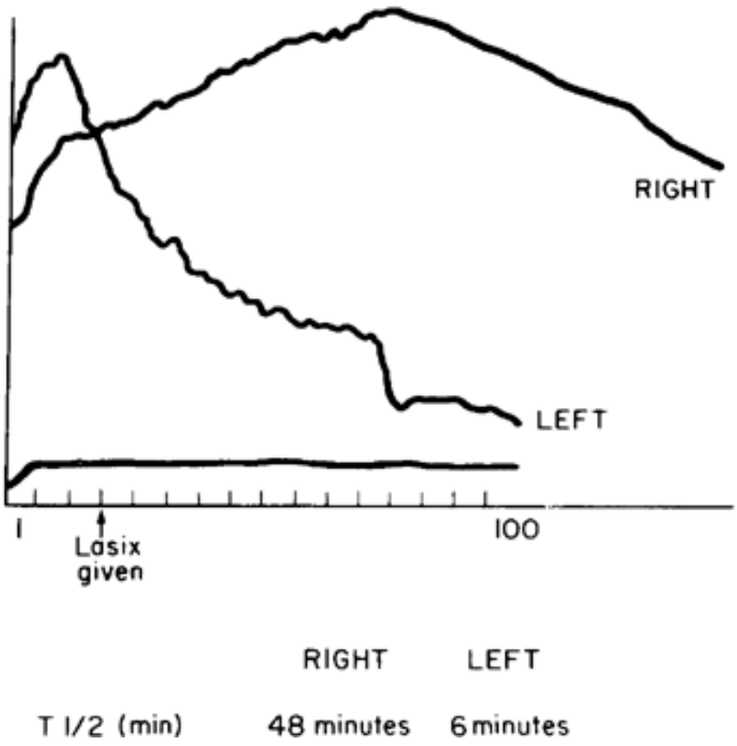

FIGURE 19.9. Lasix washout renogram performed in a patient with an obstructed right kidney. The right kidney shows an abnormal rising curve even before the Lasix is administered. On administration of the Lasix, the normal left kidney clears half of the radionuclide tracer in 6 minutes; however, the obstructed right kidney does not clear half of the tracer until 48 minutes, thus indicating its obstructed status. (From Clayman RV, Kavousi LR. Endosurgical techniques for noncalculous disease. In: Walsh PC et al, eds. *Campbell's urology,* ed 6. Philadelphia: Saunders, 1992:2269, with permission.)

In an effort to obtain more accurate information from diuresis renography, work by the Society for Fetal Urology and the Pediatric Nuclear Medicine Club of the Society of Nuclear Medicine has resulted in development of a standardized regimen for diuresis renography in children; as yet, a similar protocol is not available for adults (58). In the pediatric regimen, the bladder is catheterized; the patient receives intravenous hydration for at least 15 minutes before the study (15 mL/kg per 30 minutes); urine output response to the diuretic is measured; and the diuretic dose is standardized at 1 mg/kg of furosemide. The preferred radionuclide is 99m-technetium mercuroacetylglycylglycylglycine (^{99m}Tc MAG3) because it is rapidly cleared by the kidney and is primarily excreted by the tubules. The percent function of the affected kidney is determined; a half-life is calculated; and a clearance curve is generated. The curves can be divided into one of four groups: normal, obstructed, hypotonic pelvis, and equivocal (277). In general, a normal study would include renal function of 50% plus or minus 10% and a half-life of 10 minutes or less. If the half-life is 10 to 20 minutes, this is considered equivocal for obstruction, and a half-life greater than 20 minutes is compatible with significant obstruction (278,349).

In addition, other investigators have used the data accrued during diuretic renography to calculate a variety of other indicators that at times are useful in uncovering obstruction when the diuresis renogram is otherwise equivocal. These calculations include the normalized renal slope ratio, renal output efficiency, and calculations designed to relate renal volume to the rate of emptying of the collecting system (34,38,382). These other determinations are used to neutralize the two major causes of false-positive renal scans: compromised renal function and a dilated, phlegmatic renal pelvis. With use of these additional calculations, specificity could be increased from 85% to the 94% to 98% range using the normalized renal slope ratio, and accuracy rates of 94% were attained in patients with compromised renal function using the renal output efficiency formula. In another effort to overcome potential problems caused by a dilated system, Rossleigh and co-workers (305) have advocated obtaining an additional view after standard diuresis renography; this view is obtained after the child ambulates for 5 minutes or after the infant has been held upright for 10 to 15 minutes. In examining 12 children suspected of recurrent obstruction after a pyeloplasty; 64% of the postoperative patients who appeared to be obstructed on routine diuresis renography were not obstructed on the gravity-assisted drainage views. However, the gravity-assisted view was helpful in only 1 of 12 patients with suspected obstruction before a surgical procedure; for these children, routine

diuresis renography was satisfactory. Upsdell and associates (361) have described giving furosemide 15 minutes before administering the radionuclide (the F-15 renogram); this results in a marked diuresis at the inception of the study. The authors found that this method of performing the renogram resulted in fewer equivocal results.

The Whitaker test is the most invasive means of determining the presence or absence of functionally significant obstruction in the upper urinary tract (374) (Fig. 19.10). This test is done in the interventional radiology area under fluoroscopic control with the patient in a prone position. Usually a 20- or 22-gauge nephrostomy needle or an 8-Fr catheter is percutaneously passed into the collecting system. A Foley catheter is placed in the bladder. Using a three-way stopcock, dilute contrast is infused through the nephrostomy tube until the collecting system is fully distended. Then the flow is increased to 10 mL per minute; pressure readings of the renal pelvis and the bladder are taken at 5-minute intervals until a steady state is reached. If the pressure differential between the renal pelvis and the bladder remains less than 15 cm H_2O, the test is negative for obstruction; if the differential pressure exceeds 22 cm H_2O, the test is considered positive. Differential pressures between 15 and 22 cm H_2O are in the gray zone. For patients with an indeterminate reading, the flow rate can be increased to 15 mL per minute; the differential pressure, once a steady state is reached, should not exceed 18 cm H_2O (262).

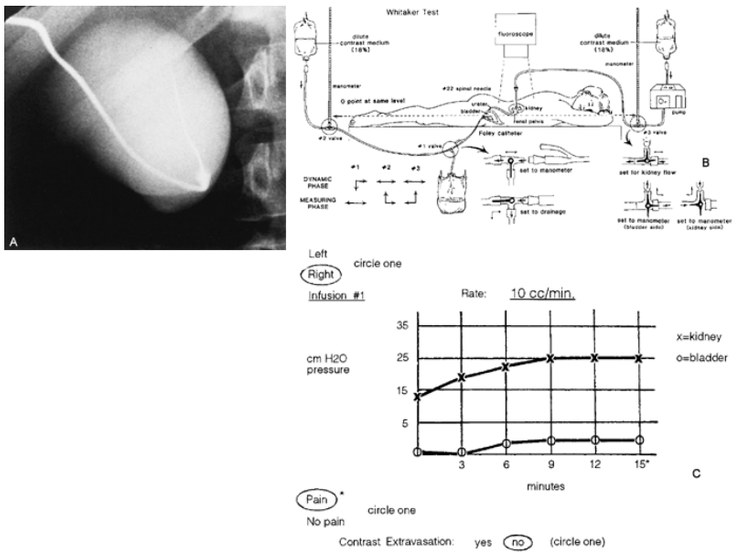

FIGURE 19.10. A: An antegrade nephrostogram reveals a hydronephrotic right kidney secondary to ureteropelvic junction obstruction. **B:** The setup for the Whitaker test consists of a pump to deliver fluid through the nephrostomy cannula, a pressure manometer connected to the nephrostomy cannula, a bladder catheter, and a pressure manometer connected to the bladder catheter. **C:** The values from the Whitaker test are plotted on a graph. In this patient, the pressure differential between the bladder and the kidney is 23 cm; the test indicates that there is a functionally significant obstruction at the ureteropelvic junction. (From Clayman RV, Kavousi LR. Endosurgical techniques for noncalculous disease. In: Walsh PC et al, eds. *Campbell's urology,* ed 6. Philadelphia: Saunders, 1992:2270, with permission.)

In contradistinction to the diuretic renogram, the most common problem with the Whitaker test is that of a false-negative study. This occurs because of inadequate filling of a large floppy renal pelvis, extravasation during the study, recording “final” pressures before a steady state has been reached, and renal intravasation caused by pyelovenous, pyelosinus, or pyelolymphatic backflow. Also, in some patients the UPJ obstruction is of an intermittent nature depending on the patient's position and the amount of urine output at a given point in time. As such, the obstruction actually may be relieved when the patient is lying prone; thus it may be necessary to repeat the Whitaker study with these patients in either a supine or sitting position.

The overall reliability of the Whitaker test is high. Laboratory studies by Ryan and colleagues (306) have confirmed the accuracy of the Whitaker test in detecting

functional obstruction in a canine model. Clinically, Bouchot and co-workers (32) reviewed their findings with Whitaker tests and diuretic renograms in 47 children. They noted that the overall accuracy of the Whitaker test was 90.5% among children with hydronephrosis. However, the Whitaker and diuretic renogram studies were *not* in agreement in 43% of the cases. Again, most of the problems were due to false-positive or equivocal renogram curves. Similarly, O'Reilly (277) and Krueger and associates (206) independently noted that in 9% to 30% of cases in which the diuretic renogram was positive, the Whitaker test was negative for obstruction. However, in the same series, the Whitaker test was inaccurate in 15% of patients largely because of a false-negative result. Overall, the most diagnostically reliable situation occurs when both the diuresis renogram and the Whitaker test are positive; this occurs in only 40% to 60% of cases overall.

THERAPEUTIC URETERAL APPLICATIONS

Part of "19 - ENDOUROLOGY OF THE UPPER URINARY TRACT: NONCALCULOUS APPLICATIONS "

Ureteral Strictures

With respect to ureteral strictures, from an endourologic standpoint, the ureter can be divided into three areas: proximal, middle, and distal. When discussing stricture disease, the proximal and distal portions of the ureter are quite short: the proximal ureter is primarily the few centimeters of the ureter just below the UPJ, and the distal ureter stretches from the ureteral orifice to just above the ureterovesical junction. The middle ureter includes the ureter beginning just below the iliac vessels, crossing the bony pelvis, and the majority of the ureter lying in the soft tissues of the retroperitoneum. The predominant cause of a ureteral stricture is iatrogenic (i.e., ureteroscopy, gynecologic surgery, or ureteral surgery). The distal ureter is most commonly the site of stricture disease.

Endoscopic ureteral dilation was described initially in 1891 by Pawlick, when he used ureteral bougies cystoscopically to dilate strictures secondary to tuberculosis (249). In 1907, Nitze designed a catheter with a terminal inflatable balloon to dilate and occlude the ureter (264). In 1926, Dourmashkin (77,78) dilated the ureter with a series of rubber bags attached to hollow bougies. He regularly dilated ureters up to 20 Fr and, on occasion, up to 30, 46, and 54 Fr, enabling a stone expulsion rate of 68% in his patients. In 1978, Gruntzig (126) reported percutaneous transluminal coronary angioplasty using a dilating catheter with a 3.0- to 3.8-mm balloon at the tip; these balloons were later used to dilate ureteral strictures. The concomitant development of the 9- and 11-Fr ureteroscope by Perez-Castro and Martinez-Pineiro (289) led to a renewed interest by urologists in the endourologic treatment of ureteral strictures. With improved optical capabilities and smaller endourologic instrumentation came the advent of diagnostic biopsy and therapeutic incision of endoscopic ureteral strictures.

Technique

Catheter Dilation

Catheter dilation is performed over a guidewire with multiple tapered, ureteral dilators passed under fluoroscopic control. The 0.035-inch, floppy-tip guidewire is passed into the upper collecting system under fluoroscopic control. The 5-Fr angiographic catheter is passed over the floppy-tip guidewire to secure access to the upper collecting system, and the guidewire is exchanged for an Amplatz superstiff guidewire. The 5-Fr catheter is removed. The ureteral dilators are sequentially passed over the guidewires, progressing from a 5-Fr up to a 14-Fr dilator. Following the dilation, a 7- or 8-Fr ureteral stent is placed for 4 to 6 weeks (378). However, serial, rather than single, ureteral dilations may be necessary for stricture resolution.

Balloon Dilation

Since the introduction of transluminal balloon dilation by Gruntzig in 1978 (126), this concept has been accepted widely by urologic surgeons as a technique to dilate the ureteral orifice and intramural ureter before ureteroscopy. Balloon dilation also has been used in the management of stricture disease.

The technique of balloon dilation of the ureter involves four steps to complete the procedure: (a) access to the upper urinary tract, (b) placement of the dilating balloon catheter, (c) activation of the dilating balloon, and (d) placement of a ureteral stent. Fluoroscopy is essential to each of these steps to ensure appropriate positioning and activation of the dilating balloon catheter.

The patient is positioned in the lithotomy position, usually under general or regional (e.g., spinal or epidural) anesthesia. Cystoscopy is performed and a 0.035-inch Bentson guidewire is introduced into the ureteral orifice. Using fluoroscopic guidance, the surgeon advances the guidewire along the course of the ureter, past the stricture, and positions it with the floppy tip coiled in the renal pelvis.

When the Bentson guidewire will not traverse past the stricture, a Terumo guidewire may be used. The lubricated, hydrophilic polymer coating of this guidewire greatly facilitates its passage through the narrowest ureteral stricture. It is essential to keep the surface of this guidewire constantly moistened with water or saline to achieve the maximum reduction of surface friction. However, because of its slippery nature, once positioned in the upper collecting system this guidewire can fall out easily. Therefore, once this guidewire has been passed, a 5-Fr angiographic catheter is passed over it. The Terumo guidewire is exchanged for a 0.035-inch Bentson or a 0.035-inch Amplatz superstiff guidewire. The 5-Fr angiographic catheter is then removed, leaving the stiffer guidewire in position in the upper collecting system.

Ureteral dilating balloon catheters are available in a wide variety of sizes (5 to 12 mm) and balloon lengths (2 to

8 cm). For dilating ureteral strictures, an 8-mm-diameter, 4-cm-long balloon is usually used; the balloon should be rated to withstand pressures of greater than 10 atm. The dilating balloon exerts a radially distributed force perpendicular to the ureteral mucosa and is designed to be inflated with fluid. A pressure gauge is placed between the syringe and the balloon; the recommended pressure limit of the balloon should not be exceeded, or else the balloon may rupture within the ureter and cause significant ureteral damage.

The dilating balloon catheter is passed over the guidewire into the ureter under fluoroscopic monitoring. Proximal and distal metal markers on the balloon catheter indicate radiographically the borders of the balloon and allow it to be positioned accurately; the balloon should straddle the "contrast"-outlined stricture. Using a handheld pressure-generating syringe (e.g., LeVeen) with an incorporated pressure gauge, the clinician inflates the balloon with a 50:50 mixture of contrast medium and saline solution under fluoroscopic monitoring. The balloon is initially inflated up to 1 atm of pressure, following which it is inflated at a rate of 1 mL of contrast mixture per minute under fluoroscopic control until the waist in the balloon at the site of the stricture disappears. If the pressure rating of the balloon is reached and the waist is still present, an endoincision (vide infra) will be necessary. Once the waist disappears, the inflated balloon is maintained in position for 2 to 5 minutes before it is deflated; the balloon is then reinflated. If the stricture has truly been torn, the balloon should now fill out at a low pressure. In contrast, if the balloon fails to fill out at low pressure, the stricture has not been treated adequately and an endoincision (vide infra) will be necessary. Following deflation of the balloon, the catheter is removed from the ureter leaving the guidewire in position. An indwelling ureteral stent (either a 7- or 8-Fr or a 7-/14-Fr stent) is then placed fluoroscopically over the guidewire. The ureteral stent is maintained for 4 to 6 weeks.

Clayman and colleagues (50) studied the effects of rapid and slow balloon dilation of the distal ureter to 8 mm (24 Fr) in the pig model. They showed that dilating the ureter to 8 mm (24 Fr) was safe. Slow dilation, over a 10-minute period, produced less residual inflammation 6 weeks following dilation compared with the rapid-dilation (less than 10 seconds) group. However, both groups had similar epithelial denudation, inflammation, and submucosal hemorrhage immediately following the dilation. Selmy and colleagues (324) studied the effect of balloon dilation of the ureter on upper tract dynamics and ureteral wall morphology in the pig model. They found that 1 week after ureteral dilation there was circumferential edema in the lamina propria and thinning of the muscularis propria; this correlated with obstructive urodynamic changes and grade 2 reflux in one-third of the animals. Over a 6-week period, there was gradual resolution of the pathologic inflammatory changes, disappearance of the obstructive changes, and return to radiographically normal ureters. Their observations favor a 6-week stinting period.

Endoincision

The development of the smaller rigid ureteroscope (6.9 Fr), the smaller flexible ureteroscope (7.5 Fr), and accompanying ancillary instruments for use with these endoscopes has made visualization and manipulation of the ureter and upper urinary tract an easier and safer procedure. Cutting modalities for incision of a ureteral stricture include the cold knife, electrosurgical probes, and the Ho:YAG laser.

Strictures in the proximal ureter are incised using a technique similar to an antegrade endopyelotomy. A percutaneous nephrostomy tract is established such that there is a straight-line access to the UPJ region and ureter. The straight posterior or posterolateral incision in the ureteral stricture is full thickness until retroperitoneal fat is seen. The caudal extent of the incision should be 1 cm beyond the area of the stricture. The cephalic portion of the ureteral incision should be into the renal pelvis. Following the incision, an indwelling 7- or 8-Fr double pigtail or 7-/14-Fr endopyelotomy stent is placed in an antegrade fashion. A small 14-Fr nephrostomy tube and Foley catheter also are inserted postoperatively. A nephrostogram is performed 36 to 48 hours postoperatively.

When there is no evidence of extravasation at the site of the ureteral incision, the nephrostomy tube and Foley catheter may be removed. The ureteral stent is usually maintained for 4 to 6 weeks (88,183,318).

The middle ureteral stricture is the most difficult to manage endosurgically. Middle ureteral strictures may be approached in an antegrade or a retrograde fashion. The antegrade approach is identical to an antegrade endopyelotomy except that the cephalad extent of the incision travels 1 cm into normal ureter rather than entering the UPJ. The retrograde approach is similar to a retrograde endopyelotomy except that the proximal limb of the incision remains in the confines of the middle ureter, and in some cases, the short rigid ureteroscope with or without an insulated sheath may be used. In the retrograde approach, after securing a guidewire across the stricture and into the upper collecting system, the intramural ureter is balloon dilated to 15 Fr. This allows introduction of the 12-Fr ureteroscope, through which a cold knife may be passed. Alternatively, ureteral dilation may be omitted and the rigid 6.9-Fr or flexible 7.5-Fr ureteroscope may be introduced, through which a 3-Fr or smaller electrosurgical device or 200-micron holmium laser probe may be passed to perform the incision (Fig. 19.11). The stricture is incised posterolaterally if it lies above the iliac vessels, anterior if it overlies the iliac vessels, and anteromedially if it lies just below the iliac vessels; the full-thickness incision through the stricture is extended 1 cm above and 1 cm below the stricture region into normal-caliber ureter.

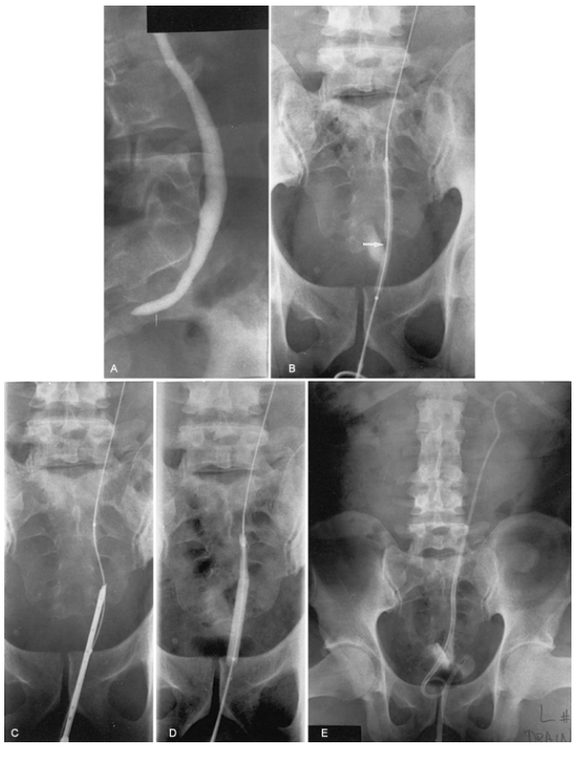

FIGURE 19.11. A: A benign, left ureteral stricture with hydroureter on intravenous pyelography. **B:** A guidewire has been passed retrograde into the upper collecting system. The ureteral dilating balloon catheter is filled to 1 atm pressure, and persistent waisting *(arrow)* of the balloon corresponds to the area of stricture. **C:** With the deflated dilating balloon catheter still in position, the short, rigid ureteroscope is inserted to the level of the stricture. A 3-Fr, right-angle electrosurgical probe is used to incise the stricture full thickness, extending the incision 1 cm above and 1 cm below the strictured region. **D:** Following incision of the stricture, inflation of the ureteral dilating balloon to 1 atm pressure demonstrates resolution of the area of waisting, confirming adequate incision of the stricture. **E:** A 7-/14-Fr double pigtail ureteral stent is positioned in the upper collecting system with the 14-Fr portion traversing the region of the ureteral incision.

In male patients, with a middle ureteral stricture above the iliac vessels, a 7.5-Fr flexible ureteroscope is recommended. A nonconducting Terumo guidewire is passed across the stricture, followed by passage of an 8-Fr dilator and 10-Fr sheath. The 8-Fr dilator is removed, and a side-arm adaptor is placed on the 10-Fr sheath; a retrograde ureterogram is performed to delineate the stricture, following which a second guidewire is passed by the ureter and into the renal pelvis. The 10-Fr sheath is removed. One guidewire is fixed to the drapes with a clamp, thereby becoming the safety guidewire. The flexible ureteroscope is passed over the second (i.e., working) guidewire. Once the ureteroscope is delivered to the ureter, the working guidewire is removed.

If the flexible ureteroscope buckles at the ureteral orifice or does not pass easily up the ureter to the site of the stricture, the flexible ureteroscope is exchanged for a ureteral access sheath. Once the 14-Fr end of the sheath is delivered well into the distal ureter, the 12-Fr dilator is removed. The flexible ureteroscope is then passed over the working guidewire through the 14-Fr sheath and into the ureter. The safety guidewire remains in place alongside the access sheath.

The flexible ureteroscope necessitates the use of a 2- or 3-Fr electrosurgical or less than 400-micron laser Ho:YAG probe. Periureteral damage from use of electrosurgical devices with a greater than 400-micron tip is similar to a cold-knife incision (75). Using visual orientation in combination with fluoroscopy in two planes, a full-thickness incision is made posterolaterally in the ureter above the iliac crossing, anteriorly in the ureter overlying the iliac vessels, or anteromedially in the ureter below the iliac vessels. Retroperitoneal or periureteral fat should be exposed by the endoincision, which extends 1 cm proximal and 1 cm distal to the ureteral stricture. After the stricture incision is completed, an indwelling ureteral stent (a 7- or 8-Fr double pigtail stent or a 7-/14-Fr endopyelotomy stent) is placed. When the 7-/14-Fr stent is used, it should be positioned such that the 14-Fr portion traverses the region of the ureteral incision. A Foley catheter is used to drain the bladder postoperatively. A cystogram 36 to 48 hours postoperatively usually confirms cessation of extravasation at the region of the ureteral incision, which permits removal of the urethral catheter. If extravasation is still present, the patient is discharged from the hospital with the urethral catheter still in place. An outpatient cystogram and catheter removal can be done 1 week later provided that a postoperative urine culture is sterile.

The distal ureteral stricture is usually at the ureteral orifice, the intramural tunnel, or just at or slightly above the ureterovesical junction. These strictures are incised such that the lower limb of the incision extends through the ureteral orifice (61). The retrograde approach is used most commonly for distal strictures. Cystoscopically, a guidewire is manipulated past the region of the stenosis and positioned fluoroscopically in the upper collecting system. An 8-mm, 4-cm-long ureteral dilating balloon catheter is passed over the guidewire after the cystoscope has been removed. Fluoroscopically, the balloon is positioned in the distal ureter such that the metal, lower radiopaque markers on the balloon lie just caudal to the ureteral orifice in the bladder. The balloon is inflated with a 50:50 mixture of contrast solution and saline stained with indigo carmine to a low pressure (i.e., 1 atm). The site of the stricture thus should be well outlined (i.e., a visible waist should appear in the balloon at the stricture site). A standard Iglesius resectoscope sheath is then inserted into the bladder. The proper positioning of the balloon catheter in the intramural ureter is confirmed visually. A right-angle, Orandi or Collins, electrocautery knife attachment is placed through the resectoscope sheath. Using 50 W pure cut, the surgeon begins the incision at the 12 o'clock position of the ureteral orifice and extends it cephalad through the ureteral orifice, ureteral tunnel, and for a distance of 1 cm cephalad to the area of stricturing. Following completion of an adequate incision, the 8-mm balloon should inflate fully at less than 1 atm of pressure. The dilating balloon is then deflated and removed. An indwelling 7- or 8-Fr double pigtail stent or a 7-/14-Fr endopyelotomy stent is placed over the guidewire; when the latter is used, the 14-Fr portion of the stent traverses the distal ureter. A Foley urethral catheter is used to drain the bladder. A cystogram 36 to 48 hours postoperatively is performed to confirm the resolution of any extravasation, following which the urethral catheter may be removed. The indwelling stent is removed on an outpatient basis 4 to 6 weeks following the stricture incision.

The Acucise cutting balloon device also has been used in the management of proximal and distal ureteral strictures (40) (Fig. 19.12). This technique involves placement of a nonconducting Terumo guidewire past the stricture and into the upper collecting system. The balloon catheter is positioned across the strictured region of the ureter under fluoroscopic control. In the proximal ureter above the iliac vessels, the cutting wire is oriented posterolateral, whereas below the iliac vessels the balloon cutting wire is directed anteromedially to avoid the branches of the internal iliac artery and vein, which are lateral to the ureter. *Strictures lying directly over the iliac vessels should not be approached with the cutting balloon device.* This type of ureteral stricture is better approached using direct ureteroscopic visualization and an electrosurgical probe because the surgeon can more accurately confirm visually the precise anterior location of the planned incision.

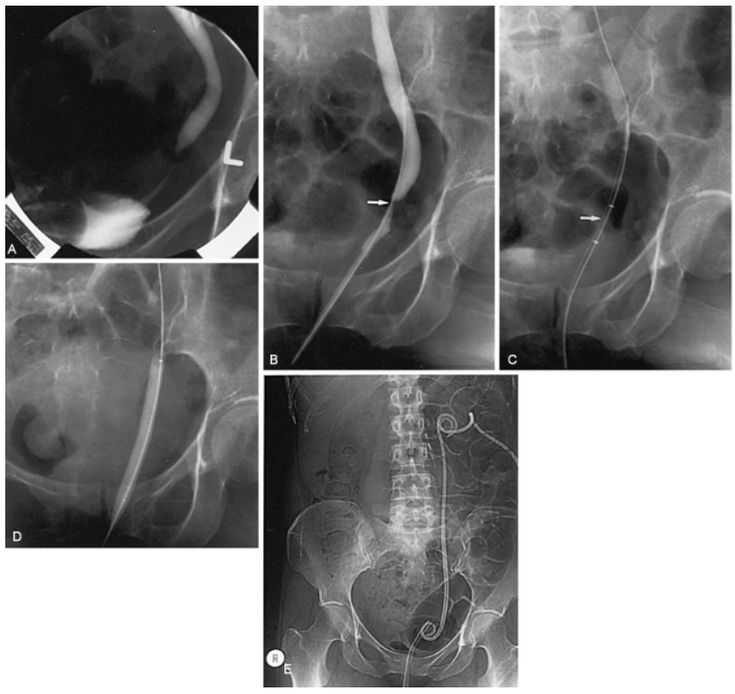

FIGURE 19.12. A: Distal left ureteral stricture with hydroureter on nephrostogram evaluation. **B:** Flexible cystoscopy is performed, and a 0.035-inch Terumo guidewire is passed through the strictured region *(arrow)* of the ureter in the upper collecting system. **C:** The cutting balloon catheter is passed over the guidewire and positioned with the cutting wire *(arrow)* oriented medially and traversing the region of the ureteral stricture. The radiopaque markers outline the exposed cutting wire, which is presented to the tissues as the balloon is inflated at a low pressure. **D:** Following incision of the stricture, a ureteral dilating balloon catheter inflated to 1 atm pressure confirms no residual waisting at the level of the stricture. **E:** A 7-/14-Fr double pigtail ureteral stent is positioned in the upper collecting system with the 14-Fr segment traversing the region of the ureteral stricture. The nephrostomy tube (placed preoperatively) and the Foley catheter are removed 24 to 48 hours postoperatively when a cystogram or nephrostogram indicates no residual extravasation at the site of the ureteral incision.

After positioning the cutting balloon catheter in the appropriate orientation, using two-plane fluoroscopy, the surgeon inflates the balloon with 2 mL of a 50:50 contrast solution and saline mixture while simultaneously activating the cutting wire with 75 to 100 W of pure cut electrical current. Inflation of the balloon carries the activated wire through the tissues. This portion of the procedure should take less than 3 seconds. The balloon is left inflated for 10 minutes, and then it is deflated and pulled retrograde. By

affixing a side-arm adaptor over the guidewire and onto the cutting balloon catheter, a retrograde ureterogram can be obtained. This study should confirm extravasation from the site of the incision. The cutting balloon catheter is then removed. A 5-Fr angiographic catheter is passed over the Terumo guidewire into the upper collecting system. The Terumo guidewire is exchanged for a 0.035-inch Amplatz superstiff guidewire, and the 5-Fr catheter is removed. An indwelling ureteral stent (a 7- or 8-Fr double pigtail stent or a 7-/14-Fr endopyelotomy stent) is passed over the guidewire and positioned fluoroscopically in the upper collecting system. The 7-/14-Fr endopyelotomy stent is positioned such that the 14-Fr portion of the stent traverses the region of the ureteral incision.

The more challenging problem, associated with ureteral stricture disease, occurs when the retrograde ureterogram reveals complete ureteral obstruction. A percutaneous nephrostomy tract is established. With the patient lying prone, the extent of the stricture can then be estimated through a combined antegrade nephrostogram and retrograde ureterogram. The latter is secured after using prone flexible cystoscopy to place the retrograde catheter; in some cases, the flexible ureteroscope can also be passed with the patient prone so a “cut-to-the-light” procedure can be done. A short (less than 1 cm) occlusion may be approached endosurgically. Bagley (11) has reported successful recanalization of complete ureteral obstructions up to 5 cm in length. However, in general, ureteral occlusions longer than 2 cm are better managed with an open surgical procedure.

The site of complete ureteral occlusion may be accessed antegrade by developing the percutaneous nephrostomy tract and passing a flexible nephroscope or short rigid ureteroscope down to the obstruction. Concomitantly, a flexible ureteroscope may be passed in a retrograde fashion to the distal end of the occlusion. If the ureteral stricture is short, the light from the retrograde endoscope may be identified and the tips of the two endoscopes may be aligned using fluoroscopy in an anteroposterior and then oblique projection. With a rigid ureteroscope passed antegrade, a direct incision using a cold knife may be performed onto the tip of the retrograde endoscope. Also, the surgeon can be guided by the light coming from the retrograde endoscope. In this case, the light through the antegrade endoscope is turned off. If the two endoscopes are properly aligned, a bright pink light should be seen through the stricture. As the incision is made toward the light, the light should become more white in appearance until the tip of the retrograde endoscope is clearly visualized. A 260-cm exchange guidewire is then passed through the retrograde instrument and retrieved by the antegrade endoscope. After establishing a guidewire across the stricture, the surgeon can complete the incision through full thickness of the scar and balloon dilation to 8 mm can be used to confirm the adequacy of the incision before placing a ureteral stent. When a flexible endoscope has been passed antegrade, an electrosurgical probe is used to incise the stricture. Alternatively, a stylet guidewire (e.g., rocket wire with a sharp tip from a Lawson retrograde nephrostomy kit) may be passed through the retrograde endoscope to create an indentation on the scarred ureteral tissue and to guide the incision by the antegrade instrument under direct visualization. Alternatively, this sharp wire can be passed, under fluoroscopic control, through the lower end of the stricture and retrieved proximally; the stricture can then be balloon dilated.

Following incision of the stricture, a long-acting steroid (e.g., triamcinolone 40 mg/mL) may be injected into the bed of the incised stricture (243). A 3-Fr Greenwald injecting needle catheter is passed via the rigid or flexible ureteroscope, and 3 to 5 mL of triamcinolone (40 mg/mL) is injected into any dense scar tissue bordering the ureteral incision. A pressure syringe (e.g., LeVeen) is helpful to inject the medication into this area.

Among patients with a particularly long stricture (i.e., longer than 2 cm), a rarely used alternative to open surgical repair is the placement of a free urothelial graft (49,243). With use of a 28-Fr Iglesius resectoscope equipped with an Orandi knife, a 2- to 4-cm-long piece of urothelium from the bladder is incised and carefully lifted off of the dome or base of the bladder. The donor site is cauterized with a roller electrode. The graft is meticulously defatted, following which the thin urothelial surface of the graft is sutured, facing inward, onto a 7-Fr ureteral stent using 5-0 chromic suture. Via a 14-Fr ureteral access sheath, the stent is fluoroscopically positioned in place so the graft-bearing portion of the stent traverses the area of the incised stricture; as the 14-Fr sheath is pulled retrograde, the stent-bearing graft is kept in place with a metal tip stent pusher. A urethral catheter is left in place and the patient is kept on bed rest for 48 hours. The urethral catheter is removed on postoperative day 7; the stent is removed after 6 weeks.

For totally occlusive strictures of the distal ureter, a percutaneous nephrostomy is placed. Through this site, a guidewire and ureteral dilating balloon catheter may be positioned into the distal ureter to the level of the obstruction. The balloon of the catheter should be constructed such that it is *flush* with the tip of the catheter. The balloon is inflated with a 50:50 mixture of contrast medium and saline solution stained with indigo carmine until a pressure of 1 atm is reached. An Iglesius resectoscope sheath is inserted into the bladder; after fluoroscopically aligning the tip of the Orandi electrosurgical knife over the balloon in two planes, an incision is made through the intervening tissue directly onto the inflated balloon. The balloon is thereby uncovered as the overlying sclerotic bladder and ureteral tissues are incised. A 260-cm exchange guidewire is passed through the balloon catheter and retrieved through the bladder. This through-and-through guidewire is then used to place a 7-Fr or 7-/14-Fr indwelling ureteral stent.

A Foley urethral catheter is inserted into the bladder to complete the procedure. A cystogram, 36 to 48 hours postoperatively, usually shows no evidence of extravasation, and the urethral catheter is removed. If extravasation persists,

the catheter is maintained for another 7 days before repeating the cystogram. The indwelling stent is removed on an outpatient basis 4 to 6 weeks postoperatively.

Recently, Nissenkorn and Gdor (263) reported their experience with a nephrovesical stent for management of complete ureteral obstruction secondary to metastatic prostate or invasive bladder cancer (Fig. 19.13). The proximal end of a specially designed 7-Fr double pigtail stent is inserted into the renal pelvis via a percutaneous nephrostomy puncture. A subcutaneous tunnel is created from the flank to the suprapubic region, down which the distal end of the stent is passed. The stent is passed into the bladder through a suprapubic bladder puncture. This stent is changed every 4 months over a guidewire, using a small flank incision to access the subcutaneous nephrovesical stent.

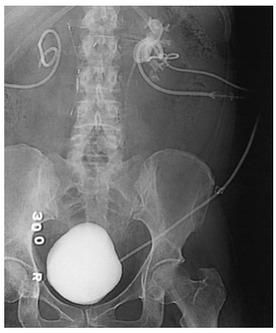

FIGURE 19.13. A left, subcutaneous nephrovesical stent has been placed in this 32-year-old woman with complete obstruction of both distal ureters secondary to metastatic breast carcinoma.

Results

When evaluating the literature with regard to the management of ureteral stricture disease, it is important to review the cause of the stricture. Ureteral strictures secondary to radiation therapy or resulting from extraluminal metastatic malignancies, causing periureteral compression, respond poorly to endoureterotomy (216). In contrast, patients with a concomitant ureteral stone and an apparent ureteral stricture usually have resolution of the stricture following removal of the stone and alleviation of the inflammatory response to the stone; incising these strictures may falsely inflate the endoureterectomy success rate.

The development of high-pressure arterial balloon-dilating catheters allowed this technology to be applied to ureteral stricture disease. Several investigators have reported favorable results with balloon dilation of ureteral strictures. Success rates range from 48% to 88%, with an overall average of 55% in 271 patients (19,24,41,170,193,203,216,261,268) (Table 19.3). However, there appears to be limited consensus among the reports of balloon dilation on the optimal balloon size and technique to perform the procedure. In the literature, the dilating balloon size varies from 4 to 10 mm and the duration of balloon inflation ranges from 30 seconds to 10 minutes for anywhere from one to several inflation cycles. Also, there is no agreement on the size of stents or duration of stinting following balloon dilation; stent sizes range from 6 to 16 Fr, and stent duration ranges from 2 days to 12 weeks. In many of the reports, the success of the procedure is assessed on the basis of subjective relief of the patients' pain or symptoms. When objective studies are provided, they are often not more than 6 months after the procedure. These criteria are unreliable and could inaccurately inflate the success rate reported by 15% or more.

Authors	No. of Patients	Balloon Size	Method of Incision	Stent Size (Fr)	Stent Duration (wk)	Overall Success Rate (%)	Average Follow-up (mo)
Balloon Dilation							
Banner and Pollack (19)	44	4 mm		7–10	4 days–12 wk	48	—
Chang et al. (41)	11	5–8 mm		8–16	4–8	88	10
Johnson et al. (170)	13	4–10 mm		5–16	2 days–mo	69	3–21
Lang and Glorioso (216)	127	4–6 mm		7–10	3–6	50	—
O'Brien et al. (268)	20	4–6 mm		—	—	60	17
Beckman et al. (23)	17	4–8 mm		7–10	4–8	82	15
Kramolowsky et al. (203)	20	5–10 mm		6–12	6	64	—
Netto et al. (261)	19	4–6 mm		8.5	2–8	53	—
Osther et al. (276)	37	10 mm		7	4–6	90	29
Total	**308**	**4–10 mm**		**6–11**	—	**67%**	—
Endoureterotomy							
Eshghi et al. (88)	40		Cold knife	6–10	4–6	88	—
Schneider et al. (318)	12		Cold knife	14	3–6	71	15
Chandhoke et al. (40)	8		Electrosurgical cutting balloon	7/14[a]	4	75	4
Cohen et al. (56)	6		Electrosurgical cutting balloon	7/14[a]	4–6	66	29
Preminger et al. (293)	40		Electrosurgical cutting balloon	7–7/14[a]	4–6	71	9
Wolf et al. (379)	38		Electrosurgical probe or cutting balloon	7–7/14[a]	4–6	82	28
Singal et al (335)	12		Holmium laser and balloon dilation	6/12	4–6	75	11
Total	**156**			**6–14**	**3–7**	**78%**	**4–29**
Surgical Repair							
Smith (338)	36		Surgical repair			97	
Kramolowsky et al. (203)	11		Surgical repair	5–7	2.5	91	21

[a]Endopyelotomy stent.

TABLE 19.3. MANAGEMENT OF URETERAL STRICTURES

Endoureterotomy, either endosurgical or fluoroscopic (i.e., cutting balloon), for middle and distal ureteral stricture disease appears to have good clinical results with success rates ranging from 66% to 88%. The overall success rate for 156 patients undergoing endoureterotomy is 78%, which appears to be better than the overall success rate of 67% noted for balloon dilation (Table 19.3). However, there is no apparent consensus on the ideal cutting modality used for the endoureterotomy. Cold-knife incision of the ureteral stricture appears to be as efficacious as electrosurgery and Ho:YAG laser in performing endoureterotomy (40,293,318,335). Figenshau and colleagues (95) investigated the acute tissue changes occurring in the pig ureter following balloon dilation (5 mm), cutting balloon, and endoscopic incision with a cold knife, Nd:YAG laser, or electrocautery as endosurgical management of ureteral strictures. This study used small 250- and 660-micron electrocautery probes. There was no significant difference in the degree of tissue injury among the various cutting modalities used except for the larger 660-micron electrosurgical probe. Unlike a ureteral incision balloon, dilation resulted in injury to the lamina propria but did not appear to split the muscularis and adventitial layers.

The optimal stent size and duration of stenting remain undetermined. Animal studies have shown that for middle ureteral stricture, the larger size stent (i.e., 14 Fr) provides similar results to a 7-Fr stent (247). Similarly, Kerbl and co-workers (187) could find no difference in the healing of ureteral strictures regardless of whether a 1-, 3-, or 6-week period of stenting was selected.

Although balloon dilation and endoureterotomy for ureteral strictures have impressive success rates, these do not

duplicate the very high 91% to 97% success rate achieved with open surgical repair of ureteral strictures (203,261). There may be several reasons for the discrepancies noted in these comparisons. The success of any treatment modality may depend on the length of the ureteral stricture, the cause of the stenosis, and the location of the stricture; until now, strictures of similar nature have not been studied in an effort to cull from the general category of ureteral stricture those strictures that would best respond to an endourologic approach.

Several investigators have noted that long ureteral strictures tend to be associated with poorer success rates despite the use of balloon dilation or endoincision. Beckmann and colleagues (24) noted that in 25 patients with strictures shorter than 2 cm, balloon dilation was successful in 84%. Conversely, among eight patients with strictures longer than 2 cm, dilation succeeded in only 50%. Chang and colleagues (41) and Netto and colleagues (261) separately concluded that strictures longer than 1 cm rarely responded well to balloon dilation. The same observation has been noted in the literature on the use of incision of ureteral strictures. Meretyk and colleagues (243) found that the best results following endoureterotomy were in those patients with strictures less than 2 cm. Schneider and colleagues (318) reported that the longest stricture they treated by cold-knife incision was 2.5 cm in length, and this patient reobstructed 24 hours after removal of the ureteral stent. Therefore it would appear appropriate to apply endosurgical management to only patients with strictures less than 2 cm in length.

The cause of the ureteral stricture also has a significant impact on the success of the endosurgical treatment results. The most common cause (23%) of ureteral stricture in the Meretyk series was postoperative fibrosis following open pelvic surgery or a ureteroscopic procedure (243). These relatively nonischemic strictures respond better to endosurgical treatments than do poorly vascularized strictures (19,41,216,243,318). Other causes of ureteral stricture include intrinsic inflammatory processes, such as schistosomiasis, tuberculosis, or radiation injury (82,170,193,261,299,328). The ischemic stricture associated with radiation responds poorly to endoureterotomy.

Extrinsic processes resulting in ureteral stricturing include retroperitoneal fibrosis, endometriosis, and retroperitoneal malignancies (170,243,261). Those processes causing extrinsic compression of the ureter do not respond to balloon dilation or incision of the ureter. As such, ureteral strictures secondary to retroperitoneal fibrosis are more appropriately managed by releasing the ureter from the retroperitoneal fibrosis and transposing it into an intraabdominal position or treating the underlying disease process.

Likewise, for ureteral strictures associated with a malignancy, a nephrovesical stent or endoluminal metal stent (i.e., Wallstent) or a permanent nephrostomy tube is indicated (62,226,263,286). Lopez-Martinez and colleagues (226) have used the nephrovesical stent in eight patients with metastatic prostate cancer. The average duration of stent patency was 19 months (range of 1 to 48 months). Five patients reobstructed because of recurrent tumor, and in two patients additional stents were telescopically placed. Three patients died of metastatic cancer with the stent *in situ.* Six patients at risk at 12 months had patent stents compared with 3 of 5 at 24 months, 2 of 2 at 36 months, and 1 of 1 at 48 months. Nissenkorn and Gdor (263) have used the nephrostomy-diverting stent in eight patients with metastatic prostate and invasive bladder cancer. With a mean follow-up of 5.5 months, the stents functioned well and eliminated the percutaneous nephrostomy during the terminal stages of the patients' disease.

The anatomic location of the ureteral stricture also has been cited as a factor affecting the success of endoureterotomy. Smith (338) showed that in a series of 28 patients with ureteral stricture disease, all 4 patients with a middle ureteral stricture failed balloon dilation. Similarly, Meretyk and colleagues (243) noted a 25% success rate for endourologic incision of middle ureteral strictures compared with an 80% success rate for distal ureteral strictures. Likewise, proximal ureteral strictures, specifically secondary UPJ obstruction, respond well (i.e., 80%) to an endoincision. As such, marsupializing one limb of the stricture into the bladder or renal pelvis appears to provide a better success rate than strictures in the middle ureter, which by definition remain bound by normal ureter above and below the treatment region.

Contrary to earlier reports, it now appears that the duration of a ureteral stricture before treatment has no significant effect on the success rate of the therapy. When the factors of stricture length, location, and cause are controlled, the duration of the stricture does not alter the ultimate outcome. Successful endosurgical therapy has been reported in strictures ranging from 8 weeks' to 18 months' duration (261).

Clearly, the success of endosurgical treatment depends to some extent on the previously described characteristics of the stricture: cause, length, and location. Unfortunately, rarely do study reports subdivide the patient groups according to their stricture characteristics. This factor, when combined with the inconsistencies of the technique of balloon dilation or endoincision and the variability in posttreatment stent size and stent duration, results in a significant amount of clinical confusion such that cumulative data on the endosurgical management of ureteral stricture can only be judged in the broadest anecdotal manner.

Meretyk and colleagues (243) have described the use of long-acting steroid injection and free urothelial grafts in the stricture region to improve the results of endoincision of ureteral strictures. Triamcinolone injection appears to be clinically beneficial in patients undergoing incision of urethral and bladder neck contractures (65,92). One of the actions of triamcinolone is to block collagen formation. In

three patients with recurrent stricture after endoscopic ureterotomy, Schmeller and colleagues (315) demonstrated that histologically the area of the ureterotomy consisted of collagen-rich connective tissue with few fibroblasts and a scarcity of smooth muscle fibers. Therefore the application of triamcinolone into the incised bed of the ureteral stricture may inhibit collagen formation and improve the success of endoureterotomy. Wolf and colleagues (379) demonstrated that a nonischemic etiology, more recent etiology (less than 24 months), shorter stricture (1 cm), use of a 12-Fr or larger stent, and injection of triamcinolone into the bed of the stricture were associated with better outcomes for ureteral strictures treated endosurgically.

Experimental results with free tissue grafts (i.e., tunica vaginalis) to repair the ureter have been inconsistent and complicated by hydronephrosis and graft sloughing (102,204,146). However, a free graft of bladder urothelium has worked well for urethral stricture disease (139) and could possibly be of value for ureteral replacement (124). In Urban's series, six patients underwent a free urothelial graft for ureteral strictures between 1.5 and 8 cm. Mean follow-up at 30 months revealed a patency rate of 83% (362). Presently, this time-consuming approach may be a reasonable procedure in high-risk surgical patients with strictures longer than 2 cm.

Several investigators have evaluated absorbable biocompatible materials as substitutes in the urinary tract (321). However, these have been unsatisfactory because of urine leakage, shrinkage of the repair site, and stone formation. Improvement in cell-culture techniques have enabled some investigators to create a monolayer of urothelial cells on synthetic graft materials before implantation (179). These studies are encouraging for improved cellular lining, prolonged patency, and selective permeability of the graft, but follow-up is limited and clinical trials have yet to be instituted. Cussenot and colleagues (62) reported on the use of a flexible, expandable, tantalum wire stent in the management of four patients with ureteral stricture disease. All of the patients had complicated pathology, including periureteral malignancy and several failed endourologic balloon dilation attempts. Radiographic and endourologic follow-up showed mucosal hyperplasia of varying intensity in all four patients and recurrent obstruction in three (75%). This hyperplastic reaction to metal stent implantation also has been observed in the human urethra. In contrast, Pauer and Lugmayr (286) used a self-expanding, stainless steel alloy, 7-mm stent (Wallstent) to treat ureteral obstruction secondary to a metastatic retroperitoneal tumor in 12 patients; an indwelling double-J stent was used during the first 4 weeks of Wallstent placement. Hyperplasia and edema of the urothelium was observed in all cases during the initial 4 weeks of stent placement; however, the hyperplasia appeared to resolve after the initial 4 weeks. However, during an average follow-up of 27 weeks, 87% of the stents remained open. Two patients developed encrustation of the stent after 30 weeks.

In conclusion, endourologic management of ureteral strictures has not acquired the same degree of acceptance as endourologic management of UPJ obstruction. Overall, the endosurgical management of distal and upper ureteral strictures less than 2 cm and not associated with radiation or other ischemic injury is highly successful and results in minimal morbidity. Also, failure to establish patency does not preclude a subsequent open reconstructive repair. Strictures longer than 2 cm and those associated with radiation or ischemic injury or a middle ureteral location may be managed more appropriately by open reconstruction because of the high failure rate associated with this group of patients treated endosurgically. Further clinical studies are necessary to determine the long-term feasibility and success of adjuvant therapy, such as triamcinolone injection and free urothelial grafting.

Ureteroenteric Strictures

Ureteroenteric strictures are a late complication of urinary diversion. There is no predilection to the type of urinary diversion and the rate of development of stenosis at the ureteroenteric anastomosis, which ranges from 4% to 8% (128,316). The mechanism of stenosis is usually idiopathic. Compression of the ureter by recurrent tumor or inflammation secondary to radiation therapy is a rare cause of late stricture formation. The patient with ureteroenteric stenosis may have flank pain, urinary tract infection, sepsis, or fever. However, these strictures often may be asymptomatic, thereby leading to permanent renal damage. For this reason, it is important to follow urinary diversion patients annually with routine evaluation of the upper urinary tract to obviate silent, slowly developing, renal obstruction.

The standard therapy for a ureteroenteric anastomotic stricture is usually exploratory laparotomy and revision of the ureteroenteric anastomosis with reimplantation of the viable ureter into the conduit. The development of percuta-neous nephrostomy drainage and external ureteral stents initially provided a therapeutic alternative to the surgical approach, especially in patients with recurrent malignant disease (304,339). However, chronic nephrostomy tubes and ureteral stents are associated with considerable morbidity and must be exchanged at regular intervals to minimize the risk of obstruction (253,371). As such, in patients without recurrent cancer, this approach is only of a temporizing value. In 1979, Smith and colleagues (339) reported endoscopic dilation of ureteroileal strictures with Teflon dilators and insertion of a Gibbons ureteral stent. Subsequently, in 1988, Kramolowsky and colleagues (202) treated nine patients with ten ureterointestinal strictures with either balloon dilation or an endoureterotomy, followed by stent removal.

Technique

It is important to completely assess the patient with regard to the etiology of the ureteral anastomotic stricture and the

location and extent of the stenosis before embarking on the endosurgical manipulation. As such, a CT scan and renal scan are helpful. If the stricture is complete or secondary to recurrent malignancy, the objective of endourologic therapy is to establish a retrograde external ureteral catheter, which may be changed on an outpatient basis every 12 to 16 weeks. If the stricture is totally occluding the ureter, a nephrostomy tube can be placed for a 4- to 6-week period. If, despite optimal drainage, the function of the affected kidney remains below the 15% level, nephrectomy may be the next best step provided the contralateral kidney is normal. Likewise, if the patient has evidence of urosepsis, a nephrostomy tube should be placed immediately.

For benign, partial ureteroenteric anastomotic obstruction of a well-functioning kidney, the goal is to reestablish a permanent, nonstinted, patent ureteral conduit. A percutaneous nephrostomy is placed. An antegrade ureterogram is performed in combination with a loopogram to determine the extent of the stenosis. The ureteroenteric stricture may be approached from an antegrade or a retrograde access or from a combined antegrade and retrograde approach.

The antegrade approach is commonly used for balloon dilation of the stricture. The patient is placed in a flank position, with the affected side superior. Both the stoma and flank are prepared and draped. Percutaneous access is easily established because the kidney is commonly hydronephrotic. After the percutaneous nephrostomy has been established, a guidewire is manipulated antegrade through the dilated UPJ and down the ureter. If the guidewire does not easily pass through the region of stenosis, a 5-Fr angiographic catheter is placed over the guidewire. The guidewire is exchanged for a Terumo guidewire, which because of its lubricity can usually pass through even the tightest stricture. The 5-Fr angiographic catheter is then advanced over the Terumo guidewire across the stenosis and into the conduit loop. The Terumo guidewire is then exchanged for a 260-cm exchange guidewire. A flexible cystoscope is passed into the conduit through the stoma, and grasping forceps are used to retrieve the end of the exchange wire from the stoma. The 5-Fr angiographic catheter is removed. An 8-mm, 4-cm-long, 7-Fr ureteral dilating balloon catheter is passed over the through-and-through guidewire under fluoroscopic control until it straddles the stricture. The balloon of the catheter should be rated to a minimum of 15 atm of pressure. A pressure syringe (i.e., LeVeen type) with an in-line pressure gauge is attached to the balloon inflation port and used to slowly inflate the balloon with a 50:50 contrast and saline mixture. The inflation is continued until the waist in the balloon at the level of the stricture disappears. The balloon is left inflated for 1 minute and deflated. This cycle of inflation followed by deflation may be repeated once or twice.

Following completion of the balloon dilation, the dilating catheter is removed. A 10- to 16-Fr nephroureteral stent is then placed antegrade, or preferably a single pigtail 12-Fr biliary urinary drainage catheter can be placed retrograde. The latter has sideholes only in the stent coil, which resides in the renal pelvis; the butt end of the tube exits the conduit stoma. A 2-0 Prolene suture is used to secure the shaft of the stent to the peristomal skin. The patient's urine collection device is passed over the end of the stent and secured in the usual manner to the peristomal skin. If a retrograde stent is placed, an 8- or 10-Fr nephrostomy tube also is positioned. On postoperative day 2 or 3, a nephrostogram may be performed, and if the collecting system is intact, the nephrostomy tube is removed. The nephrostent or retrograde ureteral stent is removed 4 to 8 weeks postoperatively.

Retrograde balloon dilation of ureteroenteric strictures also may be performed. However, this may be more difficult than an antegrade approach. Flexible cystoscopy of the conduit is performed through the stoma. If a nephrostomy tube is in place, indigo carmine–stained saline can be instilled to help identify the narrowed ureteroenteric anastomosis. Via the cystoscope, a Terumo guidewire is inserted into the ureter and advanced under direct endoscopic and fluoroscopic control. Once coiled in the renal pelvis, a 5-Fr angiographic catheter is passed over the guidewire through the strictured region and into the upper collecting system. The Terumo guidewire is exchanged for a 0.035-inch Amplatz superstiff guidewire, and the 5-Fr angiographic catheter and the cystoscope are removed. An 8-mm, 4-cm-long, 7-Fr ureteral dilating balloon catheter is passed over the guidewire until the balloon straddles the region of the stricture fluoroscopically. The same technique of balloon dilation and retrograde stent placement described for the antegrade approach is used for the retrograde approach (i.e., sideholes only in the renal pelvic coil of the stent). An indwelling ureteral stent should not be used because it may become occluded with mucus. This scenario may result in obstruction and fatal urosepsis (371). The stent is removed 4 to 8 weeks postoperatively under fluoroscopic guidance; a retrograde ureterogram is obtained.

Endoincision of a ureteroenteric stricture carries with it the risk of an inadvertent enterotomy or significant hemorrhage. Therefore these patients should receive a complete mechanical and antibiotic bowel preparation preoperatively. If the bowel is appropriately prepared, an enterotomy may be managed conservatively with an external ureteral stent and an elemental diet. In the situation of significant bleeding, an open procedure may be necessary; if the patient is stable, revision of the ureteroenteric anastomosis may be performed at the same time. In general, a left ureteral stricture that extends more than 1 cm above the ureteroenteric anastomosis site is a contraindication to an endoincision.

The endoscopic incision of the ureteroenteric stricture also may be approached in an antegrade or a retrograde fashion. In either case, the patient is placed in the flank position with the affected side superior, and both the stoma and posterior flank are prepared and draped.

To perform an antegrade endoincision of a ureteroenteric stricture, an 18-Fr nephrostomy tract should be established

in a middle or upper posterior calyx to provide straight-line access to the affected distal ureter. The flexible 7.5- or 9.4-Fr ureteroscope, or 15-Fr nephroscope, is inserted through the nephrostomy tract into the renal pelvis, and under direct visualization the endoscope is delivered to the stricture. A 0.035-inch Terumo guidewire is visually passed through the stricture and into the conduit. A flexible cystoscope is passed via the conduit stoma and is used to retrieve the end of the Terumo guidewire. The flexible ureteroscope or nephroscope is removed, and a 5-Fr angiographic catheter is passed fluoroscopically over the Terumo guidewire until the tip is through the conduit. The Terumo guidewire is exchanged through the 5-Fr angiographic catheter for a 0.035-inch, 260-cm exchange guidewire. The 5-Fr angiographic catheter is removed. A 6- or 8-mm, 7-Fr ureteral dilating balloon catheter is passed retrograde over the guidewire until the balloon straddles the stricture. The balloon is inflated with dilute radiographic contrast solution stained with indigo carmine, using a pressure syringe (i.e., LeVeen type) with an in-line pressure gauge, to 1 atm. With the balloon inflated, the flexible endoscope is introduced antegrade, and a 2- or 3-Fr straight-tip or right-angle electrosurgery probe is passed through the endoscope. A right-angle electrosurgery probe allows for highly accurate stricture incision. An incision is made in the ureter alongside the balloon using 50 to 100 W of pure cut energy. The incision is extended distally until the conduit is entered; the cut is made through the full thickness of the ureter until retroperitoneal fat can be seen. The ureteral dilating balloon should now expand to its full size; if the balloon was punctured during the incision, it is removed and replaced with a 10-mm nephrostomy dilating balloon. Visually and fluoroscopically, the balloon is positioned across the region of the incision. If the incision in the stricture is successful, the balloon should fully inflate at 1 to 2 atm without any evidence of a waist. If the scar tissue of the incised ureteral stricture appears to be particularly dense and no fat is seen, 3 to 5 mL of triamcinolone (40 mg/mL) may be injected into the bed of the incised stricture using a 3-Fr Greenwald needle mounted on a flexible shaft. A LeVeen pressure syringe is used to perform the injection into the dense scar tissue.

The balloon catheter and flexible endoscope are removed. A 12-Fr retrograde single pigtail catheter with sideholes only in the pigtail is inserted retrograde into the upper collecting system; the butt end of the catheter exits the stoma. A 14-Fr nephrostomy tube is inserted into the renal pelvis. A nephrostogram is performed on postoperative day 1 or 2, and if the collecting system is intact, the nephrostomy tube is removed. The external ureteral stent is maintained for 4 to 8 weeks postoperatively.

Retrograde endoincision is performed under direct vision with the Sachs urethrotome, 12-Fr, short, rigid therapeutic ureteroscope, or 15-Fr flexible cystoscope. The endoscope is inserted alongside the guidewire. An 8-mm ureteral dilating balloon catheter is passed retrograde, until the balloon straddles the area of the stricture. The balloon is inflated with 50:50 contrast material and saline in a pressure syringe (LeVeen type) with an in-line pressure gauge, to 1 atm pressure to delineate the stricture fluoroscopically. The balloon is then deflated and the area of the stricture is incised using a cold knife through the rigid ureteroscope. Alternatively, the balloon may be left inflated, and a 2- or 3-Fr straight-tip or right-angle Greenwald electrode may be used through the ureteroscope or flexible cystoscope to incise the ureter alongside the balloon. The incision should be extended through the full thickness of the ureter; ideally, periureteral fat should be seen. The incision is extended cephalad until the dilated normal ureter is identified. The ureteroscope is withdrawn and the 8-mm balloon is reinflated to confirm that the ureter is widely patent. A 12-Fr single pigtail ureteral catheter is passed retrograde as previously described. If on postoperative day 2 a nephrostogram shows no evidence of extravasation, the 8-Fr nephrostomy tube is removed. The retrograde catheter is removed 4 to 8 weeks postoperatively.

If the ureteroenteric obstruction is complete, a combined antegrade and retrograde approach is necessary. In the combined approach, the rigid endoscope is passed through the conduit, and the flexible ureteroscope or flexible nephroscope is passed through the developed nephrostomy tract. When the tips of the two endoscopes are fluoroscopically close (less than 1 cm), the light from the antegrade endoscope is turned off. The endoscopist then seeks the light coming from the rigid retrograde endoscope lying within the conduit, which will appear as a bright pink light transilluminating the intervening tissue. The C-arm fluoroscope is used in two planes of projection to further confirm the close alignment of the tips of the two endoscopes. At this point a cut-to-the-light procedure can be performed as previously described for treatment of the completely obstructing ureteral stricture (253). Alternatively, the light of the antegrade endoscope can be sought via the retrograde endoscope; a retrograde incision is then made (Fig. 19.14).

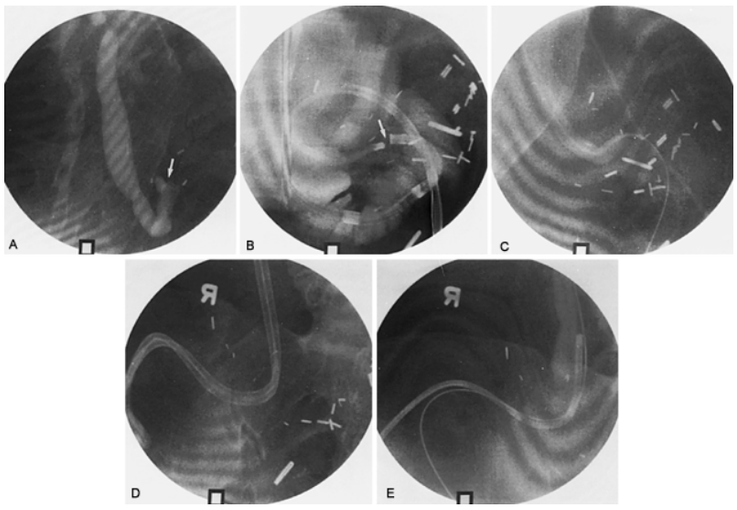

FIGURE 19.14. A: Right uteroenteric stricture *(arrow)* with moderate hydroureteronephrosis on antegrade nephrostogram. **B:** A flexible uteroscope has been passed antegrade to the level of the stricture. A flexible cystoscope is passed retrograde through the ileoconduit to the stricture. A cut-to-the-light technique is used by passing an electrosurgical cutting device through the cystoscope to incise the intervening stricture *(arrow).* **C:** After incising the stricture, a guidewire is passed antegrade and retrieved by the cystoscope to establish a through-and-through guidewire across the region of the stricture. **D:** A stent is then placed. In this case, two 7-Fr single pigtail catheters have been placed across the region of the incised stricture. Note: there are no sideholes in the shaft of the stents; the drainage holes are only in the pigtail portion. **E:** At the time of stent removal, ureteroscopy is performed through the ileal conduit to confirm patency of the incised stricture.

Once a guidewire has been established across the area of the stricture, the incision can be extended using an antegrade or retrograde technique to complete the endoincision. This incision should be performed slowly under direct endoscopic control to avoid inadvertent injury to an underlying artery or segment of bowel.

If the bowel is entered, a 10-Fr ureteral pigtail catheter is placed across the area of incision and into the renal pelvis. The fistula will usually close spontaneously over several weeks with the patient on an elemental diet (244). If an artery is incised, there will be immediate hemorrhage; a 10-mm balloon catheter or a Kaye catheter can be passed over the through-and-through guidewire to straddle the region of the incision, and the balloon is inflated to tamponade the bleeding site. The balloon can usually be deflated 2 days later. If bleeding recurs, the balloon is reinflated, and

angiography followed by selective embolization or an open surgical repair is performed. If there is no bleeding, the balloon is exchanged for a 12-Fr single pigtail retrograde external ureteral catheter.

Results

The reported experience with ureterointestinal strictures is even more limited than that of UPJ and ureteral strictures. The largest single-center series used balloon dilation to treat 37 ureteroenteric anastomotic strictures in 29 patients (329). Most of these patients had undergone cystectomy and diversion for bladder or uterine/cervical carcinoma and had received adjuvant radiation therapy before cystectomy. All but three patients underwent diversion to an isolated segment of terminal ileum; in the remainder, a colon conduit was created. All of the ureteroenteric strictures were dilated in an antegrade fashion using a 4- to 10-mm dilating balloon catheter. The goal of the dilation was to eliminate the waist in the balloon at the area of the stricture; this required between one and three inflations at the same procedure. The balloon was left inflated for 1 to 2 minutes. Most of the ureters were stinted with an 8.3- or 10-Fr stent, although six ureters had stents ranging in size from 14 to 24 Fr. The stents were placed retrograde following the dilation and were maintained for 1 to 6 weeks. In short-term follow-up, only 30% of the cases were considered to be clinical successes. At 1 year of follow-up, only 6 of 37 strictures (16%) were patent. Half of the successful cases subsequently required repeat dilation and stent placement to maintain ureteral patency; these late restenoses occurred between 14 and 73 months following the initial dilation.

These investigators were unable to identify distinguishing or predictive factors for success of balloon dilation of the ureterointestinal anastomotic strictures.

Several other investigators have reported on balloon dilation of ureterointestinal anastomotic strictures (6,24,41,170,268) (Table 19.4). There does not appear to be any consensus as to the size of dilating balloon to use, the size of the ureteral stent to place following the dilation, or the duration of stent placement. In these other series, the success rates for balloon dilation of ureterointestinal strictures range from 16% to 67%. Among all series, the overall average success rate was 29% at an average follow-up of 14 months. Of note, the highest success rate of 67% occurred among pediatric patients with a conduit and a benign etiology of the stricture (6). Many of these reports had short-term follow-up (less than 12 months) of their patients, and as Shapiro and colleagues (329) have demonstrated, longer follow-up significantly decreases the initially favorable results (Table 19.4).

Authors	No. of Patients	Balloon Size	Method of Incision	Stent Size (Fr)	Stent Duration (wk)	Overall Success Rate (%)	Average Follow-up (mo)	Complications
Balloon Dilation								
Chang et al. (41)	8	5–8 mm		8–16	4–6	50	20	0
Johnson et al. (170)		4–10 mm		5–16	2 days–mo	43	3–21	0
O'Brien et al. (268)	6	4–6 mm		—	—	17	12	—
Shapiro et al. (329)	37	4–10 mm		8–24	1–6	16	12	1 urosepsis
Beckman et al. (23)	5	4–8 mm		7–10	4–8	60	22	0
Aliabdi et al. (6)	3	6–8 mm		—	6	67	12	0
Total	**66**	**4–10 mm**		**5–24 Fr**	**1–8 wk**	**29%**	**14 mo**	**2%**
Endoincision		**Approach**						
Meretyk et al. (244)	19	Antegrade	2–5 Fr electrosurgery probe	18–20	3–6	57	29	1 ureteroenteric fistula
Cornud et al. (59)	9	Antegrade	7 Fr sphincterotome	18	8	67	8	1 urinoma
Ahmadzadeh (5)	5	Antegrade	3 Fr needle electrode	7	4	60	14	1 peritoneal urine leak 1 fever
Germinale et al. (109)	9	Antegrade and Retrograde	Balloon dilation and electrode (2) or cold knife (2)	10	8	45	12	0
Chandhoke et al. (40)	3	Antegrade	Electrosurgical cutting balloon	14	4	33	4	1 ureteroarterial fistula
Wolf et al. (379)	30	—	Electrosurgical probe or cutting balloon	7–16 Fr	4–6	50	23	1 blood transfusion, 1 sepsis 3 febrile UTI, 1 lacerated iliac artery
Singal et al. (335)	9	—	Holmium laser and balloon dilation	6/12	4–6	75	11	0
Lin et al. (224)	9	—	Electrosurgical cutting balloon	10	6	30	24	0
Total	**74**	—	—	**10–20 Fr**	**3–8 wk**	**52%**	**16 mo**	**10%**
Surgical Repair								
Kramlowsky et al. (202)	7 (9 strictures)	—	—	7–8 F	—	89	33 mo	1 peritoneal urine leak 1 conduit enterotomy 1 bowel resection caused by enterotomies

UTI, urinary tract infection.

TABLE 19.4. ENDOUROLOGIC MANAGEMENT OF URETEROINTESTINAL ANASTOMOTIC STRICTURE

The experience with endosurgical incision of the ureterointestinal anastomotic stricture also is limited. This procedure may be performed in an antegrade or a retrograde fashion, although most investigators have used the antegrade technique (5,40,59,109,224,335,379).

The largest single-center study was reported by Wolf and colleagues (379) and consisted of 30 ureterointestinal anastomotic strictures in 25 patients. Most of the patients (26 of 30) had an ileal conduit for transitional cell carcinoma or cervical carcinoma. Of 30 strictures, 16 occurred less than 24 months and 13 occurred more than 24 months from the time of the diversion procedure. A variety of approaches to the endoureterotomy were taken, including antegrade, retrograde, and combined antegrade and retrograde. The success rates of endoureterotomy for ureteroenteric strictures at 1, 2, and 3 years were 72%, 51%, and 32%, respectively. There was an improved outcome for right rather than left strictures (68% versus 17% 3-year success rates, respectively) and for strictures treated less than 24 months after the etiologic insult (37% 3-year success rate compared with 27% for those treated longer than 24 months after the insult). Stricture length, diameter, and previous treatment did not alter the results. Those strictures that were amenable to treatment in a purely retrograde fashion, as opposed to those requiring an antegrade or combined approach, tended to have a better outcome (75% and 18% 3-year success rates, respectively). More favorable results were also noted with the use of 12-Fr or larger stents (38% compared with 0% 3-year success rate when using smaller stents) and stinting longer than 4 weeks (35% compared with 26% 3-year success when stinting 4 weeks or less). The use of triamcinolone did not appear to affect the results. One of the patients in this series had a major postoperative complication. During incision with the cutting balloon device, a left ureteral–left iliac artery fistula was created. The bleeding was controlled with a high-pressure, 10-mm tamponade balloon catheter in the ureter. Angiography confirmed the presence and location of the fistula. Open surgical management was required. Overall, use of the cutting balloon for ureterointestinal strictures is advisable only if the stricture is at the ureteroenteric site and if initial attempts at an endoscopic incision have been unsuccessful.

Additional reports in the literature have shown an overall success rate of 52% for endoincision of the ureterointestinal anastomotic stricture (Table 19.4). A variety of cutting modalities have been used, including electrosurgical, cold knives of various sizes and configurations, and Ho:YAG laser (5,59,109,335,379). Following the endoincision, all patients have been stinted (10 to 20 Fr) for 3 to 8 weeks postoperatively. Kramolowsky and colleagues (202) compared their nine patients who underwent open surgical revision of a ureteroenteric stricture with their six patients who underwent endoscopic incision and balloon dilation of a ureterointestinal stricture. The ureter was patent with no ureteral stent in 89% of the patients treated with open surgical revision at 33 months and in 71% of patients undergoing the endoscopic incision at 18 months. Although the endoscopic procedure was less successful than the open surgical revision, it was associated with a significantly shorter hospitalization, decreased blood loss, reduced patient discomfort, and decreased cost compared with the open surgical procedure. Although the standard open surgical revision of a ureteroenteric anastomotic stricture is usually successful, it can be difficult to perform because of surrounding scar tissue or previous radiation therapy, making intraoperative and postoperative morbidity significant. Postoperative complications can occur in 30% of the open-surgery patients, and these problems often necessitate reoperation (202). Many patients with ureterointestinal strictures are poor surgical candidates because of age, longstanding urosepsis, or renal insufficiency. As such, the endoscopic incision of the ureterointestinal stricture provides a less invasive, less morbid approach that is successful in alleviating the problem in as many as 75% of otherwise surgical candidates (335).

In patients with known metastatic disease, the endoscopic approach allows placement of an external stent for drainage purposes. This may facilitate optimization of the patient's renal function before chemotherapy. All stents used in a ureterointestinal unit should have side drainage holes present only in the portion of the stent in the renal pelvis and at the end where the stent exits the stoma. No holes should be placed along the catheter where it traverses the conduit to preclude mucous obstruction and possible fatal urosepsis (371). Stents should be changed every 3 to 4 months as an outpatient procedure under fluoroscopic control.

Transitional Cell Cancer of the Ureter

Primary transitional cell carcinoma of the ureter (TCCU) represents only 2% of all urothelial malignancies seen in the urinary tract. Patients most commonly have hematuria,

flank pain, or urinary frequency and dysuria, although lower abdominal mass, fever, or weight loss may be the presenting complaint. Batata and colleagues (20) demonstrated that 65% of ureteral cancer patients have cancer in other parts of the urinary tract concurrent with or before or after a diagnosis of ureteral cancer. The most common malignancy of the ureter is transitional cell carcinoma (93%); rarely, squamous cell carcinoma (5%) or mucoid adenocarcinoma (2%) may occur in the ureter. Most ureteral tumors occur in the distal ureter (65%), followed by the middle (17%) and upper (12%) ureter; the entire ureteral length is affected by malignancy in 7% of ureteral tumor patients (8).

Several investigators have evaluated prognostic factors in carcinoma of the ureter (30,140). As with transitional cell carcinoma of other areas of the urinary tract, ureteral transitional cell carcinoma has an excellent (greater than 90% survival rate at 5-year follow-up) prognosis if it is well differentiated and confined to the mucosa. Eighty-two percent of patients without muscle-invasive tumor survive 5 years. However, dissemination of the carcinoma into regional lymph nodes or beyond results in a 10% patient survival 5 years from the time of diagnosis. Local extension of the tumor into the periureteral tissues also has a poor prognosis, with only 29% of patients surviving 5 years (20,234).

The accuracy of clinical diagnosis of TCCU becomes crucial in predicting the patient's prognosis and determining the most appropriate therapy. Batata and colleagues (20) showed that 72% of ureteral tumors could be diagnosed reliably radiographically by intravenous pyelography (19%), retrograde urography, or ureteral catheterization (53%). However, that leaves more than one-fourth of the patients with indeterminate radiographic studies. Neither urine cytology nor flow cytometry is consistently reliable in diagnosing transitional cell carcinoma of the upper urinary tract. Although high-grade tumors often have an associated abnormal cytology, negative urine cytology is seen in as many as 10% of patients with high-grade lesions and in up to 60% of patients with low-grade lesions (310). Flow cytometry measures cellular DNA and RNA content. A false-negative flow cytometry may be seen in 66% of superficial papillomas and in 8% of invasive cancers (242). Blute and colleagues (31a) showed that imaging studies and cytology together correctly diagnosed a ureteral tumor in only 52% of 21 patients who eventually were found to have a ureteral malignancy.

In 1929, Young (381) performed the first recorded ureteroscopic examination when he inserted a pediatric endoscope into a dilated ureter and passed it up to the level of the renal pelvis in a child with posterior urethral valves. Fifty years later, Lyon and colleagues (229) reported on their experience with endoscopy of the distal ureter using pediatric instruments. Subsequently, Perez-Castro and Martinez-Pineiro (289) created the first custom-built ureteroscope; they described their experience in ureteroscopy, including initial examination of the ureter to the level of the renal pelvis in both men and women.

First-generation rigid ureteroscopes were developed with the goal of visualizing the distal ureter and generally measured 20 cm long with a diameter of 13 to 14.5 Fr. As indications were extended into the middle ureter, proximal ureter, and renal pelvis, working lengths increased and endoscope diameters decreased. Presently, rigid ureteroscopes are available in 6.9 Fr with working lengths up to 40 cm; these diminutive endoscopes also incorporate single (4 to 5 Fr) or dual (2.3 and 3.4 Fr) working channels to allow simultaneous passage of instruments and effective irrigation. Subsequently, flexible ureteroscopes with active deflection up to 180 degrees and a diameter of 7.5 Fr have been developed. The working channel size in these endoscopes is smaller (3.6 Fr) than in their rigid counterparts, hence the irrigant must be pressurized when using diagnostic or therapeutic instruments.

Presently, the indications for diagnostic ureteroscopy include radiographic filling defects or obstruction, unilateral malignant urinary cytology, or macroscopic, essential lateralizing hematuria (149). The indications for ureteroscopic treatment of upper tract tumors are less well defined.

Technique

Ureteroscopy is an adjuvant procedure in the diagnostic evaluation of the patient. Therefore all patients should have preprocedural evaluations, including a thorough history, physical examination, and radiographic evaluation. The urethra and bladder must be examined carefully with the cystoscope to eliminate the possibility of a lower tract tumor. If this is present, it should be resected and the surgical site allowed to heal completely before manipulation of the upper urinary tract to reduce the potential risk of tumor seeding and implantation (341).

The technique for ureteroscopy in patients with suspected upper tract TCCU involves no use of an initial ureteral guidewire to avoid inadvertent injury to the collecting system (259). The procedure is initiated by passing a small-caliber (6.9-Fr), short, rigid ureteroscope to study the distal ureter and rule out any pathologic condition. Through the ureteroscope, a guidewire is advanced to the uppermost point to which the 6.9-Fr ureteroscope was advanced, and the short rigid ureteroscope is removed. A small-caliber, actively deflectable flexible ureteroscope is passed over the guidewire and into the ureter under fluoroscopic guidance, being careful not to push the guidewire any higher in the ureter. If upper tract biopsies are anticipated, it is helpful to place a ureteral access sheath to the level of the ureter visualized with the rigid ureteroscope. This facilitates subsequent placement of the flexible ureteroscope, through the distal ureter, into the upper collecting system. In addition, following biopsy of a lesion, the ureteroscope can be removed without having to pull the biopsy device through the endoscope, which may shear off the tissue of the specimen within the scope. Multiple biopsies can be performed because the flexible ureteroscope

can be easily reintroduced into the collecting system through the access sheath. Once the flexible ureteroscope is positioned at the upper level of the already examined ureter, the guidewire is removed. With the availability of smaller-caliber ureteroscopes, dilation of the distal ureter usually is not necessary.

Proximal ureteroscopy is performed, followed by examination of the renal pelvis. Systematic evaluation of the upper-, middle-, and lower-pole calices, in that order, is performed. This procedure prevents confusion due to contusion of the mouth of the upper-pole infundibulum caused by passive deflection of the shaft of the endoscope against this area during inspection of the lower-pole calices. Nonionic contrast medium is injected under fluoroscopic guidance to verify endoscopic entry into all calices of the renal collecting system. If a lesion is identified, its location is marked on the fluoroscope screen. After complete inspection of the collecting system, the lesion is addressed. The lesion is then biopsied by passing a 3-Fr biopsy forceps or a 3-Fr basket through the ureteroscope. The latter is twirled into the lesion and then closed; as it is withdrawn, the entrapped papillary fronds are detached from the tumor.

Brush biopsy catheters for the flexible ureteroscope are also available and may be of value if the biopsy material is not adequate. It is helpful to place a ureteral access sheath to facilitate passage of the flexible ureteroscope and removal of the biopsy specimen. After removal of the biopsied material, a 2- or 3-Fr electrosurgical probe or a 200- to 400-micron Nd:YAG laser probe (20 W) may be used to fulgurate the area; alternatively, if a large 12.5-Fr, rigid ureteroscope is being used, a resectoscope loop can be used to resect the tumor down to ureteral muscle (Fig. 19.15) (99). Last, the flexible endoscope is advanced into the renal pelvis, and the collecting system is systematically examined for any additional occult tumors. The aspirate and biopsy specimens should be sent immediately to the cytopathology laboratory, where they are evaluated by smear and cytospin. When any tissue fragments are visible in the specimen, a cell block is prepared.

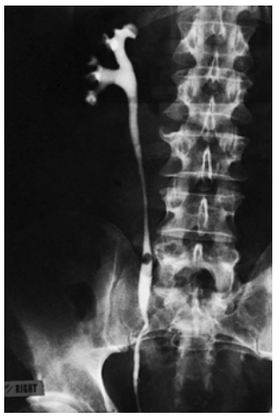

FIGURE 19.15. This midureteral filling defect is a low-grade transitional cell cancer. The diagnosis and therapy both were completed using the ureteroscope. Follow-up over 2 years revealed no recurrence.

Following resection of the primary tumor, a withdrawal retrograde ureterogram should be performed to assess extravasation. The ureteroscope is removed, and an indwelling ureteral stent is inserted over the safety guidewire; a urethral catheter is also placed. If there is no extravasation, the urethral catheter is removed on the first postoperative morning. The ureteral catheter is removed 3 to 5 days later as an outpatient. In the event of extravasation, the urethral catheter is maintained for 2 or 3 days, at which time a cystogram is performed. When the extravasation has resolved, the urethral catheter may be removed. The ureteral stent is left in place for 4 to 6 weeks.

Results

Grasso and Bagley (121) used the small-diameter, actively deflectable, flexible ureteroscope to investigate 584 patients suspected to have urothelial malignancies. They were able to successfully complete the ureteropyeloscopy in 94% of the patients. Ureteral dilation was required in only 12% of procedures. Lower-pole access required secondary or passive deflection in 60% of procedures. Keeley and colleagues (185) performed diagnostic ureterorenoscopy in 92 consecutive patients with upper tract transitional cell carcinoma. Fifty-one open surgical procedures were subsequently performed, including distal ureterectomy in four and nephroureterectomy in forty-seven. Cytologic evaluation was positive for malignancy in 48 of 51 cases (94%). Grading of ureteroscopic specimens was possible in 42 cases (82%) (Table 19.5). Transitional cell carcinoma grade on ureteroscopy accurately predicted tumor grade and stage in the surgical specimens. There was no significant perioperative morbidity.

Authors	No. of Patients	Treatment	Adjuvant Therapy	Local Recurrance Rate (%)	Metastasis	Average Follow-up (mo)
Huffman et al. (153)	17	3 segmental ureterectomy	0	33	0	15
		14 ureteroscopic excision	0	36	0	16
Eastham and Huffman (83)	4	4 ureteroscopic excision	Mitomycin C 5 mg in 20 mL saline × 30 min	25	0	8
Elliott et al. (86)	23	8 ureteroscopy/Nd:YAG	0	39	9	58
		13 ureteroscopy/electrocautery	0			
		2 PCN/Nd:YAG	0			
Martinez-Pineiro et al. (233)	22	14 ureteroscopy/Nd:YAG	BCG/mitomycin/VAC, 5-FU not specified who received what treatment	57	Not specified	30
		6 ureteroscopy/electroresect		0		
		2 ureteroscopy/electrocautery		0		
Keeley et al. (185)	18	Ureteroscopy/Nd:YAG/Ho:YAG	Mitomycin 40 mg/3 doses via ureteral catheter	28	Not specified	35
Grasso et al. (122)	8	7 ureteroscopy/Nd:YAG	0	63	0	18
		1 ureteroscopy resection	0			
Total	**92**			**47**		**28**

TABLE 19.5. ENDOSCOPIC MANAGEMENT OF PRIMARY URETERAL TRANSITIONAL CELL CARCINOMA

The success of intravesical agents in the treatment of superficial transitional cell carcinoma of the bladder has motivated some investigators to apply these agents in the management of upper urinary tract tumors (83,185,233). Among these reports a variety of topical chemotherapeutic agents have been used, including bacille Calmette-Guérin (BCG), mitomycin C, thiotepa, and interferon-α_2. There has been no standardization to determine which patients receive this adjuvant therapy, although it tends to be given to patients judged to be at high risk for recurrence. The therapy is usually administered via a ureteral catheter, after retrograde pyelography has confirmed no extravasation and

good flow around the ureteral catheter. Keeley and colleagues (185) administered 40 mg of mitomycin C in three divided doses in the immediate postoperative period in 15 patients with no attributable toxicity. Seven patients received intravesical BCG with a ureteral stent in place; again with no significant toxicity. However, no attempt was made to randomize the patients; therefore little can be determined regarding the efficacy of either treatment.

A low-grade, low-stage ureteral tumor may be associated with urothelial dysplasia and carcinoma *in situ* in other areas of the ureter in 50% and 9% to 13% of cases, respectively (140). Bloom and associates (30) reported ureteral stump tumors in 4 of 10 patients (40%) with primary ureteral carcinoma who underwent nephrectomy and partial ureterectomy. Strong and colleagues (346) had 5 of 13 patients (40%) with ureteral stump recurrences following segmental ureterectomy or incomplete nephroureterectomy for primary ureteral carcinoma. Therefore, when management other than radical surgical excision is chosen for a patient with transitional cell carcinoma of the ureter, ongoing surveillance of the entire urinary tract is mandatory. In most situations, this should follow the same regimen that is used among bladder cancer patients. Specifically, ureteroscopic examination of the ureter should be performed every 3 months for 1 year, then every 6 months for 1 year, and then on an annual basis. Although intravenous or retrograde urography and cytology may be substituted for the endoscopic evaluation, these studies may be less accurate in detecting early, diminutive, low-grade recurrences.

Kerbl and Clayman (188) described a method of transurethrally unroofing the ureteral orifice in two patients undergoing endoscopic management of upper tract transitional cell carcinoma. At presentation, neither patient had a history of bladder tumor. By creating a widely patent ureteral orifice, the clinician could perform flexible ureteroscopy (10 Fr) in the office without the need for dilation of the intramural ureter, without oral or parenteral analgesics, and without postureteroscopy stent placement. The entire length of the ureter and all of the calyces could be completely examined in this manner. These two patients have been followed for over 5 years. One patient has had a small, recurrent, superficial, papillary lesion in the renal pelvis treated with electrosurgical fulguration 4 years after the initial procedure; pathologic evaluation was not performed on this lesion. The other patient has had three small upper tract recurrences. Both patients have had grade I to II pathologic stage A bladder tumors during the 5 years of follow-up and have received intravesical BCG or interferon therapy following transurethral resection of the bladder tumor.

Incision of the intramural ureter creates low-grade asymptomatic reflux. Guthman and colleagues (133) have shown that sterile reflux in the adult does not impair renal function or result in increased urinary tract infections. The primary concern is whether reflux will result in more frequent upper tract recurrences in these patients because of seeding from the lower tract. Some investigators have shown that among patients with recurrent bladder tumors and reflux, the incidence of upper tract tumors may be as high as 20% (7,254). Long-term, clinical follow-up will be necessary to study this hypothetical concern.

A significant concern with regard to endoscopic management of patients with transitional cell carcinoma of the ureter is the potential for tumor implantation or tumor seeding. Soloway and Masters (341) have shown in an animal model that disruption of the urothelial cell layer by cauterization increased implantation of transitional cell tumors by fourfold. During balloon dilation of the distal ureter and passage of the ureteroscope, abrasion of the urothelium may occur. Kulp and Bagley (208) reported on 13 patients, all of whom underwent ureteropyeloscopy with biopsy and treatment one to four times before nephroureterectomy for TCC of the renal pelvis. Only one patient had vascular-lymphatic extension, and because of the tumor growth characteristics, extension was suspected before endoscopy. This patient had no intravascular-lymphatic free cells or clumps of cells noted on the final pathologic specimen. There were no local recurrences in the follow-up of the remaining patients, at 3 months to 6 years (average of 34 months).

Ureteral perforation and subsequent retroperitoneal tumor implantation are a concern during ureteroscopy for TCCU. Perforation is more likely to occur with electrosurgical resection of the ureteral lesion than with excisional biopsy and Nd:YAG laser fulguration of the tumor base. However, to date in none of the reports of ureteroscopic management of primary ureteral transitional cell carcinoma has there been a case of retroperitoneal seeding documented during clinical follow-up up to 21 months (83,86,122,151,187,233).

Nephroureterectomy or distal ureterectomy remains the treatment of choice in most patients with TCCU. For patients with a solitary kidney, renal insufficiency, or medical illnesses rendering them poor candidates for an open surgical procedure, endoscopic modalities for treatment of upper tract transitional cell carcinoma are reasonable alternatives for management. However, the overall long-term (i.e., longer than 5 years) efficacy of these endoscopic modalities remains unproven. Continued long-term follow-up of patients with ureteral transitional cell carcinoma managed with ureteroscopic excision and fulguration is essential to delineate the effectiveness and long-term complications and cost of this minimally invasive procedure.

Benign Ureteral Fistulae

The ureter may be damaged easily during abdominal or pelvic surgery because of its proximity to the peritoneum. Gynecologic operations are the primary cause of iatrogenic ureteral injury. The incidence of these lesions ranges from 0.5% to 1% for common pelvic operations and up to 10% for radical pelvic surgery (80). Ureteroscopy also can result

in ureteral injury. In addition, ureteral fistulae to the peritoneal space, retroperitoneum, adjacent viscera, or skin may result from other benign (i.e., regional enteritis) disease. Perforation, resection, or ligation of the ureter leads to extravasation of urine, formation of a urinoma, and late development of ureterocutaneous or ureterovaginal fistulae. Many ureteric injuries are identified at the time of the surgical procedure and managed with repair or stinting without significant sequelae to the patient. Ureteric injuries that are not recognized intraoperatively or in the early postoperative period are complicated by periureteric fibrosis or epithelialization of the fistulous tract.

Technique

The approach to urinary fistulae is based on the principle that the urine must be diverted from the site of the extravasation. The placement of a percutaneous nephrostomy tube effectively diverts the urine away from the fistula; in addition, an indwelling ureteral stent, with sideholes only in the intrapelvic and intravesical pigtail, is positioned across the fistulous tract.

The stent may be passed antegrade or retrograde. The antegrade approach is performed more easily because of the dilation of the upper collecting system. If a guidewire cannot be manipulated across the ureter, a flexible ureteroscope can be passed antegrade, and the ureter can be cannulated under direct vision. Likewise, if a retrograde approach is chosen, ureteroscopy may be helpful to cannulate the ureter. Ureteroscopy is also helpful if the obstruction and fistula formation are the result of a prior surgical procedure. In this case, retrograde rigid ureteroscopy is advisable because any visualized obstructing suture can be incised with a ureterotome before placing a stent (198).

Results

Early diagnosis and treatment are key to the successful management of ureteral injuries. Endourologic techniques have a higher success rate when instituted as soon as possible following the ureteral injury (198). Successful endourologic treatment reduces the patient's hospitalization, incidence of complications, and postoperative discomfort. Placement of the ureteral stent seems to decrease stricture formation at the site of injury (212). Chang and colleagues (41) reported 12 patients with ureteral fistulae treated with percutaneous nephrostomy and 8- to 12-Fr ureteral stents. The stent was left in place for 4 to 6 weeks. In 10 of 12 patients (83%), the ureteral fistula healed without stricture formation or further intervention. One patient required continued stinting for recurrence of a pelvic malignancy. One patient had a persistent ureterovaginal fistula and required a psoas hitch and ureteral reimplantation. At the time of surgery, the ureter was noted to be angulated as a result of cicatrization and a chronic urinoma.

Malignant Ureteral Fistulae

The most difficult ureterovaginal or vesicovaginal fistulae to manage are those associated with incurable pelvic cancer. These patients often have been treated with radiation therapy, are terminally ill, and are not suitable candidates for open urinary diversion.

Technique

Nephrostomy tube drainage is usually instituted in these patients; although the drainage of urine is diminished, it is rarely stopped by this modality alone. Usually the ureter must be occluded to truly stop the leakage of urine. This can be accomplished with either of two antegrade approaches: electrocoagulation of the urothelium of the lower ureter or fluoroscopic placement of obstructing material in the distal ureter. Ureteral coagulation is performed through a flexible nephroscope introduced via the nephrostomy tract. Beginning approximately 6 to 7 cm below the ureteropelvic junction, the urothelium is circumferentially electrocoagulated using a 3- or 5-Fr round-tip or ball electrode. The procedure is continued until 4 to 5 cm of proximal ureter has been treated; the nephrostomy tube is then replaced. Alternatively, under fluoroscopic control, an antegrade angiographic catheter can be delivered to the fistulous site. A large sponge of Gelfoam (38 inches thick, 34 inches long, 14 inches wide) is instilled through the catheter; Gianturco coils also may be delivered to the fistulous site. These materials are superior to instillation of cyanoacrylate or placement of a detachable balloon for closing the ureter (129).

Results

Gunther and colleagues (130) first attempted to perform transrenal ureteral occlusion with the tissue adhesive butyl-2-cyanoacrylate. However, long-term follow-up showed that this substance softened in urine and was expelled by ureteral peristalsis. Subsequently, they adopted a detachable balloon filled with low-viscosity silicone rubber and released in the distal ureter (129). An advantage to the occlusion balloon is that the ureter is not irreparably destroyed should ureteral surgery or diversion become necessary at a later date. In their clinical report, five patients with urinary fistulae secondary to pelvic cancer and two patients with severe painful pollakisuria underwent ureteral occlusion with a detachable balloon (129). In all patients, urinary flow via the ureter ceased by ureteral balloon occlusion and combined nephrostomy drainage. Follow-up ranged from 1 month to 6 months. No complications occurred.

Kinn and associates (194) combined the insertion of nylon plugs with injection of polidocanol for ureteral occlusion in 15 patients with vesicovaginal fistulae. Urine leakage ceased in 73% of patients; however, the plug did migrate to

the renal pelvis in six patients and was associated with pyelonephritis in one patient. More recently, a high success rate has been attained using Gianturco coils in combination with gelatin sponge material to occlude the ureter (103).

Reddy and colleagues (300) described the technique of percutaneous ureteral fulguration for occlusion of the ureter combined with nephrostomy drainage in three patients with urinary tract fistulae secondary to pelvic cancers. In their report, three patients were treated with percutaneous ureteral fulguration and nephrostomy tube drainage for lower urinary tract fistulae secondary to advanced pelvic malignancy. All patients were completely dry at the fistula site 4 to 10 days following the ureteral fulguration. Follow-up ranged from 1 to 21 months with stable renal function and no complications.

Arterial Ureteral Fistulae

Arterioureteral fistulae are rare, with less than 40 cases reported in the literature (72). The primary clinical presentation is massive hematuria, which may result in shock and cardiovascular arrest. In many cases the hematuria did not become apparent until the time of ureteral stent removal. In a review of the literature, Dervanian and colleagues (72) found that 57.5% of the arterioureteral fistulae reported in the literature were associated with prolonged (average of 5.6 months) ureteral catheterization. They hypothesized that the stent may result in ischemia of the ureter as it crosses the iliac vessels, thereby resulting in localized necrosis of the ureteral and arterial walls. Other factors that may contribute to arterioureteral fistula formation include primary iliac artery disease (e.g., mycotic infection, aneurysm), prior iliac artery surgery (e.g., endarterectomy, prosthetic graft), pelvic neoplasm, radiation fibrosis, postsurgical ischemia of the ureter, and endoureterotomy. Patients with known common iliac artery disease are poor candidates for chronic indwelling ureteral stents. In these patients, a permanent nephrostomy or a nephrovesical stent is a safer alternative.

Technique

Among patients with a chronic indwelling ureteral stent, it is advisable to remove the stent over a guidewire. This ensures the urologist's control over the upper urinary tract. The immediate treatment of sudden onset of hematuria after stent removal is to pass a 5- or 8-mm ureteral dilating balloon catheter over the guidewire until the balloon straddles the area of the common iliac vessels. On inflation, the fistulous tract is effectively occluded, thereby allowing time to stabilize the patient with intravenous fluids.

Treatment of the arterioureteral fistula is by embolization and bypass or by direct surgical repair. These fistulae are amenable to embolization. However, careful coordination between the interventional radiologist and vascular surgeon is essential to avoid lower limb ischemia. The advantage of this approach is that a femoral-femoral bypass can be performed, thereby obviating a major transabdominal procedure. The direct surgical procedure involves management of the blood vessel by ligation and bypass, direct suture repair, or patch repair. The urinary tract involvement may be managed with nephroureterectomy, cutaneous ureterostomy, ureteral resection and anastomosis, or ureteral ligation followed by percutaneous nephrostomy. The choice of surgical procedure depends on the local tissue conditions and the patient's overall medical status. However, the least invasive therapy is to embolize the common iliac vessel, proceed with a femoral-to-femoral bypass, and place a percutaneous nephrostomy tube.

Results

If an arterioureteral fistula is suspected, arteriograms and retrograde pyelograms should be performed (Fig. 19.16). Of the 33 cases in Dervanian's report, direct visualization of the arterioureteral fistula by retrograde pyelograms occurred in 27% and by arteriography in 23% of the patients studied. The common iliac artery was most often involved (55%); other vessels involved were the internal iliac artery (9%), external iliac artery (6%), inferior mesenteric artery (3%), and iliac patch angioplasty or anastomosis site (30%). The right ureter was involved in 58% of the cases and the left ureter in 42% of cases. The mortality rate of arteriovenous fistulae is approximately 15%. Knowledge of this rare problem and its efficient management are essential for all urologists.

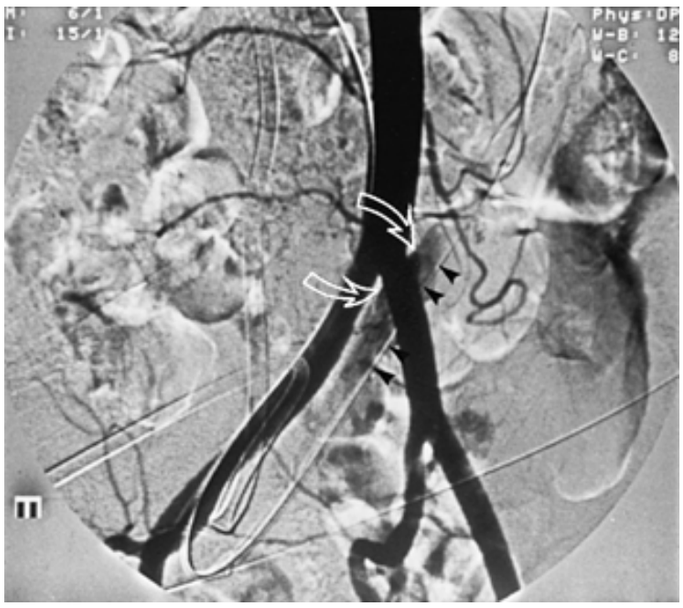

FIGURE 19.16. An arterial-ureteral *(curved arrows)* fistula is demonstrated on this flush aortogram. The arrowheads outline the ureter. This fistula developed 3 days following an endoureterotomy for a left ureteroenteric anastomotic stricture. This patient underwent an uneventful open repair of the left common iliac artery.

THERAPEUTIC RENAL APPLICATIONS

There are four areas in which endourology has a significant effect on the handling of noncalculous renal disease: obstruction, transitional cell cancer, cysts, and infection (e.g., abscess, fungal bezoar). In each of these areas, retrograde ureteroscopic and antegrade nephroscopic techniques are used. In this section, each of these four areas is reviewed from the standpoint of technique and results. Endourologic techniques as they apply to the transplant kidney are also reviewed.

Renal Obstruction

There are two types of stricture disease that affect the kidney: UPJ obstruction and calyceal abnormalities. In the latter category are the calyceal diverticulum and hydrocalyx.

Ureteropelvic Junction

Historical Aspects

Precedence in the surgical treatment of UPJ obstruction belongs to Friedrich Trendelenburg, who in 1886 performed the first recorded reconstructive procedure on the ureteropelvic junction. Unfortunately, the death of his patient probably tempered enthusiasm for this approach; it was not until 5 years later that Ernest Kuster accomplished a dismembered pyeloplasty unaccompanied by surgical mortality (257). Other innovative open surgical approaches to repairing the obstructed UPJ soon followed: renal pelvis plication, Y-V flap advancement, straight flap insertion, and spiral flap repair.

In the early 1900s, faced with what appeared to be an inoperable situation, Joachim Albarran performed the first endopyelotomy when he incised an upper tract stricture and left a catheter in place. Surprisingly, the incised-but-not-reconstructed ureter healed and remained patent; Albarran termed this fortuitous occurrence a *ureterotome externe* when he first reported it in 1909. Subsequently, during a visit to Europe, Keyes learned of the technique and brought it back to the United States in 1915. However, it was not until the 1940s that David M. Davis, in the twilight of his career in urology, rediscovered Albarran's work. Between 1943 and 1948, Davis developed the technique of “intubated ureteroplasty.” He reported an 89% subjective and a 60% objective success rate at 1- to 2-year follow-up (67,68).

Much interest resulted from Davis' reports, and during the ensuing decade many laboratory studies were undertaken in an effort to better understand how the intubated ureterotomy worked. From these studies it became apparent that the urothelium covered the ureteral incision, usually within 5 days. Ureteral muscle appeared to regenerate and grow around the incised ureter between 6 and 12 weeks; contracture appeared to play less of a role with regard to the development of an intact circumferential muscle layer. In addition, peristalsis was noted to return across the area of the incision within 6 weeks (135,136,230,274,372). Despite these revelations, by the late 1960s intubated ureterotomy had become a rarely performed procedure, having been superseded by the more successful and aesthetically more pleasing plastic reconstructive procedures of the renal pelvis, specifically the Anderson Hynes dismembered pyeloplasty.

The 1970s brought an explosion in interest in percutaneous nephrostomy; in the late 1970s, this new method for minimally invasive access to the kidney rapidly replaced open nephrostomy first, and later, open urolithiasis surgery. It was in this environment that in 1983, Mr. J.E.A. Wickham developed the concept for performing a percutaneous intubated ureterotomy by incising the UPJ from inside out (i.e., “pyelolysis”). Wickham, working with Miller, Whitfield, and Ramsey, used a cold-knife urethrotome to incise the ureteropelvic junction. Via a preplaced nephrostomy tract, the kidney was traversed, and the UPJ was incised until periureteric fat could be seen. A nephrostomy tube was placed at the end of the procedure; an indwelling stent was maintained across the incised UPJ for 4 weeks. The reported success rate was 64% (287,298).

Subsequently, A.D. Smith brought Mr. Wickham's pyelolysis to the United States; he renamed the procedure *endopyelotomy.* Using a cold-knife endoscopic technique with a newly developed hook blade, Smith, Badlani, Karlin, and associates achieved success rates of 87.5% in patients with both primary and secondary UPJ obstruction (10,176,250). In their series, a 14-Fr tapered external nephrostent was left indwelling for 6 weeks. By 1993, they had expanded their series to 189 patients; overall success rate was 86% at 6 to 96 months' follow-up regardless of a primary or secondary type of UPJ obstruction (251).

The approach and method of UPJ incision are variable. The approach may be either antegrade by endoscopic means or retrograde by endoscopic, fluoroscopic, or combined means. Nonetheless, the classic antegrade percutaneous approach is still a very popular method for performing an endopyelotomy (Fig. 19.17). Via an upper pole or middle posterior calyx nephrostomy tract, the UPJ is visualized directly and incised with a cold knife until periureteric fat is seen clearly.

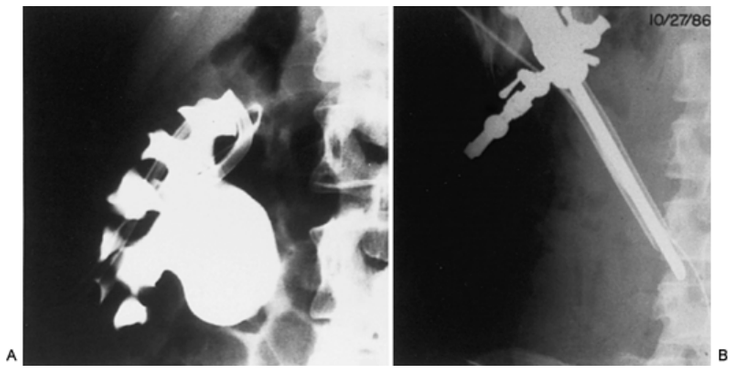

FIGURE 19.17. A: An antegrade nephrostogram reveals marked ureteropelvic junction obstruction. **B:** A cold-knife urethrotome has been introduced via the nephrostomy tract. A guidewire traverses the ureteropelvic junction. An incision in the ureteropelvic junction (UPJ) was then made along the lateral border of the UPJ.

Variations of the antegrade method include using a retrograde inflated balloon to invaginate the UPJ into the renal pelvis, using a wire-guided ureterotome blade, and a transpelvic approach. In the invagination method, the balloon is inflated just beneath the UPJ, provided the ureter has a low insertion into the renal pelvis. The inflated balloon is then pushed cephalad so that the UPJ is carried into the renal pelvis itself; as such, when the tissue overlying the balloon is incised, a double length of tissue is cut because the UPJ has been folded into the renal pelvis. This method should preclude any inadvertent incision of a crossing vessel and speeds the overall completion of the procedure (106,107). Alternatively, a wire-guided cutting instrument can be passed antegrade over the guidewire and through the

narrowed UPJ, thereby incising it. This technique has been used successfully by both Korth and Schneider (201,318). Another technique is the transpelvic approach in which the renal pelvis is purposely incised along its lateral or posterolateral surface and the urethrotome is passed *outside* of the pelvis. The UPJ is then incised from the outside inward (273).

The retrograde approach varies from a purely fluoroscopic to an endoscopic technique. In 1987, Beckman and Roth (22) reported passing a retrograde angioplasty-type balloon to dilate the obstructed UPJ. Since then there have been few reports of a similar approach (Table 19.6). In general, an 8- to 10-mm dilating balloon catheter rated to 10 to 15 atm of pressure is passed retrograde until it straddles the obstructed UPJ. The balloon is then inflated until the obstruction disappears; the inflated balloon is left in place for a variable period of time (usually 1 minute). In some cases, the balloon is then deflated and reinflated for two more 60-second cycles.

Authors	No. of Patients	Approach	Method of Incision	Stent Size (Fr)	Stent Duration (wk)	Overall Success Rate (%)	Success Rate (%)		Hospital Stay (days)	Average Follow-up (range) (mo)	Secondary Pyeloplasty (%)	Secondary Nephrectomy (%)
							1° UPJ	2° UPJ				
Balloon Series												
Beckman et al. (23)	11	Antegrade or retrograde	6 to 10-mm balloon	8–10	4–8	73	86	50	—	10 (2–22)	—	—
Webber et al.	76	Retrograde	10-mm balloon	10	6–8	67	—	—	—	(8–120)	3	11
Oakley et al. (267)	20	Retrograde (15) Antegrade (5)	10-mm balloon	6	6	67	72	33	4	22 (6–30)	—	15
Total	**80**		**10-mm balloon**	**6–10**	**4–8**	**73**	**81**	**46**	**4.2**	**17**	—	—
Antegrade Endopyelotomy												
Van Cangh et al. (365)	102	Antegrade	Cold-cut knife	10–12	6	73	—	—	6.7	60 (12–120)	11	0
Kletscher et al. (197)	50	Antegrade	Cold-cut knife	7–14	6	88	90	82	3–8	12 (4–74)	14	0
Brooks et al. (35)	13	Antegrade	Cold knife	7 or 14	4–6	77	—	—	3	20 (4–53)	2	0
Korth et al. (201)	286	Antegrade	Cold knife	Primestent PCN/EP	3–6	73	80	67	—	20 (6–120)	—	—
Gallucci and Alpi (100)	46	Antegrade	Cold knife	5 or 6	3	80	—	—	4	— (12–60)	4	—
Khan et al. (189)	220	Antegrade	Cold knife	8–12 PCN/EP	6	86.7	—	—	5.2	—	5	3
Danuser et al. (66)	80	Antegrade	Cold knife	8/14 or 7/12 PCN/EP	6	89	—	—	6	26 (1.5–72)	11	1
Shalhav et al. (326)	83	Antegrade	Electrosurgical	7 or 7/14	4–6	83	89	77	4	32	—	—
Total	**880**			**5–7/14**	**3–6**	**81**	**86**	**75**	**4.7**	**28**	—	—

UPJ, ureteropelvic junction.

TABLE 19.6. ENDOPYELOTOMY: RETROGRADE BALLOON AND ANTEGRADE TECHNIQUE

At about the same time that Beckman and Roth described their retrograde fluoroscopic technique, Inglis and Tolley (160) reported a retrograde ureteroscopic approach to performing an endopyelotomy. In their approach, the rigid ureteroscope was passed up to the site of the UPJ obstruction, and the ureter was then incised with an electrosurgical probe until periureteric fat could be seen. Subsequently, several other urologists reported on a similar approach using electrocautery or a cold knife to make the incision (Fig. 19.18) (47). To facilitate delivery of the rigid or flexible ureteroscope, Thomas suggested stinting the ureter for 1 week before the planned endopyelotomy (356).

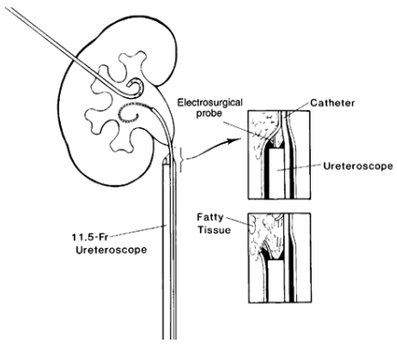

FIGURE 19.18. The 11.5-Fr long, rigid ureteroscope has been passed through the ureter; an electrosurgical probe tip can be seen protruding from the tip of the ureteroscope. The tip of the ureteroscope is covered with a nonconductive material. A nephrostomy rube remains from a preoperative Whitaker test. A safety guidewire and a 5-Fr nonconductive catheter have been placed up the ureter. The *inset* shows a close-up of the actual incision in the lateral aspect of the UPJ; the incision is continued until the full thickness of the ureteral wall has been cut and periureteral fat can be seen clearly. (From Clayman RV, Kavousi LR. Endosurgical techniques for noncalculous disease. In: Walsh PC et al, eds. *Campbell's urology,* ed 6. Philadelphia: Saunders, 1992:2277, with permission.)

A third variation on the retrograde approach was reported by Clayman and colleagues (52) in 1992. In this fluoroscopic technique, a 13-Fr electrosurgical wire-bearing, 8-mm balloon catheter is advanced over a guidewire until the balloon straddles the UPJ (Fig. 19.19). For primary UPJ obstruction before insertion over the guidewire, the balloon catheter is rotated until the electrosurgical wire faces laterally. The catheter is advanced halfway up the ureter, at which point a side-arm adaptor is placed on the throughput channel of the catheter. A retrograde ureterogram with dilute contrast is obtained, thereby defining the UPJ area. Next, the catheter is advanced across the UPJ; the electrosurgical wire should remain in a lateral orientation. The position of the electrosurgical wire is carefully checked with fluoroscopy (Fig. 19.20A,Fig. 19.20B). At this point, 0.5 mL of dilute contrast is placed in the balloon to define its position and to raise the electrosurgical wire slightly off of the catheter's shaft. Then the electrosurgical wire is simultaneously activated at 75 W of pure cutting current while the balloon is completely inflated to its full 2 mL volume (Fig. 19.20C). The inflated balloon is left in place for 10 minutes, and then it is deflated. There should be prompt extravasation from the incision site (Fig. 19.20D). If this is not the case, the cutting device can be activated one more time. If extravasation still is not appreciable, the cutting balloon catheter is deflated, pulled back to the midureter, and a retrograde ureterogram is repeated. If there is still no extravasation, the cutting balloon catheter is removed and a flexible ureteroscope can be passed to the site; if no incision in the ureter is seen, a cut can be made with a 2-Fr electrosurgical probe or a 360-micron Ho:YAG laser fiber passed through the flexible ureteroscope.

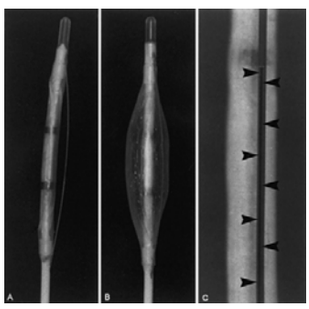

FIGURE 19.19. A: A cutting balloon (i.e., Acucise) is shown in its uninflated state. The cutting wire is clearly seen overlying the balloon. **B:** With the balloon inflated, the cutting wire is stretched over the balloon. **C:** A close-up of the cutting wire shows that the actual cutting surface of the wire *(arrowheads)* is only 150 microns in width but 2.8 cm in length.

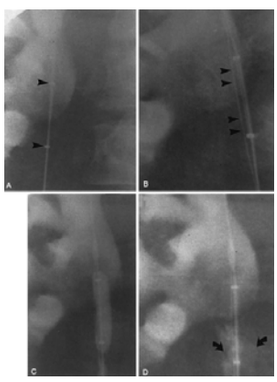

FIGURE 19.20. A: The cutting balloon has been passed up over the guidewire until the cutting wire straddles the ureteropelvic junction (UPJ) area. Note that the cutting wire lies between the two radiopaque markers *(arrowheads).* The cutting wire cannot be seen in this projection. **B:** The catheter has been turned so that the cutting wire is facing laterally *(arrowheads)* along the UPJ area. **C:** The cutting wire has been activated and the balloon has been fully inflated. **D:** As the balloon is deflated, extravasation of contrast *(arrows)* can be seen. Following this, the balloon is removed and an indwelling ureteral stent is placed along with a bladder catheter.

After the UPJ is opened, an external or internal stent varying in size from 8 to 14 Fr is placed. The stent duration is usually 4 to 6 weeks. A follow-up intravenous pyelogram

(IVP) or Lasix washout renogram is obtained 1 to 2 weeks after stent removal and again at 3 months, 6 months, 1 year, and then annually for 5 years.

Results

The results of endopyelotomy, regardless of approach or method of incision, have been highly satisfactory. Although not quite equal to open pyeloplasty, the overall success rate has been high enough that, when combined with the minimal morbidity and short hospital stay associated with the procedure, endopyelotomy has become the preferred method of many urologists for treating adult UPJ obstruction.

The largest endopyelotomy experience to date is with an antegrade approach using a cold knife to incise the UPJ. Motola and colleagues (251) reported the initial large series of patients. Among 212 patients treated by antegrade endopyelotomy over an 8-year period between 1983 and 1991, the overall success rate was 89%. For patients followed 6 months or more, the success rate hardly changed: 86%. In addition, primary UPJ and secondary UPJ obstruction fared equally well (85% versus 86% success rate). Other urologists have independently reported success rates of 73% to 89% in series ranging from 13 to 286 patients (33,35,63,66,189,197,201,326,364). Overall, results for primary and secondary UPJ obstruction were comparable (Table 19.6).

In Motola and colleagues' (251) large series, operative time averaged 90 minutes with a hospital stay of 6.2 days. When compared with open pyeloplasty at their institution, they noted that endopyelotomy resulted in a shorter hospital stay (6.2 versus 10 days) and less operative time (90

minutes versus 106 minutes). Also, convalescence was much quicker in the endopyelotomy groups: 20 days versus 42 days. Brooks and colleagues (35) compared open and endourologic approaches with UPJ obstruction in 45 patients. Successful relief of obstruction was achieved in 100% of patients undergoing open and laparoscopic dismembered pyeloplasty, 78% undergoing Acucise endopyelotomy, and 77% undergoing antegrade percutaneous endopyelotomy. The Acucise endopyelotomy resulted in shorter convalescence (1 week) than the antegrade endopyelotomy (4.7 weeks), laparoscopic pyeloplasty (2.3 weeks), or open pyeloplasty (10.3 weeks). Complication rates were similar among all the groups.

Gupta and colleagues (132) reviewed 401 percutaneous endopyelotomy procedures performed over a 12-year period. Eighty-five percent of the failures occurred within 6 months of the endopyelotomy; although 2% failed as late as 5 years following the endopyelotomy. They noted that patients with high-grade hydronephrosis and poor initial renal function were much less likely to have a successful endopyelotomy than those with moderate hydronephrosis or good renal function. Other investigators have demonstrated similar results. The success rate for endopyelotomy in patients with UPJ obstruction caused by high insertion is similar to that reported for endopyelotomy in patients without high insertion (43,326).

Complications from endopyelotomy have been relatively few. Bleeding requiring transfusion has been noted in only 1% of patients in Smith's antegrade endopyelotomy series; however, others have noted significant hemorrhage in 8% to 9% of their cases (207,245). Cassis and co-workers (37) noted an overall major complication rate of 11%. Other serious complications have included ureteral avulsion, ureteral necrosis, and arteriovenous fistula formation (232,251,347). Urinoma, hematoma, and urinary tract infection also have been reported, albeit rarely.

For retrograde ureteroscopic endopyelotomy, success rates similar to antegrade endopyelotomy have been reported (Table 19.7) (44). An overall success rate of 80% was published by Meretyk and colleagues (245); however, in their series, there was a 16% incidence of intraoperative hemorrhage and a 20% incidence of distal ureteral strictures postoperatively. This resulted in their abandoning the retrograde endoscopic approach in favor of the antegrade technique. However, Thomas and colleagues (356) reported excellent results and low morbidity with a ureteroscopic approach, providing the ureter was stinted for 1 week before ureteroscopic endopyelotomy. In their series the success rate was 87%; one patient (2.5%) required urgent nephrectomy for acute bleeding. Of note, notwithstanding the early experience of Meretyk and associates (245), other urologists have reported an 82% to 90% success rate with the electrosurgical or Ho:YAG laser cutting modality (352,356). Interestingly, in two out of the three reports a dilating balloon is used following the incision at the UPJ to dilate the area. The overall experience with this approach remains small.

Authors	No. of Patients	Approach	Method of Incision	Stent Size (Fr)	Stent Duration (wk)	Overall Success Rate (%)	Success Rate (%)		Hospital Stay (days)	Average Follow-up (range) (mo)	Secondary Pyelo-plasty (%)	Secondary Nephrectomy (%)
							1° UPJ	2° UPJ				
Ureterscopic Series												
Thomas et al. (356)	39	Retrograde	Electrocautery and 8-mm balloon	7/14	6–8	90	—	—	1.2	16 (7–37)	—	8
Tawfiek et al. (352)	32	Retrograde	Electrosurgical or Ho:YAG laser	6–7/14	6–10	87.5	87.5	87.5	—	18 (5–49)	3	16
Gerber & Kim (107a)	22	Retrograde	Electrosurgical or Ho:YAG laser + 7-mm balloon	7–7/14	6–7	82	—	—	<1	21 (4–61)	5	—
Total	**93**			**6–7/14**	**6–10**	**87**	**—**	**—**	**—**	**16**	**—**	**—**
Acucise												
Brooks et al. (35)	9	Retrograde	Acucise	7 or 14	4–6	78	—	—	0.2	24 (15–32)	2	—
Nadler et al. (258)	28	Retrograde	Acucise	7 or 7/14	4–6	81	78	100	1.6	33 (24–43)	4	4
Faeber et al. (90)	32	Retrograde	Acucise	7/14	6–8	87.5	—	—	1.8	14 (3–28)	12.5	—
Preminger et al. (293)	66	Retrograde	Acucise	7–7/14	6	77	72	100	—	7.8 (1–17.9)	—	—
Shalhav et al. (326)	66	Retrograde	Acucise	7 or 7/14	4–6	77	71	83	2.2	20	—	—
Lechevallier et al. (220)	36	Retrograde	Acucise	9	4–12	75	74	77	3	24 (6–42)	11	—
Total	**237**			**7–7/14**	**4–12**	**79**	**74**	**90**	**1.8**	**17**	**—**	**—**
Open Pyeloplasty												
Scardino and Scardino (313)	2,481	Open	Open pyeloplasty	—	—	88	—	—	—	8–10	2	3
Brooks et al. (35)	11	Open	Open pyeloplasty	—	—	100	—	—	7.3	26 (9–44)	—	—
Total	**2,492**			**—**	**—**	**94**	**—**	**—**	**—**	**—**	**—**	**—**

UPJ, ureteropelvic junction.

TABLE 19.7. RETROGRADE ENDOPYELOTOMY AND OPEN PYELOPLASTY

The retrograde, fluoroscopic approach to performing an endopyelotomy is the simplest method yet developed (Table 19.6 and Table 19.7). However, experience with either balloon dilation to 30 Fr or a balloon incision is less than with the antegrade approach. Although originally described by Kadir and colleagues (173) in 1982 in a patient with a secondary UPJ obstruction, balloon dilation of the UPJ did not undergo any significant testing until 1989, when Beckman and colleagues (23) and O'Flynn and colleagues (271) independently reported on its use in a series of 11 and 31 patients, respectively. After balloon dilation to 18 to 30 Fr, a 7- to 10-Fr stent was left indwelling for 4 to 8 weeks. Overall success rates of 68% to 73% were recorded at follow-up of 10 months. Of note, the procedure appeared to work better for primary (86% success rate) than for secondary (50% success rate) UPJ obstruction (23,173,271). Subsequently, McClinton and colleagues (236) expanded O'Flynn and colleagues' (271) original series and reported on 76 patients treated with endoballoon rupture of the UPJ using a 30-Fr balloon; follow-up of 8 months to 10 years revealed an overall success rate of 67%, with a re-treatment rate of 28%. With a single treatment, only 42% of patients had a durable successful outcome. Recent reports of balloon dilation of UPJ obstruction have used a 10-mm balloon catheter with reported success rates averaging 73%. Success with primary UPJ appears to be better than for secondary obstruction (Table 19.6). However, in a recent long-term follow-up, McClinton noted a durable response rate of only 52%.

Reports on the outcome of the endopyelotomy using a retrograde fluoroscopically guided cutting balloon are now available. In long-term follow-up of the Washington University series, at an average of 33 months' follow-up, the cure rate was 81% on diuretic renal scan evaluation (258). In this same group of patients, subjective analysis done with analog pain scales demonstrated that 61% had a favorable response with 36% totally free of pain and 25% markedly improved. Preminger and colleagues (293) reported a multiinstitutional clinical trial, with the cutting balloon catheter, in 66 patients with UPJ obstruction. With a mean follow-up of 7.8 months, the patency rate was 77% for the endopyelotomy, with 72% of the primary and 100% of the secondary UPJ obstructions remaining patent. Postoperative hemorrhage was the most significant complication, occurring in 3% of the patients, and controlled in both cases by embolization. Brooks and associates (35) compared the retrograde balloon incision to a standard antegrade endopyelotomy and to a laparoscopic pyeloplasty. The success rate for the antegrade and retrograde endopyelotomies was similar (77% to 78%) at 20 to 24 months' follow-up; however, the hospital stay (0.2 versus 3.0 days), analgesic use (1.2 versus 18 mg of morphine sulfate), and operative time (46 versus 145 minutes) were all less for the retrograde balloon

incision. However, as with all of the retrograde approaches, there is no single series with more than 75 patients, and the number of published reports is limited.

Endopyelotomy: Unsettled Issues on Indication

In an effort to maximize the success rate of endopyelotomy, numerous investigations have been made into patient selection, procedural modifications, and the fate of endopyelotomy failures. Each of these areas is of vital importance because the answers to these questions may enable the urologist to preselect patients in whom endopyelotomy will have the best chance of working while providing the surgeon with the best instrumentation and appropriate guidelines necessary to maximize the chances of a favorable outcome. In addition, knowledge concerning the fate of endopyelotomy failures is essential so that urologists can provide their patients with accurate information on which to decide between an endourologic versus open procedure.

With regard to patient selection, concerns have been voiced regarding the use of endopyelotomy in the following seven circumstances: concomitant presence of renal calculi, children, the elderly, a high ureteral insertion, poor renal function, massive hydronephrosis, and a crossing renal vessel. First, it is important that the diagnosis of a UPJ be made in the absence of renal calculi. Szewcyzk and colleagues (348) have shown that patients with renal pelvic stones may appear to have a UPJ obstruction on preliminary testing. However, following percutaneous removal of these calculi, the associated edema in the area of the UPJ region resolves, indicating that the apparent UPJ obstruction was of a secondary, transient nature. Obviously, performing an endopyelotomy in this patient group or having a large number of these types of patients in an endopyelotomy series may result in an inflated success rate (348).

Pediatric endopyelotomy has been performed sparingly. In 1987, Towbin and co-workers (360) reported on the results of endopyelotomy for primary UPJ obstruction in three children, 11 to 18 years of age; the procedure was successful in two out of the three cases. Lingeman and colleagues (225) reported on seven children undergoing endopyelotomy for primary UPJ obstruction; in their series, a successful outcome occurred in 100% of children followed for an average of 13 months. More recently, Figenshau and colleagues (94) expanded Kavoussi and colleagues' (184) earlier report on pediatric endopyelotomy to 17 children ranging in age from 3 months to 17 years old. Endopyelotomy was performed for primary (eight cases) and secondary (nine cases) UPJ obstruction; at a mean follow-up of 25 months, the success rate in the primary group was only 62%, whereas the success rate in the secondary UPJ group was 100%. In two patients with a secondary UPJ obstruction, an additional percutaneous procedure was required to obtain a successful end result. All failures were found within the first year of follow-up. Schenkman and Tarry (312) compared 8 children undergoing endopyelotomy with a contemporary group of 20 children having an open pyeloplasty for UPJ obstruction. The endopyelotomy success rate at 1.5 years of follow-up was 88%. The open pyeloplasty success rate was 93%. The hospital stay was similar for the two groups (2.5 days versus 3.4 days for the endopyelotomy and open pyeloplasty, respectively). The operative time was longer for the endopyelotomy than for the pyeloplasty (220 versus 132 minutes, respectively), and this resulted in a higher average hospital cost for the endopyelotomy group ($8,474 versus $5,931, respectively).

At the other end of the age spectrum, endopyelotomy for primary and secondary UPJ obstruction in the geriatric population has proven quite successful. Horgan and colleagues (145) reviewed 18 patients ranging in age from 66 to 83 years; the success rate in these patients mimicked the success rate in the overall adult population: 88% for either primary or secondary UPJ obstruction. There were no intraoperative complications, and the average hospital stay was 6.3 days; these results were also identical to the hospital stay for their younger adult endopyelotomy patients.

Of ongoing concern to all urologists performing endopyelotomy is that the success rate is only 72% to 88%. In an effort to better identify ideal candidates for endopyelotomy, the following factors have been studied: high insertion, poor renal function, hydronephrosis, and the presence of a crossing vessel. Several investigators have determined that high insertion of the ureter has no adverse effect on outcome (43,327,364). In contrast, it was the opinion of Meretyk and associates (245) that poor renal function (i.e., less than 20%) augured a poor outcome; indeed, for these patients a nephrectomy was recommended. Gupta and colleagues (132) have similarly shown that patients with poor renal function were less likely to have a successful endopyelotomy (54% success rate if renal function is less than 25% versus 92% success rate if renal function is greater than 40%). With regard to hydronephrosis, Van Cangh and colleagues (365), Glinz and colleagues (117), and Gupta and colleagues (132) have each independently noted that massive hydronephrosis bodes ill. In Gupta and colleagues' (132) series, fully 89% of the failed endopyelotomies were among patients with severe or massive hydronephrosis. Similarly, Van Cangh and colleagues (365) noted a 76% success rate in patients with minimal hydronephrosis versus a 66% success rate in patients with grade 3 to 4 hydronephrosis. Glinz and colleagues (117) noted that among patients undergoing a successful endopyelotomy, the average volume of the renal pelvis was less than 60 mL.

The one area that has stimulated the greatest amount of debate regarding patient selection for endopyelotomy has been the issue of the crossing vessel (343). Cassis and associates (37) had first voiced concern about the potential importance of diagnosing the presence of a crossing vessel preoperatively; for this purpose the IVP was inadequate, and only an angiogram provided the necessary information.

However, the seminal work on the impact of a crossing vessel on the outcome of an endopyelotomy was performed by Van Cangh and colleagues (365). They obtained preoperative angiograms in patients before endopyelotomy. The presence of a crossing vessel with either mild (grade 1 to 2) or severe (grade 3 to 4) hydronephrosis resulted in success rates of only 50% and 39%, respectively; whereas absence of a crossing vessel was associated with a successful outcome in 95% of patients with mild hydronephrosis and 77% of patients with moderate to severe hydronephrosis. In this series, the crossing vessel was the single most important prognostic factor (365). Including all series of open surgery, angiography, endoluminal US, and spiral CT, the incidence of crossing vessels in patients with UPJ obstruction averages 50% (33% to 79%) (131).

In the quest to diagnose a crossing vessel, the advent of two minimally invasive studies has been most timely. Today, endoluminal US and spiral CT provide the urologist with the ability to closely examine the UPJ area before proceeding with a given therapy (15,138). Endoluminal US involves the retrograde passage of a 7.2-Fr catheter over a 0.025-inch guidewire (Fig. 19.21). The tip of the catheter contains a 12.5- or 20-MHz US unit. The catheter is set up to scan 10 degrees from the perpendicular, providing a 360-degree cross section with a 1.5-cm radius. By slowly pulling the catheter through the UPJ area, the examiner can clearly identify any vein or artery crossing the UPJ and measure its size. Drawbacks to the technique, however, include the cost of the catheter (several hundred dollars), the invasive nature of the test, and the learning curve for the observer, which includes recognition of vessels, categorizing them as arteries or veins, and determining the anterior or posterior direction of vessel passage.

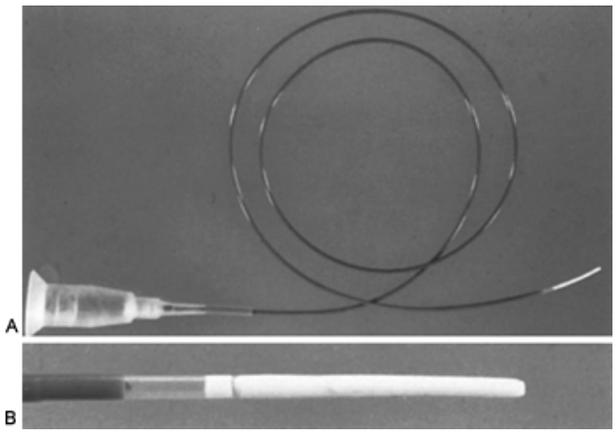

FIGURE 19.21. A: An endoluminal ultrasound catheter for intraluminal ultrasonography. The 7.2-Fr catheter passes over a 0.025-inch guidewire. **B:** The tip of the endoluminal ultrasound unit contains either a 12.5- or 20-MHz ultrasound unit capable of providing 360-degree scans of the ureter with a radius of 1.5 cm.

Nonetheless, using this method Tawfiek and colleagues (352) reported on 37 successful examinations in 27 patients with a primary UPJ obstruction and in 10 patients with a secondary UPJ obstruction. Crossing vessels were seen in 53%; the vessels crossed the UPJ anteriorly (16%), posteriorly (6%), anteromedially (9%), anterolaterally (19%), and anteriorly and posteriorly (3%); none were noted directly lateral (Fig. 19.22). This variation in vessel distribution is similar to that observed by Sampaio and Favorito (309) in their postmortem study of the normal UPJ, in which they noted 65% of patients had a crossing vessel at the UPJ; however, no vessels crossed the lateral surface. In Tawfiek and Bagley's report (352), the information gleaned from the endoluminal US study helped determine the site of endopyelotomy incision in 16 patients and changed the planned therapy in 5 patients.

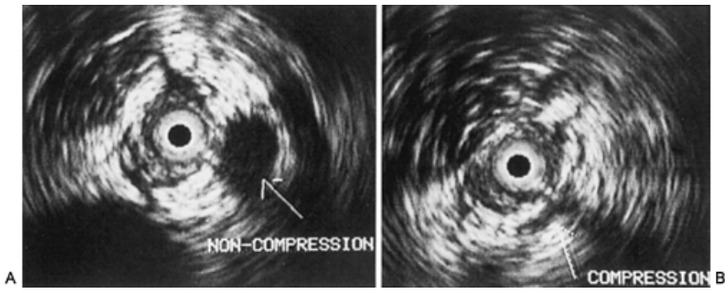

FIGURE 19.22. A: An endoluminal ultrasound study performed at the level of the ureteropelvic junction (UPJ) reveals a large vessel crossing the UPJ directly posterior *(arrow).* Noncompression refers to the conditions at the time of scanning: no manual pressure was put over the kidney area. **B:** By pressing down on the flank directly overlying the area of the scanning, the crossing vessel *(arrow)* can be compressed, thereby indicating its probably venous nature.

Spiral (helical) CT differs from the standard tomography the way a bread slicer differs from a potato peeler (138) (Fig. 19.23). In the former situation, only sections of the area of interest can be studied; although these sections can be made quite thin, an accurate reconstruction of the area is difficult. In the latter situation, a dynamic ongoing record of the entire area of interest is made; this continuous radiographic recording then can be reconfigured to provide the observer with views of the area from every conceivable angle. To accomplish this, during CT scanning the x-ray source undergoes rotation in a spiral pattern while the patient is moved through the CT scanner. With this arrangement, an entire scan of the area of interest usually can be done with a single breath hold (i.e., less than 25 seconds). Both the total amount of radiation exposure and the amount of image noise are reduced compared with conventional CT technology. With this technique, overlapping images at intervals as small as 1 mm can be obtained. The ability to detect small vessels around the UPJ is further improved by giving a bolus of intravenous contrast just before scanning. As such, vessels as small as 2 mm in size that cross the UPJ area can be detected. In addition, by reconstructing the renal pelvis, an accurate measurement of its size can be obtained, further enabling the surgeon to better determine the suitability of a given patient for endopyelotomy. Quillin and colleagues (296) imaged 24 consecutive patients, with symptomatic UPJ obstruction, with dual-phase, contrast-enhanced helical

CT. Eleven (46%) of the patients collectively had 11 anterior and three posterior vessels (2 mm or greater in diameter) crossing the UPJ on helical CT. Laparoscopy and open surgery findings were in agreement with the helical CT angiogram for five of five patients in this study. Uncomplicated endopyelotomy was performed for 11 patients in whom no significant vessels were seen posterior or posterolateral to the UPJ.

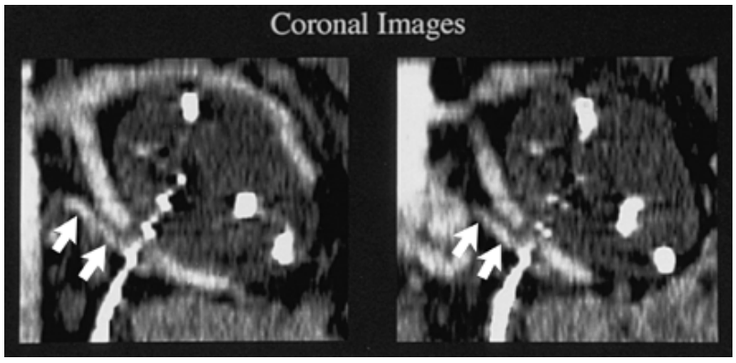

FIGURE 19.23. In this spiral computed tomography scan of a 34-year-old male patient with a UPJ obstruction, the coronal reconstruction reveals a vessel *(arrows)* crossing the UPJ posteriorly. The density of the vessel suggests that it is probably an artery.

Armed with endoluminal US and spiral CT, several investigators are seeking to corroborate Van Cangh and colleagues' (365) findings because many questions remain unanswered. Specifically, it remains puzzling that despite the presence of a crossing vessel, even in Van Cangh and colleagues' (365) series the endopyelotomy was still successful in approximately 50% of patients depending on the degree of hydronephrosis. Nakada and colleagues (260) demonstrated in 16 patients, who had undergone successful cutting balloon endopyelotomy for UPJ obstruction, with greater than 2-year follow-up, that six (38%) had anterior or posterior crossing vessels based on CT angiography. Could it be that only some and not other vessel configurations are directly responsible for the UPJ obstruction? Perhaps only an anterior crossing vessel causes problems or perhaps a crossing artery is of greater concern than a crossing vein. The next question arises that if a crossing vessel is found, what should be the next step: open pyeloplasty, laparoscopic pyeloplasty, laparoscopic exploration and incision of the vessel if it is not a major renal arterial branch, or laparoscopic exploration and incision of the vessel combined with endopyelotomy? Further clinical evaluation will be necessary to determine the significance and implication of the crossing vessel associated with UPJ obstruction. Ideally, appropriate laboratory and clinical studies will allow the urologist in the future to confidently select patients for endopyelotomy knowing that the procedure will then be as successful as its open surgical counterpart. In all respects, this continues to be the goal of each endourologic procedure: to offer the patient a minimally invasive approach of efficacy equal to, but with morbidity less than, a standard open surgical procedure.

Endopyelotomy: Unsettled Technical Issues

To what extent differences in the technical aspects of performing an endopyelotomy affect the ultimate success rate remains unknown. Controversy continues in several areas: the method of incision, the size of the indwelling stent placed after the endopyelotomy, and the period of time that the stent is left indwelling. From an incisional standpoint, although a cold-knife urethrotome continues as the preeminent method for opening the ureteropelvic junction, a variety of apparently equally efficacious methods have been described. Hulbert and colleagues (155) and Meretyk and colleagues (245) have independently reported on using a minute electrosurgical probe for making the incision; similarly, Chandhoke and colleagues (40) have reported on using an electrosurgical cutting balloon, whereas O'Flynn and colleagues (271) have written about using a 10-mm dilating balloon presumably to split the UPJ along its weakest point, and Tawfiek and Bagley (353), Gerber and Alsikafi (107b), and Renner and others (300a) have individually reported using the Ho:YAG laser to incise the UPJ stricture. As noted, the results with any of these techniques appear to be remarkably similar. Studies examining electrosurgical incisions have shown that when the cutting surface of the probe is less than or equal to 400 microns, the resulting incision and peripheral damage are indistinguishable from the incision achieved with a cold knife. However, probes that have a 1-mm or larger tip cause significantly more damage and should be avoided (75). With balloon disruption of the UPJ area, laboratory studies have shown that although the balloon splits the ureteral mucosa and muscularis, the adventitia usually remains intact, thereby precluding any significant retroperitoneal extravasation. The balloon at times splits the ureter along a single plane; however, the site of the split and the overall length of the tear are highly variable (288). With regard to other endoscopic cutting modalities, such as bipolar electrosurgical probes or special laser fibers (e.g., side-firing fiber with a KTP laser), data are unavailable.

Controversy continues over the size of the stent to leave indwelling after an endopyelotomy. For years, the notion has been that the stent serves as a mold around which the ureter heals. This philosophy was strongly endorsed in Davis's classic writings; based on his clinical experience, Davis recommended that as large a stent as possible should be placed following an intubated ureterotomy (68). As such, many urologists have advocated leaving a 14-Fr stent in place, in the hope that the healed UPJ will then assume the same size as a normal UPJ. These large stents have a dual taper so that the portion traversing the incised UPJ is 14 Fr, while the portion in the bladder is only 7 to 8 Fr. Both an external nephrostent and internal double pigtail design have been used. However, laboratory studies have challenged Davis's notion. Moon and colleagues (247) could show no difference in ureteral healing in a pig model after a cutting-balloon endoureterotomy whether a 7- or 14-Fr stent was used. Similarly, there have been a few clinical reports suggesting that the stent, rather than a mold, is actually serving as a *scaffold* along which the orderly growth of the urothelium and subsequent ingrowth of the ureteral musculature is guided, a concept attributed to Hinman (274). In several series, indwelling stents of 8 to 10 Fr have been placed; the outcomes have been highly favorable, with success rates of 83% to 88% reported (44,197,236). If stent size is ultimately shown not to affect the outcome of an endopyelotomy, the need to prestint the ureter before a retrograde endopyelotomy would be decreased, and the ease and safety of postendopyelotomy stent placement and removal would be facilitated.

Research has challenged the 6-week stent practice. Animal studies by Kerbl and colleagues (187) revealed that in a pig ureteral stricture model, stinting for 1 week with a 7-Fr stent provided results as good as stinting for 3 or 6 weeks. In the 1-week group, the results for endoureterotomy of longer strictures were statistically significantly better than in either the 3- or 6-week groups. Clinically, Kuenkel and Korth (207) noted in their series of 143 endopyelotomies that a stent for 3 weeks produced superior results to leaving a stent for 6 weeks. Abdel-Hakim (1) has noted that as short a stinting period as 4 days was successful in five patients, each of whom was stinted with a 7-Fr external ureteric catheter. However, maximum follow-up in this series was only 6 months. Kumar and colleagues (209) demonstrated that 2 weeks of stent placement were as effective as 4 weeks in the successful outcome of antegrade endopyelotomy. Obviously, in this regard we again have much to learn; prospective, randomized clinical studies of patients with similar types of UPJ obstruction are sorely needed to answer this and other questions regarding stinting after endopyelotomy.

Endopyelotomy: Fate of Failed Procedures

One last question regarding endopyelotomy is of paramount importance. Specifically, is the patient in whom an endopyelotomy fails placed at a disadvantage for subsequent surgical salvage? Certainly, if this is the case, one would be most hesitant to proceed with a minimally invasive procedure in which a failure rate as high as 30% could be expected. Kavoussi and colleagues (180) and Motola, Smith, and colleagues (252) have independently written on the fate of the failed endopyelotomy patient. Both reports noted that although salvage open pyeloplasty is at times a bit more difficult to perform than a primary pyeloplasty, the overall success rate was excellent. Among 15 patients in Motola and colleagues' (252) series and 5 patients in Kavoussi and colleagues' (180) report, all underwent a successful salvage dismembered pyeloplasty. Follow-up at 1 to 7 years revealed that all 20 patients had a successful outcome. Of note, in the Kavoussi and colleagues (180) series, one patient underwent a nephrectomy because of decreased renal function, whereas in the Smith series there were no subsequent nephrectomies.

Calyceal Diverticulum and Hydrocalyx

The calyceal diverticulum and the hydrocalyx are two entities related by the narrowness of their communication with the collecting system. Whereas in the former, there is no associated functioning renal tissue, in the latter, the relief of obstruction can have a potentially positive effect on renal function. As such, the endosurgical approach to these two conditions is quite different.

Calyceal diverticula are noted on 0.45% of intravenous urograms. Most commonly these outpouchings are unilateral and emanate from a minor calyx and are more of anatomic than clinical interest. Only one-third become symptomatic because of the development of urolithiasis, pain, hematuria, or recurrent infection (357).

Far more rare than calyceal diverticula is the hydrocalyx. This is usually an acquired condition caused by infection (e.g., tuberculosis, urolithiasis, prior intrarenal surgery). A congenital isolated hydrocalyx may be either developmental or associated with extrinsic compression from a crossing segmental renal vessel; the latter has been described most commonly in the upper pole of the kidney (Fraley's syndrome) (89,97). At times, the distinction between a hydrocalyx and a calyceal diverticulum only can be made during nephroscopy; the absence or presence of a papilla differentiates between a diverticulum and a hydrocalyx, respectively.

Calyceal Diverticulum: Technique

For the few calyceal diverticula requiring surgical therapy, the standard approach has been to excise or marsupialize the diverticulum; the neck of the diverticulum is then closed with a suture. For a very large diverticulum, partial nephrectomy is performed. However, beginning in the late 1980s these lesions began to be managed successfully endourologically by percutaneous and ureteroscopic methods. There have also been a few case reports of successful laparoscopic treatment of a calyceal diverticulum (118).

When approached percutaneously, the diverticulum should be entered directly; the renal pelvis or normal part of the collecting system is not initially entered (Fig. 19.24) (158). Once inside the diverticulum, any stones are removed. Next, the opening of the diverticulum into the collecting system is identified and cannulated with a guidewire; the guidewire is then covered with a 5-Fr angiographic catheter. With use of a roller electrode, the entire inner surface of the diverticulum, except the neck of the diverticulum, is electrocoagulated. Following this, the neck of the diverticulum is enlarged by multiple electrosurgical (less than 400-micron tip) endoscopically guided, shallow (less than 2 mm in depth) incisions, balloon dilation to 12 to 24 Fr, and/or dilation with coaxial dilators to 26 to 28 Fr. Next, a nephrostomy tube is placed such that it traverses the diverticulum and terminates in the renal pelvis. This tube is usually removed 2 to 7 days later (48,157,171,211).

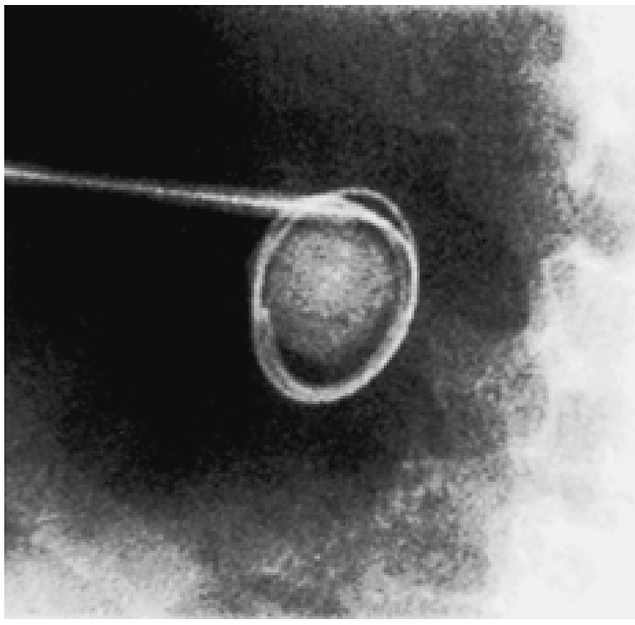

FIGURE 19.24. Direct percutaneous puncture of a stone-containing calyceal diverticulum. The wire has been coiled several times within the diverticulum to enable the urologist to dilate the tract over the stiff part of the guidewire. (From Hulbert JC, Reddy PK, Hunter DW, et al. Percutaneous techniques for the management of caliceal diverticula containing calculi. *J Urol* 1986;135:225, with permission.)

There are two alternatives to percutaneously cannulating and incising the neck of the diverticulum. In both situations, the neck of the diverticulum is not sought. In one technique, the entire inner surface of the diverticulum, including the presumably unidentified diverticular neck, is electrocoagulated under endoscopic control; a tube is left in the diverticulum for 2 to 3 days and then removed. The true collecting system of the kidney is never entered (323). In the other approach, a transdiverticular puncture into the collecting system is made; the interior of the diverticulum is either electrocoagulated as previously described or left intact. The neoinfundibulum is either dilated (12 to 18 Fr for 2 minutes), thereby creating a new drainage path, or is allowed to heal closed. In the former situation, an 8- to 10-Fr nephrostent is placed, whereas in the latter circumstance, the tip of the tube is placed only into the diverticulum. In Lang's (214) series, the stent was left in place for 4 weeks, following which it was exchanged for an indwelling stent of unspecified size and duration (27).

When approached ureteroscopically, the neck of the diverticulum is first identified, following which a safety guidewire may be passed into the diverticulum or into the renal pelvis. The lens of the ureteroscope is removed so that a 4-mm dilating balloon catheter can be passed over the guidewire through the sheath of the ureteroscope; the balloon is passed retrograde until it straddles the neck of the diverticulum. The balloon is then inflated, thereby dilating the neck of the diverticulum; the balloon is then deflated and removed. The ureteroscope's lens is replaced and the ureteroscope is advanced into the diverticulum. Alternatively, flexible ureteroscopy can be done and a nonconducting guidewire can be passed into the diverticulum. Next, a 2- or 3-Fr electrosurgical probe can be used to incise the

neck of the diverticulum; several radial incisions (less than 2 mm) are made, and the ureteroscope is advanced into the diverticulum (Fig. 19.25). The calculus is then fragmented with laser or electrohydraulic energy, and the walls of the diverticulum can be treated with either electrocautery or Nd:YAG energy. An indwelling ureteral stent is placed in the collecting system; the stent does not transverse the diverticulum. Alternatively, following dilation of the neck of the diverticulum, the calculi may be treated by shock wave lithotripsy; however, in this case the diverticulum will probably remain intact (98,157,246).

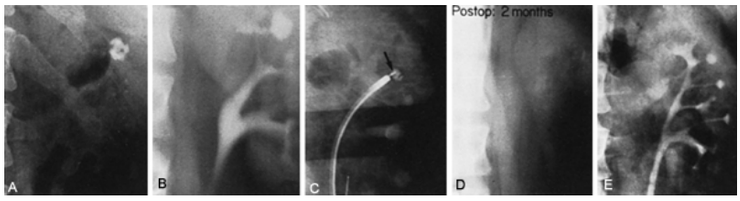

FIGURE 19.25. A: A plain abdominal radiograph reveals multiple calculi lying in the kidney just above the eleventh rib. **B:** An intravenous urogram reveals that the stones are lying in an upper pole calyceal diverticulum. **C:** The flexible ureteroscope has been advanced retrograde, and the neck of the calyceal diverticulum has been identified. With a 3-Fr electrosurgical probe, the neck of the diverticulum is incised, following which the stones are fragmented using laser lithotripsy. **D:** At 2 months after the operation, a plain abdominal radiograph reveals only a few stone flecks in the area of the diverticulum. **E:** The intravenous urogram at 2 months after the procedure reveals that the diverticulum has decreased markedly in size.

Another approach to treating the stone-bearing calyceal diverticulum is extracorporeal shock wave lithotripsy. Although this results in successful fragmentation of the stone in the majority of patients, in most cases, the stone fails to pass; however, many patients do become at least transiently asymptomatic. Of note, the diverticulum remains unaltered; hence, the potential for recurrent stone disease in the diverticulum remains a real risk. According to Streem and Yost (345), the ideal diverticulum for a primary ESWL approach is one in which the neck of the diverticulum is visibly patent on the pretreatment radiographs and the stone burden is less than 1.5 cm.

Hydrocalyx: Technique

In contrast to the calyceal diverticulum, the traditional approach to treating a hydrocalyx has been open partial nephrectomy or transposition of an obstructing vessel. Minimally invasive approaches to this problem have included both ureteroscopic and percutaneous therapy; however, the more common endourologic approach has been via a percutaneous route (165). With the endourologic approach, the goal is twofold: to open the narrowed infundibulum and to preserve the functioning calyceal tissue. A direct percutaneous approach into the hydrocalyx may be attempted. In this case, the technique is identical to that described for treating a calyceal diverticulum except that after incising or dilating the neck of the infundibulum (12- to 18-Fr balloon or 20- to 24-Fr Amplatz dilators), the walls of the hydrocalyx are not disturbed in an effort to preserve the function of the now unobstructed calyx (25).

In incising an infundibulum, it is important to limit the depth of any incision to only 2 mm in order not to injure any of the larger vessels that may surround the infundibulum (48). Anatomically, the vessels surrounding an infundibulum are most prevalent along its anterior and posterior surfaces; the superior and inferior surfaces of the infundibulum are less vascular. Based on anatomic studies, Sampaio (308) recommended that the initial incision should be on the superior surface of the infundibulum; if need be, a counterincision can be made along the inferior surface. These surfaces in a middle calyx would be akin to the medial and lateral surfaces of an upper- or lower-pole calyx; in these cases, a lateral incision has been recommended (159). Again, anterior and posterior incisions should be avoided because they may result in significant hemorrhage.

Overall, the least invasive yet most effective form of therapy for a symptomatic, stone-containing calyceal diverticulum is a direct percutaneous approach with stone removal and obliteration of the walls of the diverticulum. Using this approach, up to 100% of patients can be rendered asymptomatic; more than 90% of patients become stone free; and in two-thirds or more of cases, the calyceal diverticulum is obliterated, thereby precluding recurrent urolithiasis or infection (Table 19.8) (89,154,171,318). In these cases, either cannulation and dilation of the true neck of the diverticulum or electrocoagulation of the entire diverticulum is recommended. In contrast, balloon dilation of a newly created drainage path from the diverticulum into the collecting system results in diverticular obliteration in only 20% of cases; however, in 70% of cases, the neoinfundibulum

remains patent, thereby draining the calyceal diverticulum (214).

Authors	No. of Patients	Technique	Symptom Free (%)	Stone Free[a] (%)	Diverticulum Obliterated	Average Follow-up (range) (mo)	Catheter Duration
Hulbert et al. (154)	12	Antegrade PCN (neck dilated)	NS	100[b]	100	9 (3–15)	2 wk
Eshghi et al. (89)	14[c]	Antegrade PCN (cold knife)	NS	100	86	NS	3 days–2 wk
Jones et al. (171)	14	PCN	100	96	100[b]	35 (16–60)	—
Lang (214)	10	PCN	NS	NS	20[d]	≤7 yr	—
Lagha et al. (218)	18	PCN ± fulguration (neck dilated to 26–28 Fr)	—	100	72	1–3	2 days

[a]Stone status of diverticulum.
[b]Electrocoagulate walls of diverticulum.
[c]Did not differentiate between calyceal diverticulum or hydrocalyx.
[d]In 60% the calyceal diverticulum had a patent neck after dilation.
NS, not specified.

TABLE 19.8. CALYCEAL DIVERTICULA: PERCUTANEOUS APPROACH

The other endourologic methods for approaching this disease entity are less effective. With regard to ESWL, its success rate is highly variable dependent on how selective the physician has been (Table 19.9). In patients with a small stone burden (i.e., less than 1.5 cm) and with a patent diverticular neck on radiographic studies, Streem and Yost (345) achieved an 86% rate of asymptomatic or less symptomatic patients and a 58% stone-free rate; at follow-up 2 years later, 8% of these preselected patients had re-formed a stone in the treated calyceal diverticulum. Also, they noted that of nine patients treated in this manner who also had infection, recurrent infection occurred in 67%. Other urologists, using no selective criteria, have reported post-ESWL symptom-free rates of only 36% and stone-free rates of only 0% to 20% (101,171,294). A purely ureteroscopic approach was effective in only two of six patients treated by Mikkelsen and colleagues (246). In sum, percutaneous calyceal diverticulectomy with removal of the calculus and obliteration of the walls of the diverticulum remains the most definitive and long-lasting less invasive method of treating the symptomatic calyceal diverticulum. Other less morbid procedures are often less effective.

Authors	No. of Patients	Technique	Symptom Free (%)	Stone Free[a] (%)	Diverticulum Obliterated	Average Follow-up (range) (mo)	Catheter Duration
Garcia et al. (101)	13	ESWL	37	0	NS	NA	
Jones et al. (171)	26	ESWL	36[b]	12	NS	35 (16–60)	
Psihramis and Dretlee (294)	10	ESWL	70	20	NS	5.9	
Streem and Yost (345)	19[d]	ESWL	86[e]	58	NS	24	
Fuchs and David (98)	15[f]	URS and ESWL	87	73	7[g]	7.4	3 wk

[a]Stone status of diverticulum.
[b]Thirty-nine percent required PCN salvage because of symptoms.
[c]All stones <1.5 cm.
[d]All diverticula with radiographically patent neck.
[e]Includes symptom free and improved.
[f]Twelve were truly calcyeal diverticula.
[g]Twenty percent more had decrease in size of diverticulum.
NS, not specified; NA, not applicable.

TABLE 19.9. CALYCEAL DIVERTICULA: EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL)

Unlike with calyceal diverticula, there is scant experience in treating infundibular stenosis endourologically. Schneider and co-workers (317) reported on six patients

with a hydrocalyx among whom a cold-knife incision was successful in 66%; the catheter was left indwelling for 3 to 6 weeks. The length of follow-up was not stated. Similarly, Lang (214) reported a 67% success rate in six patients with a hydrocalyx, treated by percutaneous infundibuloplasty (i.e., balloon dilation) who were followed for 2 to 7 years. In his series, the infundibulum was dilated with a 12- to 18-Fr balloon, which was left inflated for 2 minutes. Following this, an 8- to 10-Fr nephrostent was placed; the external stent was left in place for 4 weeks, after which it was exchanged for an internalized stent of unspecified size and duration. Hwang and Park (159) reported an 80% success rate with cold-knife infundibulotomy among 10 patients with tuberculous infundibular strictures followed for longer than 1 year after their percutaneous procedure.

Transitional Cell Cancer of the Renal Pelvis

Transitional cell cancer rarely affects the upper urinary tract: 94% of all transitional cell tumors occur in the bladder, whereas only 5% are found in the renal pelvis and 1% in the ureter (51,375). Traditionally, the therapy for all upper tract tumors has been an open surgical ablative approach. For the kidney and upper ureter, this has entailed a nephroureterectomy with excision of a cuff of bladder, whereas for the distal ureteral tumor, distal ureterectomy and ureteral reimplantation usually has been sufficient. The feasibility of an endosurgical approach to these tumors was championed by Gittes (114), who in 1980 questioned why low-stage, low-grade tumors of the ureter and renal pelvis could not be treated by local excision just as it is common practice for similar types of lesions affecting the bladder. For many years, the stumbling block to this approach remained one of access. However, with the advent of percutaneous and ureteroscopic techniques in the 1980s, this minimally invasive hypothesis could be examined more directly (383,384).

A major area of contention with regard to the endosurgical therapy of upper tract TCC is the appropriate indications for such therapy. On the one hand, some urologists believe this to be “heroic” therapy and thus would limit its application to individuals with a solitary kidney, with renal insufficiency, or who are a high surgical risk. On the other hand, other urologists believe equally as strongly that for low-grade, low-stage disease, an endosurgical excision should be offered to all patients as a simpler, less morbid, renal-sparing form of therapy. This controversy continues to grow because advances in endoscopic equipment and in electrosurgical and laser technology have greatly facilitated the ability of the urologist to access and treat superficial lesions anywhere in the upper urinary tract. As such, today an endosurgical approach would technically be feasible in approximately 40% to 50% of all patients (i.e., patients with low-grade and low clinical stage disease) with upper tract transitional cell cancer (375).

Technique

When approaching transitional cell cancer of the renal pelvis (TCCP), the ureteroscope may be most effectively used if the lesion is small (i.e., less than 1 cm). In males, except for the distal ureter, a flexible ureteroscope is commonly used, and the tumor, after excisional biopsy, is usually treated with electrocautery, the Nd:YAG laser, or Ho:YAG laser (314) (Fig. 19.26). In females, a rigid ureteroscope usually can be used to reach the renal pelvis and the upper-pole calyx, whereas a flexible ureteroscope is needed to approach lesions in the middle or lower calyces (14).

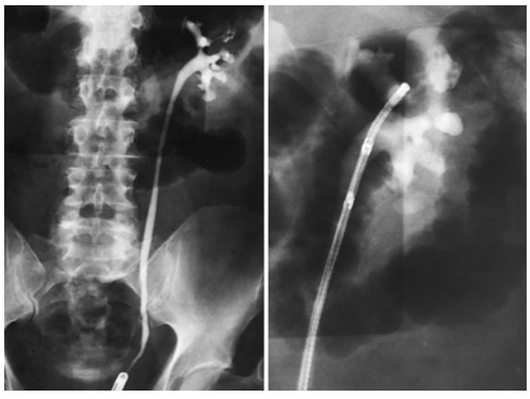

FIGURE 19.26. A retrograde ureterogram reveals poor filling of an upper-pole calyx. Flexible ureteroscopy revealed a papillary transitional cell carcinoma. The tumor was biopsied; however, because of its size and sessile nature, fulguration was not performed. The patient subsequently underwent a nephroureterectomy.

In all ureteroscopic cases, a nonconducting guidewire (i.e., Terumo or guidewire) is passed into the kidney to serve as a safety guidewire. This safety guidewire remains in place throughout the procedure and is used at the end of the procedure for the passage of an indwelling ureteral stent.

In procedures involving the upper ureter and renal pelvis, the distal ureter is dilated with a 4-mm balloon if a 9.4-Fr flexible ureteroscope is to be used or with an 8- to 10-Fr fascial dilator set if a 7.5-Fr flexible ureteroscope is available. If the patient previously has undergone diagnostic ureteroscopy and an indwelling stent was placed, the ureter usually will have dilated passively around the stent, precluding the need for active, acute dilation. Also in this situation, the surgeon is benefited by knowing the diagnosis such that the goal at the second session is therapy alone. If a preoperative diagnosis has not been obtained, the urologist will have to biopsy the lesion and then proceed with definitive therapy. In this circumstance, there is usually bleeding from the biopsy site, and subsequent therapy may be compromised because of impaired visibility. If this occurs, it is prudent to stop the procedure, place an indwelling stent, and plan to return on another day to therapeutically address the tumor.

If, during the procedure, the flexible ureteroscope cannot be easily advanced to the tumor site, the procedure should end. In the upper ureter, the ureteral wall is much thinner than in the distal ureter and it can be perforated easily. As such, it is not recommended to use a 4-mm balloon to dilate the upper ureter because ureteral perforation and possible retroperitoneal seeding may occur. In this case, it is far more prudent to place an indwelling ureteral stent and return in a few days to 1 week to perform the ureteroscopy. As previously noted, with an indwelling ureteral stent in place, the ureter will dilate passively, thereby facilitating subsequent ureteroscopy.

Throughout the ureteroscopic procedure, the irrigant pressure is kept below 100 mm Hg in order to preclude hypothetical renal backflow of any tumor cells. The only time the pressure on the irrigant is raised is when an instrument is passed through the working channel. In this situation,

the pressure on the irrigant may be increased to 150 mm Hg; as soon as the instrument is removed, the irrigant pressure should be returned to less than 50 mm Hg. Furthermore, throughout the procedure it is important not to introduce air into the collecting system. Not only will the presence of air make it more difficult to work because of the air-fluid interface and the reflection of light off of the air bubble, but also it may set up a situation in which an explosion can occur during electrocoagulation, resulting in extravasation and possible tumor spillage (9).

The goal of the treatment either is to resect or to coagulate the entire tumor. In the former circumstance, the resection is carried down flush with the urothelium. With the rigid ureteroscope this can be done with a small electrocautery loop. With the flexible ureteroscope, the cold-cup biopsy forceps is used to tediously resect the superficial portion of the tumor and biopsy the tumor's base, following which the base of the tumor is electrocoagulated or treated with the Nd:YAG laser (20 W); alternatively, the tumor can be vaporized and the base coagulated with the Ho:YAG laser. At the end of the procedure, a retrograde ureterogram is performed in order to rule out any extravasation. An indwelling ureteral stent and a urethral catheter are placed. The urethral catheter is removed on the next morning. The ureteral stent is removed in 3 to 5 days, unless a significant perforation has occurred, in which case the stent is left in place for approximately 4 to 6 weeks; in this case, a cystogram is performed before removing the urethral catheter to rule out ureteral extravasation.

The percutaneous approach is reserved for larger tumors (i.e., larger than 1 cm) (350,351). The method of resection appears to be continually evolving. Initially, a retrograde ureteral catheter usually is placed. This can be a 7-Fr, 11.5-mm balloon occlusion catheter; the balloon can be inflated in the renal pelvis and snugged down at the UPJ to preclude any tumor fragments from traveling into the ureter. The puncture into the collecting system is made such that the urologist both will have a straight approach to the tumor and yet enter the collecting system as far from the tumor as possible (Fig. 19.27). The tract is dilated to 30 Fr with a high-pressure balloon, and then a 30-Fr Amplatz working sheath is placed. The irrigant is kept at a pressure of less than 100 mm Hg. The tumor is resected piece by piece with a standard 24- or 26-Fr resectoscope. With each pass of the resectoscope loop, the tumor fragment is evacuated from the collecting system. The base of the tumor is biopsied with a cold-cup forceps and fulgurated using the Nd:YAG laser (at 20 to 30 W for 3-second exposures) or electrocautery (50 W) (125). The occlusion balloon catheter is then deflated and removed; an indwelling nephrostomy tube is positioned in the renal pelvis. Two days after the procedure, a nephrostogram is performed; if there is no extravasation, the nephrostomy tube is removed. Alternatively, the nephrostomy tube may be left in place for 9 to 12 weeks, during which

time instillation chemotherapy can be given on a weekly basis; similarly, by leaving the nephrostomy tube in place, second-look nephroscopy and tumor-base rebiopsy and fulguration can be accomplished at 6 or 12 weeks.

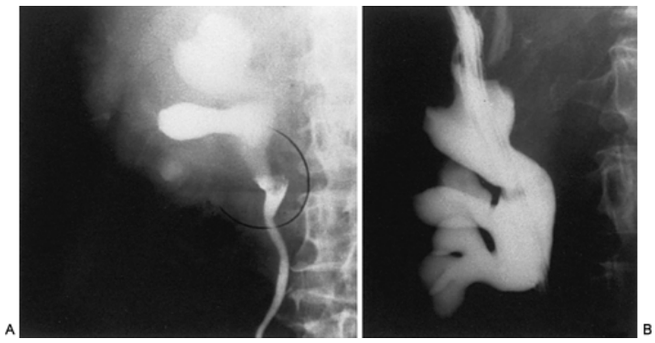

FIGURE 19.27. A: In a patient with a solitary kidney and hematuria, a retrograde ureterogram reveals a papillary filling defect at the level of the ureteropelvic junction. Subsequent ureteroscopy and biopsy showed the lesion to be a low-grade transitional cell cancer. **B:** A percutaneous nephrostomy was established via an upper-pole posterior calyx, thereby providing direct access to the tumor via a remote calyx. A standard resectoscope was then used to excise the tumor, and a nephrostomy tube was placed. (From Clayman RV, Kavousi LR. Endosurgical techniques for noncalculous disease. In: Walsh PC et al, eds. *Campbell's urology,* ed 6. Philadelphia: Saunders, 1992:2301, with permission.)

Results

The key question with regard to an endosurgical approach to TCCP is, To whom should this therapy be applied? Although there is consensus that for patients with low-grade, low-stage disease and with a solitary kidney, renal insufficiency, or high surgical risk that this minimally invasive approach is reasonable, there is significant concern about extending this approach to all patients with upper tract transitional cell cancer. In Table 19.10, series on the percutaneous treatment of TCCP are reviewed; the patients cited in these papers are also subdivided according to the grade or stage of their disease. What becomes clear is that even for low-grade or low-stage disease, the recurrence rate within the first 2 years after percutaneous resection is high: up to 33% (45,86,168,221,233,284). As such, multiple, subsequent endosurgical procedures can be expected. Also, among those patients with low-grade disease, approximately 75% underwent adjunctive therapy with iridium wires, instillation chemotherapy, or second-look procedures with further laser therapy to the tumor base. Despite all of this additional treatment, recurrences were still noted in one-third of patients. Also during the same 2- to 4-year follow-up period, 23% of patients required a nephroureterectomy (45,86,168,221,233,284).

	No. of Patients												
	Tumor Grade				Stage		Local Recurrence (%)	Bladder Recurrence (%)	Posttreatment Adjunctive Therapy (%)	Converted to Open (%)	Metastatic Disease (%)	Death from Cancer (%)	Average Follow-up (range) (mo)
Authors	G_1	G_2	G_3	CIS	O/A	B/C							
Jarrett et al. (168)	11	12	13	—	31	5	33	Not specified	BCG × 6 wk	42	Not specified	17	56 (9–111)
Patel et al. (284)	11	11	1	1	25	0	23	31	^{192}Ir to tract	15	Not specified	7	45 (1–100)
Elliott et al. (86)	Not specified				5		25	—	0	43	Not specified	19	48 (20–117)
Martinez-Pineiro et al. (233)	Not specified				18		11	17	Thiotepa, mitomycin C, BCG, interferon	6	Not specified	14	31 (2–119)
Clark et al. (45)	6	8	4	0	18	0	33	Not specified	BCG × 6 wk	12	24	18	24 (2–76)
Lee et al. (221)	20	16	13	—	46	3	12	Not specified	0	20	12	24	36 (2–150)

TABLE 19.10. UPPER TRACT TCC: PERCUTANEOUS ENDOSURGICAL THERAPY

The results of endosurgical therapy are only slightly better for patients with TCCP approached ureteroscopically; however, in most of these cases the tumors have been small (less than 1 cm) and usually low grade (G_1 to G_2) (Table 19.11). In 69 patients gleaned from various series with grade 1 tumors, there has been no report of local recurrence and no conversion to an open procedure at an average follow-up of 17 months; however, for 31 patients with grade 2 or 3 tumors, ureteroscopic resection was followed by local recurrence in up to half of the patients and conversion to an open procedure in 23% with an average follow-up of 32 months.

	No. of Patients												
	Tumor Grade				Stage		Local Recurrence (%)	Bladder Recurrence (%)	Posttreatment Adjunctive Therapy (%)	Converted to Open (%)	Metastatic Disease (%)	Death from Cancer (%)	Average Follow-up (range) (mo)
Authors	G_1	G_2	G_3	CIS	O/A	B/C							
Elliott et al. (86)	Not specified				16		38	—	0	43	Not specified	19	48 (20–117)
Martinez-Pineiro et al. (233)	Not specified				39		35	17	Thiotepa, mitomycin C, BCG, interferon	3	Not specified	14	31 (2–119)
Keeley et al. (185)	21	14	5				29	40	15 mitomycin C 7 BCG	17	0	0	30 (3–116)
Grasso et al. (122)	1	11	1	1	14	0	50	29	1 mitomycin and interferon 1 mitomycin	29	0	0	17 (6–31)

TABLE 19.11. UPPER TRACT TCC: URETEROSCOPIC ENDOSURGICAL THERAPY

Although some authors have been able to identify a patient population in whom recurrence in the short term is low, this has not been the case in other series. Most series incorporate topical chemotherapy, following the initial percutaneous resection, as the management protocol for upper tract TCC. Jarrett and colleagues (168), using this regimen, noted that among their 11 patients with a solitary, stage 0/A, G_1 lesion, there were tumor recurrences in two patients during a greater than 4-year follow-up period; one was treated by endoscopic resection and one by nephroureterectomy due to large volume disease. Clark and colleagues (45) reported a 33% recurrence rate in their similar stage and grade patients with percutaneous management and topical BCG for upper tract TCC. Orihuela and Smith (279) noted several risk factors for recurrence: lack of use of postoperative BCG instillation, a sessile lesion, a tumor larger than 2 cm in diameter, positive preoperative cytology, positive random upper tract

biopsies, and a prior history of transitional cell cancer of the bladder (TCCB).

Lee and colleagues (221) retrospectively reviewed 110 patients with localized TCC of the upper urinary tract, all of whom had 13-year follow-up. In this group, the results of open nephroureterectomy (60) and percutaneous resection (50) were compared. Of the disease-specific deaths, 65% (17 of 26) were in patients with grade 3 lesions, with a mean cancer survival period of 15.2 months after the initial procedure. Disease-specific survival rates after open and percutaneous approaches for grade 2 disease were 53.8 and 53.3 months, respectively.

Tumor grade remains the most important prognostic indicator in patients with renal TCC regardless of the surgical approach. Grade 3 tumors are more aggressive, presenting in an advanced stage, and recurrences are more often associated with metastasis. Nephroureterectomy is the management of choice in the surgical candidate. Percutaneous management of upper tract TCC is usually reserved for patients with a solitary kidney, bilateral disease, or chronic renal insufficiency. Percutaneous treatment of grade 1 or 2 renal TCCU in healthy individuals with a normal contralateral kidney mandates strict and lengthy follow-up.

Endourology for Transitional Cell Cancer of the Renal Pelvis: Adjunctive Measures

The efficacy of endosurgical therapy of TCCP has been obfuscated by the myriad treatment approaches, as previously described, and by variations in the use of instillation therapy and postresection adjunctive measures. Regarding instillation therapy, various agents have been instilled using a variety of schedules in an effort to prevent tumor recurrence. For example, de Kock and Breytenbach (69) performed local open excision of an upper tract transitional cell cancer and followed this treatment with six weekly and then ten monthly retrograde instillations of 60 mg of thiotepa in 150 mL of normal saline over 30 minutes; the ureter was not occluded. Over a 5-year follow-up period, there was no recurrence. In other series, Eastham and Huffman (83), Streem and Pontes (344), Inglis and Tolley (161), and Grossman and co-workers (125) used mitomycin C in the upper urinary tract with no adverse side effects. In these reports, one to five instillations of 20 to 40 mg of mitomycin C or two instillations of 5 mg of mitomycin C were given in the immediate postoperative period either through a nephrostomy tube or a 7-Fr, 90-cm single-J ureteral catheter. In the percutaneous method, Eastham and Huffman (83) reported giving the mitomycin C as a continuous drip infusion at 50 mL per hour (40 mg of mitomycin C in 1,000 mL of saline) for 20 hours. Pressure in the renal pelvis was maintained at 15 cm H_2O or less. In contrast, infusion by the ureteral catheter consists of slowly instilling 5 mg of mitomycin C in 20 mL of saline into the ureteral catheter; the ureteral and urethral catheters are then clamped for a 30-minute period, after which they are opened to drainage. This is done on postoperative days 1 and 2. It is essential with both methods that before instillation an antegrade nephrostogram via the nephrostomy tube or a retrograde nephrostogram via the ureteral catheter be performed; there should be no evidence of extravasation or intrarenal backflow before instillation of any chemotherapeutic agent.

The largest experience with instillation chemotherapy in the upper urinary tract is with BCG (141,366). In their series, Jarrett and colleagues (168) reported using BCG in 19 of 33 patients treated endoscopically. The BCG was administered as 50 mL through the nephrostomy tube in six weekly instillations. They were unable to demonstrate any significant difference in survival curves between the patients who received BCG and those not receiving this adjuvant therapy. Other investigators have used similar regimens with BCG following percutaneous resection of the tumor and have not conclusively demonstrated any benefit from this adjuvant therapy (45,233). Sharpe and associates (330) reported on 17 kidneys with positive selective upper tract cytology but negative radiographic studies. In these patients, a 6-week course of weekly BCG (Pasteur strain, 120 mg in 100 mL of normal saline) was given; the solution was instilled slowly over 1 hour via an external ureteral catheter. The height of the solution was kept 20 cm above the patient, who was placed in a supine position. The patients voided 1 hour after the therapy. Overall, 75% of the patients had normalization of their urinary cytology at an average follow-up of 3 years. Complications with this approach were predominantly of a minor nature (dysuria and transient hematuria). There was only one major complication: fever with BCG bacteremia. Similarly, Bellman and colleagues (26) reported only minor side effects from percutaneous transnephrostomy BCG therapy; in their series, BCG instillations did not have to be stopped because of any complications. Of interest, subsequent rebiopsy of the renal pelvis revealed asymptomatic granulomas in 25% of their patients; the presence of granuloma formation had no influence on the success of the therapy. Mukamel and colleagues (255) also have documented the lack of significant adverse reactions from BCG in the upper urinary tract among 13 patients with documented vesicoureteral reflux. As of yet, there have been no deaths from using BCG in the upper tract; however, meticulous attention to detail before and during BCG instillation is essential. Specifically, a preinstillation nephrostogram should reveal an intact collecting system, there should be no hematuria at the time of instillation, the urine must be sterile, and the instillation should always progress at a low inflow pressure (i.e., 20 cm H_2O) (36,297).

Other adjunctive treatment variations have been reported. For example, Nurse and co-workers (266), Nolan and associates (265), and Patel and colleagues (284) placed a radioactive iridium 192 wire in the nephrostomy tract for 3 to 8 days in order to deliver 4,000 to 4,500 cGy at 0.5 cm

from the wire. With this regimen they experienced no seeding of the nephrostomy tract. Taking a different approach, Orihuela and Smith (279) followed the initial tumor resection with a second-look procedure and laser application to the base of the tumor. Presently, it is difficult at this stage to select a given regimen that produces reliable high-quality results. Only through further study and careful reporting of data will the optimal endosurgical approach to TCCP become clear. However, there is a suggestion that adjunctive instillation therapy, especially with BCG, and second-look biopsy or electroresection of the tumor base may reduce recurrence rates.

Endourology for Transitional Cell Cancer of the Renal Pelvis: Unsettled Issues

In addition to the aforementioned problems of the impact of technique on outcome, four other clinical issues directly affect the efficacy of an endosurgical approach to TCCP: accuracy of diagnosis, tumor implantation, recurrence, and surveillance. Unlike for TCCU, the accuracy in diagnosis of TCCP by ureteroscopic means is disconcertingly low. Huffman (150) and Huffman and colleagues (152) noted that undergrading or understaging occurred in 60% of the renal pelvic tumors approached ureteroscopically. This is a significant problem because the procedure itself is primarily of benefit only for low-stage, low-grade disease.

Tumor implantation caused by local seeding of the upper urinary tract or retroperitoneal extravasation remains an ongoing, albeit largely undocumented, concern. With regard to local seeding, Grasso and co-workers (123) have reported one case of ureteral and urethral seeding of a renal cell cancer after a flexible ureteroscopic procedure (9.8 Fr). However, there have been no published reports of ureteral transitional cell tumors occurring after endourologic treatment of a renal pelvic transitional cell tumor. Clayman has noted a case of extensive ureteral tumors developing after a combined percutaneous and flexible ureteroscopic procedure to treat a grade 2 noninvasive transitional cell tumor in the renal pelvis of a solitary kidney. The latter patient had no prior history of transitional cell cancer. He eventually required a ureterectomy and autotransplantation with a pyelovesicostomy; no metastatic disease developed. Whether this situation resulted from tumor dissemination or the multifocal nature of his transitional cell cancer remains unsettled. To date, there have been no other reports of extensive seeding of the ureter following ureteroscopy in patients with TCCP. A second area of concern is the potential for seeding of the retroperitoneum should ureteral perforation occur during ureteroscopy or from extravasation during placement of the percutaneous nephrostomy tract. Both fears have been realized, albeit in only one case each to date. Martinez-Pineiro and associates (233) noted local tumor recurrence in a patient with TCCP T_1, G_2 who underwent a ureteroscopic procedure followed by subsequent nephroureterectomy. During the ureteroscopic procedure, the ureter was perforated; extension of the tumor into the retroperitoneum was noted at the subsequent surgical procedure, and this patient went on to develop distant metastases and died of the cancer. In another case, Huang and colleagues (147) reported seeding of a nephrostomy tract 5 weeks after percutaneous transnephrostomy (36 Fr) biopsy of a grade 3 midureteral tumor. Although these represent only isolated case reports, the small number of patients undergoing these procedures, coupled with the lack of follow-up CT scan data and the relatively short follow-up period in all series, makes one cognizant that the retroperitoneal appearance of TCCP caused by extravasation during the procedure may be significantly higher than what has been reported to date.

Another area of potential problems centers around the possibility of pyelorenal backflow and the subsequent development of distant metastases. Lim and colleagues (223) noted in one patient that following ureteroscopy the nephroureterectomy specimen revealed submucosal migration of tumor cells into the renal venous and lymphatic spaces. However, these authors were using irrigation pressures as high as 200 mm Hg. Despite this disconcerting finding, no metastatic disease developed over the ensuing 6 months in their patient. Kulp and Bagley (208) noted no problems of tumor cell backflow in 13 patients; however, in all cases, only gravity irrigation or gentle hand irrigation was used. It would appear that if the irrigation pressure is kept below 100 mm Hg, this problem may not develop.

The next concern with regard to the endourologic management of upper tract transitional cell cancer is the problem of tumor recurrence or new tumor development in the ipsilateral intact upper urinary tract. Realizing that when a ureteral stump is left after nephrectomy for TCCP the recurrence rate in the ipsilateral ureter is 40%, one can hardly be surprised by the 20% to 75% recurrence rate reported at less than 2 years after percutaneous or ureteroscopic therapy for TCCP (205,346). This is really no different than the 23% recurrence rate in the upper tract after conservative open surgical therapy for grade 1 tumors or the 54% recurrence rate after similar conservative therapy for high-grade lesions (256,370).

Given the high rate of recurrent or newly developed tumors in the ipsilateral ureter and renal pelvis, postresection surveillance of the affected upper urinary tract is of major importance. Just as most urologists believe that cytology and cystography are inferior to cystoscopy for following patients with superficial bladder tumor, cytology and intravenous urography in large part may prove to be less reliable than ureteroscopy for following patients with TCCP. In the series reported by Grossman and colleagues (125), among patients with a *known* upper tract lesion, the cytology before the lesion was endoscopically removed was positive in only 8% of patients with a grade 1 lesion and 50% with a grade 2 lesion. Similarly, in Blute's experience among patients

with a radiographically identifiable upper tract lesion, the combination of intravenous urography, retrograde ureterography, and cytology diagnosed only 55% of all renal pelvic tumors, whereas ureteroscopic evaluation correctly identified all renal pelvic tumors. As such, given the poor track record of nonendoscopic studies when a lesion is present, the use of these same modalities for surveillance appears to be ill advised; periodic ureteroscopy appears to be essential.

Problems with a ureteroscopic surveillance protocol arise if a patient is going to require intravenous sedation, a formal outpatient surgical visit, and an indwelling ureteral stent every time surveillance ureteroscopy is completed. If current recommendations for bladder tumor surveillance are applied to transitional cell tumors of the upper urinary tract, this would include at least six examinations during the first 2 years and annual ureteroscopy thereafter (108,322). This certainly is not as simple or as inexpensive as office cystoscopy. In an effort to reduce the cost and complexity of surveillance cystoscopy, Kerbl and Clayman (188) have reported deliberately unroofing the ureteral orifice and tunnel with an Orandi electrosurgical knife in two patients undergoing endourologic management of upper tract transitional cell cancers. In both patients, the resulting refluxing ureteral orifice was sufficiently patulous to permit flexible ureteroscopy without dilation or sedation in the office. To date, both patients have undergone routine surveillance, office-based ureteroscopy, for over 2 years. In one patient, a total of three diminutive upper tract recurrences have been noted and subsequently treated on an outpatient basis. In the other patient, there has been one upper tract recurrence also treated in a similar manner. Of note, these tumors were too small to be imaged on either retrograde ureterography or intravenous pyelography. However, the potential negative impact of a refluxing ureter in a patient with upper tract transitional cell cancer may be of concern because approximately one-third of these patients subsequently will develop bladder tumors. This may further compound the risk of recurrent or new tumor development on the previously affected upper urinary tract. Conflicting reports regarding the potential risk of reflux in a patient with TCCB already exist in the literature; although some authors have noted no risk of upper tract TCC development in patients with TCCB and vesicoureteral reflux, others have reported as high as a 20% incidence of upper tract tumors over a 2- to 9-year follow-up period (73,205,281).

Although one might argue that if ureteroscopy can be done safely in the office, the follow-up for TCCP should become identical to the follow-up for TCCB. The natural corollary to this reasoning is that the minimally invasive approach could then be used in all cases of low-grade, low-stage TCCP. However, the impetus for conservative, endoscopic bladder surgery is largely due to the fact that the bladder is a solitary organ, the removal of which is a major surgical undertaking associated with significant operative morbidity, lengthy hospitalization, and major changes in a patient's quality of life. For TCCP, a similar situation pertains only in the patient with a functionally or anatomically solitary kidney (319). Only in that circumstance does ablative surgery carry similar quality-of-life issues to removal of the bladder, specifically long-term dialysis and renal transplantation. Furthermore, the extension of minimally invasive therapy for TCCP to patients with two kidneys has a high price. For the dubious benefit of preserving the affected kidney, the middle-aged patient with at least a greater than 34-year life expectancy will have to undergo at least 34 separate surveillance ureteroscopic procedures in addition to the likelihood of requiring at least three additional minimally invasive procedures to treat recurrent, low-grade TCCP and a 10% to 20% likelihood of eventual nephroureterectomy because of recurrent but now invasive, extensive, high-grade, or overly extensive disease. Based on these considerations and the previously cited review of the literature, minimally invasive surgery for TCCP should be reserved only for patients with a solitary kidney, renal insufficiency, or high surgical risk; for the patient who has two kidneys and normal renal function, a nephroureterectomy remains the most expeditious, probably least expensive, and most definitive means of treatment. The possibilities that TCCP or TCCU will metachronously involve the contralateral kidney (1% to 2.5%) or that the patient with a now solitary kidney will develop renal insufficiency are not sufficient arguments to change current surgical practice for this entity in the patient with two otherwise normal kidneys (205).

Simple and Peripelvic Renal Cysts

Renal cystic disease spans the pathologic spectrum, including benign and malignant processes, acquired and inherited conditions, and infectious and noninfectious etiologies. Renal cysts may occur within the renal cortex, within the medulla, or within the peripelvic region; they may have a simple, nonloculated or a complex, septated configuration.

The most commonly occurring renal cysts are of a simple, acquired, tubular origin. Simple cysts are noted in approximately 50% of the adult population at autopsy; meanwhile, 20% to 40% of patients 50 to 80 years of age have simple renal cysts sufficiently large to be detected on CT of the kidneys (217). The prevalence of cysts appears to increase with patient age; over two-thirds of patients older than 80 years of age will have a cyst detectable by CT (217). Simple cysts are lined by detached immature tubular epithelium capable of transepithelial secretion. As such, cyst fluid contains sodium and chloride that are secreted into the cyst lumen possibly by an active transport mechanism; water osmotically follows the transfer of these ions. Fluid accumulation within the cyst also is determined by a host of pericystic regulatory factors: hormones (e.g., vasopressin, arginine), growth factors (e.g., epidermal growth factor), and other substances (e.g., prostaglandins E_1 and E_2) (120).

In this framework, the growth and, in some cases, the “malignant degeneration” of renal cysts become understandable outcomes.

In the differentiation of simple renal cysts from other, more concerning, renal masses, the diagnostic accuracy of renal US or CT is sufficiently high to preclude further invasive or costly radiographic studies. Often, this is the end of the evaluation; however, some urologists prefer to obtain a single follow-up study in 1 year to look for any changes in the size or overall appearance of the cyst in order to further corroborate its benign nature. In this regard, it is relatively rare for simple cysts to increase in size; Richter and colleagues (302) noted that only 6% of cysts increased in volume over a 1- to 10-year follow-up period. Instead, the number of cysts in a kidney is more likely to increase with time; in the study of Dalton and associates (64), approximately one-third of the patients developed additional cystic lesions during a follow-up period of 3.5 years.

Overall, simple renal cysts rarely become symptomatic. Symptoms, such as flank pain, occur when the cyst obstructs a portion of the collecting system or because of the sheer size of the cyst. Macroscopic hematuria and hypertension are extremely rare signs attributable to a renal cyst. By the same token, only in the symptomatic patient is treatment of an otherwise simple cyst indicated. Similar criteria also have been used to treat some patients with adult polycystic kidney disease either by percutaneous drainage or open surgical reduction (28). For other cystic masses, treatment is indicated only if the cyst is thought to be the result of a more serious malady, such as infection or malignancy.

Technique

There are two minimally invasive strategies for treating simple renal cysts: drainage with sclerosis or drainage with ablation. Drainage with sclerosis is performed under local anesthesia using ultrasonographic or CT guidance. First, a sheathed needle is directed into the cyst and the cavity is drained. The fluid is sent for chemical, cytologic, and bacterial evaluation. Next, the sheath of the needle is left in the cyst cavity and contrast is introduced. This enables the radiologist to carefully examine the contours of the cyst wall and determine whether the cyst communicates with the collecting system. If the cyst is smooth walled, is not peripelvic in location, and is excluded from the collecting system, a sclerosant can be instilled into the cyst cavity.

A variety of sclerosants are available (e.g., 95% ethanol, bismuth phosphate, fibrin glue, hypertonic glucose); however, ethanol is the most popular and, possibly, the most effective agent. In this technique, approximately 25% of the cyst fluid is replaced with alcohol. The alcohol is left in place for 20 minutes, during which time the patient is moved into a variety of positions to ensure bathing of the entire inner lining of the cyst. The alcohol is then drained from the cyst and the sheath is removed (21,280,290).

Drainage with ablation of a simple renal cyst or of a peripelvic renal cyst can be done in either an antegrade (percutaneous) or retrograde (ureteroscopic) manner. In the percutaneous technique, the cyst can be approached in one of three ways: transcystic, transparenchymal, or indirectly through the collecting system. In each situation, the procedure begins with passage of a retrograde ureteral catheter. This will enable the urologist to instill an indigo carmine–stained mixture of contrast material and saline into the collecting system, thereby making it easy to differentiate between entry into the collecting system (i.e., blue fluid) and entry into the cyst cavity (i.e., clear to yellow fluid).

In the percutaneous transcystic method, the cyst is punctured with a nephrostomy needle (Fig. 19.28, parts 1A to 1C). The needle is then directed across the cyst and into the renal pelvis; entry into the renal pelvis is confirmed by aspiration of blue fluid. A guidewire is passed down the ureter or coiled in the renal pelvis. The point of entry into the cyst is dilated, and a standard 24- to 26-Fr resectoscope equipped with a roller electrode is introduced. At this point, the inner lining of the cyst is electrocoagulated in all areas except where the cyst abuts the renal parenchyma or renal pelvis. Now, with the safety guidewire covered by a nonconductive angiographic catheter, the opening into the collecting system, if thin-walled, can be widened using a cold knife or electrosurgery. A transcystic nephrostomy tube is placed at the end of the procedure, such that its tip lies well within the renal pelvis.

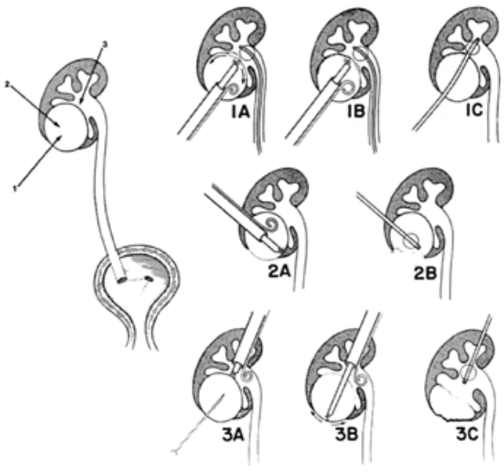

FIGURE 19.28. The three methods for percutaneously treating a renal cyst are depicted by the arrows: *1,* direct transcystic; *2,* direct transparenchymal; and *3,* indirect. **1A:** The cyst has been punctured directly and dilated; a 30-Fr Amplatz sheath has been passed, and through this a resectoscope has been introduced. The cyst wall abutting the collecting system is resected. Note that an occlusion balloon catheter has been passed up the ureter to assist in the recognition of the true collecting system. A safety guidewire catheter also has been placed in the cyst. **1B:** The remaining cyst wall is fulgurated with a roller electrode. **1C:** A transcystic nephrostomy tube is placed. **2A:** The parenchyma has been traversed in the process of entering the cyst. A 30-Fr Amplatz sheath is placed alongside a safety guidewire catheter. The outer wall of the cyst is resected, and other areas of the cyst wall are fulgurated. **2B:** A large-bore catheter is placed into the cystic cavity. The collecting system is not entered. **3A:** Via a remote calyx, the collecting system is entered and a 30-Fr Amplatz sheath is placed alongside a safety guidewire catheter. The presenting surface of the cyst is identified and resected. A needle has been placed into the cyst so that it can be readily drained and expanded, thereby aiding in its identification by the surgeon. Via the needle, normal saline stained with indigo carmine can be instilled into the cyst, thereby giving it a blue appearance and clearly delineating it from the normal collecting system. **3B:** The far wall of the cyst is fulgurated with a roller electrode. **3C:** A standard nephrostomy tube is placed in the collecting system.

In the percutaneous transparenchymal method, the cyst is entered by traversing the lateralmost portion of the renal parenchyma that overlies the cyst (Fig. 19.28, parts 2A,2B). Then a standard 24- to 26-Fr resectoscope is used to resect the outer, lateral cyst wall, thereby accomplishing a partial cyst decortication (148,291). The collecting system is never entered. If there is any bleeding at the end of the procedure, a catheter can be placed into the cyst cavity, thereby effectively tamponading the renal parenchyma.

In the percutaneous indirect method, a nephrostomy tract is placed in the kidney opposite the medial wall of the cyst (Fig. 19.28, parts 3A to 3C). A separate needle is passed percutaneously into the cyst cavity. By instilling an indigo carmine–stained mixture of contrast and sorbitol, the endoscopist is guided to the wall of the cyst that most closely abuts the collecting system and thus has a blue hue. With a resectoscope or a cold-knife urethrotome passed through the initial nephrostomy tract, the cyst wall is incised and the cyst is entered. Next, with use of a standard 24- to 26-Fr resectoscope equipped with a roller electrode, the far wall of the cyst is electrocoagulated. A nephrostomy tube is placed into the collecting system via the initial percutaneous puncture site, remote from the cyst cavity. This approach is of particular value when dealing with a peripelvic cyst (42,85,156,199).

The ureteroscopic approach to cysts is limited to smaller cysts (i.e., less than 2 cm) that have a section of their wall bulging

into a calyx or that share a common wall with the renal pelvis (i.e., peripelvic cyst) (182). If this approach is selected, it is still helpful to preplace a small percutaneous tube into the cyst cavity in order to fill the cyst with an indigo carmine–stained mixture of contrast and sorbitol. Then, via the rigid or flexible ureteroscope, a Ho:YAG laser or electrosurgical knife can be used to enter the cyst. Next, the inner surface of the cyst can be coagulated using either electrocautery or Nd:YAG laser energy (20 W).

In the rare event when a cyst has reformed despite ureteroscopic or percutaneous methods, a laparoscopic approach (i.e., drainage and cyst decortication) can be used.

Results

Drainage and sclerosis is the least invasive form of therapy for simple renal cysts. Short-term success rates for ethanol ablation are the highest of any sclerosant treatment at 97% to 100% (21,280). Cysts as large as 600 mL have been treated successfully with this method. Other sclerosants result in cyst disappearance in less than 50% of cases, especially when follow-up was extended beyond 2 years (144,290). Of note, the follow-up after ethanol ablation generally is under 1 year. Clearly, long-term follow-up studies on the durability of ethanol ablation are sorely needed.

The endoscopic treatment of renal cysts is indicated predominantly for peripelvic cysts or as salvage therapy for simple renal cysts when drainage and sclerotherapy fail. The percutaneous approach is still relatively rarely performed and hence the experience is small. For the percutaneous approach, the long-term success rate (i.e., complete cyst ablation) has been only 50% according to Plas and Hubner (291). In their series, with a median follow-up of 45.7 months, approximately 30% of the cysts recurred. The ureteroscopic approach has been reported only once (182). In one patient, the procedure was successful; however, the follow-up was less than 6 months.

Renal Abscess and Fungal Collections

A localized renal infection may occur either in the renal parenchyma (e.g., lobar nephronia, an infected renal cyst) or within the collecting system (e.g., pyocalyx caused by obstruction). The infections are due to *E. coli* in approximately one-third of cases; another one-third of patients are infected with either *Proteus mirabilis* or *Klebsiella pneumoniae* (174,307). Today, *Staphylococcus aureus* accounts for less than 10% of all renal abscesses (96). On rare occasion, a fungus is the underlying cause: *Candida albicans, Mucormycosis, Aspergillus,* or *Torulopsis glabrata* (169).

Presenting symptoms most commonly include fever, flank pain, or chills (60% to 90% of patients). Symptoms usually are present for up to 2 or more weeks before the diagnosis of a renal abscess is made. The most common associated illness is the presence of diabetes mellitus; these patients, as well as individuals with immunosuppressive disorders, are at greatest risk for developing life-threatening sequelae from an unrecognized renal abscess (96).

Today, the diagnosis of a renal abscess can be made more easily because of the advent of renal CT and US (Fig. 19.29). Fowler and Perkins (96) noted that among 61 consecutive patients with renal abscesses, CT or US provided a diagnostic accuracy of 96% and 92%, respectively.

On CT scan a renal abscess classically has a cystic, albeit thick-walled, appearance; the CT density of the abscess is usually greater than that of a cyst (134). On the other hand, the ultrasonographic appearance of an abscess is that of an irregular mass with echo-producing intralesional debris and a poorly defined back wall (373).

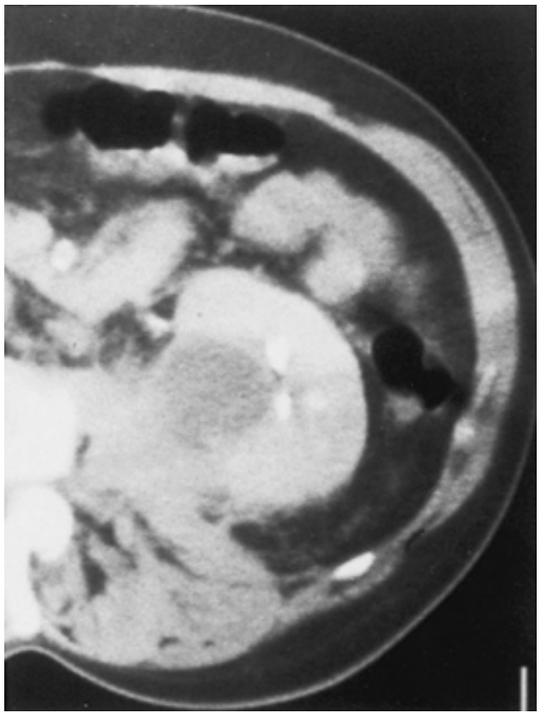

FIGURE 19.29. Computed tomography scan shows a cystic appearing lesion with debris. Puncture of the lesion confirmed the presence of a renal abscess. A drainage tube was subsequently placed inside the cavity as a therapeutic measure.

Technique

Although antibiotic therapy alone has been reported to cure the rare patient with a renal abscess, this approach has not been widely adopted. The consensus is that renal abscesses should be aspirated and, in most cases, percutaneously drained as soon as they are diagnosed. This is most easily done under US or CT guidance. Following a confirmatory diagnosis by needle aspiration, a 7- or 8-Fr self-retaining (e.g., Cope locking loop) percutaneous drainage tube is placed within the abscess cavity. An infracostal percutaneous route is selected in order to avoid any possible pleural contamination.

If the problem is one of a fungal bezoar, a standard percutaneous technique may be undertaken after the patient has been given parenteral amphotericin B and achieved appropriate serum levels. The urine at this point should be sterile. Via two retrograde ureteral catheters, the renal pelvis is irrigated with amphotericin B (5 mg/100 mL) to decrease the chances of retroperitoneal contamination by the fungus. Next, via an infracostal percutaneous approach, the fungal bezoar is removed with grasping forceps or suctioned from the kidney using the ultrasonic lithotripsy probe. At the end of the procedure, a nephrostomy tube is placed; one of the ureteral catheters is also left in place. Postoperatively, once a nephrostogram shows no extravasation and no remaining fungal bezoars, the collecting system is irrigated through the ureteral catheter with amphotericin B (50 mg/L at 50 mL per hour) for 2 to 3 days (31,137,175,377).

Results

Over the past few years, a few clinicians have reported limited success with antibiotic therapy alone for treating a renal abscess. Chakroun and colleagues (39) noted that this therapy worked in 25% of their patients, whereas Gelabert and associates (104) had only a single success among 12 patients.

Overall, the consensus remains that a renal abscess is best treated by aspiration combined with ongoing percutaneous drainage. Only in Chakroun and co-workers' (39) series was aspiration alone a viable treatment option; in this series of 12 patients, only three patients eventually required percutaneous drainage. However, for Gelabert and colleagues (104), as well as Janetschek and associates (166) and other clinical investigators, percutaneous drainage was the most definitive and effective means for treating a renal abscess. In several series, this form of therapy was effective in 82% to 88% of patients; in Fowler and Perkin's (96) extensive report of 57 renal abscess patients treated with percutaneous drainage between 1972 and 1988, the success rate was even higher at 97% (60,96,111,134,166,167). However, percutaneous drainage of a renal abscess is not an innocuous procedure; approximately 10% of patients develop hemorrhage, recurrent abscess, or urosepsis after this procedure.

Failed percutaneous aspiration and drainage of a renal abscess is fortunately rare. Most failures are due to a loculated abscess or are associated with a fungal infection. The patient with a loculated abscess can at times be salvaged percutaneously by the placement of multiple percutaneous drainage tubes. For the patient with a fungal abscess, irrigation of the abscess cavity with amphotericin B (50 mg/L at 50 mL per hour) is sometimes helpful in resolving the problem (134). However, for the most part when initial percutaneous therapy fails, the next step is open surgery, with manual fragmentation of any loculations followed by placement of large drains or, if the kidney is functioning poorly, nephrectomy; this open approach may be necessary in up to 9% of cases.

Because of the advances in antibiotic and endourologic therapy, the mortality rate from renal abscess has fallen to 7% to 9%. Today, most fatalities from renal abscess result from a delay in diagnosis rather than therapeutic failure.

As with the previously described parenchymally based renal abscesses, the best mode of therapy for infection of an obstructed portion of the collecting system (i.e., pyonephrosis

or a pyocalyx) is percutaneous drainage. In these cases, a percutaneous nephrostomy tube is placed into the obstructed area of the collecting system. This results in immediate relief of obstruction and drainage of the infection. When combined with appropriate antibiotic therapy, nephrostomy tube drainage is highly successful. In Janetschek and colleagues' (166) collected series of 21 cases, all patients with these conditions responded well to a percutaneous approach. However, two patients, despite percutaneous drainage, ultimately required a nephrectomy because of failure of the kidney to recover function (166).

Before the advent of endourologic techniques, urinary tract fungal bezoars usually were the harbinger of ureteral obstruction, urosepsis, and death; up to 80% of these patients succumbed. Today, however, successful therapy is achievable in the majority of these patients. A review of the endourologic literature reveals only a handful of cases of funguria with associated bezoar formation managed endourologically. In these cases, more than 80% of the patients have survived with an intact kidney following percutaneous drainage or extraction of the fungal mass (3,31,70,76,137,162,163,175).

Post–renal transplantation

In the renal transplant population, the frequency of a urologic complication is closely associated with the type of ureteral reimplant performed at the time of renal transplantation. Most of these complications are secondary to ureteral obstruction; the remaining, less common complications are due to urinary tract fistula formation, ureteral necrosis, and urolithiasis.

With the traditional Leadbetter-Politano reimplantation, urinary tract complications occur in 5% to 11% of patients (355). However, with the more recent adaptation of routine primary ureteral stent placement at the time of the operation or an extravesical technique for performing a ureteroneocystostomy, the incidence of urologic complications has fallen to below 4% (355). However, up to two-thirds of these problems are still due to ureteral obstruction. The obstruction may be either of an intrinsic (i.e., ureteral stricture) or an extrinsic (i.e., perirenal fluid collection, such as lymphocele, urinoma, abscess, or hematoma) nature. The development of strictures usually occurs early in the postoperative course, but in some cases ureteral stricture formation may occur as late as 5 years postoperatively (178,195,355).

When faced with a rising creatinine in the renal transplant patient, the clinician must determine whether the apparent compromise in renal function is prerenal (i.e., arterial stenosis, renal vein thrombosis, or alteration in fluid status), renal (i.e., rejection), or postrenal (i.e., obstruction or fistula). To evaluate for a ureteric or perirenal postrenal problem, a renal US study or a CT scan is of particular benefit. Either study can reveal the presence of hydronephrosis or an extrinsic obstructive lesion and assess for intrarenal filling defects. With regard to perirenal lesions, the diagnostic accuracy of the CT is slightly better than sonography; in one review, sonography detected 73% of perirenal fluid collections, whereas CT was correct in 87% of the patients (sensitivity of 64% and specificity of 94%).

An advantage of renal US is that it can be performed with duplex Doppler scanning. As such, the renal vascular RI can be determined. When the RI exceeds 0.75, the chances of an obstructive process are high. However, a normal RI argues for a nonobstructive process, such as transplant rejection or a fistula. In a study of 35 renal transplant patients with pyelocaliectasis by Platt and associates (292), the RI was elevated (average of 0.81) in 13 patients with proven obstruction; there were two false-negative diagnoses, but in both patients the obstruction was associated with a fistula. The latter problem was probably responsible for the apparently normal RI. After placement of a percutaneous nephrostomy in the obstructed patients, the RI fell to 0.67.

When obstruction is suspected, the next step should be an antegrade nephrostogram (177). This is of both diagnostic and therapeutic value. The site of obstruction can be delineated clearly; the presence or absence of an associated ureteric fistula can be determined; if need be, a Whitaker pressure study can be performed; and a percutaneous nephrostomy can be left in place after the study is completed. The Whitaker test can be most helpful in distinguishing between an anatomic and a functional narrowing. In one study, up to 25% of ureteric strictures were functionally insignificant; in these four patients, the rise in creatinine was subsequently shown to be due to rejection (177).

The other two major areas of complications following transplantation in which endourology has had an impact are ureteral fistulae and perirenal collections. The most common site of a ureteral fistula is either at the site of the ureteral reimplantation or, more rarely, along the renal pelvis. Diagnosis of this condition can be made most clearly either during an antegrade nephrostogram or a retrograde ureterogram. In either case, a ureteral stent can then be placed to “put the ureter to rest.” If an indwelling ureteral stent is placed retrograde, a urethral catheter also is indicated in order to preclude reflux and continued leakage at the fistula site. If the stent is inserted immediately after performing an antegrade nephrostogram, a percutaneous nephrostomy tube should be left in place to decompress the renal pelvis and prevent further passage of urine across the fistula.

Perirenal collections often produce symptoms of discomfort and a fullness in the lower abdomen; the usual sign is new-onset azotemia caused by ureteral obstruction. These collections may be due to one of four problems: urinoma, lymphocele, hematoma, or abscess. The CT scan is the most reliable method for diagnosing the presence of perirenal collection; at the same time the scan is done, the lesion can be drained and a self-retaining drainage tube can be placed. The obtained fluid can be sent for culture, cell blood count, and creatinine; these tests should effectively identify the nature of the collection.

Technique

The initial form of management for the majority of ureteral complications among renal transplant patients is placement of a percutaneous nephrostomy tube. Given the proximity of the transplanted kidney to the skin, the procedure can be accomplished rapidly and safely using either fluoroscopic or ultrasonographic imaging (336). The methods involved in dealing with ureteral strictures in the transplant kidney are the same as previously described for treatment of ureteral strictures in patients without a renal transplant. Likewise, the therapy for a ureteral fistula (i.e., placement of an indwelling ureteral stent) and for a perirenal collection (i.e., aspiration and drainage) do not differ from the techniques used to approach the same entities in patients with normal renal function and eutopic kidneys.

Results

Endourology has had a significant impact on the management of all types of ureteric and perirenal complications affecting the renal transplant patient. As previously noted, ureteric complications are usually due to either a ureteral stricture or a ureteral fistula. Ureteral strictures in the transplant patient have most commonly been treated with balloon dilation to 8 to 12 mm accompanied by ureteral stinting for 4 to 14 weeks with a 7- to 14-Fr ureteral stent. The success rate with this approach is 40% to 70% at an average follow-up of 2 years. Overall, strictures in the distal ureter or at the ureterovesical anastomotic site are more common than upper ureteral strictures and appear to respond better to endourologic management. In one study, the success rate with distal/ureterovesical junction (UVJ) ureteral strictures was 75%; however, only 16% of proximal ureteral strictures responded favorably to balloon dilation (93,172,177,192,283,333).

An alternative, albeit more invasive, approach to ureteric strictures is to endourologically incise the stricture. Conrad and colleagues (57) used a flexible wire-guided cold knife to endourologically treat 11 transplant patients with a ureteral stricture; all but two of the strictures were in the distal/UVJ portion of the ureter. An indwelling 14-Fr stent was placed for a period of 4 to 6 weeks. Success was achieved in 82% of patients with a mean follow-up of 28 months (2 to 61 months). Of interest, both UPJ obstructions and all six patients with very distal ureteral obstruction responded favorably to endoureterotomy; however, only two of four patients with middle or lower ureteral strictures had a favorable outcome. A similarly high rate of success has been reported by Youssef and associates (381a) using the Acucise device to cut the area of obstruction; a successful outcome was noted in five of six renal transplant patients. These data are similar to endoureterotomy data in the nontransplant patient population, among whom success rates for UPJ and distal ureteral obstruction are higher than for strictures lying in the lower or middle ureter that, after an endoureterotomy, have not been marsupialized into the renal pelvis or bladder, respectively. Overall, it would appear that an endourologic approach with balloon dilation or incision is a reasonable first step when dealing with posttransplant ureteral strictures, especially if the stricture involves the UPJ or UVJ area. Last, although endoureterotomy may be intrinsically more appealing to the urologic surgeon, at this point in time, given the small number of patients treated to date, there is no clear-cut difference in results between balloon dilation and endoureterotomy of distal strictures.

With regard to a ureteral fistula in the transplanted ureter, placement of an indwelling ureteral stent with either proximal (i.e., nephrostomy tube) or distal (i.e., urethral catheter) decompression is often effective. This is especially true if the leakage is associated with distal ureteral obstruction. However, ureteral fistulae are relatively rare, and experience with the endourologic management of this complication remains scant. In reviewing the available literature, the largest series of fistulae managed by stents was reported by Berger and co-workers (29); the procedure worked in only two of 12 patients. Subsequently, Hobarth and colleagues (143) and Irving and Kashi (164) independently reported an additional eight patients in whom either a ureteral stent or percutaneous nephrostomy was used to treat a ureteral fistula; a successful outcome was reported in five of the eight patients. One reason for the markedly improved results in the series of Irving and Kashi (164) is that these authors were careful to distinguish between a small ureteral fistula and total ureterovesical disruption as might occur with ureteral necrosis. In their series, patients with suspected ureteral necrosis were managed with direct surgical intervention. As such, endourologic methods were applied only to patients with small fistulae; among four patients with ureteral leakage unassociated with ureterovesical discontinuity, all were successfully managed endourologically.

Among perirenal collections, the most common type after renal transplantation is a lymphocele. In these cases, drainage may be followed by placement of a tube into the cavity; sclerotherapy with ethanol can be used if the lymphocele does not abut directly on the ureter or renal pelvis. Failing this, an open surgical procedure or, more recently, laparoscopic marsupialization can be performed. The latter has gained rapidly in popularity and today appears to be the treatment of choice should simple percutaneous drainage fail to resolve the problem (331). For other perirenal collections such as perirenal abscess, percutaneous drainage and appropriate antibiotic therapy is the first step. With regard to a nonexpanding hematoma, once the diagnosis is made, nothing further need be done unless the hematoma is causing extrinsic compression on the ureter. In this case, a ureteral stent can be placed until the hematoma resolves. Last, with regard to treating a perirenal urinoma, percutaneous drainage is the first step. Following this, the site of the

fistula must be identified and appropriate endourologic or surgical therapy instituted (vide supra).

EXTRARENAL APPLICATIONS

Part of "19 - ENDOUROLOGY OF THE UPPER URINARY TRACT: NONCALCULOUS APPLICATIONS "

Perirenal Abscess

Perirenal abscess can result from rupture of an acute renal abscess into the surrounding fatty tissue inside Gerota's fascia. Perirenal abscess formation usually arises as a complication of pyelonephritis, urolithiasis, penetrating trauma, and prior urologic procedures in the retroperitoneum or the collecting system. Perirenal abscess also may occur because of a secondary nonrenal etiology: enteric fistula, pancreatic abscess, and lumbar osteomyelitis. Hematogenous spread to the kidney from a cutaneous infection or intravenous drug usage also has been responsible for perirenal abscess formation. A significant number of patients with perirenal abscess will have diabetes mellitus or other coexisting debilitating conditions, such as underlying malignancy or immunosuppression.

The clinical course of a perirenal abscess is often insidious. The symptoms and signs are usually vague and nonspecific. Most commonly present is fever (58% to 83%), followed by flank or abdominal pain (20% to 70%), and a palpable mass (9% to 13%). Advanced cases may manifest with malaise, weight loss, and a draining sinus. Leukocytosis with a left shift is a routine finding. Urine cultures are usually positive; however, the bacteria isolated from the urine may not reflect the organisms isolated from the abscess in 19% of the cases. *E. coli* and *P. mirabilis* are the most common causative organisms; however, when the abscess results from hematogenous spread, *S. aureus* predominates (84,332).

Abdominal plain films may show scoliosis, loss of the psoas shadow and renal margin, urolithiasis, and gas within a perirenal mass. Intravenous pyelography can reveal thickening of Gerota's fascia, mottling of the perirenal fat, delayed renal function or nonfunction, focal or diffuse renal enlargement, presence of a mass effect, renal fixation, or hydronephrosis. Chest radiographs may be abnormal in up to 41% of cases; pleural effusion, lower-lobe consolidation, and elevation of the hemidiaphragm are the most common findings (87). Renal US characteristically will show round or oval hypoechoic lesions. However, abscesses containing large amounts of gas may be mistaken for bowel. Abscesses that contain a large amount of echogenic debris or with septations may have characteristics that are indistinguishable from a tumor (367). CT is the imaging modality of choice because it provides better definition of the extent of the abscess and its relationships to other structures than can be obtained with US. Typically, the mass has a soft tissue density (less than 20 HU) and may have a “rind sign” caused by vascular enhancement of the abscess wall after the administration of intravenous contrast (110). Rarely, scintigraphy with gallium- or indium-labeled white blood cells may be useful in determining the presence of an abscess when the diagnosis is uncertain.

Technique

Patients routinely are given broad-spectrum parenteral antibiotics before abscess drainage. The abscess is localized by US or CT. The abscess is then punctured with an 18-gauge, thin-walled needle. The puncture should be extraperitoneal and extrapleural (i.e., below the twelfth rib) to avoid seeding of the abscess contents into the peritoneal and thoracic cavities, respectively, which can result in peritonitis, pleural effusion, pyopneumothorax, and empyema. Contents of the abscess are aspirated and sent for Gram stain, culture, and sensitivities. A guidewire is advanced through the 18-gauge needle puncture and coiled in the abscess cavity. The tract is dilated with semirigid dilators under fluoroscopic or US guidance. A drainage catheter is then positioned and secured. The size of the drainage tube depends directly on the viscosity of the initial aspirate. Tube sizes generally range from 8 to 14 Fr, or occasionally, a vanSonnenberg sump catheter will be used for a very viscous collection. If the abscess is loculated, two or more catheters may be percutaneously placed to provide adequate drainage. Mean drainage times are between 5 and 20 days (213). Prolonged drainage should alert one to the possibility of an enteric or urinary tract fistula.

Saline irrigation of the catheters may be started after 48 hours to help clear debris from the cavity and prevent catheter occlusion. Sinograms may be obtained at the discretion of the urologist to monitor the size of the abscess cavity and to identify any fistulous tract. Once the drainage from the catheter has ceased, a sinogram is repeated. If the cavity is now small (i.e., not much larger than the drainage catheter), the catheter can be removed. Alternatively, if a substantial cavity persists, 95% ethanol can be used to attempt to sclerose the cavity. In this case, one must be certain that there is no communication between the abscess cavity and the collecting system or other viscera. Sclerosis is continued on a weekly basis for 3 to 6 weeks until the abscess cavity has completely collapsed around the drainage catheter, at which time the catheter can be removed.

Results

Perinephric abscess is a very serious problem that carries a high mortality rate, especially when prompt drainage and broad-spectrum antibiotics are delayed (Fig. 19.30). Even with timely percutaneous drainage, mortality rates are as high as 13%. Initial percutaneous drainage is the procedure of choice in the management of perirenal abscess and in select cases may be the only intervention necessary. Elyaderani and Moncman (87) reported that 2 of 6 perirenal

abscesses treated with percutaneous drainage resolved completely without further intervention. Lang (213) reported that 9 of 10 perirenal abscesses resolved with percutaneous drainage. These data are in agreement with results reported independently by Haaga (134) and by Gerzof and Gale (110).

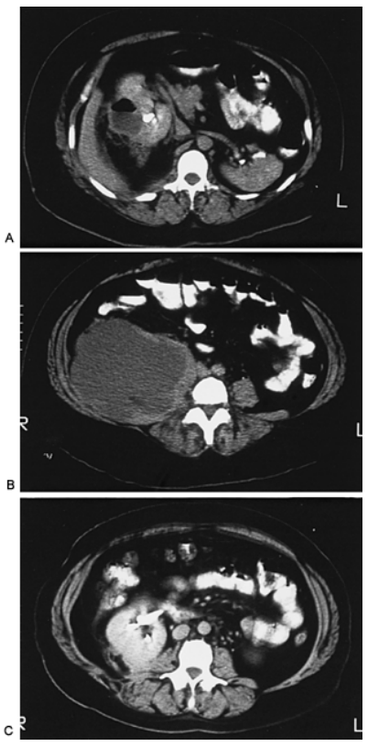

FIGURE 19.30. A: An obstructing upper-pole stone is present on this computed tomography scan. **B:** A large, retroperitoneal abscess caused by the obstruction and resulting infection. **C:** Three months after percutaneous stone removal and drainage of the abscess cavity, renal function has returned to normal and the abscess cavity has completely resolved.

Urinoma

A perirenal urinoma results from renal or ureteral trauma, urologic surgical procedures, or upper tract obstruction with associated ureteral or renal extravasation (e.g., neoplasm, surgical ligation, calculus disease). Extravasation of urine into the perirenal space is usually due to a forniceal rupture. When the amount of urine extravasated exceeds the capacity for lymphatic clearance, a perirenal fluid collection develops. Inflammation and fibrosis at the site of leakage can lead to ureteral obstruction, progressive hydronephrosis, and ultimately loss of renal function (215).

Clinically, the symptoms and signs of a urinoma include vague abdominal or flank discomfort and sometimes a palpable mass. There may be several months' delay between the causative event and presentation and diagnosis of the urinoma. In cases of a left-sided collection, one must be certain that the fluid-filled mass does not represent a pancreatic pseudocyst.

Plain films of the abdomen may reveal a mass if the urinoma is large. Findings on intravenous urography may include decreased renal function or absence of renal function on the affected side, cephalad and lateral displacement of the kidney, or contrast in the urinoma on delayed images. CT is the optimal study to define the extent and the relationship of the urinoma to surrounding structures. The wall of the urinoma may be thickened and smooth; the density of the urinoma is between -10 and +30 HU. Homogeneous enhancement of the urinoma implies a functioning kidney and presence of a communication between the urinoma and the collecting system (215). A retrograde pyelogram or antegrade nephrostogram is useful in identifying the level of obstruction and the point of extravasation.

Technique

Under US or CT guidance, a percutaneous drain is placed in the most dependent aspect of the fluid collection. The aspirated fluid is sent for creatinine determination, blood cell count, culture and sensitivities, and when indicated, amylase. The creatinine content of a urinoma should be similar to the high creatinine content of the urine.

A 10-Fr biliary urinary drainage or locking Cope loop catheter is placed. In instances where there is no longer a communication with the collecting system and no ongoing obstruction, drainage usually ceases after 48 to 72 hours. In cases of prolonged drainage, placement of an indwelling ureteral stent and urethral catheter or a percutaneous nephrostomy generally provides diversion sufficient for spontaneous closure of the fistulous tract. There are rare instances in which there is persistent drainage despite renal and bladder catheter drainage. In these cases, the urinoma drainage tract can be dilated. An endoscope can be used to identify the point of communication with the renal collecting system (156). Biopsies may be taken of the cavity to rule

out malignancy. If the point of communication is small and well away from the normal collecting system, the entire urinoma cavity and especially the base of the urinoma can be electrocoagulated with a roller electrode. If there is a larger communication, however, the urinoma cavity again can be electrocoagulated, following which a nephrostomy tube can be passed across the fistula and into the collecting system. The now dry cavity usually will collapse and seal around the shaft of the tube. In traumatic cases where there is devitalized tissue, an open surgical approach may be necessary for debridement and closure of the fistulous tract.

When the drainage has ceased, a sinogram is helpful to document collapse of the cavity. If there is still a large cavity, but drainage has stopped, and there is no demonstrable communication with the collecting system, ethanol sclerotherapy or repeat electrocoagulation can be used to facilitate collapse of the cavity.

Results

More than 90% of urinomas related to obstructive processes respond to drainage and correction of the underlying causes of obstruction. Ball and co-workers (18) found similar success in treating four pediatric patients with urinomas; all four patients responded well to percutaneous drainage of the urinoma. In urinomas resulting from trauma, success with percutaneous drainage is dependent on the viability of the tissue and the vascular supply near the fistulous tract. Cases in which there is a large amount of devitalized tissue, such as those associated with major trauma, may require open debridement and closure of the fistulous tract (248).

Lymphocele

For the urologist, a lymphocele occurs most commonly following pelvic lymphadenectomy, retroperitoneal lymph node dissection, or kidney transplantation. There is a 5% to 10% incidence of symptomatic lymphocele development following pelvic lymphadenectomy for malignancy (119). Khauli and colleagues (190) reported a 36% incidence of perirenal fluid collections following renal transplantation; among those patients, 7% had symptomatic lymphoceles that required intervention.

It is hypothesized that lymphoceles form when transected lymphatic channels are allowed to drain into a nonepithelialized space. Lymph fluid is devoid of platelets and has low concentrations of clotting factors; thus meticulous attention to ligation of the lymphatic vessels is necessary to prevent lymphocele formation. Perioperative heparin therapy, diuretic use, and high-dose corticosteroids also have been implicated as contributing factors to lymphocele formation (142,190).

The symptoms caused by a lymphocele result from compression of adjacent structures, lower-extremity edema, abdominal or pelvic mass, or bowel and bladder problems. In the transplant patient, the lymphocele may result in ureteral obstruction and a rise in serum creatinine. In the postpelvic lymph node dissection patient, the first sign of a pelvic lymphocele may be deep venous thrombosis and associated pulmonary embolus caused by partial obstruction of the external iliac vein by the lymphocele.

US is most commonly used to evaluate suspected pelvic fluid collections. In transplant patients, the US may reveal, in addition to the lymphocele, hydronephrosis or a mass effect on the bladder, colon, or iliac vessels. CT studies provide similar information.

Technique

The fluid collection is punctured under sonographic or CT guidance. The initial aspirate is sent for electrolytes, creatinine, cell count, and culture sensitivities. Additional studies that may be useful are determination of protein and cholesterol content along with cytologic analysis. The typical lymphocele fluid will have creatinine and electrolytes similar to serum, but the levels of cholesterol and protein are usually lower than serum values. Culture of the fluid should be sterile. Usually an 8- to 14-Fr drainage tube is left indwelling. When the drainage is less than 10 mL per 24 hours, the cavity is studied by contrast injection. If the cavity has collapsed around the drainage tube, the tube can be safely removed. If, despite 1 week of drainage, large amounts of fluid continue to be collected, sclerosis of the lymphocele may be attempted with 95% ethanol, povidone-iodine, tetracycline, or bleomycin (54,55,191,240). Sclerosis may be repeated, if necessary, at weekly intervals for several weeks. For patients with persistent or recurrent lymphoceles, laparoscopic intraperitonealization of the lymphocele is usually successful and has far less morbidity than an open approach (91,237,337).

Results

Small lymphoceles may not require treatment or may be managed by simple aspiration. Khauli and colleagues (190) reported an 86% spontaneous resolution rate in the management of asymptomatic posttransplant lymphoceles. For symptomatic lymphoceles, percutaneous drainage with or without sclerotherapy has a reported success rate of 69%; however, drainage may persist for up to 4 months following initial tube placement (55). For patients who fail percutaneous drainage and sclerosis and who have uninfected lymphoceles, the standard of care has been surgical exploration and intraperitoneal marsupialization with or without placement of a tag of omentum into the lymphocele cavity.

Laparoscopic intraperitonealization of the lymphocele has become popular (91,237,337). Fahlenkamp and associates (91) have reported the largest series to date with five

patients all successfully treated by a laparoscopic peritoneal window procedure, although one patient required an additional percutaneous drainage of an undrained loculated portion of the lymphocele. The enthusiasm for this procedure must be tempered by the small series of patients and the potential complications of a laparoscopic procedure. One case of division of a transplant ureter during laparoscopic lymphocele drainage has been reported (334).

In some cases, the patient's anatomy precludes intraperitoneal marsupialization of the lymphocele. Lucas and colleagues (228) have reported the successful use of an internalized Tenckhoff catheter to drain posttransplant lymphoceles in three patients with a mean follow-up of 5.3 years. In a fourth patient, the Tenckhoff catheter became occluded. At reexploration the catheter was found to be encased in omentum. Three Tenckhoff catheters were placed in tandem, and the patient has done well during a 3-year follow-up period.

Another approach to the postpelvic lymph node dissection patient with an anatomically unfavorable (i.e., not amenable to a laparoscopic approach), unresponsive lymphocele is endoscopic fulguration. McDougall and Clayman (239) reported using this approach in a patient with a refractory lymphocele after a pelvic node dissection. With the patient under intravenous sedation, a short, rigid ureteroscope could be passed into the cavity and the base of the lymphocele could be electrocoagulated. The drainage tube was not replaced, and drainage rapidly ceased; it has not recurred.

CONCLUSIONS

Part of "19 - ENDOUROLOGY OF THE UPPER URINARY TRACT: NONCALCULOUS APPLICATIONS "

With the passage of time, endourology has come to encompass a means of diagnosis and treatment for a whole host of maladies formerly approachable only by open surgery. In this regard, percutaneous and, more recently, ureteroscopic methods have prevailed, the latter being far less invasive than the former. The work that remains to be done is to further refine each of these techniques until its respective success rate routinely equals or exceeds the outcome of its open or laparoscopic surgical counterpart. To this end, the urologist and the bioengineer need to work hand in hand to develop and then critically test each new, less invasive treatment modality as it becomes available.

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20

RENAL CYSTIC DISEASE

Marguerite C. Lippert

M.C. Lippert: Department of Urology, University of Virginia Health Science Center, Charlottesville, VA 22908.

Contents

Renal cysts are abnormal dilations somewhere along the renal tubule between the glomerular capsule and the collecting system or are diverticulum-like structures possibly in continuity with the nephron. All renal cysts originate from microscopic renal tubules by proliferation of renal epithelial cells to form a diverticulum from the tubule wall and accumulation within the cyst of fluid from either glomerular filtrate or net transepithelial fluid secretion (144). Renal cysts may develop by heritable, developmental, or acquired processes. Renal cystic disease can involve both

kidneys diffusely as autosomal-dominant polycystic kidney disease (ADPKD), one particular area of both kidneys as medullary sponge kidneys, or just one kidney or part of it as multicystic kidney. Alternatively, a cystic tumor can replace normal renal parenchyma as in multilocular cyst. Finally, simple cysts can occur alone or together anywhere in the kidney.

Classification of cysts for the purpose of simplifying concepts does not necessarily provide a practical, clinical framework for such diverse cystic diseases. Hence, although the classification of Osathanondh and Potter (290), based on microdissection studies, brought a basis for future research on the pathogenesis of renal cystic disease, the clinician was not aided in making a diagnosis from history, physical examination, and radiographic studies. Meaningful clinical classifications of renal cystic disease based on clinical and radiographic features, genetic investigation, and morphology, such as those of Bernstein (28) and Gardner and Evan (127), honestly portray the diversity of renal cystic diseases, but they do not lend themselves to a simple conceptual framework. Table 20.1 gives the 1987 classification from the Committee on Classification, Nomenclature, and Terminology of the American Academy of Pediatrics Section on Urology that offers broad genetic categories but still displays adequately the diversity of renal cystic diseases (137). The advent of ultrasonography (US), magnetic resonance imaging (MRI), and computed tomography (CT) have drastically improved the clinician's ability to diagnose and differentiate the various renal cystic diseases. There has been rapid recent progress in identification or chromosomal localization of responsible disease genes, giving insights into the pathophysiology of the genetic renal cystic diseases. The importance of a careful family history is emphasized by the classification of renal cystic diseases into genetic categories. Table 20.2 shows the known linkages of genetic renal cystic diseases.

Genetic
Autosomal-recessive (infantile) polycystic kidneys (ARPKD)
Autosomal-dominant (adult) polycystic kidneys (ADPKD)
Juvenile nephronophthisis–medullary cystic disease complex (NMCD): Juvenile nephronophthisis (autosomal recessive) (NPH) Medullary cystic disease (autosomal dominant) (ADMCKD)
Congenital nephrosis (autosomal recessive)
Cysts associated with multiple malformation syndromes
Nongenetic
Multicystic kidney (multicystic dysplasia) (MCDK)
Cystic nephroma (multilocular cyst)
Simple cysts
Medullary sponge kidneys (<5% inherited)
Acquired cystic kidney disease in chronic hemodialysis patients (ACKD)
Caliceal diverticulum (pyelogenic cyst)

Adapted from Glassberg K, et al. Renal dysgenesis and cystic disease of the kidney: a report of the Committee on Terminology, Nomenclature and Classification, Section on Urology, American Academy of Pediatrics. *J Urol* 1987;138:1085, with permission.

TABLE 20.1. CYSTIC DISEASE OF THE KIDNEY

Disease	Inheritance	Chromosome
$ADPKD_1$	AD	16p31.1
$ADPKD_2$	AD	4q13-q23
ARPKD	AR	6p21
NPH_1	AR	2q12-q13
NPH_2	AR	9q23-q31
$ADMCKD_1$	AD	1q21
$ADMCKD_2$	AD	16q12
MKS_1	AR	17q21-q24
MKS_2	AR	11q13
VHL	AD	3p25.5
TSC_1	AD	9q34
TSC_2	AD	16p13.3

AD, autosomal dominant; ADMCKD, autosomal-dominant medullary cystic kidney disease; ADPKD, autosomal-dominant polycystic kidney disease; AR, autosomal recessive; ARPKD, autosomal-recessive polycystic kidney disease; MKS, Meckel's syndrome; NPH, nephronophthisis; TSC, tuberous sclerosis; VHL, von Hippel-Lindau disease.

TABLE 20.2. GENETIC RENAL CYSTIC DISEASES—KNOWN LINKAGES

AUTOSOMAL-DOMINANT POLYCYSTIC KIDNEY DISEASE

Part of "20 - RENAL CYSTIC DISEASE "

ADPKD is the most common form of cystic disease of the kidney and is caused by mutations in any one of at least three genes: PKD_1 on chromosome 16 (accounting for 85% of patients), PKD_2 on chromosome 4 (accounting for 15%), and the unmapped PKD_3 (probably accounting for rare families unlinked to the other two sites) (Table 20.3). It is the third most common cause of end-stage renal disease (ESRD), contributing 6% to 12% of patients receiving chronic renal dialysis. Fifty percent of patients typically develop chronic renal failure by age 60 (119). The highest incidence rate of ESRD from ADPKD is 1.5 per 100,000 population, occurring between the ages of 45 and 64 years (99). ADPKD occurs in about 1 in every 1,250 live births and is characterized by bilateral cystic disease in enlarged kidneys with a retained reniform shape. It is a systemic disease, and subsets of patients may develop

extrarenal manifestations such as liver cysts or cerebral aneurysms.

Disease	Inheritance	Chromosome	Gene	Mean Age Onset of ESRD (yr)	Gene Product
$ADPKD_1$	AD	16p31.1	PKD_1	54.3	Polycystin1
$ADPKD_2$	AD	4q13-q23	PKD_2	74	Polycystin2

AD, autosomal dominant; ADPKD, autosomal-dominant polycystic kidney disease.

TABLE 20.3. ADPKD—KNOWN LINKAGES

Clinical Features

Typically, for the first 10 years of life, the kidneys are normal in function and anatomy. From age 10 to 30 years, US may show the presence of cysts, although the patient is asymptomatic. However, from 30 to 40 years, the patient may be diagnosed because of symptomatic presentation such as palpable kidneys, microscopic or gross hematuria, urinary tract infection (UTI), flank pain, or renal colic from passing clots. Although elevation of creatinine may begin between 40 and 50 years of age, dialysis or renal transplantation for ESRD does not typically become necessary until after age 50. Without dialysis or renal transplantation, the mean age of death for ADPKD is 50 years (81) and patients die of uremia (59%), heart failure, and cerebral hemorrhage. However, more recent studies suggest that many patients today are being diagnosed as having ADPKD without symptomatic presentation because of modern imaging and that these patients may remain without ESRD, death, or symptoms until their seventies (73,89).

Polycystic Liver Disease and Extrarenal Cysts

Liver cysts are the most common extrarenal manifestation in patients with both PKD_1 and PKD_2 mutations. Although about 50% of ADPKD patients have liver cysts (241), liver function remains normal except in rare cases of severe massive cystic disease compressing the biliary tree, leading to biliary obstruction and obstructive jaundice (102). Unlike renal cysts, in women, liver cysts are more numerous, occur earlier, and are more extensive in women (408). Multiparity and postmenopausal estrogen therapy increase the risk of massive hepatic cystic disease (109,353). Hepatic cyst development requires somatic inactivation of the normal allele coupled to a germline mutation just as in renal cysts (401). Polycystic liver disease has rarely occurred as a genetically distinct event with no association with ADPKD (190). Liver cysts rarely have been found in children with ADPKD, although they have been described in an 8-month-old ADPKD patient (272).

Although massive hepatic cystic disease usually does not impair hepatic function, a minority of patients complain of symptoms such as abdominal swelling, intermittent attacks of pain, shortness of breath, pain on stooping, dyspnea, early satiety, nausea, heartburn, and regurgitation (280,390). When the symptoms are disabling, initial treatment can include percutaneous drainage and sclerosis or laparoscopic fenestration, especially if there is one or a small number of dominant cysts (381). However, if there are many cysts, part of the liver is spared, allowing treatment with combined hepatic resection and fenestration (280). Occasionally, symptoms remain despite fenestration procedures, at which time orthotopic liver transplantation is considered (with or without kidney transplant depending on dialysis dependency) (204). Hepatic cyst infections, although rare, can be confused with renal cyst infections and are best treated with percutaneous drainage and antibiotics that concentrate in the biliary tree, such as trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones (136).

In addition to liver cysts, ADPKD patients have developed cysts in the pancreas, lung, ovaries, esophagus, testes, bladder, thyroid, uterus, spleen, pineal gland, subarachnoid space, epididymis, seminal vesicles, and prostate. The estimated prevalence of pancreatic cysts is 98.5% in ADPKD patients older than 20 years of age (377). Complications of pancreatic cysts in ADPKD are rare, but chronic obstructive pancreatitis has been reported (254). Polycystin 1 has been found in epithelial cells of the pancreas.

Until the advent of US, seminal vesicle cysts were not described in ADPKD. However, when male ADPKD patients were screened with transrectal ultrasound (TRUS), 60% were found to have seminal vesicle cysts and 11% had prostate cysts (84). Hendry and associates (170) noted that although the TRUS appearances suggested seminal vesicle cysts in six male ADPKD patients, vasograms revealed dilation of the seminal vesicles from atonicity or failure to effectively contract with no evidence of seminal vesicle cysts (170). Ovarian cysts are not more prevalent

in female ADPKD patients than in the general population (408).

Aneurysms and Hernias

Intracranial aneurysm (ICA) rupture is the most feared extrarenal complication of ADPKD. From 0% to 40% of ADPKD patients have asymptomatic, unruptured cranial aneurysms on autopsy, prospective angiographic imaging studies, and prospective noninvasive imaging studies (35,52,64,188,368,393). Currently, the prevalence of ICAs is approaching 10% in ADPKD patients, as opposed to 2% in the general population. Familial clustering of ICA in ADPKD patients does occur (212,406), with a prevalence of 16% in those families (408). ICAs have occurred in both PKD_1 and PKD_2 families.

The risk of rupture increases with the size of the aneurysm, with most aneurysms being less than 10 mm in size in ADPKD patients. Hence, the yearly risk of bleeding is low (0.5% to 2%) but the cumulative risk remains significant and depends on expected survival, which can be about 60 years in ADPKD patients (259). However, the average patient age when ICAs rupture in ADPKD is younger than in the general population and varies from 37 to 47 years of age (63). Although most acute neurologic events in ADPKD patients do not result from ruptured ICAs, these ruptured aneurysms can result in the potential sequelae of subarachnoid hemorrhage, with greater than 50% mortality and permanent disability; however, they are potentially preventable (63,259). Systematic screening of ADPKD patients with a positive ICA family history or previous aneurysmal rupture with MRI angiography beginning in the third decade of life is recommended (259). If angiography revealed an aneurysm, treatment with either microsurgical clipping or endovascular coiling should be recommended if the individual risk of rupture is higher than the risk of treatment. Such risk is dependent on the patient's age and health and the size and location of the ICA. In general, microsurgical clipping is still the treatment of choice, when feasible, because it is curative unless the patient is older, in which case endovascular coiling is a good alternative (259).

Cardiovascular abnormalities such as cardiac valve anomalies, dilation of the aortic root, dissections of the thoracic aorta, and coronary artery aneurysms have been reported to have an increased incidence in ADPKD patients (158,381). Routine echocardiography with Doppler analysis revealed 26% incidence of mitral valve prolapse, 31% incidence of mitral incompetence, 8% incidence of aortic incompetence, and 6% incidence of tricuspid prolapse in ADPKD patients (185). Symptoms of mitral prolapse (e.g., palpitations, nonexertional chest pain) are more common in ADPKD patients than in controls (119). PKD mutations may be responsible because polycystin 1 and polycystin 2 are strongly expressed in the medial myocytes of the elastic and large distributive arteries as well as in cardiac myocytes and valvular fibroblasts (149). Other nonrenal manifestations of ADPKD involve increased incidence of inguinal hernias, hiatal hernias, colonic diverticula, and cholangiocarcinoma. Polycystin 1 has been found in the epithelial cells of the intestine.

Pain

Pain is the most common presenting symptom of ADPKD, particularly in women (408). It antedates renal palpability and occurs in 59% of affected individuals (81). Pain usually occurs in the flank or lateral abdomen but may radiate to the epigastrium or suprapubic area. Acute pain can be secondary to cyst rupture or cyst hemorrhage. The more common dull pain increases as the disease progresses and cysts enlarge, and no etiology has been confirmed. Perhaps pain results from the stretching of the renal capsule, pressure on adjacent organs, or traction on the renal pedicle. Distinguishing this chronic dull pain from the pain of a simultaneous renal disease such as obstruction, hemorrhage, infection, or tumor is difficult but of great importance for the preservation of future renal function. These latter etiologies tend to cause pain of more recent onset. Abdominal pressure from massive hepatic cystic disease needs to be considered.

Hypertension

Mild to moderate hypertension antedates the onset of ESRD in about 60% of ADPKD patients. Before renal deterioration, ADPKD patients with hypertension have more renal cystic involvement than normotensive ADPKD patients (22). Cyst decompression can transiently lower blood pressure in hypertensive ADPKD patients until renal cystic volume increases again (103,115,384). Enlarging cysts could theoretically compress renal vessels, causing renal ischemia and thereby activating the renin-angiotensin-aldosterone system. Consequently, angiotensin-converting enzyme (ACE) inhibitors are widely prescribed as first-time agents for treating hypertensive patients with ADPKD. However, in hypertensive ADPKD patients with chronic renal insufficiency and massive cystic involvement, ACE inhibitor therapy can cause reversible renal failure (61). The mild to moderate hypertension in ADPKD responds well to drug treatment. Antihypertensive treatment may or may not retard the development of ESRD. Cardiovascular disease is the most common cause of death in ADPKD patients (408). Control of blood pressure is necessary to prevent accelerated hypertension and cardiovascular events. Mild to moderate hypertension in ADPKD patients may decrease on dialysis (326). PKD_1 patients have a fourfold increase in prevalence of hypertension compared with PKD_2 patients and have an earlier age of onset (34.8 versus 49.7 years) (376).

Hematuria; Flank Masses

Hematuria, gross or microscopic, is common, occurring in up to 64% of affected individuals (89). It is the presenting complaint in 35% (225). Hematuria can result from spontaneous or traumatic cyst rupture or concomitant calculi, infection, or neoplasm. An evaluation of hematuria in ADPKD patients should include all of these possibilities. Clots can cause renal colic and obstruction of the urinary tract. The most common inciting events precipitating hematuria in ADPKD patients are UTIs (42%), followed by sports or strenuous activity (20% in males and 11% in females) (225). Approximately 60% of ADPKD patients have palpable flank masses, of which one-third are bilateral and two-thirds are unilateral. However, it is a less common (15% of patients) finding at initial presentation.

ADPKD in Children

Less than 10% of cases of ADPKD present in the first decade of life (224). It is important to differentiate between children presenting at an early age with symptoms or complications leading to the diagnosis of ADPKD as opposed to those children of affected families in whom the diagnosis is made by family screening. Those identified in childhood by US family screening may have a benign early course (348), compared with those diagnosed *in utero* or by symptoms in the first few months of life, who have an estimated perinatal mortality of 43% with a 67% complication rate for the survivors by the age of 3 years (249). Children diagnosed as ADPKD *in utero* or in the first year of life have more severe renal cystic disease. In affected fetuses, oligohydramnios can occur earlier than in autosomal-recessive polycystic kidney disease (ARPKD) because the renal developmental abnormality occurs earlier in ADPKD than in ARPKD (154). Although most ADPKD infants survive, they have a more rapid decline in their renal function and more significant hypertension than their affected adult relatives. Of 24 children diagnosed with ADPKD prenatally or up to 1 year of life, 16 developed hypertension and required treatment at the mean age of 2.9 years; 3 of the 16 developed ESRD at the mean age of 2.8 years (249). Presenting symptoms in neonates include renomegaly in mild cases and respiratory distress or stillbirth in severe cases. Presenting symptoms after 1 year of age include renomegaly, hypertension, and hematuria.

Although simple renal cysts are common in adults, they are rare enough in children that any cyst on a renal US in a child at risk for ADPKD probably indicates the presence of ADPKD (121). When 106 children younger than 18 years of age who were at 50% risk of ADPKD were screened with US by these criteria as well as gene linkage analysis, 45% screened positive for ADPKD by both modalities. Fourteen children (13%) were positive for ADPKD by gene linkage analysis but had a normal initial US, although subsequent US examinations were positive for ADPKD during this analysis (121). The US false-negative rate was 25% using these criteria and highest in those children younger than 5 years of age. Since the development of present renal imaging techniques, the number of ADPKD cases discovered in childhood appears to be almost as high as that of ARPKD patients surviving the neonatal period (123).

Children with an early onset of severe ADPKD have a PKD_1 genotype and have an affected parent whose milder disease presented in adulthood. The increase in disease severity is limited to the kidney, which has a higher number of cysts and mostly glomerular cysts (289). Even though the child or fetus carries the same stable mutation as the affected parent, 45% of the subsequent gene carrier offspring have early-onset ADPKD, even with different partners (154). A modifying gene could be transmitted from the affected parent, which might alter the rate of somatic mutation at PKD_1 (289).

A less common cause of early onset of severe ADPKD occurs when both PKD_1 and TSC_2 [the more common gene causing tuberous sclerosis (TSC)] are both deleted, resulting in a phenotype with early-onset multiple renal cysts and/or early renal failure (50). This PKD_1–TSC_2 contiguous gene syndrome can occur because TSC_2 and PKD_1 are located a few nucleotides apart on chromosome 16. Patients may show findings of TSC [renal angiomyolipomas (AMLs), facial angiofibromas, and central nervous system (CNS) lesions resulting in mental retardation and/or seizures] before or after their early-onset severe renal cystic disease.

Morphology

On gross inspection, the ADPKD kidneys are huge because they are filled with hundreds of fluid-filled cysts (Fig. 20.1). Their surfaces are distorted by innumerable large cysts. However, unlike dysplastic kidneys, they retain their reniform shape. At autopsy, the mean combined kidney weight of clinically asymptomatic ADPKD patients was 512 g; of symptomatic patients, 930 g (165); and of ESRD ADPKD patients who came to renal dialysis, 2,600 g (23). The cut surface shows extensive parenchymal replacement of cortical and medullary cysts, which vary from a few millimeters to a few centimeters in diameter (Fig. 20.2). Cyst fluid varies from clear yellow to chocolate brown and from watery to gelatinous.

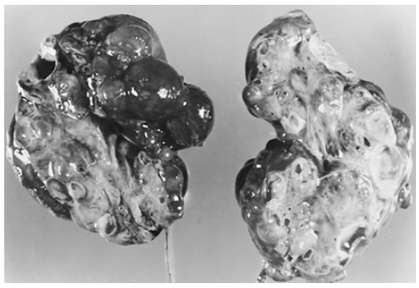

FIGURE 20.1. Autosomal-dominant polycystic kidney disease. Innumerable cysts distort the surfaces of these bilaterally enlarged kidneys. (Courtesy of Dr. S.E. Mills, Department of Pathology, University of Virginia Medical School, Charlottesville, VA.)

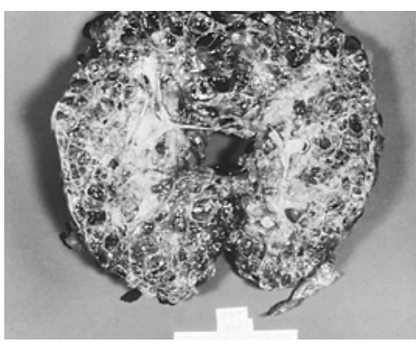

FIGURE 20.2. Autosomal-dominant polycystic kidney disease. Cut section reveals extensive parenchymal replacement by cortical and medullary cysts of varying sizes. (Courtesy of Dr. S.E. Mills, Department of Pathology, University of Virginia Medical School, Charlottesville, VA.)

On microscopic study, islands of normal renal parenchyma are found, although most parenchyma has been replaced with cysts. The cysts are lined by a single layer of flattened cuboidal or columnar epithelium, but glomerular and tubular cysts may also be recognized. Cysts involve all elements of the nephron and collecting ducts. Estimates suggest that only 1% to 2% of the 2 million renal tubules develop cysts (147).

Pathogenesis

Fewer than 5% of the nephrons develop cysts in patients affected with ADPKD. Although every cell in the kidney harbors the dominant mutations in patients with ADPKD genotypes, a “second hit” mechanism must disable the wild-type allele before a solitary tubule cell begins to divide until a microcyst is formed. When cysts become 2 mm in diameter, 70% of them separate from the tubule of origin and fill with fluid exclusively by transepithelial secretion of sodium chloride (NaCl) and fluid under central control of cyclic adenosine monophosphate (cAMP) (145). Transepithelial fluid secretion and extracellular matrix remodeling are secondary factors (143).

Hence, the rate-limiting step in a two-step process of cyst formation is inactivation of the remaining normal allele as an acquired, or somatic, mutation in patients with a germline PKD_1 mutation (319) or with a germline PKD_2 mutation (226,307,378). Epithelial cells lining the renal and biliary ducts cysts appear to have “forgotten” how big the tubule is supposed to be and continue to proliferate. Kidneys from patients with ADPKD exhibit high levels of apoptosis (programmed cell death) as well as cellular proliferation (276), just as in embryonal renal development. Cysts may be viewed as survivors of programmed cell death, whereas the surrounding tubular epithelium may be unusually susceptible to the forces that cause apoptosis (145). Cyst enlargement seems insufficient to account for development of ESRD in ADPKD, but cysts may adversely affect adjacent renal parenchyma, resulting in cystic fibrosis through paracrine and endocrine factors (407) and hence renal failure.

Genetics and Diagnosis

The mutant gene in ADPKD, either PKD_1 or PKD_2, is expressed in an autosomal-dominant pattern, with a 50% chance of inheritance. However, within a given family, there is variable penetrance and variable ages of onset. As many as

25% of patients have no family history for ADPKD (165) because (a) affected relatives died of other causes before their disease was diagnosed, (b) affected living relatives may not be aware of their diagnosis, (c) nonpaternity, or (d) spontaneous new mutations. Spontaneous mutations occur in less than 10% of ADPKD patients (119). The mutation rate for ADPKD has been observed to be high and has been estimated to be 6.9×10^{-5} (92). By the age of 30, 70% penetrance has been estimated, and 99% has been estimated by the age of 55 (92). Humans homozygous for ADPKD have not been described (143).

In 1985, Reeders and colleagues established a linkage of a PKD locus to the α-globulin locus on the short arm of chromosome 16 using reverse genetics. Now christened *PKD_1*, this gene on chromosome 16p13.3 (15) has been mapped, fully sequenced, and characterized. Mutations on this long gene (52 kb) account for 85% of ADPKD patients who have the more severe form of ADPKD (191). PKD_1's protein product, polycystin 1, among the largest reported, is predicted to function as a membrane glycoprotein involved in cell–cell or cell–matrix interactions. Both the size of the gene and its complicated genomic structure with highly homologous loci elsewhere on chromosome 16 prevent direct mutation testing for the purpose of screening at-risk individuals. Linkage-based testing is feasible, but complicated by the existence of two distinct loci (227).

PKD_2, the mutated gene in the milder ADPKD phenotype, has been localized to chromosome 4q 13-23 (222,311) and characterized (273). Polycystin 2, the PKD_2 gene product, and polycystin 1 may be involved in a common signaling pathway that links extracellular adhesive events to alteration in ion transport, possibly regulating transmembrane Ca^{2+} fluxes (273,339,383).

Because 15% of ADPKD patients were found to have no linkage to PKD_1 (297,412), a search for PKD_2 began that was far more expeditious than the PKD_1 search because the PKD_2 gene has a far less complex genomic organization. Therefore gene-based diagnosis in PKD_2 is simpler than in PKD_1. However, because only 15% of ADPKD families have this form of the disease, it is less clinically useful in the absence of effective PKD_1 gene-based mutation detection. PKD_2 has a milder renal phenotype compared with PKD_1 as judged by age at onset of hypertension, ESRD, and cyst appearance (163,297,331,376). The existence of PKD_3, a third unmapped gene, would explain why some linkage studies do not link a few ADPKD families to either PKD_1 or PKD_2 (9,85); however, evidence is inconclusive (301).

Both forms of ADPKD are caused by a second hit mechanism that disables the wild-type allele. Within PKD_1 and PKD_2 families, phenotypic variability may be explained partially by gender and partially by random somatic events (i.e., the second hits) that inactivate the normal PKD_1 or PKD_2 allele. Because familial clustering of such ADPKD complications as intracranial saccular aneurysm occurs, attempts to find genetic heterogeneity to explain variability between families has been explored in addition to PKD_1 or PKD_2 mutations. Hateboer and associates (164) found differences only in the prevalence of hypertension and hernias between PKD_1 families secondary to the different PKD_1 mutations segregating to each family within their study.

Separate modifying genes may also affect the ADPKD phenotype by altering the chance of somatic mutation such as the ACE genotype. PKD_1 patients homozygous for the ACE deletion allele are at increased risk for developing ESRD before the age of 50 years; however, they do not have a greater prevalence of hypertension (310). Another example of a modifying gene may be mutant cystic fibrosis transmembrane conductance regulator protein (CFTR) because patients with ADPKD and cystic fibrosis (CF) had less severe polycystic kidney and liver disease (normal renal function, smaller renal volumes, absence of hypertension, and no liver cysts) as opposed to family members with only ADPKD (292).

Because of the technical demands and expense of both mutation detection and linkage analysis in ADPKD, identification of the genotype is not currently possible in most cases. There may be an exception in a subset of ADPKD families who reach ESRD late in life because this subset may be enriched for PKD_2 and gene-based diagnosis is simpler for PKD_2 (358). Gene-based diagnosis of PKD_1 is currently not practical because of complications engendered in detecting mutations in the reduplicated regions of the PKD_1 gene and because of the absence of recurrent mutations (358). Molecular genetic diagnosis of PKD_1 is best done by genetic linkage studies using intragenic and closely flanking polymorphic markers to overcome the problem of recombination.

Presently, the minimum requirement for the use of the test is the testing of two related clinically affected persons (120). Increasing the number of affected persons multiplies the degree of confidence in the recognition of the haplotype with which ADPKD is transmitted within each family. This requires large families, but in such a family, the predicated gene has a less than 5% error rate, which facilitates presymptomatic detection and prenatal diagnosis of ADPKD. When flanking markers for PKD_2 are used in conjunction with flanking markers for PKD_1, accuracy of diagnosis is improved. Individuals at risk for ADPKD who have less than two affected family members are dependent on US for diagnosis or potentially direct gene-based testing in PKD_2 families.

Although more accurate, molecular analysis of ADPKD is expensive and cannot be performed everywhere. US is the preferred method of diagnosis of ADPKD because it is highly sensitive, does not involve radiation or contrast material, and is widely available and inexpensive. The sensitivity of US for PKD_1 and PKD_2 patients older than 30 years of age is 100%. However, the sensitivity for PKD_1 patients younger than 31 years is 95.2%, and for PKD_2 patients younger than 31 years, it is only 66.6% (375). Therefore, for younger persons at risk in PKD_2 families, genetic testing is an option.

The early diagnosis of ADPKD facilitates improved genetic counseling and rational decision making about reproduction but will not necessarily lead to termination of an affected pregnancy. Linkage analysis can clarify gene status in potential living-related transplant donors. Many individuals at risk for ADPKD avoid presymptomatic diagnosis because of difficulty in getting life and medical insurance as well as future employment. A questionnaire-based study of ADPKD patients showed that 87% were concerned about the availability of health insurance, although 88% were covered. Fifty-seven percent of those with employer-based health insurance (83% of the total) had this availability determine their job choice (140).

Radiologic Findings and US Diagnosis

Contrast-enhanced CT scanning is the most sensitive diagnostic procedure for ADPKD. However, US has become the preferred diagnostic imaging method for children and adults because it is highly sensitive, does not involve radiation or contrast materials, and is widely available and inexpensive (Fig. 20.3). Renal US should pick up 95.2% of at-risk patients younger than 31 years of age in PKD_1 families and 66.6% in PKD_2 families (375). In those older than 30, US should pick up 100% of ADPKD because of the larger cyst size. The US diagnosis of $ADPKD_1$ depends on the patient's age. For patients aged younger than 30 years, two cysts, either bilateral or unilateral, must be present. Two cysts are necessary in each kidney for individuals aged 30 to 59 years, and at least four cysts are necessary in each kidney in individuals older than 60 years (322). A single cyst on US in an at-risk child is suggestive of ADPKD. Both US and CT are advantageous over intravenous pyelogram (IVP) because both allow a concomitant examination of the liver for cysts. IVP may reveal calyceal distortion on the pyelogram phase (mass effect), bilateral renal enlargement, and a Swiss-cheese appearance in the nephrogram phase (Fig. 20.4).

Renal arteriography reveals stretching on vessels around avascular masses in large kidneys in the arterial phase and a mottled or Swiss-cheese appearance in the nephrogram phase (Fig. 20.5).

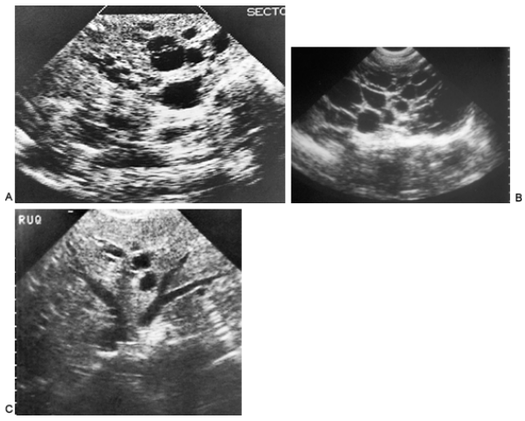

FIGURE 20.3. Autosomal-dominant polycystic kidney disease in two adults. **A:** Renal ultrasound (US) reveals multiple cysts of varying sizes in an enlarged kidney. US reveals a markedly enlarged kidney with numerous cysts of varying sizes **(B)** and two small cysts within the liver in a 37-year-old woman **(C)**.

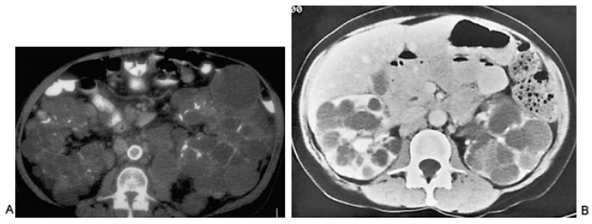

FIGURE 20.4. Autosomal-dominant polycystic kidney disease in two adults. **A:** Unenhanced computed tomography (CT) scan revealing calcifications in walls of multiple cysts in enlarged kidneys. **B:** Enhanced CT scan in a 51-year-old woman reveals bilaterally markedly enlarged kidneys with multiple cysts of varying sizes, shapes, and attenuation values. There is some enhancing renal cortical tissue remaining, but excretion into the collecting system is identified only with difficulty.

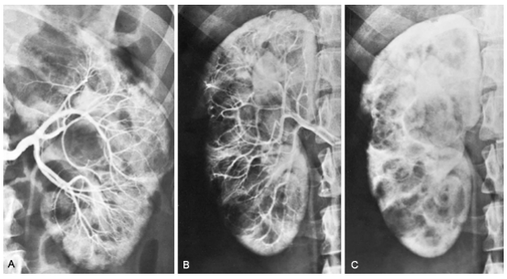

FIGURE 20.5. Autosomal-dominant polycystic kidney disease in two adults. **A:** The arterial phase of renal arteriography in a 23-year-old woman reveals stretching of the vessels around avascular masses in enlarged kidneys. **B:** The arterial phase of renal arteriography in a 30-year-old woman also reveals the intrarenal arterial branches to be stretched, elongated, and displaced by many cysts. **C:** The nephrogram phase of the same arteriogram reveals a mottled or Swiss-cheese appearance in both enlarged kidneys.

It is unfortunate that in a disease in which precise diagnosis of complications is crucial, the distorted anatomy of ADPKD kidneys often reduces the diagnostic accuracy of imaging procedures that are quite reliable in patients with normal kidneys (357). Contrast-enhanced CT scanning is the best technique for evaluating possible complications in ADPKD such as cyst or parenchymal infection, cyst hemorrhage, cyst calcifications, and renal calculi (242). Renal angiography can demonstrate renal cell carcinoma (RCC) in patients with ADPKD and can evaluate suspected renal hemorrhage and renovascular lesions. Both IVP and retrograde pyelography can localize the level of possible urinary tract obstruction in ADPKD. Retrograde pyelography should be avoided because of the high risk in ADPKD patients of introducing infection; however, it may be necessary when renal failure precludes satisfactory IVP and the level of obstruction needs to be localized. If intravenous contrast is contraindicated in an ADPKD patient, CT without contrast is the most useful test to rule out urinary tract obstruction (but not to find the level of obstruction) because US may not distinguish between parenchymal cysts and dilated calyces. Radiogallium scanning can help localize the cyst or parenchymal infection in ADPKD but false-positive and false-negative results may reduce the value of this test in individual patients. Indium-111 leukocyte scanning has potential to detect and localize infected cysts in patients with a polymorphonuclear leukocyte count greater than 2,000/mm^3 (49). MRI does not appear to offer advantages over CT, except perhaps to diagnose an acute renal hemorrhage.

Management

Therapy of ADPKD must be directed toward delaying and managing ESRD and toward managing the complications of ADPKD that occur before and after renal failure. Routine urologic diseases, such as urinary infections, calculi, and obstruction, can be very difficult problems in ADPKD patients and require special therapeutic consideration.

Renal Failure

Renal function is well preserved until late in ADPKD, at which time it decreases rapidly. Onset of renal failure is variable, but approximately 50% of ADPKD patients will have ESRD by 60 years of age (119). Time to development of ESRD in ADPKD patients is affected by genetic heterogeneity (PKD_1 versus PKD_2 mutations), random somatic events (second hits that inactivate PKD_1 or PKD_2 allele), and gender. A number of these factors predicting earlier ESRD in ADPKD patients can be identified early in ADPKD (206). For example, the median age of ESRD is 53 years for PKD_1 patients as opposed to 70 years in PKD_2 patients. Women had an additional 4 years until ESRD as compared with men (56 versus 52 years). Those patients diagnosed with ADPKD before age 30 developed ESRD at age 49 as compared with age 59 for those diagnosed after age 30. Hypertension does not appear to influence the rate of

progression of renal failure in ADPKD, but the development of hypertension before age 35 reduced renal survival by 14 years compared with those developing hypertension after age 35. Earlier gross hematuria predicted earlier ESRD in ADPKD patients. Although female patients with ADPKD with three or more pregnancies had earlier onset of ESRD, Johnson and Gabow (206) also revealed that this effect was not significant independent of the patient's age at diagnosis and presence of hypertension.

The first sign of kidney failure in ADPKD is the inability to maximally concentrate urine. The renal concentrating defect in ADPKD can develop before glomerular filtration rate (GFR) decreases. There is loss of noncystic parenchyma replaced by fluid-filled cysts in a network of interstitial fibrosis, perhaps secondary to autocrine and paracrine factors (145). The noncystic nephrons compensate by increasing their function so that the GFRs are elevated very early in ADPKD; however, the compensatory mechanisms then fail, and other signs of renal failure follow.

General medical therapy for treatment of chronic renal failure includes low-sodium diets (326) and slowing of the development of osteodystrophy with aluminum hydroxide gel and treating metabolic acidosis. The Modification of Diet in Renal Disease (MDRD) Study revealed minimal benefit of a low-protein diet in ADPKD patients with moderate renal disease (GFR of 25 to 55 mL/min/1.73 m^2) but did suggest the benefit of protein restriction in advanced renal disease (GFR of 13 to 24 mL/min/1.73 m^2) (237).

Factors that predict a greater risk of renal failure include more severe proteinuria, UTIs in male patients, hepatic cystic disease in female patients, African-American race, and sickle cell trait in African-American patients (119). Management should include attempts to treat UTIs. Whether treatment of hypertension alters time of onset of ESRD in ADPKD patients is unknown, although control of blood pressure is necessary to prevent accelerated hypertension and cardiovascular events. Surgical cyst decompression does not slow progression of renal insufficiency in ADPKD (104).

Dialysis and Renal Transplantation

Fifty percent of ADPKD patients will eventually require dialysis or renal transplantation. Surprisingly, effective peritoneal dialysis has not been hindered by the large cystic renal and hepatic masses, hernias, or diverticulitis in ADPKD patients treated by continuous ambulatory peritoneal dialysis (157). When one takes into account ADPKD patients' older age at the time of dialysis, they do as well as other ESRD patients when receiving hemodialysis (18). When on hemodialysis, 5-year survival is 10% to 15% greater in ADPKD patients than in non-ADPKD patients, probably because of lower cardiac mortality in ADPKD patients (313).

Long-term renal dialysis also markedly reduces blood pressure in hypertensive ADPKD patients (326). While on hemodialysis, the prevalence of renal pain, gross hematuria, and renal infection is significantly greater in ADPKD patients, but these complications are rarely severe (313). ADPKD ESRD patients do as well as nondiabetic ESRD patients undergoing renal transplantation in that patient and graft survival are similar (18,113,160). Although Florijn and co-workers (116) found that ADPKD patients are at risk for cardiovascular disease after renal transplantation and Andreoni and colleagues found that ADPKD patients are at risk for gastrointestinal (GI) complications after renal transplantation, others have found no increased risk of coronary events or GI complications in ADPKD after renal transplantation (313). Cysts do not develop in the transplanted kidney in ADPKD patients any more than in other patients after renal transplantation (113). Despite superior results with living-related transplantation for non-ADPKD patients, this has been somewhat limited for ADPKD patients because the disease is familial. However, if an ADPKD patient has two clinically affected family members and if the ADPKD phenotype links with the PKD_1 or less common PKD_2 locus, living-related donors can be found at any age with use of linkage analysis. For the remaining ADPKD patients, living-related donors can be identified by negative radiographic findings when 30 years of age or older or at any age with direct gene-based mutation detection in PKD_2 families. Bilateral pretransplant nephrectomies are not routinely indicated in ADPKD because of high morbidity and mortality (116), but they are indicated in situations of recurrent pyelonephritis, hematuria requiring blood transfusions, and large renal size causing vena caval obstruction or precluding placement of renal allograft into the true pelvis (24).

Urinary Tract Infections

Symptomatic UTIs are common, with an overall incidence of 53% and recurrence rate of 61% in ADPKD patients. Complicated UTIs are less common but difficult to treat. The incidence of renal infection in PKD_2 was half that of PKD_1 (163). Of 23 female patients who had symptomatic UTIs, 12 (52%) had pyelonephritis, of whom 3 developed perinephric abscess (89). Up to 90% of UTIs in ADPKD occur in female patients (357). Urine culture may or may not be sterile, depending on the location of the infection. Sklar and associates (357) divide ADPKD renal infections into three types: (a) acute bacterial interstitial nephritis (infection of the noncystic parenchyma with an unobstructed collecting system), (b) pyonephrosis (infection of upper collecting system, which may be obstructed by stone, blood clot, or compressing cyst), and (c) pyocyst (infected cysts). Although a urine culture should be positive in acute bacterial interstitial nephritis, it may be negative in pyonephrosis and in pyocyst because of the confined infection. Distinguishing between these is helpful in choosing a treatment course. A poor response to antibiotics should suggest either pyocyst or an obstructed urinary tract (pyonephrosis). Infected cysts can be successfully treated with cyst-penetrating antibiotics (333). Failure of prolonged systemic antibiotics to treat infected cysts may make percutaneous puncture and drainage (62,295), laparoscopic decortication and drainage (168), open surgical drainage, or even nephrectomy necessary because of the attendant mortality of infected cysts. The retroperitoneal route of laparoscopic cyst decortication and drainage prevents intraperitoneal contamination and can be guided by laparoscopic US (168). The incidence of serious infections complicating ADPKD seems to be decreasing because the rates of infection (26%), nephrectomy (45%), and death (7%) in a 1983 study of ADPKD patients are higher than the respective rates of 16%, 12%, and 0% in a similar 1996 study (132). Radiologic diagnosis or localization of a pyocyst can be extremely difficult. CT or gallium scan may help localize the infection to a cyst, but ^{111}In leukocyte scanning may prove to be more sensitive in detecting and localizing infected cysts in ADPKD in renal failure (49). In some cases, the presence of debris or echogenic material on CT or US aid in the diagnosis (295). ADPKD patients with renal calculi are three times as likely to have UTIs than those without calculi and the infections are more complicated (242). Obstruction should be ruled out to eliminate pyonephrosis.

Few antibiotics penetrate the cysts, and of those available, fewer still are effective against Gram-negative organisms, which cause the vast majority of UTIs in ADPKD patients. Lipophobic antibiotics such as aminoglycosides, ampicillin, and cephalosporins penetrate cysts poorly but have a favorable activity against Gram-negative enteric organisms (26). Lipophilic antibiotics penetrate all cysts but have varying ranges of activity; examples of such antibiotics include (a) clindamycin or metronidazole for anaerobes; (b) vancomycin or erythromycin for staphylococci or streptococci (357); and (c) chloramphenicol (346), cefotaxime (26), TMP-SMX (105), ciprofloxacin (333), and norfloxacin for Gram-negative enteric organisms. Gibson and Watson (132) advocate initial therapy of complicated UTI in ADPKD patients with intravenous ampicillin and an aminoglycoside, realizing that failure to respond to these antibiotics would suggest a cyst infection because aminoglycosides do not penetrate cysts. Aminoglycosides should be withheld when renal function is compromised. Others recommend initial use of TMP-SMX and fluoroquinolones for infected renal cysts (408).

Urinary tract instrumentation (cystoscopy, retrograde pyelograms, and bladder catheterizations) should be avoided when possible in ADPKD patients because of the high association of infection and mortality despite sterile urine culture before instrumentation. Of 14 ADPKD patients who underwent urinary tract instrumentation, 6 (43%) developed symptomatic UTIs, of whom 3 had pyelonephritis that led to death in 2 despite parenteral antibiotic therapy (89). Most UTIs in ADPKD patients are

believed to be ascending in origin and are more prevalent in women. With postmenopausal loss of estrogen protection, the vagina is colonized by Enterobacteriaceae instead of lactobacilli. Recurrent UTIs in postmenopausal women can be minimized by estrogen replacement therapy. Intravaginal estrogen cream may be helpful in postmenopausal ADPKD patients with recurrent UTIs if they do not have significant hepatic cystic disease.

Pain Management

Pain is reported in 61% of ADPKD patients (122) and must be evaluated to rule out obstruction, infection, neoplasms, and hemorrhage. If these causes are eliminated, chronic dull pain from ADPKD can be treated conservatively with analgesics such as acetaminophen. Nonsteroidal antiinflammatory drugs should be avoided because of their nephrotoxic potential. Pain clinics offer a multidisciplinary approach to help with this chronic pain. However, for those chronic pain ADPKD patients for whom such conservative methods have failed (usually a minority), cyst-decompression procedures are helpful. Percutaneous aspiration of three to five dominant superficial cysts under US guidance dramatically relieved pain in 11 narcotic-dependent ADPKD patients for 3 to 6 months (25). Percutaneous cyst aspiration accompanied by instillation with sclerosing agent results in a longer time period of cyst reduction than aspiration alone, but it also is likely to be limited to a lesser number of cysts decompressed as compared with open surgical drainage (384). Open surgical cyst decompression of 100 to 200 cysts per kidney in a 2- to 3-hour operation dramatically relieved pain in 80% of 26 narcotic-dependent ADPKD patients for 1 year and 62% for 2 years (104). Laparoscopic cyst decompression is limited to ADPKD patients with relatively few, but large, cysts because it provides inferior renal volume reduction compared with open surgical cyst decompression, although hospital stays and postoperative recovery are shorter (103). Cyst decortication and nephrectomy have been effectively performed laparoscopically for delayed recurrent pain after cyst aspiration and sclerosis, but only 1 to 62 cysts were decorticated at one sitting (101). Bilateral open transperitoneal cyst-reduction surgery for ADPKD allows drainage of 35 to greater than 1,000 cysts at one sitting with the option of simultaneous treatment of liver cysts by decortication or partial liver resection (115). Cyst-decompression procedures do not worsen or improve renal function in ADPKD patients long term (103).

Calculi

Flank pain in ADPKD can be secondary to obstruction of the urinary tract from clots, calculi, or cysts and is difficult to diagnose. Imaging studies must distinguish between obstructing calculi in the collecting system, renal parenchymal calcifications, and cyst wall calcifications. CT scanning with and without contrast best achieves these goals, and it can differentiate cysts from dilated calyces, which may not be possible on US (242). Levine and Grantham (242) found that CT scanning with and without contrast revealed 36% of ADPKD patients had renal calculi, whereas 25% had cyst calcifications. However, 20% of ADPKD patients were found to have nephrolithiasis when studied by review of IVPs and review of medical records, with nearly equal incidence in men and women (379). In this study, struvite was found in 10% of stones analyzed, although uric acid was found in 57% and calcium (phosphate, carbonate, and oxalate) in 77%; however, only 20% of the ADPKD stone patients had stones available for analysis. A common metabolic abnormality in ADPKD stone patients with normal renal function was hypocitricaciduria, whereas hyperuricemia was common in ADPKD stone patients taking diuretics or those with renal insufficiency (379). In all ADPKD patients (with or without calculi), hyperuricemia has been found in 71% (mean creatinine clearance of 69 mL per minute) and clinical gout in 24%, although the highest serum uric acid levels were found in ADPKD patients with the lowest GFR (268). Three times as many ADPKD patients with renal calculi have UTIs as those without renal calculi (242). There was no significant difference in the incidence of renal tract calculi between men and women or between PKD_1 and PKD_2 individuals (163). Obstructing ureteral and renal calculi have been successfully treated with extracorporeal shock wave lithotripsy (ESWL) (Fig. 20.6) in ADPKD. More than 82% of ESWL procedures were successful in ADPKD patients, but approximately half of them had residual fragments, which is higher than for patients without ADPKD (380). Retrograde procedures such as ureteroscopy with basket extraction, laser fragmentation, and ultrasonic fragmentation have been used successfully but can potentially cause ascending infections. Eighty percent of percutaneous procedures were successful in ADPKD patients (380). Alternatively, appropriate stone surgery can be done.

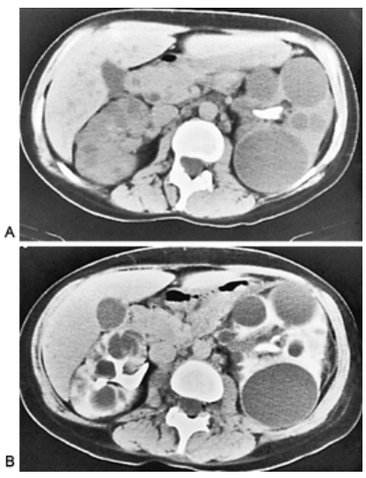

FIGURE 20.6. Autosomal-dominant polycystic kidney disease with left staghorn calculus treated by extracorporeal shock wave lithotripsy (ESWL) in a 31-year-old woman. **A:** Before ESWL, unenhanced computed tomography (CT) scan reveals a left staghorn calculus, bilaterally huge kidneys with multiple cysts of many sizes, and hepatic cysts. **B:** One day after ESWL, enhanced CT reveals no change in the renal cysts from ESWL. The residual gravel cannot be seen because of the contrast.

Obstruction, Hemorrhage, and Tumors

Obstruction of the urinary tract in ADPKD patients can also be caused by renal cyst compression, which can be treated by percutaneous, laparoscopic, or open surgical cyst decompression. Blood clots can also cause obstruction and can usually be managed conservatively. Bleeding in polycystic kidneys can usually be diagnosed by CT and treated with bed rest and observation. Cyst hemorrhage can be confined to the cystic space (causing acute pain), rupture into the collecting system (causing gross hematuria), and/or extend into the perinephric space. Intracyst hemorrhage has been treated successfully with desmopressin acetate and aprotinin administration (225). Severe hemorrhage can be treated by segmental renal artery embolization or percutaneous nephroscopic

balloon occlusion of infundibuli to preserve some renal function in ADPKD patients. Alternatives to control hemorrhage include complete or partial nephrectomy.

RCC must be excluded in ADPKD patients with flank or abdominal pain, intrarenal hemorrhage, or hematuria. However, the risk of unilateral RCC in ADPKD patients is the same as the general population. However, ADPKD patients in renal failure who are receiving dialysis can develop acquired cystic kidney disease, which has a higher incidence of RCC. Both renal arteriography and MRI can help differentiate tumor from cyst (177) (Fig. 20.4).

AUTOSOMAL-RECESSIVE POLYCYSTIC KIDNEY DISEASE (INFANTILE TYPE)

Part of "20 - RENAL CYSTIC DISEASE "

ARPKD includes a spectrum of phenotypic appearances ranging from renal failure in infants to hepatic disease in older children. In addition, newborns with the severe common form of the disease can die of respiratory disorders within a few days after birth. Affected fetuses have bilaterally enlarged echogenic kidneys and oligohydramnios due to poor fetal urine output, usually after 20 weeks of gestation. These infants have the “Potter phenotype” (pulmonary hypoplasia, characteristic facies, and spine and limb deformities) because of their oligohydramnios. The incidence of ARPKD is about 1 in 20,000, with a heterozygosity frequency of 1 in 70 (417). ARPKD is characterized by bilateral cystic disease in enlarged kidneys with retained reniform shape. ARPKD is transmitted in an autosomal-recessive pattern only and is caused by a genetic defect on chromosome 6.

Clinical Features

The clinical picture of ARPKD covers a continuum of presentations of renal failure and hepatic disease developing at different ages and to different degrees. Newborns and infants suffer more from renal failure. Children presenting after infancy are more likely to have liver disease, although a continuum exists.

More than 75% of ARPKD patients present in the newborn period, at which time the child has massively enlarged kidneys (up to ten times normal size) (80,143), causing respiratory difficulties as a result of diaphragmatic elevation and pulmonary hypoplasia. Vaginal delivery may be impeded by the massive kidneys. Most deaths occur in the first month of life and are due to pulmonary atelectasis and respiratory failure from oligohydramnios (351). Survival of all but the most severely affected neonates is now the norm. Approximately 86% of children born with ARPKD are alive at 3 months and 79% at 12 months (214). Oliguria and Potter's facies may be present, but renal failure is not the cause of death. If the child survives the newborn period, he or she most likely will have eventual renal failure and systemic hypertension, which can be particularly severe in the first year of life (123). Seventy percent of ARPKD children require drug treatment for hypertension, which is insufficiently treated in 31.2% of these patients because of its severity (416). Blood pressure elevation is intermittent during the course of the disease. After the first month, growth failure and congestive heart failure are usually the major clinical problems (232). Some patients have secondary effects of chronic renal insufficiency such as anemia, growth failure, and renal osteodystrophy (416).

After the first year of life, the clinical presentation of ARPKD is more variable because of the spectrum of renal failure and hepatic disease. As children with ARPKD grow, the renal cystic dilation can regress as the kidneys become smaller (38). These children can have either slowly progressive renal insufficiency or simply a mild renal functional impairment such as a mild inability to concentrate urine. The percentage of patients with severe renal insufficiency

increases with age from 11% at 2 years to 32% at 5 years, 36% at 10 years, 43% at 15 years, and 100% at 20 years (123). Zerres and others (418) showed a statistically significant sex difference in terms of more pronounced progress in girls. Girls with ARPKD had shorter survival probability (82% at 1 year) compared with boys (95% at 1 year) and more girls had impaired renal function, developed ESRD, and showed growth retardation (418). Systemic hypertension is common, but ß-blockers and converting enzyme inhibitors are effective (123). UTIs occur in 30% to 43% of ARPKD patients but are more common in girls (43%) than in boys (20%) and occur earlier in girls (418).

However, with time, these older children with ARPKD can develop more severe hepatic involvement. The hepatic disease in ARPKD is called *congenital hepatic fibrosis* (CHF) because the liver has an increase in the number of portal bile ducts and fibrosis of the periportal spaces. Hepatic US can be used to confirm the presence of "biliary dysgenesis" in at least half of ARPKD patients (123). CHF presents clinically as portal hypertension, which can result in massive upper GI hemorrhage from ruptured esophageal varices. More commonly, the children with ARPKD develop splenomegaly as their initial or only sign of portal hypertension due to hepatic fibrosis (317). There is no hepatocellular disease. Caroli's disease (gross cystic dilation of the intrahepatic biliary tree) is often associated with ARPKD, and the two diseases may be overlapping syndromes (416). In this older age group (older than 6 years), CHF, not the renal cystic disease, may be responsible for death. However, the continuum of renal failure and hepatic disease in older children with ARPKD also includes children symptomatic from both kidney and liver disease (266). The clinical cause and

pathologic expression of renal disease can be entirely dissimilar within the same family (125,173,215).

Morphology

The gross and microscopic characteristics of ARPKD kidneys vary with the age of the child at the time of presentation, but the disease is always bilateral. In newborns with the severe form of ARPKD, gross inspection reveals the kidneys to be adult size and reniform (Fig. 20.7). The kidney surface is smooth and studded with 1- to 2-mm cysts. The cut surface shows a striking radial arrangement of thin-walled channels extending from the pelvis to the cortex. Microscopically, these channels are dilated collecting tubules and ducts, which are the fusiform cysts of ARPKD. Interstitial edema is severe.

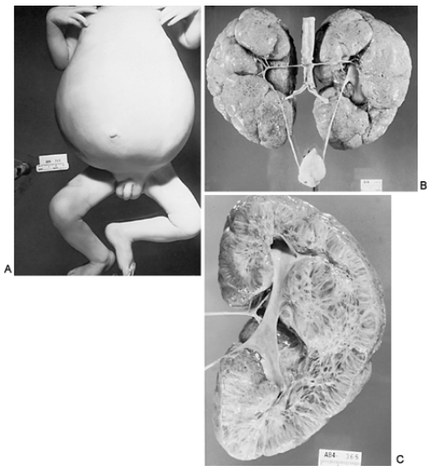

FIGURE 20.7. Autosomal-recessive polycystic kidney disease in a 7-month-old boy. **A:** Abdomen is markedly distended from the massively enlarged reniform kidneys **(B),** which have minute cysts studding the kidney surface. **C:** Cut section reveals radial arrangement of tubular-shaped cysts. (Courtesy of Dr. S. Bova.)

In children surviving the neonatal period, the kidneys become smaller, the collecting ducts become less dilated, and the remaining cysts are spherical as opposed to saccular (245). Also, variable degrees of corticotubular atrophy, basement membrane thickening, and interstitial fibrosis are present (173). These findings are also true for children who present with ARPKD after infancy. However, with time, these children are likely to develop CHF (317). Grossly, the liver in CHF is firm and enlarged with a granular surface. Microscopically, there are an excessive number of interlobular bile ducts. The liver is subdivided by bands of fibrous tissue in the periportal and interlobular spaces. Although portal hypertension is commonly attributed to a presinusoidal block because of the portal fibrosis or the portal vein abnormalities, a postsinusoidal block may be present in the same patients (31).

Pathogenesis and Genetics

The pathogenesis is unknown except that it is genetically transmitted as autosomal recessive. Heterozygotes are unaffected. Hence, a very careful family history covering at least three generations should be taken to exclude ADPKD. The ARPKD gene has been localized to chromosome region 6p21. The abnormal DNA results in the development of cysts in the renal collecting ducts, which expand to enormous size because of epithelial cell hyperplasia in the cyst walls and fluid accumulation within cyst cavities (143). Presenting newborns can have 80% of tubules involved, whereas patients presenting during adulthood have less renal involvement (10% of tubules) (351).

Because of the continuum of clinical presentation of ARPKD, four types were described by Blyth and Ockenden (40) with different ages of onset. Each type was to be transmitted as an autosomal-recessive allele and each type was to have occurred in all of the affected children of a family. However, further work has shown that not only do different clinical and pathologic courses occur within one family (125,173,215) but that ARPKD has a spectrum of phenotypic expressions and not just four genetically determined, rigidly defined subgroups (125,245). Deget and colleagues (87) revealed that intrafamilial variability of the clinical picture is small. Zerres and associates mapped the ARPKD gene locus to 6p21 codon in families with a mild ARPKD phenotype, and Guay-Woodford and associated (153) showed the severe perinatal form of ARPKD maps to the same chromosome. Together, these studies suggest there is a single ARPKD gene. Multiple allelism with only a few different alleles would account for the great variability of manifestations in different families and would also explain the relatively high intrafamilial concordance in manifestations (416).

Radiologic Findings

In infants with bilateral palpable abdominal masses, the initial study should be renal and abdominal US (Fig. 20.8). In newborns with the severe form of ARPKD, the kidneys are very large with diffusely increased parenchymal echogenicity. This increased echogenicity is caused by the sound beam bouncing off the innumerable dilated tubules. Some investigators have shown a more heterogeneous pattern with either “striped” or “pepper-and-salt” echoes (404), or a peripheral zone of normally echogenic cortex in some newborns (270). Occasionally, small cysts can be identified in the hyperechogenic medullary areas.

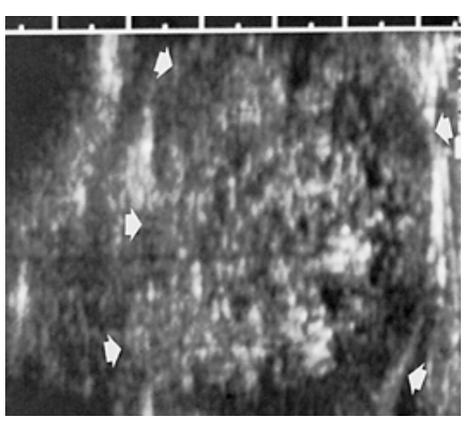

FIGURE 20.8. Autosomal-recessive polycystic kidney disease in newborn. Renal ultrasonography reveals marked renal enlargement with heterogenous pattern and myriad fine cysts. *Arrows* denote renal margin.

IVPs in infants with ARPKD may show only progressively dense nephrograms of these massive kidneys or may show the classic radial streaking of contrast in dilated collecting tubules. The collecting system is usually not seen, although contrast in the bladder may be seen on delayed films.

In the older child with ARPKD, the IVP pattern is less diagnostic because the kidneys are only somewhat enlarged and the renal pelvis and calyces are better visualized. The calyces may be blunted, or the pyramids may be opacified with a brushlike pattern. There may be an ectasia of the collecting tubules (215). US studies in the older child with ARPKD can demonstrate diffuse hyperechogenicity of the parenchyma or reveal a prominent rim of renal cortex with normal echogenicity surrounded by moderately echogenic medulla (270). Serial US studies in ARPKD patients surviving the neonatal period reveal that kidney size decreases (despite the child's linear growth) and echogenicity changed (38). Disseminated small cysts (less than 15 mm) are often visible and may be present from the neonatal period (123). US evaluation of the liver reveals increased echogenicity, dilated bile ducts, and no discrete cysts (173). CT of the kidneys in ARPKD can reveal accentuation of contrast material on the cortical layers and lacelike medullary cysts (211). CT without contrast commonly reveals bilateral renal calcifications in older ARPKD children with renal failure; however, these calcifications are not recognized on plain film (248). RARE-MR technique (rapid acquisition

with relaxation enhancement) is a noninvasive imaging study that demonstrated the pathognomonic water-filled structures in all of eight ARPKD children evaluated (aged 3 months to 14 years) (219). Both magnetic resonance cholangiography (210) and hepatobiliary scintigraphy (400) have been used to diagnose Caroli's disease in ARPKD patients.

Diagnosis and Management

Families with a severely affected child carry a high risk that additional affected children will be severely affected as well, because intrafamilial variability of the clinical presentation is small (87). Because of the poor prognosis of the severe perinatal form of ARPKD, there is a strong demand for prenatal diagnosis. If a pathoanatomic examination of a previous affected child (liver biopsy or autopsy of fetus) is available, molecular linkage analysis is now feasible for prenatal diagnosis of subsequent pregnancies if DNA analysis of the parents and the one affected child has shown that markers linked to ARPKD are informative. Because direct mutation analysis in ARPKD is not available, correct clinical diagnosis of the first affected child is paramount for accurate prenatal diagnosis of subsequent pregnancies with molecular linkage analysis. The vast majority of families who meet these criteria were informative with the highly polymorphic markers of the ARPKD interval, with precise correlation between the genotype and the predicted phenotype (417). Mücher and co-workers (274) found that the large number of flanking polymorphic loci made genetic linkage-based prenatal diagnosis of ARPKD possible for more than 99% of the families that they analyzed.

In a prenatal differential diagnosis, ADPKD, Meckel's syndrome, and Bardet-Biedl syndrome should always be ruled out. Renal cystic changes can be seen in patients with CHF, which is also autosomal recessive. Adult ARPKD patients who present with mild renal failure can be diagnosed as ARPKD only if they have a negative family history and parents (older than 30 years of age) with normal renal US studies to exclude ADPKD. They can be diagnosed as having ARPKD if they have symptoms of portal hypertension or a liver biopsy revealing hepatic fibrosis (416).

The prenatal US picture of the enlarged kidneys and/or increased echogenicity is characteristic but not pathognomonic (415). Oligohydramnios occurs after 20 weeks of gestation in severe perinatal ARPKD. Related US measurements of kidney length may be the most useful parameter.

US (small renal cysts), liver biopsy (CHF), and family history (recessive inheritance) are usually sufficient to diagnose ARPKD (351). There is no known cure for ARPKD, but genetic counseling can inform parents that siblings of an affected child have a 25% chance of being affected and a 50% chance of being heterozygous carriers. Otherwise, treatment is supportive. Respiratory resuscitation and support may be necessary for newborns diagnosed with ARPKD. When the massively enlarged kidneys restrict diaphragmatic excursion, resulting in respiratory distress in addition to pulmonary hypoplasia, ARPKD newborns may require bilateral or unilateral nephrectomy. Unilateral nephrectomy may improve respiratory status and decrease feeding difficulties without inducing renal failure in ARPKD infants (20). Peritoneal dialysis can be instituted as they await renal transplantation (367). Older children may need antihypertensive medications for hypertension, digitalization for congestive heart failure, and alkali for metabolic acidosis to permit normal growth, as well as other supportive measures for treating renal failure in growing children. Chronic dialysis and renal transplantation may be necessary eventually, but liver involvement should be evaluated first. Jamil and co-authors (200) noted that liver disease did not progress rapidly after initiation of renal replacement therapy and did not subsequently present a clinical problem. Prophylactic portacaval shunting or combined liver–kidney transplantation was unnecessary. Portal hypertension may result from CHF in ARPKD and can be treated by portacaval shunting to treat esophageal varices. However, recurrent bleeding is controllable by sclerotherapy (200).

JUVENILE NEPHRONOPHTHISIS–RENAL MEDULLARY CYSTIC DISEASE COMPLEX

Part of "20 - RENAL CYSTIC DISEASE "

The juvenile nephronophthisis–medullary cystic disease complex (NMCD) consists of a group of hereditary diseases characterized by renal salt loss, renal cyst formation at the corticomedullary junction, and progressive renal failure. These diseases have different hereditary patterns and genetic

heterogenicity but share similar clinical features and pathologic features. Both kidneys are small and reniform with small cysts at the corticomedullary junction. NMCD is uncommon, but it is the most common cause of renal failure in the adolescent.

Clinical Features and Genetics

Despite the genetic heterogeneity of NMCD, the pathologic and clinical features are similar except for the age of onset. The autosomal-recessive medullary cystic disease, juvenile nephronophthisis (NPH), affects mostly children and adolescents. The autosomal-dominant medullary cystic disease (ADMCKD) affects mostly adults. Finally, NMCD can rarely occur sporadically with no documented family history but consanguinity of parents should suggest the possibility of recessive inheritance.

NPH results in ESRD at about age 14 years and is the most common form of renal failure in adolescents (126). Because of severe salt wasting secondary to a severe defect in tubular function and the resultant inability to concentrate urine, children or adolescents present with polydipsia, polyuria, and secondary enuresis. Children can also present with growth retardation or skeletal deformity. The salt wasting occurs late in the disease and can be heralded by a decrease of already-present arterial hypertension. However, the polyuria and nocturia can be present for more than 10 years before ESRD occurs (54,60). Both sexes are affected equally. Urinary infections are not common.

Genetic heterogeneity exists within NPH (Table 20.4). Nephronophthisis type 1 (NPH_1, autosomal-recessive medullary cystic disease) has been mapped and localized to chromosome 2q12-13 (8). Within this region, the gene $NPHP_1$ was identified; this gene is deleted in more than 65% of patients with NPH_1 (175). NPH_1 is the most common type of NPH and NMCD. However, patients with the rare Senior-Løken syndrome (renal-retinal syndrome, autosomal-recessive medullary cystic disease, or NPH with retinitis pigmentosa) do not link to chromosome 2q12-13 (8). In addition, Gagnadoux and colleagues (124) described a group of infants who reached ESRD before 2 years of age with pathologic features similar to those of NPH. This disorder has been designated “infantile nephronophthisis” (NPH_2). Haider and associates (159) identified linkage of NPH_2 to chromosome 9q22-31 in a family with an autosomal-recessive mode of inheritance. Affected individuals developed hypertension, hyperkalemia, and rapid deterioration of renal function with ESRD by 3 years of age. There is emerging evidence that a third locus (NPH_3) exists for adolescence onset recessive nephronophthisis (176).

Disease	Inheritance	Chromosome	Mean Age Onset of ESRD
NPH_1	AR	2q12-q13	13 yr
NPH_2	AR	9q22-q31	7.8 mo
$ADMCKD_1$	AD	1q21	62.2 yr
$ADMCKD_2$	AD	16q12	31.5 yr

AD, autosomal dominant; ADMCKD, autosomal-dominant medullary cystic kidney disease; AR, autosomal recessive; ESRD, end-stage renal disease; NMCD, juvenile nephronophthisis–medullary cystic disease complex; NPH, nephronophthisis.

TABLE 20.4. NMCD COMPLEX—KNOWN LINKAGES

The autosomal-dominantly inherited disease, medullary cystic disease, is less common than juvenile nephronophthisis and results in ESRD at about 32 years of age (126). Many ADMCKD patients are hypertensive at an early stage of the disease, but some later develop hypotension due to excessive salt wasting. Polyuria and polydipsia are less intense in ADMCKD than in NPH. Some ADMCKD patients have gout and/or hyperuricemia (362). Christodoulou and associates (71) localized a gene ($ADMCKD_1$) for ADMCKD to chromosome 1q21 in two large Cypriot families. Affected family members also had hyperuricemia and gout, with a mean onset of ESRD at 62.6 years of age. Scolari and colleagues (347) described a second locus for medullary cystic disease, $ADMCKD_2$, on chromosome 16p12 in a large Italian family. Affected family members had hyperuricemia, gouty arthritis, and an average onset of ESRD at age 31.5 years. Diagnostic criteria for ADMCKD include (a) autosomal-dominant inheritance; (b) defective urine-concentration with polyuria, isosthenuria, and relatively normal urinalysis results; (c) normal or small-sized kidneys with occasional small medullary cysts; and (d) renal pathologic findings characterized by tubular-interstitial fibrosis (347). A third locus ($ADMCKD_3$) is possible (176).

Landing and colleagues (232) were correct that *medullary cyst disease* is not the name of a specific disease but is a useful term for a lesion that occurs in the later stages of several different genetically determined and other types of tubulointerstitial disease.

Morphology and Pathogenesis

On gross inspection, both kidneys in NMCD are contracted and pale with granular subcapsular surfaces. On cut section, there is poor demarcation between the medulla and the attenuated cortex. The cysts are actually diverticula of the distal convoluted tubules. When the cysts are macroscopic, they are typically located on cut section at the corticomedullary junction. They can range from microscopic to 1 cm in size. Cysts are usually present but occasionally are not especially early in the disease. Cysts are more common in ADMCKD than in NPH.

Microscopic examination reveals glomerular sclerosis, tubular atrophy, and interstitial fibrosis with chronic inflammation. The tubular basement membrane is markedly

thickened. Without the presence of cysts, the pathologic findings resemble those of interstitial nephritis. Indeed, NMCD has been considered a primary interstitial nephritis by some (53). Therefore a renal biopsy can be misleading if the corticomedullary cysts are missed in the biopsy specimen. Such biopsy specimens have been diagnosed as chronic interstitial nephritis initially but were changed because a later examination of the entire kidney from a subsequent nephrectomy or autopsy may show the medullary cysts (53,318). Renal biopsies may also not reveal the cysts if the biopsies are done early in the disease.

The pathogenesis of NMCD is unknown, except that it can be genetically transmitted. The gene product of $NPHP_1$, nephrocystin, may play a role in the protein–protein interaction (e.g., in signal transduction at focal adhesions, the contact points between cells, extracellular matrix). A defect in cell–matrix interaction would help explain the tubular membrane disruption in NPH (176). Perhaps a tubular basement membrane defect causes the early occurrence of the decreased urine-concentrating ability. Both NPH and ADMCKD may be the results of defects in the same developmental or metabolic pathway. Potential similarities in mutated genes may result in similar phenotypes (71).

Radiologic Findings and Management

Radiographic findings vary with the stage of progression of NMCD. Occasionally, an IVP early in the disease may reveal characteristic patterns either as streaky contrast enhancement or ring-shaped retention of contrast material in the corticomedullary region (288). More commonly, an IVP reveals normal findings early in the disease but shows bilaterally small kidneys later in the disease, at which time high-dose nephrotomography could reveal renal cysts (332). However, an IVP is of little value very late in the disease when renal function is greatly reduced. US has been shown to reveal cysts in the corticomedullary zone ranging from 2 to 10 mm in size in both patients with early and late NMCD (288). US reveals disappearance of the corticomedullary differentiation at all but the early stages of NMCD as well as small kidneys and increased parenchymal echogenicity (128,332). Although US may not show cysts until later in the disease (39), thin-section CT may (106). US, CT, or both could complement renal biopsy to diagnosis NMCD if the cysts were missed on biopsy but revealed by US or CT.

Treatment of NMCD is directed toward general therapy for renal failure. If salt wasting is present, it can be treated with salt supplementation. Control of hypertension and a low-protein diet may prolong normal kidney function if patients are diagnosed early as a result of linkage data and available flanking markers (71). Dialysis and transplantation are successful. However, recognition of genetic variants is vital to avoid selecting a living donor for transplant who is personally at risk of developing the disease (13). Molecular genetic diagnosis of NPH_1 can be performed by demonstration of the presence of deletions or point mutations of the $NPHP_1$ gene (176). In addition, if glomerular cysts are found on renal biopsy, the patient should undergo liver biopsy before renal transplant to rule out hepatic disease. Hepatic disease has occasionally been associated with juvenile nephronophthisis, more commonly if glomerular cysts are found on renal biopsy. Because hepatic fibrosis can lead to portal hypertension, hepatic biopsy should be considered before renal transplant (33).

RENAL CYSTS ASSOCIATED WITH MULTIPLE MALFORMATION SYNDROMES

Part of "20 - RENAL CYSTIC DISEASE "

Renal cystic disease, macroscopic to microscopic, has been found in some hereditary disorders. Knowledge of these disorders is important for genetic counseling.

Chromosomal Disorders

Patients with trisomy 21 (Down syndrome), trisomy 18 (Edward's syndrome), trisomy 13 (Patau's syndrome), and trisomy C can develop microscopic cysts, usually of the glomerular spaces of the renal cortex.

Autosomal-recessive Syndromes

Renal cystic disease is commonly found in Meckel's syndrome (MKS) or Meckel-Gruber syndrome (occipital encephalocele, hepatic fibrosis, renal cystic dysplasia, and polydactyly) (176), in Jeune's syndrome (asphyxiating thoracic dystrophy—small chest and renal dysplasia), and in Zellweger's syndrome (cerebrohepatorenal syndrome—high forehead and hepatomegaly). The prognosis of MKS is guarded in cases with onset of renal insufficiency in the neonatal period. Two gene loci have been mapped for MKS (Table 20.2). MKS_1 is localized in 17q21-q24 (294) and MKS_2 is localized on 11q13 (334). Zellweger's syndrome is associated with renal microcysts and an almost complete lack of peroxisomes in renal tubular epithelial cells and defects in several peroxisomal enzymes (370). Renal cystic changes have been less commonly reported in a few other autosomal-recessive syndromes such as Goldston syndrome (cerebral malformations), Majewsky and Saldino-Noonan types of short rib polydactyly, lissencephaly (microcephaly, smoothness of the brain, and cystic renal dysplasia), and the Elijalde syndrome (acrocephalopolydactylous dysplasia—gigantism and renal dysplasia).

X-linked Dominant Syndrome

Renal cystic disease occurs later in life in the orofaciodigital syndrome, type I, and somewhat resembles ADPKD.

Autosomal-dominant Syndromes

Tuberous sclerosis (TSC) and von Hippel–Lindau disease (VHL) are most likely to require the attention of a urologist as opposed to the other multiple malformation syndromes. Hence, both autosomal-dominant syndromes are described in detail.

Von Hippel–Lindau Disease

VHL (cerebroretinal angiomatosis) is caused by a genetic defect in the short arm of chromosome 3 and results in renal cysts and clear-cell renal carcinomas as well as retinal angiomas; cerebellar, medullary, and spinal hemangioblastomas; pheochromocytomas; islet cell carcinomas, cystadenomas, and cysts of the pancreas; cystadenomas and cysts of the epididymis; and endolymphatic sac (inner ear) tumors (133,244,258). The disease is inherited as autosomal dominant with a high penetrance of more than 90% by age 65 (252). Most manifestations of VHL do not become apparent until after the patient has reached the end of his or her second decade. However, retinal angiomatosis often is the earliest manifestation and has been found in an asymptomatic patient as young as 9 years of age (239). Cerebellar hemangioblastomas were once the most common cause of death in VHL. As more patients survive the cerebellar lesions as a result of improved treatment methods, the incidence of renal cysts and renal tumors in patients has increased (304), such that RCC accounts for 50% of deaths in VHL and is the most common cause of death (216). In one study, CT of the abdomen and brain and indirect ophthalmoscopy were done as screening examinations on family members at risk. Of those who were diagnosed as having VHL, 35% had RCC and 76% had renal cysts (239). RCC was found only in those patients who had renal cysts (118,239). Unlike RCC in patients who do not have VHL, RCC in patients with VHL occurs in younger patients, has an equal sex distribution, and is usually bilateral and multicentric (304). These RCCs can invade locally and distantly metastasize (31).

The VHL gene maps to chromosome 3p25-26 (233). The VHL gene functions as a recessive tumor-suppressor gene, and inactivation of both alleles on the VHL gene is the critical event in the pathogenesis of VHL neoplasms (79). The allele from the affected parent has been inherited as mutated, and the wild-type allele from the nonaffected parent has been sporadically inactivated in the VHL neoplasms. If one or both alleles are unaffected, the VHL gene encodes proteins responsible for negative regulation of cell growth. Mutations of both alleles results in loss of functions of the encoded proteins with resultant uninhibited cell growth and malignant transformation. The VHL protein (pVHL) inhibits the stimulatory effects of Elongin on transcription by binding to the Elongin B and C subunits of this protein (279). Mutated pVHL cannot compete for binding to Elongins B and C and therefore regulation of transcriptional elongation is lost resulting in tumor growth. The VHL protein downregulates vascular endothelial growth factor (VEGF) (414). The mutated VHL gene upregulates VEGF so that clear-cell renal carcinomas, hemangioblastomas of the eye and CNS, and papillary cystadenoma of the epididymis secrete large amounts of VEGF, causing new blood vessels to infiltrate these tumors, which become hypervascular (236,279). Wild-type VHL is required for exit from the cell cycle, so RCC cells with mutant VHL continue to proliferate because they cannot exit the cell cycle (414). The VHL protein also is responsible for proper assembly of the extracellular fibronectin matrix and regulates expression of carbonic anhydrases 9 and 10 (414). Chromosome 3p allele loss was found in RCC, hemangioblastoma, pheochromocytoma, and pancreatic tumors, suggesting a common mechanism of tumorigenesis in all types of tumors in VHL disease (79).

Renal Lesions of VHL

The renal cysts of VHL are multiple and bilateral and are lined by variably hyperplastic epithelium. Benign renal cysts with clear-cell cytologic features were found only in kidneys of VHL patients (395). By extrapolating from microscopic evaluation, VHL kidneys have an estimated 1,100 cysts with clear-cell lining and 600 clear-cell solid neoplasms per kidney (395). The mean volume of these renal lesions was 0.46 mm^3. Hence, a constant morphology exists as the cysts grow. Clear-cell renal lesions in VHL patients ranging from cysts to microscopic RCC to macroscopic RCC show the loss of the VHL gene (247). Nodular hyperplasia within the cyst walls have been observed progressing to clear-cell carcinoma (28). DNA quantitative studies reveal that both the RCCs and the atypical cyst lining cells have the same DNA indices in VHL, suggesting that the atypical cyst lining cells evolve into RCC (189). However, serial CT renal imaging of VHL patients revealed that the majority of solid RCCs appeared to arise *de novo* and were not initially cystic (68). Conversion from cystic to solid lesions did occur in this serial CT renal imaging study but was not the predominant sequence of events in the development of RCC in VHL.

Loss of function of the VHL disease gene may be the initial event in the renal cellular transformation that results in the development of clear-cell cysts and tumors. It is unknown whether benign cysts with clear-cell lining progress to RCC or if benign cysts with clear-cell lining, atypical cysts, and renal clear-cell carcinomas represent different accumulations of genetic defects (315).

Genotype–phenotype Correlations

Differences in phenotypes in VHL patients can be secondary to either variable mutations in the single VHL gene or the effects of other modifying genes but not mutations in genes other than the VHL gene on chromosome 3p25-26. Therefore allelic heterogeneity and not locus heterogeneity

can account for differences in VHL phenotypes. VHL can be caused by many different mutations in the VHL gene, with more than 162 different intragenic mutations described (279).

VHL germline mutations can be divided into those that produce truncated VHL proteins (type I) or those that produce intact VHL proteins with a change in a single amino acid (missense mutations) (type II) (65). Type I VHL patients may have retinal angiomas, spinal and cerebellar hemangioblastomas, pancreatic cysts, and kidney cancer. This is the most common form. Type II VHL patients may develop pheochromocytomas in addition to the tumors in type I (65,398). Type II families represent 7% to 20% of VHL families and rarely have renal and pancreatic cysts. Type II can be subdivided into certain VHL mutations with a low risk of clear-cell renal carcinomas and CNS lesions (type IIa) and high risks of clear-cell renal carcinomas and CNS lesions (type IIb). Type IIb is least common. No specific germline VHL mutation is associated with retinal angiomas or endolymphatic sinus tumors (414).

However, even related VHL family members with identical germline mutation can have variation in disease severity. Other genes may modify the effects of germline VHL mutations, such as the number of retinal angiomas in VHL patients (402). In addition, the greater the number of retinal angiomas, the greater the problem with RCC and hemangioblastoma later on.

Diagnosis, Screening, Surveillance, and Management

If the patient has a family history of VHL, the diagnosis is made if an individual has a single manifestation of the disorder as clear-cell renal carcinoma, retinal angioma, or pheochromocytoma (414). Also, multiple pancreatic cysts are uncommon in the general population and would be satisfactory for a VHL diagnosis in an at-risk individual, unlike renal and epididymal cysts (253). If there is no VHL family history, the diagnosis of VHL should be considered in an individual with two or more retinal or cerebellar hemangioblastomas; a single hemangioblastoma and a visceral tumor; familial or bilateral pheochromocytoma; familial, multicentric, or early-onset clear-cell renal carcinoma; or bilateral endolymphatic sac tumors (253). Recently, the frequency of VHL germline mutations in individuals with a single VHL manifestation without a VHL family history has been investigated with the following results: 1.6% of patients with sporadic renal carcinoma had a germline VHL manifestation, as did 2.5% to 5% of patients with an isolated retinal angioma (414). Germline VHL mutations are rare in isolated cases of pheochromocytoma but occur in 50% of patients with isolated familial pheochromocytoma or bilateral pheochromocytoma with no VHL family history (327). Some had been misdiagnosed as multiple endocrine neoplasia type 2.

Genetic linkage analysis with microsatellite flanking markers has been widely used in presymptomatic diagnosis in VHL families but is not possible for relatives of isolated cases or in families where necessary samples are not available (327). The cloning of the VHL tumor-suppressor gene has enabled direct mutation testing for VHL families. Once a patient is diagnosed as being affected, all at-risk relatives should be tested for the mutation because early detection of RCC and retinal hemangioblastoma significantly reduces morbidity and mortality. Prenatal diagnosis is possible. Annual physical and ophthalmologic examinations begin in infancy in individuals diagnosed with VHL. About 50% of VHL patients will have only one manifestation of the disease. Imaging of the abdominal organs and brain and spine should be added in teenagers and adults.

Radiographic evaluation of renal lesions in VHL is useful for screening family members and for following patients once they have been diagnosed as having VHL. IVP can reveal several mass lesions, but it cannot differentiate cysts from tumors. CT can reveal solid mass lesions and many reveal renal cysts, but it cannot differentiate between a small cyst and a small tumor, nor can it find a small tumor in the wall of the cyst. Thin-section (3 to 5 mm) contrast-enhanced CT is mandatory, and spiral geometry is desirable to decrease the chances a lesion is missed (69). US and, sometimes, angiography can fail to detect these small masses (239). US is critical to help determine whether a lesion is principally solid or cystic (69). CT scans can evaluate the adrenal glands for pheochromocytomas and the pancreas for islet cell carcinomas, cysts, and cystadenomas (186,244). Sequential CT studies are most sensitive in finding renal tumors before they become large enough to metastasize. However, a substantial proportion of renal lesions smaller than 1 cm were not detected by CT or US in VHL patients (201).

Annual studies are recommended once a diagnosis of VHL is made (216). MRI is especially useful in patients with renal failure in whom screening for RCC is still necessary (69). Contrast-enhanced MRI can be useful in determining whether a lesion is principally solid or cystic.

Annual CT renal imaging of VHL patients with renal lesions is recommended to determine the size and growth rate of the lesions and thus the appropriate management. Management can include continued observation, renal parenchymal sparing surgery, or nephrectomy. Bilateral nephrectomy can result in dialysis or renal transplantation. Walther and colleagues (397) noted no renal lesions 3 cm or smaller that metastasized in VHL patients. Renal parenchymal-sparing surgery was undertaken when the largest renal lesion reached 3 cm, at which time all visible tumors were resected from that kidney with use of intraoperative US to localize any additional tumors to be removed (397). Enucleation technique can be used because as many as 53 lesions have been removed from one kidney and lesions less than 3 cm have not been observed to penetrate

this boundary, although they have invaded it (315). Because the remaining renal parenchyma in VHL patients has a high number of remaining microscopic lesions (395), these patients must be imaged annually with CT scans after renal parenchymal sparing surgery to detect when the largest residual renal lesion becomes radiographically evident and reaches 3 cm in size. At that time, nephrectomy or repeat parenchymal-sparing surgery can be considered. Excellent long-term survival is observed when partial nephrectomy is used to remove VHL renal lesions when technically possible regardless of lesion size (363). Despite a 51% local tumor recurrence in these VHL patients treated by partial nephrectomy when technically feasible, only 2 of 25 had concomitant metastatic disease and renal function was well preserved (363).

In VHL patients with renal lesions not amenable to renal parenchymal-sparing surgery or with local recurrence after such surgery, bilateral nephrectomy may eventually be necessary. Steinbach and others (363) noted that 23% of VHL patients eventually developed ESRD after treatment for localized RCC. Management options for ESRD in the VHL population includes dialysis or renal transplantation. Renal transplantation is attractive in these relatively young ESRD patients, but the risk of immunosuppression in VHL patients with multiple potential tumors must be considered. Goldfarb and associates (139) demonstrated no statistically significant difference in graft survival, patient survival, or renal function after renal transplantation in well-selected VHL patients compared with control patients without VHL. Of the 32 VHL patients, 3 died of metastatic RCC within 45 months of transplantation. For those VHL ESRD patients after bilateral nephrectomy for RCC with higher tumor stage (pT_3 and above) or large tumor burdens with a symptomatic presentation, waiting 2 years after nephrectomy to confirm that no metastatic disease develops before proceeding with renal transplantation seems reasonable. However, in VHL ESRD patients after bilateral nephrectomy for RCC that is low stage and was incidentally discovered, no waiting period may be necessary before renal transplantation.

Evaluation of living-related renal donors for VHL patients can now be performed with direct mutation testing to evaluate presymptomatic carriers of the VHL gene. A thorough evaluation is essential for all prospective living-related donors to VHL recipients.

Pheochromocytoma in VHL patients can be managed by either partial adrenalectomy or adrenalectomy (396).

Epididymal cystadenomas were found in 54% of VHL male patients screened by scrotal US (70). Two-thirds were bilateral. Their clinical course is benign, and scrotal US is useful for diagnosis (133). Surgical excision is necessary only if the lesions become symptomatic.

The care of VHL patients requires a multidisciplinary team and urologists need to be familiar with the nonurologic manifestations of VHL.

Tuberous Sclerosis

TSC is an autosomal-dominant disorder caused by a genetic defect on either chromosome 16 or 9; it results in the presence of hamartomas, which are benign tumors composed of cellular elements normally present in tissue. The CNS lesions of TSC include tubers (cortical dysplasia) in the cerebral cortex that can cause mental retardation, epilepsy, and autism. In addition, patients may have facial angiofibromas, renal AMLs, renal cysts, retinal hamartomas, ungual fibromas, bone tubers, and cardiac rhabdomyosarcomas. In patients with TSC, renal causes of death are second only to CNS causes (352).

Genetics

Although TSC is inherited as an autosomal-dominant trait with high penetrance, two-thirds of TSC patients have no family history of TSC and probably represent new mutations (sporadic cases from new mutations). Mutations in two different genes can result in the TSC phenotype, meaning that TSC exhibits locus heterogeneity. The TSC_1 gene is located at 16p13.3 and was cloned in 1993 (108). The TSC_2 gene is located at 9q34 and was cloned in 1997 (389). About 50% of TSC families link to TSC_1 and about 50% to TSC_2 (282,316). However, TSC_2 mutations are much more common in sporadic cases than TSC_1 mutations (12,229), so TSC_2 mutations are the more common genotypes. Most studies found no observable differences between TSC_1 and TSC_2 patients (229,282), although other studies found a higher incidence of mental retardation in TSC_2 patients than in TSC_1 patients (207) and a higher incidence of intellectual disability in TSC_2 sporadic cases than in TSC_1 sporadic cases (208). Complete clinical screening of the parents of supposedly sporadic cases reveals one of the parents to be a mosaic mutation carrier 10% of the time (391).

The TSC_2 gene encodes the protein tuberin, and the TSC_1 gene encodes the protein hamartin. Hamartin and tuberin directly interact, suggesting that they are components of a singular cellular pathway, which explains why TSC_1 and TSC_2 mutations have such similar phenotypes (389). Both TSC_1 and TSC_2 seem to act as tumor-suppressor genes because both germline mutations are inactivating and loss of allelic heterozygosity at 16p13 or 9q34 occurs in AMLs and rhabdomyomas in TSC patients (148,350). Loss of heterozygosity suggests that a TSC patient inherits (or spontaneously acquires through mutation) a deletion in one copy of the gene but develops lesions such as renal AMLs only when there is a somatic mutation in the other copy.

TSC_2, the more common gene causing TSC, and PKD_1, the gene causing 85% of ADPKD, are located a few nucleotides apart on chromosome 16 in a tail-to-tail orientation. Deletions involving both TSC_2 and PKD have been identified in a small subset of TSC patients with early-onset,

multiple renal cysts and/or early renal failure (50). Thus the loss of TSC_2 and PKD_1 together describes a contiguous gene syndrome with a more severe infantile form of cystic disease than that found in TSC patients without loss of PKD_1 and a much earlier age of onset than normally found in ADPKD. Perhaps mutations of TSC_2 and PKD_1 have an additive or synergistic effect. The age of onset of renal failure in the TSC_2–PKD_1 contiguous gene syndrome sometimes varies significantly within the same family because of genetic mosaicism (338) (Fig. 20.9).

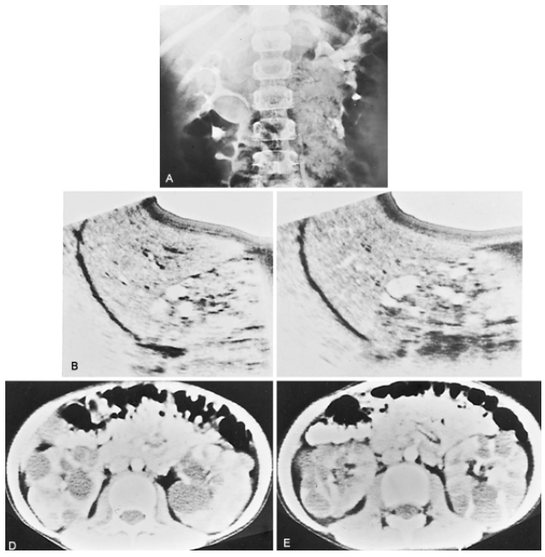

FIGURE 20.9. Tuberous sclerosis in a 10-year-old boy whose two brothers and mother were also affected. **A:** Intravenous pyelogram (IVP) reveals distortion of the collecting systems bilaterally. The splaying of the calyces could be secondary to either cysts or hamartomas. **B, C:** Renal ultrasonography reveals multiple cysts in both kidneys. **D, E:** Enhanced computed tomography reveals bilateral multiple renal cysts but no hamartomas. The presence of cysts can precede the presence of hamartomas. He had a seizure disorder, hypertension, and facial adenoma sebaceum. These radiologic findings in such a patient are typical for the TSC_2-PKD_1 contiguous gene syndrome.

Renal Manifestations of Tuberous Sclerosis

Renal disease is the second most common cause of death in TSC patients after CNS causes (352). Common renal lesions are AMLs and renal cysts. Less common renal lesions are RCC and malignant epithelial AMLs. ESRD has been reported in 1% to 15% of TSC patients (67,74,345).

Renal Angiomyolipomas.

AMLs are benign tumors consisting of variable proportions of fat-containing cells, smooth muscle cells, and arterial vessels whose thickened walls lack normal elastic tissue. AMLs have been detected in 49% (78) to 47% (364) of TSC patients but are a rare finding in the general population. Of TSC patients with AMLs, 91% had multiple lesions and 84% had bilateral AMLs, unlike the solitary AMLs in the general population (78). The incidence of AMLs increases with age in TSC patients (78), which supports the "two-hit" genetic process because the chance of somatic mutation of the second allele increases with age. AMLs in both TSC_1 and TSC_2 phenotypes have been observed to demonstrate loss of heterozygosity, which supports the idea that TSC_1 and TSC_2 act like tumor-suppressor genes (148,350). Other factors such as hormones modify the development of AMLs because pregnancy can accelerate AML growth and has been associated with rupture and hemorrhage of renal AML (96). In addition, AMLs in the general population are more common in women, AMLs in girls have a greater propensity for growth than in boys, and the larger renal AMLs occur after puberty (110). Henski and associates (171) found that 48% of renal AMLs in TSC patients (3 men and 18 women) had progesterone receptor immunoreactive smooth muscle cells but none contained estrogen receptor immunoreactive cells. Pulmonary lymphangiomyomatosis (LAM) is rare and is associated with TSC. It can have estrogen receptor and progesterone receptor immunoreactive smooth muscle cells (27). Female TSC patients with LAM can present with pneumothorax and hemothorax. The activity of the pulmonary lesions of LAM patients varies with physiologic hormonal changes and hormonal manipulation, so hormonal treatment can prolong survival and pulmonary disease (42).

The elastin-poor vascularity of AMLs makes them prone to hemorrhage into the retroperitoneum. Increasing AML size correlates with higher risk of retroperitoneal hemorrhage (91,385). AMLs are usually symptomatic if larger than 8 cm, but they tend to be asymptomatic if smaller than 4 cm (91). Rare instances of spread of AMLs to regional lymph nodes or into the inferior vena cava have been described, but no patient has had progression to widely disseminated disease (96). With regular screening of TSC patients, the incidence of AMLs may increase because routine US surveillance of affected children revealed 57% (mean age of 6.9 years) to have AMLs (110).

Renal Cysts.

Renal cysts have been found in 32% (78) to 43% (278) of TSC patients. When children with TSC were routinely screened with renal US, 10% were found to have renal cysts at initial screening (mean age of 6.9 years), but 17% were found to at follow-up (mean age of 10.5 years) (110). Simple cysts may appear or disappear in children with TSC (110). Renal cysts and AMLs tend to occur in the same patients with cysts antedating the AMLs (278). Renal cysts are usually asymptomatic. Features of TSC may present after or before the renal cysts. Although rare, renal failure in TSC is more likely to occur in patients with renal cysts (287). Children presenting with early-onset multiple renal cysts and/or early-onset renal failure may have the TSC_2–PKD_1 contiguous gene syndrome (50). When 60 children with TSC were screened with renal US, polycystic kidneys as in ADPKD patients were seen in only 1 patient. The histopathologic studies of renal cysts distinguish between TSC and ADPKD because the renal cysts of TSC have eosinophilic cells in their hyperplastic epithelium (361).

Renal Malignancies.

RCC has been described at a higher incidence in TSC patients than in the general population. TSC-associated RCC occurs at a younger age, is more likely to be bilateral, and is more likely to occur in women as opposed to sporadic RCC in the general population (31,399). Bjornsson and colleagues (36) described loss of heterozygosity in both TSC_1 and TSC_2 RCCs, indicating that increased risk is associated with both genotypes. Pea and associates (303) found alleged cases of TSC-associated RCC that were incorrectly diagnosed and concluded that RCC is less common in TSC than previously thought. Some cases called *TSC-associated RCC* were probably malignant epithelioid AMLs, and they suggested that all reported TSC-associated RCCs be reevaluated.

Renal Failure.

ESRD has been reported in 1% to 15% of TSC patients (67,74,345). ESRD in TSC is more common in females than in males (80% versus 63.1%) (74,345). Reduction in the amount of functioning renal parenchyma secondary to nephrectomy, partial nephrectomy, and/or arterial embolization to remove malignancies or control hemorrhage, as well as replacement of renal parenchyma by AMLs and RCCs, was thought to be contributory in 32% to 40% of patients (74,345). Renal failure more commonly

occurs in TSC patients with renal cysts (287). Although renal failure occurs earlier in TSC_2-PKD_1 contiguous gene syndrome, age of onset of ESRD is variable, even within the same family, and may not occur before the third decade because of genetic mosaicism (338). Clarke and associates (74) noted that on imaging, 4 of 10 TSC patients with ESRD had polycystic kidney disease.

Pathology

The pathologic findings vary with the degree of cystic involvement in TSC. Grossly, the kidneys can be enlarged, with cysts projecting throughout the renal cortex bilaterally. On cut section, multiple cysts (microscopic to 5 cm) are found throughout the cortex and medulla. Microscopically, renal cysts of TSC are easily differentiated from other renal cysts because of their hyperplastic epithelium of eosinophilic cells (361). Microdissection shows that cysts develop from all parts of the nephron.

Radiologic Findings

An IVP can reveal calyceal distortion and renal enlargement resulting from either the renal cysts of TSC or from the renal AMLs (76). US can differentiate the cysts from the hamartomas (Fig. 20.9). The AMLs appear sonographically as regions of increased echogenicity because of the presence of fat. In contrast, the cysts appear as anechoic lesions varying in size from 2 mm to 2 cm with thin uniform posterior walls and posterior enhancement (278). However, US cannot differentiate the renal cysts of TSC from those of ADPKD (unless multiple hepatic cysts are demonstrated, which would confirm the diagnosis of ADPKD). CT scanning can also demonstrate both the AMLs and the cysts of TSC. Demonstration of fat within the AML on CT makes the diagnosis of AML possible. In small AMLs (4 mm), detection of fat is difficult to achieve because of volume averaging, which makes CT confirmation of AMLs difficult. The detection of fat on US is far easier. Because all lesions seen on CT are detected by US, US is the preferred screening procedure for renal lesions of TSC (278). The renal angiographic manifestations of TSC consist of multiple AMLs, multiple renal artery aneurysms, renal cortical cysts, or some combination of these.

Management

A majority of TSC patients develop renal involvement, and a minority have significant morbidity. A baseline renal US in all TSC patients should be routine. Cooke and others (78) suggest serial renal US in TSC patients with no renal lesions and every 1 to 2 years in TSC patients with renal lesions. If there is any concern about a lesion, CT or MRI scan is appropriate. If extensive renal involvement is noted, renal function should be evaluated.

Any female TSC patient with AMLs should be monitored closely during pregnancy with renal US evaluations to allow for early diagnosis and intervention in renal hemorrhage. Female TSC patients should be cautioned about pregnancy and hormone replacement therapies. AMLs larger than 8 cm should be treated electively with arterial embolization or partial nephrectomy because most will cause complications if left untreated (91). AMLs smaller than 4 cm can be serially imaged because they are usually asymptomatic (91). AMLs between 4 and 8 cm have an unpredictable natural history because they are symptomatic 54% of the time (91). Modifying factors such as pregnancy potential should be taken into account, and patient counseling to recommend serial imaging versus elective renal sparing therapy is needed. TSC patients presenting with acute retroperitoneal hemorrhage from AML should be offered immediate arterial embolization to spare renal parenchyma (161).

MULTICYSTIC KIDNEY (MULTICYSTIC DYSPLASIA)

Part of "20 - RENAL CYSTIC DISEASE "

Multicystic kidney disease (MCDK) is the most common cause of an abdominal mass in the newborn. Although present at birth, a unilateral multicystic kidney can be clinically silent throughout adulthood. However, bilateral MCDK is fatal at birth because of insufficient renal function. The involved kidneys do not maintain a reniform shape but are replaced by clusters of cysts with fibrotic tissue. MCDK is a form of renal dysplasia and is rarely a genetically transmitted disorder (360).

Clinical Features

A multicystic kidney is present from birth but may be detected as early as 15 weeks *in utero* by prenatal US (365). Prenatal US has made *in utero* diagnosis the most common presentation of a multicystic kidney. The second most common presentation is in newborns as an asymptomatic abdominal mass that is mobile, irregular, and located in the flank and that may be transilluminated (394). Of those children diagnosed as having a MCDK, 90% were diagnosed before 1 year of age (365). A multicystic kidney is considered the most common or the second most common abdominal mass in the newborn, with congenital hydronephrosis as the alternative diagnosis (150). The widespread use of routine prenatal US has led to the observations that *in utero,* a multicystic kidney can involute and disappear. When the multicystic kidney disappears prenatally, the newborn is diagnosed as having unilateral renal agenesis, which may explain the cases of unilateral renal agenesis with an ipsilateral blind ending ureter (187). Postnatal follow-up US examinations in children with a unilateral multicystic kidney reveal that in the children followed 1 to 3 years, 47%

of the kidneys decreased in size but were still detectable and 13% disappeared. In those children followed 3 to 5 years, 23% became undetectable on follow-up US (392). Over 4.5 years, White and associates (405) noted that 17% of MCDK kidneys involuted at a mean rate of 1.02 cm per year and 30% decreased in size at a mean rate of 0.38 cm per year, although they were still detectable. Twenty-six percent of MCDK kidneys grew at a rate of 1.16 cm per year over the 4.5 years. John and colleagues (205) noted that 48% of their MCDK patients had complete involution over 2.6 years, 32% had partial involution, and 4% (one child) had increase in size. Occasionally, a transient increase in size of a multicystic kidney would be followed by involution.

Contralateral compensatory hypertrophy has been noted in older MCDK patients regardless of whether or not the patient had a nephrectomy (151). When the length of the contralateral kidney is measured at birth in MCDK neonates, hypertrophy [defined as kidney length above 2 standard deviation scores (SDS)] was found in 24%, showing that hypertrophy starts *in utero* and continues throughout childhood (205). The other 76% of the MCDK neonates had renal lengths between mean and +2 SDS. All of the contralateral kidneys in MCDK children grew at a rate greater than normal (405). Length and volume of the contralateral kidney had the most remarkable increase during the first 6 months of life (205). The presence of abnormalities of the contralateral kidney did not affect the increased renal volume (205). Size increase, size decrease, or removal of the multicystic kidney did not alter the increased growth rate of the contralateral hypertrophy (405).

In older children and adults, a unilateral multicystic kidney can be found incidentally during radiographic study being done for unrelated reasons (230). A unilateral multicystic kidney can be entirely asymptomatic in these older patients or cause abdominal pain. Resultant imaging studies to evaluate the abdominal pain result in the diagnosis of MCDK (4,359).

Indications for Nephrectomy

Surgical exploration to confirm the diagnosis of a multicystic kidney is not necessary with the current use of renal US and radionuclide renal scans. Therefore indications for nephrectomy are controversial but include hypertension, infection, pain, increasing size, and malignancy. Renin-mediated hypertension in MCDK has been established. Of 441 cases reported to the multicystic kidney registry, no case has been documented with hypertension as a causative factor (392). Serial blood pressure measurements in MCDK patients followed for approximately 4 years revealed no cases of hypertension (205,405). Although hypertension is rare in MCDK, reported cases of hypertension in patients with MCDK who were treated by nephrectomy resulted in resolution of the hypertension in pediatric patients (7,107,202) and not in adult patients (4).

Rudnik-Schöneborn and colleagues (336) found that 6 of their 204 MCDK pediatric patients required treatment with antihypertensive drugs for their hypertension. Two of the children had hypertension secondary to concomitant cardiovascular diseases, two children had spontaneous resolution of their hypertension after 6 months, one developed hypertension after nephrectomy, and one had no resolution of hypertension after nephrectomy.

Nephrectomy has rarely cured hypertension of long or unknown duration. Therefore, if patients with a MCKD are to be managed by surveillance, evaluation for hypertension must be rigorous (107) so that patients with hypertension and a multicystic kidney may benefit from a nephrectomy.

Infection involving a multicystic kidney is very rare (392) and is therefore not an indication for a prophylactic nephrectomy. UTIs may occur in patients with a multicystic kidney because of associated vesicoureteral reflux, which is more often contralateral than unilateral (114). Neither nephrectomy nor conservative management prevented the predisposition to UTI as a complication of MCDK (336). Although exceedingly rare, nephrectomy is appropriate therapy for an infected multicystic kidney (324). Pain is an indication for nephrectomy in a symptomatic patient, but this is uncommon. If the unusual circumstance of extraordinary growth of the multicystic kidney is noted over significant time or if the enlarging kidney is causing discomfort or feeding difficulty, nephrectomy is recommended (405).

Although nodular renal blastoma has been reported in multicystic kidneys (283), the development of malignancy in multicystic kidneys is so rare that prophylactic nephrectomy is unwarranted (21,392). There is a threefold to tenfold risk of Wilms' tumor compared with that in the general pediatric population (309). The mean age of presentation of MCDK children with Wilms' tumor is younger than the typical 3 to 4 years in the general pediatric population, with a mean age of 25 months (309). Screening renal US studies every 3 months up to 8 years of age is recommended to adequately screen MCDK patients for Wilms' tumor.

The Contralateral Kidney

Bilateral multicystic kidneys are less common than a unilateral multicystic kidney and are incompatible with life. Approximately 23% of fetuses with a multicystic kidney diagnosed by routine prenatal US screening were found to have bilateral disease, which is a higher incidence than that reported of births with a multicystic kidney (3,235). Bilateral disease can be associated with Potter's syndrome in which facial dysmorphia, pulmonary hypoplasia, and amnion nodosa all result from prolonged hydramnios, which results from low urinary output (47).

Males are more likely to be affected in unilateral MCDK than females at a ratio of 2.4:1, but females are twice as likely to have bilateral MCDK (235). Rarely, MCDK can

involve only a portion of a kidney, such as in a kidney with a duplicated collecting system, when the segmental MCDK typically occurs in the upper pole with atresia of the upper moiety of proximal ureter and reflux into the ipsilateral functioning lower moiety (203). Although rarely reported, ipsilateral cystic dysplasia of the testis has been associated with MCDK (329). However, because cystic dysplasia of the testis is asymptomatic and boys with MCDK do not undergo routine scrotal US screening, this lesion may be more common than is currently believed.

The prognosis of patients with a unilateral multicystic kidney depends on the status of the contralateral urinary tract, irrespective of the removal of the multicystic kidney (88). Current imaging of patients with a multicystic kidney reveal that 39% have contralateral abnormalities (vesicoureteral reflux, 18%; ureteropelvic junction obstruction, 12%), 6% have bladder wall abnormalities, and 6% have ipsilateral reflux (11). If voiding cystourethrography is routinely performed as part of the initial evaluation on all infants with a multicystic kidney, 18% to 28% are found to have contralateral vesicoureteral reflux despite a normal renal US of the contralateral kidney in most cases (114,405). Vesicoureteral reflux grades I through IV were present, with 50% spontaneous resolution or downgrading to reflux grade I in 50% of patients over 2 to 4.5 years (336). Therefore careful study of the contralateral kidney is most important in evaluating a patient with a unilateral multicystic kidney and should include voiding cystourethrography because the prognosis is otherwise excellent.

Morphology

A multicystic kidney can appear grossly as a disorganized patternless mass of variably sized cysts. The calyces and pelvis are not recognizably present grossly, and the reniform shape may not be evident. Usually, part or all of the ureter is atretic. The vascular pedicle may be atretic (93). Microscopically, immature ducts, ductules, and glomeruli, along with cysts and islands of cartilage, reside within fibrous stroma or cellular mesenchyme. Mature glomeruli may be present, although rare. The cysts are lined by low cuboidal epithelium. Contrast injection into the cysts reveals communication between the cystic spaces via tubular structures (138,344).

Pathogenesis and Renal Dysplasia

A multicystic kidney is a category of renal dysplasia in which the kidney is totally affected and cystic. Serial US examinations have revealed a multicystic kidney to decrease to a small noncystic mass (dysplastic kidney) or even to complete disappearance (aplasia) (365). The appearance by US changes from a predominant cystic dysplasia to predominant dysplasia as first the cysts involute and then the kidney decreases in size. Hence, these forms of renal dysplasia can be considered as a heterogeneous continuum of totally or segmentally involved kidneys, which may be cystic, solid, or both.

The diagnosis of renal dysplasia is made from recognizing histologic criteria thought to represent the aborted remnants of the ureteral bud or its poorly induced progeny (371). Such histologic findings include primitive glomeruli, ductules, tubules, cartilage, and primitive ducts. However, all of these features except for the primitive ducts can also be found near renal scars or in renal inflammation. Hence, primitive ducts are the only noncontroversial histologic evidence of embryonic renal maldevelopment (112).

An association exists between renal dysplasia and urinary tract obstruction. Is the cause of the obstruction (e.g., a malfunctioning ureteral bud or its branch) also the cause of dysplasia in the associated kidney or segment (371)? Support is found in the association of unilateral renal dysplasia with unilateral ureteral obstruction, bilateral renal dysplasia with posterior urethral valves, and segmental renal dysplasia with segmental obstruction. Furthermore, although the severity of the renal dysplasia relates to the severity of obstruction, the severity of both could relate to the degree of malfunction of the ureteral bud.

A defect in the ability of the branching ureteric duct and the undifferentiated metanephric blastema to communicate appears to be the basic underlying principle for the formation of dysplasia (263). Cellular communication between the ureteric duct epithelium and the metanephric blastema cells involves cellular “cross-talk” using a network of ligands and receptors on both cell types. For example, hepatocyte growth factor is expressed predominantly in the metanephric blastema, while its receptor is localized in the ureteric bud epithelium, supporting the role of the ureteric duct as inducer of the metanephric mesenchyme (263). The multicystic dysplastic kidney likely begins with a normally determined stem cell population. Aberrant expression of genes involved in the cascade of renal differentiation could result in a renal malformation. A single gene mutation may alter the ability of the ureteric bud and metanephric blastema to communicate or to respond appropriately to their reciprocal signals (263). The final phenotypic expression of MCDK may be dependent on the dysregulation or altered expression of genes that have been affected by the primary gene defect.

The high incidence of contralateral renal defects associated with the isolated multicystic dysplastic kidney is more suggestive of a generalized defect in normal induction of kidney development than of an acquired unilateral insult (263). About 24% of MCDK fetuses diagnosed by prenatal US screening have bilateral disease (3,235), suggesting a common pathophysiologic mechanism. Numerous inherited syndromes with renal malformations, such as cystic dysplasia, have been described with known specific gene and protein defects. However, the variable penetrance of renal cystic dysplasia suggests that other genes may modify normal

organogenesis (263). Associated nonrenal anomalies occur in up to 26% of unilateral MCDK patients and in 67% of instances of bilateral MCDK, suggesting an embryonic developmental field defect (235). Recent molecular techniques are expanding the understanding of the pathogenesis of MCDK.

Radiologic Findings

The frequency of the diagnosis of a multicystic kidney has increased because of the use of fetal US. A second-trimester US study is more likely to diagnose MCDK than late-trimester studies because the late-trimester studies may not identify the affected involuted kidney, thus altering the diagnosis to unilateral agenesis of unknown etiology (235). The accuracy of diagnosis in children has improved with the addition of radionuclide scanning to the point that the combination of US and renal scanning is so accurate that additional radiologic imaging is unnecessary. However, older patients may be diagnosed by other studies. A multicystic kidney appears as a nonfunctional mass on IVP. Contralateral compensatory hypertrophy occurs in 72% of children older than 2 years by US criteria (365). Because differentiation between a multicystic kidney and congenital hydronephrosis is necessary in evaluating an infant with a palpable abdominal mass, US features unique to a multicystic kidney have been described (366). The most useful criteria are (a) the presence of interfaces between cysts, (b) nonmedial location of the largest cyst, and (c) absence of an identifiable renal sinus (Fig. 20.10). Other confirmatory but not necessarily unique features on US are multiplicity of cysts that do not communicate and an absence of parenchymal tissue. Radionuclide scanning with Tc-99m DPTA reveals that 96% of multicystic kidneys demonstrate no uptake and that 4% have faint crescents of activity on delayed images (365). However, if Tc-99m DMSA is used as the tracer, 15% of MCDK kidneys show low-grade uptake, which correlates with the presence of mature cortical tissue found at nephrectomy (328). Renal angiography may show an absent or hypoplastic renal artery with no nephrogram (Fig. 20.11). Doppler US of the ipsilateral renal artery reveals marked abnormality of the waveform in a multicystic kidney (169). A retrograde urogram might reveal an atretic or absent ureter. CT is not commonly done on infants because of the requirement of prolonged periods of time without movement. However, when CT of a multicystic kidney in adults is performed, a small cystic kidney with or without calcifications can be revealed because the multicystic kidneys identified in adults tend to be smaller. Percutaneous injection of contrast material into cysts of multicystic kidneys in children has revealed communication between cysts (138,344).

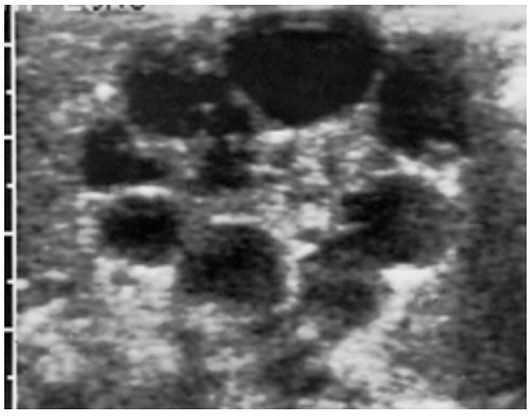

FIGURE 20.10. Multicystic kidney disease in female newborn. Renal ultrasonography at 1 week of age reveals multiple cysts in the right flank with septation between the cysts but no normal renal parenchyma. No communication was identified between the cysts, as would be present with hydronephrosis. The left kidney (not shown) was found to have ureteropelvic junction obstruction.

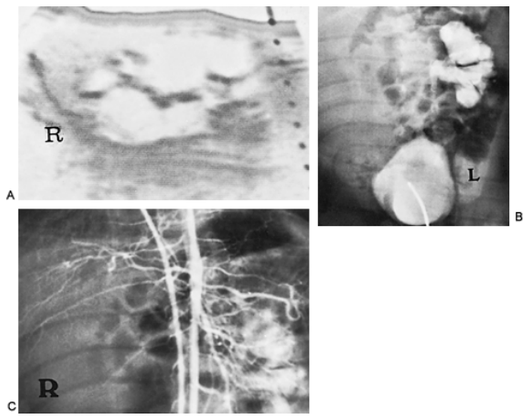

FIGURE 20.11. Multicystic kidney disease in female infant with ventriculoseptal defect and patent ductus. Although this 2-month-old had a right multicystic kidney and a left congenital ureteropelvic junction obstruction, only a right abdominal mass was palpated. **A:** Intravenous pyelogram reveals a hydronephrotic left kidney and nonfunction on the right. **B:** Midstream aortogram reveals no right renal artery. **C:** Midstream aortogram reveals no right renal artery.

Management

In the past, multicystic kidneys were routinely removed for pathologic diagnosis. However, the characteristic appearance on US plus nonfunction on radionuclide scanning allow for an accurate diagnosis without nephrectomy. Prophylactic nephrectomy is probably not indicated for pain, infection, hypertension, or malignancy because of the rarity of these disorders. However, surveillance by US and blood pressure measurements of these patients must be maintained to discover the rare cases of hypertension and malignancy.

Serial renal US studies every 3 months until age 8 have been recommended to make a diagnosis of Wilms' tumor at an early stage because of its fast growth rate (309). Monthly abdominal examinations by the parents may be as effective at diagnosing Wilms' tumor, with renal US examinations at 6 months and every 1 to 2 years thereafter until the multicystic kidney has involuted and the contralateral kidney is deemed normal.

Voiding cystourethrography should be performed as part of the initial evaluation in infants with multicystic kidneys to diagnose vesicoureteral reflux because of the risk of scarring in a solitary functioning kidney. Prophylactic antibacterial therapy is necessary until the reflux resolves spontaneously (at about 20 months of age in most of these patients) (114). Evaluation of the contralateral kidney is essential. Nephrectomy for the rare patient with pain, hypertension, malignancy, infection, or respiratory embarrassment is appropriate although US-guided percutaneous cyst decompression has been reported to definitively treat respiratory embarrassment secondary to a multicystic kidney (181). Nephrectomy for the rare young patient with

extraordinary growth of a multicystic kidney may be appropriate (405).

CYSTIC NEPHROMA (MULTILOCULAR CYSTIC KIDNEY)

Part of "20 - RENAL CYSTIC DISEASE "

Cystic nephroma (CN) is a very rare benign cystic tumor of the kidney that is usually unilateral and compresses the adjacent normal renal tissue. Hence, although CN is listed as a cystic disease of the kidney, CN does not diffusely replace normal renal parenchyma bilaterally; instead, it compresses normal renal tissue unilaterally. CN is rare, with fewer than 200 cases reported (2). Children and adults are affected with equal frequency. The cysts are limited to the area of the kidney involved with the mass and vary in size from a few millimeters to 5 cm. The tumor is completely cystic, with no solid nodules.

Clinical Features

Although children and adults are affected equally with CN, 73% of cases occurring in children younger than 4 years of age are in boys; in contrast, 89% of cases in patients older than age 4 are in females (251). Children present with a nonpainful abdominal mass, whereas adults present with a symptom such as abdominal pain or hematuria. When hematuria does occur, it is usually associated with herniation of CN into the renal pelvis. CNs often replace substantial portions of the kidney and commonly herniate into the renal pelvis (251) or renal sinus (220). The cystic mass has been observed to grow slowly in some patients (3 years) and rapidly in others (2 months) according to sequential physical examination (251). These lesions primarily occur in whites, males before age 24 months, and females between 40 and 70 years of age (59).

Eble and Bonsib (96) consider CNs in children as a different entity than CNs in adults, despite similar radiographic features. Their review concludes that tumors in young children that have been classified as CN as well as those classified as cystic partially differentiated nephroblastoma (a rare cystic benign-behaving type of Wilms' tumor) represent a single entity. Both should be considered highly cystic Wilms' tumors with little or no capacity for invasion or metastasis, and both should be classified as cystic partially differentiated nephroblastoma. Both are currently treated the same regardless of whether elements of Wilms' tumor are found, so there is no need to distinguish between the two

entities. Hence, Eble and Bonsib (96) conclude that the diagnosis of CN should no longer be applied to young children.

However, CN in adults has no connection to Wilms' tumor but is a benign cystic tumor that may rarely become malignant with secondary development of a sarcoma (96). Distinguishing CN from other extensively cystic renal neoplasms is not possible from preoperative imaging studies or fine-needle aspirates of these neoplasms (34,96). Intraoperative frozen-section analysis cannot always reliably distinguish CN from cystic RCC (34). Multilocular cystic lesions of the kidney are classified as Bosniak class 3 complicated cysts (17) in which imaging cannot distinguish malignancy from benign cystic lesions. Only 12% of RCCs are predominantly cystic, but these cystic RCCs have a slower growth rate, are identified at earlier stages and lower grades, are associated with a better prognosis and longer survival, and are even more likely to occur in males (96%) than conventional RCC (34). Fortunately, partial nephrectomy and radical nephrectomy are both effective treatments for both CN and cystic RCC because preoperative imaging and fine-needle aspirates cannot distinguish between the two entities and intraoperative frozen-section analysis could not identify malignancy in 3 of 8 cystic RCCs (although permanent sections could) (34).

Morphology and Pathogenesis

The pathologic criteria for establishing a diagnosis of CN were reformulated in 1956 by Boggs and Kimmelstiel (41). The criteria include (a) a multilocular mass, (b) no communication between cysts, (c) cysts lined by epithelium, (d) no communication between the cyst and pelvis, (e) remaining kidney essentially normal, and (f) no normal nephrons in the septa of the cysts. Joshi and Beckwith (209) further reformulated the criteria by specifying that the (a) tumor is composed entirely of cysts and their septa; (b) CN is a discrete well-demarcated mass; (c) septa are the sole solid component and conform to the outlines of the cyst without expansive nodules; (d) cysts are lined by flattened, cuboidal, or hobnail epithelium; and (e) septa contain fibrous tissue in which well-differentiated tubules may be present.

Grossly, the multilocular cystic mass is well circumscribed by a thick capsule and compresses normal adjacent renal tissue. Bilateral lesions are rare. Cut surface reveals multiple noncommunicating cysts, varying from a few millimeters to 5 cm in diameter. Microscopically, the cysts are lined by flattened or cuboidal epithelium. All cases of multilocular cystic kidneys have shown uniformly benign behavior. In adults, stromal septa have pronounced cellularity with a spindle cell pattern sometimes seen. Sarcoma was found in the septal stroma in 4 of 21 adults, with 3 of them developing metastasis containing the stromal element (251). These patients might have had multilocular sarcomas of the kidneys (59). The chemical content of the cyst fluid is similar to that of serum (1). The pathogenesis of CN is not known except that there is no familial tendency and that it behaves like a tumor in its growth and local recurrence. CN is not of developmental origin but is a cystic neoplastic lesion. The lack of normal renal tissue in its septa distinguishes CN from contiguous simple cysts and from congenital renal cystic disease with multiple cysts.

Radiologic Findings and Management

IVP of CN usually demonstrates an intrarenal mass in a normally functioning kidney. US can well visualize the multicystic nature of the tumor when the septa are seen to divide the mass into multiple loculi of regular distribution and similar size (129). CT reveals a cluster of cysts with thick walls and calcifications. However, when the cysts are small, it is more difficult for CT to confirm the cystic component of the mass (298). The septa on CT enhance with intravenous contrast medium (Fig. 20.12). MRI with gadolinium enhancement reveals enhancement of internal septa in all CN patients studied (220). Renal angiography usually reveals a hypovascular mass, sometimes with a tumor blush and neovascularity (2,251). Cytologic evaluation of cyst fluid is of limited value (2). In general, thickening of the septum to more than 1 mm, the presence of a solid component, calcification in the lesion, and neovascularity are potent signs of malignancy when imaging cystic renal tumors (82). However, US, dynamic CT, and dynamic MRI could not reliably distinguish between malignant and benign cystic tumors (178). Renal angiography was the most reliable imaging modality in distinguishing cystic RCC from benign cystic lesions by the presence or absence of tumor vessels (178), but neovascularization has been found in 20% of CNs (251).

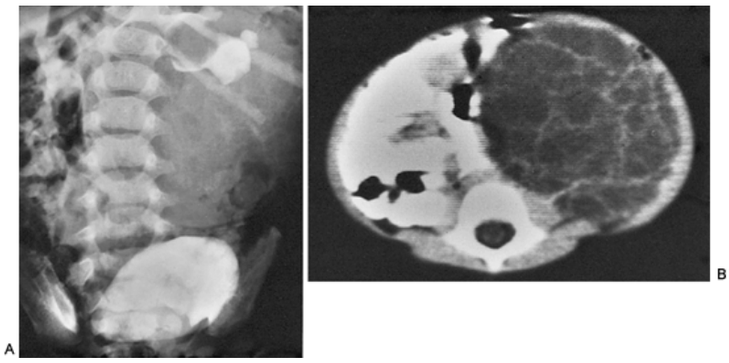

FIGURE 20.12. Cystic nephroma in a 4-year-old boy. **A:** KUB shows mass effect. **B:** Computed tomography scan with contrast reveals enhancing septa.

Therefore surgical intervention is the only effective method to differentiate CN from a malignant lesion of the kidney. A preoperative diagnosis of CN versus cystic partially differentiated nephroblastoma is of little importance because chemotherapy and radiotherapy are not used to treat either, renal-sparing surgery can be appropriate for both if technically feasible, and the two can be considered the same entity in young children (96). Nephron-sparing surgery did not result in local recurrence with 3-year follow-up (59). Complete excision of childhood CN or cystic partially differentiated nephroblastoma is possible as conservative surgery, but special care must be taken to excise the cystic lesion that penetrates the renal pelvis (66). Because radiographic methods cannot rule out malignancy, a partial nephrectomy is adequate only after the surgeon has confirmed there is no malignancy in the surgical specimen pathologically, although histopathologic confirmation by frozen section can be wrong (34,337). Cystic RCC has such a favorable prognosis that conservative surgery is appropriate, as it is for CN if technically feasible (34). Treatment by nephrectomy is appropriate after assessment of the

status of the contralateral kidney although bilateral cases are rare (66).

SIMPLE RENAL CYSTS AND COMPLEX RENAL CYSTS

Part of "20 - RENAL CYSTIC DISEASE "

Although simple cysts are an entity in their own right, concern regarding simple renal cysts is usually directed toward their differentiation from neoplastic renal masses because they are so frequently discovered as an incidental finding on radiographic studies. Indeed, 24% of routine abdominal CT scans in one study (234) and 20% in another (369) revealed unexpected simple renal cysts. Analyzing the data separately in both CT studies, 0% to 6% of patients younger than 40 years were found to have simple renal cysts, as opposed to 18% to 19% of patients 40 to 60 years of age and about 31% of patients older than 60. However, at autopsy, at least 50% of patients older than 50 years of age have grossly recognizable cysts of the renal parenchyma (223). Another autopsy study revealed a 39% overall incidence of renal cysts but a greater than 50% incidence in patients older than 50 (323). Forty-eight percent of patients had cysts less than 1 cm in diameter. These smaller cysts could have been missed by CT or US, which probably explains the discrepancy in frequency. By CT and US, the number of cysts per patient and the cyst diameter increased with the age of the patient (234,321). Such data suggest that simple renal cysts are acquired abnormalities, perhaps related to the aging process; however, the pathogenesis is unknown. They are not familial.

Renal Cysts in Children

Simple renal cysts are rare in children but may be detected at any age (373). A fetal simple renal cyst can rarely be identified by US in early pregnancy, but in the absence of associated anatomic or chromosome abnormalities, most fetal renal simple cysts will resolve during pregnancy without any sequelae (37). Before the routine use of IVP, US, and CT in children, the most common presentation of renal cysts in a child was that of an asymptomatic abdominal mass. However, in more recent series of pediatric patients, simple renal cysts were incidental findings on radiographic studies (19,141) with a reported frequency of 1 simple cyst for every 430 abdominal US studies performed (267).

Cyst Growth

Simple renal cysts are by definition unilocular, do not communicate with the collecting system, occur in a kidney that is otherwise normal, and have an epithelial lining that contains no renal elements. Grossly, cysts are tense and thin walled and vary in diameter from millimeters to 7 cm (Fig. 20.13 and Fig. 20.14). Microscopically, the cysts are lined with low cuboidal to attenuated flattened epithelium. Fluid of

simple cysts has chemical features of an ultrafiltrate of plasma (223). A dynamic equilibrium exists between production and absorption of fluid in simple renal cysts such that the cyst fluid has levels of tritiated water that reach 73% of the serum level within 2 to 5 hours after an intravenous injection of tritiated water (199). Perhaps cyst growth is dependent on the ratio of fluid production to absorption. Serial US measurements of renal cysts reveal only 28% of cysts increased in size in a 2- to 3-year period. The size change was 1 to 2 cm, and 14% of the cysts decreased in size by 1 to 2 cm over 2 to 3 years (83). However, many US and CT studies reveal increasing prevalence of simple renal cysts with age (32,56,83,234,305) and increasing diameter of cysts with age (56,234,321).

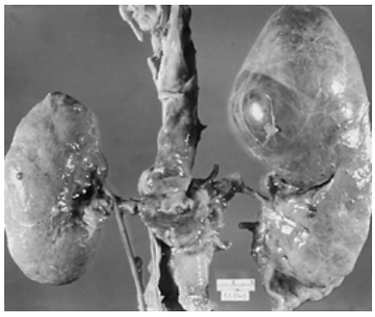

FIGURE 20.13. Simple cyst. A tense, thin-walled cyst is seen in the left upper pole. (Courtesy of Dr. S.E. Mills, Department of Pathology, University of Virginia Medical School, Charlottesville, VA.)

FIGURE 20.14. Simple cyst. A simple cyst is seen in the lower pole of this left kidney. Cyst was collapsed inadvertently at surgery. (Courtesy of Dr. S.E. Mills, Department of Pathology, University of Virginia Medical School, Charlottesville, VA.)

Radiology and Classification

Radiographic methods to diagnose a simple renal cyst have improved tremendously over the last decade. Because IVP cannot differentiate between a solid renal mass and a cystic renal mass, both of which distort the pyelocaliceal system (Fig. 20.15), renal US should be the next study. If the US requirements for a simple renal cyst are completely met on a study, investigation of a simple cyst is complete (19). The US appearance of a simple renal cyst is an anechoic mass with sharply marginated smooth walls and posterior wall enhancement (Fig. 20.16). However, if sonographic criteria for a simple cyst are not met or if lesions contain calcium, septations, or irregular margins, a CT examination is necessary (44). US is preferable as an initial study because it costs less, is less invasive, delivers no radiation, and does not require the pediatric patient to remain motionless for an extended time. The CT criteria for diagnosis of a cyst are (a) sharp margination and demarcation from surrounding renal parenchyma, (b) smooth thin wall, (c) water density content that is homogeneous throughout, and (d) no enhancement after intravenous administration of contrast material (44).

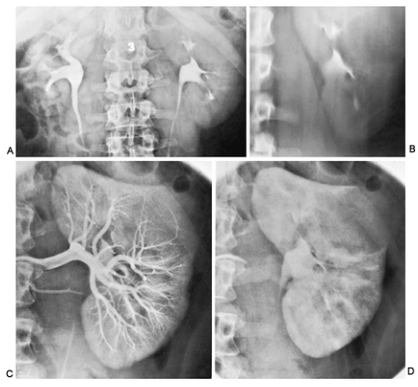

FIGURE 20.15. Simple cyst in a 36-year-old man. **A:** Intravenous pyelogram reveals bilaterally normal kidneys except for a spherical mass arising from the superolateral margin of the left kidney. **B:** Nephrotomography reveals the mass to be relatively lucent and to have smooth margins. **C, D:** Renal arteriography confirms the presence of a simple cyst by the draping of vessels around the mass, the lack of neovascularity, and its thin rim and "beaks" at its margin with the renal cortex.

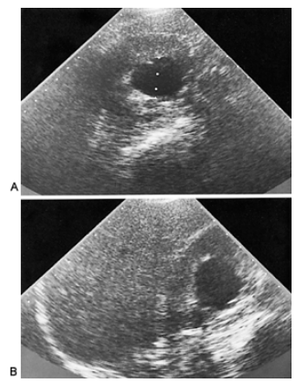

FIGURE 20.16. A–B: Simple cyst in 53-year-old woman. Renal ultrasonography reveals an anechoic renal mass with a smooth posterior wall and posterior wall enhancement.

CT scanning to evaluate a renal cyst or mass found on another imaging modality should include non-contrast-enhanced scans through the lesion as well as contrast-enhanced scans and should include 5-mm-thick sections of the lesion while there is a high level of contrast media in the blood, unless the lesion is large enough that 10-mm-thick sections are adequate. Bosniak (44) has classified cystic lesions of the kidney into four categories based on a combination of CT and US imaging to help make clinical management decisions and to approximate the risk of malignancy. *Category I* lesions are benign simple cysts diagnosed definitively by CT or US. *Category II* lesions are benign but are minimally complicated because of worrisome radiologic findings in septated cysts, minimally calcified cysts, infected cysts, and high-density cysts. Such lesions do not require surgical exploration but may need to be followed. *Category III* lesions may be malignant and are more complicated cystic lesions because of thick or irregular calcifications or irregular thick septa with solid elements at the cyst wall attachments. Such lesions require confirmation by surgery in patients without poor operative risks. *Category IV* lesions

are malignant cystic lesions and have irregular margins or solid vascular elements. They require surgical excision. Hyperdense renal cysts are in category II because they are assumed to be benign, usually contain old blood, are isodense or hypodense with surrounding renal parenchyma after intravenous contrast administration, and can be followed by serial CT (44) because cystic RCC can simulate a benign hyperdense cyst (162).

Sixteen pathologically proven cystic renal masses were retrospectively reviewed using the Bosniak classification by Aronson and colleagues (10). All category II lesions were benign, all category IV lesions were malignant, and of the seven category III lesions, three were benign and four were malignant. Similarly, 70 pathologically proven cystic renal masses were reviewed by Siegel and associates (354), with 0% Bosniak I malignant, 13% of Bosniak II malignant, 45% of Bosniak III malignant, and 90% of Bosniak IV malignant. However, Wilson and co-workers (409), in a similar retrospective review of pathologically proven cystic renal masses, found a high rate of malignancy in Bosniak categories II (80%), III (100%), and IV (100%). In addition, Cloix and associated (75), in a similar retrospective review of pathologically proven cystic renal masses, found a RCC that had been classified as a Bosniak I. However, the Bosniak classification requires devoted renal CT studies with 5-mm cuts. Cloix and colleagues (75) used 10-mm

slices in their study, and not all patients had devoted renal CT scans. Only 9 of the 20 patients in Wilson and colleagues' study (409) had undergone dedicated thin-section renal CT examinations both before and after intravenous contrast administration. Siegel and associates (354) suggest that intraobserver variation in distinguishing Bosniak II and III lesions may explain the differences between these studies. Bosniak (45) amended his original classification system by adding class 2F for minimally complicated cysts that are “somewhat suspicious” and require follow-up with serial CT scans to establish stability instead of immediate surgical exploration. Despite any shortcomings of the Bosniak classification, it is the best system currently available to classify complex renal cysts.

Spiral CT scanning eliminates respiratory misregistration; therefore the walls of cystic lesions can be visualized with great precision and specificity in the diagnosis of simple renal cyst is increased. However, small lesions can be missed by spiral CT if scanning occurs too soon after contrast injection (46).

Renal angiography is less important in the diagnosis of a simple renal cyst but would show an avascular mass with renal cortex compressed at the margins. Both contrast-enhanced power Doppler sonography and delayed CT have shown promise in demonstrating tumor vascularity/enhancement in complex renal cysts (221,261). Percutaneous cyst puncture for cytology and injection of contrast is not now as commonly needed because of the high quality of US and CT available. Of course, the diagnosis of suspected infected cysts or abscesses is benefited by percutaneous aspirate, Gram stain, and culture. MRI can help differentiate between a simple cyst and a hemorrhagic cyst (Fig. 20.17). In addition, gadolinium-enhanced MRI scans and non–gadolinium-enhanced MRI scans can be used in patients unable to receive injections of contrast media for CT. Nonenhanced and gadolinium-enhanced T_1-weighted and T_2-weighted MRI has been evaluated to determine whether imaging features could distinguish between benign and malignant complex renal cysts (16). Although mural irregularity and intense mural enhancement strongly predicted malignancy in complex renal cysts, appearances of benign and malignant lesions overlap.

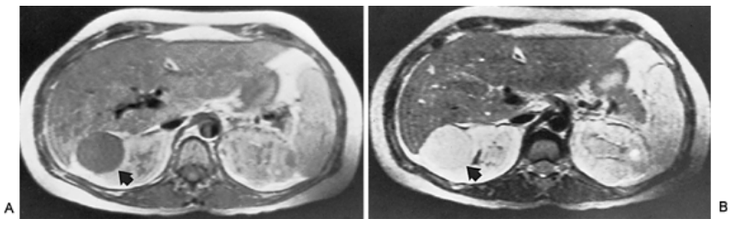

FIGURE 20.17. Simple cyst in a 44-year-old woman. **A:** Magnetic resonance imaging of a T_1-weighted image is characteristic of a simple right renal cyst *(arrow)* because of the distinct smooth margin and because of the low signal intensity (e.g., the cyst contents are very black). **B:** To confirm the diagnosis of a simple cyst, a T_2-weighted image demonstrates the cyst contents to have a high signal intensity (e.g., to be very white), which is consistent with water.

Renal Sinus Cysts

Cysts in the renal sinus deserve mention. Parapelvic cysts are usually single, larger cysts in the renal sinus originating from adjacent parenchyma and are simple cysts. Peripelvic cysts are multiple, confluent, irregularly shaped cysts that appear to arise in the renal sinus itself and that may develop from lymphatic ectasia secondary to blockage of renal hilar lymphatics (6). Autopsy studies show a 1.3% to 1.5% incidence of sinus cysts in the older population. If a sinus cyst of any size happens to be appropriately located, symptoms such as hypertension, hematuria, and localized hydronephrosis can result if a renal sinus structure is compressed, such as a vascular structure or the collecting system (6). On US evaluation, peripelvic or renal sinus cysts may be mistaken for dilated calyces and pelvis. This potential for false diagnosis may be the only clinical relevance of this condition (300).

Management of Simple Cysts

Usually, simple cysts are asymptomatic coincidental findings on imaging studies and require no treatment. However, they occasionally can present as flank or abdominal pain, infection, hemorrhage, hypertension, and impairment of renal function. Case reports elucidate the rare presentation of simple cysts as hypertension in children (14,179) and in adults (330). Increased renin release from the affected kidney has been demonstrated as well as normalization of blood pressure after open surgical or percutaneous elimination of the cyst (14,330). In ADPKD, the cause of hypertension has been proposed to be activation of the renin-angiotensin-aldosterone system by cyst compression of adjacent renal vessels causing ischemia (62). A similar mechanism may account for the hypertension in the aforementioned

case reports as well as hypertension in an aging population (305). More patients with simple renal cysts have hypertension (56). Not only are hypertension and simple renal cysts increasingly common with increasing age, but hypertension is significantly higher in individuals with cysts (305). Possibly, the association between simple renal cysts and higher arterial blood pressure arises from underlying renal disease causing both (306).

Approximately 6% of simple cysts hemorrhage, and although hemorrhagic cysts are extremely rare in children, they have been reported (325). Cyst hemorrhage can be spontaneous or secondary to trauma and may result in hematuria (296). Hyperdense renal cysts occasionally are incidentally found on CT imaging and are renal cysts containing old blood (44), suggesting minor cyst hemorrhage does not result in severe symptoms. Secondary cyst infections are rare but have been reported (131,256); these have been successfully treated with percutaneous drainage and systemic antibiotics (284). Acute urinary obstruction can cause extravasation of urine from the renal pelvis or calyces into a simple cyst (43). Except in rare cases when cysts cause calyceal or renal pelvic obstruction, simple renal cysts have no negative affect on renal function (184).

After the diagnosis of simple renal cyst has been made, no treatment is necessary except to treat symptoms such as abdominal or flank pain. Even though simple renal cysts are rare in the pediatric age group, once malignancy has been excluded appropriately by radiographic methods, no surgical exploration to confirm the diagnosis is necessary (141,320,355). Treatment of symptomatic renal cysts begins with percutaneous aspiration of the cyst to confirm that the symptom such as pain disappears. Cyst fluid can be analyzed cytologically as well as cultured to confirm diagnosis of simple cyst, but cyst fluid cytologic evaluation is not highly accurate. Twenty-four months after aspiration, cyst fluid will have reaccumulated, so there is no size difference between cysts that were aspirated and those that had no intervention (182). However, if the patient's symptom (pain) disappeared with aspiration and the cyst and symptom reoccurs, percutaneous aspiration should be repeated, followed by instillation of a sclerosing agent, such as urea cholohydrolactate, glucose, ethanol, phenol, tetracycline, bismuth phosphate, autologous blood, minocycline, Betadine (povidone-iodine), quinacrine, iophendylate, polidocanol, or ethanolamine (51,142,182,262,285,286,293,386). Cyst and symptom recurrence are significantly lower after aspiration and instillation of a sclerosing agent than after aspiration alone (182,285); however, long-term cyst reduction occurs in only 50% of cases (183). Repeated injections of a sclerotherapeutic agent over a few days into an indwelling percutaneous drain into the cyst had a higher success rate, though. Three repeated ethanol injections over 2 days into an indwelling percutaneous drain resulted in complete disappearanceof 97% of renal cysts at 3 months, with no recurrence during the mean 4-year follow-up (117). The drain was left to closed drainage between instillations.

Percutaneous resection of simple cysts is another treatment with the advantage of obtaining part of the cyst wall for pathologic analysis. Plas and Hubner (314) found that morbidity was minimal but that 50% of patients had residual or recurrent cyst tissue at 40 months, even though no patient had recurrence of their symptoms. Weichert-Jacobsen and others (403) described a modified percutaneous resection technique used only in patients with peripheral renal cysts and found no recurrence of cyst formation on US or symptoms at 19 months of follow-up. Laparoscopic excision of simple renal cysts has been reported through both abdominal and retroperitoneal approaches, with no evidence of recurrent cysts or symptoms in the initial series (155,275,281,335). Recurrence of a renal cyst

but not symptoms has been reported after laparoscopic unroofing (217). A wide section of the cyst wall is obtained for pathologic review, as is the case for open surgical cyst excision. Open surgery does have the advantage of better control of bleeding.

Most symptomatic simple cysts can be effectively managed with percutaneous drainage and sclerosis. The repeat injections into an indwelling percutaneous drain have a high success rate. However, in those few simple cysts resistant to these techniques, the percutaneous resection is effective for peripheral simple renal cysts, as is laparoscopic decortication via either a transperitoneal or retroperitoneal approach or open surgical decortication.

Management of Peripelvic Cysts

Peripelvic cysts may lie between major hilar vessels and the renal pelvis. Sclerotherapy into peripelvic cysts is considered risky. Percutaneous sclerosis with multiple injections of povidone-iodine into an indwelling drain in four parapelvic cysts relieved symptoms in all patients with 7.2 months follow-up (312). Successful marsupialization of a peripelvic renal cyst using flexible ureteronephroscopy has been reported (218). Transperitoneal laparoscopic ablation of peripelvic cysts has been successful in alleviating pain but is technically challenging (180). Open surgical repair has succeeded after a failed retroperitoneal laparoscopic ablation of a peripelvic cyst (180).

Management of Complex Cysts

Bosniak category IV complex cysts can undergo partial or radical nephrectomy depending on the size and location of the complex cyst as well as the status of the contralateral kidney. Bosniak category III complex renal cysts can undergo open surgical exploration with preparedness to perform a partial nephrectomy (410). The cyst can be visualized directly while attempts are made to prevent tumor cell spillage, and the cyst fluid can be aspirated, and the external cyst wall and biopsies of the internal cyst wall can be sent for frozen analysis. Bosniak category IIF cysts can be followed by serial CT studies. Laparoscopic evaluation of 35 patients with Bosniak category II and III complex renal cysts revealed 5 patients (14%) with cystic RCC (341). At the time of laparoscopy, cyst fluid is aspirated and the cyst wall is excised and sent for pathologic evaluation, as are biopsies of the base of the cyst if suspicious. If the pathologist confirms malignancy, an immediate radical or partial nephrectomy can be performed (341).

MEDULLARY SPONGE KIDNEY

Part of "20 - RENAL CYSTIC DISEASE "

Medullary sponge kidney (MSK) is a relatively benign entity that is diagnosed by IVP. The diagnosis is usually made in adults who present for IVP for evaluation of calculi, hematuria, or infection. The male-to-female ratio is 2:1 (240). In MSK, the kidneys retain their reniform shape, and the incidence varies from 1 in 5,000 to 1 in 20,000 (228). Although described histologically to some extent in 1908 (100), it was the onset of IVP that made possible the description and classification of MSK as a disease by Cacchi and Ricci (55). Even today, IVP is the mainstay of diagnosis.

Clinical Features

MSK is most commonly diagnosed from 20 to 50 years of age, when patients have an IVP performed to evaluate their presenting symptom, which is either renal colic (50% to 60%), gross hematuria (10% to 18%), or UTI (20% to 33%) (228). Of those who have this radiographic diagnosis made, 60% will pass calculi at some time (228). However, an uncertain number are undiagnosed because they are asymptomatic. A small number of patients with MSK have been diagnosed when they were evaluated by IVP for other conditions, such as hypertensive screening, abdominal tumors, and so on. Hence, although 60% of patients diagnosed with MSK will pass calculi, it is uncertain what percentage of all patients with MSK will pass stones, have infections, and so forth. Nephrocalcinosis in MSK is clinically benign except that it leads to stone formation and passage of calculi. Of 70 kidneys examined in affected patients, 58 had intracavitary calculi ranging in number from one to infinity (100). Stone analysis reveals that calcium phosphate stones are the most common, with calcium oxalate stones making up most of the remainder.

In MSK, the medullary cysts are dilated collecting ducts in the pyramids and papillae. Urinary stagnation in these dilated or cystic tubules may be the cause of the calcifications found in these dilated ducts. Because metabolic disorders accounting for lithiasis are found less commonly in stone patients with MSK (60%) than in stone patients without MSK (93%), MSK may cause nephrolithiasis (134). Alternatively, perhaps the biochemical composition of the urine is altered in patients with MSK who have calculi (413). Defective urinary acidification might play an important role in the mechanism of hypercalcuria and hypocitraturia in MSK patients (291). From 40% to 90% of patients with nephrocalcinosis also have hypercalciuria (174). From 15% to 21% of patients with calcium stones were diagnosed as having MSK by IVP (299,413). Ginalski and colleagues (134) found MSK on 12% of IVPs in patients with nephrolithiasis and in 1% of IVPs of patients without nephrolithiasis and without a history of stones.

Progression of MSK, as evidenced by the size or location of the dilated collecting tubules on IVP, is uncommon (228). However, nephrocalcinosis in MSK is acquired (228). Sequential US studies on six children with MSK have revealed increasing echogenicity of the renal pyramids. This increasing echogenicity proved on CT to be calcifications,

although the calcifications were too small to be seen on IVP (302). Three of these six children had hematuria, which was probably associated with their microlithiasis. Microlithiasis may be the cause of most of the hematuria seen in those MSK patients who have no demonstrable calcifications on IVP.

About 20% to 30% of patients with MSK have a UTI as their presenting symptom (228). UTI does not play a causal role in stone formation in most patients with MSK, most of whom have sterile urine (413); however, when present, infection has the potential of accelerating stone growth by alkalinizing the urine. Fortunately, infection in affected patients responds well to antibiotics, unlike in patients with ADPKD. In addition, patients affected with MSK have an incidence of hypertension similar to that found in the normal population. Occasionally, a mild urine-concentrating defect can be found in patients with MSK who otherwise have normal renal function.

Morphology, Pathogenesis, and Genetics

Grossly, the kidneys of MSK are of normal size or slightly larger and have kept their reniform shape. Cut surface reveals the larger of the dilated collecting duct cysts, which are present at the papillary tips of the renal pyramids (near the renal medulla). The smaller of the dilated collecting duct cysts may be visible only microscopically because they vary from 1 to 5 mm in diameter. Microscopically, the collecting ducts are lined by flattened epithelium, and the columns of Bertin are normal. As few as one or as many as all renal pyramids can have MSK and calcifications can be seen in the cysts clustered toward the papillary tips.

The pathogenesis of MSK is unknown, but it is probably congenital. Successive US studies in children with MSK show the progressive development of calcifications as the children grow as well as the presence of the disease in children (302). MSK has some basis for at least occasional genetic transmission because of documented family history in a few families (228) and its association with other congenital manifestations.

Radiologic Findings

The diagnosis of MSK is made by IVP (Fig. 20.18). The contrast medium stagnates in the dilated or cystic linear tubules in one or more renal papillae. These appear as linear radiations from the calyces and vary in shape from beads to strands. Whether a “pyramidal blush” is an early sign of MSK on IVP or is a normal finding is undecided. Calculi are located at papillary tips on a plain abdominal radiograph. US shows the medullary cysts only if they are large. However, in children, the renal medulla is better seen on US because there is less renal sinus fat and overlying muscle. As a result, hyperechoic areas of the pyramids are visualized and either represent ductal calcifications or dilated collecting ducts (302). On retrograde pyelography, the cysts or ectatic ducts either fail to fill with contrast or fill less prominently. The sensitivity of CT in the detection of MSK is markedly lower than that with IVP. However, CT is more sensitive than plain films and tomograms of IVP in the detection of the papillary calcifications of MSK (135).

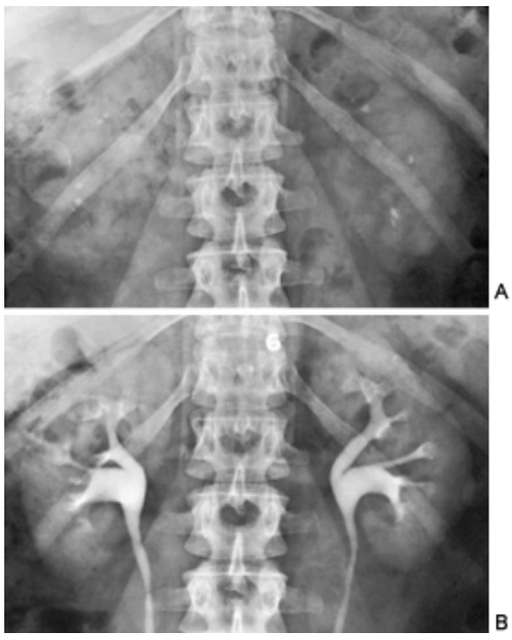

FIGURE 20.18. Medullary sponge kidney. **A:** A plain abdominal radiograph reveals bilateral nephrocalcinosis. The calculi are located at the papillary tips. **B:** An intravenous pyelogram in the same patient reveals linear radiations from the calyces. These radiations result from stagnation of contrast medium in the cystic or dilated collecting ducts.

Management

Some patients with MSK will have an asymptomatic course and require no medical intervention. Previously, 10% of the symptomatic patients had a poor prognosis because of recurrent renal calculi and infection (228), but with current therapies for infections and calculi, this number is probably lower. Infections in patients with MSK respond well to antibiotics. Prevention of stone formation can be attempted with increased fluid intake, thiazides, and inorganic phosphates (413). Urine alkalization may reduce the incidence of stone formation in these patients (90). Once calculi are formed, ESWL is effective in disintegrating symptomatic stones in the collecting system (90,277,387) but not in fragmenting the ductal (precaliceal) calcifications (90,387). Marked improvement in the frequency of renal colic and

UTIs was noted after ESWL, perhaps secondary to the reduction in stone mass and the reduced incidence of obstruction in the upper urinary tract (90). Transurethral extraction of ureteral calculi is appropriate with ureteroscopy as needed. Appropriate antibiotic prophylaxis during the perioperative period should be used because of the high risk of obstruction in these patients from passage of more calculi.

GLOMERULOCYSTIC KIDNEY DISEASE AND GLOMERULOCYSTIC KIDNEYS

Part of "20 - RENAL CYSTIC DISEASE "

Glomerulocystic kidney disease (GCKD) is a rare congenital bilateral cystic disease in which Bowman's space is dilated and thus appears as a glomerular cyst. The cysts contain some sort of glomerular tuft or tuft remnant. These multiple cysts are confined to the renal cortex in these reniform but very large kidneys. The tubular portion of the nephron is structurally normal. The lack of tubular involvement distinguishes GCKD from other cystic renal diseases in which proximal or distal tubule dilation leads to cyst formation in both the cortical and medullary regions (57).

Glomerulocystic kidneys occur in (a) GCKD, (b) heritable malformation syndromes, and (c) dysplastic kidneys (30). Glomerulocystic kidneys are a major component of heritable malformation syndromes such as ADPKD, TSC, orofaciodigital syndrome, brachymesomelia-renal syndrome, trisomy 13, short rib–polydactyly syndrome, Jeune syndrome, and familial juvenile nephronophthisis, and is a minor component in Zellweger's syndrome. Glomerular cysts can be a minor feature in dysplastic kidneys such as diffuse cystic dysplasia and renal-hepatic-pancreatic dysplasia (30). In contrast, GCKD comprises nonsyndromal heritable and sporadic forms of severely cystic kidneys in young children and to a lesser degree in adults.

GCKD has a broad range of clinical manifestations from death in early infancy to survival in adult life, with little handicap and with successful marriage and reproduction. Patients more commonly present in infancy or early childhood and have bilaterally palpable flank masses (265,349,372). Renal function can deteriorate (265) or remain stable for an unknown amount of time (349). Glomerulocystic kidneys in young infants are a common expression of early onset ADPKD (32). Many of these newborns and young children have a family history of ADPKD, whereas others are sporadic. Because no differences are found between familial and sporadic cases, the sporadic cases are potentially new mutations of the same disease (30). Children with early onset of severe ADPKD have an affected parent whose milder disease presented in adulthood. The increase in disease severity is limited to the kidney that has a higher number of cysts and mostly glomerular cysts (289). Dedeoglu and co-workers (86) described an infant diagnosed with GCKD because of classic findings on his renal biopsy, normal renal US studies of his parents, and negative family history. Seven years later, his diagnosis was changed to ADPKD because a repeat renal US of his mother (30 years old) suggested ADPKD, pathologic examination of his kidneys after bilateral nephrectomies confirmed ADPKD, and gene linkage analysis was informative for the family for ADPKD. A positive family history can point the clinician in the right direction, which may be verified by linkage analysis. Glomerular cysts have also been identified in 40% of adult ADPKD kidneys examined for their presence (30).

Less commonly, GCKD is a cause of chronic renal insufficiency in older children (411). In rare instances, GCKD has been diagnosed in adults who can present with hypertension, flank pain, hematuria, mild chronic renal failure, and ESRD (57) or who can present as coincidental findings when patients undergo renal biopsies for another renal disease such as glomerulonephritis (58). Potentially, GCKD may be more common than realized because biopsies have not been performed on otherwise asymptomatic patients. GCKD in adults and older children may also be sporadic or familial. If familial, GCKD is dominant (269). Usually, patients progress to ESRD or stable chronic renal insufficiency (57). Poor prognosis may be related to extensive involvement with glomerular cysts at an early age. Survival beyond adolescence with only mild to moderate renal functional impairment and no associated congenital abnormalities appears to improve chances for maintaining adequate renal function (57). Another category of GCKD is hypoplastic GCKD, which is rare and dominant. Unlike other GCKD patients, these patients have small kidneys and abnormal pyelocaliceal anatomy. Amir and colleagues (5) suggest that GCKD may be acquired after hemolytic uremic syndrome.

GCKD kidneys are large and reniform, with cortical cysts that vary in diameter from a few millimeters to 7 cm (349). IVP demonstrates huge kidneys and can sometimes demonstrate calyceal distortion suggesting multiple renal cysts or masses (57). US demonstrates large kidneys and may show numerous small cysts, depending on cyst size (265). Therefore the kidneys appear strongly echogenic with cortical, subcortical, and subcapsular cysts (57). Selective renal arteriography can show intrarenal vessels stretched around numerous cortical cysts (349). A renal biopsy may be necessary to establish a diagnosis (57). MRI shows multiple cortical cysts and diffuse reduction of the intensity of the renal cortex with loss of the normal corticomedullary differentiation on T_1-weighted images (98).

Treatment is appropriate management of renal failure. Both dialysis and renal transplantation have been successful (265).

ACQUIRED CYSTIC KIDNEY DISEASE

Part of "20 - RENAL CYSTIC DISEASE "

Long-term maintenance dialysis therapy is now accepted therapy for patients with ESRD. However, dialysis has ushered in a new class of renal cystic disease called *acquired*

cystic kidney disease (ACKD). ACKD was so named in 1977 by Dunnill and co-workers (95), who observed that 14 (47%) of 30 long-term dialysis patients had bilateral renal cystic disease at autopsy. None of these patients had renal cystic disease before beginning hemodialysis. Later studies revealed that hemodialysis patients and continuous ambulatory peritoneal dialysis (CAPD) patients have the same prevalence and severity of ACKD (196,343). Patients with longstanding renal insufficiency who have never been dialyzed also developed ACKD (48,72). In retrospect, ACKD was described in 1847 in patients with subacute glomerulonephritis causing such longstanding renal insufficiency (356). Because ACKD is asymptomatic in its early stages, ACKD can occur before ESRD is recognized. The uremic state promotes the development of ACKD, and dialysis extends the time that the cysts can develop. Serial CT scans of the kidneys of uremic patients suggest that cysts start to develop when serum creatinine is above 3 mg/dL (271). The incidence of ACKD in dialysis patients increases with the length of time the patient has received dialysis (241). Ishikawa and others (194) reported a 44% incidence of ACKD in patients who had undergone less than 3 years of hemodialysis, as opposed to an 80% incidence in patients who had more than 3 years. The reported prevalence rate of ACKD is increasing because of longer patient survival in dialysis therapies, higher rates of native kidney retention in transplant patients, and improved sensitivities of current imaging modalities (340). ACKD is bilateral, develops more quickly, and is more severe in men (77,198). The prevalence of ACKD in children undergoing CAPD and hemodialysis is just as high as that in adults (231,264).

Early on, ACKD patients are usually asymptomatic and are therefore not usually diagnosed unless screened radiologically as part of an evaluation for renal failure or transplantation. Alternatively, patients can present with severe intrarenal hemorrhage with or without gross hematuria. Among cases of ACKD with bleeding complications, only about 30% are related to tumor, whereas the rest are probably related to retroperitoneal hemorrhage due to rupture of a hemorrhagic cyst into the retroperitoneal space (130). Such hemorrhage can occur during anticoagulation therapy for hemodialysis, at which time patients may have such symptoms as sudden flank pain, hypotension, and decrease in hematocrit (192). Less commonly, ACKD patients may also develop a cyst infection, symptomatic distant metastases from RCC, matrix kidney stones (48), or increased erythropoietin production. The size increases of renal cysts over time in ACKD results in increased secretion of erythropoietin (97) and a rising hemoglobin (111).

Successful renal transplantation in dialysis patients can retard or lead to regression of established ACKD, as well as size reduction of the affected native kidneys (197,241), unless cyclosporine is used for immunosuppression (246). In cyclosporine-treated transplant patients, the prevalence of ACKD is essentially the same as that for hemodialysis patients. After a transplanted kidney undergoes chronic rejection, resulting in uremia, acquired renal cysts can develop in the grafted and native kidneys (195). The duration of uremia correlated with increased numbers of acquired renal cysts, just as prolongation of the dialysis period in ESRD increases not only the incidence of ACKD but also the number and size of acquired cysts.

Eighty-six percent of renal tumors in ACKD are asymptomatic and are found incidentally by imaging studies, although they can less commonly present with symptoms such as bleeding, pain, fever, hypercalcemia, or symptomatic metastatic disease. The prevalence of tumors increases with the duration of dialysis, just as kidney weight increases with duration. Increased kidney weight is secondary to increased cyst volume and epithelial proliferation, both of which can be considered premalignant. Cancer developed in 11% of tumors in ACKD kidneys weighing less than 150 g and 55.6% in ACKD kidneys weighing greater than 150 g. In addition, ACKD patients in the small kidney group did not have metastatic disease, whereas three patients in the large kidney group had metastatic disease (250). ACKD has an overall incidence of 43.6% of all dialysis patients surveyed. Renal tumors, usually multiple, are found in 7.1% of chronic dialysis patients but in 16.4% of the ACKD patients. Many of the tumors were small and were therefore considered adenomas, but 4.7% of the renal tumors had metastasized by the time of presentation (146). Considering only RCCs in ACKD, 20% are metastatic at presentation (260). In combined data from 13 studies, 4% of ACKD patients had RCC (defined as a tumor greater than 2 to 3 cm in diameter). However, this figure may be an underestimate because a pathologist will detect more tumors than a radiologist. The incidence of RCC in ACKD represents a fortyfold (in Japan) to fiftyfold (in the United States) increased risk of RCC compared with that of the general population (382).

RCC occurs at a younger age in ACKD than in the general population (45 versus 64 years) and has even higher male-to-female ratio in ACKD than the general population (6:1 versus 2:1). RCC is more common in African Americans than whites in the ACKD populations, but it is more common in whites than African Americans in the general population (260). In ACKD, RCC tends to be bilateral and multifocal, in contrast to solitary unilateral RCC in the general population.

Morphology, Pathogenesis, and Malignancy

Grossly, the renal cortex in ACKD is replaced by multiple, bilateral cysts; later, the medulla is involved to some extent. The kidneys are reniform and small initially as they decrease in size during the first 3 years of dialysis; however, they then increase in size secondary to acquired cyst development (260). Most cysts are 0.5 to 2.0 cm in

diameter but can be 4 cm in diameter. Cyst fluid is clear to hemorrhagic.

Microscopically, few glomeruli remain. Microdissection studies reveal that the cysts mainly develop in proximal tubules that survive the sclerotic process leading to the end stage kidney (388). Most cysts are lined by low cuboidal or columnar epithelium. However, some cysts have atypical proliferations of columnar, multilayered living cells in papillary formation. Although epithelial proliferation in cystic kidneys does not invariably lead to the development of macroscopic tumors and malignancy, the relative infrequency with which adenocarcinomas are found in noncystic, compared with cystic, kidneys strongly suggests a causal relationship between epithelial hyperplasia and both cysts and tumors (31). The tumors found in ACKD can be categorized histologically into three groups: (a) papillary tumors that project into the cyst lumen without invading the cyst wall, (b) parenchymal tumors that reside adjacent to but not within the cyst, and (c) solid tumors that are sheets of less differentiated cells with either foamy or acidophilic cytoplasm. Central areas may have hemorrhage (94).

RCC in chronic dialysis patients has a papillary histologic pattern in 49% of cases, as opposed to 5% of the RCCs in the general population (193). Gains of chromosomes 7 and 17 and loss of Y have been observed in papillary RCCs in ACKD similar to sporadic papillary RCC, but the nonpapillary RCCs in ACKD patients did not show loss of chromosome 3p as in sporadic nonpapillary RCCs (152). Controversy exists over whether tumors less than 2 to 3 cm in size in ACKD patients should be called *adenomas* or *adenocarcinomas,* because there is no histologic difference and tumors greater than 3 cm had once to be less than 3 cm. Ishikawa and co-workers (193) suggest that all nonpapillary renal cell tumors in ACKD be diagnosed as RCCs and that the adenoma versus carcinoma question be limited to papillary renal tumors because of different genetic alterations and different natural histories. Specifically, a nonpapillary RCC can occur any time after starting dialysis, whereas papillary RCC and ACKD occur more frequently after long-term dialysis. Sant and Ucci (340) noted that renal neoplasms of 1.5 and 1.8 cm in native ACKD kidneys showed microscopic capsular invasion and suggested all renal adenomas be considered small adenocarcinomas with metastatic potential.

RCC can occur in the native kidneys in ACKD patients after successful renal transplantation (166,243,340). Renal transplantation reduces the frequency and severity of ACKD in ESRD patients but does not completely eliminate ACKD, even in all patients with good renal function, especially if the patient is treated with cyclosporine (246). Heinz-Peer and others (166) reported a 24.9% incidence of ACKD in native kidneys after successful renal transplantation and noted that 5% of the native kidneys with ACKD were found to have RCC. The genetic alterations in renal parenchymal cells undergoing epithelial proliferation during ACKD are important rate-limiting changes toward neoplastic growth. Therefore, although ACKD can be reversible in the native kidneys of individuals who have received functioning renal allografts, the final step in progression from cyst to adenoma to adenocarcinoma may not be reversible by correction of an uremic environment (144). The multistage process of oncogenesis may be beyond the bounds of physiologic control, so the malignant potential of ACKD may persist in renal transplant recipients, even after many years of normal function (166).

The pathogenesis of ACKD is unknown, but one theory involves the accumulation of biologically active substances such as cystogenic nephrotoxins that accumulate during hemodialysis, peritoneal dialysis, or chronic uremia. Such biologically active substances may cause kidneys to develop ACKD and renal tumors if these kidneys are exposed to the biologically active substance long enough. Support for this hypothesis lies in the fact that successful renal transplantation can result in regression of established ACKD. Because ACKD does occur in patients who have longstanding renal insufficiency before beginning dialysis, dialysate-leached chemicals are not believed to be the initiators of ACKD. Hence, this suggests that although hemodialysis and peritoneal dialysis prolong life, they are not complete kidney substitutes because they may allow some biologically active substance to accumulate (146).

Another theory suggests that the loss of functional renal mass such as a critical number of working nephrons increases production of renotropic factors that promote tubular cell hypertrophy and hyperplasia leading to cyst formation and, rarely, renal tumors (144,145). Hemodialysis and CAPD may fail to eliminate the substances that promote production of renotropic factors, although successful renal transplantation may retard or lead to the regression of ACKD. Increased expression of renotropic factors, epidermal growth factors, platelet-derived growth factor, and C-erb B-2 (a protooncogene) may be involved (172,260).

The hormonal theory offers another possibility for ACKD pathogenesis because ACKD occurs much earlier in male than in female patients. After 3 years of dialysis, ACKD incidence is 100% in males and 66% in females. Furthermore, after long-term dialysis, the severity of cystic transformation is far greater in male patients and the increase in renal volume in male ACKD patients is more than twofold that reported in female patients (77). However, the size of the kidney tends to plateau after 13 years of hemodialysis in male patients, whereas significant cystic changes developed in female patients receiving long-term (more than 18 years) hemodialysis (198). Perhaps the decreased androgen-to-estrogen ratio and the increased estrogen value could result in an estrogen receptor–mediated effect on tubular epithelial cell proliferation, which could be more pronounced in male tissues because they are less adapted to

high estrogen values. In addition, androgen reduction (more severe in male patients) may upregulate epidermal growth factor (77).

Radiologic Findings, Screening, and Management

Because the incidence of ACKD increases with the length of time a patient has been receiving dialysis, asymptomatic dialysis patients should be screened after 3 years of dialysis treatment by either US or CT. A baseline predialysis renal US should be obtained for comparison purposes. If any US detects the presence of cysts, CT should be done to assess the presence of a renal tumor because ACKD patients are at increased risk for renal tumors. Unfortunately, it can be difficult for US to detect the small cysts of ACKD in these sonographically abnormal small kidneys of ESRD patients (146) (Fig. 20.19). Manns and others (257) were unable to identify 10% of the native kidneys in ACKD by US. Hence, if it were not for cost, contrast-enhanced CT would be preferable as a first test to diagnose ARCD as well as to diagnose tumor (Fig. 20.20). However, some authors have found US to be more accurate than CT to diagnose RCC in dialysis patients (374). If an ACKD patient becomes symptomatic with flank pain, hematuria, or any unexplained fever or systemic illness, appropriate imaging such as an enhanced CT scan is appropriate to evaluate for possible tumor, hemorrhage, or infected cyst. Annual CT screening of all long-term dialysis patients after 3 years would add $36 million to the Medicare budget, but data do not justify the expense (238). Screening ACKD patients on dialysis every 3 years by CT or US has been predicted to increase the 25-year life expectancy of a 20-year-old by 1.6 years but only increase the 5-year life expectancy of a 58-year-old by 4 to 5 days (342). More than half of the U.S. dialysis population would be unlikely to benefit from such screening because the median age of patients beginning dialysis is 62 years (342).

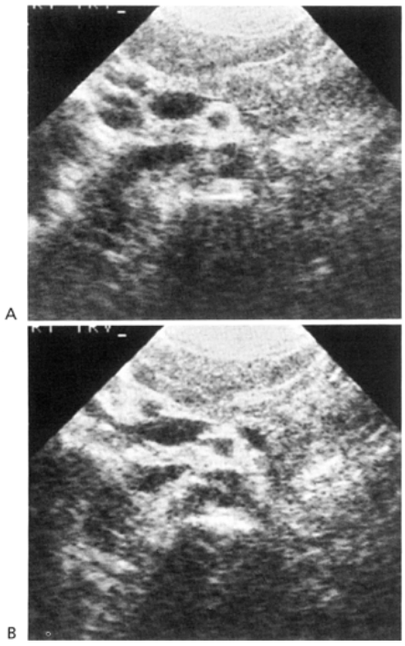

FIGURE 20.19. A–B: Acquired cystic kidney disease in a 52-year-old woman on chronic dialysis. Renal ultrasonography reveals small kidneys with increased cortical echoes as found in chronic renal disease. Multiple cysts are present and are of varying sizes.

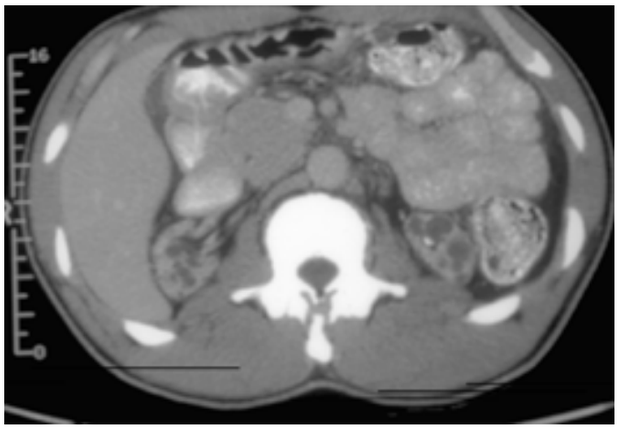

FIGURE 20.20. Acquired cystic kidney disease in a 46-year-old man on chronic dialysis who has had a left nephrectomy. Unenhanced computed tomography reveals a right small kidney with multiple cysts.

However, identification of subsets of ACKD patients most likely to benefit from annual screening is appropriate. For example, young patients with prolonged dialysis (255) and patients in good medical condition would benefit if annual renal imaging found localized RCC (238). In addition, subsets of ACKD patients with high-risk factors such as male gender (77) or large kidneys (250) would benefit. MRI is superior to US in depiction of simple and complex cysts of native kidneys in renal allograft recipients (167) but is not better than CT scanning even after gadolinium enhancement (382). The 1995 clinical practice guidelines of the American Society of Transplant Physicians for evaluation of renal transplant candidates do not recommend screening for ACKD and RCC because of the low frequency of cancer and reported regression of ACKD after transplantation (156). Gulanikar and associates (156) evaluated 206

consecutive adult patients for renal transplantation with a renal US and found 63 patients (30.6%) had ACKD and 8 (3.8%) had localized RCC (6 unilateral and 2 bilateral). Seven of the cancers were in the ACKD patients. Although US screening of the entire ESRD population for ACKD and tumors cannot be justified because of patient age and comorbidity limiting life expectancy, patients chosen for renal transplantation are younger and have less severe comorbidities. Given the expense and risk of renal transplantation, renal US screening for ACKD before renal transplantation is appropriate. Screening for tumors in native kidneys after transplantation with renal US may be justified in high-risk groups such as young men. Consideration should be given to scanning of native kidneys when a renal transplant patient undergoes US imaging of his or her graft (238).

In dialysis patients, renal tumors larger than 3 cm should undergo a radical nephrectomy unless the patient is a poor operative risk (382). Tumors less than 3 cm require radical nephrectomy if the patient is a transplantation candidate. Patients with tumors completely confined to the kidney can have a transplant immediately after the nephrectomy, but when tumors extend into the perinephric fat, a waiting period of 1 to 2 years is advised (308). Tumors less than 3 cm in the remaining ACKD patients require either radical nephrectomy or annual CT scans to access rate of growth to determine whether radical nephrectomy is appropriate. If a tumor is smaller than 3 cm and no rapid tumor growth is documented on serial imaging studies, but symptoms such as back pain or hematuria persist, nephrectomy is probably indicated because the tumor may be carcinoma and nephrectomy for intractable hematuria can reveal RCC that was not visualized preoperatively (130). Bilateral nephrectomy can be considered in ACKD-related RCC patients who are to undergo renal transplantation because posttransplant immunosuppression is a known risk factor for the development of renal neoplasms and because ACKD is a bilateral disease (382).

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21

HYDRONEPHROSIS

Jay Y. Gillenwater

J.Y. Gillenwater: Professor of Urology, University of Virginia Medical School, Charlottesville, VA 22908.

Contents

Hydronephrosis is the distention of the renal calyces and pelvis with urine as a result of obstruction of the outflow of urine distal to the renal pelvis. Prolonged hydronephrosis results in renal parenchymal atrophy. Elevated renal pelvic pressures and decreased renal blood flow are postulated to be mechanisms of injury and cellular atrophy. Obstructive uropathy progressively impairs all renal functions except urinary dilution. The longer and more complete the obstruction, the more severe the pathophysiologic changes become.

Significant changes in experimental hydronephrosis have occurred in three areas in the last 4 years. There is a better understanding of which factors and vasoactive substances cause the decreased blood flow after 24 hours of complete unilateral ureteral obstruction (UUO). There is more information on causative factors leading to tubular loss and interstitial fibrogenesis. The differences between the pathophysiology of obstructive nephropathy in the newborn and adult have been further delineated, showing that in addition to tubular atrophy and interstitial fibrosis, obstruction in the maturing kidney impairs renal growth and development.

Recent research shows a complex series of pathophysiologic events after ureteral obstruction involving more than the anatomic, pathologic, and physiologic changes previously described. A variety of vasoactive compounds, growth factors, and cytokines are activated in response to ureteral obstruction. These factors include platelet-derived growth factor, transforming growth factor-ß (TGF-ß), epidermal growth factor, insulin-like growth factor, clusterin, nitric oxide, endothelin, atrial natriuretic peptide, and angiotensin II. There are also factors that cause leukocyte infiltration, such as osteopontin and arachidonic acid metabolites (eicosanoids).

Recent excellent reviews by Gulmi and colleagues (76), Chevalier (19), Ricardo and Diamond (169), and Klahr and Morrissey (113) define current knowledge of these vasoactive mediators. My interpretation of these data is that the etiology, pathophysiology, and consequence of UUO is significantly different in the newborn and the adult. Obstruction of the maturing kidney impairs renal growth and development in addition to causing tubular atrophy and interstitial fibrosis. The renin-angiotensin system (RAS) in the maturing kidney plays a greater role in normal development

and pathophysiologic response than in the adult. In adult UUO, there is a better understanding of the development of fibrosis and the presence of various vasoactive compounds. There also appear to be species differences in responses to ureteral obstruction.

PATHOPHYSIOLOGY OF OBSTRUCTIVE UROPATHY

Part of "21 - HYDRONEPHROSIS "

Historical Aspects of Hydronephrosis

Hinman first studied experimental hydronephrosis systematically (87,89,90). These studies showed that infection plus obstruction caused severe and rapid renal damage (87). Histologic changes were noted after 1 week of obstruction, with some histologic recovery after release of 60 days of obstruction in rats (87). Denervation of the kidney did not alter the course of hydronephrosis (94). Renal arterial or venous obstruction accentuated the damage in hydronephrosis (89,92,93). Release after 2 weeks of complete ureteral obstruction with contralateral nephrectomy resulted in the return of most function to the previously obstructed kidney. The same experiment with 3 weeks of complete obstruction resulted in only a 50% return of function. The animals could not survive release of obstruction lasting longer than 2 or 3 weeks if the opposite kidney was removed at the time of release of the ureteral obstruction. The animals could survive release after 30 to 60 days of unilateral hydronephrosis if the opposite normal kidney was damaged gradually after release of the ureteral obstruction.

Pathology

Urinary tract obstruction causes proximal dilation with anatomic changes in the proximal ureter, renal pelvis, and renal parenchyma. Initially, the proximal ureter and renal pelvis react with muscle hypertrophy and hyperplasia. Production of connective tissue consisting of collagen and elastic tissue occurs later and is thought to impair myogenic impulse transmission and cause disturbance of peristalsis (42,48,65,70,116). An increase in collagen, which acts as an inelastic collar preventing distention, has been found in the obstructing segments of the ureteropelvic junction and in megaureters (77,151,152). Studies of infants with ureteropelvic junction (UPJ) obstruction showed an increase in the inner longitudinal muscle bundles, in collagen between muscle bundles, and in elastin in the adventitia (191).

Hydronephrosis eventually causes tubular dilation with cellular atrophy and interstitial fibrosis. Within 7 days, atrophy is seen in the distal nephron. By 14 days, there is progressive dilation of the distal tubules and atrophy of the proximal tubular epithelial cells. At 28 days, there is loss of 50% of the medulla with marked atrophy of the proximal tubules and thinning of the cortex. Glomerular changes are not noted before 28 days of obstruction. There is no evidence of microscopic changes in the arteries to account for the substantially reduced blood flow observed in hydronephrosis. Venous drainage is impaired, causing some of the renal damage (2,46,91,97,164,180,182,193). Urinary tract obstruction causes proximal dilation, blunting of the renal papillae after 2 to 3 days, and gradual atrophy and thinning of the renal tissue. Microscopically, the renal tubules dilate with cellular atrophy beginning in the distal nephron. In longstanding hydronephrosis, the glomeruli become sclerotic. During obstruction, there is increased cellularity of the interstitium with leukocytes, fibroblasts, and macrophages, which may have vasoactive functions. No vascular obstruction is seen to account for the increased vascular resistance associated with chronic hydronephrosis.

Fluid Turnover in Hydronephrosis

Urine exits the renal pelvis in complete ureteral obstruction by extravasation, pyelolymphatic backflow, and pyelovenous backflow. Replacement glomerular filtration maintains the hydronephrosis. Thus there is an active turnover of urine in the hydronephrotic renal pelvis despite complete ureteral obstruction. Substances injected into the hydronephrotic renal pelvis have appeared in the systemic circulation, confirming the dynamic state of the hydronephrosis: strychnine (199), phenolsulfonphthalein (17), dye (138), and indigo carmine (96). Extravasation of urine first occurs through rupture of the fornix (10,96). Narath (146) and Olsson (155) studied urine backflow during ureteral obstruction. Initially, ureteral obstruction produces pyelocanalicular and pyelosinus backflow.

With acute obstruction and high pressures, as during retrogrades or with ureteral calculi, most of the fluid exits the renal pelvis by extravasation at the calyceal fornix. With low-pressure obstruction, much of the fluid exits into the lymphatic vessels. In chronic hydronephrosis, most of the fluid exits into the renal venous system.

Renal Counterbalance, Compensatory Renal Hypertrophy, and Renal Hypotrophy

The concepts of renal counterbalance, compensatory renal hypertrophy, and renal hypotrophy (disuse atrophy) were first introduced by Hinman in 1922 (88) and later summarized in 1926. The theory of renal counterbalance is based on the premise that there is a mechanism to monitor total renal function and that the function of each kidney can be modulated up or down as appropriate. Thus, if one kidney is removed or rendered nonfunctioning by obstruction, the opposite kidney would undergo compensatory hypertrophy. If additional renal tissue is added by release of unilateral obstruction or transplantation of additional kidneys, some mechanism would modulate total renal function downward by renal hypotrophy. Renal hypertrophy and hypotrophy involve changes in function. Some misunderstandings

and controversy have resulted from efforts to comprehend renal counterbalance in terms of renal mass instead of function.

Studies have provided new information about compensatory renal hypertrophy. Two forms of renal growth have been postulated: obligatory growth thought to be under the stimulus of growth hormone and compensatory growth under an unknown humoral stimulus. Compensatory renal growth includes both hypertrophy and hyperplasia (161) and is not as great in older animals (84). After unilateral ureteral obstruction, there is a bilateral increase in renal mass the first week, followed by atrophy in the obstructed kidney and continued hypertrophy in the opposite unobstructed kidney. The increased mass in the obstructed kidney may be a local response to injury (229) or a response to the unknown humoral factor. In most models, the renotrophic factor is present in anephric animals. Renotrophic factor stimulates three forms of growth: embryonic growth, wound repair compensatory growth, and neoplastic growth (159). The renotrophic factor is thought to be humorally mediated and must be continually present to maintain compensatory growth (126). Similar renotrophic factors are present in urine and serum (80). During compensatory hypertrophy, glomeruli increase in size but not in number. Diabetes and pregnancy cause renal hypertrophy.

Chronic UUO in fetal sheep impairs growth of the obstructed kidney and stimulates compensatory growth in the contralateral kidney. The developing kidney is more susceptible to the effects of ipsilateral UUO. Adaptive growth of the contralateral kidney is also enhanced. Compensatory growth is reversible (187), whereas normal growth is not. Angiotensin acts as a growth factor in normal renal development and is not necessary in neonatal mouse. Insulin-like growth factor-1 plays a role in neonatal (but not adult) compensatory renal growth (143).

Renal hypotrophy (atrophy) is most easily understood in terms of function. When a hypertrophied kidney is experimentally transplanted into a recipient with a hypertrophied kidney, both kidneys return to their previous size (187,189). When two additional kidneys were transplanted into male rats with normal kidneys, there was no change in the size of either the two transplanted kidneys or the two normal kidneys. However, total renal blood flow and glomerular filtration showed no increase over normal conditions (170). Silber (187,189) found that after transplanting an additional kidney there was an increase in total renal mass and a 50% increase in total renal blood flow and glomerular filtration rate (GFR).

Studies in our laboratory showed that with release of unilateral complete obstruction, the obstructed kidney regains function over the next 4 months. Compensatory hypertrophy persists in the contralateral kidney during that time. Total renal function is not fully recovered to control values at 4 months. Studies in Chevalier's laboratory have confirmed the compensatory hypertrophy in the contralateral kidney in the neonate (19). These studies suggest both a humoral and a neural mechanism.

Return of Function After Complete Ureteral Obstruction

Recovery of renal function after release of complete ureteral obstruction varies with the species, total time of obstruction, presence or absence of infection, degree of pyelovenous and pyelolymphatic backflow, and whether the renal pelvis is intrarenal or extrarenal. In the dog with a normal contralateral kidney after release of 2 weeks of obstruction, the GFR can recover up to 46% of control function in 3 to 4 months. After release of 4 weeks of total ureteral obstruction, there was recovery of the GFR to 35% of control by 5 months. No return of function was noted with release after 6 weeks of total ureteral obstruction in the dog (201).

How long the human kidney can be completely obstructed and still regain function after release is not known for certain. Reports in the literature have been difficult to evaluate because the length and completeness of obstruction and the return of renal function are difficult to document adequately. With greater use of renal scanning and renal ultrasound and better awareness of possible ureteral obstruction after pelvic surgery, better documentation should be possible. The cases with the longest period of complete ureteral obstruction meeting the aforementioned criteria and showing some recovery of function are 56 and 69 days (74,120,166).

Prediction of Recovery Potential Before Release of the Obstruction

To make the right decision about nephrectomy or correcting an obstruction, the urologist needs to know whether the kidney will regain function after the obstruction is released. The two best means of assessing recoverability before surgery are the placement of temporary ureteral stents or nephrostomy tubes and the use of renal scans with sophisticated analysis. The simplest method is to place percutaneous nephrostomy tubes to relieve the obstruction and monitor creatinine clearances. If the previously obstructed kidney has not regained at least a 6 to 10 mL minute creatinine clearance by 2 to 3 months, I do not think it merits repair if the other kidney is normal.

Prediction of recoverability with the renal scans is more difficult and has not been successful in many studies. Evaluating cortical zones of interest by arbitrary mathematical analysis, however, has been successful: technetium (^{99}Tc) pentetic acid, diethylene triamine pentaacetic acid (DTPA) (121), ^{99m}Tc DMSA (dimercaptosuccinic acid) (132), and iodohippurate sodium labeled with iodine 131 (^{131}I hippuran) (66,108). That the different scanning agents measure various renal functions has not seemed to be as important as the method of quantitative analysis of the

results. ^{131}I hippuran measures renal blood flow and correlates with the GFR. ^{99m}Tc DMSA accumulates in the cytoplasm of proximal tubular cells and is used to assess functioning cortical tissue. ^{99}Tc DTPA is eliminated by glomerular filtration and correlates with cortical renal blood flow. MacNeily and associates (125) believe it is important that measurement of the radioactivity be made between 1 and 3 minutes when the radioactivity is confined to renal blood vessels and functioning parenchyma. Before 1 minute, the radioactivity can be extrarenal; after 3 minutes, the accumulation of radioactivity in the renal pelvis can cause confusion.

Intrapelvic and Renal Tubular Pressures

Normal

Normal renal pelvic pressure is 6.5 mm Hg, which slightly exceeds the intraperitoneal, bladder, and ureteral pressures. Normal proximal tubular pressure is 14 mm Hg (134).

Unilateral Ureteral Obstruction

Ureteral and renal pelvic pressures after complete unilateral ureteral obstruction rise abruptly and then decrease within 24 hours to 50% of the peak values (202). Ureteral pressures continue to decline over the next 8 weeks to 15 mm Hg despite the continued completed obstruction (202). Thus static ureteral pressure measurements have never been helpful in determining the degree of ureteral obstruction.

The peak ureteral pressures with acute complete ureteral obstruction vary with hydration, osmotic diuresis, degree of ureteral contractions, and amount of reabsorption. The maximum pressure from filtration is the stop-flow pressure of 15 to 20 mm Hg [glomerular capillary pressure (60 mm Hg) minus capillary oncotic pressure (25 to 30 mm Hg) minus hydrostatic pressure in Bowman's capsule (15 mm Hg)]. The higher pressures measured during acute obstruction are a result of filtration pressure and active muscle contractions in the ureter and renal pelvis. Ureteral pressures of 50 to 70 mm Hg have been measured after acute ureteral obstruction in humans (5,97,130,134,144,153,196). Ureteral pressure after obstruction can be further increased to 100 mm Hg by saline or mannitol diuresis (158,201).

Pressure transmitted back to the renal pelvis varies with the conditions of the obstruction. In acute unilateral obstruction in nondiuretic rats, the ureteral and proximal tubular pressure rises to 14 mm Hg, which is normal proximal tubule pressure (72,73). In diuretic rats, the maximum pressure in the ureter and proximal renal tubule rises to 40 mm Hg (72,73). Further elevation of ureteral pressure by injecting fluid to 80 mm Hg fails to transmit and does not raise proximal tubular pressure above 40 mm Hg, presumably because of compression of papillary foramina (72).

Within 24 hours, the elevated proximal tubular pressure is below normal as a result of afferent arteriole constriction (49,72). Another consequence of elevation of ureteral pressure is that the proximal and distal tubules become leaky to creatinine, mannitol, and sucrose. Studies have shown that the aqueous junctional complexes of membranes of adjacent cells are disrupted. The permeability is restored when tubular pressures return to normal (16,122).

When unilateral ureteral obstruction persists, ureteral pressure slowly declines to reach normal levels in 3 to 4 weeks (202). Michaelson (134) found an average decrease of intrapelvic pressures of 6.6 mm Hg after follow-up of six patients with partial obstruction for 8 weeks. Although ureteral and pelvic pressures decrease toward normal ranges with chronic obstruction, they must continue to be slightly elevated because something is sending signals maintaining the alterations seen in renal function during obstruction. Because relief of the obstruction promptly reverses the process, another possible explanation would be that the distention and increased tension are sending signals initiating the physiologic response.

Alterations of Renal Function During Unilateral Obstruction: Short-term Effects

Glomerular Filtration Rate

As previously described, within minutes of ureteral obstruction, the hydraulic pressure of the fluid proximal to the obstruction rises. As the proximal tubular pressure rises, the GFR falls. The decrease in the GFR is attributable to both the rise in tubular pressure and the decrease in the area of filtering membrane when the afferent arteriole constriction begins after 5 hours of obstruction. The GFRs in rats with complete obstruction were 52% at 4 hours, 23% at 12 hours, 4% at 24 hours, and 2% at 48 hours (79,162).

Renal Blood Flow

Ipsilateral renal blood flow and ureteral pressure have a triphasic relationship during the first 24 hours of acute unilateral ureteral obstruction (Fig. 21.1) (137). The initial transient (112-hour) response is an increase in renal blood flow and ureteral pressure, indicating a preglomerular vasodilation. Pretreatment with prostaglandin (PG) inhibitors prevents this vasodilation, indicating that PGE_2 and PGI_2, which dilate vessels and are produced in the kidneys, may be responsible (1,64,101,175). Nishikawa and associates (149) and Needleman and co-workers (147) measured increased production of the vasodilating prostaglandins during acute ureteral obstruction. The increase in renal blood flow caused by acute ureteral obstruction appears to be limited to cortical blood flow, with the inner cortex having the greatest

increase (190). The transient increase in renal blood flow is thought to be the result of a vasodilating prostaglandin release.

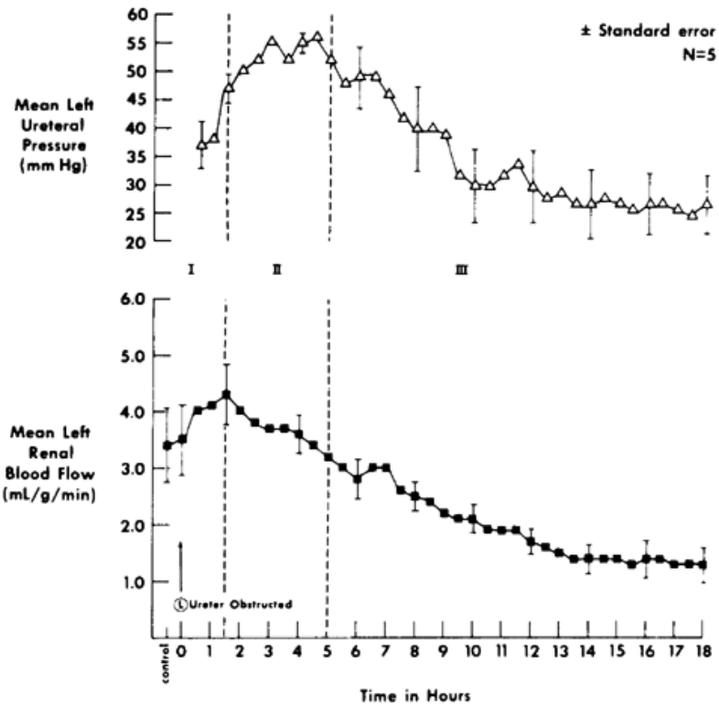

FIGURE 21.1. Triphasic relationship between ipsilateral renal blood flow and ureteral pressure during 18 hours of left complete ureteral obstruction in the dog. In phase I, both left renal blood flow and ureteral pressure increase. In phase II, left renal blood flow decreases, while ureteral pressure continues to increase. In phase III, left renal blood flow and ureteral pressure decline together. (From Vaughan ED Jr, Sorenson EJ, Gillenwater JY. The renal hemodynamic response to chronic unilateral complete ureteral occlusion. *Invest Urol* 1970;8:78, with permission.)

The second vascular phase, which consists of a decrease in renal blood flow with continuation of rising ureteral pressures, occurs 5 to 112 hours after the obstruction. The postulated mechanism is a rise in postglomerular vascular resistance.

During the third and chronic phase (5 to 18 hours), renal blood flow and ureteral pressure decrease. This fall in renal blood flow and ureteral pressure continues chronically (202). Preglomerular vasoconstriction causes the decrease in renal blood flow and lower ureteral pressure. Similar preglomerular vasoconstriction is seen in a single nephron with tubular obstruction (4).

Sheehan and associates (181) found reduced renal blood flow and thromboxane A_2 synthesis in dogs with partial ureteric obstruction. Increased renal blood flow to the nonobstructed side was associated with elevated PGE_2 formation. Elevated angiotensin I levels corresponded to maximal increases in prostaglandin synthesis.

Hemodynamic Changes in UUO

The role of vasodilator eicosanoids in phase I has been confirmed since the initial studies by Allen and associates (1), showing that pretreatment with indomethacin prevented the initial vasodilation seen with UUO. Studies have confirmed the role of vasodilator prostaglandin in causing the increased renal blood flow immediately after UUO (61,139).

The role of eicosanoids after phase III UUO is not as well established. Yarger and colleagues (227) showed a decrease in renal vasoconstriction in UUO after the administration of imidazole, a thromboxane A_2 synthesis inhibitor. Indomethacin, which decreases synthesis of both vasodilator and vasoconstrictor eicosanoids, did not increase renal blood flow.

The mechanism of the chronic preglomerular vasoconstriction in hydronephrosis has received the most experimental attention in the last 10 years. Unilateral ureteral obstruction results in decreased renal blood flow to the ipsilateral kidney and increased blood flow to the unobstructed contralateral kidney (56). The ipsilateral vasoconstriction is in part caused by thromboxanes, angiotensin, endothelin, and mesangial-cell contact (29,62,103,115,118,139,140,185,227). Increased production of vasodilators as prostaglandins opposes the vasoconstriction in the ipsilateral kidney and, in part, causes the vasodilation of the contralateral kidney (101). Chronic UUO in the guinea pig increases angiotensin-dependent renal vasoconstriction independent of renal nerves (31). Vasodilation of the opposite

kidney may be mediated by the renal nerves or contralateral renal renin suppressors (32,37). Thromboxanes have been shown to act as modulators of renal vascular resistance in UUO (78,227). Vasodilator prostaglandins appear to contribute to vasodilation of the intact opposite kidney (223).

Fern and co-workers (57) studied UUO mice with no to four functional copies of the angiotensin gene and found that angiotensin regulates at least 50% of the renal interstitial fibrotic response and that a functional renal-angiotensin system is not necessary for compensatory growth. UUO was also reported by Kinter and colleagues (112) to reduce renal antioxidant enzyme activities, including those seen with sodium depletion, thus contributing to the progression of renal injury in obstructive nephropathy.

Nitric oxide, an endothelial-derived relaxing factor (EDRF), is increased in the ipsilateral vasoconstricted rat kidney but not in the vasodilated contralateral kidney (33). Endogenous nitric oxide has a marked systemic and renal vasodilatory effect in the unobstructed normal rat (6,198,205,209,228).

Haung (82) has pointed out that in normal renal physiology nitric oxide regulates local arteriolar tone, tubular sodium handling, and mesangial-cell proliferation and causes decreased synthesis and increased degradation of matrix protein. This suggests that nitric oxide may serve as an antifibrotic in the kidney. Administration of L-arginine before UUO resulted in nearly complete restoration of renal blood flow and GFR after release of obstruction and infusion of nitric oxide synthase (NOS) inhibitor before release of the obstruction resulted in complete loss of renal function in the affected kidney. Administration of L-arginine significantly decreased the infiltrating of macrophages into the interstitium of the obstructed kidney and improved GFR (82).

Glomeruli from the contralateral vasodilated kidney produce increased PGE_2 and 6-keto PGF_{1a} (223). The increased injury to the renal medulla in obstructive uropathy has been postulated to be due to reduced O_2 as a result of reduced nitric oxide formation (13,33).

Studies from Chevalier's laboratory at the University of Virginia have shown the following:

1. In neonatal obstruction, *in situ* localization of renin and mRNA was increased with ureteral obstruction (53). In contrast, adult rats with chronic unilateral ureteral obstruction of 24-hour and 4-week duration did not manifest an increase in the distribution of immunoreactive renin or renin mRNA in the obstructed kidneys (54).
2. In chronic unilateral ureteral obstruction in newborn rats studied by El-Dahr and co-workers (53), the renal sympathetic nerves modulated renin gene expression, which leads to increased renin distribution along afferent glomerular arterioles in both kidneys.
3. EDRF modulates basal arterial blood pressure, renal vascular resistance, GFR, and effective renal plasma flow in normal rats and in rats with unilateral release of bilateral ureteral obstruction of 24-hour duration (167).
4. Neonatal unilateral ureteral obstruction in newborn rats stimulates increased renin secretion in the obstructed kidney. The increased renin secretion is from recruitment of more renin-secreting renal cortical cells and is not blocked by chemical sympathectomy (150).

The pathophysiology of obstructive nephropathy in the newborn was recently reviewed by Chevalier (19) as summarized and partly quoted here. Obstruction to urinary flow results in a complex response by the developing kidney, manifested by impaired nephrogenesis, including delayed maturation of the renal vasculature, glomeruli, tubules, and interstitial cells. In the adult, UUO stimulates renal cell proliferation. These changes may result from a combination of factors, including loss of epithelial cell polarity, a reduction in the oncoprotein bcl-2 and epidermal growth factor (EGF), and increased expression of the fibrogenic cytokine TGF-$ß_1$. UUO in the neonate causes impaired renal growth, renal tubular dilation, tubular atrophy, and interstitial fibrosis. Recent studies have focused less on the hemodynamic effects of obstruction and more on renal cellular response and the role of growth factors (18).

The developing kidney responds differently to chronic UUO than the adult kidney (18). The RAS plays a greater role in UUO in the neonate than in the adult kidney. In the neonate, there is enhanced activity of the entire RAS, which contributes to the very high renal vascular resistance during development, which normally gradually decreases. Chronic UUO in the neonatal rat results in a marked increase in renal renin gene expression, distributed along the length of the afferent arteriole and intratubular artery rather than being localized to the juxtaglomerular region. Angiotensin II is now recognized as a vasoconstrictor and an important growth factor that can stimulate proliferation or hypertrophy of renal tubular cells. Renal renin gene expression following UUO is ten times higher in the neonate than in the adult rat. Inhibition of angiotensin markedly reduces the progression of interstitial fibrosis and apoptosis (18). Compensatory renal growth in the neonate is primarily hyperplastic, whereas that in the adult is hypertrophic (47).

Activation of the RAS stimulates the expression of a variety of fibrogenic compounds, including TGF-$ß_1$, platelet-derived growth factor, adhesion molecules, and α-smooth muscle actin. The functional consequences of obstructive nephropathy in early development are hyperfiltration by remaining nephrons, followed by a progressive decrease in the glomerular filtration rate that may only develop in later life.

Chronic UUO in the developing kidney slows renal maturation. There are similarities between the renal response to UUO and cystic kidney disease, possibly in part because of the constriction of the nephron in cystic kidneys. The progressive increase in renal expression of TGF-$ß_1$ contributes

to progressive interstitial fibrosis. In response to urinary tract obstruction, renal tubular cells lose their polarity. The EGF receptors normally located on the basal surface in the adult become localized to the apical surfaces (18).

In another laboratory, Gulbins and associates (75) found that in hydronephrotic rat kidneys physiologic control of basal vascular tone in larger preglomerular arterioles is modulated by an endothelium and EDRF. Efferent arteriolar tone is predominantly controlled by EDRF. Reyes and colleagues (167) state, "The role of some vasoconstrictors and vasodilators in altered renal hemodynamics occurring during ureteral obstruction [has] been studied. Angiotensin II (163), thromboxane A (113), and antidiuretic hormone (168) decrease GFR and ERPF. Prostaglandins and platelet-activating factor (PAF) tend to maintain GFR and ERPF. Inhibition of vasoconstrictors angiotensin II (163), thromboxane (113), and antidiuretic hormone (168) or giving platelet activating factor increases GFR and ERPF but not to normal levels indicating other nonactive factors are involved." Renal macrophages have been identified as the cellular source of prostanoids in hydronephrotic kidney (176).

The role of macrophages and reactive oxygen species in experimental hydronephrosis has recently been reviewed by Ricardo and Diamond (169). Reviewing the role of the infiltrating renal macrophage as a mediator of interstitial fibrosis after UUO, they postulate that "the mechanical disturbance of the proximal tubule resulting from complete ureteral ligation, elaborates a florid pro-inflammatory and pro-fibrogenic response. The initial injurious states results in the release of an array of chemoattractant signals by the tubular epithelium, including ICAM-1, osteopontin, and MCP-1, which lead to the facilitation and recruitment of macrophages into the renal interstitium. One of the many macrophage-derived products is TGF-beta, which promotes fibrogenesis by stimulating the synthesis of extracellular matrix proteins in parallel with the downregulation of matrix metalloproteins and the upregulation of matrix metalloprotein inhibitors" (169).

The role of growth factors, cytokines, and vasoactive compounds was recently reviewed by Klahr and Morrissey (113), who found that "renal interstitial inflammation and fibrosis occurs after ureteral obstruction. Fibrosis most likely develops as a consequence of an imbalance between extracellular matrix synthesis and deposition and the degradation and removal of matrix. Angiotensin II in turn upregulates other factors (TGF-ß, tumor necrosis factor-α, nuclear factor-κB and several adhesion molecules and chemoattractants). Blockade of angiotensin II synthesis or inability of this peptide to bind to its receptor lessened the increased levels of mRNA for TGF-ß and collagen-IV. Increased levels of angiotensin II have a major role in the development of tubulointerstitial fibrosis after ureteral obstruction" (113). The predominant physiologic alteration after 24 hours of ureteral obstruction is renal vasoconstriction. This may be due to an imbalance between vasoconstrictor and vasodilatory substances. Important vasoconstrictors include angiotensin II, thromboxane A_2, endothelin, and antidiuretic hormones. In bilateral ureteral obstruction, the leukotrienes have a vasoconstrictive effect. Vasodilators that may have a role include L-arginine (a precursor of nitric oxide), platelet-activating factor, and atrial natriuretic peptide. A decrease in these substances could cause vasoconstriction (113).

Recent studies in the research laboratory of Felsen and Vaughan have further explored the pathophysiology of UUO. The mouse kidney obstructed for 2 weeks expressed significantly more TGF-ß, exhibited more tubular apoptosis and fibrosis, and had less inducible nitric oxide synthase (iNOS) expression and less total NOS activity than the contralateral unobstructed kidney. Treatment with the monoclonal antibody to TGF-ß (ID11) significantly decreased tissue TGF-ß concentration, tubular apoptosis, and fibrosis (136). Decreased nephrosis was accompanied by decreased p53 and increased bcl-2. Furthermore, iNOS expression in the obstructed kidney was restored by ID11 treatments, and tubular proliferation in both kidneys was significantly increased by ID11. These data suggest the possibility that ID11 can preserve the obstructed kidney in UUO.

The results using nitric oxide knockout mice demonstrate that nitric oxide appears to be protective against the apoptosis of UUO (135). Nitric oxide protects against the fibrosis of UUO (98). An *in vitro* study demonstrated that angiotensin II and mechanical stretch release NO and TGF-ß from a renal tubule cell line and TGF-ß is a negative regulator of NOS. In dogs, the nitric oxide system is activated during late UUO (177).

Experimental Studies of Postnatal Urinary Obstruction

Unilateral severe partial ureteral obstruction in the neonatal guinea pig results in renal growth arrest by 2 to 4 weeks (28). Three weeks after the obstruction in these animals, renal blood flow was decreased 50% and the GFR was decreased by 80%. The mechanism is thought to be ischemia caused by vasoconstriction from angiotensin II (29). Prostaglandins and thromboxane do not seem to mediate the vasoconstriction in this experimental model (26). The reduced GFR is thought to be the result of decreased renal blood flow, raised intratubular pressures, and reduced glomerular ultrafiltration coefficient. If the contralateral kidney is impaired or removed, there is less reduction of ipsilateral renal blood flow and some compensatory hypertrophy occurs in the partially obstructed neonatal kidney (21,28). The younger the age, the more compensatory hypertrophy of the contralateral unobstructed kidney is observed (195). Factors influencing the amount of injury from partial ureteral obstruction are age at the time of obstruction, severity of obstruction, and duration of obstruction. Brief (10-day)

unilateral partial ureteral obstruction in the neonate results in permanent reduction of function in that kidney. If the obstruction is relieved at 5 days, there is less impairment of function than is seen after 10 days of obstruction (22,30).

Recovery of renal function in urinary obstruction is best achieved by early relief of obstruction. A few studies in experimental animals test whether some drugs further enhance recovery. Infusion of imidazole (a thromboxane inhibitor) or captopril (an angiotensin-converting enzyme inhibitor) significantly increased GFR and renal blood flow after release from 24 hours of complete ureteral obstruction in the adult rat (227). Long-term administration of captopril improved inulin clearance and renal mass after complete unilateral ureteral occlusion of 1- to 3-week duration in adult rats. Administration of indomethacin resulted in slight improvement of GFR but not of renal mass. McDougal (131) concluded from these studies that angiotensin II production and possibly thromboxane synthesis contribute to a loss of renal function after release of obstructive uropathy in adult rats.

Chevalier and Peach (29) found in the neonatal guinea pig that administration of enalapril during ureteral obstruction significantly lowered vascular resistance. After release of neonatal unilateral chronic partial ureteral obstruction, enalapril reciprocally altered angiotensin-mediated vascular tone of both kidneys. In those experiments in neonatal guinea pigs, enalapril (angiotensin-converting enzyme inhibitor) was administered after release from 5 to 10 days of unilateral partial ureteral obstruction. Vascular resistance was not reduced in the obstructed kidney to a greater extent than systemic vascular resistance. However, vascular resistance in the intact kidney was reduced after release of the obstruction in the opposite kidney. These studies suggest that the vascular tone of the intact kidney is increased after release of obstruction on the opposite side.

Tubular Function

In partial acute ureteral obstruction, urine volume decreases, osmolality increases, and urinary sodium concentration is reduced (86,194,219). These changes result from a slower rate of tubular flow caused by a decreased GFR and higher pressures. If the ureteral pressure is elevated to 70 mm Hg, there is a 50% reduction in maximum tubular clearance of glucose and *p*- aminohippuric acid (127). After complete acute ureteral obstruction, there is an additional decrease in the glomerular filtration rate and decreased sodium concentration in the distal tubule. After release of acute ureteral obstruction of 5 to 60 minutes at a pressure of 75 to 120 mm Hg, there is a temporary concentrating defect (58,106,110).

Summary

After acute ureteral obstruction ureteral and pelvic pressures rise as high as 50 to 70 mm Hg, depending on the diuretic state. This is a higher pressure than the 20 mm Hg net filtration pressure, indicating a component of muscle contraction. Renal blood flow and ureteral pressure relationships respond in a triphasic pattern to acute ureteral obstruction. The first phase (lasting 112 hours) is renal vasodilation from vasodilating prostaglandins associated with a rise in ureteral pressure. The second phase (5 to 112 hours) consists of a continued increase in ureteral pressure associated with a decrease in renal blood flow, indicating postglomerular vasoconstriction mediated in some unknown manner. The third and chronic phase exhibits both decreasing ureteral pressure and renal blood flow, as a result of preglomerular vasoconstriction mediated in part by thromboxanes and angiotensins. During acute complete ureteral obstruction, the GFR decreases and tubular function becomes impaired. With acute partial obstruction, tubular pressure rises and the GFR decreases with a resultant decrease in urine volume because of better reabsorption, increased osmolality, and lowered urine sodium concentration.

Long-term Effects of Partial Obstruction

Studies have been performed during chronic partial obstruction in patients and experimental animal models. Evaluation of renal function during the obstruction is important because there is a different environment after release of the obstruction. Studies by Suki and associates (194), Olesen and Madsen (154), Stecker and Gillenwater (192), and Wilson (213) show significant impairment in renal functions during mild degrees of obstruction. These studies during chronic unilateral partial ureteral obstruction show reductions in renal blood flow, GFR, concentrating ability, hydrogen excretion, and sodium reabsorption. Because tubular transit time is increased, sodium reabsorption must be impaired more than the filtration rate and tubule flow rate to account for the increased urinary sodium concentrations.

Most patient studies during partial obstruction have been with bilateral ureteral obstructions. All studies have shown impairment of urinary concentration (7,9,50,51,67,129,142,200,217,218,230). Impairments of all phases of acidification (ammonia excretion, titratable acidity, and bicarbonate absorption) have been reported (7,9,51,67,129,217,218,230).

Long-term Effects of Complete Obstruction

Ureteral and Tubular Pressures

Ureteral pressures peak 3 to 5 hours after complete unilateral ureteral obstruction and within 24 hours decrease to 50% of peak values. Ureteral pressures continue to decline over the next 6 to 8 weeks to approximately 15 mm Hg (202). Proximal tubular pressure may return to normal (4) or to 70% below normal (104,225). Numerous collapsed

tubules are observed on the kidney surface (81,104). Glomerular capillary pressure is reduced (43).

Renal Blood Flow

Renal blood flow measured by flow probes during continued complete unilateral ureteral obstruction shows progressive decreases that are caused by afferent arteriole constriction. Measurement showed renal blood flow to be 70% of control at 24 hours, 50% at 72 hours, 30% by 6 days, 20% by 2 weeks, 18% at 4 and 6 weeks, and 12% at 8 weeks (137,202) (Fig. 21.2). Blood flow is decreased most in the outer cortex and inner medulla (186,190,226). The mechanism of the afferent arteriole vasoconstriction is discussed earlier in this chapter.

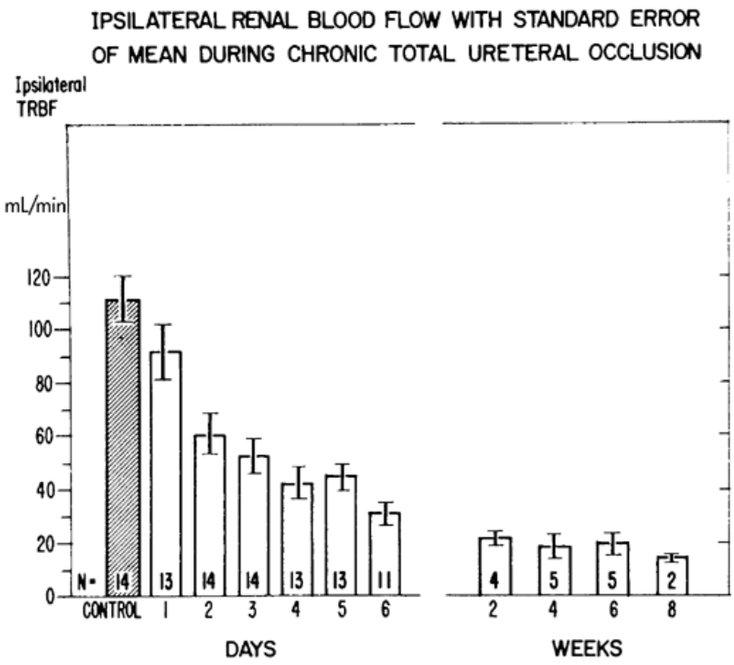

FIGURE 21.2. Changes in left renal blood flow with chronic total left ureteral occlusion in 14 dogs with chronic indwelling blood flow probes. TRBF, total renal blood flow. (From Moody TE, Vaughan ED Jr, Gillenwater JY. Relationship between renal blood flow and ureteral pressure during 18 hours of total unilateral occlusion. *Invest Urol* 1975;13:246, with permission.)

Glomerular Filtration Rate

Measurements of the GFR decrease progressively during complete ureteral obstruction in the dog, to 1.74 mL per minute at 1 week and 0.4 mL minute at 5 weeks of occlusion (145). The fluid exiting by pyelolymphatic, pyelovenous, and pyelotubular backflow is replaced by the continuing glomerular filtration. Immediately after ureteral obstruction is released, there is minimum urine flow. One week after release from 2 weeks of obstruction, the GFR was 15% of control; maximum recovery of the GFR after release from 2 weeks of obstruction was 46% of control (200). After release from 4 weeks of ureteral obstruction, the GFR was 3% and recovered to 35% of control at 5 months (201). No return of glomerular filtration was noted in dogs after 6 weeks of obstruction with a normal contralateral kidney.

Tubular Function

All tubular functions studied, with the exception of urinary dilution, are progressively impaired by complete ureteral obstruction. Perhaps urinary dilution is unimpaired because it is not a system that requires energy. Concentrating ability is severely impaired immediately after release. This tubular function is one of the first to be injured. Recovery of concentrating ability can be complete after release from 2 weeks of complete obstruction. After release from 4 weeks of obstruction, concentrating ability is permanently impaired.

During short partial ureteral obstruction, urine osmolality is higher because of slow tubular transit times in the obstructed kidney. When the partial obstruction is released, urine osmolality falls (106).

Other tubular functions that have been shown to be impaired by chronic unilateral ureteral obstruction are maximum tubular excretory capacity of *p*-aminohippuric acid and glucose, potassium excretion, sodium reabsorption, and urinary acidification (8,36,109,201).

The main tubular effect is in concentrating ability. After release of up to 24 hours of obstruction, there is a normal flow rate of dilute urine with no sodium-losing tendency (214).

Contrasting Conditions During Ureteral Obstruction

Physiologic changes are different depending on whether the ureteral obstruction is unilateral or bilateral. With bilateral ureteral obstruction, the uremic state starts with retention of substances that are normally excreted, and one or more of these substances apparently affect renal hemodynamics and tubular function. Better understanding of clinical problems, such as postobstructive diuresis, has resulted from the study of this situation.

The surface tubules in rats look normal after 24 hours of bilateral ureteral obstruction, in contrast to the poorly perfused and filtering nephrons with collapsed tubules observed in unilateral ureteral obstruction. Proximal and distal tubular pressures are elevated in bilateral ureteral obstruction but are lower than normal in unilateral ureteral obstruction. Afferent arteriole pressure is increased in bilateral ureteral obstruction and decreased in unilateral ureteral obstruction. Glomerular capillary pressure increases to higher levels when both ureters are obstructed than when ureteral obstruction is unilateral. Renal blood flow is reduced to one-third of the control value after release of both bilateral and unilateral ureteral obstruction (24 hours). The single-nephron GFR is 40% of normal in bilateral ureteral obstruction. The reason for the decreased single-nephron GFR is the elevated tubular pressure because the glomerular capillary pressure is normal.

The explanation for the differences between the renal vascular responses in unilateral and bilateral ureteral obstruction is not known (44,81,105,133,197,206,213,214,226).

Contrasting Studies After Release of Ureteral Obstruction

The contrast in the physiologic effects of chronic (24 hours or greater) unilateral and bilateral ureteral obstruction has provided a better understanding of postobstructive diuresis. The major difference is the significant natriuresis and diuresis occurring after release of bilateral ureteral obstruction. Through different mechanisms, renal blood flow and GFR are reduced to 33% of control in both unilateral and bilateral ureteral obstruction after release from 24 hours of obstruction. In unilateral ureteral obstruction, there is afferent arteriole constriction with abnormal distribution between the cortex and the medulla, with a shift of blood flow from the outer cortex to the inner cortex and medulla (104,105). In bilateral ureteral obstruction, there is efferent arteriole constriction and normal distribution of blood flow. The reduced GFR in unilateral ureteral obstruction is caused by the afferent arteriole constriction, and the reduced GFR in bilateral ureteral obstruction is the result of the increased proximal tubule pressure. After release of bilateral obstruction, the tubular pressure returns toward normal and the GFR remains low because of new afferent arteriole constriction (172,221). Wright (220) postulated that the new afferent arteriole constriction after release of bilateral ureteral obstruction is caused by the macula densa feedback mechanism responding to increased distal delivery of tubule fluid.

The role of nitric oxide is not the same in UUO and bilateral ureteral obstruction (BUO). Following release of BUO, renal nitric oxide synthase activity is decreased (167). Following UUO, NOS activity is increased, thereby counteracting the vasoconstrictor responses (33).

Urine flow is increased up to ten times that of control after release of bilateral ureteral obstruction, in contrast to the low rates of flow and solute excretion after release of unilateral ureteral obstruction. The excretion rates of potassium, phosphate, and urea are significantly increased. After release of bilateral ureteral obstruction, diuresis occurs despite the withholding of fluid and food during the period of obstruction. The diuresis persists for several days until sodium balance is restored. The concentrating defect persists several days longer than the salt loss. The impaired sodium reabsorption occurs in both the proximal and distal tubule (14,15,133). The mechanism of the postobstructive diuresis is not known, but cross-perfusion studies have shown a buildup of a natriuretic factor in the plasma of animals with bilateral ureteral obstruction (215). Wright and Howards (222) postulated that postobstructive diuresis results from two factors: (a) distention and damage to the collecting ducts by increased luminal pressure and (b) inhibition of proximal tubular sodium reabsorption by an unidentified factor that is normally excreted in the urine.

After release of 24 hours of unilateral ureteral obstruction, the previously obstructed kidney has a normal urine flow rate of dilute urine with no natriuresis. These conditions result from reduced renal blood flow and GFR, slightly impaired sodium reabsorption, and severely impaired concentrating ability.

Leahy and associates (117) studied renal injury and recovery in partial ureteric obstruction. Creatinine clearance after release of partial ureteric obstruction showed 8% of control with 60 days' obstruction, 31% of control with 28

days' obstruction, and normal function after 14 days' obstruction. Methyl-methacrylate extrusion casts of the renal microvasculature confirmed arteriolar constriction.

Clinical Postobstructive Diuresis

Patients rarely have a severe, life-threatening diuresis after release of urinary tract obstruction. Generally, diuresis occurs only if all nephron units were obstructed in a way similar to the animal studies described previously. Excellent reviews have been published by Goldsmith (68), Howards (100), Vaughan and Gillenwater (200), Wilson and Klahr (216), Klahr and Morrissey (113), Yarger (224), and Wright and Howards (222). A diuresis generally occurs after release of bilateral obstruction. The diuresis is physiologic, usually mild, and self-limiting. Patients with bilateral obstruction have a retention of sodium and water, and the diuresis is just restoring normal fluid and electrolyte balance (142).

The postulated mechanisms for the rare pathologically significant postobstructive diuresis are (a) impaired urine concentrating ability, (b) impaired sodium reabsorption, and (c) solute diuresis caused by retained urea or administered glucose. Transient peak urine flow rates of up to 69 mL per minute, with an average of 30 mL per minute, and cases of diabetes insipidus unresponsive to vasopressin have been reported (51,171).

In the clinical situation, a patient could develop major fluid and electrolyte problems if he or she had the rare pathologic sodium or water diuresis and it went unrecognized. Our plan of management after release of obstruction is to have the patient weighed and blood pressures recorded in the upright and supine positions and ask that the physician be notified if urine volume exceeds 200 mL per hour. The thirst mechanism will correct any abnormal water loss in the conscious and alert patient. Pathologic sodium loss with resultant contraction of extracellular fluid volumes can be recognized by orthostatic hypotension. Pathologic sodium loss can be replaced by 0.5N saline solution, initially at 50% of output to avoid perpetuating a possible salt and water overload. Pathologic diuresis from nephrogenic diabetes insipidus can be recognized from urine having a specific gravity value ranging from 1.000 to 1.004. Urine from patients with impaired sodium reabsorption should be isotonic.

Relationships of Hypertension and Hydronephrosis

There are two known mechanisms whereby hypertension can result from obstructive uropathy. During acute unilateral ureteral obstruction, renin-angiotensin-aldosterone secretion is increased, with an associated hypertension (208). Also, chronic partial or complete bilateral ureteral obstruction is associated with sodium, water, and urea retention, which produce a volume-related hypertension. In both types, the hypertension is corrected shortly after release of the obstruction. Vaughan and Sosa (203) have reviewed the subject extensively.

The incidence of hypertension with hydronephrosis is variable and not well documented. Most patients with bilateral chronic ureteral obstruction have a mild volume overload–related component to the hypertension, which is corrected by the postobstructive natriuresis and diuresis (200). In acute unilateral ureteral obstruction, patients had a 30% incidence of hypertension (178). In this same study, Schwartz (178) found the incidence of hypertension in patients to be 1.35% in chronic unilateral ureteral obstruction. Other studies have reported a 13% to 20% incidence of hypertension in chronic unilateral ureteral obstruction (12,207).

Thus most patients with chronic unilateral hydronephrosis are normotensive. Any hypertension is usually coincidental in most patients with chronic unilateral hydronephrosis. If significant, the kidney obstruction should be corrected to preserve renal function. In attempting to relate the hypertension and hydronephrosis, Vaughan and Sosa (203) point out that the patient's workup can be similar to renovascular hypertension if renin secretion is studied, contralateral renin suppression is shown, and a positive captopril test is obtained.

Fetal Hydronephrosis

Changing concepts in diagnosis and subsequent management of antenatal hydronephrosis were reviewed by Shokeir and Nijman (184). The increased use of ultrasonography for fetal–maternal screening has detected genitourinary abnormalities in 2 to 9 per 1,000 births, with a male-to-female ratio of 2:1. The major abnormality identified was hydronephrosis. A false-positive error rate of 9% to 22% is reported in the antenatal diagnosis of hydronephrosis. Explanations for the spontaneous resolution of antenatal hydronephrosis include the four- to six-times greater fetal urine flow rate than after delivery, fetal folds, and the increased compliance of the fetal ureter. The high fetal urine flow rate is attributed to differences in fetal renovascular resistances, GFR, and concentrating abilities. UPJ obstruction is the most common cause of antenatal hydronephrosis. Reflux is later diagnosed in 25% to 35% of cases.

The management of fetal hydronephrosis is controversial (184). Once hydronephrosis is diagnosed, ultrasound is repeated near term. If bilateral hydroureteronephrosis and a dilated bladder is diagnosed, ultrasound is recommended every 4 weeks. Other diagnostic tests available are amniocentesis, periumbilical blood sampling, chorionic villous sampling, and fetal urine sampling. None of these tests can accurately predict the degree of renal injury or predict the recoverability of renal function prenatally or postnatally. Prenatal intervention to relieve the obstruction has not been proven yet for routine use. Theoretically, the best

opportunity would be in cases of urethral valves causing bladder outlet obstruction with progressive oligohydramnios. Shunting the urine from the obstructed bladder to the amniotic cavity should relieve the urinary obstruction and prevent the pulmonary hypoplasia associated with oligohydramnios. There are no large successful series showing the practicality of this procedure.

Screening for hydronephrosis shows a 2% incidence, with 21% of these having significant structural abnormalities requiring postnatal follow-up. Prenatal intervention for hydronephrosis gives similar outcomes as postnatal detection (39,60).

Congenital obstructive nephropathy is the principal cause of renal failure in infants and children. In the maturing kidney, urinary tract obstruction permanently impairs renal development (20).

Postnatal management of suspected hydronephrosis involves doing ultrasound several days after delivery. Unless serious abnormalities such as bilateral hydroureteronephrosis are detected, further ultrasounds are deferred until 1 month of life. Neonatal oliguria the first few days of life can mask hydronephrosis, which can be detected on the studies 4 weeks later. Diagnosis and management of the various conditions causing fetal urinary tract obstruction is dealt with in another chapter.

Glomerular Development

Chronic UUO interferes with both nephrogenesis and terminal maturation of glomeruli. Human fetuses with severe obstructive nephropathy have a reduced number of glomeruli (63). In experimental animals, relief of obstruction at 10 days does not increase the number of perfused glomeruli, but under certain conditions, GFR returns to normal, indicating that the remaining nephrons have hyperfiltration (23).

The effects of UUO on the developing tubule are profound, including suppression of proliferation, stimulation of apoptosis, and the maintenance of an immature phenotype by tubular epithelial cells. Expression of transforming growth factor-β_1 and clusterin are increased. Maturation of interstitial fibroblasts is delayed. Progression of tubular atrophy and interstitial cystitis results in part from continued activation of the RAS and oxygen radicals. Unlike in the adult, in the neonate, suppression of proliferation and stimulation of apoptosis are mediated at least in part through angiotensin II receptors (35).

Obstruction in the neonatal rat is attenuated by EGF (24). EGF stimulates renal tubule epithelial cell proliferation and maturation and reduces apoptosis in the neonatal rat kidney subjected to chronic UUO (25). During the critical period of nephrogenesis, impairment of the obstructed kidney and growth of the contralateral kidney are directly proportional to the duration of obstruction; thus earlier relief of obstruction may allow greater ultimate preservation of renal mass (34). However, after 5 days of obstruction in the neonatal rat, relief of obstruction does not reverse renal vascular, glomerular, tubular, and interstitial injury. Hyperfiltration and residual tubulointerstitial damage in the postobstructed kidney are likely to lead to deterioration of function in later life (27).

SURGICAL MANAGEMENT OF HYDRONEPHROSIS

Part of "21 - HYDRONEPHROSIS "

All operative techniques for correction of ureteropelvic junction obstructions strive to achieve dependent drainage with an unobstructive anastomosis of the ureter to the renal pelvis. Attempts must be made to avoid parenchymal loss or ligation of any of the renal vessels. It must be remembered that any anastomosis heals by scar tissue, which will contract by about one-third of its original diameter as it matures. End-to-end or end-to-side anastomoses without spatulation of the ureter are doomed to failure.

Diagnostic Tests of Upper Urinary Tract Obstruction

Evaluation of the upper urinary tract is done (a) to determine whether it is dilated, (b) to determine whether the dilation represents a clinically significant obstruction, (c) to determine the effect of the obstruction on renal function, and (d) to determine the potential recoverability of function.

The tests used to diagnose upper urinary tract obstruction are ultrasonography, intravenous urography, diuretic renography, retrograde and antegrade pyelography, the Whitaker perfusion test, computed tomography (CT) scans (including helical CT scans), and magnetic resonance imaging with or without contrast agents. These tests have been recently reviewed by Shokeir (183).

Ultrasonography is often the first test used to screen for upper tract dilation. It is quick, noninvasive, accurate, readily available, and relatively inexpensive. The diuretic ultrasound has had limited usefulness to determine whether an obstruction is significant or not. Using Doppler ultrasound to determine the resistive index has been advocated by Platt and colleagues (160) to differentiate obstructive from nonobstructive dilation in adults. The resistive index is defined as peak systolic velocity minus lowest diastolic velocity divided by peak systolic velocity. A resistive index above 0.70 is used to differentiate obstruction from nonobstruction. In our hands, this test has not been very discriminatory.

Intravenous urography accurately depicts the anatomy of the calices, renal pelvis, and ureters but is not as accurate in quantitating the significance of any obstruction.

Diuretic renography was introduced by O'Reilly and associates in 1978 (157) and has since become an

established method of diagnosing and evaluating upper urinary tract obstruction. In the diuretic renogram, an isotope is administered, and at a given time, a diuretic is administered intravenously. The ideal time activity curves under conditions of nonobstruction and obstruction are shown in Fig. 21.3 . Adequate function is essential, and urethral catheters are necessary in most children. False-positive results from this test are seen in patients with poor renal function, in grossly dilated systems in which the rate of washout decreases even without obstruction, and when dehydration flattens the curves. False-negative results can occur in patients with a highly compliant (small volume, tight) renal pelvis, or when there is a forced diuresis. Accuracy is reported to be improved by deconvolutional analysis of the renogram with calculation of parenchymal transit time (212). The half-time of isotope drainage ($t_{1/2}$) after a diuretic is commonly used for evaluation. Kidneys with a $t_{1/2}$ of less than 10 minutes are considered unobstructed, and kidneys with a $t_{1/2}$ of greater than 20 minutes are considered obstructed. Those in between are equivocal. In my opinion, the accuracy of this technique is highly variable, depending on the institution where it is performed.

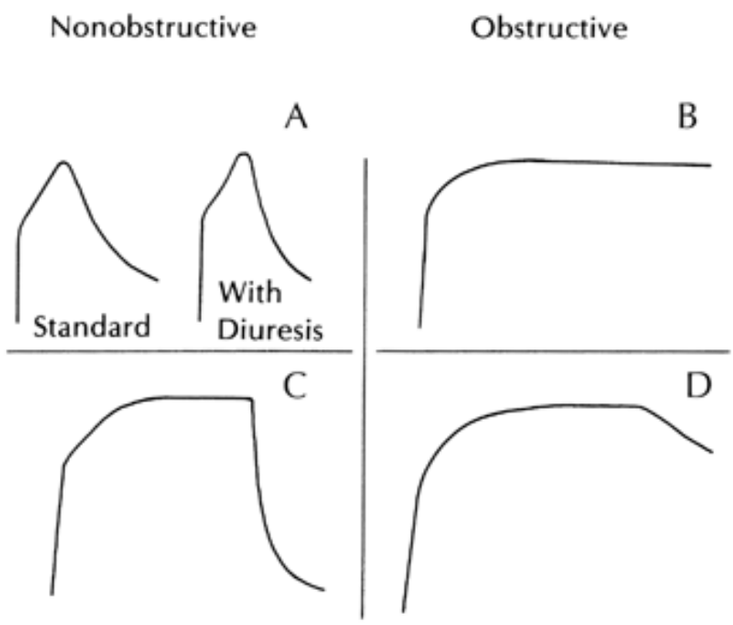

FIGURE 21.3. Typical diagrammatic diuresis renograms. *D* is where diuretics were administered; *A* is nonobstructive; *B* is obstructed with no washout; *C* is nonobstructive after diuresis; *D* is obstructive with no washout after diuresis. (Modified from Lupton EW, Richards D, Testa HJ, et al. A comparison of diuresis renography, the Whitaker test, and renal pelvic morphology in idiopathic hydronephrosis. *Br J Urol* 1985;57:119, with permission.)

Connolly and associates (38) reviewed the variability of diuresis renography interpretation resulting from the different methods used for determining postdiuretic renal pelvic clearance half-times. They found a 27.8% variation between the four methods of $t_{1/2}$ determinations, emphasizing the individual variations of studies in different institutions.

Retrograde pyelography is rarely used except to define the anatomy better in certain situations. Rapid emptying of the contrast indicates no obstruction. If a percutaneous nephrostomy tube is inserted, antegrade pyelography should be done to help define whether the system is obstructed and the site of the obstruction.

The technique and interpretation of the Whitaker test (210) requires the collecting system to be filled completely before beginning the test. Other sources of error are urine leaks when there are high urine outputs and not using a urethral catheter. Koff and colleagues (114) classified the pressure-flow patterns as simple or complex. This procedure, properly done, will help define obstruction in equivocal cases such as massively dilated systems with poor function. The obvious disadvantage is the invasiveness of placing a nephrostomy tube.

The unenhanced helical CT has become the test of choice to diagnose acute urinary tract obstruction from kidney stones and can give valuable information in other conditions with dilated upper urinary tracts.

Accuracy of the Various Tests

The available literature regarding the accuracy of these tests to determine whether an upper urinary tract dilation represents a significant obstruction was reviewed by Lupton and associates (124) and O'Reilly (156). In general, there is good correlation of the tests when there is clear-cut severe obstruction or clear-cut nonobstruction. On the equivocal cases, however, there is much disagreement.

Two studies (40,124) showed excellent correlation between diuresis renography and mean transit time through the renal parenchyma. Studies comparing diuresis renography with perfusion pressure flow studies have reported variable results, with reported correlations of 86% (179), 84% (83), 67% (124), 53% (211), and 54% (69).

Studies comparing diuresis renography with renal pelvic morphology report an 87.5% correlation between the two tests (55,71,123). Israel (102) reported a 100% correlation between diuresis renography and synchronous intrapelvic pressure measurements.

Equivocal washout studies present clinical problems. If the kidney has good function and the patient is well hydrated, O'Reilly (156) thinks an equivocal response indicates partial obstruction. When renal function is impaired, it is difficult to distinguish whether an equivocal response is caused by obstruction or by the renal impairment itself. By O'Reilly's analysis (156), 15 of 188 patients (8%) had obstruction on the diuresis renograms but normal perfusion-pressure studies. O'Reilly stated that two cases had intermittent obstruction and the other 13 had gross hydronephrosis, poor renal function, or both. Of the 188 cases, 48 (25%), including 32 previously reported by Hay and colleagues (83), had normal diuresis renograms but abnormal perfusion-pressure studies.

possible explanation put forward by O'Reilly for the discrepancies is that the systems tolerated lower flow rates but not the 10 mL per minute used in the perfusion-pressure studies.

The intrarenal resistive index is a physiologic parameter that indirectly reflects the degree of resistance in the intrarenal vasculature. In a review of the literature, Rawashdek and associates (165) concluded that the intrarenal resistive index measurements are still in a developmental phase and that this technique has yet to be recognized as a dependable parameter to determine whether a dilated renal pelvis represents significant obstruction.

Indications for Surgery

The major indications for surgical repair of hydronephrosis are relief of pain or relief of significant obstruction that will destroy renal function. Intermittent hydronephrosis classically occurs during a marked diuresis and is best demonstrated by radiologic studies during the symptomatic episodes (148). Determination of whether a mild partial obstruction is significant is more difficult. The best studies are the intravenous urogram to demonstrate calyceal clubbing and dilation, diuretic renograms, Whitaker renal perfusion studies, retrograde pyelograms with washout studies, or longitudinal follow-up urograms showing progressive dilation of the renal pelvis and calyces. When an individual case is first seen with mild to moderate dilation of the renal pelvis, it is not always possible to forecast its natural history.

Ryan and associates (172) have reported that *in situ* double-J stents impair upper urinary tract motility and experimental calculus transit time and may delay passage of ureteric calculi.

Forty-one kidneys in infants and newborns were studied with diuretic renography, showing partial obstruction or dilation with obstruction that washed out with diuretics. Twelve-month follow-up showed deterioration to significant obstruction in 20%. The deterioration was more likely to occur in the markedly hydronephrotic units (99). Bilateral hydronephrosis detected antenatally was followed for up to 7 years in 26 children. Operations were never performed on 34 kidneys, and operations were performed on 18 kidneys. There was no consistent difference in final filtration rates of the two groups (107).

I have seen patients whose previous radiologic studies showed a mild hydronephrosis, presenting with significant hydronephrosis that had progressed over periods of 1 to 10 years. Thus ureteropelvic junction obstruction is progressive in some patients.

A 17-year follow-up of 36 adults with UPJ obstruction managed without surgery showed little change in function or worsening of hydronephrosis. Forty-seven patients who had pyeloplasty (and presumably more hydronephrosis) showed split function of the obstructed kidney from 40.8% to 47.1% of total function after pyeloplasty, but total GFR did not improve (111).

Lennon and associates (119) studied *in vitro* the pharmacologic options for the treatment of acute ureteric colic. Morphine was confirmed to have a spasmogenic effect on ureteric activity, which was unaffected by naloxone. Both indomethacin and diclofenac produced an abrupt inhibition of ureteral contraction, which, because of spasmolytic effects, may be indicated as therapy for the acutely obstructed ureter.

Selection of Operative Procedures

All of the operative techniques provide a dependent and progressive funneling of the ureteropelvic junction. The two basic techniques are the use of some type of pelvic flap (41,59,173) and the dismembered pyeloplasty (3,59). Recently, balloon dilations have become popular, and they were 80% successful in 40 cases (128). Endopyelotomies have been successful as well (86%) (141). The most commonly used surgical procedure is the dismembered pyeloplasty. All the operations work, and one should not be dogmatic in declaring that one or another of the operations is best.

Meticulous care and delicate handling of the renal pelvis and ureter are essential for the success of the pyeloplasty. Small, sharp scissors and fine vascular forceps are essential to prevent crush damage of the tissues. Tissues that are frequently lifted or held should have sutures placed for traction, or skin hooks should be used. Tissue must be approximated with fine sutures (I prefer chromic catgut 4-0 or 5-0 wedged on an atraumatic needle). Knots should be placed on the outside. I prefer to use interrupted sutures beginning at the apex to avoid a “dog-ear” in this location.

I agree with Blandy (11) that too much time has been wasted arguing over whether to use stents or nephrostomies. Any urologist should know how to use both. Stents should be used if the anastomosis appears likely to kink or is obstructed by edema during the first few days. Nephrostomies are needed if renal function is unclear or if there is a high likelihood of leakage or obstruction. I generally favor using both stents and nephrostomies. In bilateral hydronephrosis, if one side is infected, that side should be repaired first. In uninfected hydronephrosis, if one side has poorer function, that side should be repaired first.

Ureteral strictures in association with ureteropelvic junction obstruction are uncommon in my experience. Ureteral strictures can be corrected during the pyeloplasty. The Davis intubated ureterotomy (45) or end-to-end anastomosis can be used.

Foley Y-plasty

The Foley Y-plasty (59) was designed for the correction of an obstructive, congenital high insertion of the ureter

into the renal pelvis (Fig. 21.4). The pelvis and ureter must be dissected free. Careful planning of the pelvic incisions is essential. The anterior and posterior pelvic incisions and the ureteral incision should be approximately the same length. I have found it helpful to mark the end of each planned incision with a 4-0 silk suture. The anterior pelvic incision is started at the ureteropelvic junction and extended laterally and downward toward the hilum of the kidney. The posterior incision is then similarly made, completing the V portion of the Y incision. The ureteral incision is then made down the lateral margin (the side facing the renal pelvis). The sharp tip of the pelvic flap is rounded off. Before closure, the nephrostomy tube and stent are placed, if they are being used. Interrupted 4-0 or 5-0 chromic catgut is used for closure, starting at the tip to avoid leaving a dog-ear in the renal pelvis. I drain the area with two drains. All tubes and drains are brought out the posterior part of the wound, because it has less sensation than the anterior portion. The Foley Y-type ureteropelvioplasty can be combined with a Davis intubated ureterotomy (45) when the ureteral structure is longer than can be corrected with the Foley Y-plasty alone (Fig. 21.5). Use of stents is essential in the Davis intubated ureterotomy to provide scaffolding for new growth. I usually place several sutures loosely from the edges across the catheter to ensure that the sides lie flat and do not curl up. Davis states that the healing by secondary intention requires 6 weeks. When exposing the

ureter, there should be minimum dissection to preserve the blood supply. Careful nontraumatic handling of the tissues is essential.

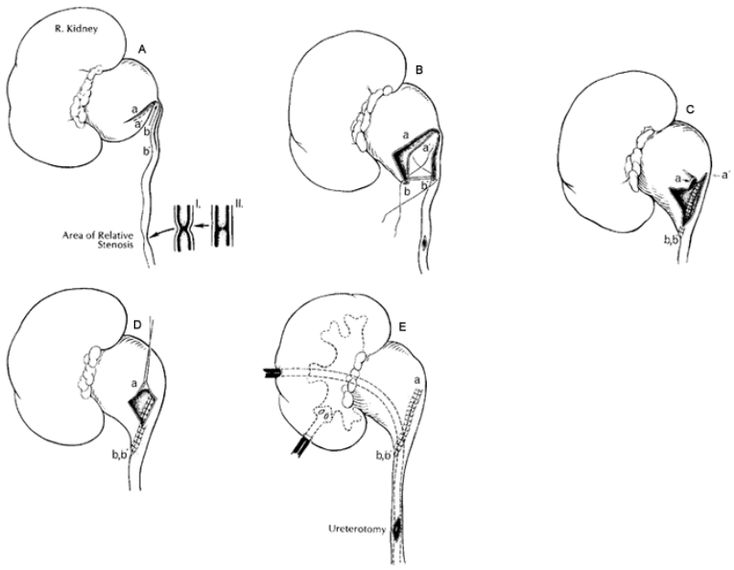

FIGURE 21.4. Classic Foley Y-plasty. **A:** Anterior and posterior pelvic incisions should be the same length as the ureteral incision. **B:** The tip of the flap and the lower end of the ureterotomy should be approximated first. **C**, **D:** The closure is started at *(b,b')* and extended upward to *(a,a')*. A dog-ear may form at point *a*. *I* and *II* illustrate the infrequent relative narrowing of the ureter, which is occasionally seen lower in the ureter. **E:** If there is a narrow segment, it can be treated by a ureterotomy or dilation. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH et al, eds. *Campbell's urology*, ed 4. Philadelphia: Saunders, 1979, with permission.)

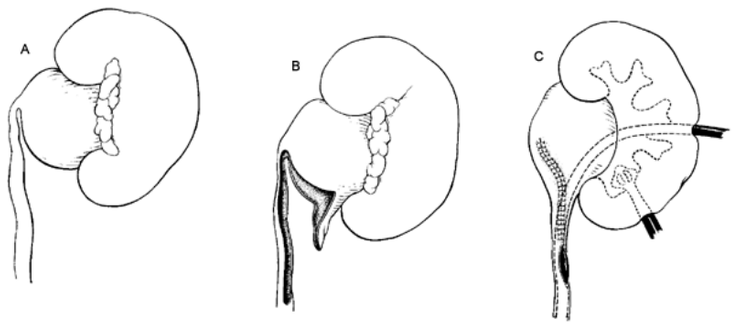

FIGURE 21.5. The classic Foley Y-plasty for high ureteral insertion with a long obstructing ureteral defect. **A:** The high insertion of the ureter into the renal pelvis. **B:** The long ureterotomy and funneling flap in the renal pelvis. **C:** The closure of the renal pelvis with the lower portion of the ureteral incision left open as a Davis intubated ureterotomy.

Dismembered Ureteropyelostomy

The operation first described by Foley in 1937 (59) and Anderson and Hynes in 1949 (3) is the most commonly used pyeloplasty and works well in most situations. The operation consists of suturing a spatulated ureter to a generous V-shaped pelvic flap. The pelvic flap is essential to provide the funneling. The kidney and ureter are dissected free, noting carefully whether there are any lower pole vessels. It is important to know how long the narrow upper ureteral segment is to plan the pelvic flap. If needed, additional length can be gained by mobilizing the kidney. Preoperative evaluation should have provided information about the length of the narrowed ureteral segment. If additional information is needed, one can open the renal pelvis and pass down a calibrating ureteral catheter or bougie à boule.

Before opening the pelvis, I plan and map out the incision, the pelvic flap, and any excess renal pelvis I am going to remove, placing marking sutures or using a marking pen. I always mark the lateral edge of the ureter where I plan to do the spatulation to prevent rotation and cutting the ureter in the incorrect place. Proper orientation is essential. It is easy to misplace the anastomosis and cause rotations or angulation if one does not pay attention, stay oriented, and properly mark the tissues. A nice aspect of this operation is that it can be used with either an intrarenal oran extrarenal pelvis. There are several ways one can fashion the renal pelvic flap (Fig. 21.6,Fig. 21.7,Fig. 21.8 and Fig. 21.9) (11).

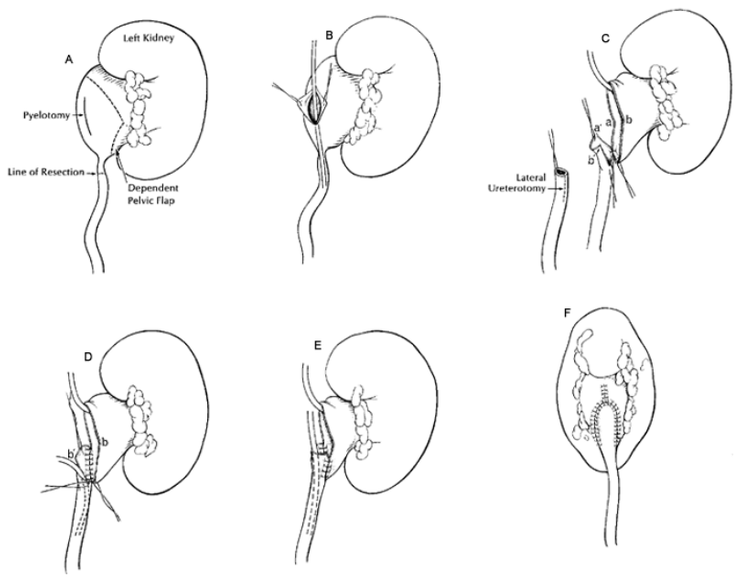

FIGURE 21.6. Dismembered Foley Y-plasty operation. The obstructing segment is excised and a dependent funneling of the pelvis is achieved. **A:** The pyelotomy and ureterotomy incisions are planned and marked. **B:** The pyelotomy incision is started. **C:** The lateral ureterotomy is done and ureteral stent passed after excising the ureteral segment. **D:** Suturing with 3-0 or 4-0 absorbable sutures is started on the posterior surface at the apex. **E:** Traction sutures are used to approximate the edges. It is important not to crush the tissue with heavy forceps. The tip of the flap is sewn to the ureterotomy. It is important to start at the apex. **F:** The funnel is completed, and any redundant pelvis can be resected. The pelvis is reconstituted. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH et al, eds. *Campbell's urology*, ed 4. Philadelphia: Saunders, 1979, with permission.)

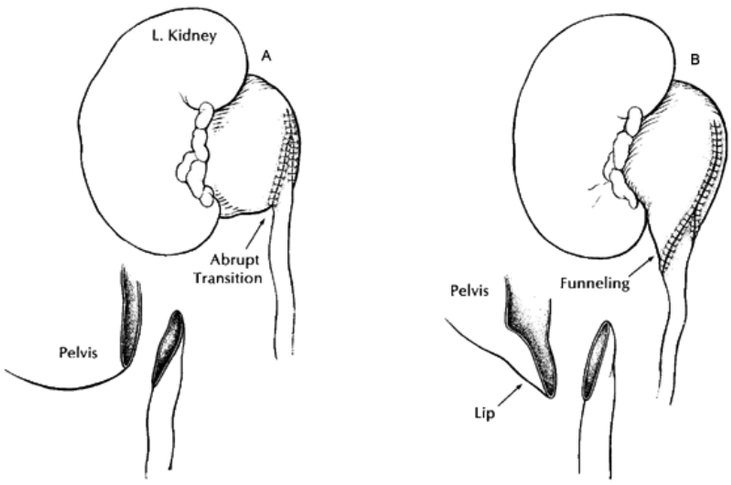

FIGURE 21.7. The value and importance of creating a funnel **(B)** in the pelvis as opposed to creating an abrupt transition between the pelvis and the ureter **(A).** Proper funneling gives dependent drainage with a nice transition between the pelvis and ureter. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH et al, eds. *Campbell's urology*, ed 4. Philadelphia: Saunders, 1979, with permission.)

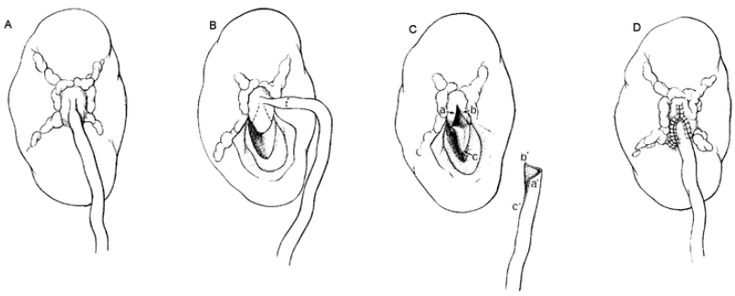

FIGURE 21.8. Difficult high-insertion repair. The Foley Y-plasty can be adapted to patients with a small extrarenal pelvis. **A:** The area of narrowing in the upper ureter with small extrarenal pelvis. **B:** Resection of renal parenchyma to expose the large intrarenal pelvis. **C:** The ureter is cut distal to the obstruction and spatulated. The pelvis flap is also formed after resection of the stenotic segment. Approximate *a-a′, b-b′,* and *c-c′.* **D:** The anastomosis is completed with a funneled and dependent pelvis. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH et al, eds. *Campbell's urology*, ed 4. Philadelphia: Saunders, 1979, with permission.)

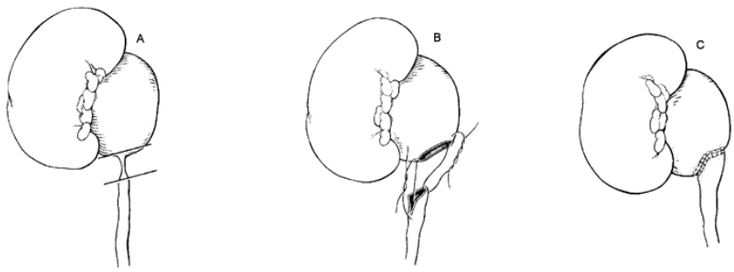

FIGURE 21.9. Simple pyeloplasties in children have been successful. The narrow segment **(A)** is excised, leaving the pelvis tunneled, and the ureter is spatulated **(B).** Closure is with 3-0 or 4-0 absorbable sutures **(C).** (Modified from Zincke H et al. Ureteropelvic obstruction in children. *Surg Gynecol Obstet* 1974;139:873, with permission.)

Ureterocalyceal Anastomosis

The ureterocalyceal anastomosis can be used when there seems to be no other option for anastomosing the kidney. This anastomosis is most useful when the renal pelvis cannot be dissected out or used. The procedure is more difficult and will have a higher failure rate than other procedures. The two different methods are removing a button of renal parenchyma over the lower calyx (Fig. 21.10) or opening the lower calyx by incising down to the calyx in the medial portion of the lower pole of the kidney (Fig. 21.11).

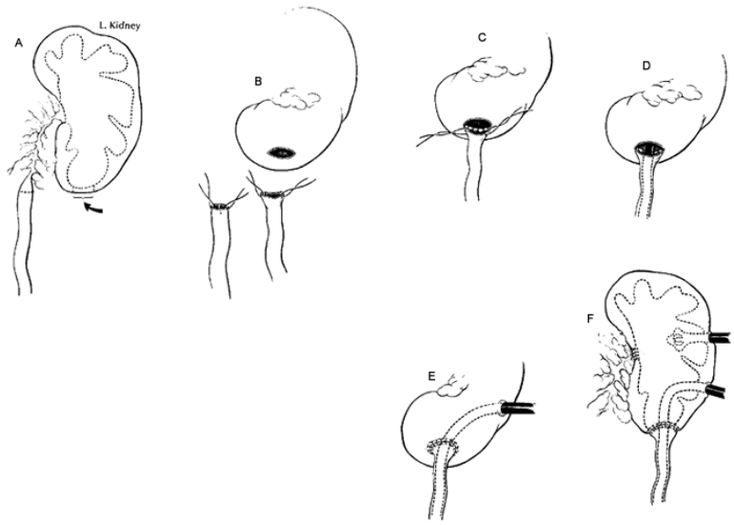

FIGURE 21.10. Ureterocalyceal anastomosis for difficult situations in which anastomosis to the pelvis is impossible. **A:** The scar tissue is excised. The renal pelvis is closed after placing a stent and nephrostomy tubes. **B:** Ureterotomies are done after orientation sutures are placed in the ureter. The ureteral opening is enlarged, ready for the anastomosis. An elliptic segment of renal parenchyma is excised. The dimensions of the opening should be the same as those of the ureter to be anastomosed. **C:** Ureter is sutured to calyceal mucosa with interrupted 3-0 or 4-0 absorbable sutures. **D:** Ureteral stent is passed after posterior anastomosis is complete. **E:** Anastomosis is completed. **F:** Diagram of funneling. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH et al, eds. *Campbell's urology*, ed 4. Philadelphia: Saunders, 1979, with permission.)

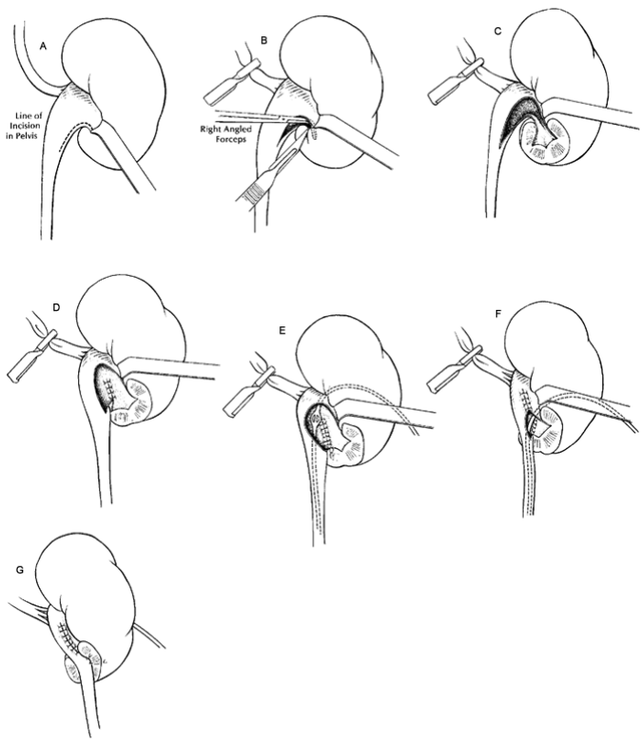

FIGURE 21.11. Ureterocalicostomy. **A:** Line of incision from ureter to renal pelvis to lower calyx. **B:** Cutting into the calyx and the lower pole parenchyma. **C:** The calyx is open and hemostasis obtained. **D:** Posterior anastomosis of the ureter to the calyx. **E:** A Cumming nephrostomy tube is used to stent the anastomosis and drain the renal pelvis. **F:** Anterior anastomosis is begun. **G:** Anterior anastomosis is completed. (Modified from Blandy J. *Operative urology*. Oxford: Blackwell Scientific, 1978, with permission.)

In ureterocalyceal anastomosis, one usually is not able to adequately dissect out the renal pelvis because of scar tissue. Usually, there is a longer narrowed segment of ureter. The ureter is cut back to normal tissue and spatulated on the lateral border. If the renal pelvis can be entered, I pass a sound down to the lower calyx and cut out an adequate button of renal parenchyma, marking the mucosal edges of the calyx for later anastomosis. If the renal pelvis cannot be entered, a guillotine type of procedure will provide access to the lower calyx.

The other type of procedure that can be used in some circumstances is the ureterocalicostomy. This procedure was devised to correct a narrow infundibulum. The renal pelvis is opened and a right-angle clamp is passed into the lower calyx. Before making the cut it is advisable to place a bulldog clamp around the renal artery, because bleeding from large veins can be tremendous. The parenchyma is cut, including the mucosa of the lower calyx. The ureter is cut on

its lateral border and sutured with 3-0 or 4-0 chromic sutures to the calyceal mucosa. The sutures should be interrupted at the apex. Nephrostomy tubes and stents should always be used, because these operations have a higher risk of failure.

Extrinsic Vascular Obstruction

The Hellstrom vascular relocation procedure (85) is a simple technique for correcting renal outlet obstruction from a crossing vessel (Fig. 21.12). This procedure should be used solely when there is extrinsic obstruction only. One has to be careful that there is no intrinsic obstruction. I have operated on at least six hydronephrotic kidneys with intrinsic obstruction that previously had been thought to have only extrinsic obstruction. Intrinsic obstruction cannot be ruled out by passing a catheter through the area in question. Some of the obstructions are caused by impaired function, not intrinsic or extrinsic scarring. If there is any doubt about an area of intrinsic obstruction, I think it should be corrected at the time of surgery. In the Hellstrom procedure, the anterior herniation of the renal pelvis is placed behind the vessels, and the vessel is fixed to the renal pelvis to relieve the extrinsic obstruction.

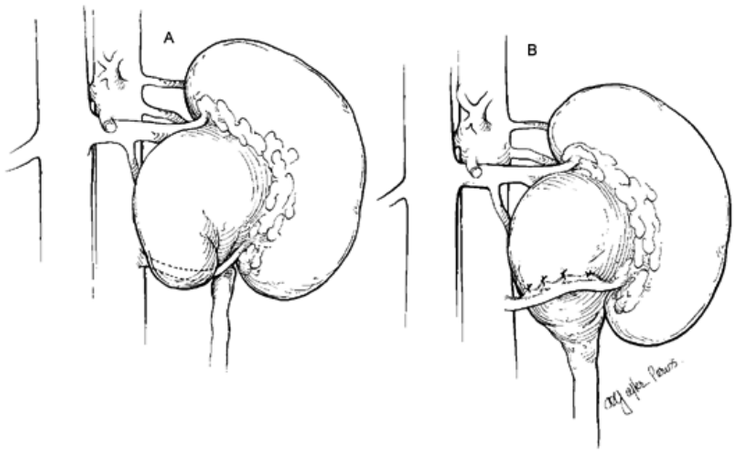

FIGURE 21.12. Hellstrom technique. The obstructing vessel is moved to a nonobstructing position. An intrinsic defect should be carefully ruled out by perfusion studies on the operating table. **A:** Anterior herniation of the renal pelvis over an obstructing renal vessel. **B:** Fixation of the renal vessels in a nonobstructing position. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH et al, eds. *Campbell's urology,* ed 4. Philadelphia: Saunders, 1979, with permission.)

Hydronephrosis in a Horseshoe Kidney

Hydronephrosis can occur in horseshoe kidneys. The obstruction is usually ureteropelvic junction obstruction and is not from pressure where the ureter crosses the kidney. The isthmus is usually medial to the obstruction and is not causing the obstruction. The problem with routine cutting of the isthmus is that one can injure major renal vessels or enter the collecting system. In my experience, most pyeloplasties can be accomplished without having to divide the isthmus. If the isthmus is thin, it should be divided with lateral placement of the lower poles.

The pyeloplasty can be done like any other pyeloplasty. The dismembered pyeloplasty is usually the preferred procedure. To expose the horseshoe kidney, one needs to make a midline or paramedian incision. The bowel is mobilized medially. The kidney usually lies in the region of the bifurcation of the aorta. Renal vessels come from the aorta and iliac arteries.

Hydronephrosis from Retrocaval Ureter

The retrocaval ureter is a congenital anomaly in which the right ureter passes behind the vena cava, causing obstruction (Fig. 21.13). The abnormality is caused by persistence of the posterior cardinal vein as the major portion of the infrarenal inferior vena cava. The kidney is approached through a flank or an abdominal incision. The renal pelvis is dissected down to where the ureter passes under the vena cava. The ureter can be cut here. The normal ureter is located as it crosses anterior to the vena cava and is cut. One then spatulates the distal ureter segments and does an anastomosis with a U-shaped flap of the renal pelvis.

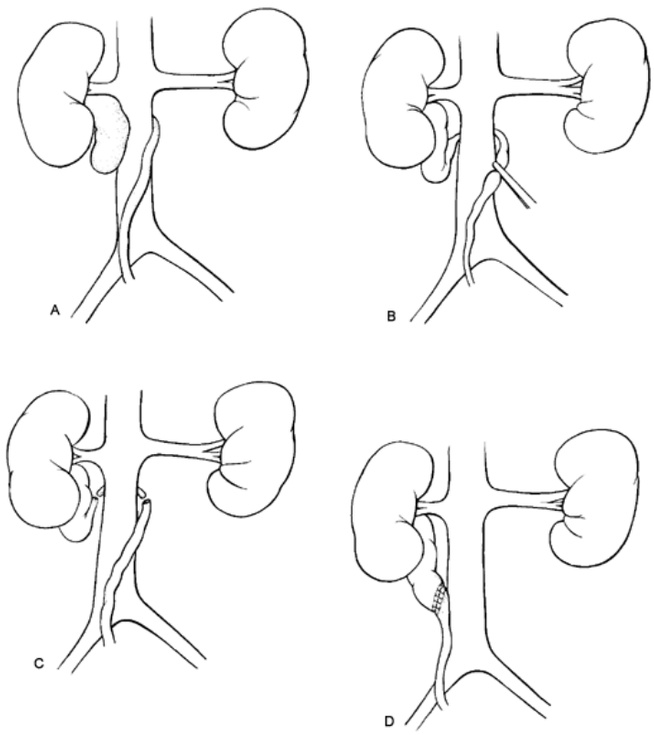

FIGURE 21.13. A: Retrocaval ureter. **B:** The renal pelvis is dissected down to where the ureter passes under the vena cava. **C:** The ureter can be cut here; the normal ureter is located as it crosses anteriorly to the vena cava, and is cut. **D:** The distal ureter segment is then spatulated, and an anastomosis with a U-shaped flap of the renal pelvis is performed.

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22

RENAL TRANSPLANTATION

Stuart M. Flechner

Andrew C. Novick

S.M. Flechner and A.C. Novick: Cleveland Clinic Foundation, Cleveland, OH 44195.

Contents

Recent years have witnessed an explosive growth in the number of patients experiencing end-stage renal disease (ESRD), as well as the number of centers providing therapeutic modalities such as hemodialysis, peritoneal dialysis, and renal transplantation. Data from the United States Renal Data System (303) reveals an annual growth in the prevalent population of ESRD patients of more than 10% (Fig. 22.1), with many treated by center hemodialysis. Currently, more than 220,000 patients with ESRD require treatment. There is an age-dependent increase in the incidence of new patients with ESRD (Fig. 22.2). The mean age is 61 years, and more than half are older than 65 years. The continued aging of the U.S. population will undoubtedly ensure continued growth of the ESRD population.

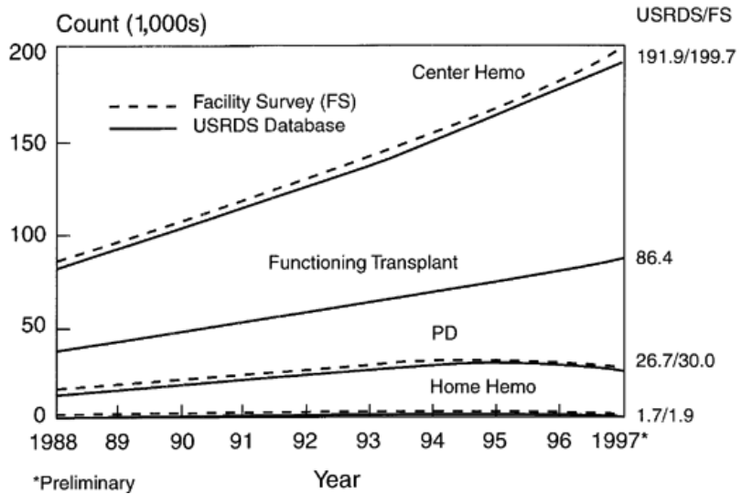


FIGURE 22.1. Point prevalence counts of patients with end-stage renal disease alive on December 31, by treatment modality and year, 1988–1997. Medicare patients only. PD, peritoneal dialysis. (From United States Renal Data System 1999 Annual Data Report. III. Treatment modalities for ESRD patients [Review]. *Am J Kidney Dis* 1999;34[2 Suppl 1]:S53, with permission.)

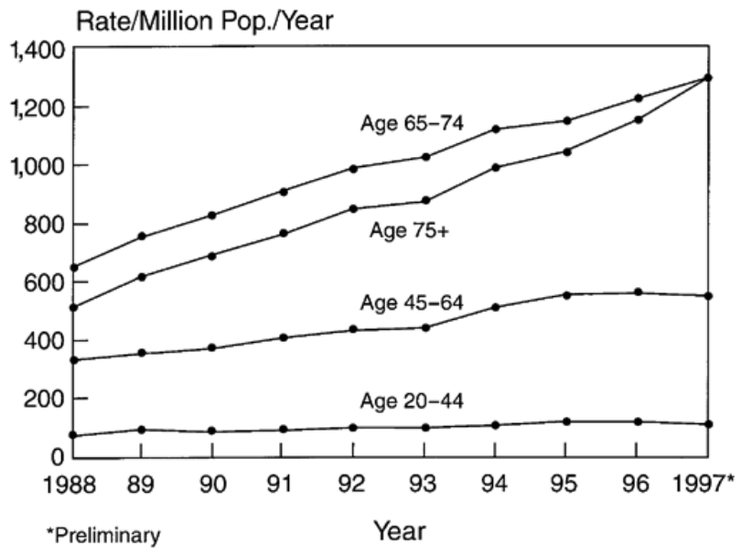


FIGURE 22.2. Incidence rates of treated end-stage renal disease per million population, by age group, 1988–1997. Medicare patients only. (From United States Renal Data System 1999 Annual Data Report. II. Incidence and prevalance of ESRD. *Am J Kidney Dis* 1999;34[2 Suppl 1]:S45, with permission.)

Although there has been continued improvement in patient survival for both dialysis and transplantation (Fig. 22.3), the mortality rate of the ESRD population continues to be approximately 20% per year. Patients with ESRD enjoy only 20% to 25% of the life expectancy of the general population (8.8 years versus 31.8 years, respectively, at ages 45 to 49). Cardiovascular events are the most common cause of death in patients with ESRD. As Fig. 22.4 indicates, death rates for dialysis patients increase dramatically for each cause among patients older than 65 years of age.

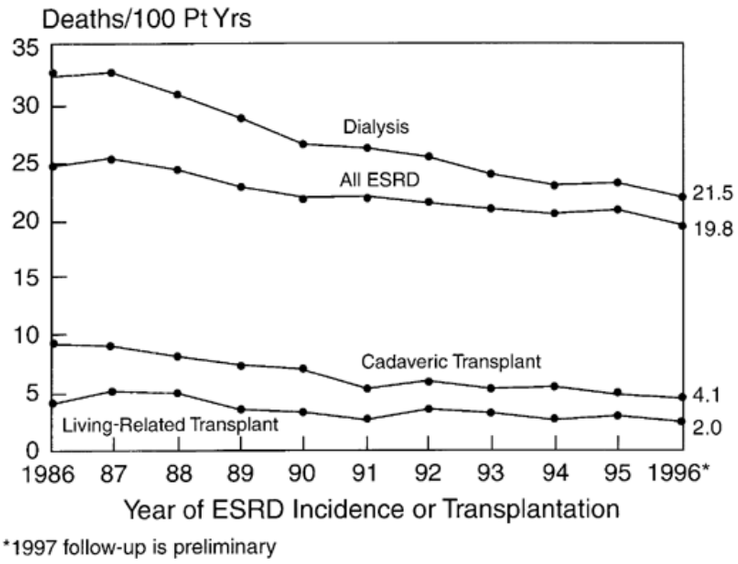


FIGURE 22.3. Death rates based on estimates from proportional hazards regression models by modality and year of end-stage renal disease *(ESRD)* incidence or of first transplantation. For each category, death rates are adjusted by age, race, sex, and diabetes to the average patient in a corresponding standard population.

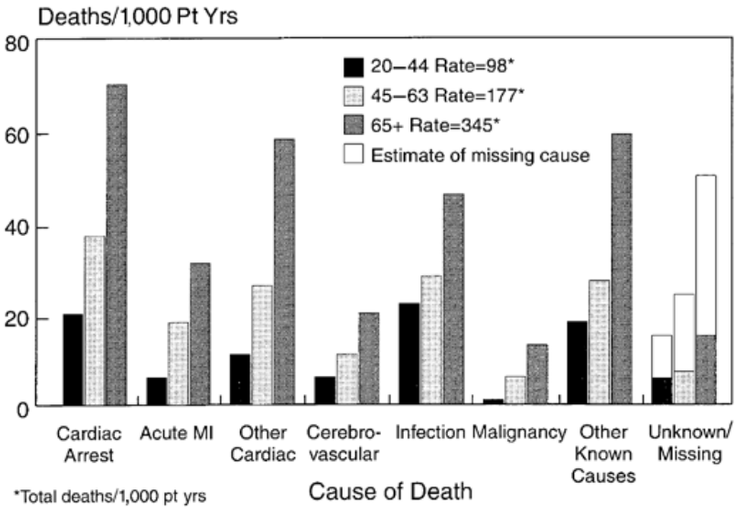


FIGURE 22.4. Cause-specific death rates for all dialysis patients by age, 1995–1997. The categories are collapsed from a death notification form. Patients younger than 20 years of age are excluded. MI, myocardial infarction. [From USRDS 1999 annual data report. *Am J Kidney Dis* 1999;34(2 Suppl 1):S88, with permission.]

The annual cost for the ESRD population in 1997 was more than $15 billion (Fig. 22.5). This is more than $43,000 per patient, with approximately 75% of this cost being absorbed by the federal Medicare program and additional amounts paid by state medicaid programs and private sources. These figures significantly underestimate the true expense because costs related to lost time from work and other expenses are not reflected.

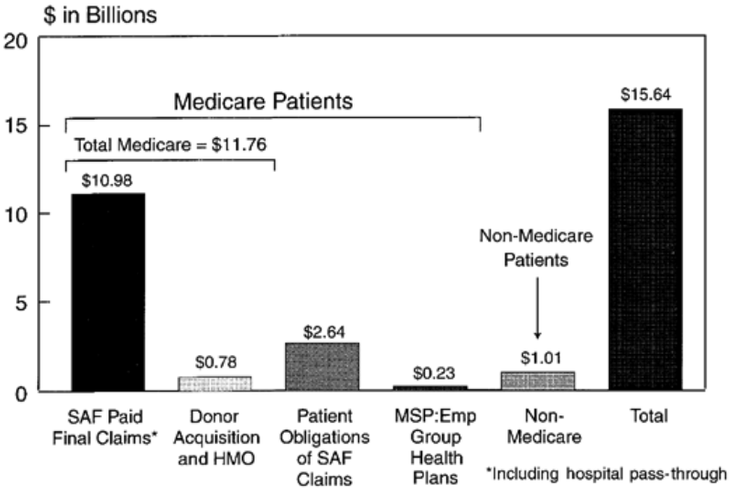


FIGURE 22.5. Estimated total direct monetary cost of treating end-stage renal disease in the United States, 1997. Separate estimates of cost are reported according to eligibility for Medicare insurance. HMO, health maintenance organization; SAF, Standard Analysis Files. [From USRDS 1999 annual data report. *Am J Kidney Dis* 1999;34(2 Suppl 1):S128, with permission.]

As a result of economic considerations, quality of life, and outcomes, renal transplantation has emerged as the preferred treatment modality for most patients with ESRD (67). However, the number of transplants performed has not kept pace with the ESRD population growth (Table 22.1), and more than 42,000 patients are now awaiting transplantation (9). As apparent from Table 22.1, the number of kidney transplants has increased over 10 years by one-third from about 8,600 to 12,000 per year. However, this has been inadequate to meet the rising number of waiting patients, which has increased more than 250% during the same period. Although there have been slight increases in the number of cadaveric organ donors, this has been attributed to an increased use of older donors (older than age 60) and those with extended criteria of organ quality (e.g., ischemia, hypertension). There has been a doubling in the number of live donor transplants in the last decade, as improved immunosuppression has permitted the use of more distant relatives and even unrelated (spouses) individuals (Fig. 22.6). Experimental work on the use of animal xenografts as a source of donor organs remains many years away from being a clinical reality (13,224), but it continues to represent the best hope to resolve the worldwide organ donor shortage problem. The severe shortage of available donor organs has had more marked implications in extrarenal (e.g., heart, liver) transplants as numerous patients awaiting transplantation die each year, and significant concerns have arisen with respect to assurance that available organs will be allocated to needy recipients in a fair and equitable manner. Federal legislation created the National Organ Procurement and Transplant Network, and the United Network for Organ Sharing (UNOS) was awarded the federal contract to develop policies for equitable organ distribution.

	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
Cadaveric transplants	6,753	7,323	7,281	7,203	7,509	7,638	7,691	7,722	7,769	8,011
Live donor transplants	1,903	2,094	2,393	2,236	2,850	3,006	3,354	3,596	3,844	4,151
Total transplants	8,656	9,417	9,674	9,439	10,359	10,644	11,045	11,318	11,613	12,162
Cadaveric donors	3,810	4,306	4,268	4,276	4,606	4,798	5,001	5,037	5,081	5,341
Patients waiting	16,294	17,883	19,352	22,376	24,937	27,498	31,149	34,646	38,270	42,392

From 1999 annual report of the U.S. Scientific Registry of Transplant Recipients and the Organ Procurement and Transplantation Network transplant data 1989–1998. Richmond, VA: UNOS; and Bethesda, MD: Division of Organ Transplantation, Bureau of Health Resources, U.S. Department of Health and Human Services.

TABLE 22.1. NUMBERS OF RENAL TRANSPLANTS, CADAVERIC DONORS, AND WAITING PATIENTS, 1989–1998

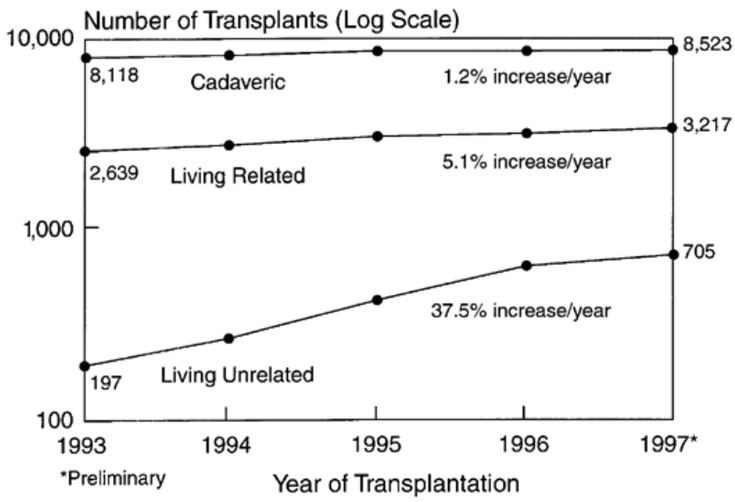


FIGURE 22.6. Total number of renal transplants by donor source and year (1993–1997) shown on log scale. Largest increase in living unrelated category. [From USRDS 1999 annual data report. *Am J Kidney Dis* 1999;34(2 Suppl 1):S96, with permission.]

IMMUNOBIOLOGY OF TRANSPLANTATION

Part of "22 - RENAL TRANSPLANTATION "

Advances in molecular biology have aided our understanding of the immunobiology of organ transplantation and rejection. A *locus* is the location of a gene on a chromosome. *Alleles* are alternative forms of a gene at a given locus on homologous chromosomes. The *major histocompatibility complex* (MHC) is a series of cell surface antigens encoded by closely linked genes. A *haplotype* is the sum of genetic material or unit of inheritance contributed by each parent. Each individual inherits a distinct haplotype from each parent. The *phenotype* is the total histocompatibility antigens expressed by an individual without distinguishing which antigens are maternally or paternally derived. The *genotype* is the total of histocompatibility antigens expressed

by an individual, designating the maternal and paternal contributions.

Many of the basic observations on transplant rejection were made through research into the mechanisms of tumor resistance. Following is a brief historical review of some of the investigators who have advanced our current knowledge of transplant immunobiology. In 1902, Carrel and Guthrie, during the development of vascular suture techniques, performed canine kidney autotransplants (same individual), allotransplants (members of same species), and xenotransplants (between species) (40). They observed that the autografts survived indefinitely, whereas the allografts and xenografts were rejected. Landsteiner (148) described the ABO blood group antigens. Haldane (103) theorized that transplanted tissues were rejected due to differences in alloantigens that were similar to differences in blood group antigens. Little and Tyzzer (156) noted that tumors survived when transplanted between mice of the same strain, but rejected when transplanted to other strains. Gorer (96), noting these observations, correlated these findings with the existence of an allelic blood group antigen that was able to be serologically detected. This important observation demonstrated that tumor rejection is not dependent on tumor-specific antigens, but on antigens present in normal tissues.

Snell (259) confirmed that it was the histocompatibility loci, and their encoded antigens, that account for both tumor and skin graft rejection. He reasoned that the distribution of these “transplantation antigens” followed a Mendelian pattern. Medawar (176) demonstrated that the rejection response was primarily a reaction rather than humorally mediated hypersensitivity. He performed full-thickness rabbit skin grafts and a few weeks later regrafts using the same

donors into the same recipients, and demonstrated the phenomenon of accelerated rejection. Billingham and associates (22), expanding on the observations of Medawar, demonstrated the phenomenon of second set or accelerated rejection in recipients sensitized by prior exposure to the donor alloantigen (i.e., the more rapid rejection of a second graft from the same donor from which a first graft had been rejected).

Through the work of these and many other investigators, the field of clinical organ transplantation has evolved. However, the success of clinical renal transplantation currently rests on the use of drugs to achieve nonspecific immune suppression to prevent allograft rejection. The ultimate goal of organ transplantation is to induce the development of *donor-specific tolerance* (defined as the state of immune unresponsiveness to the donor MHC antigens, but the host maintains the ability to respond to other foreign antigens). Several hypotheses exist regarding mechanisms of tolerance induction, which has been observed primarily in animal models, but also anecdotally seen in transplant recipients who were taken off immunosuppressive medications for medical reasons or occasionally in noncompliant patients who stopped taking their medications. These include *clonal deletion*–elimination of immunoreactive T cells; *clonal anergy*–prevention of activation and proliferation of donor antigen–specific T cells; *suppression*–inducing other cells or mechanisms to prevent the triggering of a donor-specific immune response; and *chimerism*– persistence of a small number of hematopoietic cells of donor origin in the recipient (10). Although presently not a clinical reality, tolerance induction remains the goal of transplant research worldwide.

THE HUMAN MAJOR HISTOCOMPATIBILITY COMPLEX

Part of "22 - RENAL TRANSPLANTATION "

The immune response of a patient when exposed to the “foreign” tissue of an organ transplant continues to represent the major barrier to success in spite of the many advances that have been made in immunosuppression. The human major histocompatibility complex is the primary target of immune-reactive cells that make up the rejection process. The MHC describes a region of genes that encode proteins that are responsible for the rejection of tissues between different species or between members of the same species. More important, these cell surface proteins serve as identity markers on cells interacting with T lymphocytes carrying out specific immune functions. The cell surface MHC markers are called human leukocyte antigens (HLAs) because they were first identified on white blood cells.

The HLA gene complex is found on the short arm of chromosome 6 (Fig. 22.7). Two classes of antigens, class I (HLA-A, HLA-B, and HLA-C) and class II (HLA-DR, HLA-DQ, and HLA-DP), can be differentiated by their molecular structure and their tissue distribution. The class I HLAs consist of a 44-kDa, transmembrane glycoprotein α-chain that is noncovalently associated with β_2-microglobulin on the cell surface. These molecules are found in varying densities on essentially all cells in the body.

HLA class II molecules are made up of two transmembrane glycoproteins, an α-chain of approximately 34 kDa and a ß-chain that is slightly smaller (28 kDa). Their tissue distribution is much more restricted than that seen with class I. The B lymphocytes, which express both class I and class II, are commonly used to identify class II antigens in the laboratory. The involvement of HLA class II in transplant rejection results from the presence of these molecules on the surface of vascular endothelial cells of the graft, as well as on "passenger leukocytes" that are present in the organ.

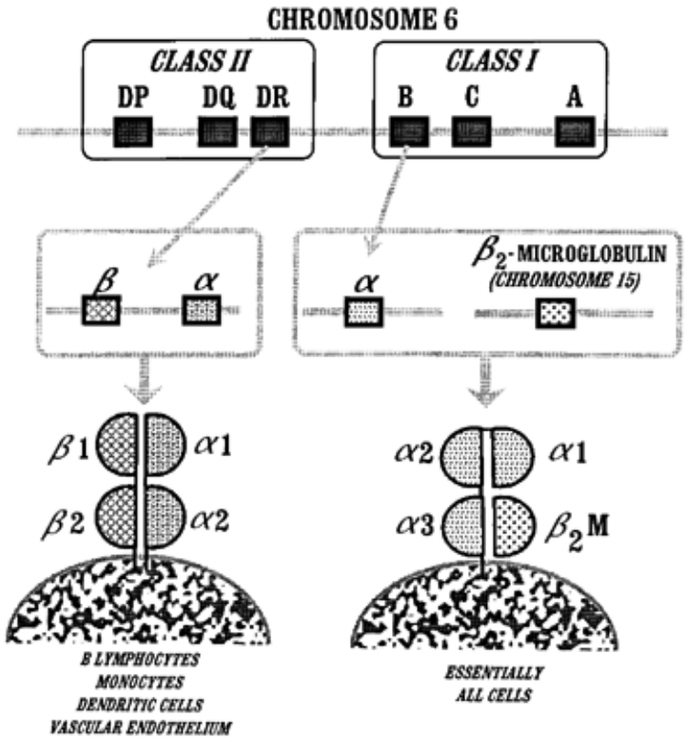


FIGURE 22.7. A simplified illustration of HLA genes and molecules.

The MHC genes are codominantly expressed, meaning that each individual expresses the HLAs that are inherited from either parent. What makes this system unique is the degree of polymorphism that is found, resulting in a great many alleles or variants of these antigens that have been identified in the population. Table 22.2 illustrates the HLA-A, HLA-B, HLA-C, HLA-DR, and HLA-DQ antigens that can be identified using standard lymphocytotoxicity methodologies. Using polymerase chain reaction (PCR)–based DNA-level testing, it is becoming abundantly clear that the degree of polymorphism is much greater than was previously thought. In 1994, the numbers of alleles that had been identified at the DNA level included 50 at

HLA-A, 97 at HLA-B, 34 at HLA-C, 106 at HLA-DR, 26 at HLA-DQ, and 59 at HLA-SP (24). All of the class I polymorphism is found in the α-chain, $ß_2$-microglobulin being invariant, and the number of class II alleles given are for the ß-chains, which are much more polymorphic than the class II α-chains.

HLA-A	HLA-B		HLA-C	HLA-DR	HLA-DQ
A1	B5	B51 (5)	Cw1	DR1	DQ1
A2	B7	B5102	Cw2	DR103	DQ2
A203	B703	B5103	Cw3	DR2	DQ3
A210	B8	B52 (5)	Cw4	DR3	DQ4
A3	B12	B53	Cw5	DR4	DQ5 (1)
A9	B13	B54 (22)	Cw6	DR5	DQ6 (1)
A10	B14	B55 (22)	Cw7	DR6	DQ7 (3)
A11	B15	B56 (22)	Cw8	DR7	DQ8 (3)
A19	B16	B57 (17)	Cw9 (w3)	DR8	DQ9 (3)
A23 (9)	B17	B58 (17)	Cw10 (w3)	DR9	
A24 (9)	B18	B59		DR10	
A2403	B21	B60 (40)		DR11 (5)	
A25 (10)	B22	B61 (40)		DR12 (5)	
A26 (10)	B27	B62 (15)		DR13 (6)	
A28	B35	B63 (15)		DR14 (6)	
A29 (19)	B37	B64 (14)		DR1403	
A30 (19)	B38 (16)	B65 (14)		DR 1404	
A31 (19)	B39 (16)	B67		DR15 (2)	
A32 (19)	B3901	B70		DR16 (2)	
A33 (19)	B3902	B71 (70)		DR17 (3)	
A34 (10)	B40	B72 (70)		DR18 (3)	
A36	B4005	B73			
A43	B41	B75 (15)		DR51	
A66 (10)	B42	B76 (15)		DR52	
A68 (28)	B44 (12)	B77 (15)		DR53	
A69 (28)	B45 (12)	B7801			
A74 (19)	B46	NM5			
	B47				
	B48	Bw4			
	B49 (21)	Bw6			
	B50 (21)				

*Revised Jan. 14, 1993.
Adapted from *Histocompatibility laboratory manual.* The Cleveland Clinic Foundation.

TABLE 22.2. LISTING OF RECOGNIZED HUMAN LEUKOCYTE ANTIGEN SPECIFICITIES*

One other system that plays a major role in histocompatibility is the ABO blood group antigens. Incompatibility at ABO can result in hyperacute rejection of a transplanted organ. The same general rules that apply for transfusion are relevant for transplantation (i.e., type O is the universal donor, type AB is the universal recipient, and so on), and confirmation of ABO compatibility should always be performed before transplantation of an organ.

HISTOCOMPATIBILITY TESTING FOR TRANSPLANTATION

Part of "22 - RENAL TRANSPLANTATION "

Three areas of histocompatibility testing are relevant for organ transplantation: (a) the typing of patient and donor to determine the degree of *match;* (b) assessment of the level of *sensitization* to HLAs in patients who have been exposed to foreign antigens via pregnancies, transfusions, or transplant; and (c) *crossmatching,* in which the serum of the patient is examined for the presence of preformed antidonor antibodies that would be potentially harmful to the graft. By examining all of these factors, it is possible to assess the degree of risk for rejection in a particular donor–recipient combination.

The mainstay of histocompatibility testing is the complement-mediated, lymphocytotoxicity assay (285). This technique involves the incubation of lymphocytes with antibodies that react with HLAs, addition of a source of complement that results in lysis of the cells if antibody is bound to their surface, and the scoring of cell death using a vital stain. T lymphocytes, which express HLA-A, HLA-B, and HLA-C, are used only for class I typing, and B lymphocytes, which express class II, are used to identify HLA-DR, HLA-DQ, and HLA-DP. The sources of HLA reagents include allosera obtained from sensitized individuals as a result of pregnancy, transfusion, or transplant rejection, and in some cases monoclonal antibodies specific for HLA. Because individuals are seldom exposed to a single mismatched HLA, a considerable amount of screening of sera is required to obtain reagents appropriate for HLA typing. HLA typing at the DNA level is a rapidly developing technology that holds much promise (204). Here it is the nucleotide sequences of the DNA that are identified, rather than the epitopes found on the HLA molecules that recognized using antibodies. Once the DNA sequence of an HLA molecule is determined, it is relatively simple to produce reagents that can identify the polymorphic sequences. This general approach has almost unlimited potential for the identification of the many HLA alleles.

Individuals inherit one set, a haplotype, of HLAs from each of their parents. Therefore matching for HLA involves two antigens each at three HLA loci. Most data regarding HLA matching have included antigens at the HLA-A, HLA-B (class I), and HLA-DR (class II) loci, including anywhere from zero to six antigens matched. However, for solid organ transplantation, the concern is to avoid mismatched antigens that the patient would recognize as foreign. Therefore assessing the number of mismatches is the more appropriate method for determining compatibility at HLA in solid organ transplantation. Sometimes fewer than six antigens are identified, which may result from an individual who inherits the same antigen at a particular locus from each parent (homozygous).

Presensitization to HLAs is the major obstacle faced by many kidney transplant candidates. The same events that provide potential sources of HLA reagents in some individuals, such as pregnancy, transfusion, and transplant rejection, may sensitize a potential transplant candidate. To assess the degree of presensitization, a patient's serum is tested against a panel of lymphocytes from individuals of known HLA type, using essentially the same lymphocytotoxicity assay used for HLA typing. A value is obtained, the percent panel reactive antibody (PRA), that represents the percentage of the population that the patient's serum would be expected to react against. Many laboratories take this a step further, identifying HLA specificities of the antibodies, as well as identifying HLAs that the patient does not have antibodies against and therefore would be “acceptable” mismatches for the patient. In general, sera are obtained and screened on a monthly basis for patients waiting for a kidney transplant. The PRA may vary from month to month, necessitating frequent antibody screening to provide current information should a donor become available. Patients not previously exposed to HLAs may be screened at longer intervals, assuming that it is possible to document changes in their status (e.g., transfusion).

Perhaps the most important activity of the histocompatibility laboratory is performing the crossmatch test. It has been known for years that the presence of antidonor antibodies, particularly IgG, anti-T cell (class I) reactions, is associated with a significant risk of hyperacute rejection (209). The class of antigen recognized by the antibodies (class I or II) by using T and B cells as targets can be determined, as can the class of antibody (IgG or IgM) using a variety of permutations of the lymphocytotoxicity technique. Not all types of antibody reactions are associated with a high degree of risk of rejection, so characterization of the reaction can assist in determining compatibility between patient and donor. Sometimes reactions may also be due to an autoantibody, which can be removed by absorption with “self” lymphocytes.

Standard crossmatching techniques have made hyperacute rejection a rare occurrence. However, the observation that a number of transplants resulted in grafts that never functioned and that this was more likely to occur in presensitized recipients has led to the development of more sensitive

crossmatching techniques. Two approaches use antibody reagents that bind to human IgG to enhance the sensitivity. In the antiglobulin crossmatch, a second anti-IgG antibody is used, allowing the detection of weak reactions and those involving noncomplement-binding IgG using lymphocytotoxicity. The flow cytometry crossmatch uses a fluorescent-labeled anti-IgG reagent, and the binding of the patient's antibodies, not the donor lymphocytes, is measured using a flow cytometer. Both the antiglobulin approach (137) and the flow cytometry technique (51) can be used to identify patients who are at high risk of graft loss, and these techniques are especially effective in cases involving retransplants.

Using the information provided by the degree of mismatch, the PRA information and the crossmatch allow an assessment of the degree of compatibility between patient and donor. In general, an extremely well-matched graft, such as an O-A, B, DR antigen mismatch, can be expected to do well. An antibody specificity against a donor antigen found in a recent serum is of more concern than one from months or years before the transplant, particularly if there is crossmatch activity (115). In terms of crossmatch reactivity, IgG is of more concern than IgM, T cell (class I) more than B cell (class II), and recent serum more than historical (114); reactions involving autoreactive antibodies, which are often IgM, do not appear to be deleterious. Essentially all transplants involve some degree of risk of rejection, but using the histocompatibility results can help avoid recipient–donor combinations at the greatest risk.

MECHANISMS OF IMMUNOLOGIC RESPONSE—ANTIGEN RECOGNITION; CELLULAR AND HUMORAL RESPONSE

Part of "22 - RENAL TRANSPLANTATION "

The purpose of the immune system is to protect the host by identifying and eradicating potentially harmful invaders and foreign substances. The cells and molecules responsible for immunity constitute the immune system, and their collective and coordinated response to the introduction of foreign substances is called the immune response. The immune response can be divided into nonspecific-innate immunity and specific-adaptive immunity. The nonspecific arm includes cells such as neutrophils and macrophages, which can phagocytose pathogens, and inflammatory molecules such as complement, which can directly kill cells. The specific arm of the immune system by contrast is able to selectively identify foreign molecules and respond and adapt to only those foreign cells. Furthermore, the specific arm exhibits memory, such that reexposure prompts a more rapid and vigorous response. It is the specific arm of the immune system that is most important in transplant rejection (296).

Adaptive immunity can be further divided into humoral (antibody) and cellular components. The humoral response derives from B cells that recognize foreign antigens via antibody receptors on the B-cell surface. When activated, the B cell matures into a plasma cell, which secretes a large quantity of its specific antibody. When a pathogen is coated by these specific antibodies, cell death can occur by complement activation or phagocytosis by other cells that recognize and bind to the “tail” of the antibody (opsonization). In organ transplantation, the presence of “preformed” antibodies in the recipient that are specific for the donor organ results in the rapid destruction of the organ (hyperacute rejection). These antibodies bind immediately to the vascular endothelium of the graft and trigger complement-dependent cytotoxicity, eventually leading to complete vascular thrombosis.

The T lymphocyte is the central component of the cellular arm of the immune response (298). T cells recognize protein antigen through their T-cell receptor only after an antigen has been processed into peptide fragments and presented on carrier MHC molecules by antigen-presenting cells (APCs). Intracellular antigens are usually presented to T cells by class I MHC molecules. Extracellular antigens, however, must first be phagocytosed by a specialized APC such as a macrophage or dendritic cell, which presents peptides bound to class II MHC molecules. The result is that the T cell must recognize both MHC and peptide in a particular arrangement for antigen-specific activation to take place (Fig. 22.8). The types of responses are also controlled by the specificity of the MHC antigens on the APCs themselves. Those T cells bearing CD8 that are programmed to

be cytotoxic require APCs to present antigen in context of MHC class I molecules; those T cells bearing CD4 that are programmed to become helper T cells require antigen to be presented in context of MHC class II molecules (178).

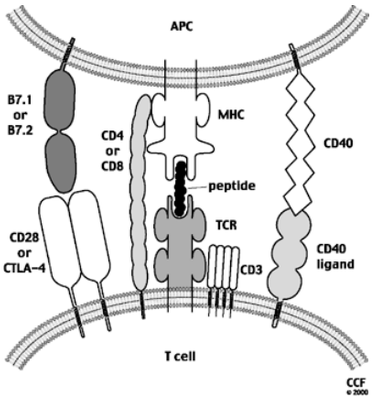


FIGURE 22.8. Presentation of foreign peptide antigen to host T cell. Signal 1 delivered as peptide is processed and presented in MHC groove of APC to T-cell receptor. Signal 2 is delivered by APC costimulatory molecule B7 or CD40 to T-cell ligand CD28 or CD40 L, respectively. T cell CD4 or CD8 molecule stabilizes the interaction.

The overall scheme of allograft rejection can be divided into five stages:

1. Antigen recognition
2. T-cell activation—requires two signals
3. Signal transduction and cytokine release
4. Cellular differentiation and proliferation
5. Target cell destruction

Graft alloantigens provide a unique potential for host T-cell activation because they themselves serve both as immunogens and as components of the activation mechanism. When a kidney is transplanted into a recipient, it brings with it an array of tissue-bound class I and II MHC molecules, as well as antigen-presenting cells. These APCs are included in the group of donor-derived white cells referred to as *passenger leukocytes,* which can be adherent to blood vessels or within the interstitial tissues. The activation of recipient T cells requires two distinct signals. Signal 1 requires the presentation of the peptide–MHC complex on an APC to the T-cell receptor of a resting T cell. Signal 2 is a costimulatory signal that is transmitted by surface glycoproteins on the APC, which interact with their ligand on the T-cell surface. The most important costimulatory signals are the B7 or CD40 molecules on an APC binding to their T-cell surface ligands CD28 (or CTLA-4) or CD40 ligand (CD154), respectively. The triggering of the T-cell receptor by signal 1 alone leads to anergy or nonresponsiveness. An APC that provides both signals 1 and 2 leads to activation of protein kinase C and other signal transduction pathways in the T cell. The resting T cell then progresses through the cell cycle from the "G_0" phase to clonal proliferation.

The immune response is provided two distinct pathways for allorecognition (99). A *direct presentation* pathway is provided by *donor APCs,* which present peptide–MHC complexes to recipient T cells. The foreign MHC molecules presented to the recipient can be a myriad of alloantigens, including the allogenic MHC molecule itself plus the many different peptides derived from endogenous proteins. Direct presentation is thought to be responsible for early acute rejection episodes. The recipient can also engage alloantigens through the *indirect presentation* pathway dependent on *recipient APCs.* Indirect presentation requires the uptake and processing of donor MHC molecules (to form peptide fragments) by recipient APCs, which present peptide–MHC complexes to the recipient T-cell receptor. Peripheral recipient APCs migrate to the graft to pick up soluble donor MHC molecules for processing. The actual site of indirect pathway T-cell activation occurs in recipient lymph nodes and is thus "self" MHC restricted. The indirect route becomes more important with time as donor APCs (required for direct recognition) diminish by senescence. The indirect pathway is thought to be more important for the development of chronic allograft rejection.

Once the recipient immune system is activated, the allograft can be attacked by several mechanisms. Recipient CD8 T cells that recognize foreign MHC class I molecules can directly damage donor cells by drilling holes in their cell membranes with a class of molecules called perforins (133). Some cytokines released by CD4 T cells can damage the allograft directly, such as tumor necrosis factor-α. Natural killer (NK) cells, which are not MHC specific but which are attracted during the immune response by opsonins, can also cause direct cell damage. Antibodies produced by B cells can fix complement, attract platelets, and destroy the organ through vascular rejection.

MODIFICATION OF THE IMMUNE RESPONSE—PREVENTION OF REJECTION

Part of "22 - RENAL TRANSPLANTATION "

Blood Transfusion Effect

For more than 30 years, the effect of blood transfusions in renal transplantation has been investigated and debated. As clinical transplantation has developed, the policies and practices regarding the avoidance or use of blood transfusions has changed dramatically on several occasions. Before 1973, transfusions were avoided in dialysis patients awaiting transplantation because of concern that they would develop deleterious antibodies (sensitization), which would have an adverse impact on success (16). Opelz and colleagues (205) described improved results in a large number of recipients who had received transfusions compared with those who had not been transfused. Subsequently, numerous reports revealed a 10% to 20% improvement in graft survival in transfused patients and a near-uniform policy of all patients receiving at least two to five transfusions before transplantation was adopted. However, over the ensuing years, refinements in HLA typing and crossmatching, as well as the development of new immunosuppressive medications, especially cyclosporine, appeared to diminish the transfusion effect. As Fig. 22.9 indicates, no discernible difference has been seen between transfused and nontransfused recipients of first cadaver transplants since 1988 (286).

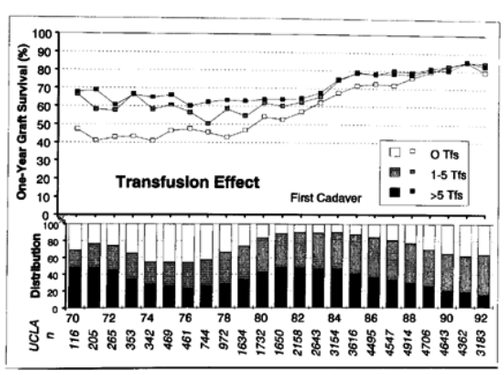


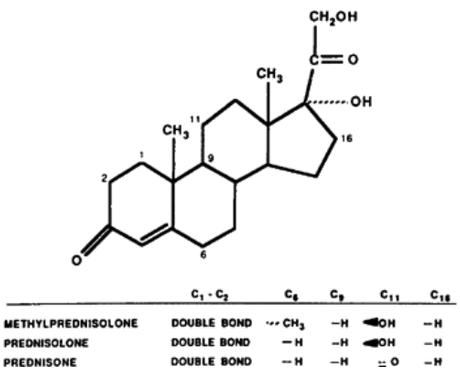
FIGURE 22.9. Effect of blood transfusions in recipients of first cadaver transplants by year, 1970–1992, demonstrating no benefit since 1988. (From Terasaki PI, Yuge J, Cecka DW, et al. Thirty year trends in clinical kidney transplantation. In: Terasaki PI, Cecka JM, eds. *Clinical transplants, 1993.* Los Angeles: UCLA Tissue Typing Laboratory, 1994, with permission.)

Similar results have been reported relative to the use of transfusions in recipients of living-related renal transplants. Salvatierra and colleagues (243) demonstrated that donor-specific (blood from the intended donor) transfusion greatly improved results in recipients of 1-haplotype–matched kidneys. This benefit was substantiated as donor-specific transfusion (DST) protocols became commonplace. Again, however, the transfusion benefits appeared to wane with the introduction of newer immunosuppressive medications (77). The major disadvantages of transfusions include the possible transmission of viral diseases and sensitization of the patient to disparate HLA phenotypes. In addition, the

availability of synthetic erythropoietin (66) has led to a substantial reduction in the number of centers currently using pretransplant transfusions.

Immunosuppressive Agents

As the molecular events in the alloantigen processing pathways have become more apparent, so has the nonspecificity of long-standing immunosuppressive therapy whose toxicities have derived from the broad impact on the body's immune system ("overimmunosuppression"). Although the ideal immunosuppressant that selectively targets only specific steps in allograft rejection while sparing all other immunologic components is not yet available, numerous promising agents are being investigated. The chemical structures of agents in current clinical use, as well as newer ones being studied, are depicted in Fig. 22.10, Fig. 22.11 and Fig. 22.12 . Their proposed mechanism of action, available results, and toxicities are reviewed next; several more comprehensive reports are available (106,279,293,296).



	C_1 - C_2	C_6	C_9	C_{11}	C_{16}
METHYLPREDNISOLONE	DOUBLE BOND	CH_3	—H	OH	—H
PREDNISOLONE	DOUBLE BOND	—H	—H	OH	—H
PREDNISONE	DOUBLE BOND	—H	—H	=O	—H

FIGURE 22.10. Chemical structure of corticosteroids. (From Thomson AW, Woo J, Cooper M. Mode of action of immunosuppressive drugs with particular reference to the molecular basis of macrolide-induced immunosuppression. In: Thomson AW, ed. *The molecular biology of immunosuppression.* New York: Wiley, 1992:161, with permission.)

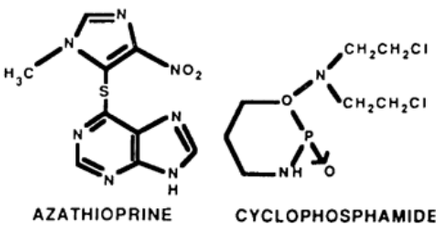


FIGURE 22.11. Chemical structure of azathioprine and cyclophosphamide. (From Thomson AW, Woo J, Cooper M. Mode of action of immunosuppressive drugs with particular reference to the molecular basis of macrolide-induced immunosuppression. In: Thomson AW, ed. *The molecular biology of immunosuppression.* New York: Wiley, 1992:157, with permission.)

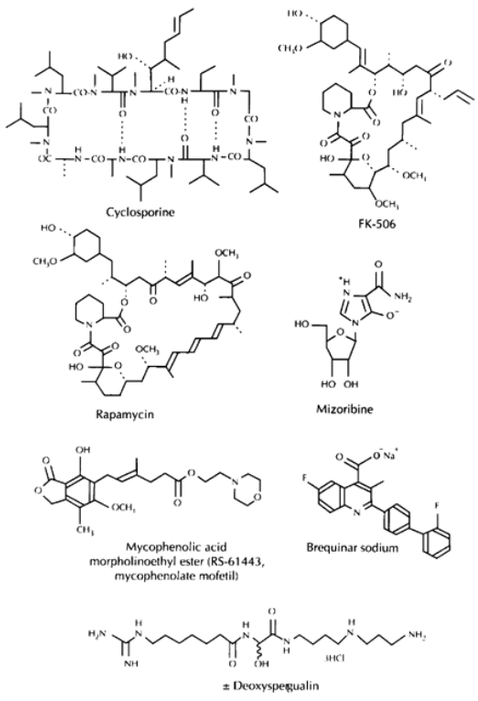


FIGURE 22.12. Names and chemical structures of cyclosporine and newer xenobiotic immunosuppressive agents. (From Lewis RM. Developments and issues in immunosuppressive therapy. *Curr Opin Urol* 1994;4:100, with permission.)

Chemical Immunosuppression

Corticosteroids

Since the initial observations more than 35 years ago that corticosteroids could prevent and treat renal allograft rejection (120), they have become the cornerstone of immunosuppressive therapy. Corticosteroids have numerous effects on the immune system (294), and their effect on T lymphocytes appears greater than that on B lymphocytes. Sequestration of lymphocytes in lymph nodes and the bone marrow results in the often observed lymphopenia. Glucocorticoids become bound to intercellular receptors, and conformational changes in the steroid–receptor complex allow for genetic interference with cytokine production. The primary immunosuppressive affect of corticosteroids is inhibition of production and monocyte release of interleukin (IL)-1with subsequent inhibition of IL-2 and interferon-γ, thus interfering with lymphocyte activation and production of effector cells.

Systemic toxicities of corticosteroids, including cushingoid features, hypercholesterolemia, hyperlipidemia, hyperglycemia, weight gain, aseptic necrosis of bone and osteoporosis, poor wound healing, growth retardation, psychiatric disturbances, and increased susceptibility to infection, are

known to all clinicians and have resulted in intense efforts to reduce steroid dosage. Alternate-day steroid dosing appears beneficial for growth in children (283), but complete steroid withdrawal appears more problematic. There have been several trials attempting to withdraw steroids form stable transplant patients (2,245). The benefits include lower blood pressure, improved lipid profiles, and diminished physical side effects attributed to steroids. However, early graft stability is often followed by acute rejection in about one-third of the patients. If attempted, withdrawal should be entertained in well-matched recipients, 1 year or more after transplant, with no prior episodes of rejection. Living-related recipients who demonstrate *in vitro* hyporesponsiveness to the donor can usually be safely withdrawn (77).

Antiproliferative Drugs

Azathioprine

Initial efforts with immunosuppression in renal transplant recipients occurred using 6-mercaptopurine and its imidazole derivative azathioprine (185). Azathioprine is metabolized *in vivo* to 6-mercaptopurine, and the antimetabolites block DNA synthesis by inhibiting purine synthesis and metabolism via competitive enzyme inhibition. Early proliferation, especially in rapidly dividing cells (lymphoblast), is inhibited, although there is no effect against activated lymphocytes (effector phase). As such, azathioprine is most effective if given immediately after antigen presentation to prevent rejection and is ineffective in treating ongoing rejection.

Adverse effects of azathioprine include myelosuppression with leukopenia and thrombocytopenia, alopecia, hepatotoxicity, cholestatic jaundice, and increased risk of infection and neoplasia. Toxicity from azathioprine will usually respond to dose reduction, although occasionally drug substitution is required. When compared directly with another antiproliferative agent, mycophenolate mofetil, azathioprine is not as potent in rejection prophylaxis. Therefore its use has been diminishing rapidly over the past few years.

Cyclophosphamide

Cyclophosphamide has historically been used in place of azathioprine, although it is much less commonly used today. It is an alkylating agent that is biotransformed by the hepatic microsomal oxidase system to active alkylating metabolites. It inhibits DNA replication and, like azathioprine, affects rapidly dividing cells and is most effective immediately after antigen presentation. Xenotransplants have renewed interest in cyclophosphamide's ability to block B-cell proliferation (268). Cyclophosphamide has a narrower therapeutic-to-toxic ratio than azathioprine, and adverse effects include myelosuppression with leukopenia, fertility disorders, and hemorrhagic cystitis.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF), developed specifically as an immunosuppressant, is a semisynthetic morpholinoethyl ester derivative of the fungal antibiotic mycophenolic acid (5). It is a noncompetitive inhibitor of the enzyme inosine monophosphate dehydrogenase, resulting in the inhibition of purine biosynthesis. MMF has markedly increased oral bioavailability compared with the parent compound mycophenolic acid, and it inhibits the proliferation of activated T and B cells and blocks antibody formation (225). It is thought to be more specific for lymphocytes, which rely primarily on *de novo* purine synthetic pathways. In experimental models, MMF prolongs the survival of skin, kidney, heart, and pancreatic islet allografts, as well as reversing ongoing rejection (183). Its role would seem to be as a substitute for azathioprine due to a decreased incidence of significant myelosuppression or hepatotoxicity. MMF is well tolerated at dosages up to 2,000 to 3,000 mg/day, with dose-related gastrointestinal (GI) disorders being its major toxicity. Initial multicenter trials comparing MMF with azathioprine in addition to cyclosporine and steroid maintenance therapy demonstrated a marked decrease in acute rejection episodes during the first year, from approximately 50% to 35% (107,262). However, patient and graft survival were not statistically different. Nevertheless, the diminished acute rejection rates translate into less clinical morbidity, and this agent has replaced azathioprine in many centers. *In vitro* MMF is a more potent inhibitor to B-cell responses than azathioprine, and it is hoped that this may have a beneficial effect on the development or severity of chronic rejection. Longer follow-up will be needed to confirm this hypothesis.

Antilymphocyte Drugs

Cyclosporine

One of the most significant advances in clinical transplantation was the isolation of cyclosporine from *Tolypocladium inflatum Gams,* a soil fungus, and the demonstration by Borel and colleagues (25) of its immunosuppressive properties, which were lymphocyte specific. Cyclosporine is a cyclic peptide that is soluble only in lipids or organic solvents. Detailed accounts of cyclosporine's proposed mechanisms of action, pharmacokinetics, results, and toxicities have been summarized (129).

Significant insight into mechanism of action was gained with the identification of immunophilins (cytosolic binding proteins). Cyclosporine binds to its specific immunophilin, cyclophilin, resulting in conformational changes and subsequent binding of calcineurin (105). Ultimately, the inhibition of calcineurin prevents the downstream gene transcription of IL-2 and other cytokines required for T-cell activation and proliferation (279). Thus cyclosporine is the prototype of a class of drugs now referred to as calcineurin inhibitors. Cyclosporine's actions are directed primarily toward T helper ($CD4^+$) cells with less effect on other T-lymphocyte subsets, and although the blockade occurs early in the lymphocyte activation pathway, it is slightly later than corticosteroid activity, thus allowing for synergistic therapy.

Initial clinical results with cyclosporine revealed significantly improved 1-year allograft survival in cadaveric recipients compared with conventional therapy with prednisone and azathioprine (37), and this improved 1-year allograft survival has withstood the test of time. Improved results led to enthusiasm to investigate cyclosporine monotherapy without steroids, although problems similar to those discussed previously for steroid withdrawal,

including increased rejection and graft loss, have been experienced (282). Therefore the agent is most commonly administered in combination with steroids and an antiproliferative agent.

Despite the marked improvements seen and broad experience gained with cyclosporine, difficulties with its use continue to be encountered. Diminished bioavailability, especially in the immediate posttransplant period, and variable patient pharmacokinetic profiles have resulted in numerous dosing strategies (129), with both 12- and 24-hour schedules widely used. Cyclosporine is metabolized by the hepatic P-450 cytochrome system, and drugs that inhibit or stimulate this enzyme system can significantly affect cyclosporine blood levels, thus making it imperative for clinicians to be informed of drug changes and their interactions (147). Primarily related to the cost of cyclosporine, drugs with more pronounced inhibition of the P-450 system, including diltiazem and ketoconazole, have been used to increase cyclosporine blood levels, thus reducing the required dosage (89). The introduction of an oral encapsulated cyclosporine has improved patient compliance (56), and a new oral cyclosporine microemulsion appears promising in addressing these concerns. Neoral is a microemulsion formulation that has been demonstrated to have more consistent absorption (increased bioavailability) and diminished pharmacokinetic variability (256).

However, the most distressing component of cyclosporine has been its toxicity, especially acute and chronic nephrotoxicity. Acute cyclosporine nephrotoxicity is mediated by pronounced vascular and, to a lesser degree, tubular alterations (239) and is manifested by oligoanuria and azotemia, clinically indistinguishable from acute rejection, and severe acute tubular necrosis in the immediate post–cadaveric transplant setting (81). Associated hyperkalemia, hyperuricemia, hypertension, hypomagnesemia, and renal tubular acidosis can also occur. A dose-dependent reduction in renal blood flow and glomerular filtration rate occur in acute cyclosporine nephrotoxicity, and although data are somewhat confusing, it appears to be mediated through an imbalance of the prostaglandin-thromboxane system rather than the renin-angiotensin system (48,141). Unfortunately, the findings of cyclosporine-induced decreased levels of vasodilating prostaglandins and elevated levels of the potent vasoconstrictor thromboxane A_2 have not resulted in the identification of specific agents effective in ameliorating cyclosporine nephrotoxicity. A number of prostaglandin analogues have been evaluated, and although some have resulted in improvement in renal function, this has not been universal. A large, multicenter, prospective, randomized, double-blind study failed to demonstrate any difference in cyclosporine toxicity in patients receiving placebo or Enisoprost (1). Similar conflicting results have been reported with the use of thromboxane synthetase inhibitors (239), and further studies will be needed to assess the potential benefit of these agents.

A number of theoretic and observed properties render calcium channel blockers ideal candidates for the treatment of cyclosporine nephrotoxicity. In addition to reducing the dosage requirement, they are effective in treating the associated hypertension. The cyclosporine-induced renal mesangial cell uptake of Ca^{2+} and resultant enhanced contractility and vasoconstriction may well be blocked by calcium antagonists, which also reverse afferent arteriolar vasoconstriction. In addition to reducing cyclosporine nephrotoxicity, verapamil administration has been associated with fewer rejection episodes, possibly related to direct immunosuppressive actions (58).

Chronic nephropathy with progressive renal deterioration was encountered in early experiences with higher doses of cyclosporine. Fortunately, fears related to high rates of graft loss have not been realized, and stable renal function has been demonstrated with long-term cyclosporine use (153). Similarly, higher incidences of lymphoproliferative disorders, including non-Hodgkin's lymphomas, appear related to excessive dosages (212). Other adverse effects of cyclosporine include hepatotoxicity, hyperglycemia, hyperlipidemia, hirsutism, gingival hyperplasia, myalgias, arthralgias, and neurotoxicity (131). Dosage reduction will often mitigate against these effects, although it must be done carefully to avoid increased risk of rejection. Cessation of cyclosporine therapy, like steroid withdrawal, has been accompanied by increased rejection and even late graft loss (244).

Tacrolimus

Tacrolimus is a fungal macrolide antibiotic isolated from *Streptomyces tsukubaensis* with very similar effects on T-cell function as cyclosporine, and it is also classified as a calcineurin inhibitor. Like cyclosporine, it binds to a cytosolic receptor protein (FKBP, a distinctly separate immunophilin class), which leads to the inhibition of a transcription activator, necessary for lymphokine (e.g., IL-2) gene expression. These events result in the inhibition of T-cell activation and proliferation (292). *In vitro,* tacrolimus is 10 to 100 times more potent than cyclosporine on a per weight basis, permitting diminished dosing. In multicenter trials, tacrolimus was found to be comparable in immunosuppressive efficacy to cyclosporine in kidney transplantation (172,222). However, the agent has a similar toxicity profile to cyclosporine. In particular, it may be just as nephrotoxic and requires careful dosage adjustments. Interestingly, histopathologic findings similar to those ascribed to cyclosporine toxicity have been seen in biopsies of tacrolimus-treated patients (231). Tacrolimus may permit a lower maintenance dosage of steroids, but it has been associated with an increased incidence of posttransplant diabetes (125). Trials of tacrolimus to reverse chronic rejection in patients initially given other agents were not successful, although (surprisingly, given the mechanism of action) it has been effective in

“rescuing” ongoing rejection refractory to steroids and antilymphocytic therapy (128).

Rapamycin (Sirolimus)

Rapamycin is a macrolide antibiotic derived from *Streptomyces hygroscopicus* with potent immunosuppressive activity. It has similar molecular structure to the calcineurin inhibitors (Fig. 22.12) and binds to the same cytosolic receptor protein (FKBP) as tacrolimus. However, its mode of action appears to be distinct from the other agents (254). Although it is a potent inhibitor of lymphocyte responses to cytokines such as IL-2, IL-4, and IL-6, it has no direct effect on the synthesis of these lymphokines. The rapamycin–FKBP complex appears to block a distinct p70 kinase called mTOR (molecular target of rapamycin). The inhibition of mTOR blocks IL-2 signal transduction pathways that prevent cell-cycle progression from G_1 to S phase in T cells. In experimental animals, rapamycin prolonged the survival of skin, heart, kidney, pancreas, and small bowel allografts. It also produced synergism with cyclosporine, which suggests an initial approach to its clinical use (although it appears antagonistic with tacrolimus). In initial clinical trials, rapamycin did not cause nephrotoxicity, unlike cyclosporine and tacrolimus. It is not hepatotoxic, nor does it induce hyperglycemia. However, it can induce thrombocytopenia and causes significant hyperlipidemia in approximately 20% of patients (27). Significant increases in cholesterol and triglycerides usually require the use of both dietary control and statin drugs. Rapamycin was first used in combination with cyclosporine and steroids in doses of 2 and 5 mg, and it was compared with cyclosporine, steroids, and azathioprine in the pivotal multicenter trials. With 2 years of follow-up, there was no significant difference in patient or graft survival between the groups. However, the incidence of acute rejection at 6 months was less, 23% versus 43%, in the patients given sirolimus (130). This exciting new agent may offer effective immunosuppression without nephrotoxicity, and it is currently being evaluated in combination with other agents.

Antilymphocyte Antibodies

Polyclonal Antibodies

Polyclonal antibodies directed against human lymphoid cells were initially used in renal transplant recipients more than 30 years ago (269). Antibodies are produced by injecting (immunizing) animals such as horses, goats, sheep, or rabbits with cells from human lymphoid tissue. Immune sera from several animals is usually pooled and the gamma globulin fractions extracted. Desired antibodies are recovered, and unwanted antibodies are removed. Minnesota antilymphoblast globulin (MALG) and antithymocyte globulin (ATGAM, Upjohn Co.), both equine derived, have been most widely used in clinical transplantation, although the former is no longer available. Recently, a rabbit-derived antithymocyte antibody (thymoglobulin, Sangstat) has been introduced.

Once injected, the antibodies bind to lymphocytes, resulting in a rapid lymphopenia. Although the exact mechanism is not known, it is probably related to complement-mediated cell lysis with clearance by the reticuloendothelial system, or the antibody may mask T-cell surface antigens, thus blocking the cell's function. A prolonged immunosuppressive effect may be the result of suppressor cell inhibition of proliferation. Polyclonal antibodies have been used primarily in cadaveric renal transplantation for the prevention and treatment of rejection. In a meta analysis including thousands of patients who received antilymphocyte induction therapy, there appeared to be both short-term advantages and long-term improvements in graft survival (280). In randomized trials, the rabbit product thymoglobulin was shown to be more effective than the equine product ATGAM in reversing acute rejection (88% versus 76%) and for rejection prophylaxis during induction therapy (30).

Because of their strong immunosuppressive effects, polyclonal antibodies are limited to short courses and other immunosuppressive agents are significantly reduced during polyclonal antibody administration. Adverse effects include fever, chills, and arthralgias related to the injection of foreign proteins and possibly the release of cytokines. These effects can be minimized by pretreatment with corticosteroids and antihistamines. There is a significant “batch-to-batch” variability, and pretreatment is required before each administration. More serious adverse effects include increased susceptibility to infections (especially viral), serum sickness, and anaphylaxis.

Monoclonal Antibodies

The introduction of hybridoma technology has opened the door for the development of more highly specific antibodies directed against single elements at the molecular level (144). Mice are generally used for the production of monoclonal antibodies after immunization with human lymphocytes. Antibody-producing B cells are recovered from the spleen and fused with an immortal murine myeloma cell line. The resulting hybrid cells (hybridomas) are isolated and grown in culture. The desired clones are then chosen for the specific antibody production. Numerous monoclonal antibodies are currently being investigated for possible use in transplantation (250). These antibodies, like polyclonal antibodies, exert their effects through a variety of mechanisms. In addition to complement-mediated lysis, blockade and inactivation of cell surface molecules, and opsonization with phagocytosis, these antibodies can induce cytotoxicity and modulation of cell surface molecules on target tissues.

OKT3 (Orthoclone)

OKT3 was the first commercially available monoclonal antibody used in transplantation. It is a murine (mouse) antibody directed against the CD3 antigen complex, a component of the T-cell receptor, which exists on the surface of all T cells. The CD3 molecule plays an important role in signal transduction and subsequent T-cell proliferation and activation. After a standard 5-mg dose, OKT3 inhibits the CD3 complex with resultant lymphocyte inactivation and results in depletion of CD3-positive T cells from the circulation via opsonization. After a few days, lymphocytes reappear but are modulated with the CD3 complex internalized or shed from the cell surface. OKT3, like polyclonal antibodies, has been used to delay the initiation of cyclosporine and for prophylaxis and treatment of rejection episodes (181).

Adverse effects of OKT3 include a first-dose response that simulates a severe flulike syndrome, consisting of fever, chills, nausea, vomiting, diarrhea, myalgias, headache, general malaise, and in severe cases, aseptic meningitis and pulmonary edema. These symptoms are caused by initial activation of resting T cells by OKT3, which is a xenoantibody, and the release of cytokines such as tumor necrosis factor and interferon-γ (43). Many of these symptoms can be diminished by pretreatment with corticosteroids (219). The use of OKT3 for induction therapy has been shown to diminish early acute rejection episodes and improve long-term graft survival (111,193). A recent randomized trial using a low-dose (2.5-mg) regimen for induction, with mycophenolate mofetil and timed doses of corticosteroid pretreatment, demonstrated that a 16% rate of acute rejection and diminished side effects could be achieved (84).

Anti–Interleukin-2 Receptor Antibodies

Another selective site for monoclonal antibody targeting of the immune response is the IL-2 receptor or Tac (CD25), present on the surface of activated immune-competent T cells. Previous studies in animals demonstrated the utility of CD25 blockade for immunosuppression using murine-derived monoclonal antibodies. However, the rapid translation of this model to the clinic has come about due to the development of humanized and chimeric forms of anti–IL-2R antibody through the use of recombinant DNA technology. Both a chimeric anti-CD25 (basiliximab) and a humanized anti-CD25 (daclizumab) bind to different epitopes on the α-chain of the T-cell IL-2 receptor, preventing further signal transduction and T-cell proliferation. The chimeric form is genetically engineered to combine human heavy and light chain constant regions with murine heavy and light chain variable regimens, which contain the antibody binding sequences. The humanized form uses multiple amino acid substitutions of human for mouse sequences to produce a more “humanlike” IgG antibody. The net effect is to produce a hybrid IgG that retains the specific anti-CD25 binding characteristics with a less xenogenic backbone. In clinical trials, each agent was shown to produce excellent antirejection prophylaxis with a diminished side effect profile (309). We have recently compared basiliximab to OKT3 for induction therapy and found comparable rates of acute rejection, 16% versus 12%, *p*= NS, and less cytokine release with basiliximab (82). These newer drugs appear easier to use than previous anti–T cell agents, and they are becoming the preferred agents for induction therapy presuming these results will be durable over several years.

Costimulatory Blockade

As previously mentioned in the section on immune activation, a new and exciting area of investigation is the role of costimulation in immune responsiveness. Blocking the costimulatory signal 2 prevents T-cell activation from occurring. Future clinical trials are anticipated to test the efficacy and safety of this approach. Agents such as the fusion protein CTLA-4 Ig, which blocks the B7–CD28 interaction, and anti-CD154, which interrupts CD40–CD40 ligand interaction, may provide a new avenue for control of allograft rejection.

Additional Agents Under Investigation

15-Deoxyspergualin

15-Deoxyspergualin is an antitumor antibiotic extracted from *Bacillus laterosporus* that has shown immunosuppressive activity in animal models. Its mechanism of action has not been elucidated, although it appears to decrease cytotoxic T-lymphocyte proliferation and inhibit antibody production by preventing lymphocyte maturation. It also may downregulate the expression of class II antigens on immune-competent cells. In experimental animals, 15-deoxyspergualin prolonged survival and reversed rejection in skin, pancreatic islet, heart, liver, and kidney allografts (234). The drug has been used clinically in Japan as part of induction therapy in living related and cadaveric renal transplantation. Although a number of reports appeared promising, in one study the drug was not as potent as steroids in reversing acute rejection, and its precise role is currently under consideration. Side effects were significant, including leukopenia and thrombocytopenia (199).

Mizoribine

Mizoribine is an imidazole antibiotic that has been available for clinical use in Japan. Like azathioprine, it inhibits purine biosynthesis and abrogates both cell-mediated humoral immune responses. Although it may posses less immunosuppressive potency than other agents, it apparently does not cause

significant myelosuppression or hepatotoxicity. In clinical trials of mismatched living related renal transplants, mizoribine was used in combination with cyclosporine and prednisone. When compared with other patients treated with cyclosporine, azathioprine, and prednisone, there was no difference in outcome (301). Data among recipients of cadaveric kidneys are not yet available. GI toxicity was reported to be related to the blood levels of the drug, which must be adjusted in patients with diminished renal function (101). It is recommended that the agent not be given to significantly oligoanuric patients, which may limit its use in cadaveric transplantation.

RECIPIENT SELECTION AND PREPARATION

Part of "22 - RENAL TRANSPLANTATION "

The increasing demand for transplantation is a natural trend that parallels the improved results enjoyed by current recipients compared with previous generations of transplanted patients (42,68). Diminished morbidity, coupled with improved graft survival, have encouraged more and more patients to seek the transplant option. At the same time, improved results have expanded the pool of potential recipients for which transplantation can be safely performed. Absolute criteria that in the past would render a patient too old, too young, too small, too debilitated, too atherosclerotic, or diabetic have been liberalized or even eliminated by most transplant centers. The primary indication for transplantation today is the patient-driven desire to return to preillness levels of activity, well-being, self-image, employment status, and sexual performance. Although a functioning renal allograft is not a cure for renal failure, renal transplantation provides the best opportunity to achieve these goals (45,68,78). However, the proper evaluation of every potential recipient and donor is of critical importance to ensure the best clinical outcome and the best use of a limited resource.

The option of renal transplantation should be entertained by any patient with permanent renal failure, even though not every patient would be medically suitable or desire a surgical form of therapy. In addition, the unique risks and responsibilities required of an individual receiving chronic immunosuppression would not be appropriate for all patients. Nevertheless, a complete discussion of treatment options can be useful to permit patients the opportunity to participate in treatment planning.

The timing of renal transplantation may also have a significant impact on outcome. Some renal physicians advocate a mandatory period of dialysis before transplantation so that patients can “get used to” their diagnosis of ESRD. In some circumstances, this may be psychologically beneficial, especially when renal function has been waxing and waning or when the etiology of renal failure is unknown. Clearly, transplantation should not be performed as an emergency, and patients who first present in florid uremia may require acute dialysis and stabilization. However, for those with slowly progressing renal failure, many highly motivated individuals have requested that the transplant be performed before the need for chronic dialysis (86,179). These patients see elective or preemptive transplantation as less disruptive to their lives, and they can avoid or delay the additional surgery required to create vascular access. Such an approach in carefully screened and selected patients can be done successfully, especially when a living donor is available. Therefore the patient with ESRD has several options to consider in the choice and timing of renal replacement therapy (Fig. 22.13).

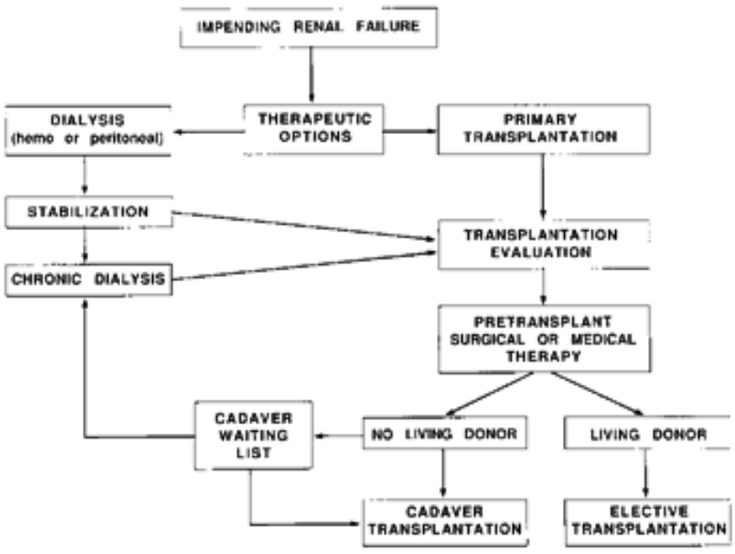


FIGURE 22.13. Patient options with end-stage renal disease.

The ever-increasing worldwide shortage of donor organs necessitates a strategy of donor allocation that provides for the best possible outcome among a given ESRD population. The altruism of donor families, which is the engine that drives organ donation, depends on the doctrine that needy recipients will have equitable access to organs and that recipient selection will be based on sound medical criteria. Therefore the option of renal transplantation should not be entertained when the risks of the surgical procedure and attendant lifelong use of immunosuppressive drugs outweigh the benefits of a functioning kidney. Each individual must be carefully evaluated for any coexisting medical or psychosocial problem that would lead to a poor outcome if left uncorrected (300).

Primary Renal Diseases

The diagnoses listed in Table 22.3 represent the most commonly encountered causes of ESRD. This large spectrum includes both congenital and acquired renal disease, those isolated to the kidney, as well as systemic diseases with renal complications. With few exceptions, patients with any of these primary diagnoses have been successfully transplanted with either a cadaveric or living-related

kidney. According to data among U.S. residents reported to the Health Care Financing Administration at the end of 1991, more than 58% of the individuals receiving dialysis were older than age 50 and 46% were female (302). In addition, nearly 30% of the transplants done that year were in individuals older than age 44 and nearly 40% were female (302).

Glomerular disease	Neurogenic bladder
Membranoproliferative glomerulonephritis	Congenital (meningomyelocele)
Rapidly progressive glomerulonephritis	Acquired
Anti–glomerular basement membrane disease	Hereditary diseases
Membranous nephropathy	Polycystic kidney disease
IgA nephropathy (Berger's)	Medullary cystic disease
Focal segmental glomerulosclerosis	Alport's syndrome
Diabetic nephropathy	Nephrolithiases
Arteriolar nephrosclerosis	Infection stones
Essential hypertension	Hyperoxaluria
Malignant hypertension	Cystinuria
Bilateral renovascular disease	Systemic diseases
Interstitial disease	Lupus erythematosus
Chronic pyelonephritis	Hemolytic uremic syndrome
Analgesic nephropathy	Amyloidosis
Toxic nephropathy	Scleroderma
Congenital disorders	Polyarteritis nodosa
Renal agenesis	Henoch-Schönlein purpura
Renal dysplasia	Infections
Posterior urethral valves	Tuberculosis
Vesicoureteral reflux	Schistosomiasis
Prune-belly syndrome	Surgical nephrectomy
Ureteropelvic junction obstruction	Trauma
	Renal malignancy

TABLE 22.3. MOST COMMON FORMS OF CHRONIC RENAL FAILURE LEADING TO RENAL TRANSPLANTATION

There has also been a shift in the most commonly encountered renal failure diagnoses among those patients eventually receiving a kidney transplant. Although all forms of glomerulonephritis are still the most common etiology (26%), diabetes is now the second most commonly encountered diagnosis (21%), followed by hypertension (14%), cystic disease of the kidney (8%), other causes (8%), urologic disorders (previously obstructive uropathy) (6%), cause unknown (7%), and missing information (9%). It is not unusual for patients to seek medical attention after they are in far advanced stages of chronic renal failure and have small, shrunken kidneys. At such a late stage, it is often impossible to determine the true cause of renal failure with a biopsy, hence the unknown etiology category. Interestingly, more than 11,000 new patients entering dialysis for the first time each year enter into this category.

As might be predicted, patients with primary glomerular diseases may develop recurrent disease in the transplanted kidney. Recurrence rates as high as 50% have been reported on posttransplant biopsies in some patients with anti–glomerular basement membrane (anti-GBM) disease, IgA nephropathy, focal sclerosis, and membranoproliferative glomerulonephritis (11,21,98,171,175). It has been postulated that the continuous use of immunosuppressive drugs after transplant may significantly slow the progression of recurrent disease. This may be true because the actual rate of graft loss from recurrent disease is quite small (218). *De novo* glomerular disease, such as membranous nephropathy, has also been reported (253,272). Although the fear of recurrence should not alter the decision to proceed with transplantation, the timing of the transplant should be considered carefully. Patients with a very rapid and aggressive course to renal failure, such as those with focal segmental sclerosis, rapidly progressive glomerulonephritis, or high titers of anti-GBM antibody, should probably wait 6 to 12 months on dialysis until the disease is quiescent.

Insulin-dependent diabetic patients make up a steadily increasing percentage of the ESRD population (302). Although not a cure for diabetes, patients with uremic diabetes often experience dramatic improvement in exercise tolerance, mobility, and well-being after renal transplantation. Much of this improvement is due to a reversal of uremic neuropathy, which often compounds the peripheral neuropathy of diabetes (200). Diabetic patients with severely compromised vision often experience a similar degree of rehabilitation as sighted patients and should not be excluded from transplantation (102). Unfortunately, progressive vasculopathy continues after transplant, which leads to a higher rate of myocardial infarction, stroke, and amputation than in the nondiabetic transplant population (151). For this reason, it is important to screen diabetic patients for correctable coronary artery, carotid, and peripheral vascular lesions before transplantation. The improving results with simultaneous pancreas–kidney transplantation may provide an additional opportunity for selected patients to slow the progression of diabetic vasculopathy (135,190).

Arteriolar nephrosclerosis, often associated with malignant hypertension, is another common cause of renal failure, especially in young African American males. Although some patients have a dramatic improvement in blood pressure control with the onset of dialysis, others may require nephrectomy to prevent cardiovascular and cerebrovascular accidents. It should be noted that control of blood pressure with medication may significantly improve renal function in previously untreated patients as well (164). Such patients should not be transplanted until irreversible renal failure has been established. The successful transplantation of patients with metabolic, hereditary, and systemic diseases can usually be accomplished. However, patients should be advised that recurrences have been reported. An especially troubling group are those patients with primary oxalosis. Oxalate

deposition and stone formation in the new transplant kidney has been observed frequently, with nonimmune graft loss as a result of recurrent disease (242). For this reason, there has been increasing enthusiasm for the simultaneous transplant of both a liver and a kidney to correct the metabolic abnormality. The transplantation of patients with a previous history of self-destructive behavior leading to renal failure, such as those with analgesic abuse nephropathy, intravenous drug abuse nephropathy, and similar behaviors, must be carefully screened and evaluated. A period of observation with required compliance to the medical regimen and random drug screens may be appropriate in certain situations. It may be helpful to seek the input of various family, community, social service, and religious support services (91,316).

Age

Chronologic age has often been a barrier to transplantation, with arbitrary cutoffs established for upper and lower age ranges in many centers. In the past, the ideal candidate may have been between 15 and 45 years of age, but improved transplant practice and delivery of immunosuppression has permitted the transplantation of small children less than 10 kg in weight and older patients in their sixties and seventies. The physiologic age of the patient is a more significant determinant of outcome (122,162). Older candidates should be aggressively screened for active cardiovascular disease. Posttransplant myocardial infarction, stroke, and peripheral vascular disease remain the most common causes of morbidity and mortality in these patients, whether they are transplanted or remain on dialysis (117). Therefore careful history and physical examination and the liberal use of noninvasive and invasive (angiography) studies, when indicated, best determine suitability for transplantation (62). The older-age patient with atherosclerotic disease should have realistic goals regarding rehabilitation and physical activity. Those patients with severe, noncorrectable atherosclerotic disease and little expectation for physical rehabilitation are probably best served by chronic dialysis, regardless of their chronologic age. On the other hand, patients with identifiable atherosclerotic lesions should have them repaired by surgery or angioplasty before transplant (61).

Small children less than 20 kg in weight have been considered high-risk recipients because of the technical difficulties associated with surgery and dialysis in this group (180). In addition, many small babies with progressive uremia are severely malnourished and have somatic and neurologic growth retardation. Refinements in pediatric anesthesia, intensive care practice, and surgical technique have substantially improved transplant outcome, and size alone should no longer be considered a contraindication (49,174,188). Although some have advocated the transplantation of small infants on an urgent basis, such practice is rarely, if ever, indicated. Small uremic children can be safely stabilized with peritoneal dialysis (72). During this time, they can be nutritionally repleted. The use of small nasogastric tubes for enteral hyperalimentation during continuous peritoneal dialysis has been a major advance. Because many such children have willing parental donors, the once high-risk endeavor of transplanting small children can now proceed in an orderly, elective fashion.

Urologic Evaluation

The purpose of the urinary tract evaluation is to uncover any functional or anatomic abnormalities that would predispose the recipient to posttransplant complications. An initial history should address the onset of renal failure and its presentation, in an attempt to identify such problems as recurrent urinary tract infection, pyelonephritis, stone disease, gross hematuria, and the presence of irritative or obstructive voiding symptoms or incontinence. Routine evaluation should include a urinalysis, urine culture, 24-hour urine collection for volume, creatinine clearance, protein excretion, and a voiding cystourethrogram. Some studies may be limited in patients with oligoanuria, and others may be required only for those with specific complaints. Patients with hematuria, filling defects, incontinence, significant prostatism, or a history of previous lower urinary tract pathology should undergo cystoscopy. Retrograde pyelograms may be required in certain patients. Selected urodynamic studies may be used for those with incontinence or suggestion of a neurogenic bladder. It should be noted that virtually all ESRD patients with a defunctionalized bladder (less than 200 mL per day urine output) demonstrate high voiding pressures, uninhibited contractions, and low flow rates. These findings invariably resolve when normal voided volumes are restored after transplantation. Men older than age 50 should have a prostate-specific antigen (PSA) blood test to screen for occult prostate cancer (41). Posttransplant prostate cancer was detected in 5.8% of men after kidney transplant in a previously unscreened recipient population (163). This suggests that the disease will become more prevalent in men as older-age patients are referred for transplant.

The increase in the number of men older than age 55 who elect the option of transplantation includes many with symptoms of prostatism. Those who produce more than 1 L per day of urine should undergo standard evaluation, and if significantly obstructed, undergo transurethral (electroresection or laser-assisted) prostatectomy. However, patients who produce small urine volumes are difficult to evaluate and have a propensity to develop bladder neck contractures and strictures after a resection (23). Such patients should await definitive management until urine volumes return to normal after transplantation. The role of pharmacotherapy for prostatic obstruction is currently evolving. Patients who develop posttransplant retention can be successfully managed

by intermittent clean catheterization until definitive therapy is instituted. Patients with urethral stricture disease should be treated by direct-vision internal urethrotomy. More complete reconstructions should be completely healed before transplant. If stricture patients produce small urine volumes, daily self-catheterization of the urethra may be required to prevent recurrent stricture disease.

The adequacy of the bladder to both store and empty can usually be elicited by history and voiding cystourethrogram, although an occasional patient may need a more detailed urodynamic assessment. If unresolved, bladder filling, emptying, and continence can be reliably tested before transplant by the placement of a small percutaneous suprapubic tube and graduated saline irrigation (143). Patients with large flaccid bladders (some diabetics) that empty poorly can be managed after transplant using intermittent catheterization if their continence mechanism is intact (76). Most small defunctionalized bladders (even those less than 50 mL) will dilate nicely after transplantation, even when anuria has been present for many years (255). However, a few patients may have contracted noncompliant and fibrosed bladders most often secondary to tuberculosis, radiation, schistosomiasis, or severe interstitial cystitis. The bladders in such patients, as well as those with total incontinence or high-pressure neurogenic bladders, are not suitable for transplantation and will require the use of intestinal segments (191,291).

If the patient has a noncompliant, high-pressure, small-capacity bladder with an intact continence mechanism, bladder augmentation with a segment of large or small bowel can be performed. If no satisfactory urethral continence mechanism remains, an abdominal reservoir with a continent stoma (a Kock pouch or variation thereof) may be considered. For many, the standard ileal loop conduit may be the procedure of choice (110). The implantation of an artificial urinary sphincter for incontinent patients can be safely performed in selected patients (201). Reconstructive bowel surgery should be performed at least 4 to 6 weeks before transplantation to permit complete healing.

PRELIMINARY SURGERY

Part of "22 - RENAL TRANSPLANTATION "

The use of continuous chemical immunosuppression after transplant increases the risk of complications for elective or emergency surgical procedures. For example, wound healing is impaired, sutured anastomoses have a greater tendency to leak, and wound hematomas are more frequently encountered. Otherwise, minor postoperative complications such as pulmonary problems or urinary tract infections may become more difficult to resolve in the immunosuppressed patient. For this reason, it is preferable to perform any necessary elective surgery before transplantation. This includes more common procedures such as hernia repair, hemorrhoids, cosmetic surgery, skin biopsies, extensive dental work, and orthopedic procedures. The following major surgical procedures may also be required to prepare a recipient for transplantation and should be completed and healed before the introduction of continuous immunosuppression.

Nephrectomy

Routine bilateral native nephrectomies are no longer considered a prerequisite for transplantation. The intended indication, removal of the stimulus that triggered immune-mediated renal injury, has been superseded by improved immunosuppression. Another common indication, hypertension, has been made more manageable by the introduction of new classes of antihypertensive agents such as α- and ß-adrenergic blockers, vasodilators, calcium channel blockers, and converting enzyme inhibitors. For dialysis-dependent patients, the retention of native kidneys has distinct advantages. They contribute to red cell production and calcium homeostasis and provide an additional source of fluid and potassium loss. A number of specific indications remain for pretransplant nephrectomy, which is required in approximately 10% to 15% of patients. These indications include recurrent bacterial pyelonephritis, infected renal cysts, active stone passage, high-grade vesicoureteral reflux with residual urine, hypertension refractory to oral agents, renal tumors, and patients with severe proteinuria causing malnutrition and edema. On occasion, patients may have massive polycystic kidneys that cause abdominal symptoms, gross hematuria, or cyst infection, or become so large that they preclude placement of the graft in the iliac fossa, and must be removed. In patients with reflux, tuberculosis, hydronephrosis, or other ureteral pathology, a nephroureterectomy may be required.

Splenectomy

Surgical removal of the spleen for the purpose of augmenting immunosuppression was once thought to be an integral component of pretransplant preparation, especially for those recipients undergoing retransplantation. Earlier reports of improved graft survival were no doubt the result of a greater tolerance for azathioprine in splenectomized patients (90). Leukopenia, which often limited the use of antiproliferative agents such as azathioprine in patients with intact spleens, is now less common in cyclosporine-treated patients. In addition, splenectomized patients are known to have a greater long-term risk of sepsis, which has further diminished the enthusiasm for this procedure (3). The rare patient may benefit from splenectomy if pancytopenia secondary to massive hypersplenism is present. More recently, recipients of ABO-mismatched kidneys have been salvaged by the combination of splenectomy, plasmapheresis, and antilymphocyte preparations (4). The spleen is apparently an essential site for the production of anti-ABO isohemagglutinins.

Parathyroidectomy

Most ESRD patients suffer from secondary hyperparathyroidism, which can be managed with oral phosphorus binders and is readily reversible with a kidney transplant. However, a few develop tertiary hyperparathyroidism often accompanied by peptic ulcer disease, metastatic calcification, pancreatitis, itching, and severe bone mineral reabsorption. Many of these patients have serum calcium levels at the upper limit of normal, but radioimmunoassay parathormone levels are elevated 10 to 100 times. These patients should undergo subtotal parathyroidectomy before transplantation.

GASTROINTESTINAL DISEASE

Part of "22 - RENAL TRANSPLANTATION "

Transplant recipients with active peptic ulcer disease are at high risk for bleeding or perforation in the early posttransplant period when doses of corticosteroids are highest (277). Therefore patients with active disease, recurrent ulcers, and a history of significant bleeding requiring transfusion should have an acid-reducing procedure before transplant. The selective vagotomy has become the preferred procedure. It is prudent to document complete healing by endoscopy before the introduction of immunosuppression.

The mortality rate associated with acute cholecystitis in transplant recipients has been reported to be up to 30%. Therefore patients with active gallbladder disease, as well as those with asymptomatic cholelithiasis, should undergo cholecystectomy before transplant (157). Laparoscopic techniques have revolutionized the management of this disease, permitting a more rapid recovery time (8). The laparoscopic approach has also been used successfully in ESRD patients who are treated with peritoneal dialysis.

The presence of colon diverticula in patients older than age 45 is of concern. Those patients with a well-documented history of diverticulitis should have a prophylactic colectomy (usually on the left side) if they are to be immunosuppressed. The mortality rate of posttransplant colon perforation has been reported to be as high as 50% (46,202). Patients with scattered diverticula and no history of bowel symptoms need to be appraised of the possibility of perforation and its consequences. Although prophylactic colectomy in these patients seems hard to justify, the decision to proceed with transplantation should not be taken lightly. If possible, these patients should have the renal allograft placed on the right side.

GENERAL MEDICAL EVALUATION

Part of "22 - RENAL TRANSPLANTATION "

It is imperative that each potential recipient undergo a complete evaluation before transplantation by the team responsible for the patient's surgery and immunosuppression (Table 22.4). The majority of this evaluation can be done as an outpatient; in a few specific instances, some tests may require hospitalization to complete. The main purpose of this evaluation is to uncover any preexisting medical or psychosocial conditions that could lead to increased posttransplant morbidity or mortality. Any such condition, if identified, should be corrected before transplant surgery and the administration of immunosuppressive therapy. The absolute list of studies performed may vary from center to center based on different practice philosophies and the distribution of various groups of ESRD patients (230). Whatever the circumstance, it is incumbent on all transplant practitioners to ensure that patients are thoroughly prepared and can therefore maximize their opportunity for a successful outcome (121).

General studies	Cultures
History and physical examination	Urine, blood, nasal
Pelvic examination, Pap smear	Selected studies
Stool for occult blood	Pulmonary function tests
Chest radiograph, electrocardiogram	Arterial blood gases
Blood chemistry	Mammogram (age older than 40)
Electrolytes, blood urea nitrogen, creatinine, Ca, PO_4, alkaline phosphatase, parathyroid hormone	Barium enema/colonoscopy (age older than 50)
Bilirubin, ALT/AST, LDH	Upper GI endoscopy
Amylase, uric acid	Cystoscopy
Cholesterol, triglycerides	Urodynamic studies
Hematologic studies	Abdominal computed tomography
Complete blood count and differential	Vascular Doppler studies
Platelets, prothrombin time, partial thromboplastin time	Stress thallium/coronary angiography
Direct Coombs' test	Echocardiogram
Cold agglutinins	Immunologic studies
Serology	Serum immunoglobulins
Cytomegalovirus, Epstein-Barr virus, herpes simplex virus, Venereal Disease Research Laboratory test	Serum complement
Human immunodeficiency virus	T-cell subsets
Hepatitis A, B, C	Panel mix lymphocyte culture (MLC)
Urologic studies	Spontaneous blastogenesis
Urinalysis	Skin testing, purified protein derivative, mumps, *Candida*, histoplasmosis
24-Hour urine for creatinine clearance, protein	Tissue typing
Voiding cystourethrogram	ABO and Rh
Radiologic studies	HLA-A, HLA-B, HLA-DR
Ultrasonography of kidneys, liver	Anti-HLA cytotoxic antibody screen
Radiograph of mandible, sinuses	Donor-specific MLC

GI, gastrointestinal; LDH, lactate dehydrogenase.

TABLE 22.4. PRETRANSPLANT EVALUATION FOR POTENTIAL RECIPIENTS

History

The initial history should address the onset of renal failure and its presentation. Hypertension, proteinuria, edema, fever, or weight gain may have resolved or may remain active. The cause of the disease and any available biopsy material should be reviewed. Associated problems, such as recurrent urinary tract infections, pyelonephritis, stone disease, or gross hematuria, should be explored. If a patient still produces urine, voiding patterns should be ascertained in an effort to diagnose bladder outlet obstruction. Symptoms related to vascular disease should be elicited, specifically looking for coronary or carotid artery disease and peripheral vascular disease. A careful GI history is important to uncover gallbladder, pancreatic, liver, or peptic ulcer disease symptoms. The family history may uncover a pattern of cancer, bleeding disorders, or inherited renal disease. Previous use of immunosuppressive drugs and any complications should be noted. The quantity and time of administration of blood products should be recorded.

Physical Examination

The initial physical examination may reflect patient compliance with dialysis and with medical therapy. Fluid overload and edema may represent intentional noncompliance. The eyes may reveal lipid abnormalities or cataracts, and the fundi can demonstrate the degree of diabetic retinopathy or arterial pathology. The cardiac examination may reveal new murmurs that have an infectious origin. All major blood vessels from the carotids to the dorsal pedis should be palpated. Diminished pulses or bruits should be evaluated further. Sources of occult infection such as otitis, dental abscesses, genital or perirectal abscesses, and the lower extremities of diabetics should be carefully inspected. The presence of lymphadenopathy in the inguinal, cervical, and axillary regions should be identified. A pelvic examination in females should include a Papanicolaou smear if not

previously done, and the rectal examination should screen for occult blood.

Laboratory Tests

Blood chemistry and serology studies are important to uncover any abnormalities or exposure to infectious agents that could complicate the transplant procedure or subsequent immunosuppressive therapy. The goal should be to normalize metabolic balance and nutrition for each potential recipient. All potential recipients should be tested for antibody to the HIV virus using confidentiality procedures and Western blot confirmation as appropriate (136). Prior or current exposure to cytomegalovirus (CMV), Epstein-Barr virus, herpes simplex virus, and hepatitis A, B, or C virus should be ascertained. Patients with positive blood or urine cultures should be treated after the source of the infection is identified. Cultures should be repeated after treatment to ensure complete response. Patients with an autoimmune etiology for kidney failure such as those with systemic lupus erythematosus, anti-GBM disease, or rapidly progressive glomerulonephritis should be screened for low complement levels, high titers of anti-GBM antibody, or circulating immune complexes. If any are present, these patients should wait 6 to 12 months on dialysis before proceeding with transplantation, to diminish the risks of recurrent disease.

Radiographic Studies

In addition to a chest radiograph, the native kidneys should be examined by ultrasound to rule out stones, tumors, acquired cystic disease, hydronephrosis, and so on. Ultrasound of the gallbladder and pancreas is necessary to screen for stones or pancreatic disease. Patients with a history of peptic ulcer disease or current symptoms should have an upper GI series or endoscopy. Patients older than 50 who may harbor diverticula or polyps or those with occult blood in the stool should have a barium enema or colonoscopy. Plain films of the sinuses, mandible, and teeth can uncover small microabscesses.

Selected Studies

Patients with extensive smoking history are instructed to stop before transplantation. Such patients, as well as those with a history of frequent pulmonary infections, should have pulmonary function tests and blood gases. Reversible

bronchospasm should be corrected medically if identified. Coronary artery disease is a significant cause of morbidity and mortality after transplant, especially in older-age patients and diabetics (75,151). Patients older than 50 with any cardiac symptoms should initially be screened with a treadmill or exercise-induced stress thallium scan (7). However, these tests are often inconclusive in diabetics and patients who fail to produce a maximal-effort heart rate (116,168). Therefore, in sedentary patients and diabetic patients, a screening coronary angiogram is strongly recommended (158,165). Potential recipients with critical coronary artery lesions should have them repaired either by angioplasty or bypass surgery before transplantation (166). Doppler studies are useful to screen for carotid and peripheral vascular lesions, especially in symptomatic patients or those with audible bruits.

LIVE DONOR EVALUATION AND PROCUREMENT

Part of "22 - RENAL TRANSPLANTATION "

Donor Evaluation

Healthy, willing, and highly motivated living relatives of the recipient such as siblings, parents, and children make up approximately 20% of the kidneys transplanted. More distant relatives such as aunts, uncles, grandparents, or cousins may also be suitable donors in certain circumstances. A second source of live donor kidneys comes from non–biologically related individuals. A healthy spouse is the most likely representative of this group, but unusually motivated “friends” of the recipient have been used in highly selective circumstances. The use of a living-related donor (LRD) in human renal transplantation has created a unique ethical dilemma for those involved with the daily care of transplant patients. In no other area in medicine is an otherwise healthy individual asked to subject himself or herself to the potential morbidity or mortality of major surgery for no apparent physical benefit. There are two basic reasons why LRD transplants are done, and each presents a variable degree of significance for a given donor recipient pair. First, LRD kidneys work better and last longer (42). This fact has been continuously observed using virtually all combinations of nonspecific chemical immunosuppression during the past 30 years. Second, there is a global shortage of cadaver kidneys (67,266). Therefore LRD transplantation will expedite the process for some recipients and may permit transplantation to be done in some patients who have been unable to secure a crossmatch-negative cadaver kidney while waiting for an extended period. These benefits, solely to the recipient, must be balanced against the potential short- and long-term harm to the donor. If more than one donor is available to a particular recipient, donors are selected based on their degree of histocompatibility, assuming that medical and psychosocial parameters are equal. Table 22.5 lists, in descending order, the degree of tissue similarity among potential donors and suggests the order of preference for a specific recipient.

Monozygotic twins
HLA-identical siblings
Haploidentical siblings, parents, children, relatives
Less than haploidentical siblings, parents, children, relatives
Distant relatives
Unrelated living donors (e.g., spouse)
Cadaveric donors

TABLE 22.5. DONOR SELECTION BY IMMUNOLOGIC SIMILARITY

Despite compelling arguments for the use of living donors, such procedures should not be done if significant morbidity or mortality were to be experienced by the donor. The concept of self-sacrifice and organ donation has been extensively examined by the medical, ethical, and legal professions. Postdonation analyses have consistently found that the donor experience was an overwhelmingly positive one, although sometimes tempered by recipient outcome (126,249). Clearly, renal donation is not an innocuous procedure; all donors experience some degree of anxiety, physical pain, and disruption of their employment schedule, schooling, and home life. In addition, a degree of pressure and coercion can be present among family members that is not readily apparent to health care professionals. For this reason, each donor must be given the opportunity to give his or her independent, informed consent to this decision. We have found that it is very important to counsel the spouse of the potential donor and to permit his or her input into the process as well. It is also helpful to allow the potential donor to determine the pace of the evaluation. Some may truly be undecided and may require more time to evaluate their commitment or desire to opt out of the process. These complex social interactions make it difficult to consider minors younger than age 18 as potential donors in all but the most unusual circumstances.

What then is the potential risk to the renal donor? Although the number of donor deaths worldwide is quite low, they have occurred. It has been reported that the 5-year life expectancy of a unilaterally nephrectomized 35-year-old healthy male donor is 99.1%, as compared with 99.3% for a matched control with two kidneys (177). Another estimate is that the mortality rate for donor nephrectomy is less than 0.1% (150). The long-term risk by actuarial methods has been calculated to equal that of commuting in a car 16 miles each working day. Fortunately, major postoperative complications such as life-threatening cardiopulmonary events or infections are rare, but minor complications such as atelectasis and urinary tract infections are reported to occur in 10% to 20% of cases (314). A flurry of concern has been generated from the findings of Brenner and colleagues (31) that rats who underwent renal ablation were subject to

hyperfiltration in the remnant kidney. This process led to glomerular sclerosis and deterioration of renal function, which was related to protein intake and time. However, several studies of renal donors with more than 20 years of follow-up failed to identify this problem in humans (238,308). Progressive renal deterioration is not observed, and the incidence of hypertension was consistent with that of the population at large. Some uninephrectomized donors did have an increased urinary protein excretion, but the implications of this are presently unknown. In an interesting comparative report, adult kidney donors followed for more than 20 years were compared with their siblings who did not donate for other than medical reasons (187). Both groups had similar renal function at the time of kidney donation. There was no significant difference in serum creatinine, creatinine clearance, blood urine nitrogen, blood pressure, or proteinuria between the kidney donors or their siblings with two kidneys. Proper informed consent and risk appraisal should continue to be the cornerstone of live donor evaluation.

The use of kidneys from living unrelated individuals, primarily a spouse, has increased in recent years. The enthusiasm for using living unrelated donors comes from three general observations. First, the continued increase in the number of waiting potential recipients and a stagnant supply of suitable cadaver organs continues to drive efforts to expand the organ donor pool (152,266). Second, the bond between two individuals, such as husband and wife, is arguably as firm as that between blood relations. The same satisfaction in helping a loved one that is attributed to living-related donation can be conveyed by spousal donation. Third, as the results of transplantation continue to improve, the expectations for success with living unrelated donors has never been better. In fact, 1-year patient and graft survival in excess of 90% has been reported using living unrelated donors (287,318). The elimination of warm ischemic injury and preservation injury to the live donor kidney, similar to that enjoyed with the LRD kidney, improves transplant outcome. One underlying concern and criticism of living unrelated transplantation relates to the possibility of commercialization and coercion of the donor. Precisely these considerations have made the sale and trafficking of human organs and tissues illegal in the United States (public law 98-507) and have been decried by virtually every transplantation organization (39,52). The decision to use living unrelated donors is not a trivial one and should be carefully individualized by any transplant unit considering this approach (317).

The purpose of the donor evaluation is to uncover any preexisting renal disease or predilection for renal disease in the potential donor. In addition, patients are screened for risk factors that would preclude major surgery and general anesthesia. Certain conditions may be identified that will not only lead to exclusion of the donor, but may require medical or surgical therapy for the donor's benefit. Therefore, before evaluation, every potential donor must be informed as to the nature of these studies and how the information will be used. It is important to maintain a strict doctor/patient relationship with donors and to accede to their requests for confidentiality. Table 22.6 lists the most commonly encountered problems that lead to exclusion of a potential donor.

Age younger than 18 and older than 65 years
Hypertension, >140/90 mm Hg, long-standing use of medications
Diabetes, abnormal GTT, HbA_{1c}, islet cell antibody
Proteinuria, >250 mg per 244 hr
Stones
GFR <80 mL/min
Significant renal abnormalities, horseshoe, fused ectopia, etc., resulting in a solitary normal kidney
Obesity >30% ideal body weight
Psychosocial problems

GFR, glomerular filtration rate; GTT, glucose tolerance test.

TABLE 22.6. EXCLUSION CRITERIA FOR LIVING DONORS

History and Physical Examination

Potential donors should be adults (age 18 or older) who are competent to give their own informed consent for renal donation. It is unusual that potential donors older than 65 would be suitable candidates (12). Donors should not have unexplained fevers, urinary tract infections, pyelonephritis, hematuria, or stone disease. Any history of urologic surgery should be documented. In general, donors with hypertension, diabetes, cerebrovascular disease, or systemic illnesses involving the kidneys are excluded. Daily medications, nonprescription drug use, and allergies should be noted. The sexual history of the donor is recorded. Donors should be reassured that donation will not alter present sexual performance (34).

Laboratory Tests

Screening chemistry and hematologic studies should be consistent with a normal physiologic state. Abnormalities such as elevated liver transaminases or prolonged coagulation profiles should be further evaluated. Serologic studies and cultures are necessary to identify present or past exposure to transmissible diseases. Donors with a previously unknown history of exposure to venereal disease should be completely treated before consideration for renal donation. Potential donors who are infected with hepatitis B or C virus or HIV should not donate organs or tissues (64,240). However, some have advocated the use of hepatitis C–positive donor organs in recipients with prior hepatitis C infection. Donors with previous exposure to CMV may

place recipients at increased risk for primary CMV disease, which will require appropriate prophylaxis.

Renal function studies are essential and should be performed in triplicate. Although no absolute criteria have been established, renal donors should have a creatinine clearance in excess of 80 mL per minute. It is not uncommon to find donors with a serum creatinine less than the laboratory-suggested 1.5 mg/dL who have a creatinine clearance under 80 mL per minute. Such donors, often thin, middle-aged women, may require an inulin clearance or radionuclide determination of the glomerular filtration rate for confirmation. The 24-hour urinary protein excretion should be less than 250 mg in adults. Patients with crystalluria on urine analysis require metabolic stone evaluation.

Radiographic Studies

The final piece to the donor evaluation confirms the anatomic integrity of the donor kidneys. An excretory urogram is performed initially to document two functioning renal units of generally normal size, shape, and position. Abnormalities, such as a solitary kidney, severe atrophy or scarring, stones, obstruction, horseshoe kidney, or tumors would exclude renal donation. If the urogram is normal, an angiogram is done to identify the abdominal aorta; determine number, position, and patency of renal vessels; and further delineate the renal parenchyma. This can be done by either standard catheter angiography or the somewhat less invasive digital subtraction techniques (79,265). Spiral computed tomography (CT) imaging is currently under evaluation as a noninvasive method to identify renal vascular and parenchymal anatomy.

DONOR NEPHRECTOMY TECHNIQUE

Part of "22 - RENAL TRANSPLANTATION "

If one kidney has a minor abnormality on radiographic studies, such as a renal scar, a single small simple cyst, or an abnormal calyx, it is considered prudent to remove that renal unit, leaving the donor with the more anatomically normal one. If both renal units are normal, the left kidney is preferred by most transplant surgeons because the left renal vein is longer, making recipient transplantation easier to perform. Multiple renal arteries exist in approximately 20% of potential donors, and removal of the kidney with a single renal artery is preferred. If a kidney with two renal arteries is necessary for transplantation, *ex vivo* bench surgery techniques can be used to facilitate transplantation in the recipient. However, the use of kidneys with more than two renal arteries of substantial size is generally not recommended. Kidneys with duplicated collecting systems have been used successfully for live donor transplantation, if care is taken to remove the ureters in a common sheath with the blood supply protected.

The surgical technique for live donor nephrectomy should in principle use the minimum surgical insult required to remove an anatomically intact and physiologically maintained kidney for transplantation. An extraperitoneal and extrapleural flank incision is suitable in most cases. The nephrectomy can be done in most cases without removing a rib. A Turner-Warwick supracostal twelfth rib incision is preferred (299). A transperitoneal nephrectomy may occasionally be used if multiple renal vessels are involved. However, this incision has been associated with an increased rate of morbidity, such as bowel obstruction and splenic injury.

During the last few years, several centers have begun to remove donor kidneys using laparoscopic methods. The left kidney is usually removed by placement of intraperitoneal ports, and a second counterincision is made for the surgeon to place a hand in the abdomen to remove the intact kidney. Those who perform the procedure state that it causes less pain and provides for a more rapid recovery (87). The kidneys removed by laparoscopy are anatomically and physiologically inferior to those removed by open nephrectomy, but appear to function normally after a short period (85). The procedure requires a dedicated team of skilled laparoscopists so as to avoid technical complications such as ureteral necrosis (192). Randomized comparative trials are lacking to compare the open and the laparoscopic approach, but the procedure is becoming more popular, especially in centers that have invested in laparoscopic equipment.

The goal of donor nephrectomy is to remove the kidney without sustaining any ischemic injury. A well-preserved kidney, when transplanted into the recipient, should function promptly and avoid posttransplant dialysis requirements.

Four things can be done by the transplant surgeon to minimize the ischemic damage to the live donor kidney. First, ischemic injury can be minimized by decreasing the energy-requiring oxidative metabolism of the kidney. Glomerular filtration is passive, driven by cardiac output, but the tubular reabsorption of the kidney requires energy expenditure, primarily by the mitochondria. Flooding the kidney with salt and water diminishes tubular reabsorption. This is done with intensive preoperative hydration of the donor, usually 150 to 200 mL per hour of intravenous fluid, which will result in a urine specific gravity less than 10.010. During the surgical procedure, diuresis can also be maintained with use of a hyperosmolar agent such as mannitol.

Second, renal ischemia can be minimized by avoiding vasospasm of the renal circulation. This is most often caused by traction on the kidney during the surgical dissection. If the kidney becomes soft or dusky in color during dissection, it is best to stop and allow the spasm to break. The application of local vasodilator drugs such as papaverine or lidocaine may be useful. Dissection can commence when the kidney becomes full and pink in color. The same problem can occur if the renal artery is surrounded with a vessel loop that is secured by a weighted metal clamp.

Third, warm ischemic injury to the kidney can be minimized by cooling the kidney after it is removed from the donor. Iced saline or perfusate at 40°C will retard mitochondrial oxidative metabolism.

Fourth, the kidney when removed is subject to cellular swelling due to the paralysis of the oxygen-dependent Na^+-K^+-ATPase pump. By perfusing the *ex vivo* kidney with a hyperosmolar solution that mimics the intracellular ionic concentrations of sodium and potassium, cellular swelling can be minimized.

It is also important during surgical nephrectomy to remove the kidney when it is in an active state of diuresis. Therefore the previously mentioned techniques to avoid spasm should be used when the kidney is removed.

The integrity of the blood supply to the ureter is essential to avoid ureteral necrosis and fistula formation in the recipient. This is done by removing a wide area of periureteral tissue with the specimen. It is generally satisfactory to transect the ureter at the pelvic brim, which will provide adequate length for transplantation.

A small rent in the peritoneum should be oversewn with absorbable suture. After the kidney is removed, the incision should be filled with water or saline and the lungs inflated to check for a rent in the pleura. A small tear can usually be oversewn around a 16-Fr Red Robinson catheter. The wound can then be closed in layers around the catheter. When closure is complete, the lungs should be expanded by the anesthesiologist, and the air in the chest can be evacuated by placing the end of the catheter under a water seal. Air bubbles will cease when the lung is fully expanded. If there is a very large hole in the pleura or the pneumothorax is not diagnosed until the patient is in the recovery room, a chest tube will have to be placed temporarily for expansion of the lung. A Foley catheter, which is placed during the induction of anesthesia, can be removed on the first postoperative day as the patient is encouraged to ambulate. We have found that the use of a patient-controlled analgesic delivery system is useful for some patients to control pain. The use of an epidural catheter for postoperative pain control and the use of intravenous ketorolac for up to 48 hours are also helpful, and decrease narcotic use (which predisposes to ileus). Donors should remain on nothing-by-mouth status for 1 to 2 days to avoid an ileus. They can generally be discharged 2 to 3 days after surgery and can return to full activity in about 3 to 4 weeks.

CADAVER DONOR EVALUATION AND PROCUREMENT

Part of "22 - RENAL TRANSPLANTATION "

Most renal transplant recipients will not have a willing family donor, and therefore they must rely on an organ from a cadaver. A well-functioning cadaveric kidney will provide the same opportunity for rehabilitation from ESRD as a live donor organ. However, a number of complicating factors in cadaveric transplantation arise from the fact that organ availability is both a limited and random event, which makes the surgical procedure nonelective in nature. Cadaver kidneys are preferably transplanted within 24 hours of recovery, but they can produce acceptable results after up to 48 to 60 hours of preservation. During this period, a previously evaluated and waiting recipient is identified and prepared for surgery. This may include dialysis or metabolic adjustments for the recipient, as well as transport of the recipient or the kidney across the country. As mandated by UNOS with some local variance, the kidney is usually placed by using a weighted system encompassing ABO blood type, tissue type, length of wait, and possibly other medical or local criteria (304).

Donor Evaluation and Maintenance

Potential renal donors generally come from individuals who have suffered irreversible head trauma, cerebrovascular accident, or anoxic brain injury (57). They should preferably be between 5 and 60 years of age. There should be no history of systemic diseases that involve the kidneys, such as nephrolithiasis, hypertension (longstanding with drug therapy), diabetes mellitus, or autoimmune disease. Patients with a history of malignant tumors other than localized brain or nonmelanoma skin cancer should not be used as organ donors. There should be no history of transmissible infectious disease or active untreated infection. A history of longstanding use of analgesics may indicate chronic renal injury. It is best not to consider individuals with high-risk behavior for HIV disease such as documented intravenous drug users, active homosexuals, hemophiliacs requiring blood transfusions, or those with known infected sexual partners (64,241). One of the great uncertainties associated with cadaver renal transplantation relates directly to the adequacy of the medical history of the cadaver donor. Many posttransplant recipient problems can be minimized or even avoided by an accurate donor history. This can be a special problem when the mortal injury occurs far from the patient's home. It is always important to obtain a medical history from someone who has had close recent contact with the individual, not merely a relative or friend.

Organs for transplantation cannot be removed until the surviving family gives specific permission for this act and brain death has been declared. The act of donation is therefore completely dependent on the good will and altruism of the public at large. The use of a signed donor card on the back of a driver's license is not sufficient consent and has been of marginal value in increasing the donor supply. Interestingly, one of the greatest impediments to identifying donors and obtaining family consent has been delayed referral or nonreferral to local organ procurement agencies by hospital personnel. It is hoped that increased local and national education policies, as well as “required request”

legislation, will expand the pool of potential donors through greater public awareness (221).

Donor Management

The process of organ procurement can begin only when an individual has been declared brain dead and family consent has been obtained. In most states, the diagnosis of brain death requires strict medical criteria to be met, and a signed declaration must be made by two physicians, neither of whom can be a member of the transplant team. Brain death remains a clinical diagnosis (Table 22.7), but it can be supported by other objective tests (208). To be declared brain dead the patient should be comatose, be unable to breathe without mechanical assistance, and have absent cranial nerve function and reflexes. The absence of perfusion of the brain on an isotopic cerebral blood flow scan is a useful confirmatory test due to its ease of performance and reliability (252). The absence of flow is not compatible with the return of brain function. It is important to make this diagnosis after ruling out hypothermia, drug intoxication, metabolic encephalopathy, and shock as confounding diagnoses.

I. Clinical criteria
a. Unresponsiveness to external stimuli (pain, sound, light, noxious, ice water calorics)
b. Absence of spontaneous breathing
c. No cranial nerve function
d. Above findings present with body temperature >90°F
e. Absence of CNS-depressant drugs
II. Clinical criteria can be supported by
a. Isoelectric electroencephalogram
b. Lack of cerebral perfusion by angiogram or radiographic flow scan
c. Absence of evoked potentials

CNS, central nervous system.

TABLE 22.7. DIAGNOSIS OF BRAIN DEATH

Once declared brain dead, the donor should be kept in a state as close to normal homeostasis as possible. Appropriate ventilatory support is required, and normothermia should be maintained. Maintenance of pulmonary care, nasogastric suction to prevent aspiration, lubrication and protection of the eyes, removal of all intravascular catheters placed without sterile technique, monitoring of vital organ function with a central venous and arterial pressure catheter, and a Foley catheter are usually required. Blood transfusion is not routinely necessary, except in cases of ongoing hemorrhage. Often, donors are volume contracted and dehydrated (the appropriate management for brain injury) and must be resuscitated with fluids. Ringer's lactate is usually sufficient. Deterioration of brain function and loss of central neurohumoral regulatory control may result in severe systemic hypertension (Cushing's reflex) due to elevated circulating catecholamines and sympathetic activity. ß-Blockers can be useful to protect the myocardium when this occurs. In some donors, brain herniation may result in bradycardia, hypotension, and diminished organ perfusion. Adequate systolic blood pressure, usually more than 100 mm Hg, is recommended. The use of vasopressors such as dopamine, which maintains renal blood flow, can be helpful. Urine output in adults should be maintained at more than 1 mL/kg per hour. Frequently, donors may develop massive urine output (more than 500 mL per hour) as a result of central diabetes insipidus, due to low levels of circulating antidiuretic hormone from the destroyed hypothalamic-pituitary axis. The resulting excessive free water loss can lead to hypokalemia, hypernatremia, hypocalcemia, and hypophosphatemia. This condition can be treated with exogenous vasopressin, which can be delivered intranasally.

The serum creatinine in the cadaver donor should be less than 2.0 mg/dL. A rising creatinine may be due to prolonged hypotension, which may cause irreversible renal ischemia. A rising serum creatinine, coupled with a markedly diminished urine output of less than 30 mL per hour before removal of the kidneys, is associated with permanent renal injury. The maintenance of the donor before surgical nephrectomy is one of the most important factors that contribute to immediate graft function after revascularization and the diminished need for posttransplant dialysis (160). Older donor kidneys, older than age 60, are especially susceptible to adverse prerecovery donor function, and every effort should be made to normalize physiologic parameters in these patients.

Donor Procurement Technique

The goals of cadaver kidney removal are to recover two anatomically intact kidneys with good physiologic function. The kidneys are removed en bloc with the midportion of the aorta and vena cava so as to preserve the origins of the renal blood vessels. Currently, most organ donors have an extra renal organ removed at the same time. If multiple organs are to be removed, the preferred sequence is the heart or lungs first, liver or pancreas second, and then the kidneys. It is important to keep the donor hemodynamically stable as long as possible during organ recovery. Most cadaver donors are given a large dose of corticosteroids to deplete circulating donor lymphocytes. Intravenous mannitol in doses of up to 1 g/kg is useful to ensure diuresis and provide some ischemic protection. A large dose of systemic heparin (10,000 to 20,000 units) is given just before organ removal. Some have advocated the use of α-blockers, calcium channel blockers, or dopamine to diminish renal vasospasm secondary to surgical manipulation.

In multiple organ recoveries, the procedure begins with a long incision from the sternum to the pubis. In kidney-only procurement, this may be modified with a xiphoid-to-pubis incision that may be widened with a cruciate extension. The

right colon and duodenum are mobilized, exposing the great vessels. The aortic bifurcation is isolated and a cannula is placed for cooling. A similar cannula is placed near the bifurcation of the vena cava. The suprarenal aorta is mobilized above the celiac trunk, as well as the suprarenal vena cava. If liver or pancreas procurement is to be done, this is more easily accomplished after the abdominal organs are removed. The ureters are divided deep in the pelvis with a generous amount of periureteral tissue intact. Once the superior mesenteric and celiac arteries are ligated, the kidneys can be flushed with ice-cold preservation fluid and circulatory arrest can ensue. Iced slush can be placed around the kidneys for additional surface cooling. At this point, wide excision of the kidneys with Gerota's fascia and the great vessels can be done, with care being given to avoid any dissection in the hilum of the kidney or posterior to the great vessels without direct visualization.

The entire en bloc specimen with aorta vena cava in both kidneys is then removed from the patient and placed in a pan of ice-cold perfusate for further dissection on a back table (Fig. 22.14). A large amount of Gerota's fat and fascia should be removed, confirming the complete flushing of all renal segments. This is rarely a problem if the return perfusate from the vena cava is clear while the organs are *in situ.* The kidneys should always be separated first by dividing the aorta on its posterior surface and then anteriorly, to leave a generous cuff of right or left aortic wall with the renal arterial circulation. This will include multiple renal arteries if present. The left renal vein can be divided flush with the vena cava and the left kidney removed separately. The right renal vein should always be kept intact with the vena cava to permit renal venous extension procedures if required in the recipient.

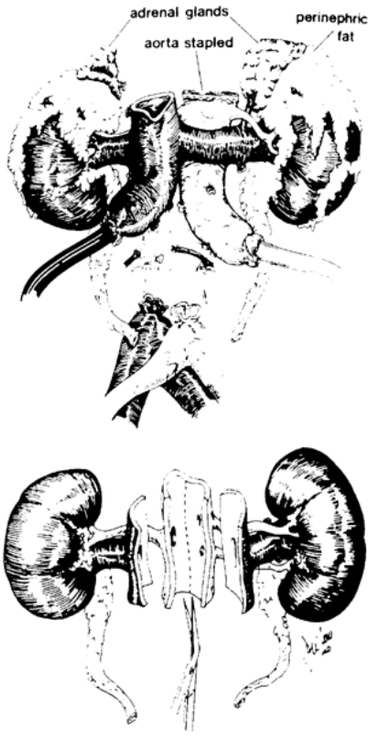


FIGURE 22.14. Technique for cadaver kidney removal. Specimen should include midaorta and vena cava with attached renal vessels. Once removed, the great vessels should be divided on their posterior surface to identify the number and location of the renal vessels. (From Barker CF, et al. Renal transplantation. In: Sabiston DC, ed. *Textbook of surgery.* Philadelphia: Saunders, 1986, with permission.)

Organ Preservation

The clinical practice of a cadaver renal transplantation requires the ability to store and preserve the kidney *ex vivo* for hours or even days. Because the acquisition of a renal donor is random, may occur at any hour, and must permit the transport of the organ over great distances, organ preservation techniques must be relatively simple, mobile, and inexpensive. In most circumstances, the process of tissue typing, crossmatching, and identification and preparation of a recipient takes at least 10 to 12 hours. In larger UNOS regions, and factoring in mandatory sharing of phenotypically identical donor–recipient pairs, this process may take up to 48 hours. In unusual circumstances, up to 60 hours of *ex vivo* time has been required. The goal of organ preservation is to provide an organ that will be protected from ischemic hypoxic damage and will function promptly in the host when revascularized.

Diminished blood flow and oxygen delivery to an organ results in ischemic injury (73). In kidney transplantation, there are two clinicopathologic consequences of ischemic injury. The first, due to a milder degree of ischemia, is acute tubular necrosis (ATN), which is reversible and results in delay of graft function after transplant. Pathologically, ATN results in sloughing and regeneration of the renal tubular epithelium with intact basement membranes. Blood flow is maintained, although glomerular filtration rate is minimal. The kidney may produce a filtrate (nonoliguric ATN) but does not remove waste products. The second form of ischemic injury is more severe and irreversible, termed *cortical necrosis.* Pathologically, necrosis of the entire renal cortex is found. Such kidneys never function (primary nonfunction), have poor blood flow characteristics, and ultimately fibrose. These pathologic findings are similar to the renal injuries suffered by patients who experience massive cardiogenic or hemorrhagic shock.

Kidneys can suffer ischemic injury at several points during organ recovery and preservation (18). *In situ* ischemia can occur in the cadaver donor during the terminal phases of brain death and organ retrieval. Hypotension is the proximate cause. Warm ischemia occurs from the time of circulatory arrest until the kidney is cooled and flushed. A human kidney can tolerate up to 20 to 30 minutes of warm ischemia, although current methods of organ procurement attempt to keep this time to zero. Beyond this time, irreversible injury ensues. Cold ischemic time refers to the period of *ex vivo* cold storage before reestablishment of the renal circulation in the recipient. A variable period of ambiothermic (room temperature) ischemia can occur during the surgical time required for anastomosis of the kidney blood vessels, although this can also be minimized by surface cooling with iced slush.

On a cellular level, ischemic injury renders the tissues hypoxic and retards oxidative, energy-requiring metabolic functions, often found in the mitochondria. One such function is the formation of high-energy phosphonucleotides such as adenosine triphosphate (ATP), required for the plasma membrane–situated Na-K and Ca pumps. Hypoxic cells lose the intermediate purine substrates required for ATP formation through degradation by xanthine oxidase. Loss of these pump functions leads to cellular swelling due to the influx of sodium and water into the cell and efflux of potassium across strong diffusion gradients. In addition, anaerobic glycolysis predominates, which produces lactic acid and hydrogen ions with resultant cellular acidosis. Acidosis is responsible for activation of lysosomal enzymes that lead to mitochondrial and cell membrane lysis. Another destructive process is the formation of superoxide anions during ischemia. These so-called oxygen free radicals can cause tissue injury during reperfusion of the kidney if they have accumulated.

Therefore solutions for organ preservation have been developed that attempt to counteract the metabolic consequences of hypoxia and anaerobic metabolism (Table 22.8). An essential ingredient in organ preservation is hypothermia. Rapid cooling at the onset of organ removal is done with iced saline slush. Perfusion and storage of the kidney at 4° to 10°C will minimize ischemic injury. Hypothermia reduces oxygen demand, slows metabolism, conserves energy in the form of adenine nucleotides, and retards catabolic enzyme activity. In addition, the ideal preservation solution would prevent acidosis, provide substrate for regenerating high-energy phosphate compounds (ATP), prevent reperfusion injury due to oxygen free radicals, and minimize cellular swelling.

Collins Solution	UW Solution
Potassium chloride	Hydroxethyl starch
Potassium phosphate	Lactobionate
Glucose	Potassium phosphate
Sodium bicarbonate	Magnesium sulfate
Magnesium sulfate	Raffinose, glutathione
Osmolality 360 mOsm/L	Allopurinol, adenosine, insulin
	Osmolality 320 mOsm/L

TABLE 22.8. MAJOR COMPONENTS OF KIDNEY PRESERVATION SOLUTIONS

The most commonly used preservation solution for kidneys was first developed by Collins more than 20 years ago. Its essential constituents mimic the intracellular rather than the extracellular fluid compartment with high K and low Na concentrations. It is made hyperosmolar with sugars to diminish the intracellular uptake of water, which causes cellular swelling. Similar preservation solutions have been made using either mannitol or sucrose as the primary osmotic agent. Each can produce adequate cold storage for up to 48 hours.

However, the advent of extrarenal organ transplantation in the 1980s required further refinements. The liver, which can metabolize glucose under preservation conditions more efficiently than the kidney, was not well maintained by the Collins solution. Therefore researchers at the University of Wisconsin (UW) developed a perfusate more suitable for the liver and pancreas, which may also provide better preservation for the kidney (226). The UW solution uses lactobionate in place of glucose as an impermeable anion to prevent cellular swelling. Raffinose and hydroxymethyl starch provide additional osmotic and colloid support for the extracellular space. The absence of glucose diminishes anaerobic glycolysis and subsequent acidosis, and adenosine provides substrate for regenerating ATP during reperfusion. Allopurinol may help reduce the formation of oxygen free radicals. The use of UW solution may extend renal preservation up to 72 hours (264).

Once cooled and perfused through the renal artery, kidneys are generally kept in a container filled with the perfusate on ice. A container with each kidney is then transported to the transplant center. This technique (so-called simple cold storage) is used by the majority of transplant centers worldwide. Some have advocated the use of machine pulsatile perfusion to preserve kidneys, which may provide for lower rates of delayed graft function with extended preservation times. The machine pulsatile perfusion method can allow the determination of perfusion pressures, resistance to flow, pH, and metabolic products, which some have suggested correlate with renal viability. Although it is more cumbersome and expensive, the machine preservation technique may be most helpful for kidneys preserved beyond 48 hours.

RENAL TRANSPLANT OPERATION

Part of "22 - RENAL TRANSPLANTATION "

Renal transplant recipients are particularly susceptible to poor healing and infection because of the complications of uremia and the altered host responses induced by immunosuppressive therapy. These considerations demand meticulous

attention to detail in performing transplantation surgery, with careful handling of tissues and strict adherence to basic operative principles of asepsis and hemostasis.

In most cases, the renal allograft is implanted into one or the other iliac fossa (197). In determining which iliac fossa to use for transplantation, one should consider both the anteroposterior relationships of the renal vessels and the anticipated method of arterial anastomosis. When end-to-side arterial anastomosis to the hypogastric artery seems likely, as in performing single-artery transplantation in young patients, it is customary to place the right kidney in the left iliac fossa, and vice versa. When end-to-end arterial anastomosis to the external or common iliac artery is expected, as in older patients or when using a Carrel aortic patch with multiple donor arteries, the right kidney will lie more comfortably in the right iliac fossa and the left kidney in the left iliac fossa. These are only relative considerations, and with proper positioning of the graft and renal vessels, either kidney may be inserted into either iliac fossa. A relative advantage of using the right iliac fossa is that the right iliac vein has a more horizontal course than the left and is more accessible for the venous anastomosis. This may assume clinical significance when transplanting a kidney with an unusually short renal vein.

In patients with a history of lower extremity thrombophlebitis, silent thrombosis of the iliac veins may have occurred and transplantation should be performed preferentially into the opposite iliac fossa. If ipsilateral transplantation is being considered, preoperative venography should be done to verify iliac venous patency. In patients with a prior failed renal transplant, the second graft is always placed in the unoperated contralateral iliac fossa.

When the recipient is anesthetized, a 20-Fr urethral catheter is inserted in the bladder. A urine specimen is sent for culture, or if the patient is anuric, the bladder is irrigated with saline and this fluid is cultured. The bladder is filled by gravity with 100 to 200 mL of 1% neomycin sulfate solution, and the catheter is clamped and connected to a closed drainage system. Shaving of the operative site is done in the operating room, and the skin is prepared with an iodine solution for 10 minutes. Before commencing the operation, a single intravenous bolus of broad-spectrum antibiotics is given.

A lower-quadrant transverse semilunar skin incision is made, extending from the midline to just above the anterior superior iliac spine (Fig. 22.15). Throughout the operation, care is taken to achieve absolute hemostasis and to minimize blood loss. The external oblique, internal oblique, and transversus abdominis muscles are divided in line with the incision. The inferior epigastric vessels are identified lateral to the rectus muscle and are then secured and divided. The rectus muscle is either retracted medially or, if exposure of the bladder is not adequate, divided at its tendinous insertion into the symphysis pubis. The round ligament in the female is ligated and divided. The spermatic cord in the male is mobilized and retracted medially to obviate postoperative hydrocele formation, which commonly occurs following high cord ligation.

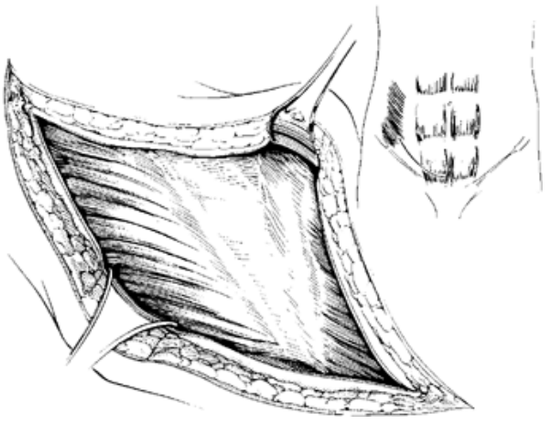


FIGURE 22.15. Lower quadrant transverse semilunar incision is used to perform renal transplantation. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

Extraperitoneal exposure of the iliac fossa is obtained by reflecting the peritoneum superiorly to the common iliac artery and medially to the bladder. A self-retaining ring retractor is then inserted to maintain exposure of the operative field (Fig. 22.16). The lateral blade of the retractor is doubly padded to avoid injury to the lateral femoral cutaneous nerve. The superior retractor blade is positioned to avoid compression of the common iliac artery, which may interfere with allograft perfusion following revascularization.

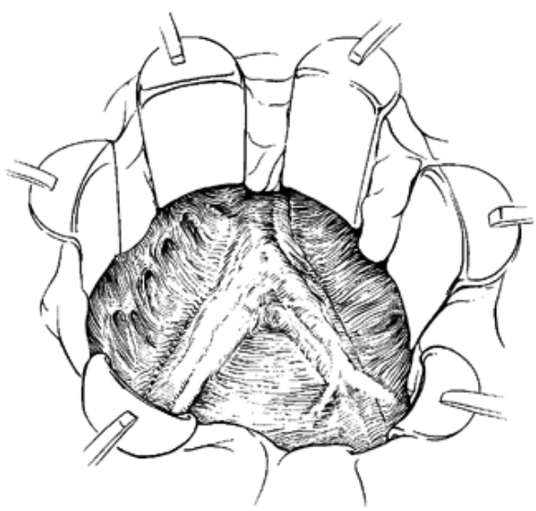


FIGURE 22.16. Extraperitoneal exposure of the iliac fossa is maintained with a self-retaining retractor. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

The external iliac vein is mobilized from the internal iliac origin to the femoral junction. To avoid postoperative lymphatic complications, all overlying lymphatic tissue is ligated and divided. If the donor kidney has a short renal vein, the internal iliac vein is divided to allow elevation of the external iliac vein and thereby facilitate the venous anastomosis. End-to-end anastomosis of the renal artery to the hypogastric artery is preferred, and the latter vessel is then mobilized from its origin to the major anterior and posterior branches. Again, all overlying lymphatic vessels are ligated and divided. In such cases, it is unnecessary to mobilize the common and external iliac arteries (Fig. 22.17).

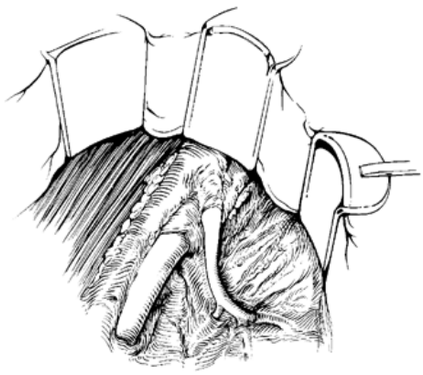


FIGURE 22.17. The external iliac vein and hypogastric artery are mobilized. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

Vascular clamps are placed proximally and distally on the external iliac vein. A venotomy is performed by excising a narrow longitudinal ellipse from the anterolateral aspect of the vein. The hypogastric artery is temporarily occluded proximally, the major branches are ligated distally, and the artery is divided proximal to the ligatures. If mild atherosclerosis of the hypogastric artery is present, endarterectomy is performed to render this vessel suitable for anastomosis to the renal artery. Heparin solution is instilled into the lumen of the hypogastric artery and external iliac vein.

The kidney is then brought into the operative field and the artery and vein are examined. Any residual tissue surrounding the origin of these vessels is removed and, if the renal vein appears short, this is mobilized from the renal sinus to obtain greater length. The kidney is lowered into the incision and end-to-side anastomosis of the renal vein to the external iliac vein is performed with a continuous 5-0 vascular suture. End-to-end anastomosis of the renal artery to the hypogastric artery is performed with interrupted 6-0 sutures after aligning these vessels carefully to avoid angulation or kinking. After the arterial anastomosis is completed, all vascular clamps are removed and circulation to the kidney is restored (Fig. 22.18).

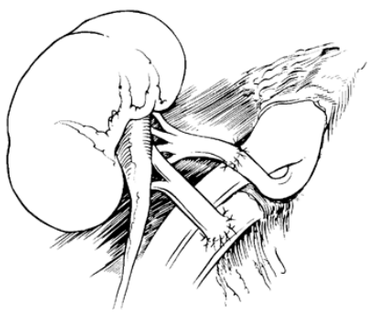


FIGURE 22.18. The renal vein is anastomosed end-to-side to the external iliac vein; the renal artery is anastomosed end-to-end to the hypogastric artery. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

The indications for end-to-side arterial anastomosis to the common or external iliac artery are extensive atherosclerosis of the hypogastric artery, significant discrepancy in size between the renal and hypogastric arteries, or multiple donor renal arteries encompassed by a Carrel aortic patch. In such cases, the external iliac artery and a contiguous segment of the common iliac artery are mobilized. Vascular clamps are placed across the common iliac, hypogastric, and external iliac arteries, and an arteriotomy in the recipient vessel is performed. In general, our preference is to perform end-to-side arterial anastomosis to the common iliac artery because of its larger caliber. This may not be possible when renal arterial length is insufficient or when there is significant atherosclerosis of the common iliac artery. In such cases, arterial anastomosis is to the external iliac artery, which lies in closer proximity to the renal hilus and is less often diseased than the common iliac artery. An interrupted-suture technique with 6-0 sutures is used unless anastomosis of a Carrel aortic patch is performed, in which case a continuous 5-0 suture is used (Fig. 22.19).

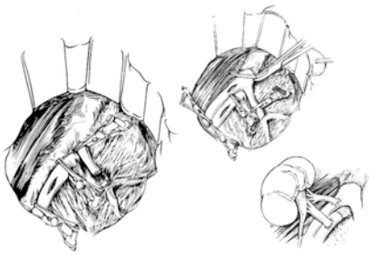


FIGURE 22.19. The renal vein is anastomosed end-to-side to the external iliac vein, and the renal artery is anastomosed end-to-side to the common iliac artery. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

After completion of the vascular anastomosis, urinary tract reconstruction is achieved by ureteroneocystostomy. This method is preferred over ureteroureterostomy or ureteropyelostomy because of a lower incidence of postoperative urinary fistulae. In performing ureteroneocystostomy, one should use the shortest length of ureter that will reach the bladder without tension because the allograft ureter receives its blood supply exclusively from branches of the renal artery. Since 1983, we have preferentially used the extravesical ureteroneocystostomy technique originally described by Lich (Fig. 22.20).

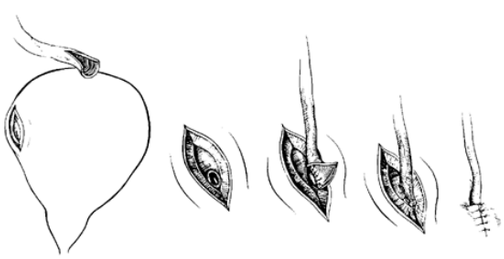


FIGURE 22.20. Extravesical ureteroneocystostomy technique. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

A 3-cm incision is made on the posterolateral aspect of the bladder. The perivesical fat, adventitia, and muscle of the bladder wall are incised to expose the mucosa over the entire length of the incision. The edges of the bladder muscle are undermined by pushing the mucosa away from the muscle. The distal end of the allograft ureter is spatulated for a short distance. A small opening is made in the bladder mucosa at the distal end of the incision, and mucosa-to-mucosa anastomosis is done between the ureter and the bladder, using interrupted or continuous 4-0 chromic sutures. At the distal aspect of the suture line, one or two bites are inserted through the entire bladder wall to anchor the ureter and prevent it from pulling out of the tunnel. The bladder muscle then is reapproximated loosely over the ureter with interrupted 3-0 chromic sutures.

As an alternative to this method, a transvesical ureteroneocystostomy technique may be used. The bladder is opened through an anterior cystotomy and a stab incision is made in the posterolateral bladder wall. The donor ureter is brought through the stab incision, and a 2- to 3-cm submucosal tunnel, directed toward the bladder neck, is fashioned. The ureter is then brought through the tunnel, taking care to avoid torsion on its longitudinal axis. The ureter is spatulated and anastomosed to the bladder with interrupted 4-0 or 5-0 chromic sutures. The sutures fixing the distal aspect of the ureter to the bladder are inserted deeply into the muscularis, while the remaining sutures are placed only through the bladder mucosa. The mucosa overlying the stab incision is closed with a continuous 5-0 chromic suture. The cystostomy incision is closed in three separate layers, with the second and third layers slightly overlapping the immediately underlying layer, to ensure a watertight repair.

The transvesical ureteroneocystostomy technique is preferred for transplantation of kidneys with a double ureter. The two ureters are left in their common adventitial sheath and are brought through the posterior bladder wall and submucosal tunnel together, as with a single ureter. Both ureteral ends are spatulated, the medial ends are sutured together, and the lateral and distal aspects are anastomosed to the bladder as with a single ureter (Fig. 22.21).

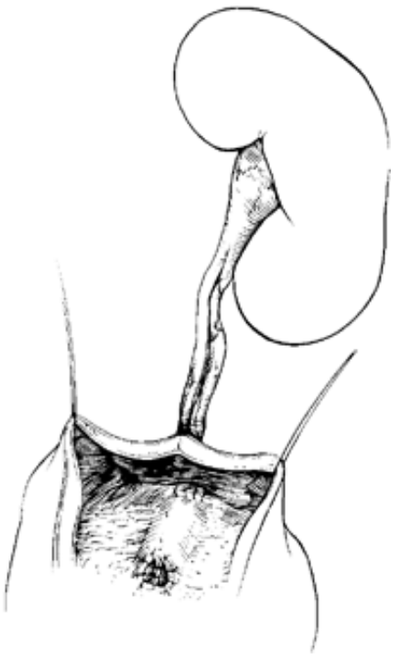


FIGURE 22.21. Transvesical ureteroneocystostomy technique for donor kidney with double ureter. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

After all anastomoses have been completed and adequate hemostasis has been achieved, the wound is irrigated with 2,000 mL of normal saline solution. This is an important local measure both in debriding the wound of small nonviable pieces of tissue and in minimizing the influence of inadvertent intraoperative contamination. The transplant incision is always closed without drainage in two separate musculofascial layers. The subcutaneous layer and the skin are also closed separately, and a pressure dressing is then used to cover the wound.

In the early postoperative period, fluid and electrolyte balance is maintained by monitoring central venous pressure, blood pressure, pulse rate, urinary output, and body weight. When oligoanuria is present despite normovolemia, 12.5 g of mannitol and 40 mg of furosemide are given intravenously. The amount of furosemide may be doubled to a maximum dose of 160 mg. Some cadaver allograft recipients remain oliguric following these measures due to vasomotor nephropathy. This diagnosis can be established only after excluding hyperacute rejection or technical problems by examining the incision for drainage, ensuring a patent urethral catheter, and obtaining an ultrasound study and an isotope renal scan. In contrast, living related allograft recipients often experience a profound postoperative osmotic diuresis, which necessitates vigorous fluid and electrolyte replacement.

Within the first 24 hours postoperatively, a technetium renal scan is routinely done to verify the patency of the transplanted renal artery. If uptake of isotope by the allograft is lacking or questionable, renal arteriography should be performed to evaluate the possibility of arterial thrombosis or hyperacute rejection. The initial surgical dressing is removed 24 hours postoperatively and is changed daily thereafter, using strict sterile technique. Systemic antibiotic therapy is administered only to patients with documented infection. A urethral catheter is left indwelling for 3 to 7 days, and the sutures from the transplant wound are removed 10 days postoperatively.

MULTIPLE RENAL VESSELS

Part of "22 - RENAL TRANSPLANTATION "

Multiple renal arteries occur unilaterally and bilaterally in 23% and 10% of the population, respectively. Important

prerequisites to successful transplantation of kidneys with multiple arteries are proper techniques of organ procurement, thorough arteriographic evaluation of potential living donors, and selection of an appropriate method of arterial revascularization. When such kidneys are transplanted, failure to recognize and preserve an accessory renal artery may eventuate in ureteral necrosis, graft rupture, segmental renal infarction, postoperative hypertension, or calyceal fistula formation. A variety of techniques are available for performing multiple artery renal transplantation (195).

Anastomosis of a Carrel aortic patch encompassing all renal arteries to the recipient common or external iliac artery is the preferred method for arterial anastomosis of cadaver kidneys with multiple arteries (Fig. 22.22). This requires that cadaver donor nephrectomy be performed en bloc with the aorta and vena cava. Use of such an aortic patch is not possible when kidneys are harvested separately, when polar vessels are injured inadvertently during removal, when there is significant atherosclerosis of the perirenal aorta, or when the renal arteries are widely separated on the aorta. Likewise, in live donor renal transplantation, a cuff of aorta should never be taken because of the increased risk to the donor.

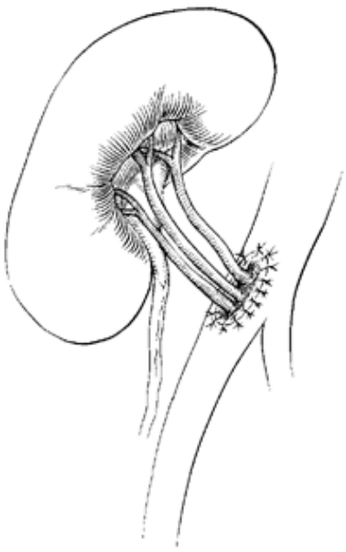


FIGURE 22.22. End-to-side anastomosis of the Carrel aortic patch with multiple renal arteries to the common iliac artery. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

When two adjacent renal arteries of comparable size are present, our preferred method is extracorporeal side-to-side anastomosis of the two vessels to create a common ostium (Fig. 22.23). This is done just before implantation, with the kidney cooled in ice saline solution. Continuous 6-0 or 7-0 vascular sutures are used for the repair, with optimal magnification provided by 3.5× loupes. Revascularization in the recipient involves only a single arterial anastomosis, preferably end-to-end to the hypogastric artery, with no increase in the warm renal ischemia time. This method is technically simple and, hemodynamically, yields less resistance to flow than do separate vascular anastomoses because of the greater cross-sectional area of the coapted vessels.

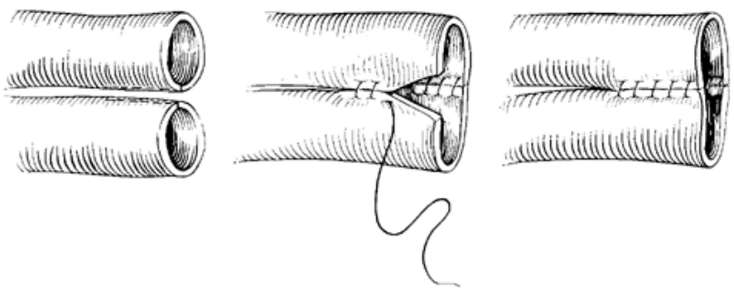


FIGURE 22.23. Side-to-side conjoined anastomosis for two renal arteries of equal caliber. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

When two renal arteries of disparate caliber are present, our preferred technique is end-to-side reimplantation of the smaller artery into the larger one (Fig. 22.24). A short linear arteriotomy is made in the side of the larger artery, without removing any of the vessel wall, to obviate narrowing of the arterial lumen. The smaller artery is spatulated, and end-to-side anastomosis to the larger vessel is done with interrupted 7-0 vascular sutures, using microvascular instruments and 3.5× loupes for magnification. A small catheter or probe may be placed through the suture line during its construction to prevent accidental entrapment of the back wall. The completed anastomosis is tested for patency and integrity by gentle perfusion of the main renal artery. The transplant operation is then done as with a single renal artery. The advantages of this method are that it is technically simple, it involves anastomosis of vessels that are similar in thickness, only one arterial anastomosis is required in the recipient, and warm renal ischemia time is not prolonged. This technique can also be used for transplant kidneys supplied by more than two renal arteries of varying caliber.

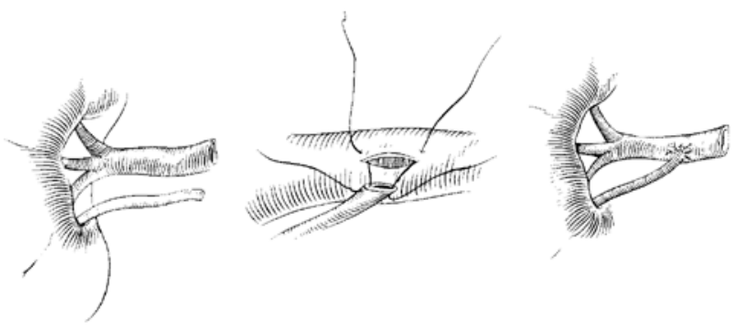


FIGURE 22.24. End-to-side reimplantation of small renal artery into larger one. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

Another method for transplanting kidneys with multiple renal arteries involves fashioning these into a single artery before implantation with a branched graft of autogenous hypogastric artery (Fig. 22.25). If atherosclerosis is present in the hypogastric artery, this can be removed after its procurement using the eversion endarterectomy technique.

Donor arterial repair is done extracorporeally under surface hypothermia with end-to-end anastomosis of the graft branches of the distal renal arteries. The kidney is then transplanted as with a single renal artery, with no added warm ischemia time. This technique is particularly useful to transplant kidneys with more than two renal arteries or when insufficient arterial length is present to permit use of the previous two methods described. Should extensive calcification of the hypogastric artery render it unsuitable as a reconstructive graft, a branched saphenous vein graft can be used alternatively in the same fashion.

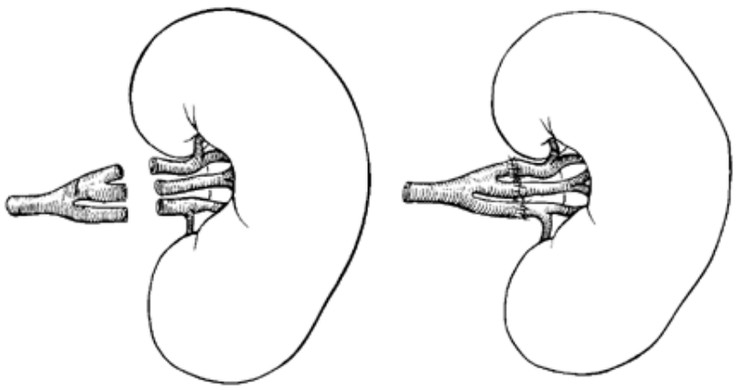


FIGURE 22.25. Use of branched autologous vascular graft to reconstruct multiple renal arteries. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

Additional techniques for performing multiple artery transplantation include arterial anastomoses to the branches of the hypogastric artery, separate arterial anastomoses to the external or common iliac arteries, separate arterial anastomoses to the hypogastric and external iliac arteries, and polar artery anastomosis to the inferior epigastric artery. These techniques all require performance of multiple arterial anastomoses *in situ* that result in a prolonged warm ischemia time. Therefore, when a Carrel aortic patch is not available, we prefer extracorporeal arterial reconstruction using one of the three methods described previously. These latter techniques have proven to be readily applicable, either individually or in combination, to most anatomic variants presented by kidneys with multiple arteries.

Multiple renal veins are less common than multiple arteries and more frequently involve the right kidney. Small renal veins can be ligated without risk. When double renal veins of equal size are present, both of these must be preserved to avoid increased intrarenal venous pressure after revascularization. The optimal method involves implanting these together with a cuff of vena cava obtained at the time of nephrectomy. When this is not available, extracorporeal venous reconstruction is performed as described for multiple arteries with either a conjoined or an end-to-side anastomosis of the two veins.

TRANSPLANTATION IN CHILDREN

Part of "22 - RENAL TRANSPLANTATION "

There are special surgical considerations when renal transplantation is performed in young pediatric patients. In children weighing less than 20 kg, the iliac fossa is too small to accommodate a kidney from an adult donor. In this event, the graft must be inserted in a more cephalad location.

A midline transperitoneal incision is made, and the cecum and ascending colon are reflected medially to expose the aorta, the vena cava, and the common iliac vessels. The graft is placed retrocecally with end-to-side anastomosis of the renal vein either to the vena cava or to the right common

iliac vein. The renal artery is anastomosed end-to-side to either the aorta or the right common iliac artery (Fig. 22.26). Immediately after revascularization of the allograft, 300 mL of albumin is administered as an intravenous bolus to replenish the suddenly depleted intravascular volume and to ensure adequate renal perfusion. The ureter generally reaches the bladder easily, remaining retroperitoneal throughout its course, and a ureteroneocystostomy is performed. An alternative surgical approach for performing transplantation in children involves the use of extraperitoneal incision extending from the tip of the twelfth rib to the symphysis pubis. This method is particularly helpful in children who have been managed with peritoneal dialysis. Very small children, weighing less than 8 kg, require transplantation of a pediatric cadaver graft.

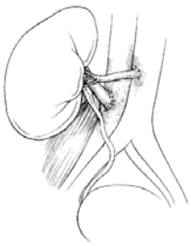


FIGURE 22.26. Technique of retrocecal renal transplantation for placement of adult donor kidney into small child. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

TRANSPLANTATION WITH URINARY DIVERSION

Part of "22 - RENAL TRANSPLANTATION "

In some patients, the bladder may be unsuitable for transplantation due either to severe neurogenic disease or to postinflammatory contracture. In such cases, renal transplantation must be performed in conjunction with supravesical urinary diversion. The most common technique involves the creation of an intestinal (generally ileal) conduit with a lower quadrant stoma at a separate operation before transplantation; 4 to 6 weeks later, the transplant operation is performed (161).

The preferred method for performing transplantation into an ileal conduit is to place the allograft retrocecally, as in pediatric transplantation, with anastomosis of the renal vessels either to the aorta and vena cava or to the common iliac vessels. This allows gravity-dependent urinary drainage and a more direct ureteroenteric anastomosis than when transplantation into the iliac fossa is done (Fig. 22.27).

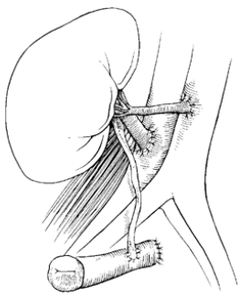


FIGURE 22.27. Technique of renal transplantation into an intestinal conduit. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

In some patients with ESRD, diversion with cutaneous ureterostomy has been performed previously and a well-functioning stoma is present. In such cases, the stoma and a short contiguous segment of distal ureter can be preserved at the time of bilateral nephrectomy. Transplantation is then performed with anastomosis of the allograft ureter to the retained native ureter just below the abdominal wall, thus obviating the need for an intestinal segment (Fig. 22.28). Using this method, satisfactory urinary drainage is achieved through the normal peristaltic ability of the allograft ureter, and the retained dilated ureter functions solely as a short conduit and stoma (161).

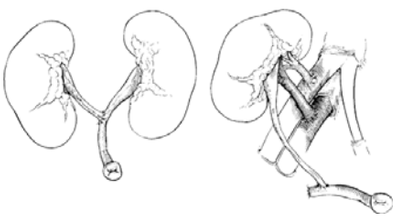


FIGURE 22.28. Technique of renal transplantation using existing cutaneous ureterostomy stoma. (From Novick AC, Streem SB, Pontes JE, et al, eds. *Stewart's operative urology.* Baltimore: Williams & Wilkins, 1989, with permission.)

RENAL ALLOGRAFT REJECTION

Part of "22 - RENAL TRANSPLANTATION "

Preventive Immunosuppressive Protocols

Immunosuppressive protocols using the agents discussed previously can be divided into two phases: induction and maintenance. *Induction* describes initial high-dose immunosuppression designed to prevent a primary immune response during the first 7 to 10 days of engraftment. Numerous factors (e.g., patient selection, organ quality) can influence immunosuppressive decisions, and transplant physician experience and judgment are key determinants of

patient management. Currently, induction therapy involves either polyclonal or monoclonal antilymphocyte agents. As previously mentioned, these agents are often used as sequential therapy with a delay in the institution of a calcineurin inhibitor drug until the kidney has sufficiently recovered from ischemic preservation injury. In general, if preservation times are short, under 12 to 18 hours, calcineurin agents can be introduced earlier without an increased risk of delayed graft function. However, when preservation times are 24 hours or longer, delayed graft function rates of 30% or more can occur, and the duration will be prolonged by the immediate introduction of calcineurin inhibitor drugs. Another consideration in induction therapy is the choice between polyclonal and monoclonal agents. Most studies have found these two classes of agents to be equally effective with respect to rejection prevention and allograft survival. The polyclonal agents are usually administered for 7 to 14 days and require central venous access due to the high protein load and vein sclerosis that occurs. The monoclonal agents can be given peripherally and are more suitable for early hospital discharge. The newer anti–IL-2 receptor blocking agents have longer half-lives and can be given only on days 0 and 4 with prolonged immunosuppression present for several weeks.

Maintenance therapy describes the lowest doses of immunosuppressive drugs necessary to prevent rejection. Unfortunately, this is often arrived at by trial and error and results in much interpatient variability. The principles of drug interactions and synergism that have been developed from multidrug protocols for cancer chemotherapy also apply to rejection prophylaxis. Multiple drugs with different mechanisms of action can be used together to permit lower dosages and less toxicity than would be obtained from higher dosages of single agents. Most centers have arrived at triple-drug maintenance regimens consisting of a calcineurin inhibitor drug (cyclosporine or tacrolimus), an antiproliferative agent (mycophenolate mofetil or azathioprine), and corticosteroids. Rapamycin is being evaluated either in combination with a calcineurin drug or as a replacement.

The following is a description of current immunosuppressive protocols used at The Cleveland Clinic Foundation and a brief review of their rationale.

Live Donor Recipients

HLA-identical siblings receive corticosteroids and cyclosporine. Cyclosporine is begun at 6 to 8 kg per day in divided doses approximately 36 hours before transplantation and subsequently adjusted to maintain trough blood levels at about 200 ng/mL. One gram of intravenous methylprednisolone is given perioperatively, and prednisone is begun at 2 mg/kg per day in divided doses from postoperative day 1. Prednisone is tapered to 30 mg per day by day 8, to 25 mg at 1 month, and lowered by 2.5 mg per month to 7.5 mg per day. Steroids are sometimes tapered off by 1 year.

Mismatched live donor recipients (1-haplotype, 0-haplotype, and live unrelated) recipients are managed with cyclosporine-based triple-drug therapy. Again, cyclosporine is begun 36 hours before transplantation at 6 to 8 mg/kg per day and adjusted by trough blood level monitoring. Steroids are given in doses similar to those described for HLA-ID recipients. Mycophenolate mofetil is begun on day 1 at 1 g twice daily and left at this dose unless specific toxicity necessitates dosage reduction. We have recently

experienced a fall in acute rejection rates to single digits in mismatched live donor recipients with the addition of basiliximab (82). The IL-2 receptor blocking antibody has now been incorporated into our protocol.

Cadaveric Recipients

Our initial concerns of cyclosporine's potentiation of ischemic injury in kidneys with prolonged preservation times were confirmed by a randomized study in which kidneys from a single donor were transplanted separately into one of two groups, the first receiving initial cyclosporine therapy while the second received sequential therapy with a delay in initiation of cyclosporine (194). Patients receiving cyclosporine had an increased incidence of delayed graft function and primary nonfunction, resulting in a diminished overall allograft survival. This was further substantiated in an experimental model in which cyclosporine was administered to rats subjected to varying times of renal ischemia (132). A protocol using sequential, quadruple therapy (MALG plus prednisone, azathioprine, and cyclosporine) was instituted at that time. Subsequent to the availability of OKT3, we initiated a randomized, prospective comparison of OKT3 versus ALG in patients with acute renal failure following cadaveric renal transplantation (270). The results revealed no difference in patient or allograft survival or rejection rates, although there was a slight increase in side effects in the OKT3 group. We subsequently demonstrated that OKT3 side effects could be diminished using lower doses and steroid pretreatment (84).

Currently, cadaveric recipients receive steroids and mycophenolate mofetil in a manner similar to that for live donor recipients. Basiliximab is given at 20 mg on days 0 and 4. The T-cell activation marker CD25 is obtained to confirm efficacy. Cyclosporine is begun after return of adequate renal function (serum creatinine 4.0 mg/dL or lower) at approximately 6 mg/kg per day and adjusted to keep trough levels at 200 to 250 ng/mL the first month. In cases of prolonged ATN, cyclosporine is delayed until day 8 to 10 and advanced more slowly.

DIAGNOSIS OF REJECTION

Part of "22 - RENAL TRANSPLANTATION "

The prompt diagnosis of rejection as the cause of allograft dysfunction is imperative to minimize irreversible damage to the kidney. Depending on the time from transplantation and the preceding level of renal function, the diagnosis can be obscure. The more classic findings of fever; a swollen, painful kidney; and diminished urine output are often absent in patients receiving cyclosporine. Differential diagnoses include ATN, nephrotoxicity, urinary obstruction or fistula, and vascular complications. A renal ultrasound (see Surgical Complications) will assist in assessing the latter causes. The findings resulting in the diagnosis of rejection are those related to renal nuclear scanning and a renal allograft biopsy.

Renal Scan

The value of sequential renal scans in the evaluation of renal transplant recipients has long been established (71). Technetium 99m diethylenetriamine pentacetic acid (^{99m}Tc DTPA) (173) and iodine-labeled orthoiodohippurate (I-OIH) (319) have been the most widely used radiopharmaceuticals. However, we now use technetium 99m mercaptoacetyl-triglycine (^{99m}Tc MAG3) to image renal transplant recipients (38,198). MAG3 is a primarily tubular-excreted compound; it shares equivalent physiologic properties with OIH that, in combination with its availability as a technetium-labeled agent, make it a preferable alternative as the radionuclide pharmaceutical. Images obtained with MAG3 are distinctly superior to those previously seen with DTPA and OIH.

Representative MAG3 scans for various clinical scenarios are depicted in Fig. 22.29, Fig. 22.30, Fig. 22.31, Fig. 22.32, Fig. 22.33, Fig. 22.34, Fig. 22.35 and Fig. 22.36 . Figure 22.29 is that of the allograft of a living-related recipient immediately after transplant and demonstrates excellent perfusion and function. There is prompt uptake of the radiopharmaceutical with early peak accumulation and a rapid excretion and clearance from the allograft. Episodes of renal function deterioration will be demonstrated in the scan, primarily manifested as a delay in uptake with the failure to reach peak accumulation (the allograft continues to accumulate throughout the duration of the study) and diminished excretion and clearance. Figure 22.30 demonstrates an immediate posttransplant cadaveric recipient with acute tubular necrosis. Figure 22.31 reveals significant improvement in the scan 1 week later as the acute tubular necrosis has resolved. Failure of the scan to demonstrate improvement in this setting or a sudden deterioration in the appearance in the scan would implicate other causes of renal failure. Figure 22.32 is a 24-hour posttransplant scan in a living-related recipient with excellent function. One month after transplant, the patient experienced an acute rise in his serum creatinine with associated deterioration of the scan (Fig. 22.33). A percutaneous renal biopsy revealed acute cellular rejection. He underwent antirejection therapy with improvement in renal function (Fig. 22.34). Figure 22.35 is that of an immediate posttransplant living-related recipient; Fig. 22.36 was obtained approximately 4 days later associated with a rise in the patient's serum creatinine. The patient was noted to have elevated cyclosporine levels, and his dosage was reduced with improvement in his renal function.

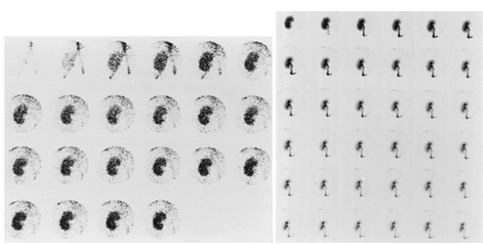


FIGURE 22.29. Renal scan in living related recipient 1 day postoperatively demonstrating excellent perfusion and function with rapid uptake and time to peak accumulation and prompt excretion and clearance.

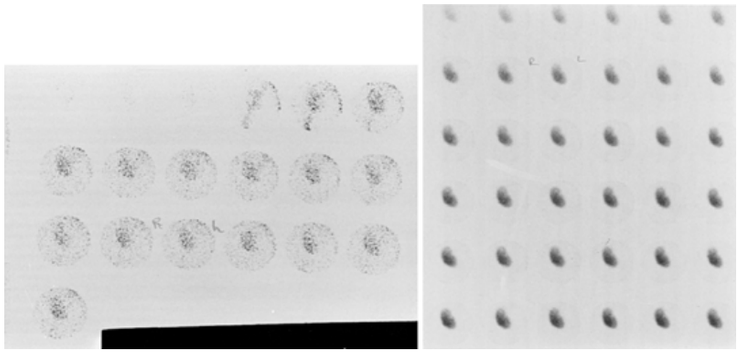


FIGURE 22.30. Baseline renal scan in cadaveric recipient with acute tubular necrosis illustrating a delay in uptake with persistent accumulation throughout the study and diminished excretion and clearance.

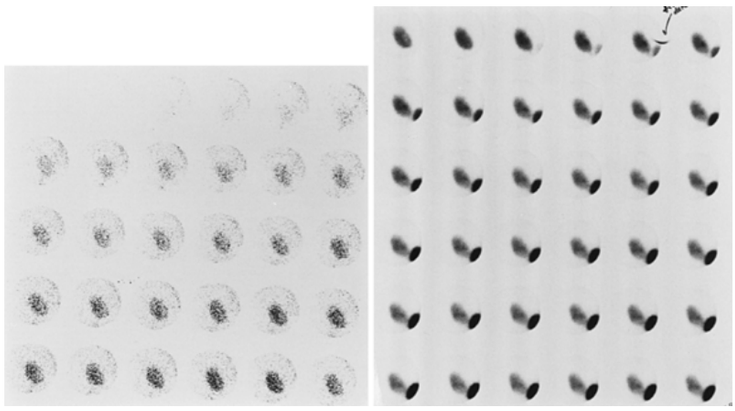


FIGURE 22.31. Renal scan in the same patient as Fig. 22.30, 1 week later, revealing improvement with resolution of acute tubular necrosis.

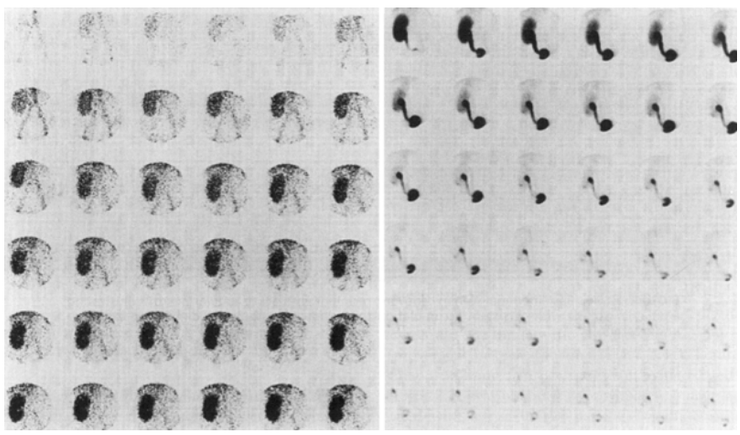


FIGURE 22.32. Baseline scan in living-related recipient with good perfusion and function.

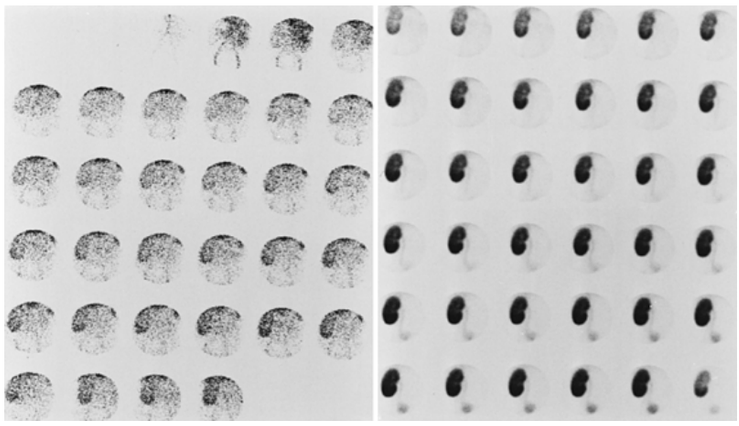


FIGURE 22.33. Scan in same patient as Fig. 22.32, 1 month later, with biopsy-proven rejection illustrating diminished perfusion and function.

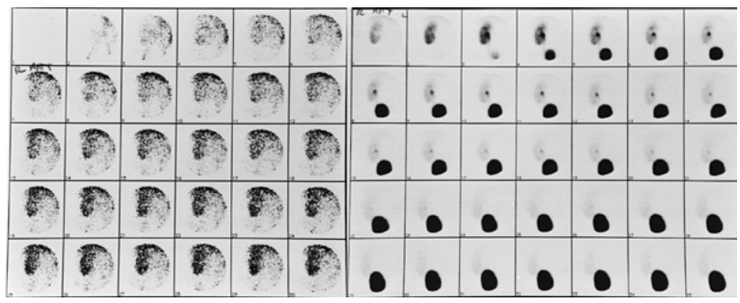


FIGURE 22.34. Scan in same patient as Fig. 22.32 following antirejection therapy with improvement in renal function.

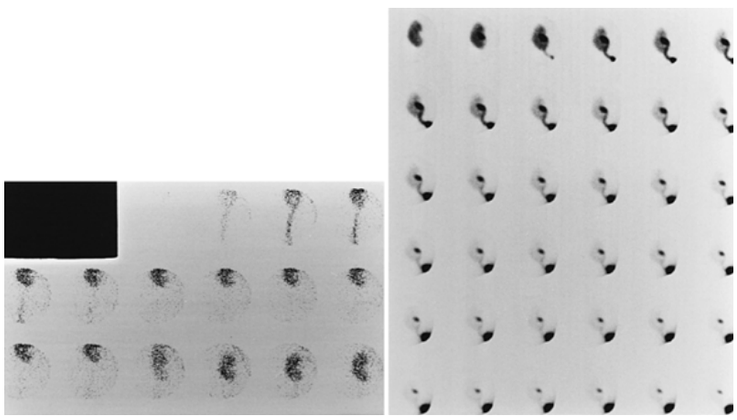


FIGURE 22.35. Baseline scan in living-related recipient, demonstrating good perfusion and function.

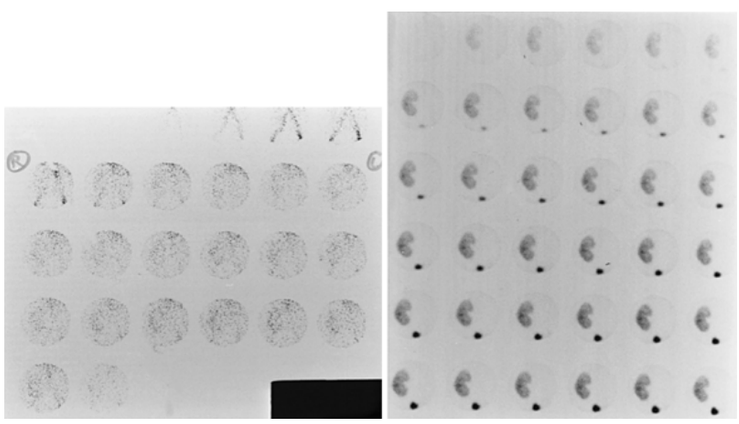


FIGURE 22.36. Scan in same patient as Fig. 22.35, approximately 4 days later, with elevated creatinine and cyclosporine levels.

Percutaneous Renal Allograft Biopsy

Although clinical and radiographic clues can arouse suspicion, the certainty of rejection requires histopathologic examination of allograft tissue. A percutaneous needle

biopsy of the kidney is often easily performed; including in the outpatient clinic, especially under ultrasound guidance. We currently perform approximately 80% of biopsies in this setting. Although the potential for significant complications, including bleeding, exists, a core biopsy can be performed safely with a high likelihood of providing needed information (140). A proposed standardized classification (Banff schema) was developed based on the premise that some findings (including tubulitis and intimal arteritis) are specific for rejection, whereas others (e.g., a cellular infiltrate) are nonspecific (Table 22.9) (261). A more recent update of the schema focused on so-called borderline cases of interstitial inflammation and severe vascular rejection (228).

Biopsy Findings	Banff Classification	Possible Clinical Approach
Normal, minor changes, or infiltrates *without* tubular invasion	Normal or "other" (nonspecific changes)	No treatment, or treat other entity
Mild lymphocytic invasion of tubules (tubulitis)	Borderline changes	No treatment, or treat other entity
Widespread interstitial infiltrate with moderate invasion of tubules	Mild acute rejection (grade I)	Treat for rejection if there are clinical signs
Widespread interstitial infiltrate with severe invasion of tubules and/or mild or moderate intimal arteritis	Moderate acute rejection (grade II)	Treat for rejection, consider ALG or OKT3 if refractory to steroids
Severe intimal arteritis and/or "transmural" arteritis, fibrinoid change, and medical smooth muscle cell necrosis often with patchy infarction and interstitial hemorrhage	Severe acute rejection (grade III)	Treat for rejection unless clinical course suggests rejection cannot be reversed, in which case consider abandoning the graft
Hyaline arteriolar thickening (new onset, not present in implantation biopsy), and/or extensive isometric vacuolization of tubules, smooth muscle degeneration, thrombotic microangiopathy	"Other," cyclosporine toxicity	Reduce cyclosporine therapy
Tubular cell loss and necrosis, regenerative changes	"Other," acute tubular necrosis	Await recovery
Interstitial fibrosis, tubular atrophy (new-onset arterial fibrous intimal thickening suggests chronic rejection)	Chronic transplant nephropathy	Temporize

From Solez K, Axelson RA, Banner B, et al. International standardization of nomenclature and criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. *Kidney Int* 1993;44:411, with permission.

TABLE 22.9. THE BANFF SCHEMA SIMPLIFIED

TREATMENT OF REJECTION

Part of "22 - RENAL TRANSPLANTATION "

Pulse Corticosteroids

As they have been for more than three decades, increased (pulse) doses of corticosteroids are the initial antirejection therapy in most programs. There are few data to support any given dose (0.5 g versus 1 g per day) or a particular route of administration (intravenous versus high-dose oral) (59). Currently, rejection episodes at our center are initially treated with 0.5 g of methylprednisolone (Solu-Medrol) per day for 3 days (271). If the rejection has not been reversed after 3 days of corticosteroid therapy or if more ominous findings are present in the biopsy (e.g., severe vasculitis), more aggressive therapy is initiated with antilymphocyte agents. Corticosteroids are administered before a biopsy is performed, and all patients undergo a biopsy before receiving antilymphocyte preparations to ensure that rejection is the cause of allograft dysfunction, as opposed to other etiologies such as acute tubular necrosis or cyclosporine nephrotoxicity.

Antilymphocyte Preparations

Both polyclonal (MALG) (274) and monoclonal (OKT3) (206) antilymphocyte preparations are extremely effective in reversing rejection when compared with corticosteroids. Although reported as primary therapy by some centers (289), we have generally reserved the use of these agents for steroid-resistant rejection episodes because of the toxicities mentioned previously. Both agents have been extremely effective with reversal rates of 70% to 90% for steroid-resistant rejection (193), although there is a slightly higher rate of re-rejection following treatment. Interestingly, approximately 50% of these rejection episodes occurring after treatment with antilymphocyte preparations for steroid-resistant rejection will respond to a course of steroids. Before re-treating with OKT3, the patient must be checked for the presence of antibodies to OKT3.

Although direct comparative studies are few, results with ALG and OKT3 for steroid-resistant rejection appear to be similar. A prospective, randomized, although small, study found slightly improved results in patients treated with OKT3 for steroid-resistant rejection compared with those receiving ALG (113). MALG is given at dosages of 15 to 20 mg/kg per day for 10 to 14 days, and OKT3 is given at a dosage of 5 mg per day for 7 to 14 days.

Plasmapheresis

Although OKT3 has been shown to be of benefit in some patients with “vascular” rejection (251), there currently exists no universally effective treatment for antibody-mediated rejection. As plasmapheresis had been shown to be successful in treating various immunologically mediated renal diseases (211), attempts were directed at using it for humoral rejection. Initial anecdotal reports indicated that plasmapheresis would be efficacious in treating antibody-mediated rejection; however, more in-depth reviews (59,211) of available data including controlled studies have failed to confirm its role in this setting. More sensitive posttransplant monitoring, such as flow cytometry crossmatches (50), may allow for antibody production detection before organ damage and thus potentially enhance the effectiveness of plasmapheresis. Additional applications of plasmapheresis have included the removal of anti–blood group antibodies in patients undergoing ABO-incompatible transplants (297). Backman and colleagues (14) reported on the use of plasmapheresis to remove anti-HLA antibodies from highly sensitized patients, thus allowing 14 of 17 patients to undergo transplantation who otherwise would have remained on dialysis. However, numerous logistical problems (e.g., waiting time before a cadaver kidney becomes available, necessity for availability of plasmapheresis at any time) have limited this potential application of plasmapheresis.

MEDICAL COMPLICATIONS

Part of "22 - RENAL TRANSPLANTATION "

Medical complications experienced by renal transplant recipients are manifestations of underlying systemic diseases (e.g., diabetes), medication-specific adverse effects, or the result of acquired immunodeficiency. Complications encompass essentially all organ systems, and virtually every recipient will require therapeutic intervention for management of medical diseases. These complications can occur at any time in the posttransplant course (early or late), and thus lifelong surveillance of the transplant recipient is necessary.

Infection

Broad-spectrum antimicrobials and prophylactic protocols aimed at more serious infectious agents (including viral) have diminished but not eradicated the significant morbidity and mortality rates suffered by immunocompromised renal transplant hosts. More than half of renal transplant recipients will experience at least a single episode of infection in the first year after transplant (240), and septicemia is second only to cardiovascular events as the leading cause of death in the posttransplant setting (302). Immunosuppressed patients are at risk not only for the usual bacterial infections experienced by the immunocompetent host, but opportunistic infections as well. Pulmonary infections have been the leading contributor to the morbidity and mortality rates seen in renal transplant recipients, and causative agents include bacterial *(Pseudomonas, Mycobacteria, Listeria monocytogenes, Legionella,* and *Nocardia asteroides),* viral (CMV, herpesvirus), and fungal *(Candida, Pneumocystis carinii, Aspergillus,* and *Cryptococcus)* (240). Significant morbidity is associated with a delay in the accurate diagnosis, which is often not possible based on sputum specimens and may require transtracheal or transbronchial aspiration or biopsy or even percutaneous or open lung biopsy. Improvements in immunosuppressive strategies (especially decreased corticosteroids) have been associated with a reduction in the incidence of and death from pneumonia in renal transplant recipients (182), which are approximately 10% and 2%, respectively, in the cyclosporine era (112). Morbidity from *Pneumocystis carinii* pneumonia, which occurs in 5% to 10% of transplant recipients, has been virtually eliminated with trimethoprim-sulfamethoxazole prophylaxis (169), which also protects against *Nocardia asteroides* and *Listeria monocytogenes.*

Urinary tract infections are by far the most common bacterial infection occurring in the renal transplant recipient, with an incidence of 35% to 79% in the nonprophylaxed patient. Approximately 60% of episodes of Gram-negative sepsis in renal transplant patients originate from the urinary system (240). The morbidity of urinary tract infections is closely linked to the timing from transplantation, with those infections in the first few months more often being associated with pyelonephritis, bacteremia, and frequent relapses, compared with those infections occurring more than 6 months after transplant, which are usually more benign. Risk factors for urinary tract infection include indwelling Foley catheters, lower urinary tract anatomic abnormalities, stones, ureteral stents, and neurogenic bladder. In addition to the described pulmonary benefit, trimethoprim-sulfamethoxazole significantly reduces the incidence of urinary tract infection and resultant bacteremia in this patient population (88). We currently administer one single-strength trimethoprim-sulfamethoxazole tablet daily in the posttransplant period. In patients with an allergy to sulpha drugs, low-dose quinoline (norfloxacin or ciprofloxacin) may be substituted, although this results in a loss of the pulmonary prophylaxis.

Chronic liver disease occurs in 10% to 15% of renal transplant recipients and is the cause of death in 8% to 28% of survivors greater than 10 years after transplant (28). Viral

hepatitis is the major cause of morbidity. Much has been learned with regard to hepatitis B virus (HBV) in this setting, and numerous questions regarding hepatitis C virus (HCV) have emerged as major considerations. The presence of a specific, sensitive, and rapid screening test for hepatitis B surface antigen (HBsAg) has rendered the transmission of hepatitis B by transplantation (with the associated risk of fulminant hepatitis), as well as the transplantation of chronically infected individuals destined to do poorly, relatively uncommon (240). A study of several thousand cadaveric organ donors revealed a prevalence of HCV by antibody testing to be approximately 5% compared with approximately 1% for healthy blood donors (215). The prevalence of virus as detected by polymerase chain reaction (PCR) was 2.4%, suggesting that half of the donors would not have transmitted virus. However, PCR is not currently available as a screening tool. A separate study from the New England Organ Bank identified 29 recipients of organs from 13 HCV antibody donors (216,217). One hundred percent of the recipients had detectable virus by PCR, although only 62% seroconverted. Forty-eight percent of the recipients developed hepatitis, including 12 with chronic liver disease and 1 with subfulminant hepatic failure. The development of chronic liver disease in posttransplant HCV disease appears more indolent than that of HBV. Rao and Andersen (232) reported a higher incidence of chronic progressive hepatitis, chronic active hepatitis, cirrhosis, and death from hepatic failure in patients 10 years after renal transplant with chronic hepatitis B compared to those with non-HBV chronic liver disease, thought to represent HCV. Until the risks are better defined, it appears that a policy of avoiding the use of HCV antibody–positive donors is appropriate, whereas the presence of HCV in a potential recipient does not represent an absolute contraindication to transplantation.

CMV is the most frequently encountered infection in renal transplant recipients, and risk factors include the serologic status of donor and recipient, as well as the immunosuppressive regimen used (240). CMV infection is reported to occur in 20% to 70% of renal transplant recipients. CMV infection occurs via one of three mechanisms. Primary infection results from the transmission of virus form a seropositive donor to a seronegative recipient; reactivation occurs when a seropositive recipient experiences reactivation of latent virus; and superinfection is a result of the transmission of a different strain (serotype) from a seropositive donor to a seropositive recipient. The term *CMV infection* is used to describe the growth of CMV in the blood or urine of the recipient. Symptomatic CMV disease describes viral growth accompanied by clinical symptoms. The most common is a clinical syndrome of fever and leukopenia. However, tissue-invasive disease involving the lungs, liver, GI tract, bone marrow, or central nervous system can occur. Approximately 60% of recipients at risk for primary infection will develop symptomatic CMV disease.

The nucleoside analogues acyclovir and ganciclovir have been used to treat CMV infection. High-dose acyclovir (800 mg four to five times a day) (15) and CMV hyperimmune globulin (260) have been used to diminish the incidence or severity of primary disease. They appear to be somewhat less effective when donors are seropositive or when antilymphocyte preparations, especially OKT3, are used. Intravenous ganciclovir at doses of 5 mg/kg twice a day for 2 to 3 weeks has proven effective in the treatment of CMV infection, as well as for preemptive therapy in patients receiving antilymphocyte preparations (210).

An oral preparation of ganciclovir has been introduced for CMV prophylaxis, although it has significantly decreased bioavailability compared with the intravenous blood levels achieved. We performed a randomized trial of oral ganciclovir versus oral acyclovir for CMV prophylaxis in renal transplant recipients considered at high risk due to induction with OKT3 (83). Only 2% of ganciclovir-treated patients compared with 36% of acyclovir-treated patients developed CMV infection. Most acyclovir failures occurred when donors were seropositive for CMV. We now administer oral ganciclovir for 90 days for all recipients of CMV-seropositive donors.

Malignancy

Renal transplant patients experience an increased susceptibility to malignancy, and the Cincinnati Tumor Registry reports a higher incidence of lymphomas, lip cancer, Kaposi's sarcoma, carcinomas of the kidney, carcinomas of the vulva and perineum, and hepatobiliary tumors as compared with the general population (214). Skin cancers are the most common and occur with similar frequency in both groups, although squamous cell predominates in the transplant patients and basal cell is more common in the general population. Lymphomas account for 20% of all cancers in transplant patients, compared with 5% of all cancers in the general population. Posttransplant lymphoproliferative disorders (PTLDs) represent a serious threat to the transplant patient. PTLDs differ from the lymphomas in the general population in that the overwhelming majority (94%) are non-Hodgkin's lymphomas and arise predominantly (86%) from B lymphocytes. Extranodal involvement is more common in PTLDs (70%); approximately 25% involve the central nervous system and 20% involve the allograft itself. Although initial reports suggested a higher incidence of PTLDs in OKT3-treated patients, it is probably a result of overall overimmunosuppression rather than a single immunosuppressive agent (214) and appears to be related to the induction of B-cell proliferation by Epstein-Barr virus (EBV) infection in the immunosuppressed patient. These relationships were demonstrated dramatically in a small series of patients in which a 12.5% incidence of PTLD was noted in patients receiving MALG induction followed by OKT3 for rejection (47). In the same study, patients at risk for primary EBV infection had a 23.1% of incidence of

PTLD compared with 0.7% for EBV-seropositive patients. Polyclonal B-cell PTLD appears to be more responsive to therapeutic measures including reduction of immunosuppression (189) than monoclonal B-cell PTLD, which appears to have a more malignant course (possibly representing progression in the continuum of the disease). The role of ganciclovir in the treatment of PTLDs is unknown at present.

Hypertension

In the cyclosporine era, 60% to 70% of patients experience hypertension following transplantation, compared with 40% to 50% before the introduction of cyclosporine, with a significant impact on patient and allograft survival (53,74). Not only has cyclosporine altered the prevalence of hypertension in the posttransplant patient, but it has also changed the mechanism and nature, and thus the treatment, of hypertension in this setting (53,74). Although the causes of posttransplant hypertension are numerous, before the introduction of cyclosporine renin-mediated causes appeared to be primarily responsible, often related to native kidney contributions or chronic rejection in the allograft. Currently, direct effects from cyclosporine predominate as the etiology of hypertension in most patients. Discussed previously (see section on cyclosporine), calcium channel blockers have emerged as the antihypertensive treatment of choice in these patients, assuming that corticosteroids and cyclosporine have been reduced to as low a dose as possible without risking rejection. Angiotensin-converting enzyme (ACE) inhibitors should be used with extreme caution because they can induce renal insufficiency, even in the absence of renal artery stenosis, as well as exacerbate existing hyperkalemia. However, the observation that posttransplant patients treated with ACE inhibitors were experiencing unexplained anemia has lead to a therapeutic benefit (310). Approximately 10% to 15% of posttransplant patients experience erythrocytosis, and through mechanisms poorly understood (although possibly related to alterations in erythropoietin production), judicious use of ACE inhibitors has been proven effective in lowering the hematocrit without creating the adverse effects mentioned previously, thus obviating the need for frequent phlebotomies, which had been the mainstay of previous treatment for posttransplant erythrocytosis (92). Provided rejection, recurrent disease, and renal artery stenosis in the allograft have been excluded, patients whose hypertension does not respond to medical therapy should be considered candidates for bilateral native nephrectomies (54).

Hyperlipidemia

Hyperlipidemia occurs in 50% to 80% of renal transplant recipients and, like hypertension, is the result of multifactorial causes, occurs with at least the same if not greater frequency since the introduction of cyclosporine, and serves as a potential risk factor for significant cardiovascular-related patient morbidity and death (119,167). Posttransplant hyperlipidemia appears to be more closely related to corticosteroid dose than cyclosporine dose (307), although unfortunately a reduction or withdrawal of steroids does not ameliorate the hyperlipidemia, and a concomitant reduction in high-density lipoprotein cholesterol with total cholesterol raises considerable doubt with regard to the cardiovascular benefit (119). Dietary management, exercise, and optimization of steroid and cyclosporine dosing constitute primary therapy for posttransplant hyperlipidemia. Persistent hyperlipidemia despite these measures requires drug intervention, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have become the preferred treatment in this setting. Although adverse effects, especially rhabdomyolysis, have been observed with higher doses of HMG-CoA, especially with higher cyclosporine doses, the cautious use of lower doses and proper monitoring of liver function test and creatinine phosphokinase levels appears to be safe and effective (44).

Hyperparathyroidism

Posttransplant hypercalcemic hyperparathyroidism occurs in approximately 30% of patients despite the normalization of urinary phosphate excretion and renal synthesis of calcitriol, defects seen in uremic hyperparathyroidism (127). Patients with a longer duration of dialysis and larger hyperplastic parathyroid glands appear to be at greater risk because glandular involution after transplant is size and time dependent. However, most patients who have spontaneous resolution and parathyroidectomy, necessary in approximately 6% to 10%, should be reserved for patients experiencing significant complications such as marked or symptomatic hypercalcemia and progressive bone disease, especially osteonecrosis (55). Transient hypocalcemia can be seen following parathyroidectomy, although long-term calcium supplementation is usually not required.

SURGICAL COMPLICATIONS

Part of "22 - RENAL TRANSPLANTATION "

Surgical problems following renal transplantation are predominantly related to either vascular or urologic complications. Improvements in surgical technique and meticulous attention to both the donor and recipient operations has led to a significant decrease in the surgical complication rate. Equally important in minimizing the morbidity associated with renal transplantation are anticipation of surgical complications and their prompt treatment when they occur (196). Surgical complications continue to occur in 10% of transplant recipients but, fortunately, are rarely the cause for allograft loss today.

Hemorrhage

Acute postoperative hemorrhage can result from disruption of a vascular suture line. Additional causes include inadequate preparation of the graft bed, an undetected or poorly ligated branch of the hypogastric artery, inappropriately ligated epigastric vessels, an unrecognized vessel in the renal pelvis, abnormal coagulation mechanisms of the recipients, and spontaneous graft rupture. The incidence of postoperative hemorrhage is increased when hemodialysis is required in the immediate postoperative period. The diagnosis of postoperative hemorrhage is usually evident on clinical grounds. The patient complains of excruciating pain around the kidney, in the back and flank. Hypovolemic shock can develop rapidly. Perinephric hematoma formation can cause functional allograft impairment by compression of the renal parenchyma, renal vessels, or ureter. Emergency exploration is usually necessary. If vascular repair or reconstruction cannot be accomplished within a reasonable time, allograft nephrectomy is indicated. Evacuation of the hematoma is important to prevent bacterial infection.

Late hemorrhage, arising months or years after transplantation, is rare but can occur as a result of rupture of a pseudoaneurysm at the anastomotic site. Hemorrhage as a result of percutaneous needle allograft biopsy has also been reported (313). The use of smaller-gauge automated needle biopsy under real-time ultrasound guidance should decrease this complication (65). Rupture of a mycotic aneurysm is another disastrous event that is fortunately rare (145). It is usually the result of a deep wound infection with secondary involvement of the vascular suture line. Transplant nephrectomy with ligation of the iliac artery and drainage of the area is the most expeditious and effective procedure (97). Salvage of the ipsilateral limb is possible with an extraanatomic revascularization procedure such as a femoral-femoral or axillofemoral bypass.

Renal Artery Thrombosis

Arterial thrombosis is a rare (less than 1%) complication that may occur as a result of hyperacute rejection, postoperative hypotension, faulty technical performance of the anastomosis, trauma to the intima of the donor artery during harvesting or perfusion, severe atherosclerosis in the recipient vessels, or wide disparity in the calibers of the donor and recipient vessels. Cyclosporine toxicity has been implicated in some cases of renal artery thrombosis on the basis of a hypocoagulable state (237). If the transplant recipient is anuric postoperatively and there is no uptake of isotope with a technetium renal scan, renal arteriography should be performed immediately. In most cases, the kidney is beyond salvage by the time the diagnosis is made, and transplant nephrectomy is the treatment of choice.

Renal Vein Thrombosis

Renal vein thrombosis is a rare (less than 1%) complication. It may result from a technical error in performing the venous anastomosis, ipsilateral femoroiliac thrombosis, external compression of the iliac or renal vein by perinephric fluid collection, or compression of the left common iliac vein between the right common iliac or aorta and the sacral promontory (silent iliac compression syndrome) (263). Additional causes in pediatric recipients include extrinsic compression in the iliac fossa (26) and kidneys from young donors less than 5 years old (109). An increased incidence of venous thromboembolism has also been noted in the cyclosporine era (306).

Venous thrombosis should be suspected when a transplant recipient has oliguria, graft enlargement, heavy proteinuria, and ipsilateral lower extremity edema. Renal flow scan shows delayed uptake with little or no excretion of the isotope. Renal venography is diagnostic and is useful in delineating the extent of the thrombus. Graft survival with renal vein thrombosis occurring within 1 month of transplantation has been poor. Early diagnosis and prompt thrombectomy occasionally have resulted in graft salvage, but more commonly, prolonged venous stasis will lead to a nonviable graft when surgical exploration is undertaken and nephrectomy is then performed. Renal vein thrombosis occurring more than 1 month after transplantation is best treated with systemic anticoagulation because, by that time, established collateral venous channels are adequate to prevent graft loss.

Renal Artery Stenosis

Hypertension following renal allotransplantation is common and may be secondary to rejection, ischemic allograft damage, retained native kidneys, steroid therapy, cyclosporine therapy, recurrence of primary renal disease in the allograft, or renal artery stenosis. Renal artery stenosis has been reported in 1% to 12% of transplant recipients and can occur at the site of anastomosis, in the donor renal artery, or in the recipient hypogastric artery (207). The causes include faulty suture technique, damage to the donor arterial intima during perfusion, intimal damage from rejection, improper apposition of the donor and recipient vessels with torsion, excessive length of the renal artery leading to angulation, or atherosclerosis in the recipient artery. An increased incidence of renal artery stenosis has been observed following transplantation of small pediatric cadaver donor kidney.

Renal arteriography is indicated whenever an allograft recipient has severe hypertension or unexplained deterioration in renal function (104). Renal vein renin measurements and captopril renography are of limited diagnostic value in this setting. Revascularization of the allograft is indicated when arterial stenosis is considered the cause

of intractable hypertension or renal dysfunction. Percutaneous transluminal angioplasty has yielded satisfactory results in these patients and is an appropriate initial option (100,233) (Fig. 22.37). Secondary surgical revascularization is indicated if angioplasty cannot be done or is unsuccessful.

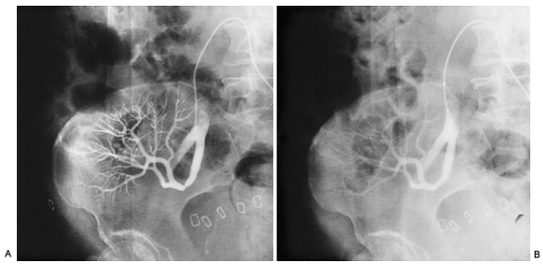


FIGURE 22.37. A: Transplant arteriogram demonstrates significant stenosis at the site of anastomosis of the recipient hypogastric artery to the donor artery. **B:** Following percutaneous transluminal angioplasty, a repeat transplant arteriogram shows complete resolution of the arterial stenosis.

A variety of techniques have been described for performing secondary arterial revascularization of a renal allograft. These include segmental arterial resection with end-to-end anastomosis, saphenous vein bypass for the proximal common iliac artery or aorta, direct reimplantation into the common or external iliac artery, patch angioplasty, or anastomosis to the hypogastric artery if this vessel is available. These are technically complex operations due to the frequent presence of dense scar tissue around the allograft; the renal vein and ureter are also often adherent to the renal artery. The results of surgical revascularization in these patients are generally satisfactory but less so than those obtained with primary revascularization of the native or transplant kidney (Table 22.10) (60,63,146,296). These operations should be performed through a transabdominal incision, which facilitates identification of the transplant renal artery. We have found that a saphenous vein bypass graft from the common iliac artery or aorta to the distal disease-free transplant renal artery is a relatively straightforward, versatile, and effective technique (Fig. 22.38). Occasionally, with a long renal artery and a short focal area of stenosis, segmental resection with reanastomosis is a satisfactory option.

	No. of Patients	No. of Successful
Dickerman, 1980[63]	16	12
Rijksen, 1982	25	18
Tilney, 1984[296]	21	14
Benoit, 1987	40	32
Lacombe, 1988[146]	63	51
DeMeyer, 1989[60]	16	15
Total	181	142 (78%)

TABLE 22.10. RESULTS OF SURGICAL REVASCULARIZATION FOR TRANSPLANT RENAL ARTERY STENOSIS

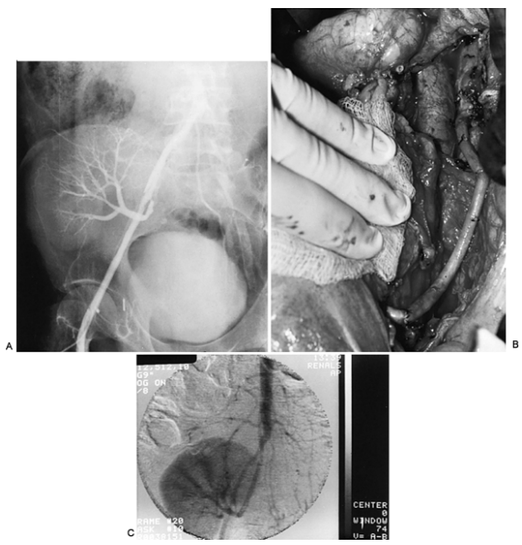


FIGURE 22.38. A: Pelvic arteriogram shows severe stenosis of proximal artery to right renal allograft. **B:** Operative photograph of completed aortorenal saphenous vein bypass. **C:** Postoperative intravenous digital subtraction angiogram shows patent bypass to renal allograft.

Renal Artery Pseudoaneurysm

Renal arterial pseudoaneurysm formation is a potentially devastating complication of renal transplantation that occurs in less than 1% of patients (94,145,235,236). Pseudoaneurysms may result from infection, injury to the renal artery during procurement or preservation, ischemic damage from excessive stripping of the artery and its vasa vasorum, faulty suture technique, or external traumatic injury. These mechanisms produce disruption of the arterial wall, usually at the site of arterial anastomosis, leading to the development of a communicating sac lined by fibrous and adventitial tissue.

The natural history of transplant renal artery pseudoaneurysm is not known, although it is clear that rupture can

occur even if the aneurysm is not affected. Hypertension and deterioration of renal function also can result from pseudoaneurysm formation, usually through extrinsic compression of the renal vessels with consequent diminished allograft perfusion. Transplant nephrectomy generally has been performed to prevent rupture (94,145,235), while *in situ* reconstruction and allograft salvage have only rarely been described (236).

We recently treated a transplant recipient with stable graft function and a 6.5-cm renal artery pseudoaneurysm causing severe hypertension and sciatic pain. Excision of the pseudoaneurysm and reconstruction were indicated to prevent rupture, reduce hypertension, and maintain stable allograft function. At surgery, extensive fibrosis was observed around the pseudoaneurysm, which enveloped the external iliac artery and renal vessels. The renal allograft together with the pseudoaneurysm and a segment of the external iliac artery were removed en bloc, and the allograft was quickly flushed with cold Collins solution. The excised segment of external iliac artery was replaced with an interposition synthetic graft. Extracorporeal renal vascular reconstruction was performed, and the repaired graft was

autotransplanted into the contralateral iliac fossa (Fig. 22.39). This approach allowed allograft revascularization to be done in a previously unoperated area using healthy recipient vessels. Extracorporeal reconstruction and autotransplantation of a renal allograft has not previously been reported but can be an effective salvage technique for selected patients with complex vascular lesions involving the transplant kidney (35).

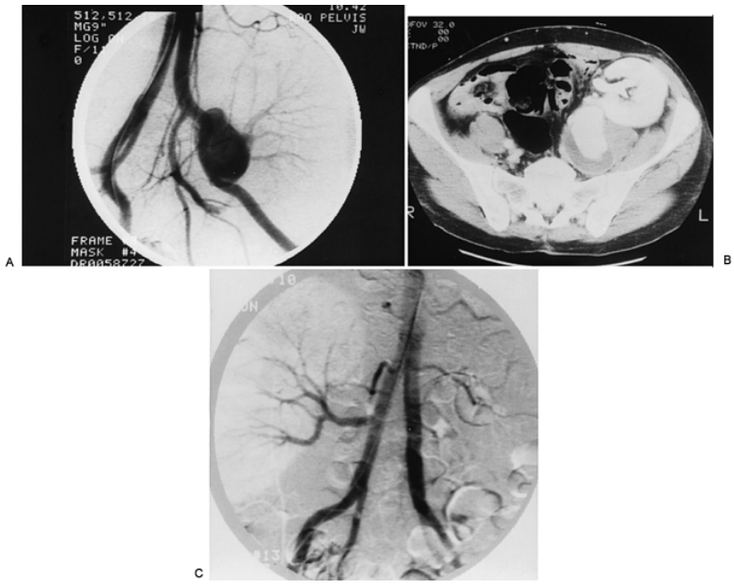


FIGURE 22.39. A: Arteriogram reveals large pseudoaneurysm arising near arterial anastomosis between renal artery and left external iliac artery. Intrarenal vasculature can be seen lateral to pseudoaneurysm. **B:** Pelvic computed tomography scan shows large renal artery pseudoaneurysm extending posteriorly in left iliac fossa. **C:** Following extracorporeal revascularization and autotransplantation, arteriogram shows patent anastomosis of reconstructed renal artery to right common iliac artery. (From Campbell SC, Gill I, Novick AC. Delayed allograft autotransplantation after excision of a large symptomatic renal artery pseudoaneurysm. *J Urol* 1993;149:361, with permission.)

Allograft Rupture

Spontaneous allograft rupture is an uncommon complication that usually occurs within the first month after transplantation (196). Graft rupture is most often seen in transplant recipients undergoing an acute rejection episode. Although this complication was formerly observed in 1% to 10% of patients, it is now only rarely encountered (less than 1%) because patients on cyclosporine maintenance therapy do not generally experience severe graft enlargement during acute rejection. Trauma, ureteral obstruction, and recent open renal biopsy are additional predisposing factors for graft rupture. Routine capsulotomy at the time of transplantation does not obviate postoperative graft rupture. The clinical picture includes sudden pain and swelling of the graft, a palpable flank mass, oliguria, and vascular collapse.

If the graft is functionally salvageable and it is technically feasible, the laceration should be repaired. If the graft has been irreversibly damaged by rejection or if multiple areas of rupture preclude a satisfactory repair, nephrectomy provides the optimum treatment.

Ureteral Fistula

Ureteral fistulae most often manifest early in the posttransplant course and may be heralded by pain or swelling over the allograft. Unilateral leg edema may also be present; occasionally, fluid will egress from the wound. A definitive diagnosis can be made by determination of electrolyte, urea, and creatinine concentrations in any fluid collected from the incision or from fluid aspirated percutaneously. This will help differentiate urine from serum or lymph. Diagnostic radiographic studies include intravenous pyelography (Fig. 22.40), ultrasound, and CT (33,220). When renal function is adequate, intravenous contrast can be given during CT scanning to differentiate urine from other fluid collections. A plain film can be taken immediately after the CT to obtain anatomic information equivalent to that with intravenous urography. As is the case for patients with transplant ureteral obstruction, however, the level of function at the time the urinary extravasation is diagnosed may not be adequate to allow administration of intravenous contrast. Retrograde studies can be difficult and have often been replaced by routine percutaneous nephrostomy placement and antegrade pyelography. In this setting, the percutaneous nephrostomy allows early proximal diversion and access for subsequent follow-up studies. It also allows precise delineation of the level of extravasation to plan further management.

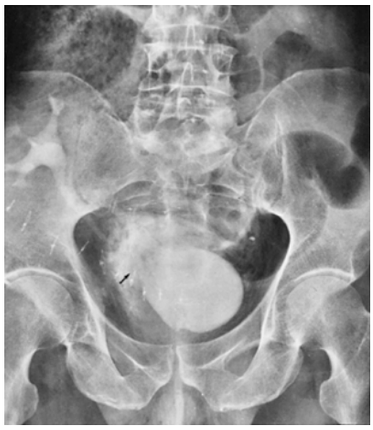


FIGURE 22.40. Intravenous pyelogram shows extravasation of contrast material from a distal ureteral fistula. (From Novick AC, Straffon RA, eds. *Vascular problems in urologic surgery.* Philadelphia: WB Saunders, 1982, with permission.)

Ureteral fistulae almost always result from compromise of ureteral vascularity, the result of which is ureteral necrosis and sloughing. As such, the distal ureter is most commonly involved, although the necrosis can involve the entire ureter. Less often, the ureteral fistula is a result of a local technical factor associated with the ureteroneocystostomy that then results in a distal ureteral leak. In any case, standard intervention for a ureteral fistula is immediate open operative intervention (196,248). For fistulae limited to the distal ureter or ureteroneocystostomy itself, a repeat ureteral reimplant can be performed and a stent temporarily left indwelling. If viability of the more proximal transplant ureter is in question, repeat ureteroneocystostomy is not appropriate. In these cases, the ureter is resected back as far as necessary to ensure that it has an adequate blood supply. Options for reconstruction then include ureteroureterostomy with anastomosis of the native ureter to the proximal transplant ureter or, when the entire allograft ureter is nonviable, a ureteropyelostomy (Fig. 22.41). In all cases, an internal stent is left indwelling for these secondary reconstructive procedures (20). If associated infection is also a factor, externalized drains should be placed near the anastomosis, and in some cases, nephrostomy drainage should be implemented (95).

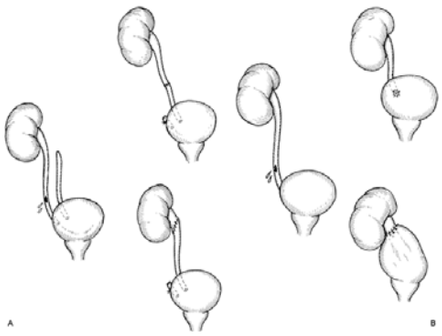


FIGURE 22.41. A: When ipsilateral native ureter is available, ureteral fistula can be repaired with ureteroneocystostomy *(top)* or ureteropyelostomy *(bottom)*. **B:** When ipsilateral native ureter is absent, ureteral fistula can be repaired with ureteroneocystostomy *(top)* or pyelovesicostomy *(bottom).* (From Novick AC, Straffon RA, eds. *Vascular problems in urologic surgery.* Philadelphia: WB Saunders, 1982, with permission.)

Percutaneous nephrostomy drainage has gained a role for adjunctive and at times definitive management of ureteral fistulae (154,275). When a ureteral fistula is diagnosed, institution of percutaneous nephrostomy drainage allows early proximal diversion and access for radiographic studies that allow precise delineation of the site of extravasation. Such antegrade studies are especially important when compromised renal function does not allow administration of intravenous contrast for urography or CT. When a percutaneous nephrostomy has been placed for diagnostic purposes, it can be left indwelling during the postreconstructive period to allow proximal urinary diversion and access for postoperative radiographic evaluation.

In some cases, percutaneous techniques can be used to obviate entirely the need for secondary operative reconstruction. Successful endourologic management of ureteral fistulae is a likely result only in select patients in whom antegrade studies suggest extravasation limited to the distal ureter and in whom contrast enters the bladder during antegrade pyelography. Proximal extravasation or failure of contrast to enter the bladder suggests extensive ureteral loss, and in such cases, percutaneous treatment will rarely prove definitive. When percutaneous management is selected, the optimal approach involves placement of a guidewire, and subsequently a stent, across the site of extravasation into the bladder. Ultimately, the patient should be left with an

internal stent and a nephrostomy tube for drainage or an internal-external stent for external drainage. Percutaneous management can be continued as long as the patient remains stable clinically and serial radiographic studies show the fistula to be resolving. Separate percutaneous drainage of a urinoma should be performed if it is infected, particularly large, or in any way symptomatic.

Although percutaneous techniques can provide long-term definitive management for some transplant ureteral fistulae, success rates will be limited. As such, we believe the primary roles of percutaneous techniques in this setting are for diagnosis and as therapeutic adjuncts before definitive operative reconstruction. In our experience, definitive percutaneous management of transplant ureteral fistulae has had a success rate of only 36%, even in highly selected patients (36).

Calyceal Fistula

Calyceal fistula is now a rare complication of renal transplantation that is essentially always the result of segmental renal infarction. Contemporary vascular techniques for management of multiple renal arteries have relegated this to a rare cause of urinary fistula. Standard intervention historically involved open exploration with debridement and drainage, along with primary closure of the involved collecting system. Unfortunately, such management was associated with unacceptably high rates of graft loss and mortality. Improved results were subsequently reported with operative placement of nephrostomy tubes and institution of external drainage. More recently, calyceal fistulae have been shown to resolve with external drainage alone. The contemporary management of this uncommon complication should consist of institution of percutaneous catheter drainage at the site of extravasation. If there is any degree of urinary obstruction associated with the fistula, percutaneous nephrostomy drainage or internal stenting should also be instituted. With adequate percutaneous drainage, calyceal fistulae should resolve without the need for open operative intervention.

Bladder Fistula

The incidence of bladder fistulae has decreased with the increasingly infrequent use of an extravesical, rather than a transvesical, ureteroneocystostomy to restore urinary continuity

at the time of transplantation (93,295). The diagnosis of a bladder fistula is relatively easy to establish with a cystogram, which generally reveals extravasation of contrast. If a catheter had not been indwelling at the time the extravasation became evident, a cautious trial of standard catheter bladder drainage alone can be instituted, although separate percutaneous drainage of a urinoma may be indicated as described earlier. Failure of this management to result in resolution should prompt open exploration with debridement and repair.

A bladder fistula diagnosed in the presence of an extravesical ureteroneocystostomy is generally diagnostic of leakage at the ureteroneocystostomy itself. In such cases, catheter drainage alone will rarely be successful. However, if the extravasation is limited to the distal ureter as defined by intravenous or antegrade pyelography, a trial of percutaneous management can be instituted as described for ureteral fistulae. A failure of or contraindication to percutaneous management necessitates prompt open operative intervention as for ureteral fistulae.

Ureteral Obstruction

Ureteral obstruction is generally a late complication of renal transplantation. The contemporary incidence has decreased to less than 5% to 10% of renal allograft recipients, but this complication still accounts for up to one-third of all significant urologic complications (139). The diagnosis is usually made during evaluation of azotemia in an otherwise asymptomatic patient, at which time standard radiographic study with ultrasonography will identify hydronephrosis. If renal function is adequate, intravenous urography may allow delineation of the site of obstruction (Fig. 22.42). Retrograde pyelography may be attempted to define the site of obstruction, although difficulty in cannulation of the neoureteral orifice has generally led to abandonment of this study in favor of percutaneous nephrostomy placement with antegrade pyelography. In some cases, the functional significance of a mildly dilated collecting system may be unclear. In these cases, the effect on renal function of prolonged percutaneous drainage can provide a definitive answer. Further evaluation with antegrade pressure/perfusion studies may also be of benefit in select cases. Definitive operative reconstruction of transplant ureter obstruction is dependent on the etiology and site of obstruction. The most common problem is distal obstruction that involves the ureteroneocystostomy. Although technical factors at the time of transplantation may have played a role, ureteral ischemia should be considered. This is especially true when longer segments of the ureter appear to be involved. Less common causes of ureteral obstruction include extrinsic compression by hematoma, lymphocele or abscess, ureteral kinking, or less commonly, previously unrecognized intrinsic ureteropelvic junction obstruction. Rarely, intermittent obstruction can result from placement of the ureteral anastomosis in the mobile anterior dome of the bladder.

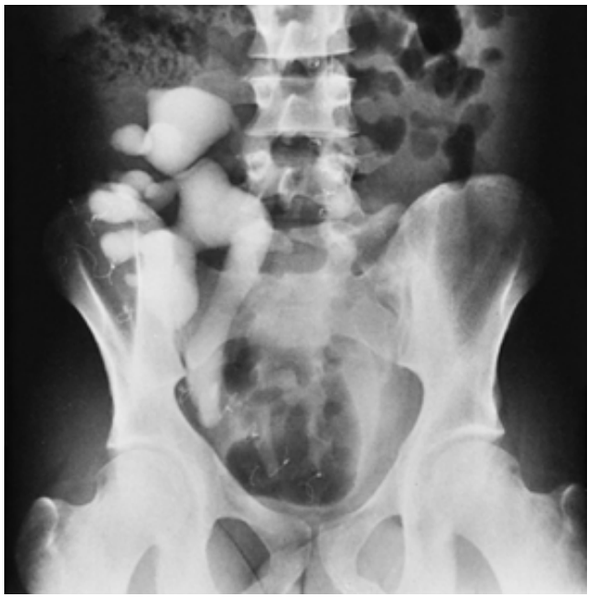


FIGURE 22.42. Intravenous pyelogram demonstrates hydronephrosis from distal ureteral obstruction. (From Novick AC, Straffon RA, eds. *Vascular problems in urologic surgery.* Philadelphia: WB Saunders, 1982, with permission.)

If the obstruction is limited to the very distal ureter, a repeat ureteroneocystostomy can be performed (196). In these cases, intraoperative placement of a soft, self-retaining internal stent that is left indwelling for 4 to 6 weeks should be considered. For extensive ureteral involvement, a nearly universally applicable reconstructive technique uses the native ureter for a ureteropyelostomy to the transplant renal pelvis (247). This avoids the need for extensive dissection of the transplant ureter and at the same time obviates the need to use a transplant ureter that may be of marginal quality. When the native ureter is used, the proximal native ureter can generally be ligated and the native kidney left *in situ* (159). However, in the presence of infection, native nephrectomy should be performed. An alternative to nephrectomy is anastomosis of the native ureter in a side-to-side fashion to the transplant renal pelvis (142). This precludes the possibility of a late complication associated with simple ligation of that ureter. Again, an internal stent is left indwelling during the early postoperative period. If a percutaneous nephrostomy had been placed before definitive repair, this also can be left indwelling during the initial postoperative period to provide temporary urinary diversion and access for postreconstructive radiographic studies.

When the native ureter is not available or is otherwise inappropriate for use in reconstruction, a variety of salvage reconstructive procedures may be used. These include vesicopyelostomy during which the bladder is anastomosed directly to the renal pelvis, with or without a bladder flap (229). An alternative to vesicopyelostomy for complicated reconstruction is an ileal interposition. In rare cases in which the transplant renal pelvis cannot be accessed either because

of peripelvic fibrosis or an intrarenal anatomy, consideration can be given to native ureterocalicostomy or vesicocalicostomy (123,312).

In recent years, transplant ureteral obstruction has been managed entirely with an endourologic approach by combining percutaneous nephrostomy drainage with transluminal ureteral dilation or endoscopic incisional ureterotomy. Those patients best suited for an endourologic approach are those with short, discrete strictures limited to the distal ureter or ureterovesical anastomosis itself (276). Midureteral narrowing suggests extrinsic compression, and long areas of stricture suggest extensive fibrosis, in which case endourologic management is unlikely to prove definitive. Similarly, ureteropelvic junction obstruction in transplanted kidneys generally results from unrecognized intrinsic ureteropelvic junction obstruction in the donor organ or from kinking at the time of transplantation. In either case, simple ureteral dilation is again unlikely to be successful. As an endourologic alternative, percutaneous endopyelotomy may have a definitive role. Reports of endourologic management of transplant ureteral stenosis have become available in larger numbers of patients, and these results suggest a 45% to 70% success rate, even after extended periods of follow-up (19,276).

Lymphocele

A *lymphocele* is a collection of lymph around the allograft. Lymphoceles may be unilocular or multilocular or encapsulated, ranging in size from a small, insignificant collection to a large obstructing mass containing more than 1,000 mL of fluid. A lymphocele is caused by lymphatic leakage from the allograft bed or the allograft itself. Care in ligation of perirenal lymphatics during donor nephrectomy and recipient lymphatics during preparation of the iliac fossa is essential in preventing this complication. Normally, severed lymphatics close within 48 hours and regenerate within 7 to 10 days. However, in transplant recipients, several factors can predispose to prolonged lymphatic leakage. These factors include rejection, open transplant biopsy, and the use of various medications such as steroids, diuretics, and anticoagulants. Retransplantation has also been implicated in the development of lymphoceles (273).

The most common initial signs and symptoms of a lymphocele are urinary frequency, suprapubic pressure, a ballottable mass adjacent to the allograft, and edema of the ipsilateral thigh and genitalia. Findings suggestive of rejection, such as hypertension, oliguria, decreased renal function, and proteinuria, may also be present. With a significant lymphocele, intravenous pyelography usually shows hydronephrosis or displacement of the bladder, with no extravasation of contrast material (Fig. 22.43). Cystography will confirm extrinsic bladder compression and the absence of extravasation. Currently, ultrasonography and CT scanning are the diagnostic methods of choice for establishing the presence, location, and extent of perinephric fluid collections. If a urinary fistula is suspected, a CT scan with contrast should be performed. Needle aspiration and determination of the creatinine and urea content of the fluid can also distinguish urinoma from lymphocele.

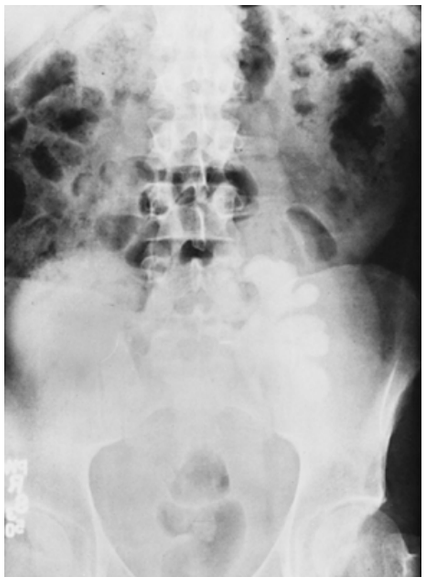


FIGURE 22.43. Intravenous pyelogram demonstrates hydronephrosis and bladder displacement from a large pelvic lymphocele. (From Novick AC, Straffon RA, eds. *Vascular problems in urologic surgery.* Philadelphia: WB Saunders, 1982, with permission.)

Small, loculated, low-density perinephric fluid collections are relatively common following transplantation. If the patient is clinically asymptomatic with no radiographic evidence of obstructive uropathy or urinary extravasation, no treatment is necessary.

When a significant lymphocele is present, a drainage procedure is indicated. Percutaneous aspiration of the lymphocele with injection of a sclerosing agent may be performed but has a variable success rate (288,315). Definitive therapy is provided by internal marsupialization of the lymphocele into the peritoneal cavity (134,320). This was formerly accomplished through a surgical abdominal incision, but laparoscopic internal lymphocele drainage can now be performed with excellent results (69,138,184,311).

Hydrocele

The incidence of ipsilateral hydrocele formation after renal transplantation has been reported to be as high as 68% when the spermatic cord is transacted at the time of transplantation (213).

Therefore this practice has largely been abandoned. Transection of the spermatic cord results in interference with lymphatic drainage of the testicle and leads to accumulation of hydrocele fluid. In addition, the testicle is rendered ischemic due to interruption of the main blood supply, making its viability totally dependent on collateral circulation. Hydrocelectomy in these patients is fraught with the potential complications of testicular loss and abscess formation (213). Aspiration of a hydrocele with tetracycline sclerotherapy is an alternative and effective treatment modality (246). Fortunately, the majority of hydroceles after renal transplantation are asymptomatic, and only a few require treatment. Symptoms are usually related to discomfort, pain, interference with sexual activity, or embarrassment related to size. The diagnosis is usually evident on physical examination and by transillumination. Ultrasound may be used to document the size and pattern of the hydrocele, to assess the testicle, and as an adjunct to aspiration and sclerotherapy.

RESULTS OF RENAL TRANSPLANTATION

Part of "22 - RENAL TRANSPLANTATION "

More sensitive histocompatibility crossmatching techniques, which have virtually eliminated hyperacute rejection episodes; careful patient selection with appropriate preoperative evaluation, reducing immediate postoperative complications; refinements in surgical techniques, minimizing technical losses; development of newer immunosuppressive drugs and strategies, lowering the incidence of early rejection; and enhanced therapy against infections, especially antiviral agents, have all contributed to an improvement in the success of renal transplantation in the past few years. One-year patient survival now exceeds 95% for all transplant groups, and 1-year allograft survival exceeds 85% for cadaveric and 95% for one-haplotype and HLA-identical recipients, respectively (Fig. 22.44). As depicted in Fig. 22.45, this enhanced 1-year survival has resulted in a slowly increasing graft survival half-life for cadaveric as well as living donor recipients (42).

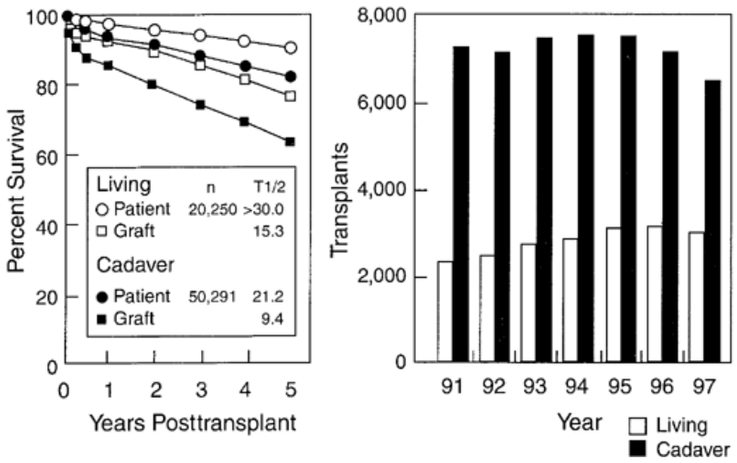


FIGURE 22.44. Patient and allograft survival by year based on donor relationship. (From Cecka JM. The UNOS scientific renal transplant registry. In: Terasaki PI, Cecka JM, eds. *Clinical transplants, 1998.* Los Angeles: UCLA Tissue Typing Laboratory, 1998:2, with permission.)

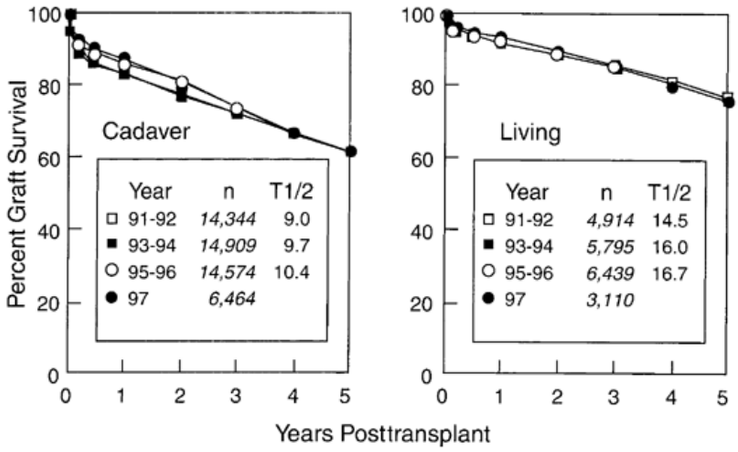


FIGURE 22.45. Allograft survival rates by year for major subgroups. (From Cecka JM. The UNOS scientific renal transplant registry. In: Terasaki PI, Cecka JM, eds. *Clinical transplants, 1998.* Los Angeles: UCLA Tissue Typing Laboratory, 1998:2, with permission.)

During the 1990s, there was a slow but persistent improvement in long-term renal allograft survival. This is best analyzed by comparing the survival half-lives of kidneys. The introduction of cyclosporine in the early 1980s resulted in improved 1-year survivals of up to 80%, but little improvement in cadaveric half-life of more than 7 to 8 years. However, further incremental advances in immunosuppression and patient management have now produced a significant prolongation in survival half-life of 21.6 years for live donor and 13.8 years for cadaveric donor recipients (108). It has been suggested that these findings may be a direct result of the decreased rates of acute rejection during the first posttransplant year, because these early rejection episodes have been shown to be a major cause of chronic rejection and late graft loss (6,70,80,124).

The influence of HLA matching on graft survival is obvious between live donor and cadaveric recipients (42). As illustrated in Fig. 22.46, 5-year survival rates are 87%, 75%, and 60% with corresponding half-lives of 24.8 years, 13.9 years, and 9 years for HLA-identical, one-haplotype, and cadaver recipients, respectively. However, the exact benefit of HLA matching within subgroups, especially cadaveric

recipients, is not so obvious. The data demonstrate 5-year graft survival of 70% for six-antigen matched kidneys versus 58% for zero-antigen matched cadaver kidneys (Fig. 22.46). More impressively, six-antigen matched kidneys exhibited a half-life of 12.7 years compared with 8.0 years for kidneys with one or more mismatched antigens. It would appear reasonable to continue policies aimed at ensuring that best matched transplants are maximized (281). Unfortunately, incremental benefits (e.g., three-antigen versus four-antigen) are not as impressive (203). One reason for this latter observation is that prolonged cold ischemia times and shipping of kidneys have a detrimental effect on graft survival. Prolonged cold ischemia times increase the incidence of delayed graft function after

transplant (Fig. 22.47). This is especially true for older-age cadaver kidneys. Delayed graft function in turn may negate any small advantage from fewer degrees of HLA matching.

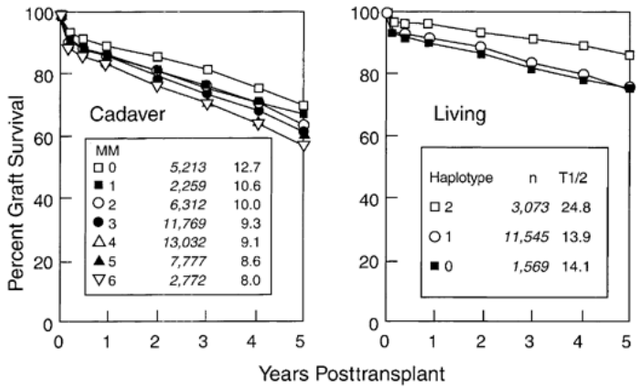


FIGURE 22.46. Rate of cadaveric and live donor graft loss at 5 years based on HLA matching. Data from more than 65,000 transplants, 1991–1997. Cadaveric transplants ranged from zero to six mismatched HLA antigens. (From Cecka JM. The UNOS scientific renal transplant registry. In: Terasaki PI, Cecka JM, eds. *Clinical transplants, 1998.* Los Angeles: UCLA Tissue Typing Laboratory, 1998:10, with permission.)

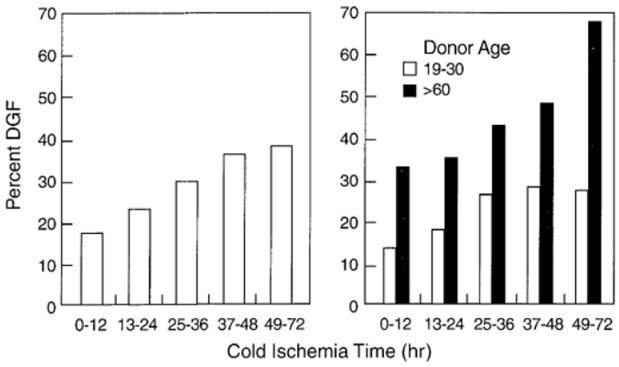


FIGURE 22.47. The effect of cold ischemia time on incidence of delayed graft function. Kidneys older than age 60 were especially susceptible, demonstrating twice the rate of delayed graft function at each 12-hour interval compared with kidneys age 19 to 30. (From Cecka JM. The UNOS scientific renal transplant registry. In: Terasaki PI, Cecka JM, eds. *Clinical transplants, 1998.* Los Angeles: UCLA Tissue Typing Laboratory, 1998:8, with permission.)

The most commonly cited cause of allograft failure after the first year is chronic rejection. Unfortunately, chronic rejection is largely an ill-defined, poorly understood process that results in unrelenting, progressive renal damage (80,118,124,170). The diagnosis of chronic rejection is usually based on histopathology, which includes among other findings interstitial fibrosis, tubular atrophy, arteriolar intimal thickening with narrowing of the lumen, and glomerulosclerosis (261). No specific treatment exists for chronic rejection other than preventing precipitating events and treating potential exacerbating factors (e.g., hypertension). A number of studies have implicated acute rejection as a risk factor for chronic rejection and subsequent allograft loss (6,70,80). Ferguson (70) reported a half-life of 16.9 years in patients experiencing no rejection versus 3.9 years in recipients experiencing more than one rejection episode. However, it is clear that not all patients experiencing acute rejection are destined to develop chronic rejection and allograft loss. In reviewing 53 patients at our institute who had functioning grafts surviving more than 20 years, Braun and colleagues (29) reported that 58% had experienced acute rejection episodes. Nevertheless, the recent increase in survival half-lives appears to be enjoyed by patients who experienced no acute rejection episodes during the first year (Fig. 22.48). Although predicting who develops chronic rejection after an acute rejection episode may not be possible, the data suggest that preventing an acute rejection episode is the most effective way to achieve long-term graft success.

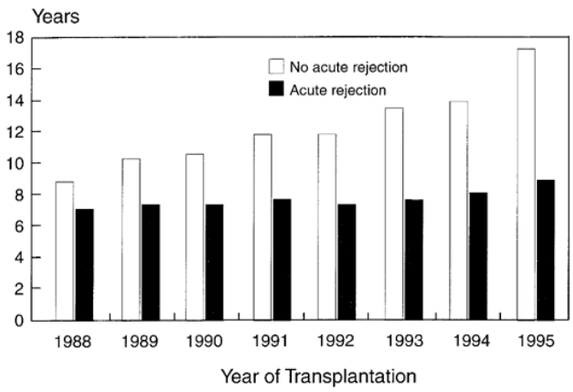


FIGURE 22.48. Projected half-life of grafts from cadaveric donors according to the presence or absence of clinical acute rejection during the first year after transplantation. (From Hariharan S, Johnson CP, Bresnahan BA, et al. Improved graft survival after renal transplantation in the United States 1988–1996. *N Engl J Med* 2000;342:605.)

Death with a functioning allograft has emerged as a major cause of long-term graft loss, especially in older recipients and diabetics. Matas and colleagues (171) have indicated that survival rates calculated counting death with a functioning graft as a cause of allograft loss are dramatically different from those calculated censoring patients who die with a functioning graft, and they have suggested that results should be reported both ways. In their series, nondiabetic living donor non–HLA-identical recipients greater than age 50 had a half-life of 9 years when death with function was considered graft loss, compared with a half-life of 62 years when data with function were censored. Other centers have reported similar results and have even demonstrated better survival in older recipients than young ones (suggesting less immunologic graft loss) when death with a functioning graft was censored (223,290). As more high-risk patients, especially diabetic and older patients, are transplanted and survive the early posttransplant period, death with a functioning graft is likely to become the predominant cause of graft loss in centers where it has not already done so.

Delayed graft function also adversely affects long-term survival, although the primary effect may be earlier (42,186,257). Although donor and organ preservation factors clearly affect the quality of initial function of the kidney

following transplantation, evidence exists suggesting that immunologic factors contribute as well. Animal models have demonstrated increased MHC antigen expression related to ischemia (258). In addition, brain death itself may cause an upregulation of cell surface immunoreactive products and release of cytokines that promote both ischemic renal injury and immunologic injury (227). Other nonimmunologic causes may be responsible for long-term graft loss as well. Brenner and colleagues (31), noting diminished results with pediatric donors, female donors, and transplants into larger recipients, suggest that “one size may not fit all” and recommend matching of kidneys based on nephron dosing as well as HLA matching. Terasaki and colleagues (284) observed that elevated serum creatinines at the time of discharge from the hospital following transplantation correlated with decreased graft survival. They suggested that the hyperfiltration hypothesis (32) could explain diminished results seen in transplants using kidneys from infant and older donors, using kidneys from female donors to male recipients, occurring in obese patients, or following early acute rejection episodes.

As stated earlier, the ultimate goal for long-term success in renal transplantation is the induction of donor-specific tolerance in the recipient. Although this is not clinically achievable at present, recent observations have generated hope of its accomplishment in the near future. Using DNA typing and other technologies, Starzl and colleagues (267) have demonstrated the peripheral migration of donor cells (chimerism) in patients with long-term allograft survival who exhibit donor-specific nonreactivity following renal transplantation. Although a direct cause and effect of microchimerism and donor-specific hyporesponsiveness has not been demonstrated, it has allowed for investigation of immunosuppressive strategies. The infusion of donor allogeneic bone marrow into a recipient who has undergone myeloablation can lead to tolerance of allografts from the same donor (278). This involves the creation of a new immune system that becomes “educated” to recognize the alloantigens as “self.” However, because of toxicity, the use of myeloablation has been limited to animals. A clinical trial using donor bone marrow and concomitant T-cell depletion with polyclonal antibodies has been encouraging, but has not resulted in tolerance (17). More recently, tolerance induction has been demonstrated in animals by blocking costimulatory signals to T cells. Costimulation is required for T-cell activation and to prevent T-cell anergy. Tolerance can be induced in animal models using blockade of the CD28–B7 interaction with a soluble recombinant fusion protein called CTLA-4Ig (155). In addition, blockade of CD154 (ligand of CD40) by monoclonal antibodies can tolerize murine skin and cardiac allografts (149). Clinical trials of costimulatory blockade are anticipated. Future improvement in results of renal transplantation will depend on utilization of knowledge of molecular events to develop more highly specific immunosuppressive agents—or, preferably, induce donor-specific tolerance, obviating the need for immunosuppressive agents altogether.

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23

RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY

E. Darracott Vaughan Jr.

R. Ernest Sosa

E.D. Vaughan, Jr. and R.E. Sosa: Department of Urology, Weill- Cornell Medical Center; Department of Urology, New York-Presbyterian Hospital, New York, NY 10021.

Contents

Sixty million Americans have high blood pressure. Hypertension secondary to renovascular disease is a leading cause of secondary hypertension in adults. The incidence of renovascular hypertension (RVH) is not known. It has been estimated that 3% to 5% of all hypertensive patients have RVH (44). An improved understanding of the renin-angiotensin-aldosterone system has permitted researchers to establish more sensitive and specific diagnostic screening tests for RVH. Advances in pharmacology, renal revascularization, and interventional radiology have steadily improved the efficacy and safety of treatment for patients diagnosed to have renovascular hypertension (127). The challenge for the physician is to accurately diagnose RVH and to select a treatment strategy suitable for his or her patient.

The importance of diagnosing RVH is multifold. First, sustained hypertension is a leading risk factor for premature illness and death. Poorly controlled or uncontrolled pressure elevation leads to small-vessel disease and end-organ damage, principally affecting the heart, kidneys, and central nervous system (59). Moreover, renin-dependent hypertension results in more severe vascular damage and hence in a higher incidence of myocardial infarctions and strokes at a younger age than is found in patients with normal or low renin hypertension, who are generally older (10). Second, RVH is difficult to manage medically (49). Even if adequate blood pressure control is maintained by pharmacologic means, progression of arterial disease is not prevented (103,135) and renal ischemia may actually worsen when the pressure is lowered to clinically desirable levels (1). Third, RVH is potentially curable by renal revascularization (21) or

angioplasty, and renal function can be stabilized or enhanced by renal revascularization (134). Fourth, renal arterial disease can lead to ischemic nephropathy, renal failure, if not diagnosed and treated (79).

This chapter presents the current understanding of the natural history and pathophysiology of RVH. A strategy for a cost-effective and reliable diagnostic evaluation of RVH is described. Established and new options for treatment are discussed and compared.

DEFINITIONS

Part of "23 - RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY "

Hypertension

It is estimated that 60 million individuals in the United States have hypertension. At what blood pressure is a person said to be hypertensive? It is difficult to define a precise cutoff that marks the upper limit of acceptable blood pressure, but it is generally acknowledged that the higher the blood pressure, the worse the resultant risk of morbidity and mortality (89). As a working definition, the 1984 Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure recommended that a sustained blood pressure of 140/90 mm Hg be considered the cutoff point between normal blood pressure and mild hypertension for all patients older than 18 years of age. Children with a sustained increase in arterial pressure greater than or equal to the 90th percentile for age are considered hypertensive. Whatever the patient's age, an elevation in blood pressure should be documented on at least three separate occasions, when measured with an appropriate-sized blood pressure cuff, to justify the diagnosis of hypertension. It is not unusual to find that a patient who is hypertensive at an initial evaluation remains normotensive at subsequent measurements (12).

Renovascular Disease

Renal disease has been recognized in association with hypertension since the early nineteenth century (8). In 1898, Tigerstedt and Bergmann (121) demonstrated that a water-soluble extract that they called renin, derived from the renal cortex of a healthy rabbit, could produce a marked and sustained hypertension when injected intravenously into a second rabbit. Interest in the relationship between renal disease and hypertension did not flourish, however, until the classic experiments by Goldblatt and associates (37) in the dog demonstrated that reversible elevation in the systemic arterial pressure could be produced by clamping the main renal artery of one of two healthy kidneys. The blood pressure returned to normal on removal of the kidney or the clamp.

The development and widespread use of arteriography in the 1950s focused attention on renal arterial disease in hypertensive patients and led to advances in renovascular surgery (34). It quickly became apparent, however, that lesions of the renal artery could be demonstrated angiographically in normotensive patients. Moreover, the results of the national cooperative study on renovascular surgery for treatment of hypertension revealed a sobering 34% failure rate in hypertensive patients subjected to renal revascularization (33). It became clear that angiographic documentation of renal artery disease in a hypertensive patient was not sufficient to justify surgical correction of the arterial lesion.

Greater insight into the pathophysiology of renal artery disease was gained by experiments in vessel hemodynamics. It was determined that the internal diameter of an artery must be reduced by greater than 70% for a significant decrease in blood flow to occur (66) and that a pressure gradient greater than 40 mm Hg across a stenosis in the renal artery was necessary to produce a significant decrease in the renal plasma flow, glomerular filtration rate (GFR), urinary sodium excretion, and urine flow rate (106).

The discovery of angiotensin (7,85) and the determination of its sequence (108) led to the eventual development of accurate radioimmunoassays to quantify the activity of the renin-angiotensin system. Researchers established that a significant decrease in blood flow to a kidney results in the activation of the renin-angiotensin-aldosterone cascade, establishing a hypertensive state. Correction of the stenosis or removal of the ischemic kidney eliminates the hyperreninemic state, allowing the blood pressure to return to normal levels.

Accordingly, *renovascular hypertension* can be defined as a sustained blood pressure elevation secondary to a physiologically significant renal artery stenosis that is correctable by repair of the lesion or by removal of the kidney. From a clinical point of view, however, it is imperative to be able to diagnose RVH prospectively. The availability of pharmacologic agents that block different steps in the renin-angiotensin-aldosterone cascade, such as converting enzyme inhibitors (CEIs) and technical advances in interventional radiology, have contributed to our understanding of the pathophysiology of RVH. On the basis of this knowledge, sensitive and specific tests that prospectively identify patients with RVH are in current clinical use.

PATHOLOGY AND NATURAL HISTORY OF RENAL ARTERY DISEASE

Part of "23 - RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY "

Atherosclerosis and fibromuscular disease of the renal artery account for most cases of RVH. Two-thirds of patients with RVH have atheromatous lesions of the renal artery. Atherosclerotic plaques typically are located in the proximal 2 cm of the main renal artery, but they also may involve the distal artery and its branches. The earliest morphologic change is vascular smooth muscle hypertrophy and hyperplasia. Angiotensin II is an important growth factor in vascular smooth muscle cells (101). The chronic administration of

angiotensin-converting enzyme inhibitors will reverse many changes of vascular hypertrophy in experimental animal models and will improve vascular compliance in the hypertensive patient. Following the onset of vascular smooth muscle hypertrophy and hyperplasia, lipid deposition occurs, with necrosis, inflammation, and formation of atherosclerotic intimal plaques that protrude into the lumen. Blood pressure elevation appears to aggravate the severity of atheromatous lesions. Calcification, surface erosion with thrombus formation, or dissection of the vessel wall may ensue (96).

Atheromatous renal arterial disease predominantly afflicts men in older age groups. The disease is often diffuse, affecting the aorta and its major branches, as well as the coronary and cerebral arteries. The renal arteries are involved bilaterally in up to 40% of cases. In the national cooperative study on RVH, patients with bilateral disease had the lowest cure rate and the highest morbidity (33). A review by Schreiber and colleagues (103) of 85 patients with atheromatous renovascular disease treated medically and followed up for a mean of 52 months revealed that the disease was progressive in over 44% of patients, with progression to complete occlusion of the renal artery in 16% of renal units. Reducing the blood pressure alone has not been shown to reduce the risk of atherosclerotic complications of hypertension. Bilateral progression has been found in 20% to 30% of patients (100).

Fibromuscular diseases of the renal artery are responsible for one-third of cases of RVH. Four pathologically different types of renal artery dysplasia have been described (114). Intimal fibroplasia accounts for approximately 10% of the fibromuscular diseases. This disorder primarily involves the intima by the circumferential accumulation of collagen, compromising the arterial lumen. The disease is progressive, and dissecting hematomas may form. Children and young male adults are principally afflicted. Vessels other than the renals may be involved. Angiographically, a smooth focal stenosis is typically seen at the midrenal artery or its branches. Dissection may alter the appearance of the stenosis and of the vessel. Because of the progressive nature of this disease, prompt repair of the lesion is advised.

Fibromuscular hyperplasia is the rarest of the fibrous dysplasias. It is characterized by hyperplasia of the smooth muscle and fibrous tissue, producing a concentric thickening of the renal artery wall. This disease afflicts children and young adults and is progressive.

Medial fibroplasia accounts for 75% to 80% of the fibromuscular dysplasias. On angiogram the diseased artery has the appearance of a string of beads. This angiographic pattern is caused by a series of collagenous rings alternating with aneurysmal dilations, involving the media of the main renal artery, often extending into its branches. Women in their thirties or forties are usually afflicted. This lesion does not dissect, and complete occlusion has not been reported. Schreiber and co-workers (103) followed up a group of 75 patients with this disease for a mean of 65 months and noted that progression of the lesions occurred in 33% of patients regardless of their age. Correction of the lesion by angioplasty is the treatment of choice.

In perimedial fibroplasia, a collar of dense collagen envelops the renal artery just beneath the adventitia. The lesions are tightly stenotic, and therefore extensive collateral vessels are commonly identified on angiography. Young women, 15 to 30 years of age, are most commonly afflicted. The lesion may be progressive, and repair is recommended.

PHYSIOLOGY OF THE RENIN-ANGIOTENSIN SYSTEM

Part of "23 - RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY "

The renin-angiotensin-aldosterone system plays an important role in the regulation of blood pressure and sodium-volume homeostasis. The renin-angiotensin system (RAS) is involved in the maintenance of a constant arterial blood pressure despite extremes of sodium intake. A decrease in sodium intake increases the formation and secretion of angiotensin II by mechanisms that are discussed later in this chapter. Angiotensin II enhances aldosterone biosynthesis by the glomerulosa cells of the adrenal cortex and increases sodium reabsorption at the proximal tubule. In states of increased sodium intake, the activity of the RAS is depressed, and excess sodium is excreted to maintain balance.

The RAS also protects the organism from the potential catastrophic effects of rapid-onset hypotension by responding to a sudden pressure decrease with an immediate increase in renin release. As discussed later, renin initiates a cascade of enzymatic reactions, resulting in the formation of angiotensin II. Angiotensin II is a potent vasopressor that helps restore the systemic blood pressure. It is particularly effective in constricting the precapillary and postcapillary resistance vessels. In addition, in the peripheral nerves angiotensin II potentiates the effects of norepinephrine at the noradrenergic neuroeffector junctions by increasing norepinephrine release, decreasing norepinephrine uptake, and increasing vascular sensitivity to norepinephrine. In summary, RAS buffers a decrease in blood pressure by direct constriction of resistant vessels, by interaction with the noradrenergic receptors in the vascular smooth muscles.

Renin is a proteolytic enzyme formed in modified smooth muscle cells known as the *juxtaglomerular cells* of the afferent arteriole. The juxtaglomerular cells are in intimate proximity of the macula densa of the distal tubule. Together, these microstructures are known as the juxtaglomerular apparatus. Renin is primarily released in response to (a) low renal perfusion pressure in the afferent arteriole (baroreceptor mechanism), resulting from either renal artery stenosis or a decrease in the mean systemic arterial pressure (this response is independent of renal innervation or of the GFR); (b) a low chloride (or sodium) concentration in the filtrate reaching the distal convoluted tubule (macula densa

mechanism); and (c) adrenergic stimulation of the β_1-adrenergic receptors in the juxtaglomerular cells. In the intact animal, decreases in mean arterial pressure and central blood volume activate baroreceptor and volume reflexes, eliciting adrenergic efferent signals that stimulate renin release (Fig. 23.1).

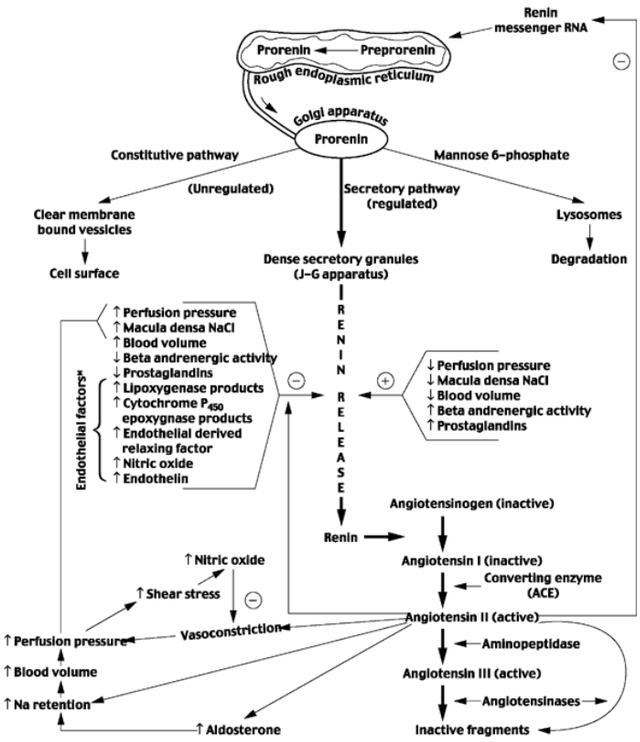

FIGURE 23.1. Renin-angiotensin-aldosterone system. (Modified from Felsen D, Vaughan ED Jr. In: Rajfer J, ed. *Urologic endocrinology.* Philadelphia: Saunders, 1986:112, with permission.)

The enzymatic action of renin splits angiotensin I off the α_2-globulin angiotensinogen. Angiotensin I generally is considered an inactive molecule. Angiotensin-converting enzyme then cleaves a dipeptide off angiotensin I to produce angiotensin II.

Angiotensin II has a wide range of biologic activities. It is the protagonist through which the RAS regulates blood pressure and fluid-volume homeostasis. It is believed that angiotensin II plays an important role in renal autoregulation at low renal perfusion pressures. Normal dogs with an intact RAS subjected to graded decreases in mean renal perfusion pressure are able to maintain normal GFR. However,

if the activity of the RAS is blocked by high salt intake or by CEIs, a decrease of mean renal perfusion pressure to the same levels is associated with a decrease in GFR (41). At low renal perfusion pressures, angiotensin II produces a selective efferent arteriolar vasoconstrictor to increase the glomerular capillary hydrostatic pressure and thus maintain GFR. Clinically, it has been shown that use of CEIs in patients with bilateral renal artery stenosis or stenosis of a renal artery to a solitary kidney is associated with azotemia that reverses when the drug is suspended. However, lowering of the pressure to the same level with antihypertensives that do not interfere with the RAS does not appear to compromise renal function (1,95,97). Use of CEIs in patients with unilateral renal artery stenosis also has been shown to decrease the GFR and renal blood flow of the ipsilateral kidney but not of the contralateral normal kidney (131).

PATHOPHYSIOLOGY OF RENOVASCULAR HYPERTENSION

Part of "23 - RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY "

Our current understanding of the pathophysiology of RVH has been derived to a large extent from work in experimental models of hypertension. Goldblatt and associates (37) first demonstrated that clamping one renal artery in a normal dog produced hypertension that was correctable by removing the clamp or the ischemic kidney. Currently, two models of RVH have been identified and characterized. The two kidney–one clip model is prepared by clipping the renal artery to one of the two kidneys. The ischemic kidney is designated by the ipsilateral kidney, and the untouched kidney is the contralateral kidney. In the one kidney–one clip model, the renal artery to the one kidney is clipped, and the contralateral kidney is removed. The degree of hypertension is similar for these two hypertensive models, but the mechanisms of hypertension differ in some respects.

The decrease in perfusion pressure and blood flow to the ipsilateral kidney in the two kidney–one clip model is associated with a decrease in the ipsilateral GFR, filtered sodium load, and urine sodium excretion (113). An increase in the reabsorption of water and electrolytes is dictated by glomerular-tubular balance in the ipsilateral kidney, increasing the urinary concentration of nonreabsorbable solutes and hence of urine osmolality. The decrease in mean renal perfusion pressure stimulates the baroreceptor mechanism and the decrease in the filtered load sodium (or chloride) activates the macula densa mechanism to increase renin secretion from the ischemic kidney.

The increase in the plasma renin activity invokes an angiotensin II–induced increase in mean systemic arterial blood pressure. The contralateral GFR does not change significantly, but a pressure-induced natriuresis and diuresis can be observed (112). Contralateral renin secretion is totally suppressed as the baroreceptor and macula densa mechanisms are turned off by the described physiologic changes. Tubular absorption of electrolytes and water is less marked than in the ipsilateral kidney because GFR is maintained. The contralateral urine osmolality is accordingly lower than that of the ipsilateral kidney.

The increase in arterial blood pressure in the one kidney–one clip model of hypertension is initially maintained by the vasoconstrictive properties of angiotensin II. If the renal artery clip is maintained for several weeks in the dog or rat, plasma renin activity is noted to return to normal or below normal levels. In this “chronic phase” of RVH, the degree of pressure elevation is equal to that observed in the acute phase, but salt and volume retention primarily account for the hypertension. The short-term administration of RAS blockers does not have a significant depressor effect. Sodium deprivation at this point increases the plasma renin activity and reestablishes sensitivity to the depressor effects of RAS blockers (35).

There is also evidence that other mechanisms are active. These include decreased nerve traffic (57) and increased production of nitric oxide. Nitric oxide inhibitors exacerbate hypertension in experimental renovascular models (76). In addition, there is evidence for a role of prostaglandin endoperoxides because the T_xA_2/PC-H_2 receptor antagonist (ifetroban) also lowers blood pressure in both the acute and chronic phase of the two kidney–one clip model (132).

PHARMACOLOGIC PROBES FOR THE RENIN-ANGIOTENSIN SYSTEM

Part of "23 - RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY "

Insight into the physiology of the RAS has been gained from the development of pharmacologic compounds that inhibit the release of the renin, block the conversion of angiotensin II, or are specific angiotensin II receptor analogs (Fig. 23.1).

The first drug that specifically blocked the action of angiotensin II was saralasin. Saralasin is an angiotensin II analog with affinity for the angiotensin II receptor, but with partial agonist activity (86). Administration of saralasin to two kidney–one clip hypertensive models or to patients with RVH produces a depressor response. However, saralasin lost favor as a screening agent for RVH because of its agonist activity, which produces an increase in blood pressure and hence an underestimation of the contribution of angiotensin II to the maintenance of hypertension.

CEIs prevent the conversion of angiotensin I to angiotensin II. Naturally occurring CEIs initially were found in snake venom (3). Captopril, an orally active synthetic CEI with a rapid onset of action, currently is used in a screening role for renin-dependent hypertension (see Single-dose Captopril Test) and to treat RVH in select cases.

More recently, a number of oral drugs have been developed that block the action of angiotensin II at the receptor level. Losartan is the prototype. At present, the angiotensin II subtype AT_1 receptor appears to be the primary angiotensin receptor in the kidney and vasculature (38).

CLINICAL EVALUATION OF RENOVASCULAR HYPERTENSION

Part of "23 - RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY "

It is now clear that the angiographic finding of a stenosed renal artery in a hypertensive patient is insufficient evidence on which to diagnose RVH. In this regard, hypertensive patients with a renal artery stenosis may not improve after renal revascularization (33). Moreover, radiologic (28) and autopsy (46) series have shown that normotensive patients can have severely diseased renal arteries. Patients with atherosclerotic disease elsewhere have a 20% to 50% chance of having renal arterial disease (129,136).

Until recently, means by which to reliably identify patients with a physiologically significant renal artery stenosis have eluded the clinician. There are no pathognomonic clinical characteristics that reliably lead to the diagnosis (107), but certain clinical features should arouse suspicion that RVH may be present (Table 23.1).

Clues	Comment
Historical	
Hypertension in the absence of any family history of hypertensive disease	Suspect if family history negative; however, about ⅓ of patients with RVH have a positive family history.
Age of onset of hypertension <25 or >45 yr	The average age of onset for essential hypertension is 31 ± 10 (SD) yr. Children and young adults usually have fibromuscular disease; adults >45 yr are more likely to have atherosclerotic narrowing of arteries.
Abrupt onset of moderate to severe hypertension	Essential hypertension usually begins with a "labile" phase before mild hypertension becomes established; usually has a more telescoped natural history, often first appearing as moderate hypertension of recent onset.
Development of severe or malignant hypertension	RVH often becomes moderately severe and is prone to produce acceleration- or malignant-phase hypertension; both forms of hypertension involve markedly increased renin release.
Headaches	Essential hypertension is usually asymptomatic. There seem to be more headaches with RVH, possibly related to its severity or to high levels of angiotensin II, a potent cerebrovascular vasconstrictor.
Cigarette smoking	In a survey (78a), 74% of patients with fibromuscular renal artery stenosis were smokers; 88% of those with atherosclerotic disease smoked.
White race	RVH is uncommon in the African American population.
Resistance to or escape from blood pressure control with standard diuretic therapy or antiadrenergic	Probably the most typical feature of RVH is that it responds poorly to diuretics and often only transiently to antiadrenergic drugs.
Excellent antihypertensive response to CEIs such as captopril	CEIs block the RAS most effectively and are therefore highly specific agents.
Examination and routine laboratory results	
Retinopathy	Hemorrhages, exudates, or papilledema indicate acceleration or malignant phase.
Abdominal or flank bruit	A helpful clue, but commonly present in elderly individuals, and occasionally it is present in younger patients who have no apparent vascular stenosis.
Carotid bruits or other evidence of large-vessel disease	Commonly the vascular disease is not limited to the renal bed.
Hypokalemia—in the untreated state or in response to a thiazide diuretic	Increased aldosterone stimulation by the RAS tends to reduce the serum potassium level. In untreated essential hypertension this does not occur. Thiazide diuretics accentuate this phenomenon in RVH.

CEIs, converting enzyme inhibitors; RAS, renin-angiotensin system.
From Vaughan ED Jr, Case CB, Pickering TG, et al. Clinical evaluation of renovascular hypertension and therapeutic decisions, *Urol Clin North Am* 1984;11:393, with permission.

TABLE 23.1. CLINICAL CLUES SUGGESTIVE OF RENOVASCULAR HYPERTENSION (RVH)

Taking these clinical findings altogether, Mann and Pickering (67) have defined patients who are at low, moderate, or high risk for renovascular hypertension (Table 23.2). Patients at moderate or high risk warrant further study (90).

Index of Clinical Suspicion
Low (should not be tested)
▪ Borderline, mild, or moderate hypertension in the absence of clinical clues
Moderate (noninvasive tests recommended)
▪ Severe hypertension (diastolic blood pressure >120 mm Hg)
▪ Hypertension refractory to standard therapy
▪ Abrupt onset of sustained moderate to severe hypertension at age <20 or >50 yr
▪ Hypertension with a suggestive abdominal bruit (long, high-pitched, and localized to the region of the renal artery)
▪ Moderate hypertension (diastolic blood pressure >105 mm Hg) in a smoker, a patient with evidence of occlusive vascular disease (cerebrovascular, coronary, peripheral vascular), or a patient with unexplained but stable elevation of serum creatinine
▪ Normalization of blood pressure by an angiotensin-converting enzyme inhibitor in a patient with moderate or severe hypertension (particularly in a smoker or patient with recent onset of hypertension)

Modified from reference 90.

TABLE 23.2. TESTING FOR RENOVASCULAR HYPERTENSION: CLINICAL INDEX OF SUSPICION AS A GUIDE TO SELECTING PATIENTS FOR WORKUP

The lack of reliable clinical clues stimulated further study in laboratory animals in pursuit of understanding the physiologic profiles that characterize laboratory models of Goldblatt's hypertension. These endeavors have resulted in the delineation of a variety of approaches to screen for patients with RVH.

The emergence of methods to reliably assay the activity of the RAS and the development of pharmacologic probes that block specific steps in the renin-angiotensin cascade have led to the use of renin determinations to diagnose RVH. Goldblatt's initial animal work led to the assumption that the underlying derangement in RVH is excess renin secretion resulting in angiotensin II formation. The hypertensive animal model most analogous to human RVH is the two kidney–one clip Goldblatt preparation. In this model, the hypertension initially is depending on the increased renin secretion from the clipped kidney. The administration

of CEIs or competitive angiotensin II analogs (9) can prevent or reverse the hypertension. This early phase of two kidney–one clip hypertension exhibits four characteristics: increased secretion of renin from the clipped kidney, absence of renin secretion from the opposite kidney, decreased renal blood flow to the clipped kidney, and elevated pressure secondary to angiotensin II–induced vasoconstriction. The identification of these characteristics permitted the development of a rational approach to the use of plasma renin activity determinations and angiotensin blockade in the diagnosis of RVH (90,127) (Fig. 23.2).

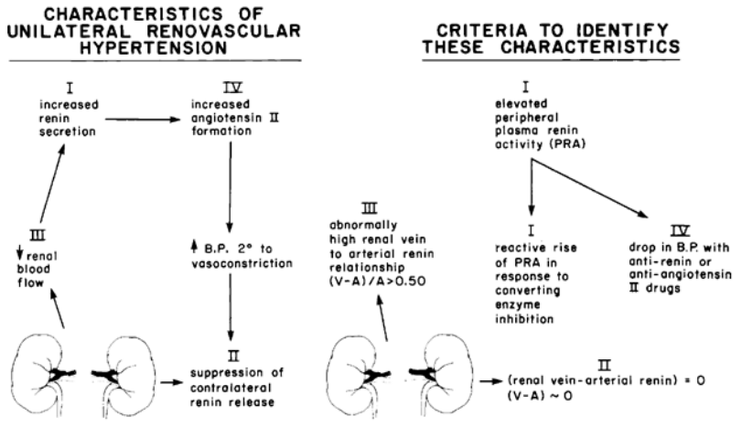

FIGURE 23.2. Characteristics of the early phase of two kidney–one clip Goldblatt's hypertension in the rat *(left)* and the criteria derived from the animal model that identify the patient with correctable renal hypertension. (From Vaughan ED Jr, Case DB, Pickering TG, et al. Clinical evaluation of renovascular hypertension and therapeutic decisions. *Urol Clin North Am* 1984;11:393, with permission.)

Until recently, the combined analysis of the peripheral renin level and determination of differential renal vein renin levels was the standard methodology for identifying potentially curable patients with renovascular hypertension (127). Less invasive tests that give both anatomic and physiologic evidence for curable renovascular hypertension are currently being explored. These tests include captopril renography, color Doppler sonography, spiral computed tomography (CT) angiography, and magnetic resonance angiography (MRA) (52,88).

However, before discussing these tests, it is important to review the use of renin determinations to understand the pathophysiology of renovascular hypertension.

PERIPHERAL PLASMA RENIN ACTIVITY

Part of "23 - RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY "

Peripheral ambulatory plasma renin activity samples are collected in a standardized setting that requires that the patient be salt replete and off all antihypertensive medicines that influence plasma renin activity for at least 2 weeks. In addition, the plasma renin activity is sampled after 4 hours of ambulation and is indexed against a 24-hour urine sodium determination.

The rationale for emphasizing the peripheral plasma renin activity determination is that it is an index of renin secretion (105). In a study of hypertensive patients who had

successful angioplasty, the peripheral plasma renin activity was elevated in 80% before angioplasty (93). The plasma renin activity always decreased and usually returned to normal after successful angioplasty (Fig. 23.3).

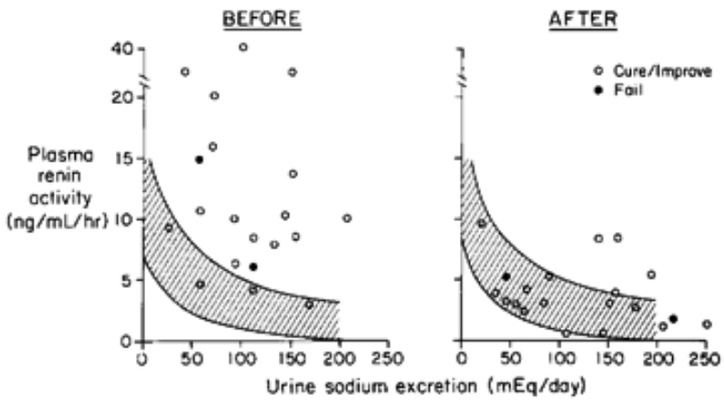

FIGURE 23.3. Effect of angioplasty on peripheral plasma renin activity indexed against 24-hour sodium excretion. *Left panel:* Before angioplasty. *Right panel:* 6 months after angioplasty. *Hatched area* shows normal range. (From Pickering TG, Sos TA, Vaughan ED Jr, et al. Predictive value and changes of renin secretion in hypertensive patients with unilateral renovascular disease undergoing successful renal angioplasty. *Am J Med* 1984;76:394, with permission.)

The 20% false-negative rate places definitive limitations on the use of peripheral plasma renin activity as a screening test for RVH. In addition, many patients with proved RVH have severe, life-threatening hypertension that precludes cessation of antihypertensive medications before blood sampling. Performance of plasma renin activity determinations while the patient is taking medication invalidates the accuracy of the test and eliminates the quantification of peripheral plasma renin activity as a practical screening tool. A third factor is the finding that 16% of patients with essential hypertension also have high plasma renin activity when indexed against a 24-hour urine sodium determination (10). Thus the positive predictive value is poor.

Enhanced Accuracy of Peripheral Plasma Renin Activity by Stimulation with Angiotensin-blocking Agents

The first angiotensin-blocking agent used for testing in human hypertension was saralasin. The initial results demonstrated that the compound, as predicted, lowered blood pressure in high-renin forms of hypertension (9).

A second approach to the use of angiotensin blockade to expose RVH came from experience after the development of CEIs that block angiotensin II formation. One of the peptides, teprotide, was shown to block the vasopressor effect of angiotensin II, and it was possible to demonstrate a close direct correlation between the pretreatment level of plasma renin activity and the magnitude of the depressor response (17).

The success of teprotide was a potent stimulus to the development of the orally active CEI captopril. Captopril has the potential for use as a diagnostic probe, like teprotide, because it has a rapid onset of action (within 10 to 15 minutes), reaching a peak effect by 90 minutes (16) (Fig. 23.4).

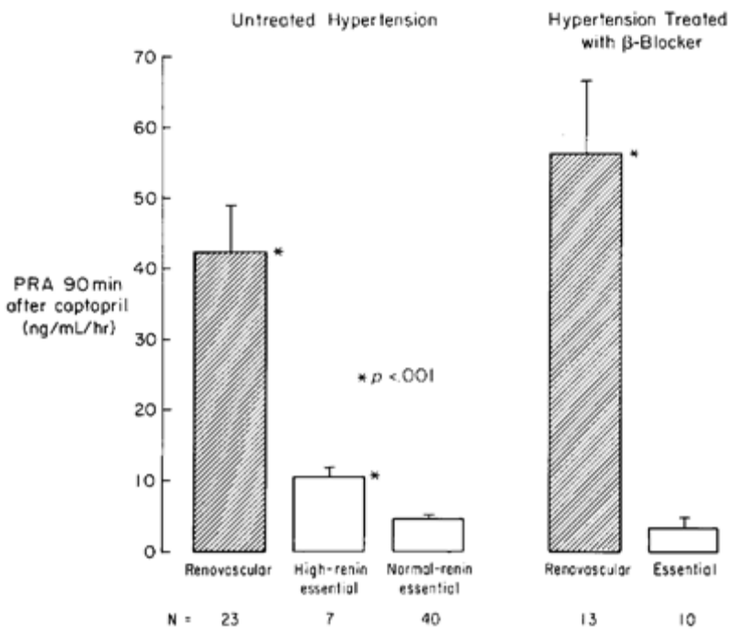

FIGURE 23.4. Levels of plasma renin activity in renovascular hypertension (RVH) and essential hypertension 90 minutes after a single dose of captopril. A marked reactive hyperreninemia was found in the group with RVH whether or not they were already receiving ß-blocker therapy. (From Case DB, Atlas SA, Laragh JH. Physiologic effects and blockade. In: Laragh JH, Buhler FR, Seldin DW, eds. *Frontiers in hypertension research. New* York: Springer-Verlag, 1982, with permission.)

During the early studies of the effect of these agents on blood pressure in hypertensive patients, it was noted that

angiotensin blockade resulted in a marked rise in plasma renin activity in selected patients. Accordingly, the induction of marked rises in plasma activity appeared to be a more specific test for RVH than the induction of depressor responses.

Single-dose Captopril Test

The captopril test is a reliable screening test well suited for outpatient use. Diuretics and preferably all other antihypertensive medications are discontinued at least 2 weeks before testing. Patients are advised not to restrict their salt intake. Twenty to thirty minutes before testing, the patient is seated comfortably in a quiet room, during which time an intravenous catheter is placed for blood sampling, and baseline blood pressure is taken for a baseline plasma renin activity determination before the oral administration of 25 mg of captopril. Blood pressure measurements are then taken every 15 minutes for 1 hour. Venous blood sampling is repeated at 30 and 60 minutes after captopril administration. A depressor renin activity level (92) is seen in patients with renin-dependent hypertension (diastolic pressure decrease of 15% or more). However, the change in blood pressure has low specificity, because patients with essential hypertension also may have a depressor response.

Formation of angiotensin II is greatly decreased by captopril. The resulting decrease in systemic blood pressure in patients with renin-dependent hypertension further decreases the blood flow to the ischemic kidney. The lower perfusion pressure produces a decrease in the glomerular capillary hydrostatic pressure, diminishing the GFR. In addition, the efferent arteriole, which undergoes angiotensin II–induced vasoconstriction at low perfusion pressures to maintain glomerular filtration, relaxes as angiotensin II formation is blocked, thus decreasing the ipsilateral GFR further. The macula densa and baroreceptor mechanisms are activated, and more renin is released from the ischemic kidney. In renin-dependent hypertension, but not in essential hypertension, inhibition of the converting enzyme is associated with a rise in plasma renin activity to 12 ng/mL per hour or greater, an increment in plasma renin activity of 10 ng/mL per hour or more above baseline levels, and a percent increase in plasma renin activity of 170% or more (or 400% if the baseline plasma renin activity was less than 3 ng/mL per hour). If these three criteria are present in a patient with normal renal function off diuretics, RVH can be distinguished from essential hypertension with a specificity of 100% and a sensitivity of 95% (75). Prior sodium depletion by diuretics or by dietary restraint increases plasma renin activity and abolishes the specificity of this test. Patients in treatment with ß-adrenergic blockers remain responsive to captopril as described previously unless their baseline plasma renin activity is less than 2.5, in which case the test may be unreliable (Table 23.3).

Drugs
Discontinue all antihypertensive medicines for at least 2 wk, if possible; otherwise, maintain β-blocker but avoid diuretics, CEIs, and nonsteroidal antinflammatory drugs for at least 1 wk, ideally 2 wk.
Diet
A diet with normal or high sodium content is necessary. Too low a sodium intake will produce false-positive results. If there is a question about diet, a 24-hr urine collection for sodium will closely reflect the intake.
Procedure
The patient is seated comfortably for 20–30 min before testing and maintained in this position for the duration of the test.
Blood pressure is measured at 20, 25, and 30 min (obtain three stable baseline measurements), then blood is sampled for plasma renin activity (in a lavender top Vacutainor kept at room temperature).
A 25-mg captopril tablet is crushed (to ensure that it dissolves) and 30 mL of water added to prepare a suspension. The patient is instructed to drink the suspension, wash the contents out twice, and drink those also.
Blood pressure and plasma renin activity are remeasured after 30 and 60 min.

CEIs, converting enzyme inhibitors.
From Vaughan ED Jr, Case DB, Pickering TG, et al. Clinical evaluation of renovascular hypertension and therapeutic decisions. *Urol Clin North Am* 1984;11:393, with permission.

TABLE 23.3. SINGLE-DOSE CAPTOPRIL TEST

In summary, the single-dose captopril test appears to accurately separate patients with RVH from those with essential hypertension. In addition, a 24-hour urine collection is not necessary, and the patient can remain on ß-blockade.

Captopril Renogram Insert

The captopril renogram is performed in a similar fashion as the single-dose captopril test. A crushed tablet of 25 mg of captopril is given 1 hour before the procedure. Numerous isotopes have been used (Table 23.3), with ^{99m}Tc mercaptoacetylglycylglycyl-glycine (MAG3) being most commonly used today. Interpretation depends on the isotope chosen and the parameter calculated. Commonly used parameters are (a) split renal function percent uptake left to right; (b) maximum activity (A_{max}); (c) single-kidney GFR or renal blood flow, depending on which isotope is used; (d) time to peak activity (T_{max}); (e) the transit time; and (f) residual cortical activity indicating slow isotopic washout. Often, the renogram curves are graded. If the test is positive, imaging studies are necessary because there can be positive tests in patients with parenchymal disease (78). Table 23.4 lists the recent literature concerning the captopril scan, including predictive value (88). False-negative scans can occur in azotemic patients with segmental branch disease. Taken altogether, along with color Doppler sonography,

the captopril renogram is gaining popularity as the initial test to identify RVH.

Reference	RAS	EH	Sensitivity	Specificity (%)	Positive Predictive Value	Negative Predictive Value
DTPA						
Pedersen, et al. (1989)	14	10	93	100	100	91
Dondi, et al. (1990)	52	80	92	96	97	95
Chen, et al. (1990)	23	27	91	93	91	93
Mann, et al. (1991)	35	20	51	100	100	54
Setaro, et al. (1991)	58	55	91	87	88	91
Svetkey, et al. (1991)	31	109	74	44	27	86
Pedersen, et al. (1992)	26	16	76	94	94	96
Dey, et al. (1993)	45	43	89	84	85	88
Mittal, et al. (1996)	45	41	82	90	90	82
IOH						
Mann, et al. (1991)	35	20	43	90	88	47
Erbsloh-Moller, et al. (1991)	28	22	96	95	95	96
Svetkey, et al. (1991)	31	109	71	41	26	83
MAG_3						
Nitzsche, et al. (1991)	18	50	94	88	74	98
Roccatello and Picciotto (1997)						
Standard evaluation	29	20	79	70	79	76
Expected renogram	29	20	79	95	96	76
DTPA or IOH						
Geyskes, et al. (1987)	15	19	80	100	100	86
Fommei, et al. (1991)	208	157	63	84	85	63
Roccatello, et al. (1992)	35	32	92	94	94	91

DTPA, ^{99m}Tc-diethylenetriaminopentaacetate; EH, essential hypertension; IOH, ^{131}I or ^{125}I-ortoiodohippurate; MAG_3, ^{99m}Tc-mercaptoacetylglycylglycylglycine; RAS, renal artery stenosis.
Modified from Pedersen EB: New tools in diagnosing renal artery stenosis. *Kidney Int* 2000;57:2657.

TABLE 23.4. ANGIOTENSIN-CONVERTING ENZYME INHIBITOR RENOGRAPHY WITH DIFFERENT TRACERS IN DIAGNOSING RENAL ARTERY STENOSIS

Contralateral Suppression of Renin Secretion and an Elevated Renal Vein–to–Arterial Renin Relationship: Use of Differential Renal Vein Renin Determinations

The emergence of the captopril renogram coupled with noninvasive imaging of the renal arteries has relegated renal vein renin determinations to a supportive role in difficult cases. However, the understanding of renal vein renin secretion enhances our understanding of RVH.

In view of limitations of the traditional renal vein ratio analysis, a method for analysis of renal values has been devised and is based on the characteristics of experimental two kidney–one clip Goldblatt's hypertension (Table 23.5) (Fig. 23.2).

Collection of samples (moderate sodium intake ± 100 mEq/day)	
Ambulatory peripheral renin and 24-hr urine sodium excretion under steady state conditions (i.e., not on day of arteriography)	
Collection of blood for PRA before and after converting enzyme blockade	
Collection of supine:	
Renal vein renin from suspect kidney (V1) and inferior vena caval renin (A1)	
Renal vein from contralateral kidney (V2) and inferior vena caval renin (A2)	
Enhancement of renin secretion by converting enzyme blockade if initial renin sampling is inconclusive	
Criteria for predicting cure	
High PRA in relation to UNaV	Measurement of hypersecretion of renin
Contralateral kidney: (V2 – A2) = 0	An indicator of absent renin secretion from the contralateral kidney
Suspect kidney: (V1 – A1)/A1 = 0.50	Measurement of reduced renal blood flow
$\frac{(V-A)}{A} + \frac{(V-A)}{A} = 0.50$ in patients with high PRA means	
Incorrect sampling	
Segmental disease	Repeat with segmental sampling

PRA, plasma renin activity.
From Vaughan ED Jr, Sosa TA, Sniderman KW, et al. Renal vein renin secretory patterns before and after transluminal angioplasty in patients with renovascular hypertension: verification of analytic criteria. In: Laragh JH, ed. *Frontiers in hypertension research.* New York: Springar-Verlag, 1981, with permission.

TABLE 23.5. RENIN VALUES FOR PREDICTING CURABILITY OF RENOVASCULAR HYPERTENSION

Hypersecretion of renin, as determined by the renin-sodium index or captopril stimulation, serves as the primary criterion for the diagnosis of RVH. A second criterion is the demonstration of the absence of renin secretion from the contralateral (or noninvolved) kidney. Suppression of renin secretion from this kidney can be determined by subtracting the arterial plasma renin activity (A) from the renal venous renin activity (V). Because the inferior vena caval (IVC) renin and aortic renin are the same, the IVC renin value can be substituted for A in this equation (105). Hence, patients with curable RVH exhibit an absence of renin secretion from the opposite kidney; that is, V – A = 0, also called *contralateral suppression of renin* (115,123). Contralateral suppression of renin indicates that the noninvolved kidney is responding in an appropriate, "normal" fashion to the elevated blood pressure, increased circulatory angiotensin II levels, or increased sodium chloride at the macula densa by shutting off renin secretion. This phenomenon is at times present not only in patients with unilateral renal arterial lesions but also in patients with bilateral disease demonstrated by arteriograms who have a dominant lesion on one side (91).

A third criterion is based on studies of renal vein and arterial vein relationships in patients with essential hypertension. The mean renal venous renin level has been determined to be about 25% higher than arterial plasma renin activity (105). Hence, a total renin increment (both kidneys) of approximately 50% is necessary to maintain a given peripheral renin level: (V – A)/A = 50%. However, a reduction in renal blood flow also influences the renal venous renin level. In this setting, the renal venous renin

concentration is misleadingly high, shifting the renal vein-to-arterial renin relationships upward. Thus the elevation of the increment above approximately 50% becomes an index of the severity of the reduction in blood flow consequent to the obstructing vascular lesion (Fig. 23.5). The combination of these criteria found in a group of patients managed by renal revascularization is shown in Fig. 23.6 (124).

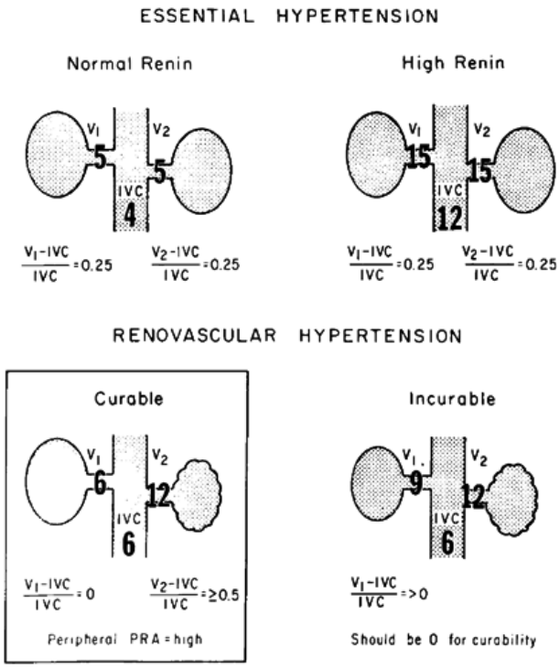

FIGURE 23.5. Renal vein renin diagnostic pattern. In essential hypertension *(top)* at all levels of renin secretion the renin level of each renal vein is approximately 25% greater than either the peripheral arterial or venous levels. In the setting of unilateral renin secretion (curable RVH) the active kidney is solely responsible for maintaining the peripheral renin levels. Hence, the increment is 50% (0.5) and becomes progressively greater as renal blood flow is reduced. Unequal bilateral renin secretion *(bottom right)* indicates bilateral disease and decreases the chance of cure after corrective unilateral surgery. (From Laragh JH, Sealey JE. Renin sodium profiling: why, how and when in clinical practice. *Cardiovasc Med* 1977;2:1503, with permission.)

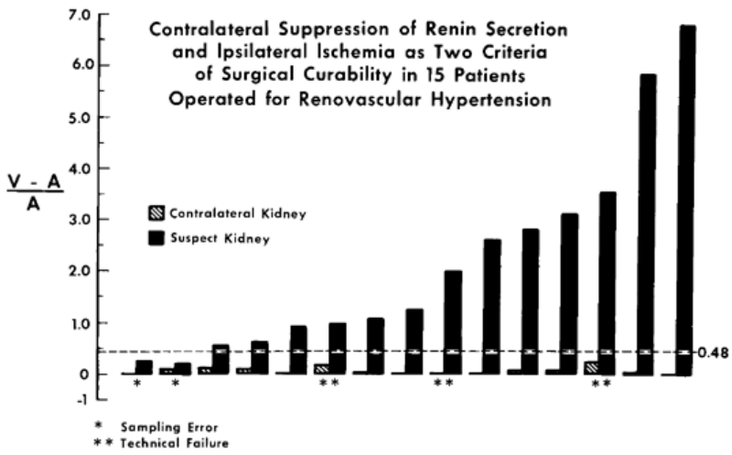

FIGURE 23.6. Of 15 patients with renovascular hypertension, 13 exhibited (V – A)/A in excess of 48% from the suspect kidney and a suppressed value from the contralateral kidney. V is renal venous plasma renin activity; A is arterial or infrarenal inferior vena cava plasma renin activity. Asterisks (**) denote the three patients who had values suggesting surgical curability yet had residual or recurrent hypertension resulting from technical failure. (From Vaughan ED Jr, Carey RM, Ayers CR, et al. A physiologic definition of blood pressure response to renal revascularization in patients with renovascular hypertension. *Kidney Int* 1979;15:S83, with permission.)

An additional aid to renal vein sampling is the utilization of segmental renal venous sampling (102), especially in cases in which sampling of blood from the major renal vein fails to demonstrate a combined renin increment of 50% from both kidneys, suggesting either a technical error or segmental disease. This approach may be particularly helpful in children with segmental parenchymal disease (87).

The patterns of renal vein renin activity in bilateral RVH are less consistent than in unilateral disease (92).

Validation of the Four Criteria

In addition to a favorable clinical response to renal angioplasty, we also have had the unique opportunity to study the effect of restoration of blood flow on renal vein renin concentration and renin excretion (92,126). To accomplish this goal we have monitored the immediate effect of successful angioplasty on renal renin secretion. Thirty minutes after angioplasty, a marked reduction was noted in the renal vein renin from the previously stenotic side (Fig. 23.7). The residual ipsilateral increment of renal vein renin was approximately 50% above the peripheral level, whereas contralateral renin suppression persisted. This 50% increment has been predicted previously to occur in the setting of unilateral renin secretion and normal renal blood flow (105).

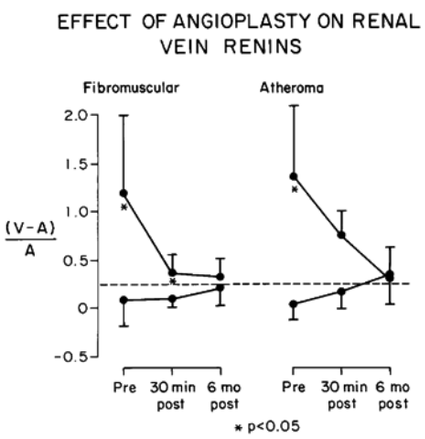

FIGURE 23.7. Effect of angioplasty on renal vein renins. Samples were taken immediately before angioplasty, 30 minutes after, and 6 months later. The higher values were for the ischemic kidney, the lower for the contralateral kidney. Asterisks (*) indicate significant difference between the two kidneys, and the *dotted line* is the normal level of (V – A)/A (0.24). (From Pickering TG, Sos TA, Vaughan ED Jr, et al. Predictive value and changes of renin secretion in hypertensive patients with unilateral renovascular disease undergoing successful renal angioplasty. *Am J Med* 1984;76:398, with permission.)

The finding that the renal renin secretory characteristics of RVH reverse after successful angioplasty with correction of the hypertension is strong support that they truly reflect the abnormal secretory behavior of renin in curable RVH.

Color Doppler Sonography

Renal sonography has rapidly evolved from a technique that gave only anatomic information to a functional test. The advances include the use of a Doppler probe (116), the color

technique, the use of contrast (74), and the captopril Doppler sonogram (128). Similar to the captopril renogram, several indexes have been used: peak systolic velocity, renal aortic ratio, end-systolic index, acceleration time, and acceleration index. The overall results as compiled by Pedersen (88) are shown in Table 23.6 .

	Patients N		Arteries N						
Reference	EH or Controls	RAS	Controls	Stenotic Arteries	Degree of Stenosis	Sensitivity	Specificity (%)	Positive Predictive Value	Negative Predictive Value
Postma, et al. (1992)	46	24		29	50	63	86	83	68
Stavros, et al. (1992)	30	26		32	60	95	97	92	98
Kliewer, et al. (1993)	23	23		28	80	66	67		
Schwerk, et al. (1994)	53	19		19	50	82	92		
Olin, et al. (1995)			63	124	60	98	98	99	97
Spies, et al. (1995)			153	42	50	93	92	77	98
Krumme, et al. (1996)	47	88		107	50	89	92	92	88
Miralles, et al. (1996)	34	44	98	58	60	87[c]/76[d]	91[c]/92[d]	86[c]/86[d]	92[c]/87[d]
Missouris, et al. (1996)			24	16	60	85[e]/94[f]	79[e]/88[f]		
Postma, et al. (1996)	52[d]	19			50	47	97		
Nazzal, et al. (1997)			70	73	50	89[b]/63[g]	92[b]/98[g]	85[b]/91[g]	94[b]/87[g]
Riehl, et al. (1997)	161	53		59	70	93	96	93	98

[a]Technical failure in 15 of 61 patients.
[b]Test parameter was acceleration index.
[c]Test parameter was peak systolic velocity in the renal artery.
[d]Technical failures in 5 of 57 patients.
[e]Without ultrasound contrast enhancement.
[f]With ultrasound enhancement.
[g]Test parameter was acceleration time.
[h]Test parameter was renal/aortic ratio.
EH, essential hypertension; RAS, renal artery stenosis.
From Pederson EB. New tools in diagnosing renal artery stenosis. *Kidney Int* 2000;57:2657.

TABLE 23.6. COLOR DOPPLER SONOGRAPHY IN DIAGNOSING RENAL ARTERY STENOSIS

The major difficulties have been in the development of competent personnel with experience. Moreover, obesity and intestinal gas are limitations. Other variables include whether attention is placed on intrarenal vessels, which cannot always be localized (99), or directly on the main renal artery (73). Regardless of differences in technique, the test is gaining wider usage (52). Again, a positive test requires anatomic confirmation.

Imaging Studies

Following a positive screening test, the traditional approach has been renal angiography followed immediately by angioplasty if possible. In a patient in whom there is a high index of clinical suspicion, angiography is still preferred (Fig. 23.8) (90).

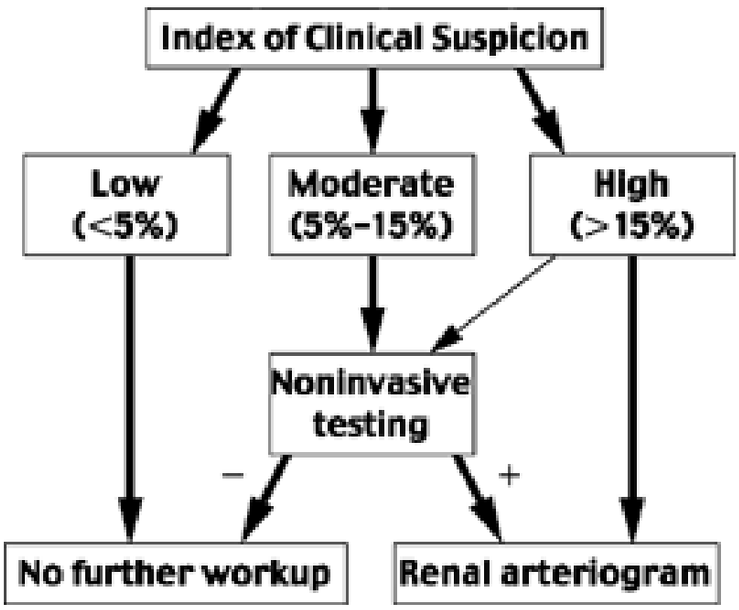

FIGURE 23.8. Suggested workup of a patient suspected of having renovascular disease. (From Pickering TG, Blumenfield JD. Renovascular hypertension and ischemic nephropathy. In: Brenner BM, ed. *The kidney.* Philadelphia: WB Saunders, 2000:2007.)

Recently, two newer, less invasive techniques are being used to diagnose renal artery stenosis.

Spiral Computed Tomography Angiography

The development of spiral CT has permitted data acquisition during a single breath hold. The scanning time is

approximately 35 seconds, the examination time is approximately 20 minutes, and the data analysis takes approximately 30 minutes. The results are impressive (Fig. 23.9). This technique is now being used routinely to evaluate renal donors (94). The reported sensitivity ranges from 88% to 98% and the specificity ranges from 82% to 98%, giving a positive predictive value greater than 85% (88). The one caveat is that a relatively high volume (150 mL) of contrast is given peripherally; thus there is a risk of nephrotoxicity. In addition, the accuracy appears to be decreased in azotemic patients.

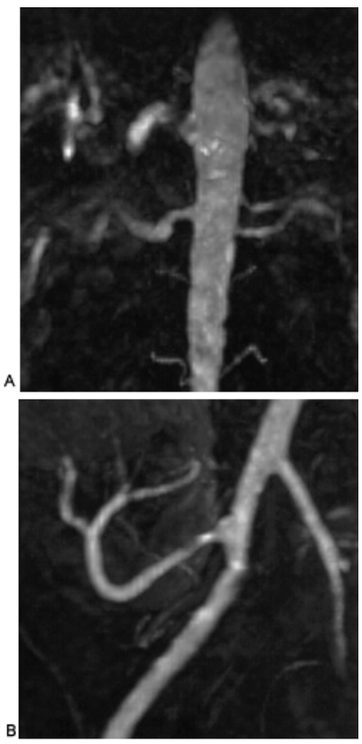

FIGURE 23.9. Spiral computed tomography scans showing bilateral renal artery stenosis **(A)** and stenosis of a transplant renal artery **(B)**.

Magnetic Resonance Angiography

The two MRA techniques used are time-of-flight and phase-contrast sequences. MRA avoids the problem of renal toxicity but is limited to visualization of the main renal artery and the larger branches (39) (Fig. 23.10). The use of gadolinium may enhance the sensitivity of the technique (109). The technique is most useful in patients with atherosclerotic

disease where the lesion is in the proximal renal artery, particularly if the patient has impaired renal function.

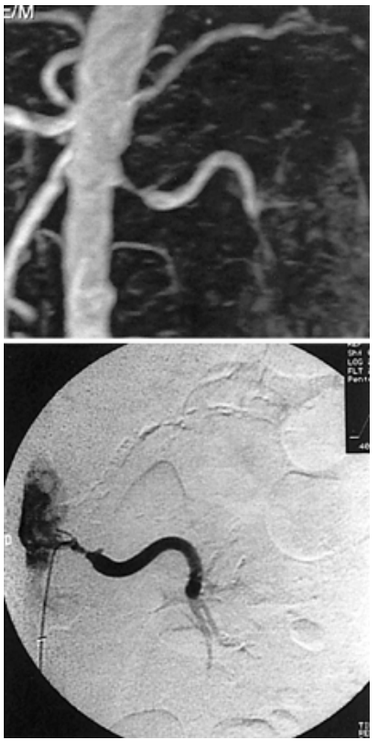

FIGURE 23.10. Three-dimensional, gadolinium-enhanced magnetic resonance angiography showing a thrombosis of the left renal artery and severe stenosis of the left renal artery. [From Grenier N, Trilland M. 2000;86(Suppl):84.]

Identifying the Potentially Curable Patient

The approach of Pickering and Blumenfeld (90) already alluded to (Fig. 23.8) seems rational. Thus the low-risk patient, in whom screening tests have low predictive value, is initially treated without evaluation. In contrast, for high-risk patients (Table 23.2), angiography is the initial study. Patients at moderate risk begin their evaluation with either a captopril renogram or a color duplex Doppler scan. If the test is negative, no additional studies are done. If the initial test is positive, anatomic localizing tests are necessary.

Ischemic Nephropathy

The other entity associated with renal artery stenosis is ischemic nephropathy. Thus renal artery stenosis is an important cause of chronic renal insufficiency due to a reduction in GFR (50,79,100).

Hypertension is now the most common cause of end-stage renal disease (ESRD) in patients older than 65 years of age (56). The subset of these patients with renal artery stenosis is unclear. However, in one study, 83 of 687 dialysis patients (12%) were found to have renal artery disease (65). Novick and colleagues (82) established the following criteria

for screening for atherosclerotic renal artery disease: (a) evidence of generalized atherosclerosis, (b) a unilateral small kidney, and (c) mild to moderate azotemia (serum creatinine greater than 1.5 mg/dL). If the patient was found to have a high-grade stenosis (greater than 75%) bilaterally or in a solitary kidney, intervention was recommended (82).

Preservation of renal function has been demonstrated after renal revascularization (4) or angioplasty (13,104). However, randomized trials, now in progress, are necessary to prove that intervention is more successful than medical management in forestalling ESRD.

In addition, the evaluation previously described using peripheral and renal vein renin determinations are often inaccurate in azotemic patients. Thus color Doppler or MRA studies are necessary to exclude ischemic nephropathy as the cause of azotemia.

TREATMENT OF RENOVASCULAR HYPERTENSION

Part of "23 - RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY "

The therapeutic options for the treatment of RVH include percutaneous transluminal angioplasty, renal artery stent placement, surgical revascularization, autotransplantation, pharmacologic interference of the RAS, and removal of the ischemic kidney.

Renal Artery Angioplasty for Renovascular Hypertension

Percutaneous transluminal angioplasty was first introduced by Dotter and Judkins in 1964 for the treatment of peripheral vascular stenoses. The introduction of flexible, double-lumen balloon catheters by Gruntzig and Hopff (40) permitted the development of percutaneous transluminal angioplasty of renal artery stenoses. The fibromuscular dysplasias and unilateral, nonostial, nonoccluded atherosclerotic renal artery stenoses are the most suitable lesions for treatment with percutaneous transluminal renal angioplasty (PTRA). The ability to avoid a general anesthetic and the relatively low morbidity of this procedure have allowed renal revascularization in patients who might have been deemed unsuitable for surgery secondary to concurrent present diseases. However, PTRA does have inherent limitations and is not suitable for dilation of ostial lesions or arterial occlusions. Therefore careful patient selection is necessary. In addition, percutaneous transluminal angioplasty is not universally available because it can be performed only by well-trained and skilled interventional radiologists with a vascular surgical team backup.

Technical success is defined as complete if the residual stenosis is 50% or less and as partial if the residual stenosis is 50% to 70% (110). The criteria to determine blood pressure are those of the national cooperative study on RVH (33). A decrease in the diastolic blood pressure to less than 90 mm Hg in the absence of antihypertensive medication is considered a cure, and a decrease in diastolic blood pressure of 15% or greater with or without antihypertensive medication is considered an improvement. A decrement in diastolic blood pressure of less than 15% is considered a failure.

Renal artery angioplasty is technically successful in approximately 80% of patients with atherosclerotic renal disease. However, the cure rate is only about 30%, with 50% improved, probably due to generalized disease. Nonostial, nonoccluded unilateral lesions were noted to be most amenable to angioplasty. Ostial lesions, total renal artery occlusions, and bilateral lesions, which often tend to be ostial and occluded, did not respond satisfactorily to angioplasty. The technical success rate in these patients as a group was 12% (110). Ostial lesions result from aortic plaques that impinge on the renal artery orifice. Inflation of the balloon catheter displaces the plaque, with recoil and assumption of the original position, occurring at deflation of the balloon. Martin and colleagues (70) reported a 25% blood pressure benefit with no cures for a group of 20 patients with ostial lesions. The development of renal artery stents now allows ostial lesions to be treated successfully with percutaneous angiographic techniques. In patients with bilateral RVH, the cure rate was a disappointing 5% and the improvement rate 41% in contrast to a 25% cure and a 47% improvement rate for patients with unilateral disease.

Renal artery angioplasty has been more successful in the treatment of the fibromuscular dysplasias. In approximately 90% of patients, the stenosed arteries are dilated successfully. Of this subgroup, 88% enjoyed a blood pressure benefit as a result of the treatment (38% cured and 50% improved). Restenosis after dilation occurred in fewer than 5% of cases in a review of long-term follow-up (117).

Complications of PTRA are reported in 10% of cases and include trauma to the access vessels (femoral or axillary) with hemorrhage. Renal artery damage by dissection, aneurysm formation, perforation, and balloon malfunction or rupture has been reported (19,31,117). Cholesterol embolization of the kidney with resulting loss in renal function or of the lower extremities resulting in distal vascular compromise have been reported. Complications of angioplasty resulting in the loss of renal unit have been infrequent, and associated deaths have been rare.

Renal Artery Stents

Patients whose renal artery strictures cannot be adequately dilated by angioplasty or whose arteries restenose following an initially successful dilation have limited therapeutic alternatives. However, an exciting alternative treatment currently is being used for these patients. A stainless steel balloon-expandable stent may be placed across a stricture to reestablish the renal artery lumen. The stents (Fig. 23.11) are 1 to 3 cm in length and may be expanded to a diameter of 4 to 9 mm (medium stents) or 8 to 12 mm (large stents).

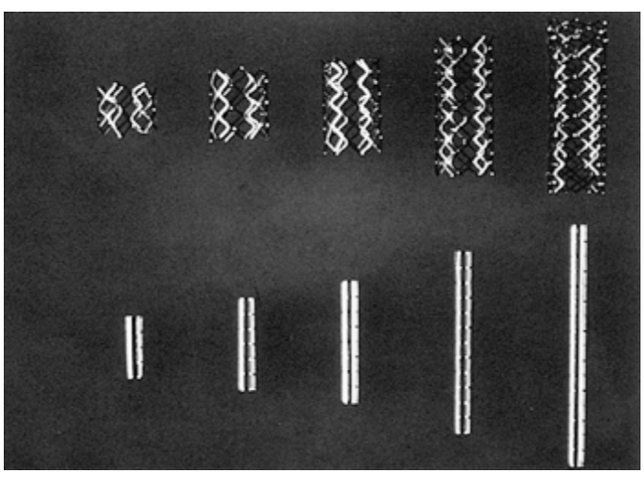

FIGURE 23.11. Palmaz stents for treatment of renal artery stenosis. Stents of various lengths are seen in the *lower row.* The *upper row* shows the stents after balloon expansion.

The renal artery stents are placed by angiographic techniques. Percutaneous transluminal angioplasty precedes introduction of a renal artery stent. If adequate dilation is not established, a stent is positioned across the renal artery stricture and is balloon expanded to reestablish the lumen. The Department of Radiology at the New York Hospital–Cornell Medical Center placed 24 stents to treat 23 renal artery stenoses in 21 patients between May 1989 and December 1993 (122). One patient was treated for a transplant renal artery stenosis. The remaining 20 patients had ostial, atherosclerotic renal artery lesions, which are generally refractory to percutaneous angioplasty. Eight stents (33%) were placed immediately following an inadequate percutaneous renal artery angioplasty. Sixteen stents (66%) were placed following a restenosis.

The percent stenosis for this group of patients was angiographically determined to be 86.3% ± 9.8%. Immediately after stent placement, the percent stenosis decreased to 1.67% ± 8.1%. At a mean angiographic follow-up of 7.6 months (range of 3 to 12 months), the percent stenosis was found to be 44% ± 23% (p < 0001 when compared with the prestent angiogram). Restenosis appeared to be due to endothelial ingrowth into the stent and not to stent compression or kinking. In 11 patients, the hypertension was cured (3 patients) or improved (8 patients). Although individual patients enjoyed improvement in renal function (7 of 11 patients with a creatinine greater than 1.5 mg/dL improved), the change in renal function for this small group as a whole was not statistically significant. Of 21 patients, 15 (71%) benefited from this procedure by an improvement in renal function, an improvement in blood pressure control, or both.

In looking at these preliminary results, it must be borne in mind that patients with recurrence of ostial renal artery lesions have a high failure rate when managed by angioplasty alone. Surgical revascularization is associated with much greater morbidity and mortality rates than angioplasty. Medical management can be complicated by progressive loss of renal function despite good blood pressure control. Table 23.7 reviews renal function after angioplasty (90).

TABLE 23.7. RENAL FUNCTION AFTER RENAL ANGIOPLASTY

Reference	Patients	Outcome			
		Improved	Stable	Worse	Death
Luft, et al. 1983 (64)	12	3 (25)	5 (42)	4 (43)	0 (0)
Pickering, et al., 1986 (93)	55	26 (47)	19 (35)	10 (18)	NA
Bell, et al., 1987 (5)	20	7 (35)	10 (50)	3 (15)	0 (0)
O'Donovan, et al., 1992 (84)	17	9 (53)	2 (12)	6 (35)	5 (29)
Martin, et al., 1992 (69)	79	34 (43)	45 (57)[b]		1 (1)
Canzanello, et al., 1989 (11)	69	36 (52)[c]		33 (48)	
Dorros, et al., 1998 (26)	163				3 (2)
	124 unilateral	41 (33)	41 (33)	42 (34)	
	39 bilateral	15 (38)	16 (42)	8 (21)	
Total	**415**	**171 (41)**	**138 (33)**	**106 (26)**	**9 (2)**

[a]Indicates renal artery stent placement during angioplasty.
[b]Indicates sum of stable and worse.
[c]Indicates improved and stable.
( ), percent of patients from each study; NA, data not available.

Case I

A 73-year-old woman, following a right nephrectomy many years before, had a 30-year history of hypertension. She was found to have a significant ostial lesion that could not be dilated by percutaneous transluminal angioplasty (Fig. 23.12). She underwent renal stent placement (Fig. 23.13). Seven months after stent placement, her renal artery remains patent and her creatinine and blood pressure are improved and stable (Fig. 23.14).

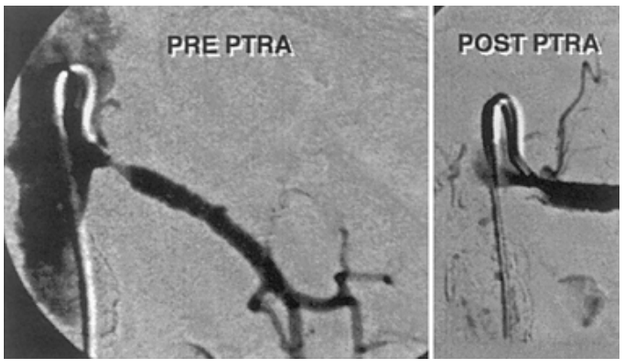

FIGURE 23.12. An ostial, left renal artery lesion is angiographically defined before percutaneous transluminal renal angioplasty **(PTRA).** After dilation, the lumen is larger. The renal artery stent can be positioned on an angioplasty balloon across the stenosis and expanded.

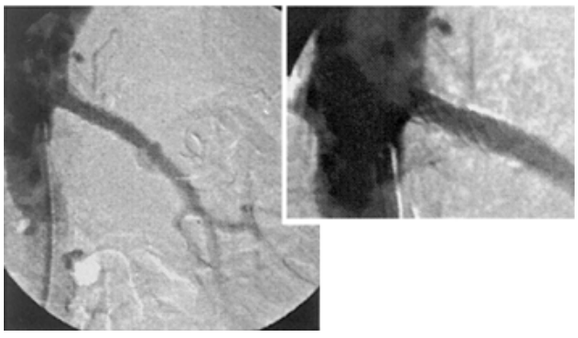

FIGURE 23.13. Poststent. A wide-caliber ostium and renal artery can be seen after the stent is expanded. The cone-down view on the inset allows the expanded stent to be recognized across the ostium and proximal renal artery.

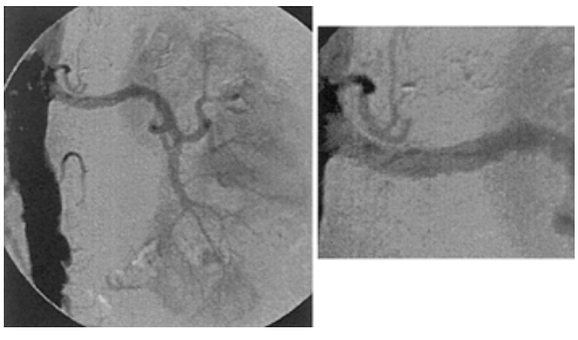

FIGURE 23.14. At a 7-month angiographic follow-up, the left renal artery and ostium remain open.

Case II

A 53-year-old white woman with a long history of hypertension has bilateral atherosclerotic ostial lesions. Percutaneous transluminal angioplasty on two lesions failed to correct her stenoses. The patient had diabetes mellitus, hypertension, and gradients of 100 mm Hg across each stenosis (Fig. 23.15). Renal artery stents were placed bilaterally (Fig. 23.16), with disappearance of the gradients and improvement in her blood pressure control.

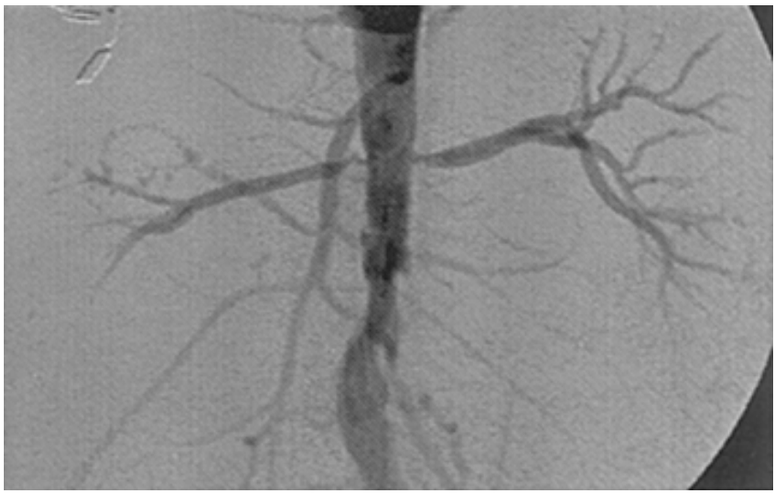

FIGURE 23.15. The angiogram of a 53-year-old white female with IDDM, hypertension, and an abdominal bruit reveals bilateral atherosclerotic ostial lesions. The gradient measured across each stenosis was 100 mm Hg (see Case II).

FIGURE 23.16. An angiogram performed immediately following bilateral renal stent placement reveals wide-open lumina. There was no pressure gradient across the ostia.

Surgical Treatment for Renovascular Hypertension

The first surgical treatment described for RVH was nephrectomy (61). During the 1940s and 1950s, small kidneys

were removed from hypertensive patients with the idea of controlling the blood pressure. In 1956, a careful review of the effects of nephrectomy on the treatment of hypertension revealed a dismal 19% success rate. However, it was appreciated that patients with unilateral renovascular disease fared somewhat better than patients with unilateral renal parenchymal disease (120). This observation plus the development and widespread use of angiography in the 1950s redirected the focus of surgical treatment of renovascular disease to revascularization of ischemic kidneys. Freeman and colleagues (34) pioneered revascularization of ischemic kidneys by performing aortic and bilateral renal artery thromboendarterectomy to treat hypertension. Aortorenal bypass quickly became the preferred method of renal revascularization, and angiography was relied on as the definitive test to predict blood pressure response to surgical correction.

The national cooperative study on RVH (33) reviewed the efficacy of surgically correcting renal artery lesions to cure hypertension. Despite a 51% cure rate, the results revealed a disappointing 34% failure rate and an unacceptable operative mortality rate approaching 10%. The patients at highest risk for operative morbidity and mortality were those with concurrent coronary or cerebrovascular disease or with bilateral renovascular disease often associated with azotemia.

In the past decade, the results of surgical renal vascularization have improved as a result of better patient selection, which can be attributed to a better understanding

of the natural history of renal artery disease, to a better understanding of the physiology and pathophysiology of the renin-angiotensin-aldosterone system, and to the development of pharmacologic probes that serve as highly reliable screening tests. There is growing recognition that patients with decreased renal function, even those with total occlusion of a renal artery, may recover renal function and enjoy a blood pressure benefit after renal revascularization (63). In the latter group, angiography demonstrates a delayed nephrogram because of a rich network of collateral vessels that preserve renal morphology and function. In patients with a preoperative serum creatinine level of less than 3 mg/dL, postoperative renal function was stable and improved in 89%. Conversely, renal revascularization in patients with a baseline serum creatinine level of greater than 4 mg/dL was not worthwhile because advanced underlying renal parenchymal disease prevented improvement in renal function. Table 23.8 reviews renal function after surgical revascularization (90).

		Outcome			
Reference	Patients	Improved	Stable	Worse	Death
Luft, et al., 1983 (64)	12	8 (67)	2 (17)	2 (17)	2 (17)
Jamieson, et al., 1984 (51)	23	15 (65)	0 (0)	8 (35)	4 (17)
Novick; et al., 1987 (83)	153	93 (61)	50 (33)	140 (6)	5 (3)
Hallett, et al., 1987 (42)	91	20 (22)	48 (53)	23 (25)	6 (7.1)
Hansen, et al., 1989 (43)	25	12 (48)	11 (44)	2 (8)	2 (8)
Dean, et al., 1991 (24)	53	31 (59)	15 (28)	7 (13)	5 (9)
Messina, et al., 1992 (71)	17	12 (71)	2 (12)	3 (18)	1 (6)
Bredenberg, et al., 1992 (6)	40	22 (55)	10 (25)	8 (20)	NA
Libertino and Beckmann, 1994 (62)	91	45 (46)	31 (32)	15 (16)	6 (7)
Fergany, et al., 1994 (30)	18	4 (22)	13 (72)	1 (6)	0 (0)
Total	**523**	**262 (50)**	**182 (35)**	**79 (15)**	**31 (6)**

(), percent of patients.

TABLE 23.8. RENAL FUNCTION AFTER SURGICAL REVASCULARIZATION

The previously unacceptable operative morbidity and mortality rates associated with renal revascularization have improved substantially by careful patient selection and preparation. It has been recognized that concurrent coronary and cerebrovascular disease and bilateral renovascular disease with azotemia greatly increase the risk of operative intervention (81). Accordingly, cardiac and cerebral revascularization are performed, when appropriate, before renal revascularization. Using this protocol, operative morbidity and mortality rates have been greatly reduced. Novick and colleagues (81) achieved a 91% blood pressure benefit in 100 consecutive renal revascularizations for atherosclerotic RVH. Bilateral revascularization is not routinely performed. Instead, the more severely affected kidney is revascularized first. Contralateral repair is reserved for patients with persistent hypertension in whom repeat renal vein renins lateralize to the unoperated side.

Aortorenal bypass with an autogenous vascular graft is the surgical treatment of choice for renal revascularization. The saphenous vein is employed most commonly. Patients with branch renal artery stenosis can be treated with multiple branch grafts employing microsurgical techniques *in vivo* or with *ex vivo* bench surgery (82). Branch intraparenchymal stenoses also may be amenable to intraoperative dilation with rigid dilators (Fig. 23.17) or angiographic-type balloon catheters introduced through the main renal artery. Most patients with bilateral disease require repair of only one side (82,118). If a bilateral repair is planned, it is performed most safely as a staged procedure.

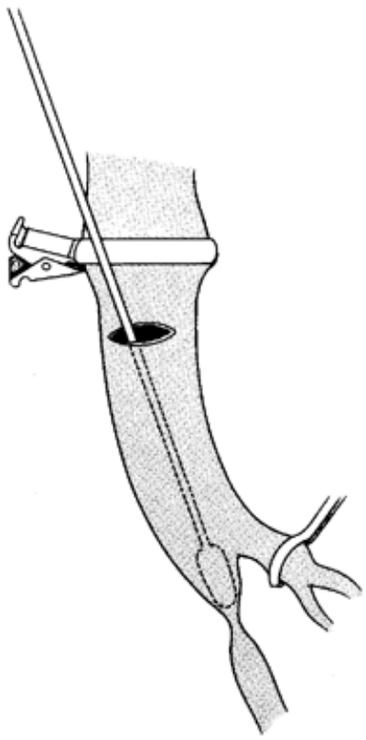

FIGURE 23.17. Intraoperative dilation of a stenosed renal artery branch with a rigid dilator.

In patients with severe aortoiliac disease, it is possible to revascularize the kidneys without performing a complete aortic replacement. Libertino and colleagues (63) developed and described hepatorenal and splenorenal bypass operations

to revascularize the right and left kidneys, respectively (18). The splenorenal bypass requires patent celiac and splenic arteries. A single end-to-end vascular anastomosis is fashioned (Fig. 23.18). The spleen is preserved and nourished by collateral short gastric arteries.

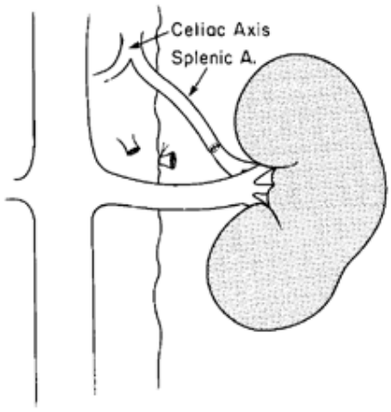

FIGURE 23.18. End-to-end splenorenal bypass to the left kidney.

The hepatic artery is ideal for bypass to the right kidney because this vessel rarely is involved by atherosclerotic disease. The most common method of hepatorenal bypass is interposition of a saphenous vein graft, end-to-side to the common hepatic artery, just beyond the gastroduodenal artery (Fig. 23.19). If the right hepatic artery is used, the gallbladder becomes ischemic, and an adjunctive cholecystectomy is necessary (Fig. 23.20). An end-to-end gastroduodenal-renal anastomosis with saphenous vein interposition also is feasible (Fig. 23.21), although the gastroduodenal artery is difficult to mobilize. Results of follow-up studies of 1 to 8 years (mean of 4 years) after hepatorenal bypass are encouraging (18). The operation was successful in 33 of 36 patients (92%). There was no evidence of permanent hepatic impairment, graft stenosis, or late complications within this period of follow-up.

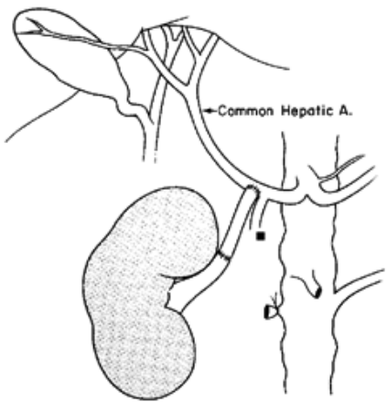

FIGURE 23.19. End-to-side hepatorenal bypass, from the common hepatic artery to the right renal artery with a saphenous vein graft interposition.

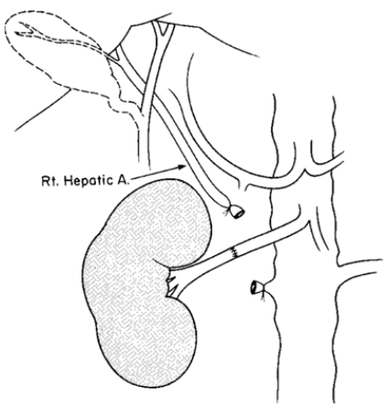

FIGURE 23.20. End-to-end hepatorenal bypass from the right hepatic artery to the right renal artery. An adjunctive cholecystectomy is necessary, because the gallbladder loses its nutrient artery.

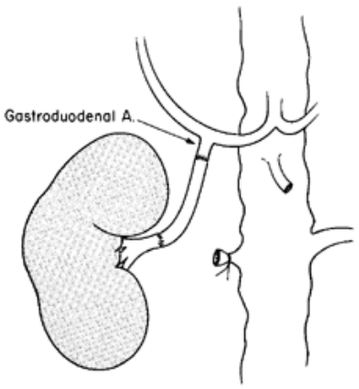

FIGURE 23.21. End-to-end gastroduodenal-renal artery anastomosis with a saphenous vein interposition.

Renal autotransplantation and iliorenal bypass with a long saphenous vein graft are useful alternative techniques for renal revascularization in patients with severe aortic atherosclerosis and absence of severe iliac disease (Fig. 23.22 and Fig. 23.23). However, the atherosclerotic process may progress to involve the iliac vessels and compromise the blood flow of the revascularized kidney. Accordingly, Novick and colleagues (82) recommend that renal autotransplantation be considered only when a splenorenal or hepatorenal bypass cannot be performed. Early results after renal revascularization are favorable. However, data on the durability of vascular anastomoses and the long-term blood pressure benefit are more limited. Dean (22) reviewed

the 20-year experience at Vanderbilt University with aortorenal bypass. He found that blood pressure was cured or improved in 95% of patients with fibromuscular renal artery disease and in 78% of patients operated on for atheromatous renal artery disease. The beneficial effect of operative treatment was maintained in this group over a follow-up period of up to 23 years. Dean (22) noted that the fate of a bypass graft is determined by several factors. These include the graft material, its length, and the flow through the conduit, as well as the surgical prevision of the anastomosis. A short graft length and high flow rate are favorable for long-term patency. An autogenous artery would seem the ideal graft to use.

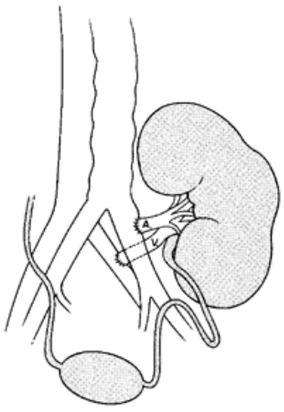

FIGURE 23.22. Renal revascularization by autotransplantation leaving the ureter intact.

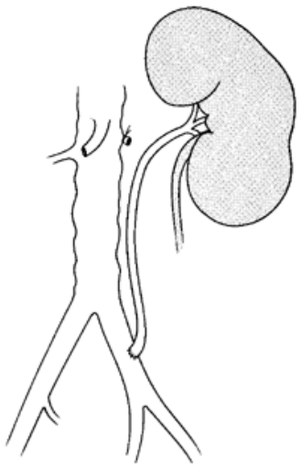

FIGURE 23.23. Renal revascularization by ileorenal bypass by means of a long saphenous vein graft.

Wylie (133) used the hypogastric artery for renal revascularization. He reported 98% patency and no late degenerative changes at a 5-year follow-up. The hypogastric autograft has particular appeal in the pediatric patient, because the graft enlarges with age in proportion to the increased demand for flow. However, the iliac arteries are not immune from the fibromuscular and atherosclerotic diseases involving the renal arteries and may succumb to these same disease processes or may already be involved at the time that renal revascularization is planned.

Venous autografts are structurally weaker than arterial autografts and represent an increased risk for aneurysmal degeneration. The saphenous vein has been used frequently in aortorenal revascularization. There is a 3% to 7% degeneration in follow-up of at least 1 year (22,27). Dacron was previously employed as a synthetic graft, but recently, polytetrafluoroethylene (Gore-Tex) grafts are preferred because of greater ease in suturing. Synthetic grafts also have the advantage of being available in a variety of sizes. However, they are subject to anastomotic aneurysmal degeneration and stenosis.

The results of surgical revascularization from the experience at the Cleveland Clinic are shown in Table 23.9 (80). The surgical techniques used in this series are shown in Table 23.10 . The postoperative renal function was improved or stabilized in 89% of the patients with atherosclerotic renovascular disease who underwent renal revascularization.

TABLE 23.9. RESULTS OF SURGICAL REVASCULARIZATION OF RENOVASCULAR HYPERTENSION AT THE CLEVELAND CLINIC

		Postoperative Blood Pressure			
	No. of Patients	Cured (%)	Improved (%)	Failed (%)	Follow-up (mo)
Atherosclerosis	180	55 (31)	110 (61)	15 (6)	6–117
Fibrous dysplasia	104	66 (63)	31 (30)	7 (7)	10–115

From Novick AO. Surgical management of renovascular hypertension. In: Kaplan NM, Brenner BM, Laregh JH, eds. *The kidney in hypertension.* New York: Raven Press, 1987, with permission.

TABLE 23.10. SURGICAL REVASCULARIZATION TECHNIQUE FOR RENAL ARTERY DISEASE AT THE CLEVELAND CLINIC

	Atherosclerosis (n = 254)	Fibrous Dysplasia or Aneurysm (n = 126)
Aortorenal bypass	138	82
Splenorenal bypass	42	4
Hepatorenal bypass	29	0
Iliorenal bypass	19	0
Autotransplantation	8	1
Aortic replacement	11	0
Ex vivo repair and autotransplantation	0	37
Other	7	2

From Novick AO. Surgical management of renovascular hypertension. In: Kaplan NM, Brenner BM, Laregh JH, eds. *The kidney in hypertension.* New York: Raven Press, 1987.

Darling and co-workers (21) recently published a large series that emphasizes the success of renal artery reconstruction in a series of 568 complex cases. The cases were selected because of extensive disease in the angioplasty era. For example, 406 patients had a coexisting abdominal aortic aneurysm, 125 had aortoiliac occlusive disease, and in only 156 (23%) was renal revascularization the primary procedure. Remarkably, the death rate was only 5.5% and the occlusion rate was only 2.8% (21). Moreover, the long-term (5 years) patency rate was 95%. In patients who underwent reconstruction for symptomatic lesions, 26% improved, 68% stabilized, and 6% worsened.

Medical Management of Renovascular Hypertension

Medical management of RVH has been unsatisfactory in the past. Hunt and colleagues (49) followed up 214 patients with RVH for 7 to 14 years. One hundred patients were selected for surgical therapy after failing to respond to 3 months of medical therapy. Patients treated medically had a higher mortality rate (40% versus 16%) and overall less effective control of their blood pressure than their surgically treated counterparts. Dean and colleagues (23) medically treated 41 patients with RVH. They found that the arterial

stenosis progressed in 41% of patients and that progression to complete occlusion occurred in 12%. In all fairness to the medical management of RVH, it must be pointed out that the drugs used in these studies were far less specific to control a hyperactive RAS than the ß-adrenergic blockers and CEIs available today. These newer drugs have been more effective in controlling blood pressure in patients with fibromuscular dysplasia than in those with atherosclerotic renovascular disease. Patients in the latter group tend to be older, have more target organ damage, and require more drugs for blood pressure control than the younger patients with fibromuscular disease.

Despite the greater specificity of these drugs for the RAS, their safety and efficacy in the treatment of RVH remain in doubt. Many reports have documented the onset of reversible decrease in renal function associated with use of CEIs in patients with bilateral renal artery stenosis or stenosis of the renal artery to a solitary kidney (54). The decrement in renal function does not appear to be caused entirely by the depressor effect of these drugs, because lowering the blood pressure to the same degree with a drug that does not interfere with the RAS does not usually lead to a comparable decrease in renal function. Micropuncture studies suggest that at low perfusion pressures the glomerular capillary hydrostatic pressure is increased by an angiotensin II–dependent constriction of the efferent arteriole (41). Inhibition of angiotensin II formation in the setting of a decreased perfusion pressure lowers glomerular filtration. Discontinuation of the CEI restores renal function to baseline.

Unfortunately, the drug-induced decrease in renal function is not limited to patients with bilateral renal artery disease. Experimental administration of CEIs in two kidney–one clip animals reveals that the ischemic kidney has a severe decline in GFR, whereas the contralateral kidney remains unaffected (130). Clinically, Wenting and colleagues (131) demonstrated, with the use of nuclear renal scans, significant impairment of renal function in the ischemic kidney of patients with unilateral renal artery stenosis treated with captopril.

Textor and colleagues (118) argued against medical management for RVH beyond the use of CEIs, possibly to implicate a wide range of antihypertensive medications. In eight patients with bilateral renal artery disease in which both renal arteries had luminal stenoses of 75% or greater, decreasing the blood pressure from a baseline of approximately 200/100 to 140/85 mm Hg by graded increases in intravenous nitroprusside produced significant decreases in total renal plasma flow and GFR. Nitroprusside is known to increase renin secretion, and therefore interference with the autoregulatory actions of angiotensin II cannot be implicated. It appears that renal units whose blood flow is already compromised cannot tolerate reduction in blood pressure to clinically relevant levels.

Four of those eight patients underwent unilateral renal revascularization of the more ischemic kidney. Although renal function per se was not significantly improved by surgery, repeated challenge with graded nitroprusside infusions, attaining the same lower levels of blood pressure, did not lower renal plasma flow or GFR. This observation strongly suggests that revascularization may protect the kidneys from loss of renal function when the blood pressure is lowered to clinically desirable levels by antihypertensive medicines (118).

Finally, it must be borne in mind that RVH is a vascular disease whose manifestations can include loss of renal function

and renin-dependent hypertension. Pharmacologic treatment of the hypertension does not address the cause of the problem. However, despite the superior results generally achieved by the revascularization of a renal artery stenosis, there is a role for medical management in the treatment of RVH. Medical management must be employed in patients who have not benefited from angioplasty or surgical revascularization, in patients who are not candidates for intervention because of the presence of other serious diseases, and in those who have refused intervention. Whatever the case, all patients with RVH who are treated pharmacologically must be evaluated carefully and routinely for changes in renal function and size (25).

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24

THE URETER

Robert M. Weiss

R.M. Weiss: Section of Urology, Department of Surgery, Yale University School of Medicine, Yale–New Haven Hospital, New Haven, CT 06520.

Contents

The function of the upper urinary tract is to transport urine from the minor calyces toward the bladder and to protect the renal parenchyma and cranial portions of the urinary tract from distally generated backflow and back-pressure. Peristaltic activity begins with the origin of the electrical activity at pacemaker sites situated in the proximal portion of the renal collecting system (20,34,66,106,211,231,242). The electrical activity is transmitted distally from cell to cell and gives rise to the ureteral contraction wave, which propels the bolus of urine distally. Efficient collection and propulsion of urine is dependent on the passive and active properties of the ureter and on the ability of the ureter to coapt its walls completely (240). Urine passes into the bladder via the ureterovesical junction (UVJ), which under normal conditions permits antegrade transport of urine from the ureter into the bladder and prevents retrograde passage of urine from the bladder into the ureter.

ANATOMY

Part of "24 - THE URETER "

Gross Anatomy

The ureter is a 25- to 30-cm-long tube extending from the renal pelvis to the bladder. The three narrowest areas of the ureter are (a) at the ureteropelvic junction (UPJ), (b) at the site where the ureter crosses the iliac vessels, and (c) at the intramural portion of the distal ureter. It is at these sites that calculi most frequently become impacted.

As the ureter descends in a medial direction from the kidney, it lies on the psoas muscle in close apposition to the peritoneum, to which it is attached. In its abdominal course, both ureters are crossed anteriorly by the gonadal vessels, and they in turn cross anterior to the genitofemoral nerve (Fig 24.1A). On the right side, the descending portion of the duodenum usually lies in front of the ureter, and more distally the right ureter is crossed anteriorly by the right colic and ileocolic vessels in the root of the mesentery (Fig. 24.1B). The appendix may overlie the right ureter. On the left side, the ureter is crossed anteriorly by the left colic vessels, and as it passes over the pelvic brim, it passes behind the sigmoid colon.

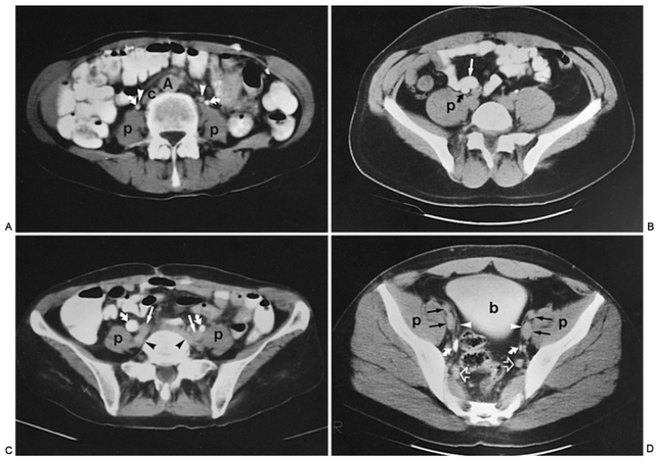

FIGURE 24.1. Computed tomography scans. **A:** Transverse section showing ureters *(curved arrows)* lying on top of psoas muscle *(p).* The gonadal vessels *(arrowheads)* are located anterior and medial to the ureter. A, aorta; C, vena cava. **B:** Close relationship between right ureter *(curved arrow)* and bowel *(straight arrow).* Right ureter is dilated. p, psoas muscle. **C:** Ureters *(curved arrows)* passing over common iliac arteries *(straight arrow)* and veins *(arrowheads).* Ureters are dilated. p, psoas muscle. **D:** Ureters *(curved arrows)* are crossed anteromedially by vasa deferentia *(arrowheads). Straight arrows* show external iliac arteries and veins; *open arrows* show hypogastric vessels. p, iliopsoas muscle; b, bladder.

As the ureters descend into the true pelvis, they pass over the terminal portion of the common or the first portion of the external iliac arteries (Fig. 24.1C). At this point, the two ureters are approximately 5 cm apart. After crossing into the pelvis, the ureters first diverge laterally and then converge medially toward the trigone. In the male, the pelvic ureter passes anterior to the internal iliac (hypogastric) artery and then just before it enters the bladder it is crossed anteriorly by the vas deferens (Fig. 24.1D). In the female, the pelvic ureter passes anterior to the internal iliac (hypogastric) artery, below the root of the broad ligament of the uterus,

and then runs along the lateral aspect of the cervix, passing under the uterine artery. The ureter is crossed by the obliterated umbilical vessels in both males and females.

Blood Supply

The ureter is supplied by a variable number of segmental arteries that arise from the aorta and from a variety of its branches or subbranches, including the renal, gonadal, adrenal, common iliac, internal iliac, external iliac, superior vesical, inferior vesical, vesiculodeferential, uterine, obturator, gluteal, vaginal, and middle hemorrhoidal arteries (39). As these segmental vessels reach the ureter, they divide into ascending and descending branches that run in the adventitial layer of the ureter. The descending branches of proximally located segmental arteries anastomose with the ascending branches of more distally located segmental vessels, thus forming long, longitudinally running vascular channels. These anastomosing arteries may give off secondary branches that form arterial plexuses in the adventitial layer of the ureter. Tributaries from the adventitial plexus pierce the muscular coat and form delicate plexuses in the submucosal layer.

Lymphatic Supply

Ureteral lymph vessels begin in communicating submucosal, intramuscular, and adventitial plexuses (239). Lymphatics from the proximal ureter may join lymphatics of the kidney, which follow the course of the renal vein to end in the lateral aortic nodes, or they may drain directly into the lateral aortic nodes near the origin of the gonadal arteries.

Lymphatics from the midureter drain into the lumbar nodes along the aorta and inferior vena cava, and lymphatics from the lower ureter terminate in the common, external, and internal iliac glands.

Nerve Supply

In a syncytial-type smooth muscle such as the ureter, there is a diffuse release of transmitter from nerve bundles, with the subsequent spread of excitation from one muscle cell to another (25). The lack of discrete neuromuscular junctions in such a system accounts for the difficulty in anatomically demonstrating the presence of ureteral innervation.

The nerves to the ureter arise from the celiac, aorticorenal, and mesenteric ganglia and also from the aortic, superior hypogastric, and inferior hypogastric plexuses. The sympathetic fibers arise from T-11 to L-1. The parasympathetic fibers to the upper ureter are derived from the vagus, and those to the lower ureter are from S-2 to S-4. In humans, the lower ureter receives a denser innervation than the upper ureter (49).

The ureter also is supplied by capsaicin-sensitive primary afferent nerve fibers that contain the tachykinins, substance P (SP), neurokinin A (NKA), neuropeptide K (NPK), and calcitonin gene–related peptide (CGRP) (45,88,130,189). The afferent innervation is densest proximally and decreases caudally (136).

Cross-sectional Anatomy

Histologically, the ureter is composed of three layers:

1. An inner mucosal layer, consisting of urothelium and its supporting lamina propria
2. A muscular layer
3. An outer adventitial layer

The inner lining of the ureter, or urothelium, is composed of transitional cell epithelium. In the contracted state, the urothelium assumes a stellate appearance, with the lumen of the ureter being completely occluded. Beneath the urothelium and separating it from the muscular coat is the lamina propria, which contains both elastic and collagenous fibers.

In humans, typical spindle-shaped smooth muscle cells, grouped together in compact bundles and rich in nonspecific cholinesterase, originate in the distal part of each minor calyx (43). These cells, which compose the outer muscle layer of the calyces and renal pelvis, are continuous with the muscular coat of the ureter.

There have been a variety of descriptions of the arrangement of the fibers in the muscular coat of the ureter. A classic description is that the muscular coat consists of an inner and outer longitudinal layer separated by a circular layer (37). Satani (179) noted that the musculature of the upper ureter ran haphazardly in all directions, whereas that of the lower ureter consisted of inner longitudinal and outer circular fibers. Murnaghan (149) described the muscle bundles as a long spiral that begins proximally as longitudinal strands in the outer region of the musculature, forms a middle circular layer as the spiral turn is made, and terminates in a distal longitudinal inner layer. Tanagho (204) emphasized that ureteral muscle bundles assume a helical or spiral configuration. More recently, Gosling and Dixon (67) noted that individual muscle bundles do not spiral around the ureter but rather form a complex meshwork of interweaving and interconnecting smooth muscle bundles without distinct longitudinal and circular layers. A scanning electron microscopic study of the guinea pig ureter showed a primarily circular arrangement in the upper ureter with a few outer longitudinal and obliquely oriented fibers, a highly irregular orientation of interlacing muscle bundles in the midureter, and predominantly longitudinally oriented muscle bundles with an underlying circular muscle coat in the lower ureter (201). The adventitia of the ureter is composed of areolar and fibroelastic connective tissue, which contains the blood vessels, lymphatics, and nerve fibers that subdivide, ramify, and enter the ureter proper.

Cellular Anatomy

The primary functional anatomic unit of the ureter is the smooth muscle cell, whose main function is to contract. The cell is extremely small, approximately 250 to 400 µmm long and 5 to 7 µmm in diameter, which permits a significant proportion of the calcium (Ca^{2+}) involved in the contractile process to enter the cell from extracellular sources at the time of excitation. The nucleus of the cell is ellipsoid and contains a darkly staining body, the nucleolus, and the genetic material of the cell. Surrounding the nucleus is the cytoplasm or sarcoplasm, which contains the structures involved in cell function. In the cytoplasm, frequently in close approximation to the nucleus, are *mitochondria,* which perform many of the nutritive functions of the cell (Fig. 24.2). Also within the cytoplasm are lattice-shaped structures called *endoplasmic* or *sarcoplasmic reticulum.* These structures serve as a site for internal storage of calcium, which plays an important role in the contraction of the smooth muscle cell.

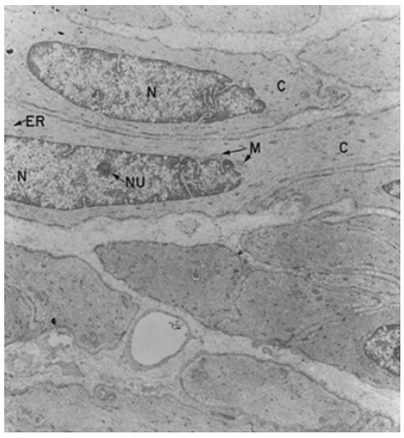

FIGURE 24.2. Electron micrograph of human ureter. C, cytoplasm (sarcoplasm); ER, endoplasmic (sarcoplasmic) reticulum; M, mitochondria; N, nucleus; NU, nucleolus. (Modified from Weiss RM. Ureteral function. *Urology* 1978;12:114, with permission.)

Dispersed in the sarcoplasm are the contractile proteins, actin and myosin, which interact—depending on the local Ca^{2+} concentration—to result in contraction or relaxation. The actin is dispersed through the sarcoplasm in hexagonal clumps and is interspersed with the less numerous clumps of the more deeply staining myosin. Attachment plaques are dark bands along the cell surface that serve as attachment devices for the actin. Any process that leads to an increase in Ca^{2+} concentration in the region of the contractile proteins results in contraction, and, conversely, any process that leads to a decrease in Ca^{2+} concentration in the region of the contractile proteins results in relaxation.

Along the periphery of the cell are numerous cavitary structures, some of which open to the outside of the cell, referred to as *caveolae.* These structures may serve a role in the nutritive functions of the cell or in the transport of ions across the cell membrane. Surrounding the cell is a doubled layer cell membrane. The *inner plasma* membrane surrounds the entire cell, whereas the *outer basement membrane* is absent at areas of close cell-to-cell contact, referred to as *intermediate junctions* (Fig. 24.3).

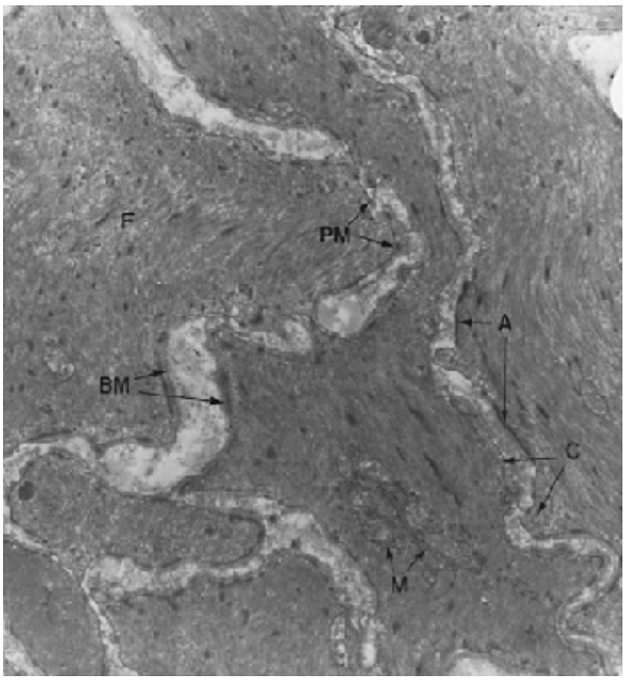

FIGURE 24.3. Electron micrograph of human ureter. A, attachment plaques; BM, basement membrane; C, caveolae; F, actin and myosin filaments; M, mitochondria; PM, plasma membrane. (From Weiss RM. Ureteral function. *Urology* 1978; 12:114, with permission.)

PHYSIOLOGY

Part of "24 - THE URETER "

Electrical Activity

The electrical properties of excitable tissues depend on the distribution of ions on the inside and outside of the cell membrane and on the relative permeability of the cell membrane to these ions (81). When a ureteral muscle cell is in a nonexcited or resting state, the electrical potential difference across the cell membrane, or transmembrane potential, is referred to as the resting membrane potential (RMP). The RMP is primarily determined by the distribution of potassium ions (K^+) across the cell membrane and by the preferential permeability of the resting membrane to potassium (76,222). In the resting state, the tendency for the positively charged K^+ ions to diffuse from the inside of the cell, where they are more concentrated, to the outside of the cell, where they are less concentrated, creates an electrical gradient in which the inside of the cell membrane is more negative than the outside. The electrical gradient that is formed tends to oppose the further movement of K^+ ions outward across the cell membrane along its concentration gradient. Thus an equilibrium is reached with a greater concentration of K^+ on the inside of the membrane and with the inside of the cell membrane being negatively charged with respect to the outside of the cell membrane.

The RMP in smooth muscle is lower than that which would be expected if the resting cell membrane were exclusively permeable to potassium. The RMP in the ureter is in the range of -33 to -70 mV (99,222). In the resting state, the sodium concentration on the outside of the cell membrane is greater than that on the inside. If the resting membrane were somewhat permeable to Na^+, both the concentration and electrical gradient would support an inward movement of Na^+ across the cell membrane, with a resultant decrease in the electronegativity of the inner surface of the cell membrane. Such a process could be a factor in the maintenance of a low RMP in smooth muscle. The RMP also may be maintained in part by an active mechanism capable of extruding Na^+ from within the cell against a concentration and an electrochemical gradient, and also by the relative permeability and distribution of chloride (Cl) ions across the cell membrane (105).

The transmembrane potential of an inactive or resting ureteral cell remains stable until it is excited by an external stimulus, whether electrical, mechanical (stretch), or chemical,

or by conduction of electrical activity from an already excited adjacent cell. When a ureteral cell is stimulated, depolarization occurs, with the inside of the cell membrane becoming less negative than it was before stimulation. If a sufficient area of the cell membrane is depolarized rapidly enough to reach a critical level of transmembrane potential, referred to as the *threshold potential,* a regenerative depolarization, or action potential, is initiated (Fig. 24.4). The action potential has the capacity to act as the stimulus for excitation of adjacent quiescent cells, and through a complicated chain of events gives rise to the ureteral contraction.

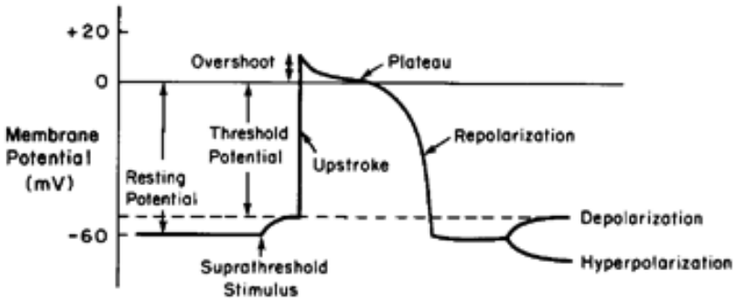

FIGURE 24.4. Schematic diagram of ureteral action potential.

When the ureteral smooth muscle cell is excited, its membrane loses its preferential permeability to K^+ and becomes more permeable to Na^+ and Ca^{2+} ions, which move inward across the cell membrane and give rise to the upstroke of the action potential (21,100,188,218,219). As the positively charged Na^+ and Ca^{2+} ions move inward across the cell membrane, the inside of the membrane becomes less negative with respect to the outside and may even become positive with respect to the outside at the peak of the action potential, a state referred to as *overshoot.* The rate of rise of the upstroke of the ureteral action potential is relatively slow, 1.2 ± 0.06 V per second in the cat (99), and accounts in part for the slow conduction velocity in the ureter.

After reaching the peak of its action potential, the ureter maintains its potential for a period of time (plateau of the action potential) before the transmembrane potential returns to its resting level (repolarization). The plateau phase appears to depend on the persistence of a high inward Na^+ conductance, and the repolarization phase appears at least in part to be due to an outward movement of K^+ across the cell membrane (21,103,104,188). The duration of the action potential in the cat ranges from 259 to 405 milliseconds (98).

In summary, the transmembrane potential of the resting ureteral cell (RMP) is approximately –33 to –70 mV and is primarily determined by the distribution of K^+ ions across the cell membrane and by the relative selective permeability of the resting cell membrane to K^+. When excited by a suprathreshold stimulus, the membrane becomes less permeable to K^+ ions and more permeable to Na^+ and Ca^{2+} ions, which move inward across the cell membrane and provide the ionic mechanism for the development of the upstroke of the action potential. Calcium also plays a prominent role in the contractile mechanism. After reaching the peak of its action potential, the membrane maintains a depolarized state (plateau of the action potential) for a time before the membrane potential of the activated cell returns to its resting level, repolarization. The plateau appears to be related to a persisting inward Na^+ current, and repolarization of the membrane probably is related to a decrease in the membrane permeability to Na^+ and Ca^{2+} and a renewed increase in permeability to K^+.

Pacemaker Potentials and Pacemaker Activity

Cells that develop electrical activity spontaneously are referred to as *pacemaker cells.* Pacemaker cells differ from nonpacemaker cells in that their resting transmembrane potential tends to be lower (less negative) than nonpacemaker cells (108) and does not remain constant but rather undergoes a slow spontaneous depolarization. If the spontaneously changing membrane potential reaches the threshold potential, the upstroke of an action potential occurs.

Dixon and Gosling (42,43,65,66,68) provided morphologic evidence of specialized pacemaker tissues in the proximal portion of the urinary collecting system. In humans, Dixon and Gosling (43) identified atypical smooth muscle cells in the region of attachment of each minor calyx to the renal parenchyma that are devoid of nonspecific cholinesterase. These distinctive cells, loosely arranged and separated from one another by connective tissue, form a thin sheet of muscle that covers each minor calyceal fornix. The atypical cells run across the renal parenchyma that lies between the renal attachments of the minor calcyes and thus serve as a connector between the minor calyces. Atypical cells are arranged longitudinally as an inner layer of the muscle coat of the minor and major calyces and of the renal pelvis. They appear to be closely applied to and to interconnect with typical muscle cells in these structures, but they do not extend beyond the UPJ into the ureter. The atypical cells may act as pacemaker cells or as a preferential conduction pathway. Lang and colleagues (107) described fibroblast-like cells in the proximal portion of the guinea pig renal pelvis that resemble the interstitial cells of Cajal that act as pacemaker cells in the intestine.

In the multicalyceal kidney, Morita and associates (146,147), using extracellular electrodes, recorded low voltage potentials, which appear to be pacemaker potentials, from the junction of the minor calyces and the major calyx. They noted that the contraction rhythm varied in each calyx. Calyceal contractions, with resultant coaptation of the walls of the calyces, facilitate outflow of urine from the papillae and protect the renal parenchyma from pressure increases transmitted from the renal pelvis. At normal urine flow rates in the multicalyceal kidney, pacemaker contractions of the calyces occur at a rate of approximately six per minute. At normal rates of flow, the contraction waves are

frequently blocked in the renal pelvis or at the UPJ (146). With increasing flow, there is a cessation of this block, and a 1:1 relationship is observed between pacemaker and ureteral contractions (33). In other words, at high flows, ureteral contractions occur at the same frequency as that of the calyces, whereas at low flows, calyceal contraction frequencies are greater than those of the ureter.

Under normal conditions, electrical activity arises proximally and is conducted distally from one muscle cell to another across the intermediate junctions (113,212). These close cellular contacts are similar to nexuses, which have been shown in other smooth muscles to be low-resistance pathways for cell-to-cell conduction (8). Although the primary pacemaker for ureteral peristalsis is located in the proximal portion of the collecting system, latent pacemakers are present in all regions of the ureter (90,140). Action potentials arising at these sites can propagate proximally and distally. Under normal conditions, these latent pacemaker regions are dominated by activity arising at the primary pacemaker sites. When the latent pacemaker sites are freed of their domination by the primary pacemaker, they in turn may act as a pacemaker.

Contractile Activity

The contractile event is dependent on the concentration of free sarcoplasmic Ca^{2+} in the region of the contractile proteins actin and myosin. Any process that results in an increase in Ca^{2+} in the region of the contractile proteins favors the development of a contraction; any process that results in a decrease in Ca^{2+} in the region of the contractile proteins favors relaxation.

Contractile Proteins

In smooth muscle, the most widely accepted theory suggests that phosphorylation of myosin is involved in the contractile process. With excitation, there is a transient increase in the sarcoplasmic Ca^{2+} concentration from a steady state concentration of 10^{-8} M to 10^{-7} M to a concentration of 10^{-6} M or higher. At this higher concentration, Ca^{2+} forms an active complex with the calcium-binding protein calmodulin (223) (Fig. 24.5). Calmodulin without Ca^{2+} is inactive. The calcium–calmodulin complex activates a calmodulin-dependent enzyme, myosin light-chain kinase, which in turn catalyzes the phosphorylation of the 20,000-Da light chain of myosin (Fig. 24.6). Phosphorylation of the myosin light chain is a prerequisite for activation by actin of myosin Mg^{2+}-adenosine triphosphatase (ATPase) activity, with resultant hydrolysis or adenosine triphosphate (ATP) and the development of smooth muscle tension or shortening (Fig. 24.7).

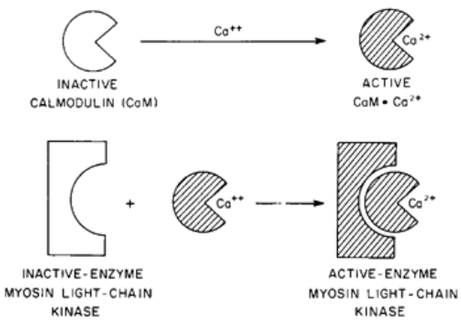

FIGURE 24.5. Schematic representation of contractile process in smooth muscle. Calmodulin is activated by Ca^{2+}. The activated calcium–calmodulin complex activates the enzyme myosin light-chain kinase. (Modified from Weiss RM. Physiology and pharmacology of the renal pelvis and ureter. In: Walsh PC, et al, eds. *Campbell's urology,* ed 5. Philadelphia: Saunders, 1986, with permission.)

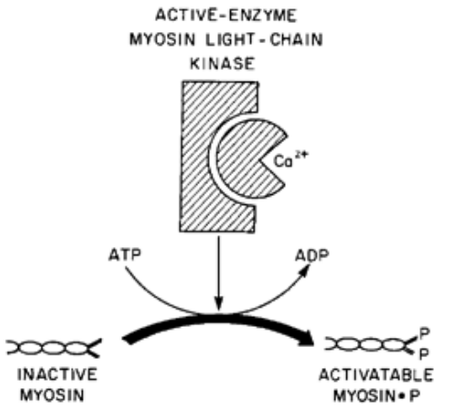

FIGURE 24.6. Schematic representation of contractile process in smooth muscle. The activated enzyme, myosin light-chain kinase, catalyzes the phosphorylation of myosin. Myosin must be phosphorylated for actin to activate myosin ATPase. (Modified from Weiss RM. Physiology and pharmacology of the renal pelvis and ureter. In: Walsh PC, et al, eds. *Campbell's urology,* ed 5. Philadelphia: Saunders, 1986, with permission.)

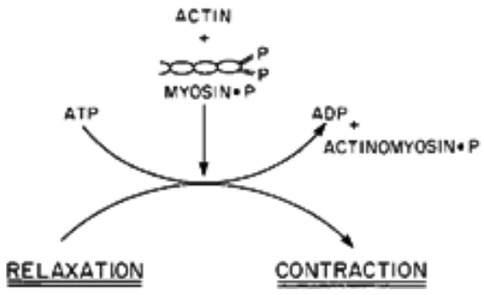

FIGURE 24.7. Schematic representation of contractile process in smooth muscle. Actin activates ATPase activity of phosphorylated myosin with the resultant development of contraction. (Modified from Weiss RM. Physiology and pharmacology of the renal pelvis and ureter. In: Walsh PC, et al, eds. *Campbell's urology,* ed 5. Philadelphia: Saunders, 1986, with permission.)

When the Ca^{2+} concentration in the region of the contractile proteins is low, myosin light-chain kinase is not activated, because calmodulin requires Ca^{2+} to activate the enzyme. This prevents activation of the contractile apparatus,

because the myosin light chain cannot be phosphorylated, a process that must precede tension development. Furthermore, a phosphatase dephosphorylates the myosin light chain, preventing actin activation of myosin ATPase activity, and relaxation results.

The calcium involved in the ureteral contraction is derived from two main sources (Fig. 24.8). Because smooth muscle cells have a small diameter, the inward movement of extracellular Ca^{2+} into the cell through L-type calcium channels during the upstroke of the action potential provides a significant source of sarcoplasmic calcium (79,125). Calcium release from a more tightly bound storage site, that is, the endoplasmic (sarcoplasmic) reticulum, is another possible source of sarcoplasmic calcium (218), although pharmacologic evidence suggests that Ca^{2+} release from the sarcoplasmic reticulum does not play a significant role in ureteral contractions, at least in the guinea pig (122,124,125). Relaxation results from a decrease in the concentration of free sarcoplasmic Ca^{2+} in the region of the contractile proteins. The decrease in sarcoplasmic Ca^{2+} can result from uptake of Ca^{2+} into intracellular storage sites (124,125) or from extrusion of Ca^{2+} from the cell (24).

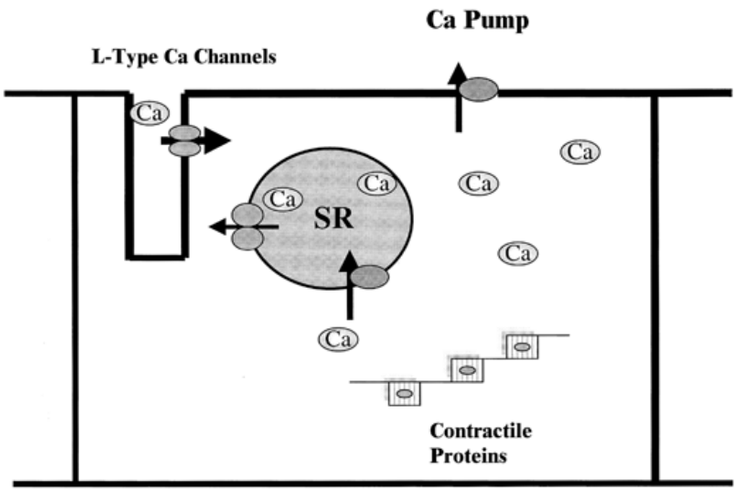

FIGURE 24.8. Schematic representation of calcium *(Ca)* movements involved in ureteral contraction. Ca involved in contractile process may be derived from extracellular sources or from tightly bound intracellular storage sites. SR, sarcoplasmic reticulum.

Role of Nervous System in Ureteral Function

The ureter is a syncytial type of smooth muscle without discrete neuromuscular junctions. Because peristalsis may persist after transplantation (155) or denervation (234), and because normal antegrade peristalsis persists after reversal of a segment of ureter *in situ* (142), it is apparent that ureteral peristalsis can occur without innervation. Further evidence indicating that an intact innervation is not required for ureteral peristalsis is that neither pacemaker activity nor the propagation of ureteral peristalsis is affected by the neural poison tetrodotoxin (61,185). It is, however, also apparent that the nervous system plays at least a modulating role in ureteral peristalsis. Autonomic drugs may affect the rate of urine transport through the ureter by modulating not only peristaltic frequency but also bolus volume (148). There is strong evidence to support the presence of excitatory α-adrenergic and inhibitory ß-adrenergic receptors in the ureter (139,171,225). Support for the presence of excitatory α-adrenergic and inhibitory ß-adrenergic receptor mechanisms in the ureter includes the demonstration of adenylyl cyclase activity in the ureter (230,236), the demonstration of α- and ß-adrenergic receptors in the ureter using receptor binding techniques (110,111), and the finding that the application of a given intraluminal pressure results in a greater degree of ureteral deformation in rabbits depleted of catecholamines by the administration of reserpine than results from the application of the same pressure load to a ureter of a normal non-reserpine-treated animal (226). Furthermore, electrical stimulation with high-intensity, high-frequency, short-duration pulses has been shown to release catecholamines, presumably from neural tissue intrinsic within the wall of the ureter (225) and renal calyx (116), and catecholamine-containing nerve fibers and cells have been demonstrated in the ureter (163).

Available data suggest that cholinergic (parasympathetic) agonists potentiate ureteral and renal pelvic contractility by directly stimulating cholinergic receptors (128,164,220) or

by indirectly causing the release of catecholamines (171). The ureter contains acetylcholinesterase-positive nerve fibers and cells, with the intravesical ureter being the most densely innervated (164), and cholinergic (muscarinic) receptors have been demonstrated in the ureter (110,111). DelTacca's demonstration (41) of acetylcholine release from isolated guinea pig, rabbit, and human ureters during field stimulation, and the inhibition of this release by the neural poison tetrodotoxin, provides further evidence for a role of the parasympathetic nervous system in the control of ureteral activity.

Anatomic support for a role of the nervous system in the modulation of peristalsis is provided by the demonstration of adventitial nerves in the human ureter (152,153) and the immunohistochemical demonstration of nerves and nerve cells beneath the muscularis and adventitia in the human and pig ureter (93).

Release of the tachykinins SP, NKA, and NPK from capsaicin-sensitive sensory nerves of the ureter has an excitatory effect on ureteral peristalsis, whereas release of CGRP from these nerves has an inhibitory effect on ureteral peristalsis (87). The excitatory effect of the tachykinins involves excitation of NK2 receptors in guinea pig and human ureters (158). The inhibitory effect of CGRP is associated with an increase in cyclic adenosine monophosphate (cAMP) (177). Maggi and associates (132) noted that the excitatory effects of tachykinins are more prominent in the renal pelvis than in the ureter and that the inhibitory effects of CGRP are more prominent in the ureter than in the renal pelvis. Histochemical studies have shown that the tachykinins and CGRP colocalize in the same nerves in the guinea pig and human ureter (88). Peptidergic neurons containing neuropeptide Y (NPY) and vasoactive intestinal polypeptide (VIP) also are present in the rat, cat, guinea pig, and human ureters (3,5,49,162). NPY potentiates the contractile responses to norepinephrine (162). VIP decreases ureteral peristaltic frequency and amplitude (109).

Nitric oxide (NO) and NO donors cause an increase in cyclic guanosine monophosphate (cGMP), with resultant relaxation of the renal pelvis and ureter (91,92). Nerves displaying immunoreactivity for nitric oxide synthase (NOS) or nicotinamide-adenine-dinucleotide phosphate (NADPH) diaphorase are present in the human ureter (60,91,193). There is some evidence that NO may be a transmitter in the ureter and renal pelvis, but there may be species and anatomic differences. NOS inhibitors have been shown to block nonadrenergic, noncholinergic (NANC) nerve-mediated relaxations of pig intravesical ureter (77), but they do not influence the spontaneous motility of isolated guinea pig renal pelvis or guinea pig and sheep ureter (57,127).

Physiology of the Ureteropelvic Junction

Griffiths and Notschaele (70) described the dynamics of urine transport within the ureter. As the renal pelvis fills, there is a rise in renal pelvic pressure, and urine is ultimately extruded into the upper ureter, which is initially in a collapsed state. After transporting the urine into the upper ureter, renal pelvic pressure declines to its baseline value, and the cycle of pelvic filling, increase in pressure, and launching of urine into the ureter occurs again. The closed UPJ may be protective to the kidney in dissipating back-pressure from the ureter, because ureteral contractile pressures are higher than renal pelvic pressures.

The mechanism for urine launching into the upper ureter is not completely understood, and abnormalities in a rather complicated regulatory mechanism may cause the hydronephrosis associated with functional UPJ obstructions in which urine transport is impaired, even though large-caliber catheters can be passed readily through the UPJ. Whereas in the normal system, peristalsis is controlled by pacemaker cells that generate high-frequency action potentials in the proximal pelvicalyceal region, in the chronically dilated system, the frequency gradient in the renal pelvis is lost. This can be associated with latent pacemakers initiating dystropic orthograde peristaltic activity or retrograde contractions. Obstruction alters the hierarchic organization of the multiple coupled pacemakers that normally coordinate peristaltic activity (31). Such disruption causes uncoordinated pelvic contractions that may result in hypertrophy of the renal pelvic smooth muscle and impaired transport of urine into the ureter. Whether these functional changes are secondary to or the cause of the dilation is not certain.

Murnaghan (150) related the functional abnormality at the UPJ to an alteration in the configuration of the muscle bundles, and Foote and associates (54) observed a decrease in musculature at the UPJ in patients with a UPJ obstruction. Hanna (73) noted in severe UPJ obstruction abnormalities in the musculature of the renal pelvis and disruption of intercellular relationships at the UPJ itself. Gosling and Dixon (64) also observed histologic abnormalities in the dilated renal pelvis. In some instances, there may be areas of actual narrowing or valvelike processes at the UPJ. Furthermore, a vessel or adhesive band crossing the UPJ may potentiate the degree of dilation in any of the forms of UPJ obstruction.

Propulsion of Urinary Bolus

Following extrusion into the ureter, the urine forms a bolus owing to a ureteral contraction ring that completely coapts the ureteral walls (70). The contraction ring at the rear end of the bolus progresses distally at a constant velocity, while the velocity of the leading edge of the bolus varies along the ureter (46). Therefore the width and length of the bolus is not uniform as it moves from the renal pelvis to the bladder. The bolus of urine that is pushed distally in front of the contraction ring lies almost entirely in a passive, noncontracting part of the ureter (224). Contraction waves normally occur two to six times per minute in the normal human ureter (47) and are conducted at a velocity of

approximately 2 to 5 cm per second (26). Baseline (resting) ureteral pressure is approximately 0 to 5 cm H_2O, and contractile pressures may range from 20 to 60 cm H_2O (47). The major component of the recorded pressure is derived from the contraction wave, with only a small component derived from the bolus pressure. The urine bolus is forced into the bladder by the advancing contraction wave, which dissipates at the UVJ (Fig. 24.9). When functioning properly, the UVJ ensures one-way transport of urine.

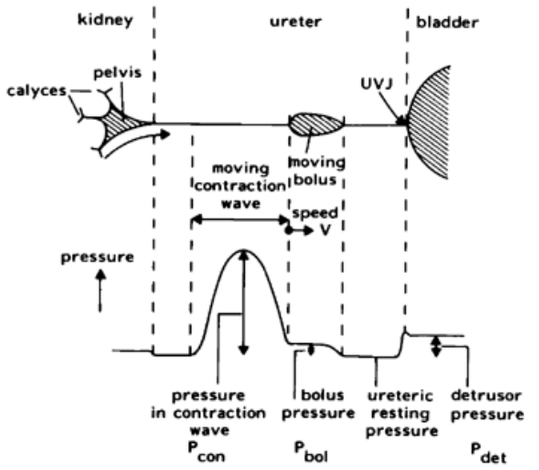

FIGURE 24.9. Schematic representation of a single bolus in the ureter moving from the renal pelvis to the bladder. Corresponding distribution of pressure within the urinary tract is shown *(lower tracing).* UVJ, ureterovesical junction; V, speed of bolus movement. (From Griffiths DJ, Notschaele C. The mechanics of urine transport in the upper urinary tract. I. The dynamics of the isolated bolus. *Neurol Urodynam* 1983;2:155, with permission.)

As with any tubular structure, the ureter can transport a set maximum amount of fluid per unit time. Under normal flows, in which bolus formation occurs, the amount of urine transported per unit time is significantly less than the maximum transport capacity of the ureter. At high flows, the ureteral walls do not coapt, and fluid is transported in a continuous column rather than in a series of boluses.

Changes in the dimensions of the ureter that occur in pathologic states may in themselves account for inefficient urine transport, even if the contractile force of the individual fibers remains unchanged (11,70,227). The Laplace equation expresses the relationship between the variables that affect intraluminal pressure:

$$\text{Pressure} = \frac{\text{Stress} \times \text{Wall Thickness}}{\text{Radius}}$$

An increase in ureteral diameter in itself can cause a decrease in intraluminal pressure and result in inefficient urine transport.

The Laplace relationship also may provide a rationale for ureteral tapering of the dilated ureter. With ureteral tapering, muscle thickness and the ability of the ureter to contract remain unchanged. The decrease in radius occurring with ureteral tapering may in itself account for higher intraluminal pressure, with resultant improved urine transport. The tapered ureter can coapt its walls more readily and generate a higher intraluminal pressure, even though the material itself has not been changed (227). Diagrammatically, with ureteral tapering, force or the number of blocks remains unchanged, but intraluminal pressure increases as the load is supported over a smaller area; thus pressure or the height of the pile of blocks increases (Fig. 24.10).

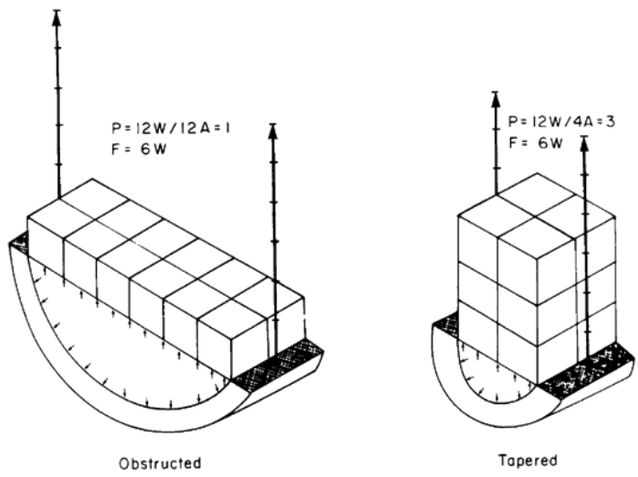

FIGURE 24.10. Diagrammatic representation of changes that occur with tapering of the obstructed ureter. A, area over which force is distributed; F, force developed by each half of ureter; P, pressure; W, blocks or weights representing load proportional to force. (From Weiss RM, Biancani P. A rationale for ureteral tapering. *Urology* 1982;20:482, with permission.)

Effect of Diuresis on Ureteral Function

The upper urinary tract alters its characteristics according to the amount of urine to be transported. Smooth muscle function is affected by the amount of stretch and the rate with which the stretch is applied. The initial response of the ureter to an increase in urine flow is an increase in the frequency of peristalsis. At relatively low flow rates, small increases in flow result in large increases in peristaltic frequency. At higher flow rates, relatively large increases in flow result in only small increases in peristaltic frequency. With increasing urine flow, peristaltic frequency increases to a maximum, and further increases in urine transport occur by means of increases in bolus volume (32). As the volume of the bolus increases, the leading edge of the bolus approximates the contraction ring of the preceding bolus. The pressure in the bolus increases because of increased resistance at the leading edge of the bolus, where it touches the preceding contraction wave. At very high flows, the pressure within the bolus exceeds the contraction pressure in the ring, and the contraction pressure is no longer sufficient to coapt the ureteral wall. The boluses then coalesce, and the ureter becomes filled with a column of fluid and dilates. At high flows, urine is transported through an open tube by columnar flow rather than by a series of boluses.

Physiology of the Ureterovesical Junction

Griffiths (71) analyzed the factors involved in urine transport across the UVJ. Under normal conditions and at normal flow rates, the contraction wave that occludes the ureteral lumen propagates distally with the urine bolus in front of it. When the bolus reaches the UVJ, the pressure within the bolus must exceed intravesical pressure for the bolus of urine to pass across the UVJ into the bladder. For the contraction wave to coapt the ureter walls and move the urine bolus distally, the pressure generated by the contraction wave must exceed the pressure within the urinary bolus. The UVJ does not relax (228).

Blok and co-workers (14) demonstrated fast and slow pressure waves at the UVJ. The fast pressure waves originate from intrinsic ureteral contractions, are related to retraction of the distal ureter within its sheaths, and are accompanied by bolus ejection of fluid into the bladder. This telescoping,

dynamic event decreases the UVJ resistance to flow and thus facilitates urine passage into the bladder. The slow pressure waves originate from the surrounding detrusor muscles and represent the influence of detrusor activity on flow through the UVJ. Coolsaet and associates (36) demonstrated that resistance to flow through the UVJ is due to (a) stretch of the bladder base and UVJ, (b) intravesical pressure transmitted to the submucosal ureteral segment, (c) activity of the detrusor muscle surrounding the UVJ, and (d) dynamics of the ureteral segment composing the UVJ.

The relationship between upper urinary tract function and resistance to outflow at the UVJ is of major clinical importance. The pressure within the bladder during the storage phase is of paramount importance in determining the efficacy of urine transport across the UVJ. This is the pressure that the ureter must work against for the greatest period of time. During filling of the normal bladder, sympathetic impulses and the viscoelastic properties of bladder wall inhibit the magnitude of the intravesical pressure rise. With filling, the normal bladder maintains a relatively low intravesical pressure (138). The low intravesical pressure facilitates urine transport across the UVJ and prevents ureteral dilation.

Renal function and the functional integrity of the upper urinary tract are at risk in individuals with noncompliant or hyperactive bladders. In the noncompliant fibrotic bladder and in some forms of neurogenic vesical dysfunction, the bladder is autonomous, and relatively small increases in bladder volume result in large increases in intravesical pressure with impairment of ureteral emptying. Regular emptying of these bladders may not be sufficient to protect the upper tracts, and intravesical pressure may need to be lowered by reduction in detrusor tonus. Furthermore, outflow resistance at the UVJ may be high in the overdistended bladder even at low intravesical pressures. This results from stretch of the UVJ and decreased retractability of the submucosal ureteral segment. Intravesical volume thus should be kept at reasonable levels, which may require intermittent catheterization. Increased resistance to bolus outflow across the UVJ can occur when there is obstruction at the UVJ, when intravesical pressure or volume is excessive, or when flow rates are so high as to exceed the transport capacity of the UVJ. Under such conditions, in which the bolus of urine cannot freely pass into the bladder, the pressure within the bolus, propelled by the ureteral contraction ring, increases and may exceed the pressure within the contraction ring. Under these conditions, the contraction wave will be unable to coapt the ureteral wall and intraureter reflux will occur. This impaired bolus transport will cause secondary widening of the ureter and weaker ureteral contractions, with only a fraction of the bolus volume passing distally. Griffiths (71) presented theoretic evidence to show

that a similar situation of impaired bolus transport across the UVJ would be expected if the ureter was wide or weakly contracting, even if the UVJ was perfectly normal. Under these conditions, a similar breakdown of bolus discharge into the bladder can occur in the wide or weakly contracting ureter at high flow rates, even if the UVJ is normal.

There is some evidence that gravity may assist urine transport and that the erect position, by enhancing hydrostatic loading of the UVJ, may facilitate urine transport across the UVJ, especially in individuals with wide upper tracts (181). From a clinical viewpoint, some workers have suggested that bed rest may be deleterious to renal function in the patient with urinary retention and dilated upper urinary tracts (58).

Relationship Between Vesicoureteral Reflux and Ureteral Function

The intravesical ureter is approximately 1.5 cm long and takes an oblique course through the bladder wall. It is composed of an intramural segment, which is surrounded by detrusor muscle, and a submucosal segment, which lies directly under the bladder urothelium (203). The relationship between the length and diameter of the intravesical segment of ureter appears to be a factor in the prevention of vesicoureteral reflux (156). Trigonal function also may be a factor in the prevention of vesicoureteral reflux (202). Furthermore, the development of vesicoureteral reflux in individuals with bladder outlet obstruction and neurogenic vesical dysfunction provides evidence that increased intravesical pressures also may be a factor in certain instances of reflux.

Although an abnormality of the UVJ is the primary etiologic factor in most cases of reflux, there is evidence to suggest that decreased ureteral peristaltic activity may be a contributory factor (96,141,228). Support for this contention may be derived from the findings that a normal ureter may not reflux, even when reimplanted into a bladder without a submucosal tunnel (40), and that a defunctionalized refluxing ureter may cease to reflux when a proximal diversion is taken down and urine flow through the ureter is reinstated (206,233). Furthermore, the success rate of antireflux procedures is less with poorly functioning dilated ureters, and, although this may be related to technical factors, decreased peristaltic activity may be a reason for failure in many instances.

Studies in normal and mildly refluxing systems have shown that there is a high-pressure zone in the distal ureter with a resultant pressure gradient across the UVJ (228). With bladder filling, the resultant UVJ–bladder pressure gradient increases in nonrefluxing systems, whereas it decreases and may disappear in refluxing systems (228) (Fig. 24.11). This decrease in the pressure gradient in refluxing systems may be related to lateralization of the ureteral orifice and shortening of the intravesical tunnel and may correspond to the time when reflux occurs.

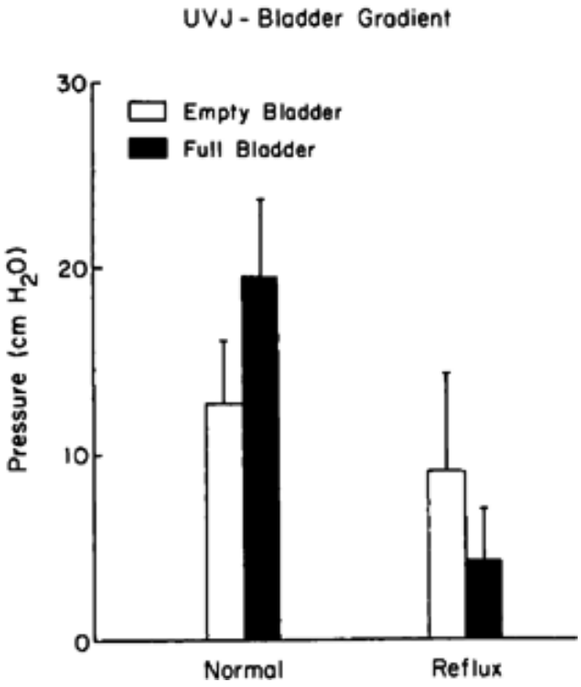

FIGURE 24.11. Pressure gradient across the ureterovesical junction *(UVJ)* in normal and mildly refluxing (grades II and III) systems. (From Weiss RM, Biancani P. Characteristics of normal and refluxing ureterovesical junctions. *J Urol* 1983;129:858, with permission.)

Effect of Infection on Ureteral Function

Infection within the upper urinary tract may impair urine transport. Bacteria and endotoxins have been shown to inhibit ureteral activity (95,165,205), and pyelonephritis in the monkey has been associated with decreased peristaltic activity (168). Furthermore, Rose and Gillenwater (170) have shown that infection can potentiate the deleterious effects of obstruction on ureteral function.

In humans, irregular peristaltic contractions, often with a decreased amplitude, have been recorded with infection. In more severe cases, absence of activity has been noted (173). Furthermore, ureteral dilation may occur with retroperitoneal inflammatory processes secondary to appendicitis, regional enteritis, ulcerative colitis, or peritonitis (134). Infection also may reduce the compliance of the intravesical ureter and permit reflux to occur in situations in which the UVJ is intrinsically of marginal competence (35).

Effect of Calculi on Ureteral Function

Factors that can affect the spontaneous passage of calculi include the size and shape of the stone (213); areas of narrowing within the ureteral lumen; ureteral peristalsis; the hydrostatic pressure of the column of urine proximal to the calculus (190); and edema, inflammation, and spasm of the ureter at the site of the stone (82).

Two factors that appear to be most useful in facilitating stone passage are an increase in hydrostatic pressure proximal to a calculus and relaxation of the ureter in the vicinity of the stone. In support of the theory that increased hydrostatic pressure facilitates stone passage, it has been shown in the rabbit and dog ureter that artificial concentrations with holes move more slowly than those without holes (190). Furthermore, ureteral ligation proximal to a concretion has been shown to decrease hydrostatic pressure, with resultant inhibition of stone passage (190). Theoretically, high fluid intake will increase hydrostatic pressure proximal to a stone and thus may aid in its passage; however, the elevated hydrostatic pressure, if prolonged, is potentially deleterious to the kidney.

With respect to the potential facilitative effect of ureteral relaxation on stone passage, Peters and Eckstein (161) showed that the spasmolytic agents phentolamine, an α-adrenergic antagonist, and orciprenaline, a ß-adrenergic agonist, dilated the canine ureter at the level of an artificial concretion and thus permitted increased fluid flow beyond a partially obstructive concretion. It appears that resistance to urine flow in this experimental model was caused in part by the artificial concretion and in part by local spasm and that the resistance could be decreased by spasmolytic drugs, such as phentolamine and orciprenaline. Although it has not been determined whether this spasmolytic effect would aid in stone passage, the same principle has been used to float upper ureteral stones proximally into the renal pelvis as a prelude to percutaneous nephrostolithotomy. Obstruction of the ureter with a balloon catheter leads to dilation of the ureter, with the impacted stone then being able to migrate proximally (9). Furthermore, placement of a nephrostomy tube proximal to a steinstrasse appears to facilitate passage of the stones. This may result from decreasing peristaltic activity that acts as a spasmodic factor in the region of the stone.

Although these data can be interpreted to imply that ureteral relaxation in the region of a concretion would aid in stone passage, a controlled study currently is not available. Such a study with an agent known to have strong relaxant effects on the ureter, such as theophylline (69,230), would be of value, but the interpretation of the data obtained might be difficult because of the marked variability of spontaneous stone passage in the clinical setting.

Ureterolithotomy

With the advent of ureteroscopy, percutaneous nephrostolithotomy, and extracorporeal shock wave lithotripsy (ESWL), open ureterolithotomy has become a less frequently used procedure. However, it may still be the preferred technique for the removal of large midureteral stones that are impacted at the level of the iliac vessels. For upper ureteral calculi, a standard flank incision below or through the bed of the twelfth rib has been the standard approach, although a posterior lumbotomy has a role in the management of larger, well-impacted calculi. During the procedure, avoidance of stone migration, especially proximally, should be ensured by control of the ureter above and below the calculus with vessel loops or Babcock forceps. A longitudinal incision in the ureter is made directly over the stone, and the stone is extracted. A small catheter is passed proximally into the renal pelvis for irrigation and to ensure that the system is unobstructed. Although distal passage of the catheter into the bladder can be used to assess distal obstruction, it can cause edema at the UVJ, with prolongation of flank drainage postoperatively. For this reason, the use of distal catheter passage can be individualized depending on the clinical situation.

Some authors favor a loose closure of the ureter with only one or two fine sutures, and others seek a watertight closure with either interrupted or continuous fine sutures. Both methods work. Our preference is multiple interrupted 5-0 chromic adventitial sutures, which avoid excessive prolonged leakage yet provide a means for urine egress, if necessary. One or two Penrose drains brought to the exterior through a stab wound provide for drainage.

The technical details for removal of midureteral stones are essentially the same as for upper ureteral calculi. The approach can either be via a subcostal flank incision or via an anterior extraperitoneal approach, using a horizontal incision beginning below the tip of the twelfth rib and extending anteriorly, with the patient in the supine position with a roll of towels beneath the shoulder and buttock. This approach, classically employed for sympathectomy, can involve muscle splitting, or the muscle layers can be divided.

Lower ureteral calculi can be approached through a modified Gibson's incision as used for renal transplantation or through a vertical suprapubic incision with retraction of the bladder toward the contralateral side. At times, with a periureteral inflammatory reaction or scarring from previous surgery, the ureter and stone may be difficult to identify. Identification of the ureter proximally, where it crosses the bifurcation of the common iliac artery, may facilitate its localization, and opening the peritoneum with visualization of the ureter through the posterior parietal peritoneum can be helpful. Identification and division of the obliterated umbilical vessels also can aid in localizing the ureter and facilitating removal of the calculus. The technique for stone removal is similar to that employed for higher stones, and early control of the ureter proximal to the calculus with a vessel loop is imperative.

For calculi in the most distal portions of the ureter, such as in the intramural portion of the UVJ, a transvesical approach can be used. If the stone can be palpated with the bladder open, an incision is made in the vesical mucosa directly over the calculus. If the stone is somewhat more proximal, proximal ureteral control with a vessel loop is obtained extravesically, and the incision in the ureter can be extended proximally from within the bladder. If there is

concern about distal ureteral damage in cases in which there is significant periureteral inflammation, a ureteroneocystostomy using a short submucosal tunnel may be required and would be preferable to the development of a ureteral obstruction necessitating a secondary procedure. In women, a transvaginal approach can be used for distal ureteral calculi.

Effect of Pregnancy on Ureteral Function

Hydroureteronephrosis of pregnancy begins in the second trimester of gestation and subsides within the first month after parturition. It is more severe on the right than on the left side, and ureteral dilation does not occur below the pelvic brim. Roberts (169) presented a strong argument in favor of obstruction as the primary etiologic factor in the development of hydroureteronephrosis of pregnancy. Others have suggested a hormonal mechanism for the ureteral dilation of pregnancy (216). As emphasized by Roberts (169):

1. Elevated baseline (resting) ureteral pressures consistent with obstruction have been recorded above the pelvic brim in pregnant women, which decrease when positional changes permit the uterus to fall away from the ureters (176).
2. Normal ureteral contractile pressures have been recorded in pregnant women, suggesting that hormonally induced ureteral atony is not the prime factor in ureteral dilation of pregnancy.
3. Women whose ureters do not cross the pelvic brim, that is, those with pelvic kidneys or ileal conduits, do not develop ureteral dilation of pregnancy.
4. Hydronephrosis of pregnancy usually does not occur in quadripeds whose uterus hangs away from the ureters (210).
5. Elevated ureteral pressures in the pregnant monkey return to normal when the uterus is elevated from the ureters at laparotomy or when the fetus and placenta are removed from the uterus.

Studies of the effects of hormones of pregnancy on ureteral function have been conflicting. Although several studies have shown an inhibitory effect of progesterone on ureteral function (89,102) this has not been a universal finding (159,182). Progesterone has been noted to increase the degree of ureteral dilation during pregnancy and to retard the rate of disappearance of hydroureter in postpartum women (119). Furthermore, hydronephrosis has been reported in women taking oral contraceptives (72,137). Others, however, failed to induce changes in ureteral activity in women by the administration of estrogen, progesterone, or a mixture of these drugs (29,135). Thus, although obstruction appears to be the primary factor in the development of hydronephrosis of pregnancy, it is possible that a combination of hormonal and obstructive factors is involved (52).

Effect of Age on Ureteral Function

Aging affects the structure and function of the ureter. In a human autopsy study of subjects ranging in age from 12 weeks of gestation to 12 years of age, Cussen (38) noted a progressive increase in the population of smooth muscle cells and a small increase in the overall size of the individual smooth muscle cells with age. This is accompanied by an irregular increase in the number of elastic fibers. A progressive increase in ureteral cross-sectional muscle area is also observed in the ureter of the guinea pig between 3 weeks and 3 years of age, accompanied by an increase in developed force (85) (Fig. 24.12). The increase in force developed between 3 weeks and 3 months of age seems to be attributable to an increase in contractility, because there is an associated increase in active stress, or force per unit area of muscle. The increase in force developed between 3 months and 3 years of age can be explained by an increase in muscle mass alone, because there is no change in active stress between these two age groups (Fig. 24.13). Although changes in the force–length relationships of guinea pig ureter occur with age, the force–velocity relationships do not change with age (12).

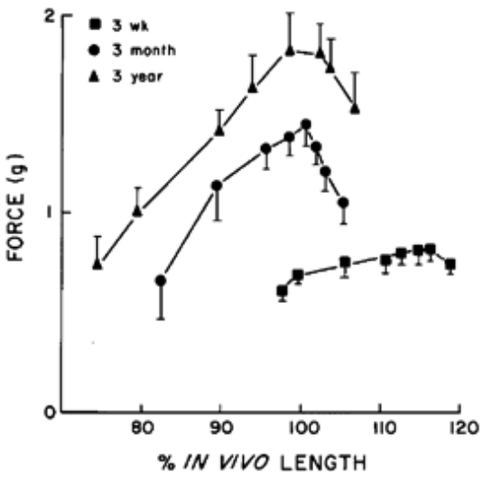

FIGURE 24.12. Active force–length curves of isolated guinea pig ureteral segments as a function of age. Developed force increases with age. Data are shown as mean ± SEM. (Modified from Hong KW, Biancani P, Weiss RM. Effect of age on contractility of guinea pig ureter. *J Urol* 1980;17:459, with permission.)

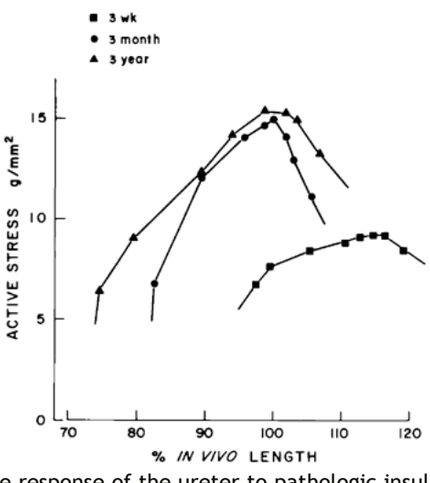

FIGURE 24.13. Active stress (force/unit area) – length curves of isolated guinea pig ureteral segments as a function of age. Stress increases between the 3-week and 3-month age groups and then remains constant with further aging. (Modified from Hong KW, Biancani P, Weiss RM. Effect of age on contractility of guinea pig ureter. *J Urol* 1980;17:459, with permission.)

The response of the ureter to pathologic insults depends not only on the magnitude and duration of the pathologic insult but also on the age of the individual affected. The neonatal rabbit ureter undergoes greater degrees of deformation in response to an applied intraluminal pressure than does the adult rabbit ureter (1). This decrease in compliance with age also is noted clinically, where more marked degrees

of ureteral dilation occur in the neonate and young child in response to obstruction than in the adult. Experimental data suggest that aging has effects on the mechanical and biochemical properties of the ureter (1,85,236), and these changes may affect the response of the ureter to pathologic insult.

URETERAL PHARMACOLOGY

Part of "24 - THE URETER "

The ureter is affected by both the parasympathetic (cholinergic) and sympathetic (adrenergic) branches of the autonomic nervous system.

Parasympathetic (Cholinergic) System

Acetylcholine (ACh), the prototype cholinergic agonist, serves as the neurotransmitter at (a) neuromuscular junctions of somatic motor nerves (nicotinic sites), (b) preganglionic parasympathetic and sympathetic neuroeffector junctions (nicotinic sites), and (c) postganglionic parasympathetic neuroeffector sites, such as smooth muscle cells (muscarinic sites). ACh, synthesized in the nerve terminals from acetyl coenzyme A (CoA) and choline by the enzyme choline acetyltransferase, is released into the synaptic cleft and interacts with postganglionic receptor sites to elicit a functional response. ACh subsequently is hydrolyzed (degraded) by the enzyme acetylcholinesterase (AChE). The muscarinic effects of cholinergic agonists can be blocked by the parasympatholytic agent atropine. The effects of nicotinic agonists can be blocked by nondepolarizing ganglionic blocking agents or by high concentrations of the nicotinic agonist itself, which may cause ganglionic blockade by desensitization of receptor sites after an initial period of ganglionic stimulation.

ACh and other cholinergic agonists, such as methacholine, carbamylcholine (carbachol), and bethanechol (Urecholine), have in general been observed to have an excitatory effect on ureteral function, that is, they increase the frequency and force of contractions (171,220). The excitatory responses to carbachol and ACh appear to be more marked in ureters from younger than from older guinea pigs (232).

Anticholinesterases (anti-ChEs) prevent hydrolysis of ACh by cholinesterases and thus potentiate the actions of ACh. The effects of anti-ChEs, such as physostigmine and neostigmine, parallel the excitatory effects of ACh and other parasympathomimetics on the ureter (121). Although atropine, a competitive antagonist of the muscarinic effects of ACh, has been shown to inhibit the excitatory effects of parasympathomimetic agents (121,220) and physostigmine (121) on a variety of ureteral and calyceal preparations, the majority of studies have shown that atropine itself has little direct effect on ureteral activity in many species, including humans (94,167). Even when atropine has been observed to inhibit ureteral activity, its effects are frequently minimal and inconsistent (172), providing little rationale for its use in the treatment of ureteral colic.

Sympathetic (Adrenergic) System

Most investigators have noted that α-adrenergic agonists, such as norepinephrine and phenylephrine, stimulate ureteral activity (74,139,171,220,225). Norepinephrine, the chemical mediator responsible for adrenergic transmission, is synthesized in the neuron from tyrosine. Once released from the nerve terminal, some of the norepinephrine combines with postsynaptic receptors on the effector organs, such as smooth muscle, leading to a physiologic response. There are both α_1- and α_2-postsynaptic receptors in smooth muscle, and stimulation of either results in a contractile response. Presynaptic α_2-adrenergic receptors in the neuron inhibit the release of norepinephrine from the nerve terminal, and thus excitation of these receptors is inhibitory to smooth muscle function (Fig. 24.14). Reuptake or neuronal uptake of norepinephrine into the neuron limits the amount of time that norepinephrine is in contact with the innervated tissue and thus regulates the magnitude and duration of the catecholamine-induced response. Agents such as cocaine and imipramine (Tofranil), which inhibit neuronal uptake, potentiate the physiologic response to norepinephrine. The enzymes monoamine oxidase (MAO) and

catechol- *O*-methyltransferase (COMT) provide degradation pathways for norepinephrine.

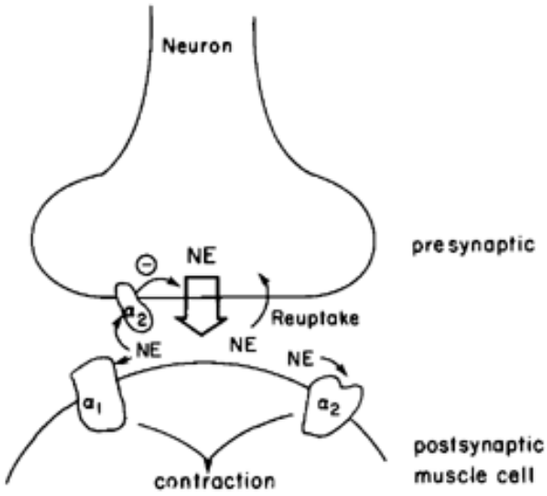

FIGURE 24.14. Diagrammatic representation of the role of presynaptic and postsynaptic α-adrenergic receptors. Norepinephrine *(NE)* released from nerve terminals may combine with postsynaptic α_1- and α_2-adrenergic receptors on smooth muscle to cause contraction. Norepinephrine combining with presynaptic α_2-adrenergic receptors on the nerve terminal prevents further release of NE from the neuron.

ß-Adrenergic agonists, such as isoproterenol, inhibit ureteral activity (139,171,220,225). The relaxant effects of isoproterenol are greater in ureters from young than from old guinea pigs (232,235). It appears that the ß-adrenoceptor subtype involved in the relaxation response is species specific (209). Tyramine, whose adrenergic agonist effects are primarily due to the release of norepinephrine from adrenergic terminals, has a stimulatory effect on the upper urinary tract (53,115).

The α-adrenergic antagonists phentolamine and phenoxybenzamine (Dibenzyline) have been shown to inhibit the stimulatory effects of norepinephrine and other α-adrenergic agonists in a variety of ureteral preparations (53,74,115,139,171,220,225). The ß-adrenergic antagonist propranolol has been shown to block the inhibitory effects of ß-adrenergic agonists, such as isoproterenol, in a variety of ureteral preparations. A prototype α_1-adrenergic antagonist is prazosin, and a prototype α_2-adrenergic antagonist is yohimbine.

Second Messengers

Adrenergic and cholinergic agonists regulate physiologic processes via their interaction with a variety of specific membrane-bound receptors (6,56), and the responses to these agonists are mediated via "second messengers," such as cAMP, cGMP, Ca^{2+}, inositol 1,4,5-trisphosphate (IP_3), and diacylglycerol (DG).

cAMP mediates the relaxing effects of ß-adrenergic agonists in a variety of smooth muscles including the ureter (230,235,236). The ß-adrenergic agonist, such as isoproterenol, combines with a receptor on the outer surface of the cell membrane (Fig. 24.15). The ß-adrenergic agonist itself does not enter the cell. The agonist–receptor complex in turn activates the enzyme adenylyl cyclase on the inner surface of the cell membrane with the conversion of ATP to cAMP. A stimulatory guanine nucleotide-regulatory protein (G protein), G_s, acts as a functional communication between the hormone-occupied receptor and the catalytic or active unit of the adenylyl cyclase. Age-dependent changes in the ability of isoproterenol to activate adenylyl cyclase play a role in the effect of age on isoproterenol-induced ureteral relaxation (236). cAMP acts as a second or "internal" messenger for the response elicited by the ß-adrenergic agonist. cAMP, through activation of a protein kinase and subsequent phosphorylation of proteins, has been suggested to lead to the uptake of Ca^{2+} into intracellular storage sites, such as the endoplasmic reticulum, with a resultant decrease in free sarcoplasmic Ca^{2+} and the development of relaxation (7).

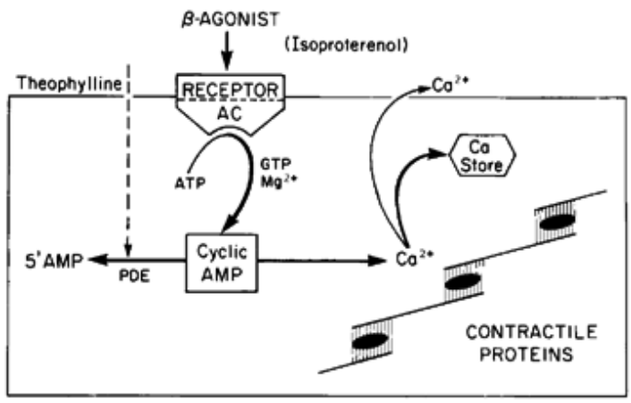

FIGURE 24.15. Diagrammatic representation of the role of cyclic adenosine monophosphate (cAMP) in ß-adrenergic agonist–induced relaxation of smooth muscle. Agonist combines with receptor on the outer surface of the cell membrane. The receptor–agonist complex, in turn, activates the enzyme adenylyl cyclase on the inner surface of the cell membrane, which in the presence of Mg^{2+} and guanosine triphosphate (GTP) results in the conversion of adenosine triphosphate (ATP) to cAMP. cAMP is postulated to cause an increased uptake of Ca^{2+} into intracellular storage sites with a resultant decrease in Ca^{2+} in the region of the contractile proteins, resulting in relaxation. cAMP also may act directly on the contractile proteins to inhibit the contractile process. The enzyme phosphodiesterase *(PDE)* degrades cAMP to 5'AMP. Theophylline is a PDE inhibitor and thus also can increase cAMP with resultant smooth muscle relaxation.

cAMP levels may be increased by increasing its synthesis or by decreasing its degradation. Synthesis of cAMP involves activation of the enzyme adenylyl cyclase, and degradation of cAMP involves activation of the enzyme phosphodiesterase. Two agents that relax ureteral smooth muscle increase cAMP levels: isoproterenol, by increasing synthesis, and theophylline, by decreasing degradation (28,196,229,230). Further support for a role of cAMP in relaxation of smooth muscles can be derived from the finding that

dibutyryl cAMP, which more readily diffuses into the intact cell and is more resistant to breakdown by phosphodiesterase than cAMP, can relax smooth muscle (235).

Some of the actions of the α_2-adrenergic and muscarinic cholinergic agonists appear to involve the inhibition of adenylyl cyclase via stimulation of an inhibitory G protein, G_i (Fig. 24.16) (114). Other actions of muscarinic cholinergic agonists and some actions of α_1-adrenergic agonists and a number of hormones or neurotransmitters, whose actions are associated with an increase in intracellular Ca^{2+}, are related to changes in inositol lipid metabolism. Interaction of these agents with a receptor leads to the hydrolysis of polyphosphatidylinositol 4,5-biphosphate (PIP_2) by a phosphodiesterase (phospholipase C) with the formation of IP_3 and DG (10) (Fig. 24.17). IP_3 is involved in Ca^{2+} mobilization from intracellular stores, such as the endoplasmic reticulum (198). IP_3 initiates the flow of information in the calmodulin branch of the calcium messenger system and is thought to be responsible either for brief contractile responses or for the initial phase of sustained responses (157). DG binds to protein kinase C (PKC), causes its translocation to the cell membrane, and, by reducing the Ca^{2+} requirements for PKC activation, allows the enzyme to become more active. The physiologic response to DG depends on protein phosphorylation (151). The PKC branch of the calcium messenger system is thought to be responsible for the sustained phase of the contractile response (157) and is responsive to hormonally induced changes in intracellular calcium. DG, by activating phospholipase A, serves as a source of arachidonic acid (AA), the substrate for prostaglandin synthesis (133). Arachidonic acid may be involved in the stimulation of guanylyl cyclase with the formation of cGMP (10). This would explain the calcium-dependent increase in cGMP associated with the smooth muscle contractions induced by the cholinergic agonist, carbachol, and the α_1-adrenergic agonist, norepinephrine. These increases in cGMP follow the onset of the contractile event. cGMP itself appears to be inhibitory to smooth muscle function. 8-Bromo cGMP relaxes the ureter and other

smooth muscles, and sodium nitroprusside–induced smooth muscle relaxation is associated with an increase in cGMP (27,184).

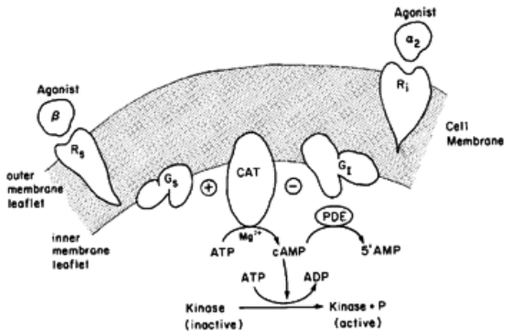

FIGURE 24.16. Diagrammatic representation of the relationship between the functional response to ß- and α_2-adrenergic agonists and the cyclic nucleotide system. ß-Adrenergic agonists activate the enzyme adenylyl cyclase and increase cyclic adenosine monophosphate *(cAMP)* production by working through a stimulatory receptor, R_s, and a stimulatory G protein, G_s. α_2-Adrenergic agonists inhibit adenylyl cyclase activity by working through an inhibitory receptor, R_i, and an inhibitory G-protein, G_i. The enzyme phosphodiesterase *(PDE)* degrades cAMP to 5'AMP. CAT, catalytic subunit of adenylyl cyclase.

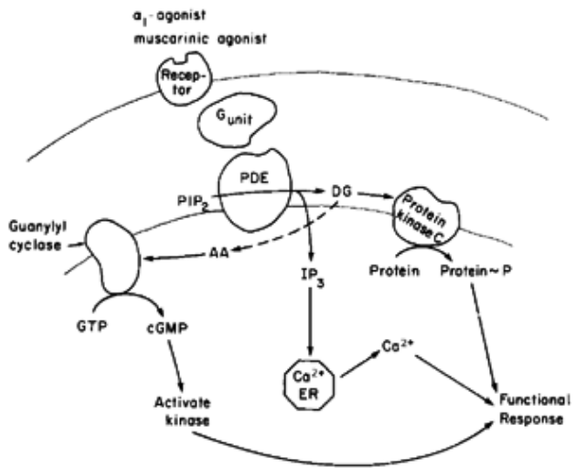

FIGURE 24.17. Diagrammatic representation of the role of inositol lipid metabolism in smooth muscle function. Agonists, such as α_1-adrenergic agonists and some muscarinic agonists, interact with a receptor, with the resultant hydrolysis of polyphosphatidylinositol 4,5 biphosphate (PIP_2), by a phosphodiesterase (phospholipase C) with the formation of 1,4,5-trisphosphate (IP_3), and diacylglycerol (DG). The functional response resulting from IP_3 is related to Ca^{2+} mobilization. DG activates protein kinase C, with the resultant functional response being dependent on protein phosphorylation. There is some evidence that DG may cause an increase in cyclic guanosine monophosphate (cGMP), which may explain the increase in cGMP observed in association with the contractile response to some autonomic agonists. AA, arachidonic acid; ER, endoplasmic reticulum; GTP, guanosine triphosphate.

Studies indicate that NO is a mediator of smooth muscle relaxation (23). NOS converts L-arginine to NO and citrulline (Fig. 24.18). The NO, in turn, activates an enzyme, guanylyl cyclase, that converts guanosine triphosphate (GTP) to cGMP, which results in smooth muscle relaxation. Nitric oxide also may cause smooth muscle relaxation by opening potassium channels (16,78).

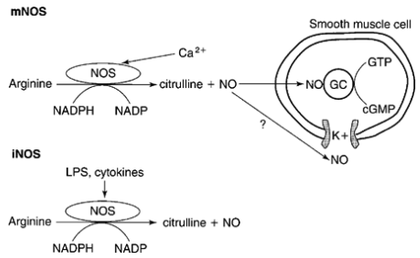

FIGURE 24.18. Schematic representation of nitric oxide synthase (mNOS, iNOS). GC, guanylyl cyclase; K^+, calcium-dependent potassium channel; LPS, lipopolysaccharide.

There are multiple isoforms of NOS. Neuronal NOS (nNOS) is Ca^{2+} and NADPH dependent (22). Neuronal excitation activates this enzyme, and the NO produced may result in smooth muscle relaxation. Endothelial NOS (eNOS) is also Ca^{2+} and NADPH dependent (186). Inducible NOS (iNOS) is NADPH dependent but Ca^{2+} independent and has been identified in ureteral (194) and other smooth muscles, and NOS-immunoreactive nerve fibers have been demonstrated in human ureter (195,197). NOS has been reported to colocalize with VIP, NPY, and tyrosine hydroxylase in nerves supplying the human ureter, including the intravesical segment (48,91,193).

Studies of isolated human ureteral segments suggest that the NO pathway may be involved in human ureteral relaxation (197). The NO donor 3-morpholinosyndonimine (SIN-1) can relax human ureteral segments, an action inhibited by the guanylyl cyclase inhibitor, methylene blue. The L-arginine–NO–cGMP pathway also may play a role in the function of the ureterovesical junction (91). NO donors inhibited agonist-induced contractions of isolated pig and human intravesical ureteral segments, and this inhibition was associated with an increase in cGMP levels.

Other Pharmacologic Agents

There are numerous reports of the excitatory effects of morphine and meperidine (Demerol) on the ureter, although these findings have not been universal (94,172). Both morphine and meperidine may have ureteral spasmogenic effects that theoretically would detract from their value in the management of ureteral colic. The efficacy of these agents in treating ureteral colic depends on their central nervous system actions, which decrease the perception of pain.

The primary prostaglandins (PGs), PGE_1, PGE_2, and $PGF_{2\alpha}$, are synthesized from the fatty acid, arachidonic acid. Two cyclooxygenase (COX) isoforms, COX-1 and COX-2, are the key regulatory enzymes in the biosynthesis of PGs from arachidonic acid (217). Indomethacin and aspirin can inhibit PG synthesis, and relatively specific COX-1 and COX-2 inhibitors have been developed. The functional response to PGs varies with the specific smooth muscle. In the ureter, PGE_1 activates adenylyl cyclase activity (236), increases cAMP levels (221), and inhibits activity. In contrast, $PGF_{2\alpha}$ is excitatory (19,30). Prostacyclin (PGI_2), a prostanoid, is synthesized in the urothelium of the ureter (2).

Indomethacin has been employed in the management of ureteral colic (83). COX inhibitors such as indomethacin inhibit pyeloureteral motility (30,177,208,242). The pain relief resulting from indomethacin, however, probably is due to inhibition of the prostaglandin-mediated vasodilation that occurs subsequent to obstruction (4,191). This prostaglandin-mediated vasodilation aids in preserving renal function, and thus, although indomethacin may provide pain relief, it is potentially deleterious to renal function (160). Endothelins (ETs) are potent vasoconstrictor peptides that exist in three isoforms (i.e., ET-1, ET-2, and ET-3). Endothelins have been shown to initiate contractions in isolated guinea pig and porcine ureters (50,129). There are two major endothelin receptor subtypes, ET_A and ET_B, with the ET_A receptor subtype being the predominant subtype in the ureter (112).

Histamine and the H_1-receptor agonist 2-(2-pyridyl) ethylamine cause contraction of the ureter, an effect that is antagonized by the H_1-receptor antagonist dimethindene. The H_2-receptor antagonist cimetidine does not affect the contractile response to histamine. These data show that the excitatory effects of histamine are mediated by the H_1-receptor subtype (44). Histamine and the H_2-receptor agonist impromidine relax precontracted ureteral segments, actions that are antagonized by cimetidine. These data are consistent with H_2-receptors mediating ureteral relaxant effects (44). 5-Hydroxytryptamine induces concentration-dependent contractions of isolated human ureteral segments (59).

Because Ca^{2+} is necessary for the development of the action potential and contraction of the ureter, agents that block the movement of Ca^{2+} into the cell would be expected

to depress ureteral function. Calcium channel blockers, such as verapamil, diltiazem, and nifedipine, have been shown to inhibit ureteral activity (62,80,84,125,174,175,218), and calcium antagonist receptors are present in the ureter (241). L-type voltage-dependent calcium channels mediate K^+-induced contractions in the guinea pig ureter (127). This is supported by the finding that the L-type calcium agonist Bay K 8644 potentiates K^+-induced contractions.

Potassium channel openers, such as pinacidil, cromakalim, and BRL 38227, hyperpolarize smooth muscle membranes and decrease spontaneous activity of the smooth muscle (55). BRL 38227 and cromakalim have been shown to inhibit ureteral activity (101,126). The effects of cromakalim are inhibited by glibenclamide (126).

In the clinical situation, the ureter's relatively sparse blood supply limits the distribution of drug to the ureter. In addition, many drugs that have theoretic potential use in the management of ureteral pathology have untoward side effects when used in the necessary concentrations. Although many drugs can affect ureteral function, their current clinical usefulness is limited.

URETERAL REPLACEMENT

Part of "24 - THE URETER "

Many clinical conditions have provided an impetus for the use of ureteral substitutes. Indications for ureteral replacement include recurrent calculi, ureteral trauma, hydronephrosis, ureterovaginal fistulae, ureteral obstruction, inflammatory disease, ureteral tumors, retroperitoneal fibrosis, and a variety of undiversions. Methods for ureteral replacement can be classified as synthetic prostheses, free grafts, and pedicle grafts. The use of free grafts and prosthetics has primarily been experimental, with most of the success being found with pedicle grafts.

A variety of synthetic materials have been used as ureteral substitutes, including Vitallium (117), tantalum (118), polyvinylchloride (215), silicone (183), Teflon (214), Dacron (13), polyethylene tubing (75), and silicone rubber (15). These materials have not gained general acceptance because of the occurrence of salt deposits and the lack of peristalsis, resulting in a functional obstruction. Studies continue toward finding a suitable biocompatible synthetic material. A tube of collagen sponge has been tried in an effort to capitalize on the regenerative growth potential of the ureter (200). The collagen sponge acts as a biodegradable scaffold for the regenerative activity of the ureter.

Free grafts have included bladder mucosa (86), peritoneum (51), vessels (187), stomach (145), and fetal umbilical vessels (97). Disruption and the lack of peristalsis have interfered with the clinical use of these materials.

In clinical practice, ureteral replacement has in general involved the use of pedicle grafts. Bladder flaps (Boari flaps), with or without hitching the bladder to the psoas muscle, have been a highly effective means of replacing the lower ureter (154). Flaps of the renal capsule have been used to enlarge the UPJ (207). Although pedicle flaps of the fallopian tube and appendix have been tried, they have not provided the required peristaltic function, and hydronephrosis has resulted (143,180).

Ileum has been the most widely used pedicle graft and the most successful (18,63,192). Proponents of the use of the ileum for replacement of the entire ureter have cautioned against its use in individuals with a serum creatinine level of 2 mg/dL or greater because of the ensuant electrolyte abnormalities (17). Middleton (144) suggested that the absorptive surface of the ileal ureter could be minimized by tapering the segment. This procedure also could aid in the construction of an antirefluxing ileovesical anastomosis. When using the ileum to replace the ureter, the ileum should be used in an isoperistaltic manner, and there should be no evidence of distal obstruction. Immediately following the procedure, there may be considerable mucus in the urine, but this tends to clear with time. Normal saline or acetylcysteine (Mucomyst) may aid in preventing mucous clogging of the urinary tract. Colon also has been used as a ureteral substitute, but less widely (199).

Lytton and Schiff (120) used a short, isolated segment of ileum to replace a segment of ureter, with the distal anastomosis of the ileum being to the ureter. This interposition, rather than replacement, gives one the opportunity to take advantage of a normal, nonrefluxing UVJ and diminishes the risk of electrolyte disturbances, especially in the patient with mild renal insufficiency. The ileal segment is tapered on its distal antimesenteric surface and, if possible, placed retroperitoneally by passing it through a window in the mesentery. The long-term results with this procedure have been excellent.

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25

DISEASES OF THE RETROPERITONEUM

Brian E. Nicholson

Dan Theodorescu

B.E. Nicholson and D. Theodorescu: Department of Urology, University of Virginia, Charlottesville, VA 22908.

Contents

> Many a clinical reputation lie buried behind the peritoneum. In this hinterland of straggling mesenchyme, with its vascular and nervous plexuses, its weird embryonic rests, and its shadowy fascial boundaries, clinicians are often left with only their flair and their diagnostic first principles to guide them (Editorial, Periureteral fibrosis. *Lancet* 1957;2:780).

The retroperitoneum contains some of the major organs that fall under the jurisdiction of urology, most notably the kidneys, ureters, adrenal glands, and the retroperitoneal lymph nodes. Inflammatory processes, benign and malignant primary tumors, as well as regional lymph node metastases are found within this space. Because diseases within the retroperitoneum fall into the realm of urology and urologists often access this space during operative procedures, it seems prudent to provide a global view of the retroperitoneum.

A detailed discussion of renal pathology, adrenal conditions, and metastatic testes tumors is provided in other chapters of this text. The aim of this chapter is to provide information relating to the other diseases that occur within this “hinterland.” The conditions that present in the retroperitoneum are some of the most challenging to manage, in terms of both diagnosis and treatment. It is vital to have a thorough understanding of these disorders to successfully care for patients with disease of the retroperitoneum.

The first section of this chapter addresses retroperitoneal tumors: benign primary retroperitoneal tumors as well as the more common and clinically more significant malignant primary retroperitoneal tumors, primarily retroperitoneal sarcomas. Second, inflammatory diseases of the retroperitoneum, including retroperitoneal fibrosis and pelvic lipomatosis, are discussed. This chapter concludes with consideration of retroperitoneal abscesses and spontaneous retroperitoneal hemorrhage.

ANATOMIC CONSIDERATIONS

Part of "25 - DISEASES OF THE RETROPERITONEUM "

The retroperitoneum, or spatium retroperitoneale, is a potential space between the parietal peritoneum and the posterior abdominal wall that is occupied by the retroperitoneal connective tissue (Fig. 25.1). This retroperitoneal connective tissue is comprised of three layers called *strata.* The inner stratum lies immediately behind the peritoneum and covers the gastrointestinal (GI) viscera along with their blood supply. The intermediate stratum envelops the adrenals, kidneys, ureters, and great vessels. The outer stratum forms the fascia of the posterior abdominal wall (255). The boundaries of the retroperitoneum are the muscular diaphragm superiorly, the posterior parietal peritoneum anteriorly, the body wall both posteriorly and laterally, and the pelvic diaphragm inferiorly. Urologic, vascular, GI, lymphatic, and neural structures lie within the retroperitoneum >Table 25.1). A detailed description

of the anatomy of the retroperitoneum can be found in Chapter 1 .

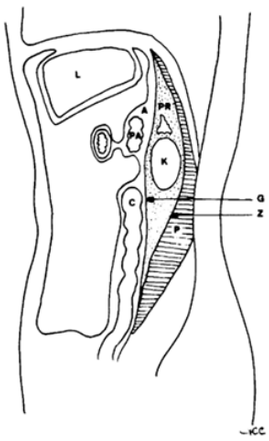

FIGURE 25.1. The retroperitoneal space and its subdivisions (sagittal section). A, anterior renal space; C, colon; G, Gerota's fascia; K, kidney; L, liver; P, posterior renal space; PA, pancreas; PR, perirenal space; Z, Zuckerkandl's fascia.

TABLE 25.1. STRUCTURES WITHIN THE RETROPERITONEUM

Urologic	Kidneys Ureters Adrenal glands
Vascular	Great vessels (aorta and inferior vena cava and their branches) Portal veins
Gastrointestinal	Pancreas, portions of duodenum and colon Rectosigmoid
Lymphatic	Parietal and visceral lymph nodes and channels Cisterna chyli Thoracic duct
Neural	
Nerve plexuses	Celiac, superoinferior hypogastric, sacral, sympathetic trunks
Nerves	Ilioinguinal, iliohypogastric, lateral cutaneous, femoral, genitofemoral, obturator, sciatic, pudendal

TUMORS OF THE RETROPERITONEUM

Part of "25 - DISEASES OF THE RETROPERITONEUM "

Retroperitoneal tumors comprise a heterogeneous group, of which metastatic carcinoma is the most common. Primary retroperitoneal tumors are defined as neoplasms originating from the retroperitoneal connective tissues. Excluded from this category are tumors of the kidney, ureter, adrenal glands, and pancreas. Approximately 85% of primary retroperitoneal tumors are malignant, with soft tissue sarcomas accounting for roughly half of these cases. A classification, as well as approximate frequency, of retroperitoneal tumors is given in >Table 25.2 . These tumors are of importance to urologic surgeons because, with the exception of the lymphomas, primary treatment is surgical and the outcome is determined by the completeness of resection and the extent of adjacent organ involvement. Although histology does affect the biologic behavior and prognosis following treatment of these tumors, they can be considered together for the purposes of assessment and treatment planning because they tend to present similarly and management is largely independent of their histiogenic origin.

TABLE 25.2. CLASSIFICATION OF PRIMARY RETROPERITONEAL TUMORS

Tumor Type	%
Benign	**15**
Neural	30
Cysts	22
Lipoma	16
Fibroma	6
Hemangioma	6
Leiomyoma	5
Other	15
Malignant	**85**
Soft tissue sarcoma	50
Lymphoma	25
Carcinoma	10
Undifferentiated/unclassified	13
Germ cell	2

Data obtained from references 27, 72, 143, 148, 193, 202, and 233.

Clinical Presentation

Although the retroperitoneum is a distinct anatomic compartment of the abdomen, it does not have rigid boundaries. Instead, it consists of loose, areolar connective tissue that provides little barrier to the growth of tumors. Hence, these retroperitoneal lesions can reach a considerable size before becoming symptomatic, resulting in most patients being diagnosed late in the course of their disease. Presenting

symptoms are characteristically vague and nonspecific:Anorexia and weight loss, general malaise, poorly localized abdominal discomfort, and backaches are common. Abdominal distention and GI complaints, such as nausea, vomiting, epigastric discomfort, and change in bowel habits, occur in some patients, and advanced tumors may actually present with intestinal obstruction. Obstruction of the urinary tract is unusual. At times, ascites, lower-extremity edema, or abnormal abdominal venous collaterals occur secondary to obstruction of the vena cava. Fever is typical not only of lymphomas but also of large sarcomas that have substantial necrotic areas. Because of the insidious onset and the nonspecific nature of the symptoms, there is typically a considerable delay, ranging from 5 to 7 months, between the onset of symptoms and clinical presentation. At the time of diagnosis, most patients complain of pain in the abdomen, flank, or back, and most will have a palpable abdominal mass on physical examination (46,52,168,233,280). Because most of these series that have documented the presenting symptoms are more than 10 years old, it is conceivable that current tumors are diagnosed at earlier stages due to the relatively high prevalence of ultrasound examinations of the abdomen in routine clinical practice. Such increased detection of early tumors as a result of increased abdominal ultrasound use has been shown for renal cell carcinoma (156,259).

Diagnostic Approach

By obtaining a careful history and physical examination along with appropriate imaging studies, the diagnosis of most retroperitoneal masses can be made. Because of the nonspecific and vague presenting symptoms, various radiologic studies are often obtained initially. These studies may include abdominal ultrasound, upper and lower GI contrast studies, and excretory urography. In particular, abdominal ultrasonography is often the first study obtained in patients presenting with nonspecific GI symptoms. This technique provides excellent accuracy in recognizing the solid or cystic nature of mass lesions, but it is often limited by the presence of bowel gas (157). When the mass is clearly delineated, ultrasonography provides a means for guidance of percutaneous biopsy techniques but currently is not the most common modality for this because of its dependence on patient body habitus.

The most important imaging technique is abdominal computed tomography (CT) scanning, which has revolutionized the diagnosis and staging of retroperitoneal masses. This study not only demonstrates the retroperitoneal location of the mass but also provides information about the nature of the lesion that is important in the differential diagnosis. Such information includes the composition, whether cystic or solid, the presence or absence of necrosis, the extent of involvement of adjacent structures, and the presence of intraabdominal metastases (143,198). Indeed, the diagnosis of a soft tissue retroperitoneal sarcoma is often strongly suspected on the basis of CT findings demonstrating a heterogeneous, irregular retroperitoneal mass with patchy areas of necrosis (Fig. 25.2).

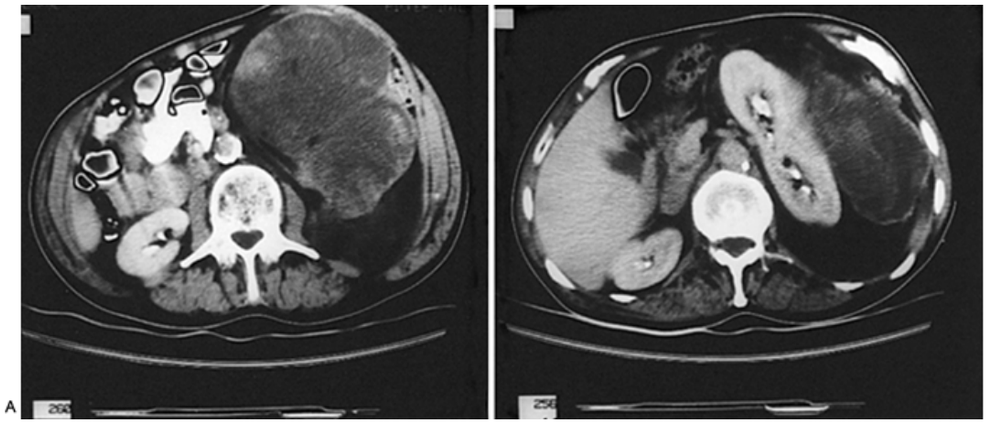

FIGURE 25.2. A: Computed tomography scan through upper abdomen demonstrates the presence of a huge, left-sided retroperitoneal liposarcoma. The mass is composed of tissues of varying densities, including soft tissue and fat. In contrast to benign lipomas, retroperitoneal sarcomas frequently demonstrate only minimal amounts of fat. **B:** Scan from same patient several cuts lower demonstrates relationship of mass to medially deviated left kidney that was resected en bloc with the tumor.

Findings on CT scan are also valuable in differentiating sarcomas from other primary and metastatic retroperitoneal malignancies. For example, the demonstration of the involvement of multiple retroperitoneal lymph nodes in association with a retroperitoneal mass may suggest

a lymphoma that may be confirmed by a lymph node biopsy. This is an important distinction to make because treatment for lymphoma is nonsurgical. A high index of suspicion for males at risk for testicular carcinoma is also warranted in patients presenting with large retroperitoneal masses. In this situation, a careful testicular examination with and without scrotal ultrasonography, and evaluation of serum α-fetoprotein and ß-human chorionic gonadotropin (ß-hCG) should be carried out. Similarly, when symptoms and signs suggest a tumor all of adrenal origin, tests of adrenocortical and medullary function are indicated. In contrast, the CT scan cannot provide conclusive evidence that a lesion is benign or that it is malignant. This is primarily because benign lesions are seen to enhance in 30% to 100 % of cases (104). However, despite these limitations, several groups are exploring the development of scoring systems combining multiple factors such as tumor size, presence of symptoms, absence of calcifications, presence of irregular margins, and the presence of necrosis to predict whether a lesion is benign or malignant (184).

When a soft tissue sarcoma of the retroperitoneum is suspected on the basis of CT scanning, magnetic resonance imaging (MRI) with gadolinium contrast administration provides important staging information (51,75). This technique delivers no ionizing radiation and requires no contrast. It offers the additional advantage of imaging in multiple planes, which can be helpful when planning tumor resection. MRI often provides information superior to that of CT scanning because it more clearly shows the anatomic relationships of the mass to adjacent structures, especially vascular structures, and the extent of tumor involvement of adjacent structures. This applies especially to sarcomatous infiltration along nerve roots with possible involvement of spinal foramina. Further uses of CT, MRI, and other imaging modalities are discussed later in the section on the preoperative evaluation.

Benign Primary Retroperitoneal Tumors

Approximately 15% of primary retroperitoneal tumors are benign.>Table 25.2 lists the pathologic findings compiled from 13 series for 158 benign retroperitoneal tumors. As can be seen, most of these lesions are stromal neoplasms and cysts. In contrast to their malignant counterparts, most of these lesions can be completely resected with a low risk of recurrence and an excellent prognosis. At times, complete resection may be difficult because of the considerable size of these masses and their proximity to vital structures. Three of twenty benign tumors in the series of Pinson and colleagues (202) and two of the thirteen tumors in the study of Braasch and Mon (27) were unresectable; one patient in the latter group ultimately died of his disease.

Lahey and Eckerson (140) classified retroperitoneal cysts as urogenital, lymphatic, teratomatous, mesocolic, paracytic, or traumatic in origin. Urogenital cysts arise from persistent wolffian remnants and are therefore more common in females. Urogenital cysts may be differentiated from mesocolic cysts at the time of surgery by the relationship of the cysts to the gonadal vessels: Mesocolic cysts are anterior to the vessels and urogenital cysts are posterior (193).

Teratomas and dermoid cysts are seen most commonly in children and usually originate in the gonads or anterior mediastinum. However, 5% of these tumors have been reported in the retroperitoneum (63). From 10% to 25% of these are malignant, and an aggressive surgical approach is warranted for all such lesions in an effort to prevent local recurrence (72,141). For sacrococcygeal teratomas, the resection must include the coccyx because a 33% recurrence rate has been cited for patients in whom the coccyx was not removed (72,148). This underscores the principle that the most important goals in managing any of these benign tumors are to completely resect them and to rule out malignancy. Liberal use of intraoperative frozen sections to ensure that the lesion is benign may eliminate the need for extended resection involving normal adjacent organs.

Soft Tissue Sarcomas

Soft tissue sarcomas are malignant, nonepithelial tumors that arise from the extraskeletal connective tissues of the body, excluding the supporting structures of the various parenchymal organs. Sarcoma is derived from the Greek word *sarkoma,* meaning “fleshy growth.” With the exception of malignant peripheral nerve tumors, which are derived from embryonic ectoderm, these tumors have a common embryonic origin—the primitive mesoderm. Although these tumors are often grouped together because of similarities in management, there is increasing evidence that biologic behavior depends on the histologic type and molecular characteristics of these various lesions. Such nuances are discussed later. In most cases, these tumors present a formidable challenge to the surgeon, primarily because complete surgical resection provides the only possibility for long-term disease-free survival. Therefore the surgeon must have a clear understanding and appreciation of the biology of these unusual neoplasms and their relationships to adjacent organs.

Although retroperitoneal sarcomas share the same histiogenic origin and biology of soft tissue sarcomas found elsewhere, they are rendered unique by virtue of their anatomic location. In the retroperitoneum, even when the surgeon achieves an apparently complete resection, tumor margins are often positive in most patients (37). In addition, this anatomic location renders the application of adjuvant treatments such as radiation more problematic. Unfortunately, the improved survival and quality of life gained over the last decade in the management of extremity sarcomas have not been paralleled in the retroperitoneum (19,203). In fact, a retroperitoneal location is a poor prognostic

indicator for patient survival in soft tissue sarcoma (109,118,158,277).

Epidemiology and Etiology

Soft tissue tumors (including those of the heart) constitute less than 1% of all malignancies in adults, with an estimated 8,700 new cases and 4,400 deaths projected for 2001 (93). Approximately 15% of these new cases will occur in the retroperitoneum. These tumors occur equally in males and females, with a peak incidence occurring in the sixth decade of life.

In 1940, James Ewing wrote, “Of the specific etiology of sarcoma, little is definitely known.” Today, our understanding of epidemiologic or etiologic factors in patients with soft tissue sarcomas continues to remain limited. However, several clinical conditions are associated with these tumors. Sarcomas are reported to occur with increased frequency in patients with a number of genetic diseases, such as tuberous sclerosis, Werner syndrome, and intestinal polyposis (79,210,257). Patients with Gardner's syndrome also have an increased incidence of benign soft tissue tumors and may develop a desmoid fibrosarcoma of the mesentery (209).

Patients with neurofibromatosis or von Recklinghausen's disease have an approximate 10% lifetime incidence of neurofibrosarcoma (101,152). Neurofibromatosis is one of the most common autosomal-dominant disorders, affecting approximately 1 in 3,500 in the general population. It is characterized by abnormalities affecting tissues derived from the embryonic neural crest. These patients are predisposed to a variety of benign growths, including neurofibromas and benign and malignant tumors arising from peripheral nervous structures, including pheochromocytomas, schwannomas, and neurofibrosarcomas. The NF-1 tumor-suppressor gene responsible for this syndrome has been localized to the long arm of chromosome 17 (97).

Patients with Li-Fraumeni syndrome, characterized by germ line mutations in the p53 tumor-suppressor gene, have an increased incidence of soft tissue sarcomas, as well as breast cancer, osteosarcoma, brain tumors, leukemia, and adrenal cortical carcinoma (154). There is also evidence that patients treated for retinoblastoma in childhood are predisposed to the development of sarcoma in later life (225). The protein products of the p53 (17p13) and retinoblastoma (13q14) genes are intimately involved in cell-cycle control, angiogenesis, and various other cellular phenotypes, and mutations in these genes have been implicated in the tumorigenesis and progression of many human malignancies (266).

Sarcomas also are known to occur at increased frequency in patients previously exposed to ionizing radiation. At The University of Texas M.D. Anderson Cancer Center, 5% of the 331 chest wall sarcomas that occurred between 1944 and 1984 were radiation induced (244). Halperin and colleagues (99) reported an increased frequency of sarcomas following radiotherapy for Hodgkin's disease. These investigators have calculated a risk of sarcoma of nearly 1% in 5-year survivors of Hodgkin's disease. The latent period for tumorigenesis following radiation therapy is in the range of 10 to 15 years. Although extraskeletal osteosarcomas appear to be the most common, other tumors commonly associated with radiotherapy are fibrosarcomas, malignant fibrous histiocytoma, mixed mesodermal sarcomas, and mesotheliomas (271).

Chemical carcinogens, such as polycyclic hydrocarbons, as well as viruses, can produce sarcomas in experimental animals. There is no convincing link in humans, however, between exposure to chemical carcinogens or viral transformation and sarcoma development.

Pathology

Histologic Classification

Soft tissue tumors are a large and diverse group of histologically distinct but often grossly and biologically similar neoplasms. The pathologic classification of these tumors is based on the presumed cell of origin and is reviewed in abbreviated form in >Table 25.3 .

TABLE 25.3. HISTOLOGIC CLASSIFICATION OF SOFT TISSUE TUMORS

Histogenic Origin	Benign	Malignant
I. Tumors of fibrous tissue	Fibroma	Fibrosarcoma
II. Tumors of adipose tissue	Lipoma	Liposarcoma
	Angiolipoma	
	Angiomyolipoma	
	Myelolipoma	
	Diffuse/pelvic lipomatosis	
III. Tumors of muscle tissue		
A. Smooth muscle	Leiomyoma	Leiomyosarcoma
B. Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
IV. Tumors of blood vessels	Hemangioma	Hemangiosarcoma
	Hemangiopericytoma	Kaposi's sarcoma
		Malignant hemangiopericytoma
V. Tumors of lymph vessels	Lymphangioma	Angiosarcoma
VI. Tumors of synovial tissue	Giant cell tumor	Synovial sarcoma
VII. Tumors of mesothelial tissue	Mesothelioma	Malignant mesothelioma
VIII. Tumors of peripheral nerves and ganglia	Neurilemoma (benign Schwannoma)	Malignant Schwannoma
	Neurofibroma	Neuroepithelioma
	Neurofibromatosis	Neuroblastoma
	Ganglioneuroma	Ganglioneuroblastoma
	Paraganglioma	Malignant ganglioma
		Malignant paraganglioma
IX. Tumors of pleuripotential mesenchyme	Mesenchymoma	Malignant mesenchymoma
		Malignant fibrous histiocytoma
X. Tumors of uncertain histiogenesis	Myxoma	Alveolar soft part sarcoma

Modified from Enzinger FM, Weiss SW. Soft tissue tumors, 2nd ed. St. Louis: Mosby, 1988a.

The varied soft tissues can give rise to either benign or malignant tumors. Malignant transformation of benign lesions is rare. The histologic distribution of retroperitoneal sarcomas is given in >Table 25.4 . Even the abbreviated histologic classification scheme as presented is complex and can be confusing to clinicians unfamiliar with sarcomas. Compounding this confusion are changes in the histologic classification of soft tissue tumors that have occurred over the past 15 years. For example, the recognition of malignant fibrous histiocytoma (MFH) as a separate category has generated wide variations in the reported incidence of specific histologic types in the literature.

TABLE 25.4. HISTOLOGIC DISTRIBUTION OF RETROPERITONEAL SARCOMAS

	Total	%
Liposarcoma	291	32
Leiomyosarcoma	265	29
Malignant fibrous histiocytoma	89	10
Fibrosarcoma	62	7
Rhabdomyosarcoma	53	6
Malignant peripheral nerve tumor	57	6
Undifferentiated/unclassified	37	4
Hemangiopericytoma	12	1
Other	56	5
	922	100

Compilation of data reported from 1981–1994 from references 7, 46, 52, 124, 168, 224, 233, 260, 273, and 280.

Although virtually absent from series reported before 1980, MFH has become one of the most common histologic types, especially in older patients. This category includes tumors previously considered fibrosarcoma or pleomorphic rhabdomyosarcoma and many undifferentiated sarcomas (74). Although originally thought to originate from histiocytes, recent evidence suggests that the cell of origin of MFH is a pluripotential primitive mesenchymal cell. Interestingly, the poorly differentiated component found in dimorphic dedifferentiated sarcomas is often of the MFH type. It has thus been postulated that MFH may represent not only a distinct histologic entity but also a dedifferentiated state. As such, MFH may be viewed as the final common pathway in the transformation of most malignant soft tissue tumors from differentiated to undifferentiated (33).

Tumor Staging

The 1997 TNM/AJCC classification and staging system for soft tissue sarcomas >Table 25.5) is currently used. Although

tumor size has been shown to be an important prognostic factor for extremity sarcomas, influencing both outcome and propensity for local recurrence, it is much less important for retroperitoneal sarcomas. Although the AJCC stage grouping takes into account tumor size by assigning B subgroups for tumors larger than 5 cm, at presentation, nearly all retroperitoneal tumors are larger than 5 cm (52). In the Mayo Clinic series of 116 retroperitoneal sarcomas reported by Dalton and associates (52), 92% were larger than 5 cm. The experience from the Royal Marsden Hospital, reported by Alvarenga and associates (7), is similar, with 90% of 120 retroperitoneal sarcomas presenting as larger than 5 cm. In fact, most of these tumors are much larger than 5 cm. McGrath and associates (168) reported median sizes of 114 cm in tumors that were completely resected and 28 cm in those that were incompletely resected.

Rules for Classification

There should be histologic confirmation of the disease and division of cases by histologic type and grade. The following are the procedures for assessing T, N, and M categories:

T categories	Physical examination and imaging
N categories	Physical examination and imaging
M categories	Physical examination and imaging

Anatomic Sites

Connective, subcutaneous, and other soft tissues, peripheral nerves (C47, C49)
Retroperitoneum (C48)
Mediastinum (C38.1, 2)

Histologic Types of Tumor

The following histologic types of malignant tumor are included, the appropriate ICD-O morphology rubrics being indicated:

Alveolar soft part sarcoma	9581/3
Angiosarcoma	9120/3
Epithelioid sarcoma	8804/3
Extraskeletal chondrosarcoma	9220/3
Extraskeletal osteosarcoma	9180/3
Fibrosarcoma	8810/3
Leiomyosarcoma	8890/3
Liposarcoma	8850/3
Malignant fibrous histiocytoma	8830/3
Malignant hemangiopericytoma	9150/3
Malignant mesenchymoma	8990/3
Malignant schwannoma	9560/3
Rhabdomyosarcoma	8900/3
Synovial sarcoma	9040/3
Sarcoma NOS (not otherwise specified)	8800/3

The following histologic types of tumor are not included: Kaposi's sarcoma; dermatofibrosarcoma (protuberans); fibrosarcoma grade I (desmoid tumor); and sarcoma arising from the dura mater, brain, parenchymatous organs, or hollow viscera.

Regional Lymph Nodes

The regional lymph nodes are those appropriate to the site of the primary tumor.

TNM Clinical Classification

T	**Primary Tumor**
T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_1	Tumor 5 cm or less in greatest dimension
T_{1a}	Superficial tumor[a]
T_{1b}	Deep tumor[a]
T_2	Tumor more than 5 cm in greatest dimension
T_{2a}	Superficial tumor[a]
T_{2b}	Deep tumor[a]
N	**Regional Lymph Nodes**
N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
M	**Distant Metastasis**
M_X	Distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis
pTNM	**Pathologic Classification**

The pT, pN, and pM categories correspond to the T, N, and M categories.

G	**Histopathologic Grading**
GX	Grade of differentiation cannot be assessed
Gl	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

After the histologic type has been determined, the tumor should be graded according to the accepted criteria including cellularity, cellular pleomorphism, mitotic activity, and necrosis. The amount of intercellular substance such as collagen or mucoid material should be considered as a favorable factor in assessing the grade.

[a]Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

TABLE 25.5. TNM/AJCC CLASSIFICATION OF SOFT TISSUE TUMORS (ICD-O C38.1, 2, C47-49)

Tumor Grading

Although there is no universally accepted grading system, in general, histologic grading is based on the degree of cellularity, nuclear pleomorphism, frequency of mitoses and pretherapeutic necrosis, and infiltrative qualities (48). Histologic grading defines a wide spectrum of biologic behavior from slow growing, locally recurrent, low-grade tumors that rarely metastasize to anaplastic, high-grade lesions that develop hematogenous metastasis in many cases. Note that these tumors may be heterogeneous, with areas of different histologic grade juxtaposed. Furthermore, recurrent tumors often manifest as progression to a higher grade, which is indicative of the genetic instability of these tumors. To reflect its prognostic significance, grade is an element of the TNM/AJCC and classification system >Table 25.5).

In most series of retroperitoneal sarcomas, approximately 40% of tumors are low grade (grade I), with the remainder equally divided between grades II and III (7,124,168,260,280). Regarding stage at presentation, between one-half and two-thirds of patients present with stage III or IV disease (7,52,124).

Incidence and Patterns of Metastasis

There is a wide range in the reported frequency (4% to 35%) of metastasis at the time of presentation, but most series report an incidence of 15% to 20% (7,52,124,168,233,273,280). Retroperitoneal sarcomas metastasize principally by the hematogenous route to the lung (30% to 60%), liver (20% to 60%), bladder (15%), and bone (10%) (46,168,273). Lymphatic spread, clinically apparent at the time of initial treatment, is uncommon for most histologic types of sarcomas. However, when present, nodal disease portends a poor prognosis and is more commonly associated with certain histologic types (alveolar rhabdomyosarcoma, angiosarcoma, epithelioid sarcoma, clear cell sarcoma) (9,66). As with lymphatic spread, histologic type also influences the frequency of distant hematogenous metastasis. Liposarcomas generally tend to metastasize relatively late, whereas MFH is characterized by early dissemination (66). Finally, tumor grade is an important risk factor for the development of metastatic disease (111).

Diagnosis

Imaging

The diagnostic imaging approach to retroperitoneal masses in general has already been discussed.

Biopsy

Fine-needle Aspiration Biopsy or Core-needle Biopsy.

In the past, most authors have recommended formal open biopsy to establish the histologic diagnosis of retroperitoneal masses, contending that fine-needle aspiration biopsy or core-needle biopsy generally does not yield enough tissue to provide the necessary information for differential diagnosis, regardless of whether the tumor is a sarcoma, lymphoma, or other visceral neoplasm localized in the retroperitoneum (124,249). However, other authors have advocated fine-needle aspiration biopsy, which minimizes the potential for peritoneal seeding during open biopsy (243). This procedure can be guided by either ultrasound or CT imaging and is reliable in differentiating potentially sarcomatous lesions from other neoplasms such as lymphoma and germ cell tumors. A significant caveat of all needle biopsies is its limitation in diagnosing well-differentiated tumors from their benign counterparts (57). In addition, such approaches can mistakenly lead to a benign diagnosis of cellular inflammatory pseudotumor instead of an inflammatory fibrosarcoma (169). Therefore great care and judgment should be exercised in the application of this technique.

Open Biopsy.

When an open biopsy is required, extreme care and planning of the biopsy are critical. The technique of biopsy is paramount in preventing peritoneal seeding of the tumor. In one study of patients with retroperitoneal sarcomas, none manifested intraabdominal sarcomatosis without having previously undergone biopsy (249). An incisional biopsy should be carried out by a laparotomy under general anesthesia in most cases. Every effort should be taken to prevent tumor spillage (249). This includes isolating and packing off wound edges and normal structures and performing minimal dissection in the area of the tumor. The tumor capsule should be incised and a small wedge of underlying tumor excised. Closure of the tumor pseudocapsule, with the meticulous attainment of hemostasis, is important to prevent tumor spill or spread by the formation of a hematoma. If a definitive diagnosis cannot be made with frozen sections, the procedure should be terminated, with definitive management awaiting the final diagnosis, which may require the use of immunohistochemical, cytogenetic, or other special studies. It should be emphasized that the tissue planes in the area of the tumor should not be disturbed. Also, a well-defined pseudocapsule characterizes soft tissue sarcomas, such that enucleating the tumor within this plane invariably leaves behind gross or microscopic tumor.

Special Studies.

Occasionally, histologic diagnosis may be difficult, and special studies, including the use of special stains, ultrastructural analysis, immunohistochemistry, and cytogenetic analysis, may be required. Combining standard histologic analysis with these techniques, a definitive diagnosis can be made in virtually all soft tissue sarcomas. Immunostaining of a number of antigens, including vimentin, cytokeratin, desmin, factor VIII–related antigen, and S-100 protein, has proven valuable in the characterization and diagnosis of soft tissue sarcomas (48). Furthermore, many of the soft tissue sarcomas have recently been found to contain characteristic chromosomal aberrations that have documented diagnostic relevance (77). However, an in-depth discussion of these techniques and their use is beyond the scope of this chapter, and the reader is referred to two excellent recent reviews (65,76).

Evaluation for Metastatic Disease and Adjacent Organ Involvement

Before definitive management of a retroperitoneal sarcoma is begun, further investigations are necessary to rule out the presence of metastatic disease and to assess other vital structures that may require en bloc resection at the time of definitive surgery. Metastatic evaluation should include abdominal and pelvic CT or MRI imaging and a CT scan of the chest. It is important to note that hepatic metastases may have MRI appearances similar to hemangiomas but harbor subtle distinctions from the latter (245). A bone scan to rule out osseous metastasis is also indicated. Suggestive lesions in any of these locations can usually be accessed by percutaneous biopsy techniques.

Although these tumors are uncommon and no large prospective studies have addressed their management, the collective experience of specialized cancer centers illustrates

several important principles for the successful management of these tumors. We cannot overemphasize the importance of preoperatively obtaining the information necessary for making rational treatment decisions. This includes obtaining an idea of the anatomic structures that are likely involved and that will therefore require en bloc resection with the tumor. Since the advent of the routine use of MRI vascular studies and newer CT techniques (e.g., spiral CT with contrast), which provide excellent visualization of vascular structures, the need for routine use of angiography largely has been eliminated (139). When MRI angiography is insufficient in establishing vascular involvement, conventional angiography is useful when further knowledge concerning the anatomy of the tumor blood supply is deemed important for planning the surgical procedure (Fig. 25.3). This is especially important when there is a possibility of aortic or other major vascular resection. MRI venography has virtually eliminated the need for conventional venacavography because MRI provides excellent visualization of the presence and extent of tumor thrombus within the vena cava. Occasionally, if not already obtained in the course of previous evaluation in patients often presenting with nonspecific abdominal complaints, contrast-enhanced upper and lower GI studies and endoscopy may be necessary to define the extent of involvement of the GI tract, which is also often resected en bloc with retroperitoneal sarcomas.

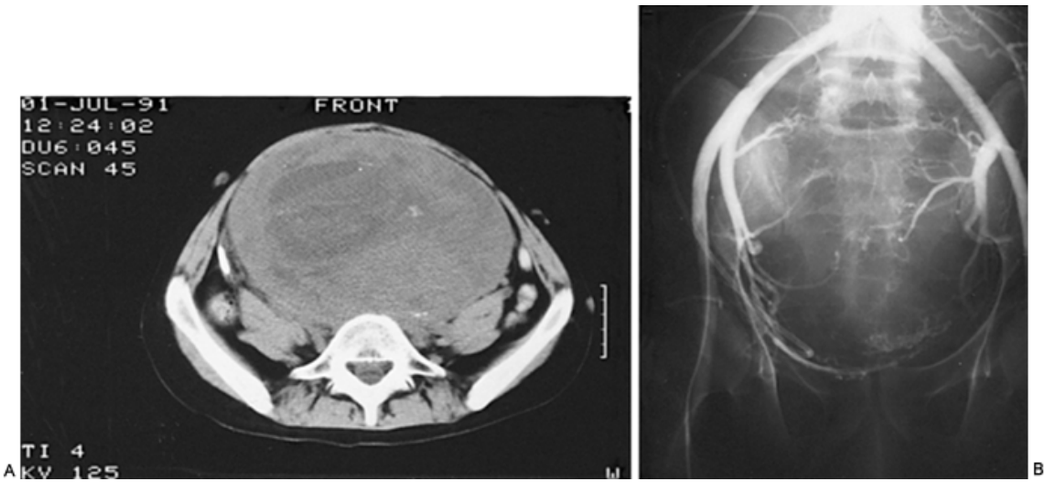

FIGURE 25.3. A: Computed tomography scan of the pelvis demonstrates huge recurrent malignant Schwannoma. **B:** Arteriogram demonstrates vascular anatomy and tumor blood supply. Resection of this tumor required performance of a hemipelvectomy.

Preoperative Assessment and Preparation

Bilateral renal function must be assessed in patients with retroperitoneal sarcomas; the kidney is the most commonly resected adjacent organ in these patients (52,124). In a recent series from Memorial Sloan-Kettering (220), 75 (20%) of the 371 retroperitoneal sarcoma patients who underwent resection needed concomitant nephrectomy. In this series, the most common reasons for renal resection were incasement by sarcoma in 53% of patients and adherence of the tumor to kidney in 28% of patients. Interestingly, on pathologic examination, the kidney was involved in only 27% of cases. Although often accomplished by documenting a normal contralateral kidney on excretory urography or a contrast-enhanced CT scan in a patient with normal renal function, more precise characterization of renal function is often necessary, such as by radionuclide renal imaging with and without the evaluation of glomerular filtration rate. This situation arises when there is a significant size discrepancy between the two kidneys, one kidney has sustained previous damage or undergone surgery, or one kidney has a preexisting lesion such as a stone. Although most cases involving large retroperitoneal sarcomas generally require sacrifice of both right and left sympathetic trunks, if future reproductive potential is an issue, patients should be counseled regarding preoperative sperm banking, as is often recommended before retroperitoneal lymph node dissection for testicular cancer (237).

The preoperative preparation is for the most part routine and not different from that for the typical, often elderly, and at times debilitated, patient undergoing a major intraabdominal oncologic procedure. These patients also are often nutritionally depleted, and optimization of their nutritional status by either the enteral or parenteral route is an important part of their preoperative care. Because of the potential for significant blood loss, the surgeon must also ensure that adequate blood is available. All patients should have a thorough mechanical and antibiotic bowel preparation. Based on the imaging workup of the primary tumor,

patients should be asked for consent for the removal of adjacent organs likely to be involved by the tumor and for possible either temporary or permanent urinary and fecal diversion. As dictated preoperatively by the location and extent of the tumor, the placement of retrograde ureteral catheters at the time of surgery may facilitate identification, dissection, and preservation of the ureters.

It is also important to recognize that the successful treatment of complex and extensive retroperitoneal sarcomas necessitates a multidisciplinary surgical approach. Therefore appropriate preoperative consultations should be sought to from general surgical, vascular, orthopedic, microvascular/plastic, neurosurgical, and cardiothoracic surgical specialties as dictated by the preoperative appearance and extent of the tumor. Multiorgan resections have been facilitated greatly over the past decade by the development of techniques for reconstruction.

Surgical Management of Patients with Clinically Resectable Disease

General Principles

Currently, the best chance of survival in patients with retroperitoneal sarcomas is provided by complete surgical resection of the tumor with microscopically tumor-free margins. Invasive monitoring of continuous arterial blood pressure and central venous pressure, and often pulmonary artery occlusion pressure, is required. There has been a trend toward an improvement in the operative mortality over the past 15 to 20 years, with current figures in the range of 2% to 4% (52,124,224,260).

The first principle in the management of these tumors is that of en bloc resection including adjacent involved organs or other structures. Although the optimal extent of visceral resection in the management of these tumors has been debated, most studies suggest that extended resection improves outcome in these patients. In general, attempts at limiting the extent of the en bloc resection result in inadequate margins and subsequent development of locally recurrent disease (22,52,260).

A second important principle in the management of these tumors is that these tumors characteristically have a well-developed pseudocapsule, and invariably, the lesions extend well beyond the confines of this structure. Therefore dissection should be performed well outside this plane because positive margins will be found in virtually all cases in which dissection is carried out at the pseudocapsule. Even when all gross disease is completely resected with an apparent margin of normal tissue, a significant percentage of cases will have microscopically positive margins on subsequent pathologic analysis. In two series that have examined the relationship of positive margins in patients deemed to be macroscopically completely resected, the incidence of positive margins ranged from 12 of 41 (29%) in the Memorial Sloan-Kettering series (124) to 39 of 45 (87%) from the Princess Margaret hospital series (37).

The prevention of possible spillage or tumor rupture is an additional important principle in the management of these tumors. The potential for tumor rupture is greatest when tense lesions, often with extensive cystic or necrotic areas, are encountered. In this situation, resection may be facilitated by decompression of the cystic or necrotic areas, taking care to prevent tumor spillage by using a vacuum trocar secured with a purse-string suture (249).

Incisions

Obtaining adequate exposure is the key to successfully resecting these lesions. Through proper preoperative planning, in most cases, the surgeon can select the incision that will provide optimal exposure. In addition to being large enough to allow delivery of the tumor through the wound, the incision must also provide access to surrounding anatomic landmarks, most importantly, the vascular supply. Regardless of the particular incision, a transperitoneal approach that allows thorough exploration of the abdomen, evaluation of the possible presence of metastasis, and evaluation of the resectability of the lesion is necessary. A vertical midline incision from xiphoid to pubis usually allows adequate exposure for resection of most moderate-sized retroperitoneal sarcomas. However, tumor extension above the crus of the diaphragm or liver, necessitating extension of the incision into the chest for adequate exposure, is not infrequently found at exploration. Because of this, the patient should be prepped preoperatively for possible extension of the incision into the chest.

A thoracoabdominal incision extending from the midaxillary line posteriorly in the eighth, ninth, or tenth interspace and extending inferiorly as a vertical midline incision is well suited for most large retroperitoneal tumors located in the upper abdominal quadrants. In addition to providing excellent intraabdominal exposure, this incision allows palpation of the mediastinum and ipsilateral lung parenchyma, as well as control of the great vessels above the diaphragm. This incision also facilitates exposure by allowing mobilization and cephalad retraction into the chest of the liver or spleen. A Chevron incision that may be extended as a median sternotomy is also an excellent alternative for large, upper retroperitoneal masses.

For tumors localized in the lower abdominal quadrants or pelvis, a midline incision is generally warranted. If necessary, this incision may be extended as an abdominoinguinal incision (129,130). This latter incision, as popularized by Karakousis (128), is especially well suited for exposure and resection of pelvic tumors with lateral fixation. Such exposure has been reported to facilitate the resection of tumors previously considered unresectable and may decrease the need for hemipelvectomy in these difficult cases (74).

Laparotomy and Determination of Resectability

There has been a trend toward improved rates of resectability over the past 15 to 20 years. A compilation of data on

1,031 retroperitoneal sarcomas from 14 major series reported between 1981 and 1994 revealed that in 49% of cases, a complete resection was obtained >Table 25.6). The definitive determination of resectability can be made only at the time of laparotomy. It is important to recognize that tumor fixation is not an indication of unresectability per se. In essence, almost no structure is sacred. However, the determination of the extent of resection must be individualized and based on the patient's general medical condition and ability to withstand the proposed procedure. For example, a sarcoma extensively involving the pancreas may be completely resected by performing an en bloc pancreaticoduodenectomy. Although this procedure may be a viable choice in a relatively young healthy patient, it would be a poor choice for an elderly patient who may not be able to withstand such an extensive resection.

	%
Complete resection	49
Incomplete resection[a]	51
Overall survival	35
Survival after complete resection	56
Overall local recurrence	57

[a]Includes patients undergoing partial resection or biopsy only.
Compilation of data reported from 1981–1994 from references 7, 46, 52, 124, 168, 202, 224, 233, 260 ,273, and 280.

TABLE 25.6. RESECTABILITY, 5-YEAR SURVIVAL, AND LOCAL RECURRENCE RATE FOLLOWING COMPLETE RESECTION OF 1,031 RETROPERITONEAL SOFT TISSUE SARCOMAS

In most cases, the basis for unresectability at the time of laparotomy will be the discovery of unsuspected metastases, in the form of either distant metastases or peritoneal seeding of the tumor. This was the case in approximately 50% of unresectable cases from the Memorial Sloan-Kettering series (124). Another common basis for unresectability is extensive vascular involvement and disease involving irreplaceable structures, such as the root of the mesentery and the spinal cord (124).

In 50% to 80% of patients in whom a complete resection is attained, the removal of adjacent organs is required (46,52,124). Organs most commonly removed are the kidney/adrenal (12% to 46%), pancreas (5% to 15%), spleen (5% to 10%), colon (5% to 24%), and small bowel (5%). Major vascular resections involving the aorta, inferior vena cava, or other major vascular structures (e.g., the iliac vessels) is reported in approximately 5% to 10% of cases (7,46,52,124). However, essentially any intraabdominal organ, as well as the spine, mesentery, and abdominal wall, may require resection to obtain adequate margins.

Overview of Surgical Technique

Wide exposure following the mobilization of pertinent intraabdominal structures is necessary for the safe and adequate resection of these neoplasms. In most cases, when a midline or Chevron transabdominal approach is selected, mobilization is similar to that required for the performance of transabdominal retroperitoneal lymphadenectomy for metastatic testis cancer, as popularized by Donohue and colleagues (59). For right-sided tumors, the mobilization involves incising the posterior peritoneum, mobilizing the hepatic flexure, and extending the incision around the cecum. The incision is then extended up the root of the mesentery to the ligament of Treitz. In the process, the duodenum is kocherized and the superior mesenteric vessels defined. At this point, the ascending colon and entire small bowel, along with the pancreas, are mobilized on the superior mesenteric artery pedicle and wrapped in moist laparotomy pads; they are then placed on the anterior chest wall out of the operative field. Extreme caution must be exercised not to occlude or injure the superior mesenteric artery by excessive traction, and the bowel should be examined periodically during the procedure. Occasionally, when approaching a large, right upper quadrant retroperitoneal lesion, mobilization of the limbs by dividing the coronary and triangular ligaments and short hepatic veins and retracting the liver superiorly into the chest is necessary. Following this mobilization, the surgeon has access to the entire right retroperitoneum and the great vessels.

Mobilization for left-sided tumors is similar. The peritoneal incision should extend from the splenic flexure around the sigmoid colon to the pelvic brim. Occasionally, it is necessary to combine the mobilization as described for right- and left-sided lesions to achieve adequate exposure. Division of the inferior mesenteric artery facilitates mobilization of the descending colon. If division of the inferior mesenteric artery is necessary, the surgeon must ensure preservation of the marginal artery. In most patients, especially younger patients, division of the inferior mesenteric artery can be done with relative impunity. Occasionally, older patients may develop symptoms such as intermittent abdominal pain and diarrhea, resulting from ischemia following ligation of this vessel. If ischemic damage or significant tumor involvement of the colonic mesentery is noted during the procedure, the colon should be resected en bloc with the tumor. When approaching a large, left upper quadrant retroperitoneal lesion, the surgeon must also mobilize the spleen and tail of the pancreas, a maneuver termed *transabdominal medial visceral rotation* (MVR) (211). Following this mobilization, the surgeon has access to the entire left retroperitoneum.

Following retroperitoneal exposure by mobilization of the intraabdominal contents, the surgeon's attention is then turned to control of the vascular supply, which almost always arises from the midline. This control necessitates the mobilization of the ipsilateral great vessel and, at times, the contralateral great vessel as well. Division of the lumbar vessels below the renal pedicles obtains this mobilization. Because the spinal cord ends at the level of L-1, ischemia to the cord is rare. The blood supply to the cord is from the anterior and posterior spinal arteries that arise from the

vertebrals. Additional blood supply comes from the radicular branches that arise from higher lumbar and intercostal arteries.

Tumor invasion of the aorta and vena cava is uncommon. However, to free a retroperitoneal tumor from the vessels, it is sometimes necessary to dissect within a subadventitial plane. Aortic resection also may be required for complete excision, with subsequent reconstruction. When there is extensive tumor involvement of the inferior vena cava, it is usually best to resect the vena cava en bloc with the tumor. In this situation, the tumor has usually resulted in venacaval obstruction with the development of extensive collateral flow. Part of this collateral flow is due to the development of large, very friable retroperitoneal veins that may cause troublesome bleeding if not meticulously controlled during the dissection. In the unusual case in which resection of the vena cava requires ligation above the level of the renal veins, a venous drainage procedure using either the splenic or portal vein to the right renal vein is necessary. When the right kidney is resected en bloc with the tumor and vena cava, it is also prudent to make every reasonable attempt to preserve the connection of the left renal vein with the vena cava. Despite the greater collateral flow through the gonadal, lumbar, adrenal, and capsular veins, the incidence of postoperative acute tubular necrosis requiring temporary dialysis following ligation of the left renal vein has been reported to be as high as 50% (164).

With dissection carried out along the great vessels, a significant number of large lymphatic channels are also encountered. Care should be taken to ligate these vessels, and it is also important to identify and ligate or clip the cisterna chyli, which is medial to the right crus of the diaphragm posterior to the right renal pedicle between the aorta and vena cava. Although most cases involving a large retroperitoneal sarcoma generally require sacrifice of both right and left sympathetic trunks, if future reproductive potential is an issue and it does not compromise the resection, the surgeon should attempt to preserve one side.

Outcomes and Follow-up

Local Recurrence

With a carefully performed preoperative evaluation and a meticulous surgical approach employing a multidisciplinary team experienced in the management of these neoplasms, most retroperitoneal sarcomas can be completely resected. However, a compilation of data on 1,031 retroperitoneal sarcomas from 14 major series reported between 1981 and 1994 revealed that only in 49% of cases was a complete resection obtained >Table 25.6). Unfortunately, the incidence of positive margins even in patients who were completely resected ranges from 29% to 87% (37,124).

Soft tissue sarcomas tend to be locally aggressive neoplasms spreading along anatomic planes created by fascia, blood vessels, nerves, and muscle bundles. As a result, even following apparent complete resection, retroperitoneal sarcomas characteristically have a tremendous propensity for local recurrence. The propensity for local recurrence in this situation is a function of multiple factors, with an overall incidence ranging from 30% to 90% (7,37,110,124). Of the patients who succumb to this disease, only approximately one-third ever develop distant metastasis, most of which occur in patients with high-grade tumors (111,158). The remainder experience progressive recurrent locoregional disease that ultimately leads to death (22,52,84,124,249). Most patients develop progressive, locoregional disease and eventually succumb to late complications, such as GI bleeding and intestinal obstruction. Sepsis and multiple organ failure are common terminal events.

Although the time to local recurrence following complete resection depends on tumor grade, most series report a median interval of 15 months, with 90% of recurrences developing within 5 years (52,124,260). This interval defines a period of intensive follow-up for disease recurrence. Patients should be followed up with physical examination every 3 to 4 months for the first 2 years. Asymptomatic patients should also have a CT scan of the abdomen and pelvis and a chest radiograph every 6 months for 2 years, and yearly thereafter. Low-grade tumors may recur much later, often many years after tumor resection.

Metastatic Recurrence

As mentioned, of the patients who succumb to this disease, only approximately one-third ever develop distant metastasis, most of which occur in patients with high-grade tumors (111,158). Although not as common as local recurrence, nevertheless, appearance of metastatic disease must be monitored during follow-up with regular chest radiographs.

Overall Survival

Overall 5-year survival following surgical resection is reported to be between 29% and 82%, with disease-free survival being significantly less >Table 25.7). The wide range in overall survival is due to the heterogeneity of tumor factors among the various series (see Prognostic Factors section).

TABLE 25.7. OUTCOME OF SERIES OF RETROPERITONEAL SARCOMAS

Author	Year	*N*	Site	5-Year Survival [10-Year Survival]
Alvarenga, et al. (7)	1991	120	Retroperitoneum	29%
Catton, et al. (37)	1994	104[a]	Retroperitoneum	36% [14%]
		45[b]	Retroperitoneum	55% [22%]
Eroglu, et al. (67)	1999	33[c]	Retroperitoneum	82%
Hendricks (109)	1997	155[d]	Retroperitoneum (N = 106) Trunk/Limbs (N = 32) Others (N = 17)	72%
Heslin, et al. (111)	1997	198	Retroperitoneum	25% [15%]
Jaques, et al. (124)	1990	114[e]	Retroperitoneum	60 mo—complete (median) 24 mo—incomplete (median) 12 mo—unresectable (median)
Kilkenny (133)	1996	49[b]	Retroperitoneum	41 mo (median)
		14[f]	Retroperitoneum	9 mo (median)
Lewis, et al. (153)	1998	500[g]	Retroperitoneum	72 mo—primary (median) 28 mo—recurrence (median)
Linehan, et al. (158)	2000	*460*[h,h]	Extremity/Trunk (65%) Retroperitoneum (35%)	42 mo (median)
Zornig, et al. (280)	1992	51[i]	Retroperitoneum	35% [15%]

[a]Surgery with external beam radiation, mix of primary and recurrence and metastatic, multiple histologies.
[b]Complete resection.
[c]Complete resection and hyperthermic total abdominal perfusion.
[d]Dedifferentiated liposarcomas.
[e]Complete resection in 65%.
[f]Incomplete resection or biopsy.
[g]56% primary and 44% recurrent.
[h]Liposarcomas, primary and recurrent.
[i]Complete resection in 59%.

Prognostic Factors

Upon analyzing the major series reporting the treatment of retroperitoneal sarcomas, many variables are associated with prognostic importance for recurrence and survival >Table 25.8). However, primarily two variables are reliable independent predictors of ultimate survival in most series: (a) the completeness of tumor resection and (b) tumor grade. The histologic type is far less significant than the histologic grade of the tumor in assessing malignant behavior. The importance of histologic grade in predicting the biologic behavior and subsequent prognosis in retroperitoneal soft tissue sarcomas has been borne out in virtually every series reported on these tumors. Jacques and associates (124) reported a 20-month median survival for 65 patients with high-grade

retroperitoneal sarcomas, compared with an 80-month median survival for 49 patients with low-grade retroperitoneal sarcomas. Similarly, Storm and Mahvi (249) reported a 5- and 10-year overall survival of 74% and 42%, respectively, in patients who had completely resected low-grade retroperitoneal sarcomas. This compares with overall survival rates of 24% and 11% at 5 and 10 years, respectively, for grade II or III lesions following complete resection. It is presently unclear whether DNA ploidy analysis adds any additional prognostic information over that already provided by grade. In general, low-grade tumors tend to be diploid, and high-grade tumors tend to be aneuploid. In some cases, ploidy analysis may be helpful. Similarly, the degree of the differentiation in liposarcomas has also been an important factor in prognosis (102,109).

Prognostic Factor	Reference
Patient factors	
Age	(37,111,118)
Performance status	(7)
Tumor factors	
Tumor grade	(7,110,124,133,153)
Degree of differentiation (liposarcoma)	(102,109)
Presence of metastasis	(7)
Histologic type	(37)
Surgical factors	
Completeness of excision/ resectability/extent of tumor	(7,37,110,111,118,124, 133,153)
Molecular factors	
MIB-1 expression	(102)
p53 expression	(201)
p27 (kip1) expression	(189)

TABLE 25.8. PROGNOSTIC FACTORS FOR SURVIVAL/RECURRENCE IN RETROPERITONEAL SARCOMAS

In most series, tumor size and either adjuvant radiotherapy or adjuvant chemotherapy are not significant prognostic factors, but the statistical power to evaluate a negative result in these studies is probably low in view of the small number of patients.

Recently, more emphasis has been placed on the evaluation of molecular prognostic markers. Because of these associations of sarcomas with clinical syndromes characterized by altered tumor-suppressor genes (see Etiology section), a number of investigators recently have performed analysis of tumor-suppressor gene loci in sarcomas. These preliminary studies suggest that alterations involving the RB, p53 (69,201), and mdm-2 genes may be important in sarcoma tumorigenesis and progression and may have prognostic significance (34,69,146,201,274). In addition, low levels of the p27 (kip) gene product appear to be a poor prognostic factor in liposarcomas (189).

Adjuvant Therapy

Overview

The alarming incidence of local disease relapse following the surgical resection of retroperitoneal sarcomas underscores the need for effective multimodal therapy. Significant advances in the management of sarcomas at other sites combining surgery, radiotherapy, and chemotherapy have not been duplicated in the retroperitoneum in large part because the opportunity for delivering high-dose intraarterial chemotherapy and radiotherapy to retroperitoneal structures is not as feasible as it is for sarcomas of the extremity. Currently, the role of adjuvant radiotherapy and chemotherapy has not been established for retroperitoneal soft tissue sarcomas. Although these modalities are commonly used, there is no evidence that the results of surgery plus adjuvant radiotherapy and/or chemotherapy are better than those of surgery alone.

Radiotherapy

Most of the data regarding the efficacy of adjuvant radiotherapy for retroperitoneal sarcomas are from uncontrolled, retrospective studies of relatively small numbers of patients. Parameters that vary significantly between series include the histologic composition of the tumors and treatment technique and dose. Because of the lack of prospective, controlled studies, meaningful conclusions are difficult. Some series report a benefit of adjuvant radiotherapy, usually decreased local recurrences (37,46,111,168,260,280). Conversely, others report no benefit using adjuvant radiotherapy (124).

Relatively high doses of radiation are required to effectively treat these tumors. Although well tolerated in other sites (e.g., the extremities), the situation is different in the retroperitoneum because of the presence of radiosensitive adjacent organs, such as the kidney and small bowel. To circumvent this problem, trials using radiation sensitizers and intraoperative radiotherapy (IORT) have been established. Both methods attempt to deliver larger effective doses of radiation to the tumor without compromising radiosensitive adjacent structures. A prospective, randomized trial using IORT was recently completed at The National Cancer Institute (238). Fifteen patients who received IORT plus low-dose (3,540 Gy) postoperative external beam radiotherapy were compared with 20 patients treated with high-dose (5,055 Gy) postoperative radiotherapy alone. There was no difference in survival between the groups after a median follow-up of 8 years. However, there was a significant improvement in local tumor control in patients receiving IORT. The local recurrence rate in these patients was 40%, compared with 80% for patients treated with postoperative radiation alone. There was also a significantly lower incidence of radiation enteritis in IORT-treated patients, although 60% experienced radiation-induced peripheral neuropathy compared with only 5% of patients receiving postoperative radiation alone.

Novel approaches aimed at limiting such toxicity have included the use of inflatable prostheses to displace radiosensitive organs away from the radiation field during treatment, followed by their removal subsequent to treatment completion (13). In addition, abdominal hyperthermia has been used in an attempt to decrease the rate of local recurrence when used in conjunction with complete surgical resection. Very early results on 33 patients reveal promising results (67).

Chemotherapy

The role of adjuvant chemotherapy in the treatment of retroperitoneal sarcomas is also not established. Furthermore, as with adjuvant radiotherapy, meaningful conclusions concerning the efficacy of chemotherapy are made difficult by the relative lack of prospective, controlled trials of adequate size. Several drugs have been shown to have activity against these tumors when used singly or in combination; these include doxorubicin, vincristine, iphosphamide, DTIC, and methotrexate (46,84). The role of multiagent systemic chemotherapy in the treatment of these tumors is the subject of a number of current trials. To date, however, there is no evidence of a significant survival benefit of its use in this setting. At present, the successful management of retroperitoneal sarcomas depends on appropriate preoperative assessment and aggressive complete surgical resection.

Management of Patients with Clinically Unresectable Disease

Surgical Approaches

Currently, the best chance of survival in patients with retroperitoneal sarcomas is provided by complete surgical resection. Unfortunately, as mentioned earlier, up to 50% of patients are unresectable at a laparotomy. Although incomplete tumor resection does not improve eventual outcome, it may in some cases effectively palliate complications of the tumor, such as severe pain and bowel obstruction.

Radiotherapy

Studies in small groups of patients have shown that three-dimensional conformal pion radiation has some beneficial results in patients. However, these studies have included patients with both retroperitoneal and truncal/extremity sarcomas, the latter having better prognosis then the former (94,95).

Treatment of Locally Recurrent Disease

The local recurrence rate 5 years after complete tumor resection ranges from 35% to 79% and at 10 years has been

reported to be as high as 90% (249). Only approximately one-third of patients, most with high-grade tumors will develop distant disease, alone or in combination with locally recurrent disease. Therefore the most common pattern of failure following complete tumor resection is recurrent locoregional disease occurring in 75% of patients (206).

Following a thorough evaluation for the presence of disseminated disease, an aggressive surgical approach should be undertaken for locally recurrent disease. With recurrent disease, however, resectability rates decline and the incidence of another local recurrence increases, with a shorter interval from resection to disease relapse. Jacques and associates (124) reported that 49%, 42%, and 33% of first, second, and third recurrences, respectively, were completely resected. Contributing to the lower resectability rates and the increased aggressiveness of recurrent retroperitoneal tumors is their propensity to undergo grade progression. However, there are reports of patients benefiting with prolonged survival following resections of recurrent retroperitoneal sarcomas (37,133,153). Recently, models based on CT scan imaging have been constructed for the outpatient determination of prognosis following surgery for locally recurrent disease (199). If validated in larger studies, these models help further delineate which patients should undergo reoperation.

Treatment of Recurrent Metastatic Disease

A significant body of evidence also supports an aggressive surgical approach for metastatic disease isolated to the lungs (35,123,181). A thorough evaluation for extrapulmonary disease with special attention to the liver is necessary because patients with extrapulmonary disease are not candidates for lung metastasectomy. In a series of 56 patients who had isolated lung metastasis resected, 40 (71%) were rendered free of disease with an actuarial 3-year survival rate of 40% (206). The median survival of patients with isolated pulmonary metastasis deemed unresectable is dismal and in the range of 7 months (35). Surgical resection of recurrent pulmonary metastasis also may result in long-term survival. A 22% 3-year actuarial survival has been reported from the National Cancer Institute (219) for 29 patients undergoing two or more resections for long metastasis. The M.D. Anderson Cancer Center experience has been similar. In a series of 38 patients with recurrent isolated pulmonary metastasis, 34 were rendered disease free after resection, with a median overall survival of 28 months, compared with 65 months for patients from whom a solitary pulmonary metastasis was completely resected (35).

Most patients treated surgically for pulmonary metastasis also have received systemic chemotherapy. Although complete plus partial response rates approaching 50% have been reported, they have not been durable and the response to chemotherapy does not predict survival following surgical resection (144). It does, however, appear logical to treat these patients before metastasectomy with several courses of systemic chemotherapy. This approach may allow the selection of responders that may benefit from further chemotherapy postoperatively. It also allows aggressive pulmonary disease and initially unsuspected extrapulmonary disease to manifest, thus sparing an unnecessary thoracotomy (243). Despite the occasional need for extended parenchymal resections including the chest wall, diaphragm, and pericardium, these procedures are surprisingly well tolerated. In the M.D. Anderson series (35), mean postoperative hospitalization was 6 days with no operative mortality.

Although resection of pulmonary metastases is the most well-established approach to metastatic lesions, recent data from patients with solitary hepatic lesions have been provided. In a very small study on 11 patients, resection of hepatic lesions from leiomyosarcoma resulted in prolonged survival (41). In addition, surgical debulking of intraabdominal metastases may offer improved survival in select cases (130).

INFLAMMATORY DISEASES OF THE RETROPERITONEUM

Part of "25 - DISEASES OF THE RETROPERITONEUM "

Retroperitoneal Fibrosis

Although the eponym assigned to retroperitoneal fibrosis is *Ormond's disease,* it was the French urologist Albarran who first reported the occurrence of hydronephrosis and a fibrous mass discovered in a patient's retroperitoneum at the time of surgery (3). Ormond published the first description of retroperitoneal fibrosis in the English literature in 1948. In his paper (192), he described two patients with generalized malaise, flank pain, anuria, and anemia associated with an inflammatory perivascular retroperitoneal process. In addition to *retroperitoneal fibrosis* and *Ormond's disease,* many terms have been used to describe this malady, including *periureteritis fibrosa, periureteritis plastica, chronic periureteritis, sclerosing retroperitoneal granuloma,* and *fibrous retroperitonitis.* Since the 1960s, the term *retroperitoneal fibrosis* has been favored because it closely reflects the cellular process involved.

The disease is characterized by the presence of an inflammatory proliferation of fibrous tissue within the retroperitoneum, which encases the great vessels, nerves, and ureters. The disease is classified into two varieties: (a) idiopathic retroperitoneal fibrosis, the most common cause, and (b) retroperitoneal fibrosis of a known origin, such as ergot derivative ingestion, retroperitoneal malignancies, previous radiation treatment, and infectious/inflammatory processes.

Pathology

On gross examination, retroperitoneal fibrosis appears as a firm woody mass, tan to white in color, that envelopes the retroperitoneal structures, including the great vessels and

often the ureters. Ureteral involvement can occur from the renal pedicle to the pelvic brim, although usually most prominent over the region from the fourth lumbar vertebra to the first sacral vertebra (258). The fibrosis tends to cause medial deviation of the middle third of the ureters in one-half to two-thirds of patients. Encasement of the ureters will lead to hydronephrosis and can cause varying degrees of renal failure. On rare occasions, the process can proceed superiorly and continue as mediastinal fibrosis and has been related to disseminated vasculitis and intrahepatic sclerosing cholangitis (108,178). Great vessel involvement is common, although not often leading to vascular obstruction. Arterial obstruction is rarely significant, whereas venous obstruction does occur and can lead to lower-extremity edema with involvement of the inferior vena cava or the common iliac veins (212). Extrahepatic portal vein involvement has also been reported (80). The size of the mass may vary significantly and may occasionally involve other retroperitoneal as well as intraabdominal organs, including the duodenum, jejunum, ileum, colon, pancreas, spleen, and kidneys; the mass may also extend into the pelvis proper (151).

Histologic examination of biopsy specimens most often reveals fibrous tissue consisting of collagen fibrils and fibroblasts. There is a spectrum of findings, from a predominantly cellular chronic inflammatory tissue to less cellular, more fibrotic collagenous tissue. In the early part of the disease process, the inflammatory cells present consist primarily of B and T lymphocytes, plasma cells, and macrophages, although eosinophils and polymorphonuclear leukocytes are also appreciated (197). Heterogeneity in the amounts of fibrous and cellular composition often occurs from biopsies taken from different areas of a mass. Many authors conclude that contraction of this cellular fibrous tissue with advanced disease may draw the ureters medially, resulting in typical findings found on IVP. Reports have noted the invasion of the psoas muscles and the ureters by the fibrous process (107).

Etiology

No associated etiologic factor is found in two-thirds of cases, and therefore they fall into the category of idiopathic retroperitoneal fibrosis. Some factors that have been associated with retroperitoneal fibrosis include drugs [most notably methysergide (Sansert)], hemorrhage, trauma, urinary extravasation, chronic urinary tract infections, retroperitoneal malignancy, perianeurysmal inflammation or leaky aneurysm, prior radiation therapy, prior surgery, inflammatory bowel disease, ruptured appendix or hollow viscus, Henoch-Schönlein purpura, ascending lymphangitis, biliary tract disease, sarcoidosis, tuberculosis, collagen disease, and fat necrosis (39). Recently, asbestos exposure and intravesical formalin use have been reported as possible etiologic agents for this disease (73,226).

The most notorious etiologic association is ingestion of the ergot derivative methysergide for the treatment of migraine headaches. This association was first reported in 1964 by Graham (91) and has been noted by many authors since. Graham (92,137) later reported a 1% incidence in a large series of patients receiving this drug and a history of methysergide intake in 10% to 12% of patients with retroperitoneal fibrosis. Methysergide has also been linked to fibrosis in other areas, including the chest (myocardium, lungs, and pleura) and the GI tract. Other ergot derivatives, such as lysergic acid diethylamide (LSD), as well as other drugs, including methyldopa, amphetamines, reserpine, phenacetin, adrenergic ß-antagonists, and recently pergolide (Permax), have also been implicated as etiologic factors (2,122,176).

The mechanism by which ergot derivatives and other drugs induce retroperitoneal fibrosis is poorly defined, and several theories have been proposed. The ergot derivatives, including methysergide and LSD, are serotonin receptor antagonists and act by competitive inhibition of receptor sites. Increased amounts of endogenous serotonin have been associated with fibrosis in the carcinoid syndrome (232). The most widely held theory as to the mechanism of drug-induced retroperitoneal fibrosis is that the drug may act as a hapten, resulting in a hypersensitivity or autoimmune reaction (267).

Retroperitoneal malignancy is also a well-documented cause of retroperitoneal fibrosis. In their review of 491 patients with retroperitoneal fibrosis, Koep and Zuidema (137) reported a 7.9% incidence of malignancy. Lepor and Walsh (151) described three types of malignant processes that could induce retroperitoneal fibrosis: (a) periureteral metastasis with fibrosis, (b) primary retroperitoneal tumor, and (c) serotonin production by carcinoid tumor. Metastatic breast, stomach, prostate, lung, kidney, and colon cancer are most commonly associated with periureteral metastases (240). Primary retroperitoneal tumors, including lymphomas and sarcomas, may cause an extensive desmoplastic response, resulting in fibrous proliferation. Pathologic analysis in this situation often reveals a predominance of fibrous tissue with small islets of tumor cells interspersed. Authors have stressed biopsy at the time of surgical exploration to differentiate idiopathic from malignant retroperitoneal fibrosis (151).

Previous radiation therapy is also associated with retroperitoneal fibrosis. Periureteral fibrosis has been noted in approximately 1% of patients treated with irradiation for pelvic tumors (54). In general, the radiation-induced fibrosis becomes clinically apparent several years after radiation therapy. On pathologic analysis, the fibrous tissue has a characteristic appearance, exhibiting large collagen fibers and extensive hyalinization. The blood vessels also show evidence of endarteritis obliterans (117).

Infection has been implicated in the etiology of retroperitoneal fibrosis as well. Urinary tract infection, gonorrhea,

syphilis, brucellosis, and tuberculosis may cause a disseminated fibrous inflammatory response (191). Despite their association with fibrosis in general, as well as a report of the association of histoplasmosis with mediastinal fibrosis, active infectious diseases have not been reported concurrently with retroperitoneal fibrosis (151,183).

Retroperitoneal fibrosis is related to and associated with a number of other disease processes characterized by fibrous proliferation. These include mediastinal fibrosis, generalized mesenteric fibrosis, sclerosing colitis, Riedel's thyroiditis, Dupuytren's contracture, Peyronie's disease, keloid formation, pseudotumor of the orbit, systemic lupus erythematosus, and diffuse pleural fibrosis (137,151). On the basis of these associations, some authors have proposed that retroperitoneal fibrosis may be a manifestation of a systemic disease, such as a collagen vascular disease or a generalized autoimmune process (159,279). The frequent favorable response of retroperitoneal fibrosis to steroid therapy and to other immunosuppressive drugs, such as azathioprine, provides circumstantial evidence to support this hypothesis (47,177). Until recently, however, testing for autoantibodies or other markers of autoimmune diseases has rarely been positive. De Luca and associates (53) reported that human leukocyte antigen-B27 (HLA-B27) stained positive in 44% of cases; HLA-B27 is also associated with autoimmune disorders such as Reiter's syndrome and ankylosing spondylitis. A conflicting report by Chevet and associates (42) found no HLA-associated markers and argued against HLA-B27 being linked to the disease. A genetic predisposition has also been reported; two sets of twins with retroperitoneal fibrosis have been described, and a small number of patients have been found to share certain HLA haplotypes (87,263,272).

Finally, it is clear that essentially any process that results in injury or inflammation of the retroperitoneum can elicit the development of a fibrotic process. Postsurgical changes, trauma with subsequent hematoma formation or spontaneous retroperitoneal bleeding, hollow viscus perforation (appendicitis, diverticulitis, or ulcers), and urinary extravasation are all possible etiologic factors for such a process (137,151).

In the two-thirds of patients in whom no etiologic agent can be identified, the diagnosis of idiopathic retroperitoneal fibrosis is made. Evidence has accumulated over the past decade that indicates that “idiopathic” may in fact be a misnomer—the condition may have a defined cause in most cases. CT scanning has shown that the inflammatory process has a striking distribution closely associated with the aorta and often extends along the bifurcation of the common iliac vessels. This distribution, also noted at the time of surgery, led several authors to suggest that it may represent a process of vasculitis. Both Mitchinson (174) and Parums (195) have proposed the unifying concept of “chronic periaortitis” to include not only idiopathic retroperitoneal fibrosis but also the related conditions of perianeurysmal retroperitoneal fibrosis and inflammatory abdominal aortic aneurysm. Also included is subclinical periaortitis associated with atherosclerosis, which can often be demonstrated on postmortem examination (16,58,174,196). Recently, antineutrophil cytoplasmic antibodies (cANCA), which are associated with systemic vasculitis, have been demonstrated in a biopsy of a retroperitoneal fibrosis mass (127).

It appears that idiopathic retroperitoneal fibrosis, inflammatory abdominal aortic aneurysm, perianeurysmal retroperitoneal fibrosis, and subclinical chronic periaortitis merely represent a spectrum of the same disease (Fig. 25.4). These entities share identical histopathologic features, and differences in the clinical and radiologic findings between these conditions relate mainly to whether the aorta is dilated and the extent of the periaortic process (31,195). The pathogenesis of periaortitis and its development into idiopathic retroperitoneal fibrosis or its variants are believed to result from an immunologically mediated inflammatory process directed to a component of the atherosclerotic plaque. Although the exact mechanism of this process awaits further studies, ceroid, an insoluble product of oxidized lipid and protein found in atherosclerotic plaques, has been found to be associated with immunoglobulins in patients with chronic periaortitis. Antibodies directed against ceroid are also detectable in patients with severe chronic periaortitis (195).

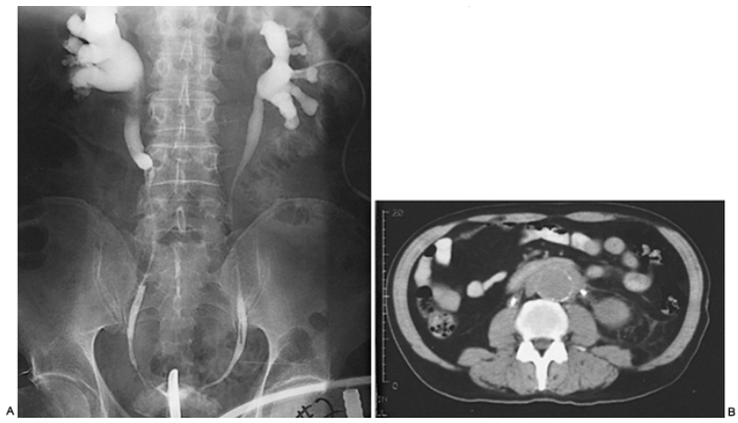

FIGURE 25.4. A: Bilateral retrograde pyelograms of a 61-year-old man presenting with anuria. Note bilateral hydroureteronephrosis and medial deviation and narrowing of both ureters. **B:** Computed tomography scan in same patient following establishment of urinary tract drainage by bilateral double-J stents. Demonstrated is retroperitoneal fibrosis surrounding a calcified inflammatory aortic aneurysm.

Further evidence that idiopathic retroperitoneal fibrosis represents clinical chronic periaortitis in the setting of an undilated aorta is that the inflammatory cells in idiopathic retroperitoneal fibrosis are identical to those seen in inflammatory aneurysms and subclinical periaortitis (195). The aforementioned striking vascular distribution of the disease and the significant frequency of aortic dilation and wall calcification demonstrable by CT also support this concept (31,58). Furthermore, because 2% to 10% of abdominal aortic aneurysms are inflammatory, a significant number of patients with abdominal aortic aneurysms may present with urologic complaints; recognition of this fact is important for the practicing urologist.

Clinical Features

Most patients diagnosed with retroperitoneal fibrosis are in their fourth through seventh decades of life, although the disease has been reported in the elderly and in children as young as 7 years of age (12,40,96,151). There does not appear to be any racial predominance; however, the disease is two to three times more common in men than in women.

Retroperitoneal fibrosis tends to be insidious. There are no specific symptoms or signs suggestive of the diagnosis; rather, a complex of symptoms helps identify patients in the earlier stages of disease. Clinical features commonly seen at the time of presentation are reviewed in Fig. 25.5 . Clinical features commonly seen early in the disease process are often vague, nonspecific, and similar to those of other inflammatory

disorders. Many patients present with generalized malaise, low-grade fever, anorexia, weight loss, and nonspecific GI complaints. An elevated erythrocyte sedimentation rate (ESR) is present in most patients, as are anemia, hypertension, and varying degrees of renal functional impairment. Most patients present with a complaint of pain localized to the flank, back, or abdomen, perhaps as many as 90% of cases (258). Pain localized to the testis is also reported in up to 10% of patients (151). Interestingly, cases involving the testes and scrotum have been reported (194,230). The pain may vary significantly. Early in the course of the disease, it is often insidious in onset and described as being dull and noncolicky. It also often originates in the lower back and may at times radiate anteriorly to the lower abdominal quadrants and into the groin. The pain is characteristically not influenced by position or activity but has been reported to be relieved in this stage by antiinflammatory agents, such as nonsteroidal antiinflammatory drugs (NSAIDs). Narcotics are usually ineffective in relieving pain in the early stages of disease. Curiously, this noncolicky pain, not otherwise characteristic of obstruction of the urinary tract, is typically relieved following ureterolysis, without any attempt to resect the fibrotic process.

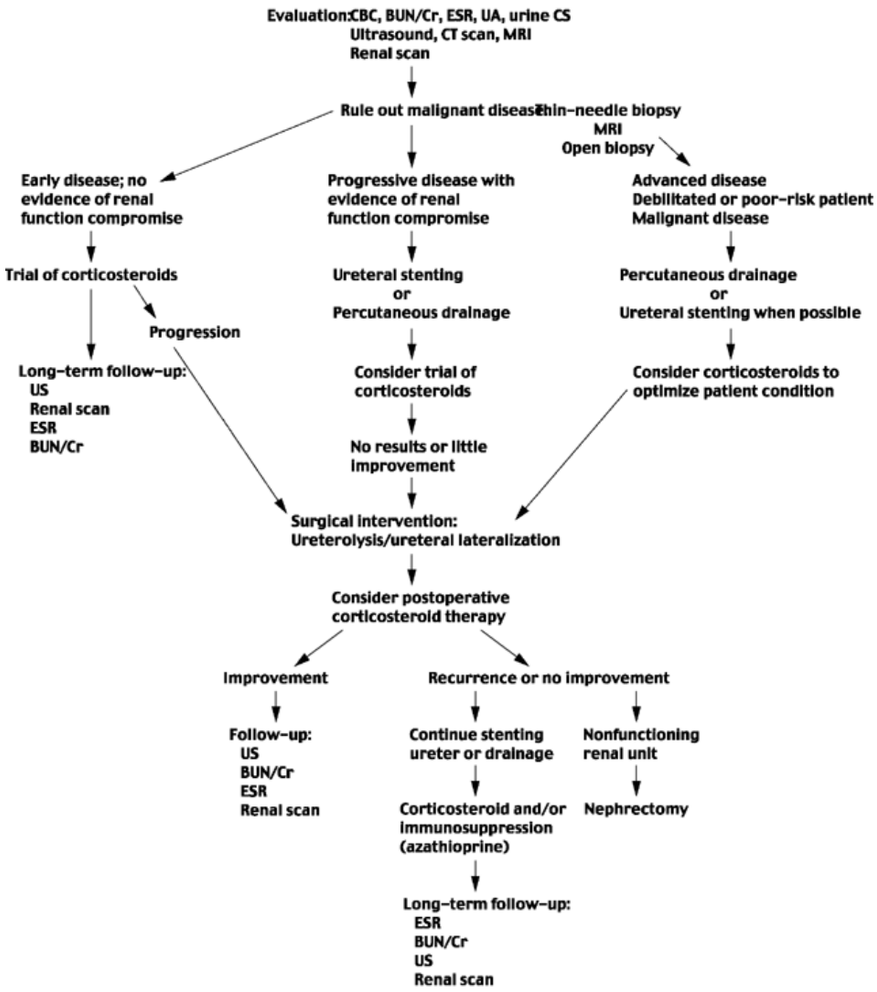

FIGURE 25.5. Algorithm for evaluation and treatment of patients with retroperitoneal fibrosis. BUN/Cr, blood urea nitrogen-to-creatinine ratio; CBC, complete blood count; CS, culture and sensitivity; CT, computed tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; UA, urinalysis; US, ultrasound.

Because of the insidious nature and vague symptoms, there is often a several-month interval from the onset of symptoms to clinical presentation. With disease progression, signs and symptoms reflect the involvement of the retroperitoneal great vessels and ureters because there is often increasing pain, oliguria (which may progress to anuria), lower-extremity edema, and even ischemic pain from arterial compression (151). The disease may mimic other processes such as large bowel obstruction, pancreatic cancer, or an abdominal aortic aneurysm.

Physical examination is usually unrewarding. The most common findings, each occurring in less than 10% of patients, are a palpable mass, uremia, lower-extremity edema, and the presence of a hydrocele. Signs of significant vascular disease, including neck and abdominal bruits, may be appreciated. The insidious onset and progressive nature of this disease are underscored by the fact that at the time of presentation, up to one-third of patients have been reported to have a nonfunctioning kidney and up to 10% have uremia secondary to bilateral ureteral obstruction and anuria (12).

Diagnostic Evaluation

Strictly defined, the diagnosis of retroperitoneal fibrosis requires pathologic confirmation, although it is usually strongly suggested on the basis of history and imaging studies.

As mentioned previously, laboratory testing is generally completely nonspecific and reflects only the presence of a chronic disease state with an elevated ESR and some degree of anemia, often correlating with the extent of azotemia that is noted at the time of presentation in most patients (12,137,151). Because retroperitoneal fibrosis is a pathologic diagnosis and retroperitoneal malignancy must be excluded, it is of paramount importance to obtain biopsy specimens. This is usually done at the time of surgical exploration; however, CT-guided fine-needle aspiration biopsy or transcaval Tru-Cut needle biopsy under fluoroscopic guidance has been reported to be possible in patients in whom surgery presents too high a risk (200,246).

The degree of renal function impairment, which ranges from none to chronic renal failure with anuria, guides the strategy for intervention and is a strong prognostic indicator. Intravenous pyelogram (IVP) findings can suggest the diagnosis relatively early in the disease process. Classically, IVP demonstrates medial deviation of the ureter, in contradistinction to retroperitoneal neoplasms and abdominal aortic aneurysms that tend to displace the ureters laterally. Medial deviation usually occurs in the middle third of the ureter at the region of the third to fourth lumbar vertebra. This finding is accompanied by varying degrees of ureteral obstruction and resultant hydronephrosis. Lateral deviation of the ureters has also been reported (228). Ureteral obstruction is generally most prominent at the level of the iliac vessels, usually bilateral, and typically involves several centimeters of the ureter. A completely normal IVP is rare and was found in only 2.5% of the cases reviewed by Koep and Zudima (137). Medial deviation of the ureter on the IVP is, however, not pathognomonic of retroperitoneal fibrosis; there is a significant fraction of patients who have medial deviation of a ureter as the sole abnormal IVP finding. Ureteral deviation in retroperitoneal fibrosis tends to extend higher, and the ureters usually appear more linear than in variant-type medial deviation (223).

Retrograde pyelography can be useful in the diagnosis of retroperitoneal fibrosis and may be performed in patients with impaired renal function that precludes the administration of intravenous contrast or when there is poor visualization following an IVP (Fig. 25.6). It is also often a therapeutic maneuver because placement of retrograde ureteral stents is generally possible. In fact, the ability to pass a 5- or 6-Fr ureteral catheter beyond the area of obstruction is a characteristic feature of retroperitoneal fibrosis.

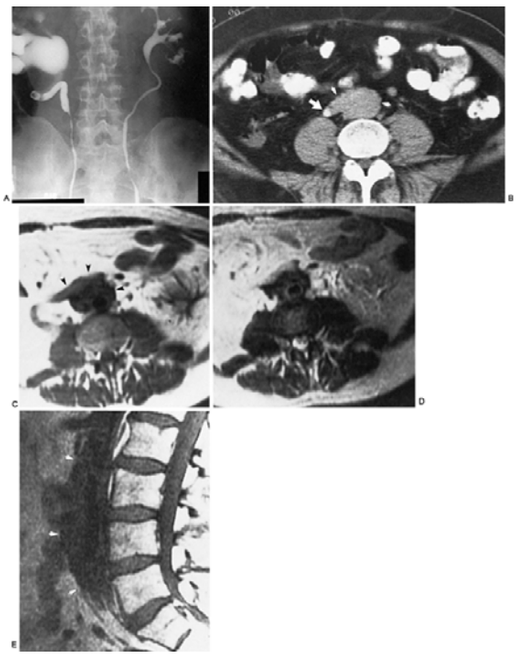

FIGURE 25.6. Benign idiopathic retroperitoneal fibrosis. **A:** Retrograde pyelography demonstrates medial displacement of both ureters at the level of L-5. The right midureter is narrowed, and there is associated right hydroureteronephrosis. **B:** Computed tomography (CT) scan demonstrates plaquelike deposition of fibrous tissue surrounding and obscuring both the aorta and inferior vena cava *(arrowheads).* The right ureter is entrapped by an extension of the fibrous process to the right of the midline *(arrow).* **C:** T_1-weighted magnetic resonance imaging (MRI) scan at 1.5 T demonstrates that the plaque *(arrowheads)* is of low signal intensity consistent with fibrous tissue. Note how the fibrous tissue encompasses both the aorta and inferior vena cava, rendering them almost indistinguishable. Note also the extension of the fibrous plaque to the right as demonstrated in the previous CT scan. **D:** T_2-weighted axial image demonstrates no change in the signal intensity of the retroperitoneal plaque, indicating that it is comprised entirely of fibrous tissue, confirming the diagnosis of benign retroperitoneal fibrosis. The wall of the aorta has increased slightly in intensity, making it now visible. **E:** T_1-weighted sagittal MRI demonstrates the plaque in profile *(arrowheads).* The lesion is extensive and extends from L-1 to L-5.

In the unusual situation in which there is extension of the disease process through the ureteral wall and/or retrograde placement of a catheter is not possible, percutaneous nephrostomy tube placement may be a valuable maneuver. This provides immediate upper tract drainage and allows subsequent anatomic study by antegrade pyelography. This situation should heighten suspicion of a malignant process. Percutaneous nephrostomy is also the procedure of choice in the patient presenting with urosepsis in the setting of retroperitoneal fibrosis and high-grade obstruction.

Ultrasonography is uncommonly used to diagnose retroperitoneal fibrosis, largely because CT is the radiologic examination of choice and can more accurately define the extent of disease. The sonographic findings consist of an extensive retroperitoneal, extrarenal, anechoic, well-marginated, and irregularly contoured mass (68). These findings may be apparent on ultrasound examination for elevated creatinine with flank pain.

CT has become the most useful imaging test for diagnosing retroperitoneal fibrosis. The CT findings consist of a dense mass of variable thickness encompassing the great vessels and ureters, with attenuation values similar to those of muscle. With the administration of an intravenous contrast medium, variable enhancement is present, most prominent in areas of active inflammation and less pronounced in areas where fibrous tissue predominates (71). The extent of the process is variable, but it often extends from the level of the renal pedicles along the great vessels and the bifurcation of the common iliac vessels and laterally to, or beyond, the lateral margin of the psoas muscles. In general, the mass is usually symmetrically distributed and encases the great vessels. The mass in retroperitoneal fibrosis shown by CT scanning also typically lies anterior and lateral to the aorta, sparing the posterior aspect; complete encirclement of the great vessels is rare and should increase suspicion of malignant nodal disease (31,32,55). However, the typical CT findings, although highly suggestive of retroperitoneal fibrosis, are nonspecific and nondiagnostic because other benign (e.g., amyloidosis) and malignant (e.g., sarcomas, metastatic carcinoma, lymphoma, multiple myeloma) processes may produce similar findings (85,222,247).

The features of CT imaging that may allow the differentiation of retroperitoneal fibrosis from malignant processes have been previously noted and have been reviewed by Brooks (31) and Degesys and co-workers (55). The differentiation between retroperitoneal fibrosis and malignant disease is readily made when there are multiple discrete enlarged periaortic lymph nodes clearly separable from the great vessels; at other times, matting of cancerous lymph nodes obscures the delineation. Factors suggestive of malignancy are the finding of an asymmetric nonconfluent mass with prominent skip areas, lack of enhancement with intravenous contrast, and the finding of discrete periaortic and/or mesenteric nodal enlargement. The mass of retroperitoneal fibrosis is usually confluent, with continuous encasement of the great vessels.

Findings comparable or superior to those obtained with CT imaging have been reported with the use of MRI. MRI has been shown in several reports to provide more information than CT scans, particularly those performed without intravenous contrast, showing the extent of disease better and with greater sensitivity for demonstrating sclerosis as

compared with CT (10,31,278). MRI has the advantage of allowing imaging in multiple planes, which may better delineate the relationship of the inflammatory process to adjacent structures. MRI typically identifies a mass with relatively low signal intensity, equal to or less than that of muscle on T_1- and T_2-weighted images (121). This low signal intensity on T_1-weighted and heterogeneous low to medium signal intensity on T_2-weighted images may provide valuable information for differentiating idiopathic retroperitoneal fibrosis from that secondary to malignant disease, which characteristically exhibits a higher signal intensity (177,182,278). Yuh and associates (278) found that all of the patients in their series had relatively low signal intensities on T_2-weighted images, suggesting benign disease. The availability and affordability of CT gives it an advantage over MRI and will suffice in most cases as the

treatment is usually based on renal function and not extent of disease.

Evaluation of renal function is important, before extensive use of CT one-third of patients presented with a nonfunctioning kidney due to long-term obstruction. Whitaker (269) demonstrated urodynamic evidence of obstruction due to retroperitoneal fibrosis. The cause of obstruction is hypothesized to be interruption of ureteral peristalsis by periureteral inflammation. The caliber of the ureter is characteristically 5 to 6 Fr except in the rare cases of ureteral invasion. Differential radioisotope renography may be helpful to identify the split function of the kidneys.

Natural History

There are very limited data from which to draw conclusions about the natural history of retroperitoneal fibrosis because most patients undergo surgical treatment, usually consisting of biopsy and ureterolysis. Although uncommon, the long-term resolution of symptoms after surgical exploration and biopsy, as well as spontaneous clinical and radiographic regression, has been reported (70,108). The disease, however, is best characterized as progressive in nature with a propensity for relapse, often many years following initial treatment, therefore necessitating lifelong follow-up. It is interesting to point out as well that several authors have reported instances of rapid progression of the disease with marked growth in the inflammatory mass and the rapid development of complications over a period of several weeks to a few months (11,258).

Management

Overview

The primary goals of management of patients with retroperitoneal fibrosis are making a prompt diagnosis, minimizing the effects of obstructive uropathy, and providing careful long-term follow-up. Treatment of retroperitoneal fibrosis is individualized and depends on the cause, the extent of the disease, and its effect on the urinary tract (Fig. 25.5).

For suspected drug-induced retroperitoneal fibrosis, cessation of the drug has been reported to result in resolution of the disease process; however, this resolution may be uncommon, and progression following the discontinuation of the drug has been reported in several cases (231). Patients should be thoroughly questioned about both medications and illicit drug intake; any known offending agent should be stopped immediately. Although the efficacy of immunosuppressive corticosteroid therapy in this setting has not been well defined, it is commonly used at the time of withdrawal of the offending agent. Smith and cohorts (242) documented a rapid reduction in the size of a retroperitoneal fibrosis mass with corticosteroid therapy.

The type of tumor encountered, the overall prognosis, and the general medical condition of the patient dictates treatment for patients found to have retroperitoneal fibrosis secondary to a malignancy. In most cases, the urologist is called upon to render palliative care and relieve ureteral obstruction by either ureteral stenting or placement of percutaneous nephrostomy tubes.

Classical treatment of idiopathic retroperitoneal fibrosis is surgical exploration with performance of multiple deep biopsies (to rule out a malignant process) and bilateral ureterolysis. Improved imaging modalities, new concepts of the pathogenesis of the disease, and the documented response of the disease to immunosuppressive therapy have made surgical management somewhat controversial. Surgical treatment is still the mainstay for most patients but recently has been combined with immunosuppressive drugs or other medical therapies. Heidenreich and colleagues (105) reported a recent retrospective study on 39 patients in whom combination therapy with oral prednisolone and azathioprine was instituted for 3 months; 3 patients demonstrated complete remission upon reevaluation, whereas 36 had stable or progressive disease and underwent operative correction.

Steroid Therapy

Although many authors continue to recommend formal open biopsy and the surgical relief of obstruction, a significant number of reports now advocate and demonstrate the efficacy of steroid therapy, including its use as primary treatment (4,12,166,177,242). In a study by Higgins and associates (116), most of their 17 patients were managed with primary corticosteroid therapy following initial relief of obstruction by percutaneous nephrostomy. Patients typically received initial dosages of prednisolone between 30 and 60 mg daily and were gradually tapered to 5 to 10 mg daily. Steroid treatment was discontinued at varying intervals, from several months to more than 2 years. These authors reported that, in general, ureteral obstruction resolves rapidly, often within 1 to 2 weeks. These and other authors have concluded that when the diagnosis can be made with near certainty using modern CT and MRI, nonoperative management with primary immunosuppressive therapy is a viable option. It should be emphasized, however, that failure to respond within 2 to 3 weeks following initiation of corticosteroids is an indication for open exploration and biopsy. Several investigators have suggested that the ultimate outcome will be little affected if the diagnosis of an extensive retroperitoneal malignant process is delayed by 2 to 3 weeks (4,32,116).

It should also be pointed out that temporary establishment of urinary tract drainage and corticosteroid therapy may be efficacious in the management of retroperitoneal fibrosis associated with an inflammatory abdominal aortic aneurysm when the aneurysm is to be managed nonoperatively. Furthermore, when the aneurysm is to be approached surgically, surgical correction of the aneurysm may not solve the problem of fibrosis. Persistent fibrosis was associated

with ureteral entrapment in 30% of these cases and resulted in renal compromise in 49% as reported by von Fritschen and associates (264). They further demonstrated hydronephrosis, not present at the time of operation, developed in 19% of patients, despite improving or stable inflammatory lesions. This is contrary to the previously held concept that surgery resulted in the resolution of the ureteral obstruction (50,234).

Alternative Medications

Many drugs have been used, with varying success, in the treatment of retroperitoneal fibrosis. Azathioprine, another immunosuppressive drug, has been used both as primary therapy and for recurrence after cessation of steroids with some success (47,100). Harreby and associates (100) also reported using penicillamine in combination with methyl-prednisolone pulse therapy in their article. Tamoxifen, which has some benefit in desmoid tumors, has been used effectively in small numbers of patients either alone or in combination with steroids (44,207). Use of the antimetabolite methotrexate has been reported in one group (229). Cyclophosphamide use has been reported for one patient with retroperitoneal fibrosis and concomitant systemic lupus erythematosus, as well as in one patient also diagnosed with periarteritis nodosa (25,160). Azathioprine or penicillamine as an alternative to corticosteroid therapy and tamoxifen, a nonsteroidal antiestrogen, may have some role in the medical treatment of retroperitoneal fibrosis; however, steroid therapy remains the best choice to date.

Surgery

Despite the documented role for primary nonoperative management, most urologists continue to recommend traditional surgical management consisting of exploratory laparotomy through a midline incision and multiple deep biopsies to establish a pathologic diagnosis. After confirmation of the diagnosis, ureterolysis is carried out. Incising the posterior peritoneum in the midline from the duodenum to the pelvic brim and developing flaps of peritoneum laterally may expose the ureters (112). Alternatively, incising the posterior peritoneum laterally and mobilizing the ascending and descending colon may expose the ureters. In most cases, the dissection is best carried out by localizing and freeing the normal but dilated proximal ureter and following it distally to the point where it is encased in the retroperitoneal mass. Occasionally, when the fibrotic process extends quite superiorly, the normal distal ureter may be identified in the pelvis and traced cephalad.

In most cases, ureterolysis can be accomplished without undo difficulty. The surgeon dissects anterior to the ureter with a right-angle clamp, and the overlying inflammatory tissue is incised sharply. The dissection is facilitated by the preoperative placement of ureteral catheters or double-J stents, which aid palpable identification of the ureters and allow for initial urinary drainage. However, extreme care is important to minimize the risk of ureteral injury. At times, the ureter appears very thin, such that the stent is readily visualized through the ureteral wall. Actual invasion of the ureteral wall by the process is uncommon, but if encountered, segmental resection and primary ureteroureterostomy may be required. Common to all ureteral procedures, the surgeon must be prepared to use any of an extensive armamentarium of reconstructive techniques. These techniques may include the use of a psoas hitch with or without a Boari flap and ureteral reimplantation, dismembered pyeloplasty, ileal replacement of the ureter, or autotransplantation (23,26,136,172).

Following the complete mobilization of the ureters, they may be handled in one of several ways. Care must be taken to prevent ureteral kinking with any operative maneuver; reapproximating the previously incised posterior peritoneum behind the ureters will leave the ureters in an intraperitoneal position. Alternatively, the ureters may be transposed laterally, using an interposition of retroperitoneal fat to buffer the ureter and the fibrotic process. The ureters may also be wrapped using pedicle flaps of omentum (150,254). De Luca and associates (53) reported excellent long-term correction of ureteral obstruction with a mean follow-up of 58 months using omental wraps and ureterolysis. Because of the variable natural history of retroperitoneal fibrosis, with its tendency toward progression and relapse, most authors recommend bilateral ureterolysis, even in the setting of unilateral ureteral obstruction. However, there does not appear to be an indication for ureterolysis for a nonfunctioning renal unit (12). If significant arterial stenosis is present, aortolysis may be required and can be carried past the aortic bifurcation to free the iliac arteries if needed.

Adjuvant Therapy

The optimal role of postoperative steroids has not been established. Numerous reports (mostly anecdotal) tend to suggest an adjuvant role for corticosteroids (12,116,175). In a multiinstitutional, retrospective review of 31 patients with idiopathic retroperitoneal fibrosis, however, Cerfolio and associates (38) concluded that steroids did not influence the restenosis rate following surgical management, including in those patients with “early” idiopathic retroperitoneal fibrosis indicated by a predominance of cellular inflammatory tissue on biopsy.

Outcome and Follow-up

The ultimate outcome of patients with retroperitoneal fibrosis is generally satisfactory, the primary determinant of outcome being the degree of renal functional impairment encountered at the time of diagnosis. Long-term follow-up studies reveal that a number of patients do experience recurrence of ureteral obstruction, often many years after

initial treatment. Recurrence of disease also may accompany cessation of corticosteroids or immunosuppressive medications. Ureterolysis with omental wraps, with or without adjuvant immunosuppressive medications, has a 5% recurrence with long-term follow-up (105).

It follows that patients with retroperitoneal fibrosis warrant scrupulous follow-up for the rest of their lives. Monitoring of renal function and imaging of the urinary tract (via ultrasound, radioisotope renal scan, or IVP) should be carried out at regular intervals. Some authors have advocated monitoring the ESR to follow the inflammatory process. The ESR has been noted to return to normal after both surgical and medical therapy. If the ESR increases after treatment or remains elevated, steroid therapy may be considered.

Pelvic Lipomatosis

Pelvic lipomatosis is an obscure and poorly understood entity that was first recognized in 1959 by Engles. In this report, Engles (64) described five patients with marked deformities of the pelvic viscera, who at exploration were found to have multiple fibrous adhesions and an excessive overgrowth of pelvic fat. In 1968, Fogg and Smyth (78) described five similar patients and first used the term *pelvic lipomatosis* to describe the condition. Since the first description in 1959, approximately 130 reports describing more than 200 patients with pelvic lipomatosis have appeared in the literature.

Incidence

The true incidence of this uncommon disease is unknown. The incidence has been estimated to account for approximately 1 in 100,000 hospital admissions in the United States between 1967 and 1975 (187,208). The largest single-center experience is from the Medical College of Virginia, where 18 patients with pelvic lipomatosis were seen over 35 years (135). Few cases of pelvic lipomatosis in females are reported in the literature, and the youngest patient reported is of an 8-year-old girl (15,120). Although pelvic lipomatosis is rare based on the number of reports in the literature, it is probably significantly more common than is generally appreciated because of the lack of physician awareness and likely underreporting of the disease (18,68,163,179).

Pathologic Features

At surgical exploration, dense, often vascular, excessive fatty tissue characteristically is found enveloping the pelvic organs (18,135). Several reports also have documented extension of the disease process cephalad, with involvement of the perirenal space, retroperitoneum, omentum, and small bowel mesentery (98,115). Heyns and colleagues (113) reviewed the pathologic findings from pelvic biopsies reported in the literature in 67 patients with pelvic lipomatosis. In 70% of patients, the only finding was that of mature fat tissue without evidence of atypia or local invasion. Additional findings documented in 30% of patients included chronic inflammatory changes, fibrosis, and increased vascularity. Evidence of cancer is uniformly lacking.

Pelvic lipomatosis may be considered a distinct, although peculiar, type of lipodystrophy. Other conditions characterized by an abnormal proliferation of fibroadipose tissue include adiposis dolorosa (Dercum's disease), nodular nonsuppurative panniculitis (Weber-Christian) disease, sclerosing lipogranulomatosis, benign symmetric lipomatosis, nodular circumscribed lipomatosis, and lipomatosis of the ileocecal region (17,114,187,218). In Heyns and colleagues' (114) review, however, only 5% of the 130 patients reported in the literature had documented extrapelvic lipomatous masses, and the authors emphasize that pelvic lipomatosis should be considered a separate clinicopathologic entity because of the absence of involvement characteristic of the other forms of lipodystrophy.

Etiology

Which etiologic factors are important in the pathogenesis of pelvic lipomatosis are unknown. Initially, a number of investigators hypothesized that the proliferation of fibroadipose tissue within the pelvis is part of an inflammatory response resulting from chronic lower urinary tract infection. In most patients with pelvic lipomatosis, however, there is no documented evidence of concomitant or a prior history of urinary tract infection. Other authors have speculated that pelvic lipomatosis may represent a localized manifestation of obesity. Interestingly, there have been two reports of obese patients with pelvic lipomatosis treated by diet; a decrease in the amount of pelvic fat was demonstrated with weight loss, and an increase in the amount of pelvic fat was associated with weight gain (135,221). However, obesity does not appear to be a primary etiologic factor in that, although many patients have a tendency toward being overweight, few are actually morbidly obese (113).

A number of other factors have been proposed to be potentially important in the etiology of pelvic lipomatosis, including localized abnormalities in lipid metabolism, endocrine dysfunction, venous stasis, and an allergic phenomenon, although there is no firm evidence to implicate any of these in the etiology of this disorder.

Clinical Features

Although pelvic lipomatosis has been reported in children and the elderly, most patients are in their third to sixth decades of life. There is also a marked sex, as well as racial, predominance with 94% of patients being male and approximately

66% being African American (114). Although occasionally diagnosed incidentally, most patients have presenting symptoms referable to the pelvis or urinary tract. Urinary symptoms and signs are most common and are reported in one-half to three-fourths of patients at the time of presentation. Most commonly, these consist of irritable voiding symptoms and hematuria; obstructive symptoms are occasionally noted. GI symptoms are also common, with patients frequently complaining of nausea, vomiting, and constipation. Other occasional presenting features include suprapubic pain or fullness; low back, flank, or pelvic pain; and lower-extremity edema.

Hypertension also is commonly noted in patients with pelvic lipomatosis. In the Medical College of Virginia experience reported by Klein and associates (135), 5 of 18 patients were discovered during evaluation for hypertension. In Heyns and colleagues' review (114) of 130 patients with pelvic lipomatosis, of the 61 in whom blood pressure was documented, 74% were hypertensive, with moderate to severe hypertension in one-third. As pointed out by Heyns and associates (114) and others, although the true incidence of hypertension in patients with pelvic lipomatosis cannot be accurately determined from case reports, it appears that the incidence is substantially higher than that in the adult United States' population. However, the cause of the hypertension in these patients remains unknown.

In addition to hypertension, pelvic lipomatosis has also been associated with cystitis cystica, cystitis glandularis, and adenocarcinoma of the bladder (114,125). The rectum and colon are often involved in this disease, leading to constipation or bowel obstruction (114,126). Furthermore, patients with pelvic lipomatosis appear to be predisposed to deep venous thrombosis and/or pulmonary embolism, which were documented in 7% of the patients reported in Heyns and colleagues' (114) review. This association has led several authors to advocate prophylactic heparin administration when surgery is performed in these patients (1). In 1992, Goswami and associates (90) described a syndrome linking crossed renal ectopia, pelvic lipomatosis, and translocation of chromosomes 1 and 6. Two groups simultaneously reported an association between achondroplasia and pelvic lipomatosis in 1999 (138,190). Other putative disorders connected with pelvic lipomatosis are the *Proteus* syndrome and nontropical chyluria (49,214).

Natural History

As a result of the displacement and encasement of the pelvic organs by fibroadipose tissue, a number of complications may occur, including obstruction of the urinary tract, rectum, iliac veins, and vena cava. Obstructive uropathy is the most common complication requiring the attention of the urologist. In Heyns and associates' (114) review, nearly half of the patients had some degree of ureterectasis or hydronephrosis, usually bilateral. Of the 18 patients reported by Klein and associates (135), 7 required operative intervention for obstructive uropathy. Interestingly, four of these patients required operative intervention shortly after diagnosis because of moderate to severe azotemia present at the time of diagnosis. The other three patients, however, underwent a diversionary procedure 6, 9, and 12 years following diagnosis for progression of upper tract obstruction and worsening renal functional impairment. One of the patients in this series ultimately died of complications of uremia. In most cases, hydronephrosis can be attributed to encasement of the ureters in the pelvic fibroadipose tissue, although some authors have attributed it to obstruction at the ureteral orifices secondary to proliferative cystitis (276). Vesicoureteral reflux with hydronephrosis has also been reported (5). It should be emphasized that the variable and unpredictable natural history of pelvic lipomatosis dictates prolonged follow-up to prevent progressive upper tract deterioration and demise of renal function.

Association with Proliferative Cystitis

It is well documented that a large percentage of patients with pelvic lipomatosis have bladder epithelial lesions characterized as proliferative cystitis, and a very few with adenocarcinoma of the bladder (114,125,276). Proliferative lesions include bullous edema, von Brunn's nests, cystitis cystica, cystitis glandularis, and cystitis follicularis. In the Medical College of Virginia experience reported by Klein and associates (135), all 12 patients who underwent bladder biopsy had evidence of proliferative cystitis, usually cystitis cystica and/or cystitis glandularis. In Heyns and associates' (114) review of the literature, 78% of patients in whom the bladder mucosa was evaluated demonstrated evidence of proliferative cystitis, usually cystitis cystica and/or cystitis glandularis.

The reason for the high incidence of proliferative epithelial changes in association with pelvic lipomatosis is unknown. Yalla and associates (276) have hypothesized that lymph and venous stasis as a result of encasement of the bladder by the fibroadipose tissue results in mucosal edema, which leads to an altered microenvironment conducive to epithelial proliferation. The true significance of these proliferative lesions in patients with pelvic lipomatosis is likewise unknown. A number of investigators consider cystitis glandularis to be a premalignant lesion, based partly on the frequent association of cystitis glandularis with primary vesical adenocarcinoma (134,180), as well as the documented progression of cystitis glandularis to primary adenocarcinoma of the bladder (62,134,180,235). Furthermore, there have now been three cases reported in the literature of patients with pelvic lipomatosis and adenocarcinoma of the bladder (89,114,125). Two patients with pelvic lipomatosis and adenocarcinoma of the bladder have been seen at The University of Texas M.D. Anderson Cancer Center over a 13-year period. Both patients presented with pelvic lipomatosis

and adenocarcinoma (Fig. 25.7). Radical cystoprostatectomy is difficult in this situation because the anatomic cleavage planes are obliterated and the bladder pedicles are greatly thickened, making the dissection extremely difficult. One patient in the M.D. Anderson experience (125) sustained a rectal injury during the procedure, necessitating construction of a temporary diverting colostomy at the time of the operation. Pathologic analysis in both M.D. Anderson cases showed extensive cystitis cystica and cystitis glandularis in addition to invasive adenocarcinoma. In the case of adenocarcinoma and pelvic lipomatosis reported by Heyns and associates (114), the patient initially presented with pelvic lipomatosis associated with cystitis cystica and cystitis glandularis 6 years before the diagnosis of adenocarcinoma.

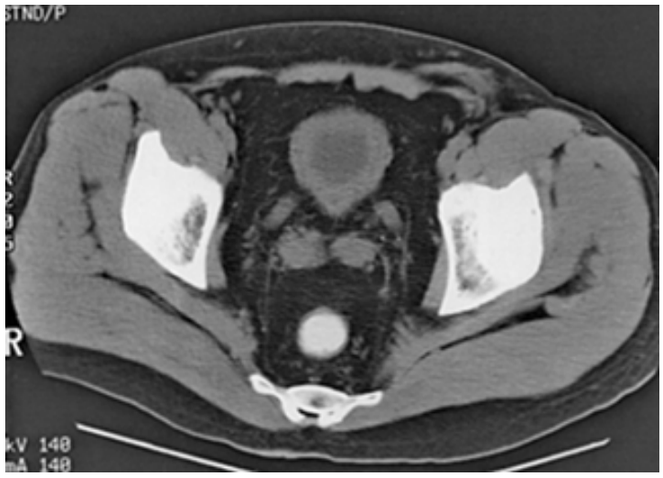

FIGURE 25.7. Computed tomography scan of the pelvis in a patient who presented with pelvic lipomatosis and primary adenocarcinoma of the bladder. Note encasement of bladder and rectum by homogeneous-appearing fat tissue and the increased distance between the seminal vesicles and posterior bladder wall secondary to fat deposition.

Despite the possible premalignant potential for some forms of proliferative cystitis, its true significance remains controversial given its high prevalence in the general population, as revealed in autopsy studies and in urologic patients (8,132,267,270). Regardless, it seems prudent to consider patients with pelvic lipomatosis and proliferative epithelial changes in the bladder to be at an increased risk for adenocarcinoma.

Diagnosis

As mentioned, there is no presenting feature characteristic of pelvic lipomatosis. When symptoms are present, they are usually vague but localized to the pelvis and urinary tract. Complaints include irritative voiding symptoms, hematuria, suprapubic discomfort, perineal pain, low-grade fever, and backache. Despite the deformity of the bladder and posterior urethra, only half of patients describe obstructive voiding complaints (14). Physical examination is only occasionally helpful. A suprapubic mass or fullness representing the displaced bladder is commonly palpable. Rectal examination often reveals a high-riding prostate gland. Owing to venous stasis secondary to iliac vein or venacaval obstruction, lower-extremity edema may be present.

Pelvic lipomatosis is generally first suspected and subsequently diagnosed on the basis of imaging studies. The diagnosis may be suggested on a kidney–ureter bladder (KUB) plain film that demonstrates increased radiolucency in the pelvis (115). Characteristic findings of excretory urography are also generally appreciated. The ureters are usually medially deviated, and often, there is a spectrum of urinary tract obstruction from distal ureterectasis to severe hydroureteronephrosis. Although the ureters typically are deviated medially in their lower third, they also may be laterally deviated. The bladder also has an abnormal appearance. Classically, it is elevated anterosuperiorly and compressed bilaterally, largely in symmetric fashion, with absence of the prostatic indention. This gives a characteristic appearance to the bladder that has been described as teardrop-shaped or pear-shaped. A voiding cystourethrogram, in addition to demonstrating the bladder abnormalities often appreciated on the IVP, also demonstrates an elongated posterior urethra (187). Barium enema typically demonstrates elongation, straightening, and narrowing of the rectosigmoid, producing the so-called “tower” rectum (Fig. 25.8) (135,219). Before the advent of CT scanning, these findings were considered pathognomonic (103). When the diagnosis was still in question, pelvic arteriography was often obtained; although there is often increased vascularity, no neovascularity or other changes characteristic of malignancy are typically seen with this technique (187). Before CT scanning, exploration and biopsy were required in most cases (114,268).

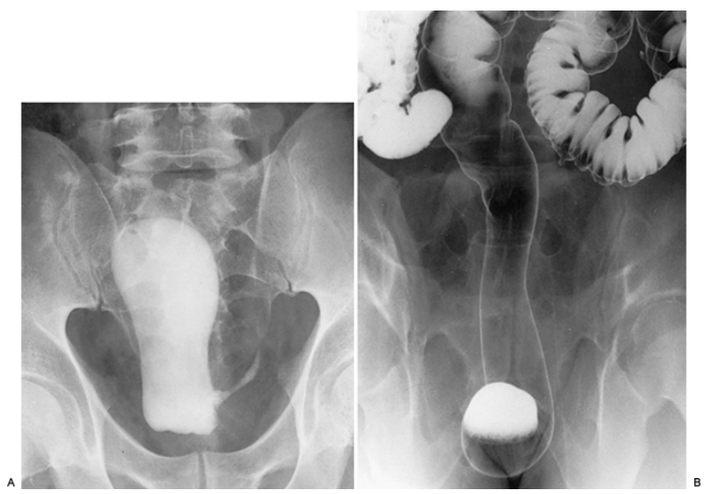

FIGURE 25.8. A: An intravenous urogram in a patient with pelvic lipomatosis demonstrates marked bilateral extrinsic compression and elongation of the urinary bladder producing the typical pear-shaped deformity. **B**: Double-contrast barium enema in the same patient demonstrates narrowing and elongation of the rectosigmoid portion of the colon attributable to the marked deposition of pelvic fat.

Since the advent of CT, in most cases, the diagnosis can be made noninvasively. CT is the diagnostic modality of choice, demonstrating the displacement and encasement of the pelvic organs by homogeneous-appearing fat tissue with low attenuation identical to that found in the subcutaneous fat. An additional CT finding considered characteristic is an increased distance between the seminal vesicles and posterior bladder wall secondary to fat deposition (135). Other CT findings consistent with the diagnosis of pelvic lipomatosis include nonenhancement of the fibroadipose tissue, the preservation of anatomic planes, and the lack of additional pelvic soft tissue masses (135,227,268). The use of MRI in pelvic lipomatosis has been reported in a limited number of patients. It does, however, allow diagnostic confirmation similar to that provided by CT scanning (56). Ultrasonography use has been reported in a few cases and does not seem to be as advantageous as CT (215).

The differential diagnosis of a pear-shaped bladder is reviewed in >Table 25.9 . Iliopsoas muscle hypertrophy is particularly important to consider because of its prevalence

in young, African American males. Obviously, the most important differential to be made is from that of a malignant process, particularly liposarcoma. In most cases, the CT or MRI findings allow differentiation because liposarcomas typically demonstrate aggressive local invasion and marked asymmetric growth. Areas of localized high density, suggesting a soft tissue mass, are also typical of liposarcoma. However, if the diagnosis remains questionable following the use of the imaging studies available, percutaneous fine-needle or core-needle biopsy or open exploration and biopsy is warranted.

Diagnostic Entity	Comment
Perivesical hematoma, urinoma, abscess, bilateral lymphoceles	Suggested by history, demonstrated by ultrasound or CT
Iliopsoas hypertrophy	Demonstrated by measured ratio of psoas muscles to pelvis
Pelvic lipomatosis	Barium enema or CT scan confirms diagnosis
Malignant infiltration of pelvic nodes	Usually due to lymphoma
Inferior vena cava obstruction	Due to enlarged venous collaterals and edematous pelvic muscles
Bilateral iliac aneurysm	Usually unilateral; physical examination and ultrasound establish diagnosis
Bladder scarring or edema	History suggestive
Pelvic fibrosis, pancreatic pseudocysts, lipoplastic lymphadenopathy	Rare
Bilateral hip replacement with extruded cement or severe bladder prolapse	Diagnosis should be clear on cystogram or intravenous urogram alone
Ureteral compression balloons	Can cause artifact on urogram

CT, computed tomography.
Modified from Saxton HM. Pelvic lipomatosis. In: Pollack HM, ed. Clinical urography: an atlas and textbook of urological imaging. Philadelphia: WB Saunders, 1990:2458, with permission.

TABLE 25.9. THE DIFFERENTIAL DIAGNOSIS OF A PEAR-SHAPED BLADDER

Because most patients present with urologic symptoms, including irritable voiding complaints, suprapubic pain, or fullness, and sometimes have hematuria, panendoscopy and biopsy are integral diagnostic studies. However, cystoscopy is usually difficult in these patients and at times impossible because of the elongated posterior urethra and bladder displacement. Use of a flexible cystoscope may facilitate the examination.

Management

There is no specific medical therapy that is successful in the management of patients with pelvic lipomatosis. Although antimicrobial therapy, steroids, dietary control, and radiotherapy have been tried, they play no role in the specific management of this condition. Most patients can be managed conservatively, with intervention reserved for the management of complications, primarily ureteral obstruction resulting in obstructive uropathy. Although a few authors have reported that the lipomatous tissue could be excised satisfactorily, most have found this to be extremely difficult or impossible as a result of the absence of cleavage planes between the fat and surrounding pelvic viscera (78,162). Most authors have found excision of the lipomatous tissue and ureterolysis to be difficult without compromising the ureteral blood supply.

The usual treatment for ureteral obstruction associated with pelvic lipomatosis has been supravesical urinary diversion or ureteroneocystostomy performed into the dome of the bladder. As reported by Klein and associates (135), these procedures have been successful in preserving renal function if performed before significant renal parenchymal damage. Use of an ultrasonic assisted lipectomy device was reported to be helpful with ureterolysis in one difficult case (98). Because of the difficulty in performing endoscopic procedures in these patients, transurethral resection, when necessary, may require a perineal urethrostomy for access.

Outcome and Follow-up

Limited information is available concerning the long-term follow-up of patients with pelvic lipomatosis. In the Medical College of Virginia experience reported by Klein and associates (135), after a mean follow-up of 7.5 years, 16 of 18 patients were alive. One patient was lost to follow-up, and one died of uremic complications of the disease. In all, 7 of the 18 patients required diversionary procedures for obstructive uropathy.

From the limited data in the literature concerning the long-term outcome of these patients, it appears that most patients' disease does not progress and can be managed conservatively with a favorable outcome. A significant percentage (approximately 30% to 50%), however, require operative intervention to relieve urinary tract obstruction. Because it is impossible to predict which subset of patients will in fact have disease progression, long-term urologic follow-up is critical. However, specific recommendations and guidelines for follow-up are difficult. It seems reasonable to obtain a renal ultrasound or nuclear renal scan yearly in stable patients and more frequently if there is any evidence of ureteral obstruction. Cystoscopy, as well as bladder biopsy, also may be indicated at the time of presentation because of the association with proliferative cystitis and its possible premalignant potential. Periodic urinary cytology may obviate the need for cystoscopy (135).

MISCELLANEOUS DISEASES OF THE RETROPERITONEUM

Part of "25 - DISEASES OF THE RETROPERITONEUM "

Retroperitoneal Abscess

In the past, retroperitoneal abscess was considered an insidious and challenging clinical entity that, if left untreated, would lead to death in virtually 100% of cases (6). With the widespread use of antibiotics, the incidence of retroperitoneal abscess has decreased significantly (0.9 to 4.0 cases per 10,000 hospital admissions) (253). Advances in diagnostic imaging (ultrasonography and CT scanning) and the development of percutaneous drainage techniques have dramatically improved the management of retroperitoneal abscess (81,82,119). Despite these advances, retroperitoneal abscess remains a diagnostic challenge and should be suspected in any patient presenting with pyelonephritis in whom fever persists despite institution of antibiotic therapy (253). Prompt diagnosis and treatment will prevent the high morbidity and mortality once associated with this entity.

Etiology

The etiology of retroperitoneal abscesses is related to either renal or perinephric infection or to inflammatory processes originating in the GI tract, such as appendicitis, Crohn's disease, diverticulitis, pancreatic abscess, or malignancy (161,167,213). Predisposing conditions for perinephric abscess include urolithiasis, diabetes mellitus, a history of urinary tract infections or urinary tract obstruction, and polycystic kidney disease (250,253). Between 36% and 42% of patients have been reported to be diabetics and 20% have calculi (171,253). Several cases of retroperitoneal abscess

occurring after normal pregnancy and delivery have been reported (45). Postsurgical abscess formation in the retroperitoneum, generally associated with surgery of the kidney or of the GI tract, is now relatively rare (28). Less common causes of retroperitoneal abscess include tuberculosis, osteomyelitis, and epidural abscess with extension. An incompletely resorbed retroperitoneal hematoma may lead to the formation of an abscess (186,265).

Clinical Presentation

Typically, a patient harboring a retroperitoneal abscess will present with fever, generalized malaise, and occasionally, diffuse abdominal pain. These symptoms will have been present for more than 2 weeks in most patients, and this is useful in distinguishing patients with acute pyelonephritis, who typically present with symptoms present for only a few days (253). Physical examination may reveal fever and a tender abdominal mass. Most often, flank or costovertebral tenderness is noted (236). A positive psoas sign may also be elicited. Further extension of the infective process may cause irritation to the retroperitoneal nerves, and patients will experience tenderness in the groin, lower abdomen, flank, and upper thigh. Irritation of the diaphragm may cause pleuritic chest pain. Clinical evidence of sepsis is present in up to 60% of patients (88).

Failure to diagnose a retroperitoneal abscess or a delay in treatment, in most cases, leads to spread of the infectious process, to sepsis, and ultimately to death. Spontaneous drainage of retroperitoneal abscess by a fistula to the skin or bowel has been reported (60). Finally, extension of the infective process to the psoas muscle is a well-recognized complication of retroperitoneal abscess (188).

Diagnostic Modalities

Laboratory testing is most often nonspecific: Leukocytosis is noted in two-thirds of patients, 42% of patients will have some degree of anemia (hemoglobin less than 10 g/dL), and most patients exhibit an elevated ESR (171,256). Urinalysis will demonstrate pyuria in most patients, and hematuria may be noted, although in only approximately one-third of patients. Radiographic evaluation may include a plain film of the abdomen, ultrasonography, and CT. In the past, urologists depended on the IVP, retrograde pyelography, and renal angiography, but the newer, less invasive radiologic techniques have provided greater accuracy in reaching a diagnosis.

The plain radiograph of the abdomen is abnormal in about 40% of cases (253). When observed, abnormalities are nonspecific and include (a) obliteration of the psoas muscle border on the affected side, (b) displacement of bowel gas or a pattern of ileus, (c) lumbar scoliosis, (d) perinephric gas, and (e) displacement of the kidney. On the IVP, a poor or nonfunctioning renal unit is present in more than half of patients; ureteral dilation, deviation, or both may be noted; and a significant percentage of patients will have coexistent urolithiasis (248). Abdominal ultrasound serves as an excellent screening test and may be performed when a perinephric abscess is suspected. However, it is limited in diagnostic ability in the retroperitoneum by overlying bowel gas, large body habitus, and its relative lack of specificity (119). Although sonography is able to clearly image fluid collections in and around the kidneys, it is unable to detect fascial planes or distinguish the nature of the fluid collection; therefore needle aspiration of the fluid may be necessary to arrive at the correct diagnosis. On the other hand, CT scanning provides more detailed information about the size, content, and extent of the retroperitoneal process, making it the diagnostic procedure of choice in the evaluation of retroperitoneal abscess (82,119,142). Typical findings include the demonstration of air–fluid levels within the mass and the frequent extension of the process along fascial planes that may even reach the pelvis. Its accuracy has been reported to be as high as 96% (170). Angiography and radionuclide imaging in the evaluation of retroperitoneal abscess have not proved to be of great help in enhancing the diagnostic capability and are therefore seldom, if ever, used (170). MRI is useful in detecting and diagnosing retroperitoneal abscesses (252). However, the availability, lower cost, sensitivity, and ability to drain an abscess at the time the diagnosis have made CT the modality of choice.

Management

The most important aspect in the management of retroperitoneal abscesses is to avoid a delay in diagnosis so that prompt and effective drainage may be attained. Relatively large retroperitoneal abscesses may be treated by percutaneous drainage and antibiotic therapy (28,83,88). As stated by Gerzof and co-workers (83), the basic principles of percutaneous drainage of retroperitoneal abscesses are (a) evaluation of the extent of the abscess by cross-sectional imaging (CT scanning being the preferred method); (b) identification of a safe, extraperitoneal, percutaneous window; (c) diagnostic aspiration (because cross-sectional imaging may not be entirely specific); and (d) placement of an indwelling catheter for drainage of the abscess cavity. Multilocular abscesses may also be treated using multiple drainage catheters (261). Adequate drainage of the abscess cavity and resolution of the process can be studied by cross-sectional imaging and injecting contrast material into the cavity (21). CT imaging, aspiration for diagnosis and culture, and drain placement can all be performed without the patient ever leaving the CT suite.

Antibiotic coverage for skin flora is best administered before aspiration and drain placement; Gram stain results will then guide coverage until culture and sensitivity results return. Broad-spectrum antibiotic coverage may be used in

patients with clinical sepsis or poor reserves. Antibiotic therapy will be tailored to the culture and sensitivity testing of the aspirate based on identification of the offending organism. In a report on 161 adults, Brook and Frazier (30) highlighted the predominance of polymicrobial aerobic–anaerobic nature of retroperitoneal abscesses. Aerobes were recovered from only 21% abscesses and anaerobes from only 21%, whereas 82% of abscesses were polymicrobial. The most commonly cultured aerobic and facultative organisms included *Escherichia coli* (37%), *Klebsiella pneumonia* (12%), and group D streptococcus (12%), whereas the most predominant anaerobes were *Peptostreptococcus* species (59%), *Bacteroides fragilis* (41%), *Prevotella* species (14%), and *Clostridium* species (14%). Brook (29) also reported the microbial growth from 41 children with retroperitoneal abscesses; 83% of infections were polymicrobial, with 54% containing *Bacteroides* species, 46% containing *E. coli*, 44% having *Peptostreptococcus* species, 15% having *Staphylococcus aureus*, and 12% containing *Prevotella* species. Gram stain of the aspirate is mandatory because a culture will be negative in 5% to 10% of cases (236).

The drainage catheter is removed when signs of clinical improvement, minimal drainage, and little or no fluid remaining in the abscess cavity are noted. Excellent results have been reported, with cure rates between 70% and 85% (21,28,88,262). Abscess recurrence has been observed in 10% of cases (21,262).

Surgical management is still required for large abscesses and for cases in which percutaneous drainage would be hazardous or have little chance of success (e.g., in cases with large, multiloculated abscesses and in those with thick, purulent material), for recurrent abscesses unsuccessfully treated by percutaneous modalities, and for patients with a nonfunctioning kidney in whom nephrectomy is carried out at the time of abscess drainage. In addition, surgical correction of any obstructive process must be considered to alleviate an underlying cause of abscess.

Spontaneous Retroperitoneal Hemorrhage

Spontaneous retroperitoneal hemorrhage is most commonly the result of trauma or rupture of an abdominal aortic aneurysm. If these causes are ruled out, a variety of uncommon causes, often with genitourinary significance and with significant potential for morbidity and mortality, must be considered. Because treatment depends on the specific cause, an awareness of the potential causes and an aggressive diagnostic approach are essential. Pode and Caine (204) published an excellent in-depth review of this subject.

Etiology

The causes of spontaneous retroperitoneal hemorrhage are reviewed in Table 25.10 . As can be seen, many of these entities are of urologic significance; in fact, excluding retroperitoneal trauma and ruptured abdominal aortic aneurysms, in most cases, the bleeding is from the kidney or adrenal gland.

Renal Disease
Tumors
Benign (angiomyolipoma)
Malignant (renal adenocarcinoma)
Renal parenchyma
Infection (pyelonephritis, renal abscess)
Acute/chronic nephritic syndromes
Nephrosclerosis
Renal vascular disease
Vasculitis (polyarteritis nodosa)
Atherosclerosis
Renal artery aneurysm, thrombosis, infarction
Renal vein thrombosis
Arteriovenous malformation
Renal transplantation
Acute/chronic rejection
Adrenal Disease
Tumors
Benign pheochromocytoma, myelolipoma, cysts
Malignant pheochromocytoma, carcinoma
Adrenal "stress" hemorrhage
Adrenal apoplexy
Local Retroperitoneal Causes
Pancreas (tumors, cysts, pancreatitis)
Primary and metastatic retroperitoneal tumors
Spontaneous hemorrhage from retroperitoneal veins
Systemic Conditions
Vasculitides
Polyarteritis nodosa, Wegner's granulomatosis
Coagulopathy
Anticoagulant/thrombolytic therapy
Blood dyscrasias
Hemodialysis

TABLE 25.10. CAUSES OF SPONTANEOUS RETROPERITONEAL HEMORRHAGE

Retroperitoneal hemorrhage secondary to spontaneous rupture of the renal parenchyma was first reported by Bonet in 1700 and described and classified by Wunderlich in 1956; it has been referred to as *Wunderlich's disease* or *syndrome* (205). McDougal and associates (165) reviewed the English literature up to 1974 and reported the findings in 78 cases. A subsequent review of the literature between 1974 and 1984 reported by Cinman and associates (43) documented an additional 27 cases. From these reviews and other subsequent reports, it is clear that most cases of retroperitoneal hemorrhage caused by spontaneous renal parenchyma rupture are associated with tumors of the kidney. Benign and malignant tumors occur with equal frequency in this setting. Although spontaneous renal parenchyma rupture has been associated with a variety of benign tumors, including lipomas, adenomas, and cysts, most cases are associated with angiomyolipoma. This tumor

is highly vascular and is prone to hemorrhage. In one review of patients with angiomyolipomas, approximately half of patients with tumors larger than 4 cm presented with retroperitoneal hemorrhage, and a significant number, approaching 10%, presented with symptoms and signs of shock (185). There is an increased tendency for hemorrhage with angiomyolipoma associated with the hemodynamic changes of pregnancy.

As with benign renal tumors, a number of histologic types of malignant renal lesions have been reported in association with spontaneous retroperitoneal hemorrhage; however, most are renal adenocarcinomas. Although fewer than 1% of patients with renal carcinoma present with retroperitoneal bleeding, because of its overall relative incidence, it is the most common cause of spontaneous retroperitoneal hemorrhage (239).

Other renal diseases associated with spontaneous retroperitoneal hemorrhage include pyelonephritis with or without renal or perirenal abscess, other renal inflammatory disorders, and renal vascular disease. A renal vascular cause is present in approximately 20% of patients with spontaneous retroperitoneal hemorrhage. This cause may be renal involvement in a systemic vasculitic syndrome, such as polyarteritis nodosa, or it may take the form of a ruptured renal artery aneurysm, renal vein thrombosis, or arteriovenous malformation. Polyarteritis nodosa is a well-recognized cause of spontaneous retroperitoneal hemorrhage (204,241). This condition, which is an immunologically mediated disease affecting small and medium arteries, is associated with renal involvement in more than 80% of cases. As with renal artery aneurysms in general, there appears to be an increased risk of bleeding in the setting of uncontrolled hypertension and pregnancy.

The adrenal gland is also a well-documented source of spontaneous retroperitoneal hemorrhage. In most cases, clinically significant hemorrhage from an adrenal source is in the setting of severe stress (e.g., pregnancy, trauma, sepsis, burns). Massive bleeding has also been reported in association with adrenal tumors, including pheochromocytoma, myelolipoma, and adrenal carcinoma (86,145,147). Rarely, retroperitoneal bleeding originates from an otherwise normal adrenal gland without recognizable precipitating factors or underlying systemic disease. This condition, referred to as *adrenal apoplexy,* is difficult to diagnose unless it is specifically included in the differential (36,217,251).

Other causes of spontaneous retroperitoneal hemorrhage include diseases of the pancreas, as well as primary and metastatic retroperitoneal tumors. Rarely, spontaneous hemorrhage may arise from retroperitoneal veins. Most of these cases, often involving the common iliac vein or its branches, are associated with proximal venous obstruction secondary to thrombosis (204). Iatrogenic retroperitoneal hemorrhage may occur after groin access is used for percutaneous vascular studies and procedures. Poupart's ligament distinguishes the external iliac vessel from the femoral vessel, and access obtained superior to the inguinal ligament may be difficult to compress; therefore bleeding can occur within the retroperitoneal space. Systemic conditions resulting in spontaneous retroperitoneal hemorrhage include a number of vasculitides, such as polyarteritis nodosa, and coagulopathic states, most notably, iatrogenic anticoagulant and thrombolytic therapy, as well as blood dyscrasias. Also included here are patients receiving long-term dialysis, who, in addition to undergoing frequent systemic anticoagulation, have intrinsic platelet dysfunction because of their uremic state. It should also be emphasized, as pointed out by Pode and Caine (204), that there is a possibility that the coagulopathic state may merely unmask an additional local factor, such as a tumor, that caused the retroperitoneal hemorrhage.

Clinical Features

The clinical signs and symptoms of patients with spontaneous retroperitoneal hemorrhage are protean and nonspecific. As a result, a high index of suspicion and an aggressive diagnostic approach are necessary for a satisfactory outcome. Clinical presentations can range from a patient with vague abdominal or flank pain that gradually developed over several days to a severely ill patient with clinical features suggestive of an intraabdominal catastrophe. In addition to the presence of localized abdominal or flank pain in most patients, other findings may include microscopic or gross hematuria, occurring in most patients with retroperitoneal hemorrhage secondary to a renal cause, and evidence of significant blood loss. Patients also commonly have nonspecific GI complaints, such as nausea and vomiting, and may have a palpable mass and tenderness over the involved area. Peritoneal signs or diaphragmatic irritation also are occasionally present. Variable degrees of renal functional impairment are common. Important historical factors include trauma, anticoagulant use, vasculitis, tuberous sclerosis, hemodialysis, and pregnancy.

The diagnosis of bilateral spontaneous adrenal hemorrhage occurring in the clinical setting of severe stress requires a high index of suspicion. This clinical scenario usually occurs in an already critically ill patient who subsequently exhibits progressive deterioration. Clinical features that may suggest the diagnosis include mental status changes, low-grade fever, hypotension refractory to treatment, fluid and electrolyte abnormalities (most commonly hyponatremia), and variable degrees of renal functional impairment (204,275).

Diagnosis

Currently, based on clinical findings and the use of modern imaging modalities, a diagnosis of spontaneous retroperitoneal hemorrhage and the underlying cause can be determined before surgical exploration in most cases (20,204).

In contrast, before the advent of CT scanning, when imaging studies were based largely on excretory urography and angiography, the specific diagnosis was rarely made before surgical exploration (165). CT is currently the most valuable imaging modality for patients with spontaneous retroperitoneal hemorrhage. CT readily demonstrates the presence and extent of the hematoma and also may demonstrate the underlying pathology responsible, such as a solid renal mass suggestive of a renal carcinoma or, if fatty tissue is identified within the tumor, an angiomyolipoma.

In a recent study of 18 patients with spontaneous retroperitoneal hemorrhage, Belville and associates (20) reported a diagnostic accuracy of 92% in 12 patients whose preoperative CT scans revealed a solid mass. In the remaining six patients, no mass was appreciated at the time of the initial study. One of these patients had CT findings characteristic of renal infarction; in two others, follow-up CT scans obtained after the hematoma had been reabsorbed revealed a small renal cell carcinoma, enabling an accurate diagnosis and appropriate subsequent treatment. The other three patients underwent exploratory laparotomy and nephrectomy, which revealed a small renal cell carcinoma in one patient, an angiomyolipoma in another, and no apparent abnormality accounting for the bleeding was discovered in the third patient.

CT scanning may also indicate the presence of polyarteritis nodosa, with multiple wedge-shaped defects present on the contrast-enhanced scan indicative of severe ischemia or infarction (106,204). When a mass is not appreciated on the initial CT scan in the presence of a retroperitoneal hemorrhage, Bosniak (24) has stressed the importance of technique in CT imaging. Optimally, both precontrast and postcontrast scans should be obtained, with thin cuts (5 mm) taken through the adrenal and renal beds. Furthermore, until the hematoma is completely reabsorbed, follow-up serial CT scans are crucial. Follow-up scans allow detection of a small renal mass previously obscured by the hematoma.

Although angiography was more important before the advent of CT scanning, it is still recommended in patients with spontaneous retroperitoneal hemorrhage, primarily to rule out the presence of a vascular cause. It may also add valuable diagnostic information if the CT findings are equivocal (204). Furthermore, angiography may be therapeutic, allowing selective embolization of active bleeding sites. Other diagnostic maneuvers may be useful depending on the presumed cause of retroperitoneal hemorrhage. For example, tests of adrenocortical and adrenomedullary function are mandatory in the presence of a suprarenal mass associated with retroperitoneal hemorrhage.

Ultrasound is also an important diagnostic imaging modality in the setting of spontaneous retroperitoneal hemorrhage. In addition to allowing one to rapidly rule out the presence of an abdominal aortic aneurysm, in most cases, an ultrasound examination will reveal the presence and the location of a retroperitoneal hematoma. Although less useful than a CT scan, it also may suggest the underlying pathology by demonstrating a renal or suprarenal mass associated with the hematoma. However, in most cases, ultrasound is unable to discriminate a solid mass from a hematoma.

Management

Optimal management of patients with spontaneous retroperitoneal hemorrhage depends on a high index of suspicion, an awareness of potential etiologic factors, an aggressive and systematic diagnostic approach, and treatment tailored to the specific cause. Occasionally, patients with spontaneous retroperitoneal hemorrhage may be critically ill, with symptoms and signs of hypovolemic shock at presentation, perhaps even necessitating an emergency exploratory laparotomy for definitive diagnosis and treatment. In most cases, however, patients can be resuscitated and stabilized such that the necessary diagnostic studies can be performed and a preoperative diagnosis made.

Patients with spontaneous retroperitoneal hemorrhage in a setting of a systemic coagulopathy should be managed conservatively because an obvious bleeding source is almost never found at the time of exploration (173). Furthermore, angiography also generally fails to reveal a specific bleeding site in this situation (204). Therefore management should focus on measures to correct the bleeding diathesis and restore blood volume as indicated.

Spontaneous retroperitoneal hemorrhage in the setting of systemic vasculitis, most commonly secondary to renal involvement by polyarteritis nodosa, is also best approached conservatively. The importance of a renal-sparing approach in this situation is underscored by the nearly always bilateral involvement of the kidneys in this disease and the propensity for progressive renal deterioration. Medical management using immunosuppressive agents may be effective (149). When the clinical situation dictates a more aggressive approach, nephrectomy should still be avoided if possible; selective embolization and partial nephrectomy are viable options (204,241).

If the CT scan reveals a renal tumor, the possibility of angiomyolipoma must be entertained. When a diagnosis of angiomyolipoma is made, especially in the setting of tuberous sclerosis with a high frequency of bilateral involvement, a renal-sparing approach, usually in the form of a partial nephrectomy, may prove optimal. If a solid tumor suggestive of renal malignancy is identified, in most cases, one may then properly evaluate the patient preoperatively, as one would for any patient with a solid renal mass suggestive of malignancy.

In the past, most authors have advocated prompt surgical exploration in the setting of spontaneous renal hemorrhage arising from the kidney with no apparent lesion on imaging analysis (61,131,165). This philosophy was based largely on experience before CT availability; on exploration in this situation, a large number of kidneys were found to harbor

renal adenocarcinoma. However, in a number of cases, otherwise normal kidneys were also removed. With the advent of CT scanning, it seems prudent to monitor the regression of the hematoma by serial CT scan examinations with thin cuts through the adrenal and renal beds until the hematoma is completely reabsorbed, thereby avoiding unnecessary exploration with the risk of removal of a normal kidney (20,24).

If the cause of spontaneous retroperitoneal hemorrhage is an adrenal tumor, tests of adrenal medullary and cortical function are mandatory. Because of the extremely high mortality rate associated with the resection of an unsuspected pheochromocytoma, every effort should be made to diagnose this tumor preoperatively and to prepare the patient properly for surgery. Furthermore, a high index of suspicion for the presence of bilateral adrenal hemorrhage in the setting of severe stress should lead to further diagnostic evaluation with functional adrenal studies and the prompt administration of corticosteroids as indicated.

CONCLUSION

Part of "25 - DISEASES OF THE RETROPERITONEUM "

This chapter addressed a number of conditions that pose major diagnostic and therapeutic challenges to the urologic surgeon. A high index of suspicion is necessary to provide proper care for patients with disease of the retroperitoneum. In some cases, it is prudent to take a multiteam approach to surgical procedures, at times involving the general surgeon or vascular surgeon.

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26

VOIDING FUNCTION AND DYSFUNCTION

Contents

26A VOIDING FUNCTION: RELEVANT ANATOMY, PHYSIOLOGY, PHARMACOLOGY, AND MOLECULAR ASPECTS

Stephen A. Zderic

Samuel Chacko

Michael E. Disanto

Alan J. Wein

Part of "26 - VOIDING FUNCTION AND DYSFUNCTION "

S.A. Zderic: Department of Surgery, University of Pennsylvania School of Medicine; Division of Pediatric Urology, Children's Hospital of Philadelphia, Philadelphia, PA 19104.

S. Chacko: Department of Pathobiology, University of Pennsylvania Medical Center, Philadelphia, PA 19104.

M.E. Disanto and A.J. Wein: Division of Urology, University of Pennsylvania School of Medicine, Philadelphia, PA 19104.

The past 30 years have seen an exponential rise in the literature characterizing normal and pathologic bladder function. Earlier reviews placed a heavy emphasis on the physiology of micturition (352) and the pharmacology of the urinary bladder (213,340). Basic neurophysiology research with identification of neural pathways controlling micturition began to appear in the literature with increasing frequency and ever greater sophistication (44,87,94). With the development of monoclonal antibodies, it now is possible to look at specific aspects of protein expression to study how physiology and microanatomy are altered by normal development, aging, and obstruction. The last 10 years have seen a remarkable increase in the number of papers using modern molecular techniques such as Western blotting (to probe for protein expression) along with Northern blotting and polymerase chain reaction technology (to probe for mRNA expression). Research studying bladder function in knockout and transgenic mice is just beginning to appear in the urology literature. DNA microarray technology now is readily available, which allows for the simultaneous comparison of thousands of genes between two tissues (i.e., normal versus pathologic). A growing number of basic scientists now are conducting active research in bladder function, and the urologic literature in the basic sciences will expand at an even faster pace. Even the most current research monographs (12,23,26,230,366,366a) will have an effective scientific half-life of 2 or 3 years.

With these ideas in mind, we wish to briefly express our objectives for this chapter. If we attempted to cover every aspect of urinary bladder function in maximal detail, the overwhelming amount of information would result in an unwieldy chapter of limited use to the practicing clinician. This makes it necessary for us to exercise judgment regarding which literature and viewpoints will be emphasized; however, every effort will be made to present divergent viewpoints. In addition to summarizing current views on the structure and function of the lower urinary tract, we wish to prepare the reader for the challenge of keeping up with this literature over the next 5 years.

The lower urinary tract functions as a group of interrelated structures whose integrated function allows for the normal voiding cycle to occur. In brief, the normal voiding cycle consists of bladder filling and storage at low pressure with perfect continence, and the subsequent voluntary and efficient expulsion of urine also at low pressure. With normal filling, a gradual rise in intravesical pressure occurs despite large increases in volume; the bladder is one of the most compliant structures in the body. Bladder filling is accompanied by an increase in proximal urethral resistance resulting from increased tension in the urethral striated muscle, called the *striated sphincter*. Normal bladder filling is not accompanied by phasic involuntary smooth muscle contractions or a significant tonic increase in intravesical pressure; contractility is suppressed until the proper moment. Under normal conditions, there is no urinary leakage, even with increases in abdominal pressure. At some point, sensory pathways convey to the central nervous system (CNS) the sensation of fullness, and if the situation is appropriate, micturition is initiated. At this point, a complex series of coordinated neural signals initiates the detrusor contraction, which must be accompanied by simultaneous funneling of the bladder neck and relaxation of the bladder outlet. During this voiding phase, the neural excitatory input to the striated musculature of the pelvic floor ceases. Once voiding is completed, the tension returns to the bladder outlet, and the detrusor muscle relaxes to allow a new cycle of filling to begin.

Each aspect of this voiding cycle is described in detail in this chapter. This requires an integration of basic concepts from several major disciplines. For example, the urinary bladder's main distinguishing feature is its remarkable compliance—the ability to store large volumes at low pressures.

To explain this one property requires an understanding of biomechanics, neurophysiology, smooth muscle physiology, pharmacology, extracellular matrix (ECM) biochemistry, and basic molecular cell biology.

Because it is impossible to list all the data in an order that is entirely logical on the first reading, we suggest an initial rapid review of the chapter to capture the major features. This can be followed by an in-depth reading with the use of bibliographic references to enhance understanding of some of the more complex topics. Schematic diagrams have been included; they are simplifications of complex biologic systems, but serve to introduce the reader to essential basic concepts. We wish to avoid presenting pure experimental data without correlating them with some aspect of the micturition cycle. In the bibliography, we place an emphasis on current review articles and thus apologize to those authors whose classic references have been omitted.

The reader of this chapter is encouraged to be critical of our views. Over the previous editions of this chapter (354), we have offered the following recommendations (with only minor revisions) when considering this contribution, as well as the current and future literature.

1. A bewildering array of experimental models exist, which must be considered carefully. A small change in one model may make the results impossible to compare with another.
2. Significant differences do exist within species; results in one animal species do not necessarily hold up in another species nor in humans.
3. Results obtained in another organ or tissue (e.g., cardiac or vascular, intestinal, or uterine smooth muscle) may not be equivalent in the smooth muscle of the lower urinary tract, even if the tissues compared are from the same species or are anatomically adjacent.
4. Substantial changes in anatomy, physiology, pharmacology, and molecular properties of the smooth muscle of the lower urinary tract may be secondary to alterations associated with or induced by gender, normal aging, hormonal status (e.g., menopause, pregnancy), denervation, decentralization, stretch, and drug effects (including those used in laboratory and clinical anesthetics).
5. *In vitro* experimental results are not always equivalent to *in vivo* findings, and neither of these is necessarily equivalent to "normal."
6. The lack of an adequate control group makes experimental work in human tissues far more difficult to interpret. This is not to imply that such studies have no merit, as long as this limitation is acknowledged; if properly performed and presented, these studies can contribute a great deal to the literature.
7. Anatomy or histology do not necessarily imply a specific function or physiologic finding will be present, and vice versa.
8. Any *in vivo* or *in vitro* effect induced by an agonist or antagonist does not necessarily impart a major physiologic significance to this neurotransmitter or its associated component of the nervous system under normal systems.
9. Pressure- or tension-generating ability in the whole organ or a strip does not necessarily correlate with contractility, and neither need correlate with bladder emptying ability.
10. The presence of receptors in a tissue in and of itself does not imply innervation or function.
11. Changes in mRNA expression alone are not necessarily of physiologic significance, unless accompanied by an associated change in protein expression that can be correlated with the physiologic findings.
12. Even a seemingly simple concept such as bladder compliance is a highly complex biologic property that probably involves the expression of multiple proteins in the correct chronologic order as well as proper anatomic domain with the proper spatial orientation. It is unwise to assume that variation in expression of one protein alone is responsible for change in the observed physiology.
13. The physiology of any portion or type of normal and abnormal bladder function usually can be explained by at least a part of one complete theory of micturition. This does not validate the entire theory or invalidate another.
14. Authors (ourselves included, despite our best efforts) must be somewhat selective in their citation of references. References that cite an author's point of view tend to be cited more conspicuously and more favorably than those that do not.

RELEVANT ANATOMY

The Bladder

The urinary bladder is a hollow muscular organ that, from an anatomic viewpoint, may be divided into the detrusor and trigone. From a pharmacologic and physiologic standpoint, the bladder is best divided into a body and base, because these two zones of the bladder differ substantially (123,292). The urinary bladder wall consists of three layers: an outer serosal layer primarily composed of connective tissue, a smooth muscle layer, and an inner mucous membrane completely lining the interior. In the human, the outer serosal layers and the smooth muscle layers are less distinct when viewed histologically.

Mucosal Layer

The mucosa of the bladder is composed of two zones: (a) the urothelium, composed of transitional epithelial cells that rest on (b) the lamina propria, a supporting structure. The lamina propria contains ECM components, fibroblasts, and sparse smooth muscle cells. Evidence suggests that the

fibroblasts (334) and smooth muscle cells (127) may become activated during obstruction to increase the secretion of matrix components in this layer. The transitional cells are a specialized epithelial layer whose structure allows the cells to unfold and expand their size as the bladder fills. These cells also are highly active metabolically, with significant enzymatic activity for enzymes involved in the tricarboxylic acid cycle, which are most likely required because of the tremendous osmotic gradients that exist between the cytosol and the bladder lumen (158). The urothelium also is important during normal embryologic development and bladder regeneration in ways that still are not fully understood. Baskin and colleagues (23,24) have shown that urothelial cells must be present if primitive mesenchyme from the fetal rat bladder is to differentiate into smooth muscle. Sutherland and associates (327) also have shown that in an acellular matrix graft inserted into the rat bladder, urothelial ingrowth precedes the appearance of smooth muscle. These studies imply that the urothelium secretes factors that act locally to affect cellular growth and differentiation. Freeman and co-authors (129) have demonstrated that cultured urothelium is capable of secreting heparin-binding epidermal growth factor, which is a potent mitogen for fibroblasts and smooth muscle.

Detrusor

The detrusor smooth muscle layer is heterogeneous, consisting of smooth muscle cells, fibroblasts, collagens, proteoglycans, elastin, and numerous other molecules in various stages of being identified. The actual smooth muscle fraction in a cross-sectional area of detrusor smooth muscle as determined by morphometric analysis may vary from 50% to 60%, and this fraction may diminish in the face of obstruction (287,305,320). Interspersed between these smooth muscle cells and bundles are zones of connective tissue (i.e., fibroblasts embedded within the ECM) that allow for force transmission from cell to cell. Smooth muscle has no skeleton upon which to exert its forces to allow for the propagation of energy. It also is generally agreed upon that, in the resting position, the detrusor smooth muscle bundles lack a particular uniform orientation, unlike striated or cardiac muscle. Histologic evidence also suggests that as the bladder is stretched, these muscle bundles (347) and matrix elements (227) become reoriented.

The bundles of the detrusor smooth muscle merge into the trigone and bladder base. The bladder base is defined as that zone below a circumferential line, determined by the level at which the ureters enter posteriorly. As such, it has an anterior and a posterior zone. The posterior zone includes the urethra and ureteral orifices, and is called the *trigone*. If one views the urethrovesical junction smooth muscle in cross section, these muscle bundles appear to form a structure analogous to the shutter of a camera (Fig. 26A.1). At baseline when these fibers are at rest and during passive filling, occlusion of the bladder outlet occurs. Realignment and coordinated relaxation of these fibers during micturition is critical if the outlet is to open and allow for low-pressure voiding. The trigone may be divided into a superficial and a deep smooth muscle layer, and continuity has been reported between the deep layer of the detrusor (123,137) and ureter (333).

FIGURE 26A.1. Smooth muscle bundles in the area of the bladder neck. (From Woodburne RT. Anatomy of the bladder. In: Boyarsky S, ed. *The neurogenic bladder*. Baltimore: Williams & Wilkins, 1967, with permission.)

Female Urethra

The adult female urethra is approximately 4 to 6 cm in length and 6 mm in diameter. It extends from the bladder neck behind the pubic symphysis and lies embedded in the anterior wall of the vagina until it reaches the meatus at the perineum. The wall of the female urethra is composed of an outer muscular layer and an inner epithelial layer. This inner epithelial layer generally is thrown into folds that form a mucosal seal (Fig. 26A.2), which is thought to contribute to the continence mechanism (373). The smooth muscle component extends throughout the length of the inner epithelial layer, and most agree on the existence of an inner longitudinal layer (137,332). Tanagho (332) believes that the outer longitudinal layer is substantial and represents a direct continuation of the detrusor layer, but this is disputed by Gosling (137,138) and Dorschner and co-workers (111), who believe that no such continuity exists. Arner and associates (16) have shown that different shortening velocities for fibers exist within the inner and outer smooth muscle layers of the rabbit urethra. The urethral smooth muscle cells are embedded in ECM, which, according to Hickey and co-authors (147), may account for

the major structural component in the human female urethra. These distinctions will prove important in future research, considering how much active urethral smooth muscle "tone" is involved in maintaining continence. The striated component of the female urethra is discussed in a subsequent section.

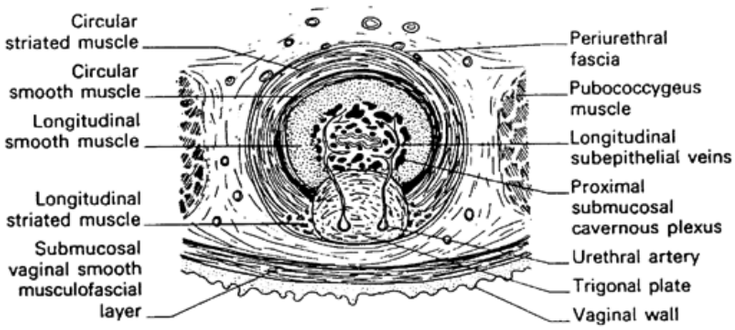

FIGURE 26A.2. Cross-sectional view of the female urethra showing the longitudinal arrangements of the smooth muscle fibers and the circular striated fibers. This diagram emphasizes the richly vascularized submucosal layer, which helps create a seal effect. (From Asmussen M, Miller A, eds. *Clinical gynaecologic urology.* Oxford: Blackwell Scientific, 1983, with permission.)

Male Urethra

The male urethra has been divided into prostatic, membranous, bulbar, and anterior zones, with the latter two zones functioning as conduits with minimal urodynamic significance. The preprostatic urethra has been described as being 1 to 1.5 cm in length and contains smooth muscle bundles embedded in collagen oriented in a distinct circular collar that becomes continuous distally with the prostatic capsule. The prostatic urethra is 3 to 4 cm long. The male posterior and membranous urethra contains an inner longitudinal and outer circular layer of smooth muscle, with poor development in the dorsal midline (331). These smooth muscle fibers are in continuity with the apex of the prostate, and distally with the bulbar urethra.

Anatomic Continuity Between Bladder and Urethra

Many authors support the view that trigonal smooth muscle bundles extend down into the urethra (193,330,360,361). This extension is consistent with the hypothesis that, during micturition, there is an opening and funneling of the bladder neck associated with a readjustment of the urethrovesical junction (angle) that depends on these anatomic relationships. Others disagree with this view and believe that the urethral smooth muscle is in no way connected with the trigone (137,246). A current view is that the unique physiology and pharmacology of the trigone and urethra are more likely to explain the funneling of the bladder neck seen with micturition (111) as opposed to anatomic relationships.

Striated Muscle Component

The once-classic view of the external sphincter—that of striated muscle fibers within the leaves of a "urogenital diaphragm" that, when contracted, will stop the urinary flow (352)—is no longer valid. The current view is that the urethral striated musculature has both an intrinsic component (i.e., within the urethral wall) and extrinsic or extramural components (42). The intrinsic layer, or *rhabdosphincter,* wraps around the urethral lumen in an oblique spiral pattern, and its fibers interdigitate with the outer muscular layer of the urethra. These fibers have a more circular orientation in the male, are thinner posteriorly, and extend from the verumontanum to the striated pelvic floor musculature. The middle third of the female urethra contains the most prominent intrinsic skeletal muscle, and it also is deficient in the posterior midline.

In both sexes, the distal end of the intrinsic striated muscle component is described as lying adjacent to a bulky skeletal muscle group oriented in the horizontal plane of the pelvic floor and encircling the membranous urethra. This is the classic description of the "external urinary sphincter" of standard anatomy texts. This extrinsic skeletal muscle is separate from the urethral wall despite anatomic apposition, and is related to the levator ani muscle group. The older literature implies a clear-cut separation between the intrinsic and extrinsic striated sphincter groups. In truth, this distinction cannot always be made on gross inspection of the sphincter, but relies on a histologic assessment. Oelrich (275) thinks that the skeletal muscle in the male urethra is derived from a single primordium extending from the bladder to the perineal membrane. The prostate, which evolves from glandular differentiation within the urethra,

grows predominately into the posterior midline and creates atrophy of these striated muscle fibers (Fig. 26A.3). This also can help explain why striated muscle fibers may be seen in radical prostatectomy specimens at points far removed from the apex.

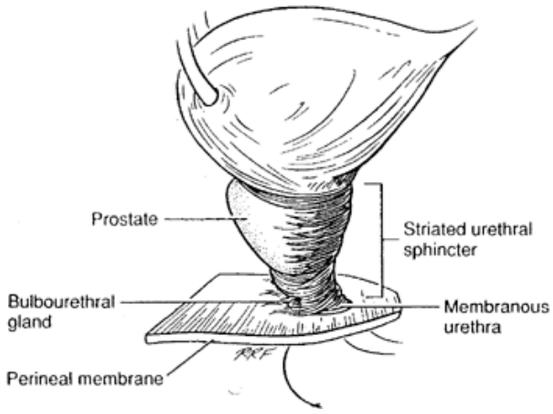

FIGURE 26A.3. This schematic representation conveys Oelrich's concept of the striated urethral sphincter in the male, which varies in its circumferential extent as it extends from the vesicoprostatic junction down to the level of the perineal membrane. (From Angermeir KW, Devine CJ. Anatomy of the penis and male perineum. *AUA Update Series* 1994;XIII:3, with permission.)

Oelrich (274) describes two striated muscle components in the female: one surrounding the urethra alone, and one enveloping the urethral and vaginal introitus. Both of these striated muscle groups become infiltrated with smooth muscle, making these descriptions histologic as opposed to surgical. A separate bundle of striated muscle fibers loop around the ventral aspect of the urethra and has attachments to the ischiopubic rami, serving as a "compressing" muscle. Again, it must be stressed that these muscles are all in continuity with one another and, taken together, form the urogenital hiatus of the pelvic diaphragm. The use of dynamic or functional magnetic resonance imaging (MRI) will help unravel the functional impact that these muscle groups have in maintaining continence. Mikuma and colleagues (250) reported on MRI scanning in young male volunteers and noted that, with pelvic floor contraction, the urethra thinned in the sphincteric area, and the entire urethra and prostate were pulled anteriorly toward the pubic bone, effectively narrowing the retropubic space (Fig. 26A.4).

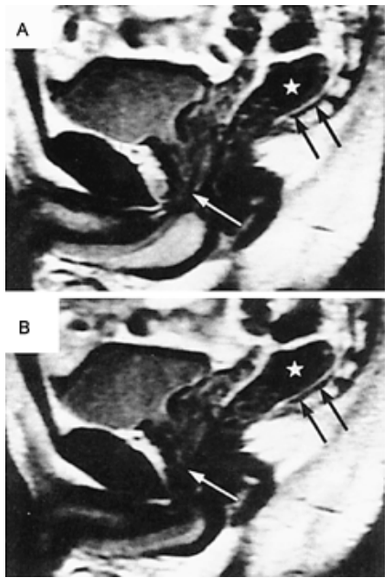

FIGURE 26A.4. Sagittal magnetic resonance images of the male pelvis taken at rest **(A)** and during contraction of the pelvic floor muscles **(B).** These functional magnetic resonance images show that with contraction of the pelvic floor there is an elevation of the prostate and bladder base such that the membranous urethra is elongated (an average of 0.5 cm) and the retropubic space narrows. (From Mikuma N, Tamagawa M, Morita K, et al. Magnetic resonance imaging of the male pelvic floor: the anatomical configuration and dynamic movement in healthy men. *Neurourol Urodyn* 1998;17:591, with permission.)

Sphincter Concept

Smooth Sphincter

No classic anatomic "sphincter" exists at the bladder neck that is analogous to the coils of the anal sphincter. Instead, there is a shutterlike opening (Fig. 26A.1) that consists of swirls of smooth muscle bundles that are rich in collagen and elastin. Thus the tone exerted on the lumen of the bladder neck is dependent on the passive recoil forces caused by the ECM components and the active tone of the smooth muscle. Tone in this region and in the proximal urethra increases as the bladder fills, so that urethral pressure exceeds intravesical pressure. With normal micturition, this smooth muscle ("sphincter") tone is reduced, then followed by a rise in detrusor contractile force to produce low-pressure voiding. A functional obstruction can occur at this point resulting from incoordination between the bladder neck and the detrusor (smooth sphincter dyssynergia), although this is rare clinically. Dyssynergia is far more likely to result from incoordination between the detrusor and the striated sphincters.

Striated Sphincters

The striated sphincters comprise both intrinsic and extrinsic components surrounding the female urethra and the posterior

male urethra. This sphincter is not essential for continence if the bladder neck is competent (146). For example, in a male with a pelvic fracture and urethral avulsion injury, the external sphincter may be rendered incompetent, yet the patient remains continent. However, if this patient were to undergo a transurethral resection of the prostate (TURP) with cuts into the bladder neck, he very well could be rendered incontinent. *Striated detrusor sphincter dyssynergia* refers to the involuntary contraction of the striated external sphincter during a bladder contraction in a patient with neurologic disease, and implies a neurologic disease or lesion is present between the brainstem and sacral cord. The one exception to this is the urodynamic findings of what appear to be detrusor sphincter dyssynergia in the absence of any "overt" neurologic findings on clinical examination or MRI. In its extreme case, this can result in a trabeculated bladder with upper urinary tract decompensation, also known as the *Hinman syndrome,* which is seen almost exclusively in children (149).

SMOOTH MUSCLE STRUCTURE AND FUNCTION

The literature describing the physiology, structure, and molecular basis for bladder smooth muscle function continues to expand. In this section, traditional views of smooth muscle are presented and integrated with newer molecular concepts. Normal function is emphasized, but some examples of how bladder smooth muscle changes in response to outlet obstruction are offered.

Structure

Smooth muscle is composed of long slender cells, whose exact dimensions vary greatly depending on the conditions under which the tissue is studied. The average diameter of the fibers is 2 to 5 μm and the length ranges from 50 to 200 μm (298,347). Cell length, diameter, and volume are some of the most difficult experimental measurements to make, because they depend on the degree of distention that the smooth muscle is subjected to at the time the tissues are fixed. The cell membrane surface is coated with numerous pits or indentations, called *caveolae,* which probably are involved in the uptake and release of humoral substances from the muscle cell (Fig. 26A.5). These caveolae increase during normal development in rat bladder (363), and diminish with aging (125).

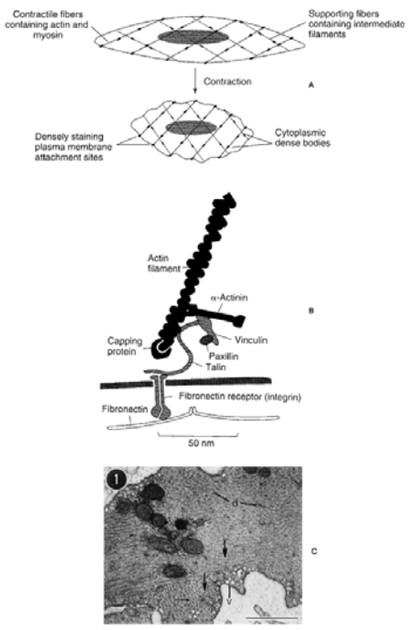

FIGURE 26A.5. A: A schematic representation of how smooth muscle contracts, which features the role of actin and myosin *(dark lines)* and their relationship to the intermediate filaments of the cytoskeleton *(light lines)*. As the actin and myosin interact, these fibers shorten to produce a significant change in cell dimensions. Changes in the ratios of actin, myosin, and intermediate filaments will alter the cell's ability to contract. **B:** A schematic representation of the complex cytoskeletal elements involved in anchoring the contractile filaments to the plasma membrane. These complex interactions allow for the force of the contractile elements to be transmitted to the plasma membrane and, via the transmembrane fibronectin receptor (integrin), allow for force transmission to the extracellular matrix. **C:** An electron micrograph of a smooth muscle cell taken from the abdominal aorta fixed *in situ* and cross sectioned. Shown are the thick filaments (myosin) *(large arrows)* and small filaments (actin) *(small arrow)*. Dense bodies *(d)* and surface vesicles or caveolae *(v)* also are identified. The bar in the lower right-hand corner is 1 micron. (From Alberts B, Bray D, Lewis J, et al. *Molecular biology of the cell,* 2nd ed. New York: Garland Publishing, 1989; and Chacko S, Blose SH, Adelstein RS. Phosphorylation and calcium regulation of actin activated ATPase activity of myosin isolated from cultured aortic and vas deferens smooth muscle cells. In: Casteels R, ed. *Excitation contraction coupling in smooth muscle*. New York: Elsevier/North Holland Press, 1977, with permission.)

Within the cell membrane, the cytosol contains several major organelles and a growing list of thick and thin filaments that merit discussion. The classic organelles of smooth muscle include the nucleus, mitochondria, ribosomes, and endoplasmic reticulum. Smooth muscle contains myosin and actin similar to striated muscle systems, but the myosin content is far less and actin is the predominant myofilament (Fig. 26A.5). With the increasing availability of monoclonal antibodies, a whole new family of cytoskeletal filament proteins have been described (224). Vimentin, desmin, spectrin, and caldesmon are thought to offer structural support and have been identified in bladder smooth muscle, with changes in their composition noted after outlet obstruction (74,219,371). Ankyrin, vinculin, talin, and tensin serve to anchor these filaments to the cell membrane (Fig. 26A.5). Controversy remains regarding whether these elements act merely as passive supports or, as in the case of caldesmon, actually contribute to the generation of contractile force (68,219).

Less controversy exists regarding the roles of actin and myosin in generating contractile force in bladder smooth muscle. As in striated muscle, these two proteins interact after phosphorylation of the 20-kilodalton (kDa) myosin light chain to allow for advancement of the myosin molecules along the actin filaments. The finer points of this interaction and its molecular basis are discussed in the section on excitation-contraction coupling. It is known that myosin filaments are present at ratios of 1:10 as opposed to the 1:1 ratio seen in striated muscles. Despite this difference, smooth muscle is capable of exerting tremendous contractile force equal to, and in some cases surpassing, striated muscle. However, smooth muscle has a much slower velocity of contraction.

In addition to these intracellular elements that contribute to smooth muscle tone and contractility, a major consideration is the role of the ECM. It is impossible to offer a current review of bladder smooth muscle without discussing the role of the connective tissue. Unlike skeletal muscle, which transmits its force by tendons attached to bone, smooth muscle cells can transmit force only by contracting against one another. The fibroblasts, collagens, elastins, and glycosaminoglycans are the elements of the ECM that serve to bind the smooth muscle cells together. Depending on the way in which the morphometric measurements are made, this matrix component may occupy up to 50% of the cross-sectional area on histologic examination. Molecular aspects of the ECM are discussed in greater detail in a subsequent section.

Fiber Arrangement and Spread of the Contractile Impulse

Two broad categories of smooth muscle have been proposed on the basis of general physiologic characteristics: multiunit and unitary (or syncytial). The multiunit smooth muscle receives a rich 1:1 innervation between the neurons and muscle cells. A thin glycoprotein layer shields these cells from one another so that they act truly independently in response to stimulation. These systems tend to be under direct control of the nervous system, and such an arrangement confers major advantages for fine muscle control. Examples include the ciliary and iris muscles of the eye. In contrast, unitary (or syncytial) smooth muscle differs by receiving a much less extensive innervation, with cells arranged

in sheets or bundles. Instead of having insulating glycoproteins between the adjacent cells, gap junctions function as bridging ion channels connecting one cell to another. Motor function in these muscle groups is highly dependent on myogenic conduction from one fiber to another. Classic examples of such muscle groups are the ureter and uterus. Despite the fact that no gap junction proteins have been identified in bladder smooth muscle, it appears to share some characteristics of both multiunit and unitary types (78). Using a guinea pig model, Mostwin and colleagues (255,256) have demonstrated that bladder smooth muscle has some cable properties, implying that some cell-to-cell communication exists.

Innervation

Some current concepts in the structural relationships of the peripheral autonomic nervous system to the bladder smooth muscle cells should be reviewed (153). Neuroeffector junctions are elaborate in smooth muscle, with long neurons sprouting off small varicosities 1 to 2 μm in diameter in a zone that is free of enveloping Schwann cells. As the nerve is depolarized along its axis, these varicosities release their neurotransmitters from stored secretory vesicles. Each varicosity is located adjacent to a cleft 20 to 50 μm wide across which these transmitters diffuse (Fig. 26A.6). Vesicles containing neurotransmitters are a histologic hallmark of the autonomic nerve endings, and are identified via immunohistochemical techniques (169).

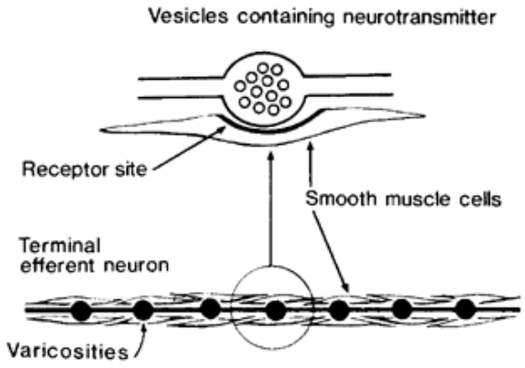

FIGURE 26A.6. Peripheral autonomic neuroeffector junction. (From Mundy AR. Clinical physiology of the bladder, urethra, and pelvic floor. In: Mundy AR, Stephenson TP, Wein AJ, eds. *Urodynamics: principles, practice, and application.* New York: Churchill Livingstone, 1984, with permission.)

Excitation-contraction Coupling

Once a neurotransmitter crosses the postsynaptic cleft, the molecular changes that lead to force generation are complex. The overall process of force generation following ligand binding is called *excitation-contraction coupling*. It is useful to divide this general topic into two distinct headings: (a) the molecular events leading to cell contraction, and (b) those events associated with cell relaxation. A simplified schematic representation of these molecular events is outlined in Fig. 26A.7 (contraction) and Fig. 26A.8 (relaxation), and serve as a useful starting point for this discussion.

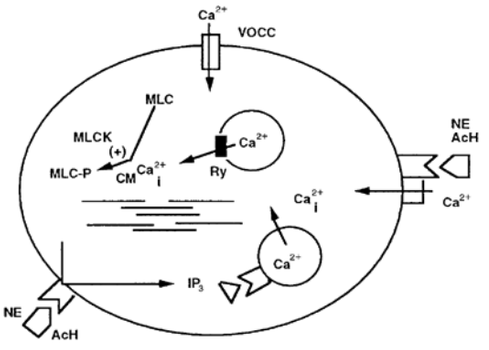

FIGURE 26A.7. A schematic outline of the events underlying excitation-contraction coupling. Excitation is induced by a ligand (NE/AcH) binding to specific cell surface receptors (adrenergic or muscarinic), which produces a rise in cytosolic free calcium. This increased cytosolic calcium may be secondary to extracellular calcium influx across the plasma membrane, or via calcium release from intracellular storage sites triggered by one of several secondary messengers such as IP_3. The release of intracellular calcium takes place via a calcium channel that, in many species, is sensitive to the effects of ryanodine *(Ry)*. The rise in free cytosolic calcium triggers the phosphorylation of myosin light chain kinase, which initiates the development of contractile force. CM, cellular matrix; MLC, myosin light chain; MLCK, myosin light-chain kinase; MLC-P, myosin light chain phosphate; VOCC, voltage-operated calcium channel.

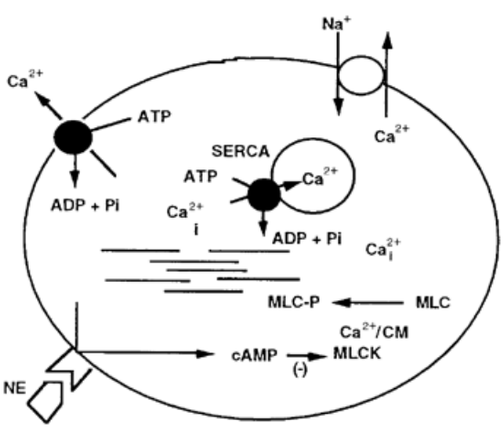

FIGURE 26A.8. A schematic outline of the events associated with relaxation of smooth muscle. The process of relaxation begins as the cytosolic free calcium concentration drops back into the normal range. This is accomplished by several mechanisms, including active pumping into intracellular storage sites by the sarcoplasmic–endoplasmic reticulum calcium ATPase (SERCA); active pumping of calcium out across the plasma membrane; and a passive exchange of sodium and calcium across the plasma membrane driven by the sodium gradient. In addition, the binding of epinephrine to a ß-receptor triggers an increase in cyclic adenosine monophosphate (cAMP), which in turn inhibits the effects of myosin light-chain kinase (MLCK). ADP, adenosine diphosphate; ATP, adenosine triphosphate; CM, calmudulin; MLC, myosin light chain.

Resting smooth muscle cells maintain a cytosolic free calcium–ion concentration of less than 0.1 μM. Total intracellular calcium concentrations are higher (most intracellular calcium is protein bound), but only free cytosolic calcium is involved in generating force and maintaining tone. With excitation of the smooth muscle cell by either ligand-specific receptor stimulation or membrane depolarization, the first step in force generation is a rise in cytosolic free calcium levels above a threshold level of 20 to 30 nM, with full activation occurring at levels approaching 300 nM (145,298,362). Given its central role in initiating contraction,

the cell is adapted with a number of mechanisms to help maintain calcium homeostasis (167,288). Cytosolic calcium may rise owing to ligand binding to a receptor coupled to an adjacent ion channel, which then opens allowing for calcium influx (Fig. 26A.7). Alternatively, such a receptor might activate a G-protein that couples this binding to the generation of a second messenger. G-proteins are located on the cytoplasmic face of the plasma membrane and serve to couple the binding of a ligand and its receptor with a secondary intracellular event such as the production of cyclic guanosine monophosphate (cGMP) (132,221). This second messenger then serves to activate the release of calcium from intracellular storage sites. The second messenger family may include cyclic adenosine monophosphate (cAMP), guanosine triphosphate (GTP), and inositol triphosphate (IP_3), and is discussed subsequently. In the case of the bladder body, the muscarinic cholinergic receptors are activated by the binding of acetylcholine to initiate the influx of calcium, which triggers contraction. In addition to the receptor-activated calcium channels, voltage-sensitive channels exist within the plasma membrane, which are opened with changes in the cell's membrane potential. Unlike neurons in which sodium influx alters the membrane potential, calcium ion influx accounts for the cell membrane depolarization in bladder smooth muscle.

The smooth muscle cell then must transform this signal, in the form of a rise in free cytosolic calcium, into force mediated by several steps and protein interactions. Calmodulin is a calcium-binding protein with an affinity constant for the free calcium ion of 100 nM. This means that as soon as the free cytosolic-cell calcium exceeds 100 nM, the calmodulin calcium-binding sites begin to fill, altering the three-dimensional conformation of this molecule (247). Once this conformational change has taken place, the calmodulin is able to bind to and activate the enzyme, myosin light-chain kinase (MLCK) (4). This enzyme serves the crucial function of phosphorylation of the 20-kDa myosin light chain (LC_{20}), with adenosine triphosphate (ATP) as the necessary cofactor. The actin-activated adenosine triphosphatase (ATPase) activity is increased with phosphorylation (67,69), and myosin light chain phosphorylation has been correlated with force development (165,259). With the light chain phosphorylation, the actin and myosin filaments interact, changing their three-dimensional conformations to slide past one another (Fig. 26A.9). This cycle may be repeated until the stimulus has been removed or the muscle reaches a new resting length. The events that lead to smooth muscle cell contraction are summarized in Table 26A.1 .

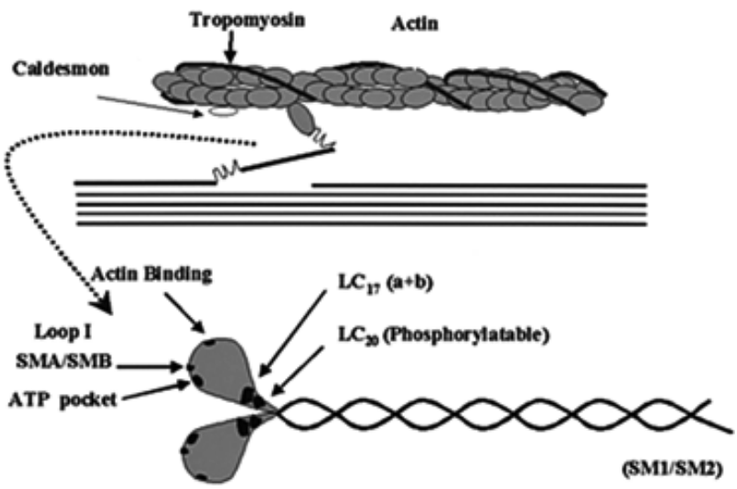

FIGURE 26A.9. This figure demonstrates a schematic representation of the smooth muscle contraction apparatus. The *top portion* of this figure shows a myosin head protruding from the thick filament to interact with the actin of the thin filament. A caldesmon molecule with its N-terminal region binding to actin and its C-terminal region binding to the flexible hinge region of the myosin is also indicated. The *bottom portion* shows a detailed view of the myosin molecule. The regions of the myosin heavy chain where the SM1/SM2 (C-terminus) and SMA/SMB (near the ATP binding site) isoforms differ, as well as the actin-binding region are shown. Also shown are the sites where the pairs of the myosin light chain (LC_{17} and LC_{20}) wrap around the myosin heavy chain. ATP, adenosine triphosphate. [From DiSanto ME, et al. Lower urinary tract physiology and pharmacology. *Curr Urol* 2001 *(in press)*.]

1. Binding to cell surface receptors triggers a rise in free cytosolic calcium
2. Extracellular calcium influx and/or release from intracellular storage sites
3. Cytosolic calcium in excess of 0.1 μM binds to calmodulin
4. The Ca^{2+} calmodulin complex binds to myosin light-chain kinase
5. Myosin light chain is phosphorylated
6. Force is developed as myosin and actin interact

TABLE 26A.1. EVENTS LEADING TO SMOOTH MUSCLE–CELL CONTRACTION

The relaxation of smooth muscle begins when the agonist binding to the receptor is degraded, either by uptake of the ligand-receptor complex into a vacuole or by enzymatic degradation within the neuromuscular junction. Stimulation

of ß-adrenergic receptors or nitric oxide (NO) also may result in smooth muscle relaxation. Regardless of which of the aforementioned mechanisms is used, relaxation of the cell is accomplished by pumping calcium out of the cell or into sequestration sites within the cell (i.e., sarcoplasmic reticulum). These ion pumps translocate the calcium ion against large gradients, allowing for calcium concentrations of 2 mM in the serum, and less than 300 nM in the cytosol. These pumps, called the *Ca^{2+}-Mg^{2+}-ATPases*, consume energy in the form of ATP. Three sarcoplasmic–endoplasmic reticulum calcium ATPase (SERCA) isoforms exist: type I, fast (skeletal and cardiac muscle); type II, slow (slow twitch fibers and smooth muscle); and type III, non-muscle. Both the plasma membrane and SERCA ATPases share in common a site for binding of the calcium-calmodulin complex and cAMP (62). This implies that as soon as the muscle is stimulated, the cell already is activating its system for the restoration of calcium homeostasis.

In addition to the previously mentioned two pumps (located on the plasma membrane and sarcoplasmic reticulum) that consume ATP, a third "pump" exists in most systems that allows for extrusion of cell calcium. The sodium calcium exchanger is a passive system that allows for ion exchanges along an electrochemical gradient (290). Under ordinary circumstances, the pump operates to extrude one calcium ion from the cytosol by exchanging it for one sodium ion on a one-to-one molar ratio. When the cell membrane is depolarized, this pump may become uncoupled and allow for calcium influx. This is an exchange pump that does not use energy directly to affect these ion transfers (energy is still required because the pump depends on the sodium gradient across the membrane that is maintained by a sodium-potassium ATPase). A brief outline of the events contributing to smooth muscle–cell relaxation is presented in Table 26A.2 .

1. Cytosolic calcium exceeds 0.1 μM and binds to calmodulin
2. The calcium calmodulin complex activates the Ca^{2+} ATPases of both the plasma membrane and the sarcoplasmic reticulum
3. In response to β-agonists, cAMP increases and binds to the Ca^{2+} ATPases
4. Nitric oxide (NO) also stimulates calcium sequestration via increasing cGMP
5. The Na-Ca exchanger pumps calcium out of the cytosol
6. The receptor ligand complex is inactivated by vacuolization within the cell
7. Degradative enzymes (acetylcholinesterase) break down the excess neurotransmitter within the cleft

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate.

TABLE 26A.2. EVENTS LEADING TO SMOOTH MUSCLE–CELL RELAXATION

The resting membrane potential of smooth muscle cells is maintained on the order of –50 to –60 mV (i.e., 30 mV less than striated muscle). In unitary (syncytial) smooth muscles such as ureter, the action potentials are similar to those in skeletal muscle. In pure multiunit smooth muscle (such as the iris), action potentials do not seem to occur. In some visceral smooth muscle, the resting potentials change with time until the threshold level of –35 mV is achieved, triggering depolarization and subsequent contraction. In the ureter, pacing cells perform this function, which induces depolarization that then spreads downstream as a result of cell-to-cell coupling (356). In the bladder, there is no evidence of such a pacing system, and some question exists regarding whether the bladder has spontaneous slow-wave fluctuations. From the standpoint of bladder function, which is to store urine for prolonged periods at low pressure, such a system would be counterproductive.

Intracellular calcium stores exist within bladder smooth muscle that may be released upon the arrival of a specific intracellular signal (84,254,366,367). The sarcoplasmic reticulum of striated muscle has a detailed and well-described histologic structure. In smooth muscle, the sarcoplasmic reticulum lacks this classic histologic appearance and consists of small vacuoles of the endoplasmic reticulum that have differentiated into performing this function. Second messengers implicated in the release of such intracellular calcium stores include IP_3, cGMP, and even free Ca^{2+} (calcium-induced calcium release) (314). Calcium release from the sarcoplasmic reticulum into the cytoplasm occurs via the ryanodine-sensitive ion channel. In the rabbit, the ryanodine channel is functionally active, and its expression appears to be developmentally regulated (136,367). However, despite being present in bovine and murine (157) bladder smooth muscle, its physiologic role could not be demonstrated functionally. This distinction is important because it illustrates two major points about this literature:

1. Molecular findings, such as an ion channel being present based on a ligand-binding study or an immunoblot, must always be correlated with a functional (i.e., physiology) study.
2. Variations do exist between species and must be considered when comparing studies.

The molecular events that comprise the process of excitation-contraction coupling and force generation in smooth muscle have been simplified for the sake of this discussion. A large and growing literature exists for each of the points that have been mentioned (37,252). The next section illustrates how two of the components mentioned in this section are altered by partial bladder outlet obstruction.

Molecular Consequences of Bladder Outlet Obstruction

The challenge of understanding bladder function at a molecular level is demonstrated nicely by considering myosin heavy-chain (MHC) expression, a critical element of the molecular motor for contraction. The MHC expressed in smooth muscle is the product of alternative splicing at several sites within the precursor mRNA molecule. As shown in Fig. 26A.9, two major isoforms of MHC exist that are the result of changes at the tail carboxyl terminus. These changes result in the SM1 and SM2 MHC isoforms, which differ slightly in their molecular weights allowing for their resolution by SDS-polyacrylamide gel electrophoresis. SM1 and SM2 MHC isoform expression have been shown to be altered by normal development (219) and obstruction (70,350). However, the shift from SM1 to SM2 has not been correlated consistently with alterations in the ability of smooth muscle to generate tension or velocity of contraction.

Additional MHC isoforms are produced by insertion of a small 21-nucleotide sequence that encodes an additional seven-amino-acid stretch in the N-terminal region near the ATP binding site to produce the SMB MHC isoform (Fig. 26A.9B). The MHC SMB isoform has been associated with a higher rate of ATPase activity (the active site for the ATPase is adjacent to this insert) and a higher shortening velocity (107,170). Comparison of the relative SMB expression between the aorta (minimal) and bladder body (maximal) correlates with the roles that these structures play. Structures that must undergo rapid contraction will express the SMB isoform, as opposed to aorta, in which tone is merely slowly adjusted. In the lower urinary tract, the amount of SMA MHC isoform is increased in the urethra (159,364). Following partial outlet obstruction, MHC expression is altered in the urinary bladder. A shift has been reported in the SM1-to-SM2 ratio after outlet obstruction, which is reversed after the obstruction is relieved (68,70). Similarly, the expression of SMA and SMB isoforms is altered by obstruction, and then shows signs of recovery after the reversal of the outlet obstruction and recovery (71) (Fig. 26A.10).

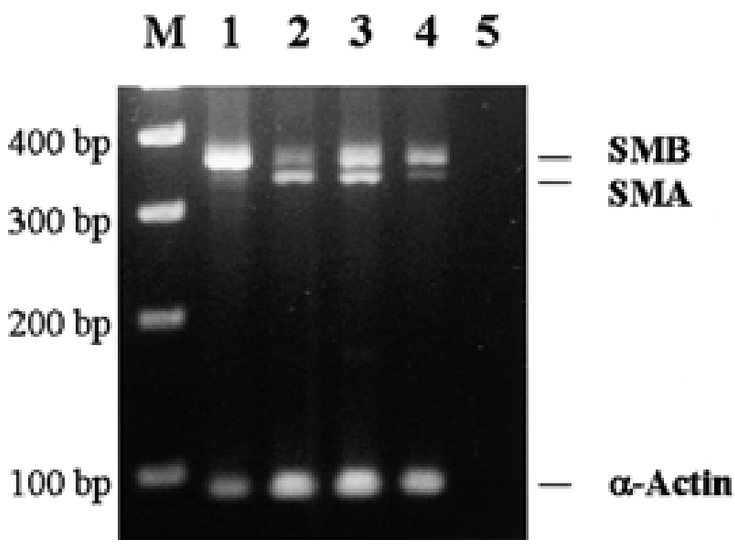

FIGURE 26A.10. Modulation of the SMA/SMB composition by the bladder in response to partial bladder outlet obstruction (PBOO). The expression of bladder mRNA coding for myosin isoforms with (SMB) and without (SMA) the seven-amino-acid insert in response to PBOO was determined using reverse transcriptase-polymerase chain reaction (RT-PCR) with specific upstream and downstream nucleotide probes designed to amplify a region of the myosin heavy chain (MHC) containing this alternative splice site. The normal bladder smooth muscle contains predominantly the SMB isoform *(lane 1),* whereas smooth muscle from 7-day obstructed bladder expresses significant amounts of the noninserted SMA mRNA transcript *(lane 2)*. Upon reversal of the obstruction for 7 days *(lane 3),* the expression of SMA declines, reaching near-normal levels by 14 days postreversal *(lane 4)*. *Lane 5* is a negative control in which no RT was added to the PCR reaction. Primers that specifically amplify α-actin were coamplified as an internal standard. A 100-bp DNA ladder as molecular size standard also was run *(lane M)*.

The generation of active force by smooth muscle takes place when the 20-kDa myosin light chain is phosphorylated by MLCK. Initial reports suggested that the degree of light chain phosphorylation is unaffected by obstruction. However, Su and Moreland (323) have offered evidence to suggest that although maximal light chain phosphorylation values are not affected by obstruction, the basal level of phosphorylation is increased significantly. They also have shown that although the peak tension developed in bladder smooth muscle strips is unaffected by the obstruction, the velocity of contraction drops tenfold. One possible mechanism for this elevated baseline phosphorylation is raised by the demonstration of alterations in the sarcoplasmic reticulum, which could produce altered basal cytosolic calcium. Other possible mechanisms for such a finding include alterations in the kinase and phosphatase pathways.

The existence of the slow isoform of the Ca^{2+}-Mg^{2+}-ATPase (SERCA2) has been confirmed in bovine and rabbit bladder smooth muscle. Protein and mRNA for SERCA2 expression in rabbit bladder increase with normal development while the bladder is doing increasing volume work in the absence of anatomic obstruction (366,368). Ryanodine increases significantly during normal development (136). Loss of SERCA2 and ryanodine expression also has been reported following partial outlet obstruction in a rabbit model, implying that major perturbations are taking place in the sarcoplasmic reticulum (Fig. 26A.11) (318,319,320 and 321,368,369). These findings are noted in the absence of any major shifts in the expression of the voltage-operated calcium

channels, suggesting a strong association between the presence of functional sarcoplasmic reticulum and the bladder's ability to empty. These alterations in the proteins of the sarcoplasmic reticulum return toward normal only in those bladders that experience recovery of function after the obstruction is relieved. Alterations in these calcium-regulatory proteins would suggest that basal cytosolic calcium rises with significant outlet obstruction, which in turn may result in altered contractile performance or serve as a signal to trigger cellular hypertrophy.

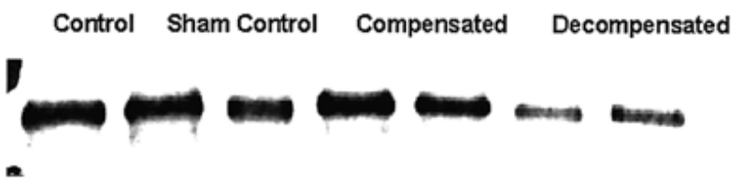

FIGURE 26A.11. A Western blot showing the loss of sarcoplasmic–endoplasmic reticulum calcium ATPase (SERCA)-2 expression following outlet obstruction for the categories of response. Equal amounts of membrane protein were subjected to SDS gel electrophoresis, and bands were visualized with a primary monoclonal antibody to SERCA2 and a chemiluminescence detection system coupled to a secondary antibody. Control and sham control bladders had no change in terms of bladder mass, voiding frequencies, voided volumes, or *in vivo* and unsedated videourodynamic performance. In contrast, bladder mass, voiding frequencies, and voiding pressures were elevated in the compensated group and significantly elevated in the decompensated group. The average voided volumes declined in both groups following outlet obstruction. Bladder decompensation was accompanied by a loss of SERCA2 expression, which was mediated by a downregulation of mRNA expression (Northern blot not shown). (From Stein R, Hutcheson JC, Gong C, et al. The decompensated detrusor III: the impact of bladder outlet obstruction on SERCA protein and gene expression. *J Urol* 2000;164:1026, with permission.)

It is clear that the preceding paragraphs are simply a beginning in terms of our ability to understand the molecular basis for smooth muscle function after bladder outlet obstruction. Other findings noted following outlet obstruction include bladder wall hypoxia (19,40,41,141), alterations in mitochondrial function (206,345), ECM deposition (127,287), and alterations in the nervous system (98), to name a few. Each of these pathways will be investigated fully in the next 10 years, using the ever-more sophisticated tools of molecular biology.

Passive Properties

If a strip of bladder smooth muscle is stretched, a sharp rise in the tension recorded by a force transducer will be seen, followed by a rapid decline to a new equilibrium (Fig. 26A.12). There is an energy cost for increasing the length of the bladder smooth muscle strip, which has several components.

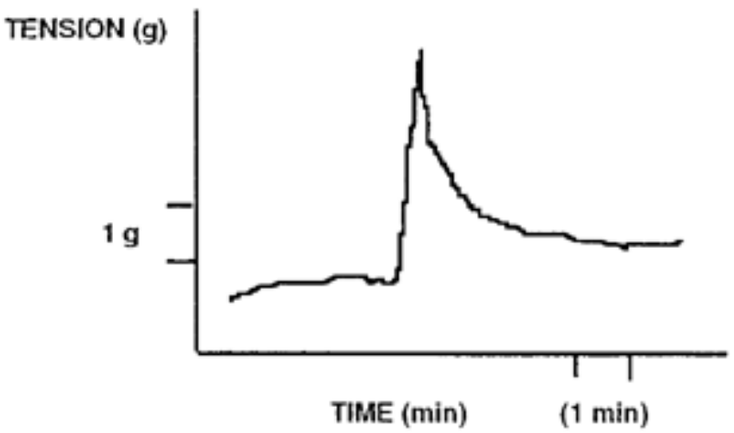

FIGURE 26A.12. The length-tension relationship for bladder smooth muscle as measured on a recording strip. A muscle strip is suspended in an organ bath with one end attached to a force transducer. The muscle strip is stretched rapidly by 25% of its resting or slack length. The recorded tension rises rapidly, then falls quickly to a new equilibrium value. The strip's resistance to deformation has at least four components: (a) baseline actin-myosin cross-bridging; (b) a transient rise in intracellular calcium during the deformation; (c) the cytosol and cytoskeleton of the cells must undergo a realignment; and (d) the extracellular matrix.

1. It is necessary to overcome the actin-myosin interactions that are present while the muscle is resting at equilibrium. Even in a muscle that is not actively contracting, actin-myosin cross-bridges are formed, and their realignment expends energy.
2. As the muscle is stretched, there is a transient rise in intracellular calcium, which triggers new actin-myosin interactions.
3. With all of its intrinsic components, the cell itself offers resistance to deformation because it must undergo a geometric (cytosol and cytoskeleton) reorientation.
4. The ECM components also offer a resistance to this displacement.

A simplistic model might consider each of these components as separate springs arranged in parallel in a system that one is trying to pull apart. Such a model might lead one to consider the application of Hook's law, which states that the force of displacement *(f)* is equal to a constant *(K)* multiplied

by the displacement length *(x):* (f = Kx). However, bladder smooth muscle does not follow Hook's law, because an additional feature of the bladder is its elasticity. Once the bladder is mechanically deformed, it will slowly return to its baseline shape even in the absence of an active contraction, whereas the spring retains memory and, upon release, returns to its baseline state in a linear fashion (Fig. 26A.13).

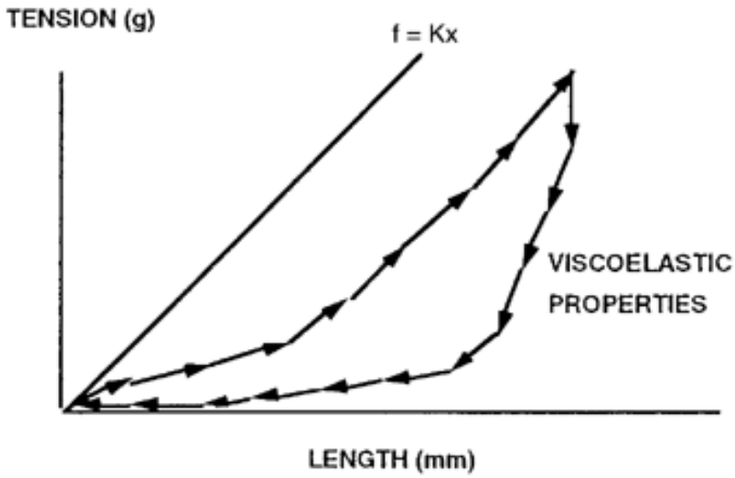

FIGURE 26A.13. The concept of elastic versus nonelastic properties. A spring would follow Hook's law, in which tension is related to displacement in a linear fashion. The normal bladder demonstrates viscoelastic properties. As shown in this diagram, progressive linear displacements produce very gradual increases in tension until a critical length is reached. Furthermore, if this process is reversed and an equal displacement is made in the reverse direction, there is a much greater fall in tension. These viscoelastic properties represent a complex interaction between the smooth muscle cells undergoing geometric rearrangements, and the extracellular matrix rich in collagens types I and III and elastin.

Extracellular Matrix

A full review of ECM physiology, structure, and molecular biology is beyond the scope of this chapter; however, the urologic aspects have been reviewed by Macarak and Howards (225,226 and 227). The ECM is a difficult component of smooth muscle to study, because these high-molecular-weight proteins are extremely insoluble. Selective proteases or cyanogen bromide–cleavage (which cleaves the peptide bond on the N-terminal side of a methionine residue) techniques break down these large macromolecules into peptide fragments that can be studied using more conventional methods of protein chemistry. In addition to the difficult protein chemistry, raising monoclonal antibodies for further research is extremely difficult, and only certain peptide fragments will have a unique enough antigenic configuration to produce a useful reagent. Despite these technical challenges, antibodies are now available that recognize the collagens in several species and these genes have been sequenced. Metabolism of the ECM consists of a biosynthetic and a degradative phase, and each is covered in this chapter, because they will increasingly become targets for future urologic therapy.

Four basic elements compose the ECM: fibrillar proteins (collagen and elastin), microfibrillar proteins, nonfibrillar proteins (the glycosaminoglycans), and fibroblasts. The cross-sectional area occupied by the matrix will vary from 30% to 70% depending on which tissues are sampled. Shapiro and associates (305) have used morphometric analysis to determine the muscle matrix ratio in both normal and pathologic states, and have demonstrated an increase in the matrix component in patients with spina bifida. However in cadaveric studies (163), no difference in smooth muscle cross-sectional areas was found between those bladders with and those without outlet obstruction. These kinds of studies are of great importance because they are performed in human tissues obtained at the time of surgery. However, chemical-based staining procedures will not differentiate the collagen types, a process that requires monoclonal antibodies or the techniques of peptide fragment analysis.

Collagen biosynthesis is a complex process that originates in either the fibroblast or the smooth muscle and involves the expression of complex gene structures. The DNA transcription into mRNA produces a long initial transcript that contains a great deal of additional genetic information (58). The mechanical, hormonal, and other unknown factors that regulate the expression of collagen genes are under active investigation. Following their biosynthesis, the collagen and elastin fibers are extruded from their cells of origin, and deposited in the extracellular space. Here, ionic bonds hold them in alignment until covalent linkages can form to provide long-term stability (Fig. 26A.14). Were these linkages not present, strength would be absent, and the smaller matrix molecules would be more soluble. The importance of

proper cross-linking is illustrated by the urologic findings in the Ehlers-Danlos syndrome, in which proper cross-linking is precluded resulting in a more compliant bladder with associated diverticula (105). Once this large mesh of fibrillar proteins is assembled, smaller microfibrillar proteins and glycoproteins are inserted into this matrix, giving it additional physiologic properties. Other complex matrix elements include fibronectin (which anchors the cell membrane to collagen), heparin, and complex glycoproteins (359). The urologic aspects of matrix biosynthesis have been commented on by Ehrlich (115), Macarak and Howards (225,226 and 227), and Rosenbloom and co-workers (297).

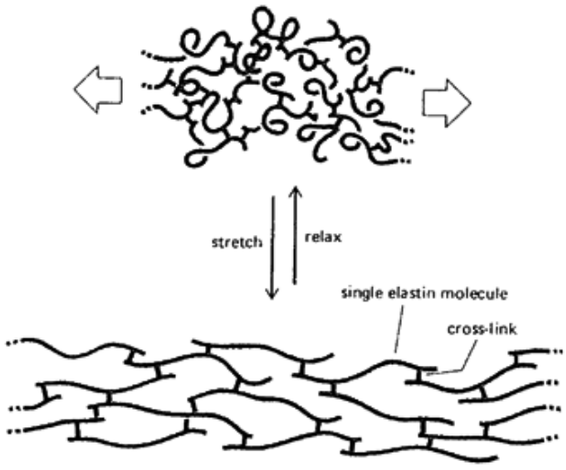

FIGURE 26A.14. Elastin molecules are joined together by covalent bonds to produce an extensive cross-linked network. The properties of the elastin molecule allow it to stretch and recoil over wide distances. The cross-links are essential in determining just how far the network may distend. (From Alberts B, Bray D, Lewis J, et al. *Molecular biology of the cell,* 2nd ed. New York: Garland Publishing, 1989, with permission.)

In response to outlet obstruction, bladder smooth muscle undergoes hypertrophy and expansion of the matrix component (237,346), which is partly reversible if the obstruction is relieved early enough. The cell's ability to synthesize matrix is balanced by its ability to break down the matrix, allowing for remodeling to take place. Fibroblasts and smooth muscle cells have acquired the ability to secrete collagenases capable of local action that remodel the immediate extracellular spaces. The collagenases are a family of metalloenzymes that predominantly use zinc as a cofactor [matrix metalloproteinases (MMP)] and are capable of breaking down collagen fibrils. The collagenases are assisted by other enzymes such as the elastases. In this manner, smooth muscle cells embedded within lattices of collagen are capable of undergoing realignment in response to stress, as has been shown experimentally (115).

The unopposed release of collagenases would result in detrimental tissue destruction; thus tissues have acquired a natural set of collagenase inhibitors. Tissue inhibitors of the metalloproteinase (TIMP) system are of growing importance in understanding how the remodeling process is kept in check. Obviously the regulation of the ECM depends on achieving a balance between synthesis and degradation (Fig. 26A.15). The urologic aspects of the collagenases and the TIMP system have been reviewed by Corcoran and associates (81). Peters and co-authors (286,287) have demonstrated a decreased production of MMP and an increase in TIMP levels following bladder outlet obstruction in the fetal lamb. These changes would alter the balance in favor of an increased deposition of the ECM.

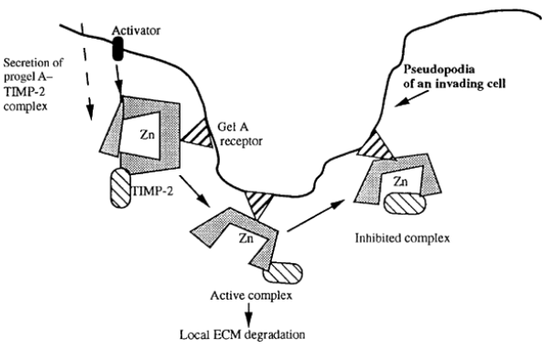

FIGURE 26A.15. The regulation of the extracellular matrix (ECM) is a delicate process balancing new synthesis against degradation. This diagram illustrates the degradation pathway via the cellular secretion of the matrix metalloproteinases, which require a zinc (Zn) cofactor. When activated in the extracellular space, these enzymes will break down the extracellular matrix products. In turn, these proteases will be regulated by inhibitors called *tissue inhibitors of metalloproteinases* (TIMP). If the TIMP concentrations rise in tissue, as has been shown in fetal bladder outlet obstruction, the net effect will be an increase in collagen accumulation. (From Corcoran ML, Kleiner DE, Stetler-Stevenson WG, et al. Regulation of matrix metalloproteinases during extracellular matrix turnover. In: Zderic SA, ed. *Muscle, matrix, and bladder function.* New York: Plenum Press, 1995, with permission.)

Striated Muscle of the Lower Urinary Tract

Skeletal muscle fibers exist in two major forms: fast and slow twitch. Skeletal fast-twitch muscle, like cardiac muscle, must be able to exhibit rapid bursts of contractile force and velocity over a wide range of physiologic demands. Fast-twitch

muscles are rich in myosin ATPase that catalyzes the actin-myosin interaction. In addition, expression of SERCA1, the fast isoform, will predominate in fast-twitch muscles. Examples of such muscle groups include the biceps and rectus femoris. Slow-twitch fibers are found in muscles that require more sustained tension, such as the pelvic levators, soleus, and abdominal wall muscles. These muscles show diminished actin-activated myosin ATPase activity and an increased expression of the slow isoform, SERCA2. No muscle group contains a pure population of fast or slow forms, but rather a blend of these fiber types.

Gosling and colleagues (140) suggested that the human external urinary sphincter primarily is composed of slow-twitch fibers. These fibers give rise to the background electromyographic activity seen during a cystometrogram (CMG). Within this sphincter exists a population of fast-twitch muscle cells that are “recruited” to increase this muscle's tone during sudden rises in intraabdominal pressure. This finding is not always correlated with the fiber distribution in other species. In the dog, only 35% of the fibers are slow twitch (27), whereas in the rabbit, fast-twitch fibers and fatigue-resistant, slow-twitch fibers are found (337). The intriguing potential for altering the fast- and slow-twitch content of the striated muscle of the outlet, by pacing or other forms of stimulation, continues to challenge investigators (329).

Summary of Smooth Muscle Properties

This section has been devoted to a discussion of the factors involved in the production of tone, force generation, and the bladder's viscoelastic qualities. These are complex biologic properties and, under normal circumstances alone, the challenge of understanding the underlying physiology and molecular biology is substantial. Out of necessity, this discussion has considered the smooth muscle as consisting of intracellular and extracellular components. In the ensuing sections, attention focuses on an understanding of the nervous system and its ability to interact with the bladder smooth muscle. Once the basic scientific principles underlying the functioning of the nervous system are reviewed, attention is directed to integrating these concepts with the preceding information.

NEURAL CONTROL OF THE LOWER URINARY TRACT

Overview

Micturition is a complex function that involves coordinated interactions between the smooth muscle of the detrusor, bladder neck, and urethra. The central and peripheral nervous systems serve to coordinate these actions. Neural regulation of the lower urinary tract requires the use of both the autonomic (involuntary) and somatic (voluntary) nervous systems. In the infant, voiding is autonomic and involuntary, but with normal maturation, somatic control over lower urinary tract function develops. In the somatic nervous system, one neuron arises in the anterior horn of the spinal column, exits the vertebral column, and courses to the muscle it serves. At the neuromuscular junction, the activated somatic neuron releases its neurotransmitter (acetylcholine). In contrast, the following points demonstrate why the autonomic nervous system is more complex:

1. Autonomic innervation involves a preganglionic fiber that travels from the spinal cord to a collection of synapses (e.g., ganglia or peripheral plexuses) from which a second postganglionic fiber travels to the neuromuscular junction.
2. These ganglia, or peripheral plexuses, give rise to distal autonomic fibers that tend to be nonmyelinated. In contrast, somatic nerves are myelinated in their entirety (myelination increases nerve conduction velocity).
3. Severing a somatic nerve may induce muscular atrophy, whereas ablation of an autonomic nerve has less pronounced changes. This may be interpreted as the autonomic system having a greater plasticity, because the extensive ganglionic connections make it easier to reroute the signals.

Classic Views of the Autonomic Nervous System

The classic sympathetic and parasympathetic categorization refers to an anatomic division of the autonomic nervous system. In the sympathetic system (Fig. 26A.16), the preganglionic

neurons exit the thoracic and lumbar spinal segments to reach the first synapse in one of three possible ganglia: (a) adjacent to the vertebral bodies (paraganglia), (b) in between the vertebrae and the organ (preganglia), and (c) located with the end organ (peripheral ganglia). The parasympathetic nervous system (Fig. 26A.17) differs in that the cranial or sacral preganglionic neurons exit the spinal column and travel long distances to peripheral ganglia, which are located either within or adjacent to the target organ. These observations apply to the portion of the autonomic nervous system controlling motor functions. For sensory roles, most of the autonomic nervous system's afferent fibers leave the organ and pass through the ganglia without making any synaptic contacts until the spinal column is reached. For both divisions of the autonomic system, preganglionic fibers are myelinated, whereas postganglionic fibers are not. In the classic view, the preganglionic neurotransmitter was acetylcholine, whereas the neurotransmitters of the postganglionic fibers were either acetylcholine (parasympathetic) or adrenergic (sympathetic). It is now clear that this view is an oversimplification.

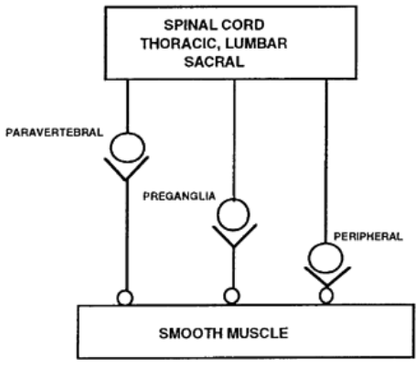

FIGURE 26A.16. A simplified schematic diagram of the sympathetic nervous system demonstrating the origins of preganglior fibers from three levels of the spinal cord. In addition, the ganglia may be divided into three categories depending on their anatomic location.

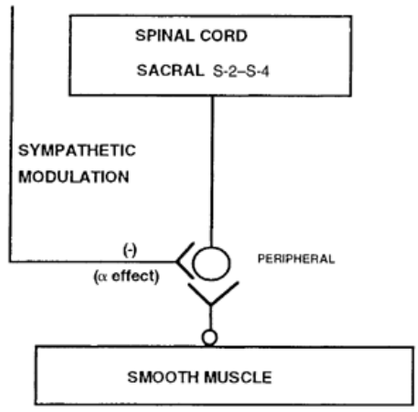

FIGURE 26A.17. A simplified schematic diagram of the parasympathetic nervous system demonstrating the origins of preganglior fibers in the sacral segments S-2 through S-4. The parasympathetic ganglia are located predominately near their organ of innervation. A major feature in this diagram is the sympathetic input into the ganglia, where adrenergic stimulation via α-receptors can produce an inhibitory effect on parasympathetic transmission.

Contemporary Views of the Autonomic Nervous System

The motor innervation of the lower urinary tract primarily is supplied by postganglionic neurons, also known as the *urogenital short neuron system*, which arise from ganglia within or in extremely close proximity to the bladder wall. A complex intraganglionic network of fibers link one ganglion to another and can modulate the activity of these synapses. Evidence suggests that in some cases urogenital fibers arise from the smooth muscle, travel to the peripheral ganglion, and synapse with an efferent neuron (which triggers a muscle response), all of which takes place independently of the spinal cord (161). It is also now accepted that the sympathetic system via α-receptors may act at the parasympathetic ganglia to modulate motor activity to the bladder (96,97) (Fig. 26A.17).

The traditional autonomic neurotransmitters were acetylcholine and norepinephrine. It now is apparent that many other molecules serve as neurotransmitters within the central and peripheral nervous system. These noncholinergic nonadrenergic neurotransmitters include ATP, serotonin, histamine, prostaglandins, peptides, and nitric oxide, and most likely play a critical role in the modulation of autonomic neurotransmission. In the traditional view, one neuron delivered one neurotransmitter to the effector endplate; it now is known that single neurons contain packages of different transmitters that often are released in groups. A currently accepted concept is of a cotransmitter—a molecule or peptide that alters the response of a postjunctional cell to the primary neurotransmitter.

Neurotransmitters and Receptors

Once the appropriate neuron is stimulated, an action potential travels down the axon to the synapse, and via an increase in calcium ion concentration in the cell, the secretory vesicles empty their transmitters into the postsynaptic cleft. This neurotransmitter crosses the postsynaptic membrane to reach the cell membrane of the smooth muscle. On this membrane, cell surface receptors are present that recognize the neurotransmitter and bind it in a specific manner. This interaction between ligand and receptor triggers the process of excitation-contraction coupling by initiating a rise in the free cytosolic-calcium concentration within the target or effector cell.

Cholinergic Receptors

Cholinergic receptors are membrane proteins to which acetylcholine binds to exert its effects as a neurotransmitter. Neurons whose transmission is cholinergic include somatic fibers, all preganglionic autonomic fibers, and all postganglionic parasympathetic fibers. The two major subdivisions of cholinergic receptors are (a) nicotinic and (b) muscarinic. This classic terminology resulted from an old observation that the alkaloid muscarine inhibits some cholinergic transmission, and low doses of nicotine mimic acetylcholine effects at other sites. The nicotinic receptors are found in skeletal-muscle motor endplates and in the autonomic ganglia. These nicotinic sites are not identical, and their structures, which are composed of six high-molecular-weight

subunits, are very complex. Recent evidence suggests they have a role in the autonomic control over bladder function (106,114).

The muscarinic receptor is found in all autonomic effector cells such as sweat glands, large and small bowel, gallbladder, and bladder. There are at least five subtypes of muscarinic receptors, and these differ in terms of their anatomic location and the effects they produce upon being activated. The muscarinic-receptor proteins are classified as M_1 through M_5. The capital "M" designates the protein, whereas the lower-case "m" defines the message RNA coding for these receptors. This distinction is important because the muscarinic-receptor proteins are similar enough in structure that their biochemical differentiation becomes quite difficult. For example, it has been possible to distinguish the M_1 and M_2 receptors based on the high affinity of the M_1 receptor for the agonist pirenzepine (45). However, the molecular distinction between the M_2 and M_3 proteins is more difficult. For some receptors, the mRNA coding for the protein structure has been studied far better than the actual receptor protein itself (228).

These distinctions among muscarinic receptors are clinically relevant when considering pharmacologic therapy of the lower urinary tract (73,162). M_1 muscarinic receptors primarily are confined to the CNS, glands, and sympathetic ganglia. M_3 receptors are seen on the cell surface of the peripheral target organs, whereas M_2 receptors also reside on the neuron's synaptic membrane (Fig. 26A.18). Presynaptic M_2 receptors (with some contribution from M_4 type) bind acetylcholine once its concentration reaches a certain level in the postsynaptic cleft, and inhibit the release of more acetylcholine; this serves as a negative feedback loop. Despite accounting for only 20% of the muscarinic-receptor density in the bladder, it is the activation of the M_3 receptor that triggers a rise in intracellular cytosolic calcium levels and initiates bladder contraction. New studies suggest that M_2 receptors also exist on the smooth muscle cell surface and contribute to force generation by inhibiting adrenergic pathways (which under pure adrenergic conditions would cause the muscle to relax) (46,73,322).

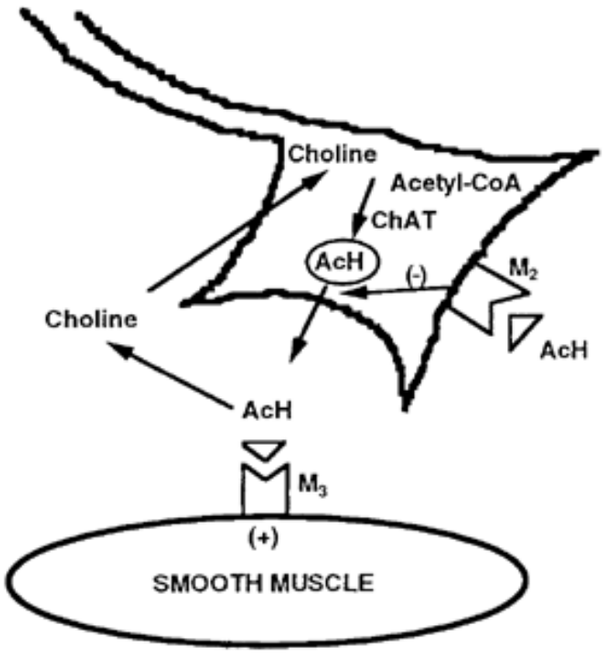

FIGURE 26A.18. A simplification of muscarinic cholinergic neuromuscular transmission. Acetylcholine is synthesized by the acetylation of choline by choline acetyl-transferase in the neuron and packaged into vesicles. The vesicles release their acetylcholine content into the neuromuscular cleft in response to a rise in axonal calcium. The acetylcholine binds to an M_3 receptor to effect a contractile response. It also will bind to a presynaptic M_2 receptor, which will inhibit the release of more acetylcholine (130). The bladder contains both M_2 and M_3 receptors. Acetylcholine is broken down in the neuromuscular cleft by the serine protease, acetylcholinesterase, and the choline moiety is recycled. This sequence of events may be modified by the addition of cotransmitters such as nitric oxide or adenosine triphosphate (ATP).

The muscarinic cholinergic receptor is composed of a single peptide chain with seven hydrophobic or transmembrane domains (66,152,357). These membrane-spanning segments are quite similar among the five receptor subtypes, and the real diversity comes when looking at the cytoplasmic loops. This allows each of the subtypes to perform a slightly different intracellular function. With some muscarinic receptors, the cytoplasmic domain is attached to a G-protein that serves to produce a second messenger such as IP_3. In other cases, the cytoplasmic portion of the muscarinic receptor is linked to proteins that affect cytosolic levels of cAMP and or cGMP.

Muscarinic cholinergic-receptor density is affected by hormonal factors such as pregnancy (downregulation) (217), estrogen (upregulation) (306), spinal cord injury (46,312), acute obstruction (187,237), and diabetes (339), and by contractile activity itself (204). The molecular basis for contractile activity regulating the receptor density was tested by Levin and colleagues (210), who showed that if the detrusor smooth muscle was stimulated repeatedly, the muscarinic binding sites were decreased. This most likely is explained by a receptor binding its ligand, and the entire complex being subjected to endocytosis by the cell. The mechanisms by which cholinergic-receptor density is altered by hormones or spinal cord injury are not understood. In samples taken from patients with myelodysplasia, Lepor and associates (200) demonstrated a decrease in the expression of the muscarinic cholinergic receptor.

Acetylcholine is synthesized in neurons from acetyl-coenzyme A, and choline is synthesized by the enzyme, choline acetyltransferase. Once acetylcholine is released into the synaptic cleft, it has four possible actions (Fig. 26A.18):

1. It may bind to an M_3 receptor and initiate smooth muscle contraction.
2. It may bind to an M_2 receptor and inhibit further acetylcholine release.
3. It may bind to either receptor and be taken up into the cell by endocytosis.

4. It may be broken down by acetylcholine-esterase, a serine protease that functions to cleave the hormone into inactive fragments.

Although the neuron will not take up unbound acetylcholine, it will reabsorb choline and recycle it for further use.

Adrenergic Receptors

The sites at which catecholamines act as the primary neurotransmitter are classified as adrenergic, and include most of the postganglionic sympathetic fibers. Norepinephrine is the catecholamine released into the postsynaptic cleft, at which point it diffuses across to the effector cell to bind to an adrenergic receptor. Adrenergic receptors classically are defined as α or ß depending on the physiologic reaction they elicit. The α-receptors produce vasoconstriction and smooth muscle contraction. Norepinephrine and methoxamine are the primary α-agonists eliciting a maximal response, whereas epinephrine has a weak effect at α-receptors. Stimulation of ß-adrenergic receptors will increase myocardial contractility and elicit some smooth muscle relaxation (bronchodilation). Maximal ß-effects are seen with isoproterenol, moderate with epinephrine, and minimal with norepinephrine.

Adrenergic receptors are composed of one polypeptide chain of approximately 500 amino acids with seven hydrophobic regions spanning the cell membrane. When a transmitter binds to the active site at the plasma membrane, conformational changes result in realignment of the intracellular receptor components. This in turn activates several pathways (G-proteins and others) and second messengers that produce smooth muscle contraction or relaxation. Distinguishing between α- or ß-receptor proteins using classic radioligand methods is limited because the differences in recognition sites are subtle. The major molecular differences are in the intracellular regions, which enable the receptor subtypes to carry out their diverse functions. Some subclassifications of adrenergic receptors cannot be made on the basis of ligand specificity, but by DNA sequence analysis only. Excellent reviews of the molecular aspects of the adrenergic receptors have been compiled by Hoffman and Lefkowitz (150) and Ruffolo and associates (299).

The α-receptors traditionally were divided into types 1 (postsynaptic) and 2 (presynaptic) depending on their location within the synapse (Fig. 26A.19). It now is apparent that type-2 receptors are located in postsynaptic and nonsynaptic sites (such as vascular smooth muscle). The α_1-receptors were then classified further, using ligand-binding studies, into two subtypes (A and B), and molecular cloning studies revealed a third (D), as well as a fourth related receptor, referred to as *a-1-L* (which may be a close variant of α_{1A}) (86). The α_{1A}- and α_{1B}-receptors are located in smooth muscle, where they elicit a contraction by coupling either with a G-protein (to produce IP_3) or to a dihydropyridine-sensitive calcium channel (222). The α_{1d} type has been identified in bovine brain, and its mRNA has been identified in the prostatic stroma (289). Smooth muscle contraction in the lower urinary tract is mediated predominately by the α_{1A}-receptors (109,249,304). The family of human α_1-adrenergic receptors has been localized to chromosome 5q (283). Three human type-2 α-receptors have been classified and their chromosomal locations have been mapped. In contrast to the $\alpha_{1A,B,D}$ class, these receptors have been mapped to three different locations in the genome: α_{2A} to chromosome 10q, α_{2B} to chromosome 2, and α_{2C} to chromosome 4 (283).

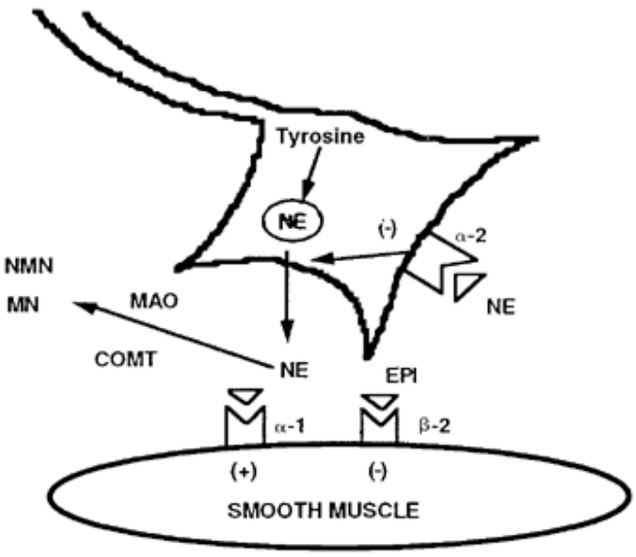

FIGURE 26A.19. A simplification of adrenergic neuromuscular transmission. Tyrosine serves as the ultimate precursor of epinephrine and norepinephrine, which, following their biosynthesis by well-described pathways (150), are packaged in vesicles. The vesicles release their contents into the cleft. Norepinephrine (NE) binds preferentially to α_1-receptors to effect a contraction of smooth muscle, whereas epinephrine (EPI) binds preferentially to α_2-receptors to produce relaxation. Feedback may occur at α_2-receptors to inhibit the release of more adrenergic neurotransmitters. NE and EPI are broken down by monoamine oxidase (MAO) and catecholamine-O-methyltransferase (COMT) into metanephrine (MN) and normetanephrine (NMN). This diagram may be modified by the addition of cotransmitters such as nitric oxide or adenosine triphosphate (ATP).

The ß-adrenergic receptors exist in at least three major forms designated as subtypes 1, 2, and 3, with the genes located on chromosome 5q. The $ß_1$-receptors are postsynaptic and produce a positive chronotropic and inotropic effect in the heart. Norepinephrine has a higher affinity for the $ß_1$-receptors, whereas epinephrine has a greater affinity for the $ß_2$-receptors. The $ß_2$-receptors are found in the presynaptic and postsynaptic membranes and in the urinary bladder, uterus, intestinal tract, and bronchi. Stimulation of the $ß_2$-receptors causes relaxation of these smooth muscle groups. A $ß_3$-adrenergic receptor has been defined

recently in the digestive tract, skeletal muscle, and adipose tissues (283).

The catecholamines are synthesized from the amino acid, tyrosine, as a precursor by well-defined biochemical pathways (150). Once the catecholamines are released into the synaptic cleft, several events may take place (Fig. 26A.19). The catecholamines may bind to a postsynaptic effector cell to cause either contraction or relaxation. They may be taken back up into the presynaptic membrane and recycled, or bind to a presynaptic receptor and inhibit further neurotransmitter release. They may be metabolized and inactivated by either monoamine oxidase (MAO) inhibitors or by catechol-O-methyltransferase.

Clinical Relevance of Receptor Molecular Biology

These differences among receptor populations are important in selecting drugs for clinical urologic applications. In the past, urologic medical therapy tended to have minimal uroreceptor selectivity. Therapy for benign prostatic hypertrophy (BPH) using α-blockers will benefit from an improved understanding of this pharmacology, because the prostatic capsule and stroma are rich in these receptors. Conventional drugs such as phenoxybenzamine bind to both the α_1- and α_2-receptors; although producing an enhanced urinary flow rate (α_1 prostatic effect), vasodilation and orthostatic hypotension may result (α_2 effect in vascular smooth muscle). Even a drug such as prazosin, with greater α_1 specificity, will have some vasodilating side effects. Although these side effects may be minimal in a young, healthy patient, they may become problematic in the older patient with BPH. The development of long-acting selective α_1-blockers such as terazosin, tamsulosin, and doxazosin has provided a greater urologic benefit in the management of prostatism while minimizing side effects (202). Current pharmacologic therapy with α-blockers has been reviewed well by Langer (191) and Blaivas (35).

The traditional drug for bladder instability, oxybutynin hydrochloride, also binds to ocular, gastrointestinal, or salivary gland sites. Subsequent side effects result, which often make these drugs unacceptable to the patient at doses with a urologic benefit. Radioligand-binding data demonstrate that tolterodine binding is eightfold lower in the parotid gland when compared with bladder (266). In a pooled analysis of four multicenter trials, this translated into better compliance while still minimizing the episodes of incontinence for those patients treated with tolterodine versus oxybutynin (13).

Other Receptors in the Lower Urinary Tract

Contraction and relaxation of smooth muscle of the lower urinary tract can occur *in vitro* in response to a large number of agonists and antagonists in addition to acetylcholine and norepinephrine. Many of these substances may occur as modulators of neurotransmission. The ability of a substance to elicit a contraction *in vitro* does not imply that it is functionally active in the *in vivo* setting under normal physiologic conditions. For a substance to be categorized as a neurotransmitter, it must meet certain specific criteria (57).

1. The presynaptic neuron should have the enzymes needed to synthesize the substance or its precursor.
2. The substance should be imaged in the presynaptic neuron using chemical, immunologic, or fluorescent methods.
3. At the postsynaptic membrane, the substance should reproduce the specific events of transmission.
4. These events should occur at concentrations that are equivalent to those obtained in the synapse at the time of transmitter release, secondary to nerve stimulation.
5. The effect should be blocked by a known antagonist in a dose-dependent manner.
6. A mechanism to terminate the action of the proposed transmitter, such as a degradative enzyme, must be available.

Receptor Distribution Within the Lower Urinary Tract

Levin and Wein (214) were the first to investigate receptor-binding methods to quantitate the expression of adrenergic and cholinergic receptors within the lower urinary tract. The bladder body has abundant muscarinic receptors, and this pattern extends down into the proximal urethra (119,123). The expression of these receptors is hormonally sensitive. Levin and colleagues (217) showed a diminished response to bethanechol stimulation and a 50% reduction in cholinergic-receptor density among pregnant rabbits.

Muscarinic receptors determined by radioligand-binding assays were expressed at higher concentrations in the bladder body and at lower levels in the bladder base, with no change in the dissociation constant. Similar muscarinic-receptor distributions within the bladder have been reported in guinea pigs (268), rabbits (201), and humans (267). The predominate muscarinic receptor in the bladder is the M_2 (80%) variant (3,210,300), but the M_3 variant (20%) actually is responsible for bladder contraction (73). Evidence now suggests that M_2 stimulation also contributes to the development of active force generation via an inhibitory effect on the intracellular cascade downstream from the ß-adrenergic receptor (73). By inhibiting the ß-adrenergic effects that induce relaxation, M_2 stimulation contributes to active force generation.

Adrenergic binding sites are expressed within the bladder body with a predominance of ß subtypes (11). Several groups have offered data to support rich cholinergic innervation

of human bladder smooth muscle (85,117,137). Ek and co-authors (117,118) have described a similar but less extensive innervation of the proximal urethra. Numerous studies agree on the general concept that the smooth muscle of the bladder neck and proximal urethra have a rich adrenergic innervation (123,188). The adrenergic and cholinergic innervation of the bladder appears to be hormonally sensitive. Using immunohistochemical methods, atrophy of the bladder-base adrenergic fibers was noted in pregnant rats (291). This was confirmed by physiology studies in the rabbit, where Tong and associates (338) demonstrated less adrenergic response among pregnant rabbits.

Adrenergic fibers in the human lower urinary tract are localized primarily in the trigonal region (59,326), with minimal expression in the bladder body (29,326). Gosling and Dixon (136a) and Kaneko and co-workers (166) reported adrenergic nerve supplies to the male bladder neck; a dissenting view is provided by Kluck (180), who found little evidence of such fibers. Gosling and Dixon (136a) further noted that such adrenergic innervation was distributed predominately right at the junction of the bladder neck and prostate, and they speculated that its functional role was in the prevention of retrograde ejaculation as opposed to the maintenance of continence. Considering the high incidence of retrograde ejaculation and low incidence of urinary incontinence after radical retroperitoneal lymph node dissection for testes cancer, this explanation makes sense. El Badawi and Atta (120) pointed out that before accepting such significant gender differences in innervation, it is wise to consider the actual studies themselves. A heterogeneity of human tissue is available for study, and none of the material studied in his review of the literature could truly meet the criteria of “normal.”

Striated Sphincter Receptors and Innervation

The striated sphincter is thought to be innervated by the pudendal nerve, which emanates from the S-2 to S-4 cord segments (99,122). The major innervation of this striated sphincter is believed to be somatic by most authors. Transection of the pudendal nerve in the rat has been shown to diminish the striated muscle component of the external sphincter and diminish average fiber size (146). In humans, somatic control of the external sphincter is such that there is activation of these neurons during progressive filling and a loss of activity just before and during micturition. Inhibition of this somatic nerve activity during micturition requires supraspinal mechanisms, which accounts for the failure of the external sphincter to relax in paraplegic patients (99).

Some authors have implicated adrenergic control over the striated external sphincter; however in a study of clinical specimens, Wein and Raezer (352) and Lincoln and associates (220) concluded that the only evidence of adrenergic innervation to the striated component of the external sphincter was associated with blood vessels. Whereas the cholinergic receptors associated with smooth muscle are classified as muscarinic, those responsible for striated muscle contraction are nicotinic. Anticholinergic drugs such as oxybutynin are active at muscarinic sites only, and will have no effect on skeletal muscle. The nicotinic receptors of the striated sphincter can be blocked for up to 3 months with endoscopically placed botulinum toxin (Bo-Tox). Such treatment has been utilized successfully in the therapy of dysfunctional voiding refractory to biofeedback therapy (303) or in paraplegic patients as an alternative to sphincterotomy.

Sensory Innervation

Although much is known about the contractility of the urinary bladder, much less is known about its sensory function, reflecting the experimental difficulties in studying sensory phenomena in animal models. Afferent nerve fibers have been demonstrated in the pelvic, pudendal, and hypogastric nerves (99,190). deGroat and Booth (89) showed that afferent receptors serving the sensation of bladder distention originate in the bladder wall and travel in the pelvic nerve, whereas mechanoreceptors are found in the hypogastric nerve. Both of these nerves carry nociceptive afferents. The afferent neurons from the striated sphincter and urethra transmit sensations of temperature, pain, and urinary distention, and these travel in the pudendal nerve.

Tucker and Moss (342) describe an *in vivo* model in which intravesical potassium chloride (KCl) produces irritation, which is detected by monitoring action potentials in the transected pelvic nerve. Afferent neurons were labeled in the bladder by intravesical injections of wheat germ agglutinin (WGA)–horseradish peroxidase or pseudorabies virus, followed by immunostaining of the spinal cord segments (Fig. 26A.20) (87,316), which showed the sensory neurons localized to discrete zones within the dorsal horn. This area also contains dendrites of neurons that supply the lower urinary tract with motor efferents. If the bladder is subjected to chemical irritation, sectioning of these same spinal segments followed by immunostaining for c-fos expression will show reactivity in the same distribution (Fig. 26A.20) (33,349). Birder and deGroat (34) also correlated these findings with evidence of increased c-fos gene expression. A major discovery in the study of bladder afferent neurons was that capsaicin blocked this population of neurons and diminished *c-fos* protein and gene expression (235,349). Capsaicin is a natural product isolated from hot red peppers, with the unique ability to bind to sensory neurons and to induce rapid membrane depolarization by the opening of an ion channel that is followed by a prolonged (but reversible) blockade. In addition to blocking small-diameter nociceptive fibers, capsaicin acts to inhibit inflammatory neuropeptide release from peripheral nerve ending (31). The potential

clinical use for capsaicin and an extensive review of its pharmacology was updated recently by Maggi (236).

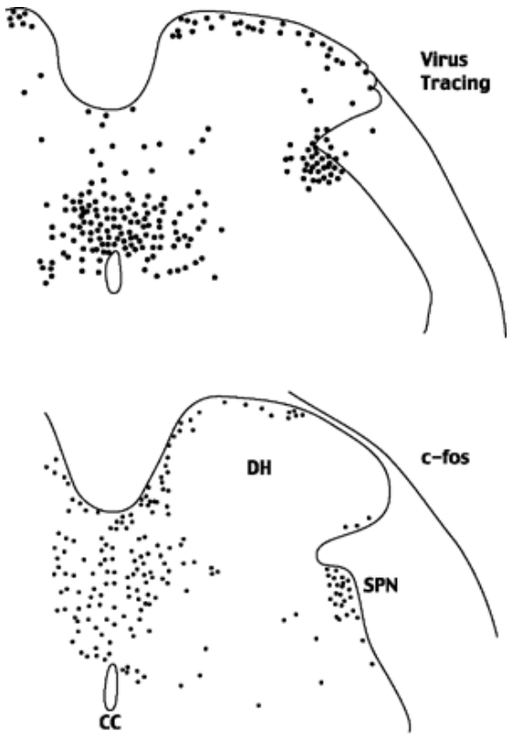

FIGURE 26A.20. Bladder afferent projections at the L-6 level of the rat spinal cord. **A:** The afferents were identified by the retrograde axonal transport of intravesically administered pseudorabies virus followed by immunohistochemical staining. Viral uptake is localized to very discrete regions within the spinal cord. **B:** The spinal cord segment has been stained for the expression of the oncogene c-fos, which is activated following the chemical irritation of the bladder. CC, central canal; DH, dorsal horn; SPN, sacral parasympathetic nucleus. (From deGroat WC, Booth AM, Yoshimura N. Neurophysiology of micturition and its modification in animal models of human disease. In: Maggi CA, ed. *Nervous control of the urogenital system*. London: Harwood Publishers, 1993, with permission.)

Denervation

If the autonomic fibers leading to the bladder are divided, the smooth muscle increases its sensitivity to neurohumoral transmission. Decentralization refers to those injuries in which the *preganglionic* fibers have been divided, whereas denervation refers to those injuries in which the *postganglionic* fibers have been divided. This supersensitivity effect is most pronounced when the postganglionic fibers are transected (352). Westfall (358) suggested several possible mechanisms for this supersensitivity: (a) increased neurotransmitter (possibly caused by diminished reuptake or degradation) with unchanged muscle, (b) altered smooth muscle cells rendered more sensitive to neurotransmitters, and (c) increased muscle-receptor density. No changes in smooth muscle–receptor affinity or density have been documented following experimental peripheral denervations. Saito and colleagues (301) induced denervation in a rabbit model and demonstrated increased force generating capacity with no change in the effective median dose (ED_{50}) for acetylcholine. They also demonstrated significant shifts in the calcium dose-response curves, implying that denervation induces some major, and as yet unknown, alterations in intracellular calcium handling in bladder smooth muscle.

Ample evidence suggests that muscles and nerves communicate with one another to maintain a homeostatic relationship independent of full-fledged contraction. Studies have shown that the peptide hormone, nerve growth factor (NGF) (343) is secreted by bladder smooth muscle cells in response to both obstruction (284) and denervation (343). NGF has been shown to induce the replication of cultured Purkinje cells, and is believed to be responsible for increases in the sizes of pelvic ganglia after experimental obstruction or denervation (316,317). These changes also have been shown to correlate with levels of mRNA coding for NGF. Gabella and Uvelius (131) have shown that, in the obstructed rat bladder, smooth muscle and ganglionic hypertrophy will occur even in the presence of decentralization (i.e., interruption of the preganglionic nerve fibers). The ganglionic hypertrophy was greater if the preganglionic fibers were left intact on one side of the pelvis. They concluded that, in the face of obstruction, smooth muscle can induce changes in the peripheral nervous system independent of the spinal cord. Brading (41) has demonstrated strong evidence in favor of denervation occurring after outlet obstruction, and believes that this destruction of the postganglionic fibers probably is mediated by bladder wall hypoxemia, which arises secondary to increases in intravesical pressure (141). Brading (41) also has noted that regional variations of denervation within the bladder wall after outlet obstruction can be attributed to differences in wall perfusion.

Skehan and co-authors (311) reported on decentralization injuries in a cat model and noted a loss of compliance with significant increases in autonomous wave activity, which could be partly overcome by the use of prazosin or acute sympathectomy. This led them to suspect that, in this decentralization model, the loss of bladder compliance was modulated by a peripheral pathway including α_1-receptors.

Most clinical examples of denervation injury are manifested by insults to the preganglionic fibers, such as the injuries incurred during radical hysterectomy or an abdominal perineal resection for rectal carcinoma. These injuries are better classified as decentralization because the postganglionic neurons are still intact leading to the bladder. Denervation in its purest sense implies injuries to the neurons immediately leading up to the smooth muscle.

NEURAL INFLUENCES ON LOWER URINARY TRACT FUNCTION: THE ROLE OF THE PERIPHERAL NERVOUS SYSTEM

In considering neural control over the lower urinary tract, this discussion begins first with a review of how the peripheral nervous system interacts with the lower tract end-organ structures. This is then followed in a subsequent section by a detailed analysis of how the CNS provides ultimate control and integration over lower urinary tract function.

Cholinergic Effects

Muscarinic-receptor sites that can be stimulated with a variety of cholinergic agonists and inhibited by atropine have been demonstrated in the bladder body and base of numerous species including dog (292), rabbit (172,211), fetal lamb (181), and humans (30,212). Stronger muscle strip responses are noted in the bladder body, and weaker responses in the bladder base. Levin and colleagues (211) found that the response to cholinergic stimulation of the bladder was not uniform and was substantially greater in the dome than in the base (Fig. 26A.21), and correlated these physiologic findings with cholinergic receptor–density levels. The bladder responds to cholinergic stimulation with a biphasic contraction (Fig. 26A.22). In bladder smooth muscle strips, application of bethanechol produces a rapid rise in tension to a peak value, followed by a 10% to 30% decline to a plateau value. It is during this plateau phase in a whole organ model, that bladder emptying takes place (207). Although the initial peak pressure is important, it is the sustained plateau pressure that primarily is responsible for the emptying phase. The plateau phase is most sensitive to alterations in extracellular calcium concentrations. If extracellular calcium is depleted and the muscle strips are contracted, the plateau force is lost first, followed by a gradual decline in the peak force (370).

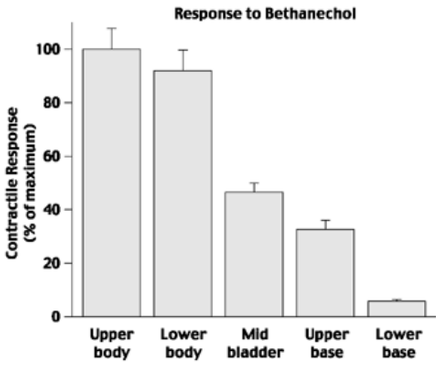

FIGURE 26A.21. Contractile response of sequential strips of isolated rabbit urinary bladder to bethanechol. Bladders were harvested and separated into five sequential longitudinal strips. The response to bethanechol (1 to 500 μM) was determined for each strip. Each bar represents the mean ± standard error of the mean of the maximum response of each strip to bethanechol (*N* = 4 to 6). There were no significant differences in the EC_{50} values (dose required to produce 50% of maximal response). (From Levin RM, et al. Neuropharmacologic investigations of the lower urinary tract. *World J Urol* 1990;8:180, with permission.)

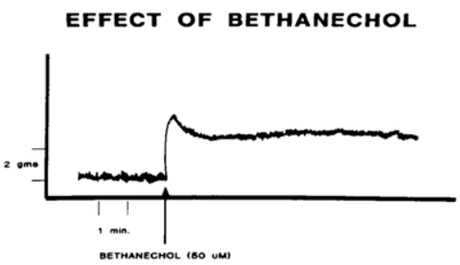

FIGURE 26A.22. Representative response of an isolated longitudinal strip of bladder body to bethanechol. The bladder body was separated into four individual longitudinal strips mounted in individual isolated baths containing 15 mL of oxygenated Tyrode's solution at 37°C. An example of the biphasic response to bethanechol (50 μM) from one strip is presented in this figure.

Muscarinic receptors also are found within the urethra; *in vitro* study of human urethral strips has shown a modest contractile response to acetylcholine that could be blocked by atropine (118). In the rat, Ekstrom and Malmberg (119) reported rapid and forceful contraction of the urethral smooth muscle in response to cholinergic stimulation, which they concluded was secondary to direct action at muscarinic receptors. Minimal responses to cholinergic stimulation were noted in rabbit urethral smooth muscle (172).

Parasympathetic Effects

Sustained increases in intravesical pressures are produced by stimulation of the pelvic nerve (Fig. 26A.23), and most investigators have come to agree that activation of this pathway is responsible for bladder emptying during normal micturition (99,340). However, it is increasingly apparent that acetylcholine is not the sole neurotransmitter released under these circumstances, because atropine blocks the response of the bladder to pelvic nerve stimulation only partially (55). In a fetal lamb model in which voiding was triggered by slow fill cystometry, Kogan (181) demonstrated

that voiding pressures diminished (but were not eliminated) with the administration of atropine, implying that other transmitters were still exerting their influence. However with atropine administration, voiding was less efficient, as noted by a major increase in postvoid residual urine. It was Burnstock and associates (55) who first advocated the concept of cotransmitters, and they have identified evidence of direct release of ATP from guinea pig bladder nerves (53,54). Substantial progress has been made in the field of autonomic neurotransmission to the urinary bladder and urethra, and this progress has been reviewed by Hoyle and Burnstock (153).

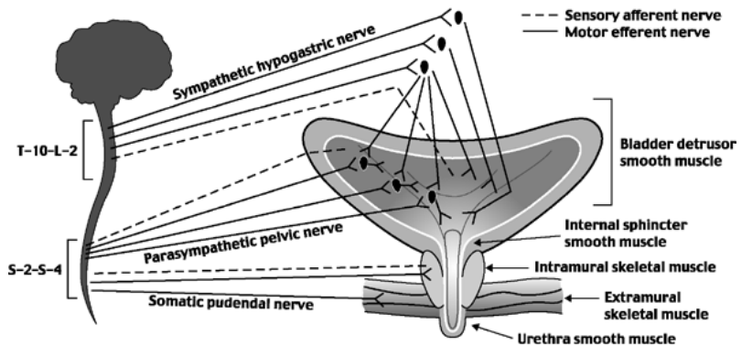

FIGURE 26A.23. A current conceptualization of lower urinary tract innervation. During the storage phase, low-level vesical afferent firing results in (a) increased sympathetic outflow to the bladder base, (b) increased pudendal outflow to the striated urethral sphincter, and (c) suppression of parasympathetic transmission in the ganglia. These neural pathways provide continence in a variety of situations, such as during sudden increases in intraabdominal pressure. It is important to note the coordinated interaction between the somatic efferents to the striated urethral sphincter, the sympathetic efferents via the hypogastric nerve, and the parasympathetic efferents via the pelvic nerve. In particular, there is a sympathetic inhibition of transmission in the parasympathetic ganglia. (From Abrams P, Wein AJ. The overactive bladder—a widespread and treatable condition. Stockholm: Erik Sparre Medical, 1998, with permission.)

Although pelvic nerve stimulation leads to increases in intravesical pressure, there must be associated synergistic effects (under normal circumstances) in the urethra. McGuire and Herlihy (241,245) offered evidence that urethral smooth muscle relaxes in response to pelvic nerve stimulation. The studies were performed with the bladder in a diverted and an undiverted state, and in both instances the urethral smooth muscle was demonstrated to relax. Furthermore, it was observed that urethral relaxation in response to pelvic nerve stimulation could be blocked by propranolol, implying that this is a ß-adrenergic response. These data are supplemented by a growing literature that supports a role for NO-mediated relaxation of the urethra and bladder neck during bladder contraction measured *in vivo* (48,248,285). Such a coordinated relaxation of the urethra and bladder neck in conjunction with a detrusor contraction are essential if efficient low pressure voiding is to occur.

The aforementioned studies were *in vivo* demonstrations of parasympathetic function in the lower urinary tract; ample *in vitro* studies have shown that atropine is capable of inhibiting the response to neural stimulation. In human bladder strips, neural stimulation results in contractions that are blocked only partially by atropine (148). This atropine inhibition is variable, is species dependent, and may be affected by pathologic processes. The atropine-resistant contribution to bladder contraction will be influenced by the methodology employed (e.g., neural stimulation by electrical field stimulation at low or high frequencies). This discussion is clinically relevant because it may explain the mechanism by which many of the anticholinergics used to treat the unstable bladder fail to produce an optimal outcome. In some instances, it might make better sense to opt for two drugs with differing modes of action (353).

Some representative *in vitro* data show that, in response to neural stimulation, atropine inhibits active force by 60% in the guinea pig (186), 20% in the cat (263), 50% in the rat (3), and 50% in the human female (82). In rabbit bladder smooth muscle, Sibley (307) demonstrated atropine resistance of 60% at higher frequencies, and 15% at lower frequencies, which may be explained by the fact that higher frequencies of *in vitro* neural stimulation produce greater cholinergic contributions to the contraction.

Brading (39) summarized results showing that, although atropine resistance to field stimulation was prominent in many species, it seemed to have little representation in pigs and none in normal humans. Hutcheson and co-workers (157) demonstrated in a murine *in vitro* whole bladder preparation, that atropine abolished all response to neural stimulation. Kinder and Mundy (175) demonstrated virtually complete atropine inhibition of the response to field stimulation in 13 patients with normal CMGs. In sharp contrast to this, Sjögren and colleagues (310) demonstrated that atropine diminished the response to neural stimulation by 50% in patients with a diagnosis of bladder instability. Using similar techniques, Palea and associates (277) demonstrated an increase in noncholinergic neurotransmission in bladder strips taken at the time of surgery from patients with interstitial cystitis. It appears that noncholinergic nonadrenergic pathways of activation may become more prominent in certain pathologic conditions such as bladder instability or interstitial cystitis. These conflicting data between animal and human studies serve to illustrate again the basic observations that were laid out at the beginning of this chapter. Data from animal species do not necessarily hold up in human studies, and findings in human tissues are often from patients with known or unappreciated urologic conditions, making the definition of “normal” a major challenge.

Atropine Resistance and the Role of Purinergic Neurotransmission

Although many theories have been proposed to explain bladder smooth muscle response to *in vivo* pelvic-nerve or *in vitro* field stimulation in the presence of atropine, the accepted view today is that a substantial fraction of parasympathetic neurotransmission is mediated by noncholinergic and nonadrenergic transmitters (55,153,160,209,239). Burnstock and partners (53,56) suggested that ATP is an excitatory neurotransmitter involved in the detrusor response to pelvic nerve stimulation and used quinacrine fluorescence histochemistry to identify these purinergic neurons. They also demonstrated a bladder contraction in the presence of atropine associated with ATP release from these nerves. Downie and Dean (110,112) also demonstrated a role for ATP in rabbit bladder contraction. ATP acts at purinergic receptors that can be classified as P_2 and P_1 (57,335). The use of arylazido-aminoproprionyl ATP ($ANAPP_3$), a photoaffinity antagonist of the P_2 receptor, inhibits the effects of ATP in the cat bladder (336).

In vivo bladder contraction in response to pelvic nerve stimulation has two distinct phases; an initial peak pressure is followed by a plateau phase. Theobald (336) and Maggi and colleagues (233) demonstrated that atropine had no effect on the initial peak pressure, whereas $ANAPP_3$ produced a loss of pressure. However, although atropine had a minimal effect (10% inhibition) on the first phase of bladder contraction, it did block the second phase of pelvic nerve contraction (60% inhibition). These *in vivo* experimental data suggest that ATP and acetylcholine truly function as cotransmitters.

Results obtained using the *in vitro* whole bladder model give similar results in terms of a two-phase response to electrical field stimulation (Fig. 26A.24). Neural stimulation (via electrical field stimulation) is one of the most realistic means of studying bladder contractility *in vitro,* because it causes neurotransmitter release from peripheral neurons within the bladder wall. In the rabbit, Levin and co-authors (203) demonstrated that atropine is capable of inhibiting 50% of the peak response and completely eliminates the tonic or plateau phase, offering evidence that cholinergic stimulation is an important contributor to these phases of the contraction. With ATP stimulation alone, the pressures generated were equal to those developed in response to field stimulation in the presence of atropine. However, the ejection fraction in the presence of ATP alone was 15%, as opposed to the 95% or more expelled in response to baseline field stimulation. The cholinergic component is decreased and the purinergic component of neurotransmission is increased by pregnancy in the rabbit (217). Long-term incubation (20 minutes) of the bladders with ATP rendered them insensitive to field stimulation with atropine. These data can be explained by the studies of Acevedo and colleagues (2), who demonstrated evidence that intrasynaptic ATP is cleaved to adenosine, which then is taken up by an adenosine receptor located on the presynaptic

membrane. This serves as an inhibitory stimulus to the release of further ATP from the neuron. The role of presynaptic and postsynaptic adenosine receptors has been reviewed by Collins and Hourani (77).

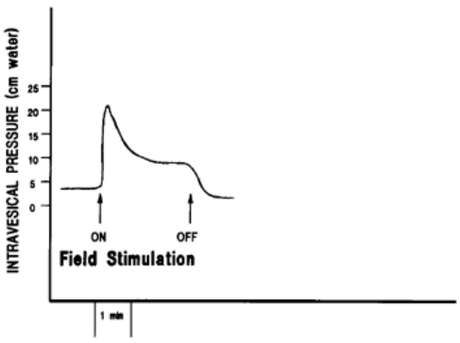

FIGURE 26A.24. Representative response of the whole rabbit bladder preparation to field stimulation. The bladder was harvested, mounted as an intact organ on an electrode-tipped catheter, and placed in an isolated bath containing 300 mL of oxygenated Tyrode's solution at 37°C. The bladder was filled to 20 mL with saline solution, and the intravesical pressure was monitored continually with a pressure transducer and recorded on a polygraph. This figure presents a representative biphasic response of the whole bladder preparation to field stimulation (80 V, 32 Hz, 1 ms). (From Levin RM, et al. Neuropharmacologic investigations of the lower urinary tract. *World J Urol* 1990;8:180, with permission.)

Brading (39) believed that atropine resistance is nonexistent in normal human bladder smooth muscle, and that the purinergic component is not related to contractile events. This does not mean that the purinergic receptors in bladder have no role in bladder function; it merely means that their role may be much more complex than was initially thought. Evidence has accumulated in a mouse with a deletion of the purinergic P2X3 receptor of alterations in sensory neurotransmission (76). These mice show detrusor hyporeflexia with bladder filling and reduced pain-related behavior to noxious stimuli. More work is required to separate the roles for purinergic neurotransmission under both normal and pathologic conditions.

Adrenergic-receptor Distribution, Stimulation, and Blockade

Urologic investigators agree that the smooth muscle of the bladder body, base, and proximal urethra contain both α- and ß-adrenergic receptors, and these findings hold true in a variety of species as well as in humans. The α responses predominate in the bladder base and proximal urethra (211), whereas ß responses predominate in the body (11). Responses to α- and ß-adrenergic stimulation as a function of location within the bladder are presented in Fig. 26A.25 and Fig. 26A.26 . Methoxamine, an α-agonist, has its greatest effect in the base of the bladder with only minimal force generated in the upper and lower body (Fig. 26A.25). In notable contrast, isoproterenol, which is a $ß_2$-agonist, exerts its greatest effects in the upper and lower body as well as in the midbladder, with minimal relaxant responses in the base (Fig. 26A.26). Although mild ß effects have been reported, the relaxation of the bladder neck and urethra during active bladder contraction more likely appear to be mediated by NO release than by ß-agonists (48,50,196,248,285,328).

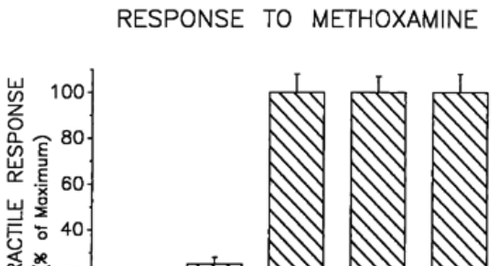

FIGURE 26A.25. Contractile response of sequential strips of isolated rabbit urinary bladder to methoxamine. The bladders were harvested and separated into five sequential longitudinal strips. The response to methoxamine (2 to 1,000 µm) was determined for each strip. Each bar represents the mean ± standard error of the mean of the maximum response of each strip to methoxamine (*N* = 4 to 6). There were no significant differences in the EC_{50} values. (From Levin RM, et al. Neuropharmacologic investigations of the lower urinary tract. *World J Urol* 1990;8:180, with permission.)

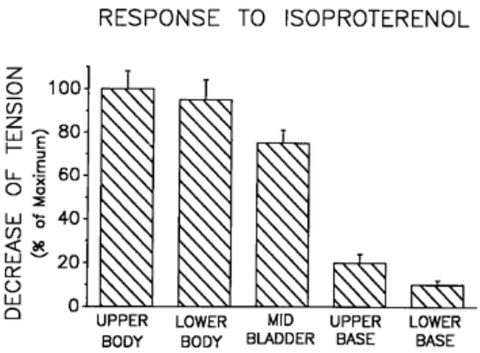

FIGURE 26A.26. Relaxant response of sequential strips of isolated rabbit urinary bladder to isoproterenol. The responses to isoproterenol were determined from 0.1 to 100 µM for each strip. Each bar represents the mean ± standard error of the mean of the maximum response of each strip to isoproterenol (*N* = 4 to 6). There were no differences in the EC_{50} values. (From Levin RM, et al. Neuropharmacologic investigations of the lower urinary tract. *World J Urol* 1990;8:180, with permission.)

The molecular basis for these physiologic findings was made clear by the application of radioligand-binding studies to these same anatomic divisions of the bladder. The α-receptors predominate in the bladder base of humans, dogs, and rabbits, and ß-receptors predominate in the bladder body (216). There is some disagreement about whether these are $α_1$- or $α_2$-receptors. In the rat, Maggi and Meli (231) found that the sites were of the $α_2$ class, whereas Anderson and Marks (6) found 80% of rabbit receptors to be of the $α_2$ class and 20% to be of the $α_1$ family. Levin and colleagues (210) reported $α_2$-receptors predominated in both the human and rabbit bladder. Functional studies show that these $α_1$- and $α_2$-receptors are active in the production of force. Tong and co-authors (338) have shown that the contractile force produced by the female rabbit bladder base in response to α-agonists is significantly diminished by pregnancy. Given the gestation-induced changes in the muscarinic cholinergic receptor seen in the maternal rabbit bladder, it is not unreasonable to expect that the α-receptor density also will be regulated.

Adrenergic Effects Mediating Bladder Function

The preceding findings regarding the adrenergic contribution the storage phase of the voiding cycle can be summarized (Fig. 26A.23) as follows:

1. Neurons stimulating α-receptors at the bladder base and urethra increase outlet resistance and thereby facilitate storage.
2. Neurons stimulating ß-receptors in the bladder body increase bladder compliance and thereby facilitate storage.
3. Adrenergic neurons and associated α-receptors suppress parasympathetic transmission in the pelvic ganglia and therefore inhibit bladder contractility.

These points serve to confirm the major theme established by deGroat and Saum (96); the main role of the adrenergic system is to favor storage at low pressures within the bladder. Over a 30-year span, ample evidence has supported these initial views (87,98). Despite this fairly straightforward view, many authors disagree on the extent to which the sympathetic system affects lower urinary tract function, and some believe its physiologic contribution is of lesser importance (257,272).

Hypogastric nerve stimulation in cats causes a transient rise in intravesical pressure followed by inhibition of spontaneous or evoked bladder contractions (190). According to deGroat and Saum (96), two major mechanisms account for such findings: (a) depression of bladder body contractility by $ß_2$ stimulation and (b) a depression of parasympathetic activity in the pelvic ganglia, mediated by α-receptors (87,91). Also consistent with this view that the adrenergic axis facilitates storage are the facts that surgical or chemical (with α-blockers) sympathectomy produces increased spontaneous activity and a diminished bladder capacity (with a leftward shift of the CMG, that is, a less compliant bladder) in the cat (96) or dog (269,351). Furthermore, deGroat and Theobald (97) thought that this inhibitory pathway is activated only by afferent impulses in the pelvic nerves, which transmit the sensation of intravesical pressure. Considered together, these data suggest a spinal reflex exists in which afferent projections sense bladder distention, and efferents located in the thoracolumbar and sacral sympathetic chains are activated to produce a tightening of the bladder neck. This basic reflex arc and its modulation by the CNS are discussed in greater detail in a subsequent section.

Kleeman (177) first reported that electrical stimulation of presacral nerves and administration of α-adrenergic agonists produced bladder neck closure in dogs, and he is credited with the first observation that α-antagonists could be of use in promoting bladder emptying. The concept of a physiologic internal bladder neck sphincter controlled by adrenergic influences began to evolve (18,184,185). McGuire (242,243 and 244) proposed that with bladder filling there was stimulation of the urethral α-receptors mediated by adrenergic fibers. In his view, the ability of urethral smooth muscle to contract would be independent of any parasympathetic influence, and would be completely lost if the thoracolumbar sympathetic chain were destroyed. Numerous authors agree that under normal conditions of bladder filling, the adrenergic system increases its activity and increases bladder outlet resistance.

Although proponents of the adrenergic system could readily define how increased adrenergic stimulation could enhance bladder outlet resistance, it proved more difficult to understand how this system could be “shut down” to allow for voiding at low pressures. McGuire (243) speculated that this occurred via ß-receptor activation mediated by parasympathetic stimulation. This concept is that parasympathetic stimulation leads to contraction of the bladder body and simultaneously leads to diminished outlet resistance at the bladder neck by acting at a ß-receptor site. El Badawi (123) also endorsed the concept that “the storage phase of micturition is controlled primarily by the sympathetic system, and the voiding phase by parasympathetic vesicourethral innervation.” He argued that the initial ß-mediated relaxation was balanced by tone adjustments in the trigone and posterior urethra was mediated by cholinergic stimulation. Today, much more is understood about which molecular mechanisms may account for the relaxation of the bladder neck and urethra since the discovery of the NO pathway.

Equally strong arguments have been made against such a powerful role for the sympathetic system in controlling the bladder neck during the storage or voiding phases of micturition. Klevmark (178), studying anesthetized cats, noted no difference in slow-fill CMGs before and after sympathectomies, leading him to conclude that the sympathetic system had little effect on bladder activity with filling. Clinically, Wein (353) has observed that patients on α-blockers for hypertension do not experience a clinically significant loss of bladder capacity. Nordling (272) also noted that ample evidence existed to support the notion that the role of the sympathetic system in the normal micturition cycle is minimal. He correctly noted that in the normal individual, “sympathectomy” or retroperitoneal lymphadenectomy almost never produce voiding dysfunction.

Adrenergic Effects on the Striated Sphincter

Today, the striated sphincter is believed to be under somatic control. Some evidence was reported in favor of an adrenergic contribution to the striated external sphincter. Nanninga and associates (261) found that external sphincter electromyelographic (EMG) activity decreased after α-blockade with phentolamine, which they attributed to a direct effect on the striated muscle. Nordling and co-workers (271) demonstrated that clonidine and phenoxybenzamine,

which cross the blood-brain barrier, decreased the urethral pressure profile and EMG activity in five normal women. When phentolamine, which does not cross the blood-brain barrier, was used, the urethral pressure decreased with no change in the EMG. The authors concluded that phentolamine's effect was a result of smooth muscle relaxation, whereas clonidine and phenoxybenzamine had a centrally induced change in striated urethral tone.

Lincoln and colleagues (220) carried out a detailed immunohistochemical analysis of the striated external sphincter in normal patients and in patients with spinal cord injuries. They concluded that any adrenergic nerves identified in the sphincter were associated with blood vessels, and that there was no adrenergic component to this group of striated fibers, findings similar to Wein and associates' original study (355). Heidekamp and co-workers (146) demonstrated that transection of the pudendal nerve in the rat leads to significant atrophy of the striated external sphincter both in terms of muscle cross-sectional area and average fiber diameter. However in these animals, voiding frequencies or volumes were not affected.

Nitric Oxide Pathway

To fully understand lower urinary tract physiology, it is important to review the NO pathway. Andersson and associates (9) described the electrically mediated relaxation of the isolated human and rabbit urethra following contraction with noradrenaline. In other words, the ability of neural stimulation to relax the urethra could be “unmasked” only by first precontracting the muscle. At the time of that publication, NO was unheard of, but this report made it clear that other neurotransmitters had to be involved in the physiology of the bladder base and urethra. In the last 18 years, the literature devoted to NO has increased exponentially, and the urologic implications of this pathway are becoming more apparent.

This field had its inception in the search for an endothelial-relaxing factor, so named because cardiovascular physiologists noted that the endothelium had to be intact if vascular smooth muscle strips were to relax *in vitro*. If this endothelium was removed, the strips lost their ability to relax. Although logic might dictate that in biologic systems, such a relaxing factor would be a peptide or complex molecule, the actual molecule turned out to be NO (278). It is ironic that this simple molecule, which under ordinary circumstances exists as a gas, is an air pollutant, is toxic at high enough concentrations, and also proves to be an important neurotransmitter. Its synthesis takes place from L-arginine, which is enzymatically transformed by the calcium- and calmodulin-dependent nitric oxide synthase (NOS) (Fig. 26A.27). NO biosynthesis requires two nicotinamide adenine dinucleotide phosphate (NADPH) cofactors.

This is significant, because the NOS may be imaged histologically by staining for NADPH diaphorase. In addition, this system has a known inhibitor of NOS in the form of *N*-nitro-L-arginine monomethyl ester (L-NAME), which acts to prevent the two oxidation steps. Of the two (D and L) enantiomers, only L-NAME is active in this inhibition. Many physiology studies employ D-NAME as a control, and if L-NAME is applied, any relaxation attributed to NO should disappear. Once NO is produced by the endothelium or neuron, it may diffuse across to the adjacent smooth muscle cell, where it increases cGMP levels, which in turn stimulate the Ca^{2+}-Mg^{2+}-ATPases that pump calcium out of the cytosol and bring about relaxation. Nitroglycerin and nitroprusside, long known to be effective vasodilators, have been shown to exert these effects after their metabolism in the endothelium into NO. At higher concentrations, NO has cytotoxicity and results in degradation of cell nuclei, with breaks in DNA strands (240). It is very important to note that several NOS isoforms exist including endothelial (eNOS), inducible (iNOS), and neuronal (nNOS). Several reviews have presented a larger overview of NO and its role in a number of biologic and urologic systems (47,52,251).

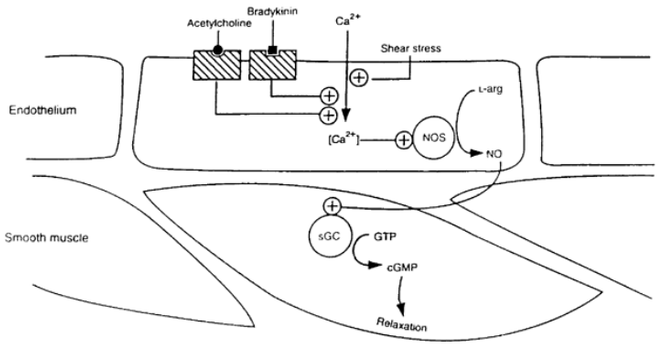

FIGURE 26A.27. A schematic diagram showing the biosynthetic pathway for nitric oxide. In response to cholinergic receptor–mediated stimulation, other ligands (bradykinin), or mechanical stress, intracellular calcium concentrations rise. This results in calcium binding to calmodulin, and this in turn activates the enzyme, nitric oxide synthetase (NOS). NOS allows for L-arginine to be broken down into NO with a required nicotinamide adenine dinucleotide phosphate (NADPH) cofactor (not shown here). NO then diffuses into the adjacent smooth muscle cell to raise cyclic guanosine monophosphate (cGMP) levels by activating soluble guanylate cyclase (sGC). It also is possible for cytokines to bind directly to smooth muscle cells and trigger a calcium-independent synthesis of NO (pathway not shown). GTP, guanosine triphosphate. (From Moncada S, Higgs A. The L-arginine nitric oxide pathway. *N Engl J Med* 1993;329:2004, with permission.)

A growing literature from many research groups suggests a major role for NO in genitourinary smooth muscle. Rajfer and co-workers (293) and Burnett and co-workers (51) have offered strong evidence to suggest that NO is the major final mediator of penile erection. In bladder and urethral smooth muscle, the effects of NO are demonstrated best after muscle strips are precontracted in response to cholinergic or adrenergic stimulation. Once a stable plateau tension is reached, the strips are subjected to field stimulation, and the NO results in a loss of active tension. The effect of NO-induced relaxation may then be expressed as a percentage of the starting baseline tension. The use of D-NAME or L-NAME then establishes that these effects are caused by NO, because only the application of L-NAME should result in a loss of this relaxation. Studies supporting a role for NO in lower tract smooth muscle come from *in vitro* and *in vivo* studies of urethra, fetal models, and detailed phenotypic characterization of the neuronal knockout mouse.

Lee and associates (197) studied the comparative pharmacology of the male and female rabbit bladder neck and urethra. They found that the urethral smooth muscle was significantly more likely to relax than the bladder neck (Fig. 26A.28), and these relaxations were abolished completely by the addition of L-NAME. The degree of NO-mediated relaxations was not different between the sexes. In the pig, Bridgewater and colleagues (48) performed *in vivo* and *in vitro* studies of the urethral smooth muscle. In one series of *in vivo* experiments in anesthetized animals, urethral pressure was monitored simultaneously with intravesical pressure. Urethral pressures were shown to increase with bladder filling. However, just before and even as the intravesical pressure was rising to initiate micturition, the urethral pressures were dropping. *In vitro* urethral smooth muscle strips in the pig also were shown to undergo relaxation in response to field stimulation that was abolished by L-NAME. In the rat, Persson and co-authors (285) demonstrated that intraarterial administration of L-NAME decreased bladder volume and increased spontaneous bladder contractions. Strips from the detrusor had no response to field stimulation, whereas strips from the urethra showed relaxations of 90% to 100% of the baseline tension.

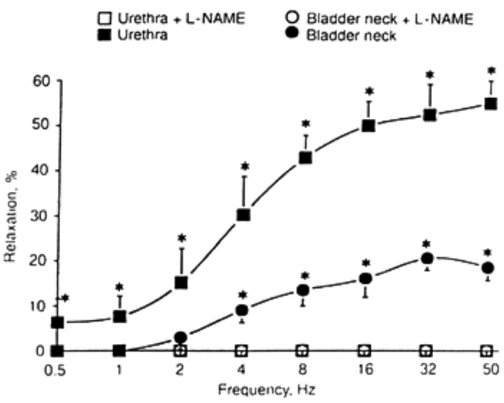

FIGURE 26A.28. The effects of L-NAME, an inhibitor of nitric oxide (NO) synthesis, on the response of the rabbit urethra and bladder neck to field stimulation following precontraction of the strips with phenylephrine. The relaxation of these strips increased with increasing frequency of field stimulation, and was abolished completely by L-NAME. These types of experiments offer evidence in support of the release of NO by neurons within the urethra and bladder neck. [From Lee JG, Wein AJ, Levin RM. Comparative pharmacology of the male and female rabbit bladder neck and urethra: involvement of nitric oxide. *Pharmacology* 1994;48(4):250, with permission.]

Lee (196) and others (183), using bovine fetal bladders, demonstrated that the bladder base showed a greater NO-induced relaxation than the body. They also demonstrated that this relaxation peaked in the last trimester, which coincides with the growing ability of the detrusor to generate tension. Gobet and co-workers (134) demonstrated that urachal ligation alone in the male sheep fetus induced bladder wall hypertrophy, and dilation of the upper tracts suggesting that a patent urachus offers protection from an immature and high-resistance bladder outlet. Kogan and Iwamoto's group (44) developed an *in vivo* fetal lamb model in which the bladder was catheterized to allow for CMGs *in utero* before and after intravenous pharmacologic manipulation. They showed that, after perfusion of L-arginine, it was impossible to fill the bladder to allow a CMG to be performed, and that this effect persisted for several hours. Ligation of the urethra and administration of L-arginine did not enhance bladder capacity on a subsequent CMG. In contrast, the application of L-NAME increased bladder capacity (248,265). In addition, with staining techniques selective for NADPH diaphorase, this group has demonstrated that NOS activity is clustered primarily at the

bladder neck. Considered together, these studies suggest that NO is critical in maintaining low muscle tone at the bladder neck and minimizing outlet resistance during fetal development.

In vivo or *in vitro* studies of the NO pathways using L-arginine or L-NAME have made valuable contributions to the understanding of bladder physiology. However, such studies have a major limitation in that the use of L-arginine or L-NAME do not distinguish among the three basic isoforms of NOS. One advantage of knockout technology is that it allows for study of a specifically targeted genetic deletion. Although knockout and transgenic studies will play a great role in urologic science over the next decade, it must be pointed out that, at this time there are no bladder-specific genetic models. This point is illustrated well in the phenotypic study of the murine model in which the second exon of the neuronal NOS gene underwent a targeted deletion. Burnett and partners (50) studied this murine phenotype, commenting on the prominent bladder wall hypertrophy; $nNOS^-$ bladders weighed a striking 60% more than their wild-type mates (Fig. 26A.29). In addition, this group of investigators measured the responses of bladder and urethral muscle strips, and demonstrated significantly blunted responses to the effects of L-arginine and L-NAME. In contrast, histology studies showed no change in the expression of eNOS, implying the knockout was nNOS specific. With evidence of bladder wall hypertrophy, these investigators also studied the *in vivo* voiding patterns. They noted a significant increase in the number of voids from 2.2 to 4.5 during an 8-hour observation period. However, Mevorach, Bogaert, and Kogan (248) studied this same population of mice, and found that when corrected for water intake, urinary frequency was identical within both groups. That these knockout mice are thirstier than their wild type controls suggests that nNOS deletion probably has other effects that influence water consumption. Mevorach, Bogaert, and Kogan (248) also reported that the $nNOS^-$ mice had a higher leak point pressure and a larger bladder capacity in urodynamic studies performed under anesthesia. Considered together, these two studies provide further support for the theory that bladder neck and urethral tone are very much dependent on NO. The discrepancy in water intake between the wild-type and knockout mouse also serves as a reminder that no technology is available at this time to create a bladder- or urethra-specific gene deletion.

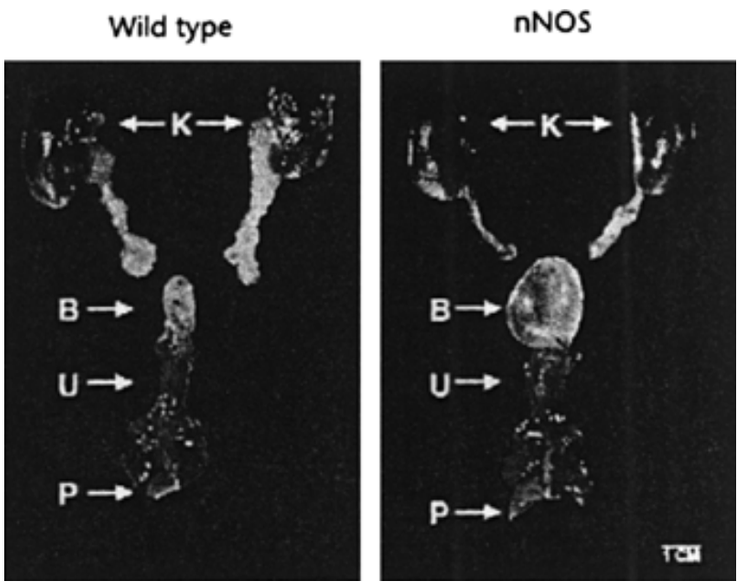

FIGURE 26A.29. A comparison of the urinary tracts from wild-type versus $nNOS^-$ knockout mice. The bladders from the $nNOS^-$ strain weighed 60% more than their wild-type controls (51). The bladders also were shown to have larger capacity and a higher leak point pressure under anesthesia (248). B, bladder; K, kidneys; P, prostate; U, urethra. (Reprinted from Burnett AL et al. Urinary bladder sphincter dysfunction in mice with targeted disruption of neuronal nitric oxide synthase. *Nature Med* 1997;3:571, with permission.)

In summary, a number of independent investigators have shown that NO plays a major role in bladder neck and urethral smooth muscle relaxation, with a lesser role in the bladder body. This has been demonstrated in a number of species, in fetal and adult tissues, and includes *in vivo* and *in vitro* studies, as well as a knockout mouse model. Based on all this evidence, it appears that NO plays a major role in the relaxation of the bladder neck that allows the “shutter mechanism” to open, and in the lowering of urethral pressures. When these events are timed properly, followed by detrusor contraction, voiding proceeds with synergy at low pressures. As molecular methods improve (e.g., antibodies, nucleic acid probes), it will be possible to probe small biopsy specimens to assess patients with clinical voiding dysfunction, by looking for disruptions in NO pathways.

Prostaglandins

It is well established that the bladder is a site of prostaglandin synthesis. This has been shown by the release of prostaglandins following bladder distention (133) or distention and pelvic nerve stimulation (171). The rate-limiting enzyme involved in prostaglandin synthesis is cyclooxygenase (COX), which exists in two isoforms (1 and 2), and the expression of COX-2 has been shown to diminish during fetal gestation in the mouse (280). Although no changes were shown in COX-1, COX-2 protein and gene expression are induced in mature mice via bladder distention (279,280). The deletion of the COX-2 isoform results in a mouse with normal bladder morphology, but these mice later die of renal insufficiency (253). Thus it is clear that, although COX-2 is regulated developmentally and its synthesis is increased with distention, its expression clearly is not mandatory for bladder development and normal function. This does not imply that prostaglandin synthesis in the bladder is unimportant; it does point out that during bladder development, other pathways compensate for the loss of COX-2 expression, and that bladder emptying is not prostaglandin dependent.

The potential roles for prostaglandins in the lower urinary tract might include stimulating smooth muscle contraction, triggering sensory receptors, and altering the microcirculation. Andersson and Sjögren (10) noted that prostaglandin E (PGE) and prostaglandin F (PGF) produce contractions of bladder smooth muscle strips. These contractions were slower to develop and of longer duration than those induced by acetylcholine and were not influenced by tetrodotoxin, atropine, or phenoxybenzamine. This would suggest that prostaglandins are capable of acting directly on the smooth muscle. However, despite such experimental evidence, most authors today believe that prostaglandins do not contribute to normal bladder contraction. Topical application of PGE2 onto the dome of a partially filled rat bladder induced a contraction *in vivo,* and this contraction is abolished if the animal is pretreated with capsaicin (which blocks the C fibers). On review of the collected literature, Andersson and Sjögren (10) concluded that it is unlikely that prostaglandins are involved directly in bladder emptying, but rather serve as modulators of neurotransmission (7). In support of this concept, Downie and Karmazyn (113) observed that mechanical irritation of the epithelium increased the basal tension and active responses to field stimulation. These effects were related to the intensity of the trauma; were mimicked by prostaglandins of the E, F, and I series; and were blocked by prostaglandin-synthesis inhibitors.

Substance P

Substance P, a peptide hormone, originally was detected in extracts from gut and brain and was prepared as a powder (hence the designation P). Its pharmacologic effects are varied, including vasodilation; contraction of bronchial, intestinal, and other smooth muscle; and stimulation of salivary secretion. Small amounts are found in the bladder in a suburothelial position, as well as in the dorsal root ganglion and dorsal horn of the lumbosacral cord (5,258). Substance P also has been shown to be present in cholinergic neurons (108). *In vitro,* substance P produces a bladder contraction that is atropine resistant (258), but does not alter the response to field stimulation. Most authors conclude that substance P is not a mediator of excitatory noncholinergic transmission, but rather serves as a sensory neuromodulator. Mallory and deGroat (238) demonstrated that when injected intrathecally, substance P could inhibit bladder activity, and this effect was reversed by naloxone, indicating that it was mediated by opioid intermediates.

Vasoactive Intestinal Polypeptide

Vasoactive intestinal polypeptide (VIP) contains 28 amino acids and was first isolated from the intestinal tract. It has a wide range of effects, including stimulation of cardiac contractility, glycogenolysis, and potent vasodilation. It serves to relax a variety of smooth muscle systems and stimulates the secretion of pituitary and hypothalamic hormones. VIP is the most common peptide hormone found in all the bladder layers, but its expression is especially prominent submucosally. As with other peptide hormones, *in vitro* studies have demonstrated contraction, relaxation, or no effect directly on bladder smooth muscle; it now appears that VIP may exert its influence at the level of the spinal cord. Igawa and co-workers (161) have shown that VIP given either intraarterially near the bladder or intrathecally leads to diminished bladder capacity and increased spontaneous contractions (intravenous doses had no effect). The use of hexamethonium (a ganglionic-blocking agent) abolished the effects of the intrathecal doses of VIP, but not the intraarterial doses. This led the authors to conclude that VIP may be facilitating the micturition reflex at the spinal cord and ganglionic levels. These views would be supported by studies using immunohistochemical techniques, where VIP has been located in the neurons, ganglia, and spinal segments (169). In addition to serving as a possible modulator of bladder contractility, the presence of VIP in afferent neuron groups has raised the possibility that it is involved in sensory pathways.

Neuropeptide Y

A peptide hormone, neuropeptide Y (NPY), contains 36 amino acids and occurs in numerous locations, including the bladder. Some authors have noted a role in bladder (258) or urethra (374). However, Peekan and associates noted that an NPY agonist had no effects of lower urinary tract smooth muscle. Furthermore, they could not identify

specific receptors for NPY in bladder or prostatic smooth muscle. Dixon and colleagues (108) identified strong immunohistochemical evidence of NPY in cholinergic neurons within the bladder. As is the case with substance P and VIP, NPY may play more of a role in modulating sensory signals from the bladder for processing by the peripheral and central nervous systems.

Enkephalins

The role of opioids in the lower urinary tract has tended to center on their CNS action. However, evidence that opioids bind to specific receptors in the urinary bladder exists, and it has been suggested that the enkephalins may function as inhibitory neuromodulators at the peripheral and ganglionic levels (93). Administration of naloxone to normal patients produces notable changes in their CMGs, with a significant decrease in bladder compliance. This correlates with the studies of Sillen and Rubenson (308), who demonstrated that intravesical instillation of morphine into the bladder produces diminished frequency and amplitude of spontaneous contractions. This work has clinical significance in the postoperative management of patients following intravesical surgery such as open prostatectomy or ureteral reimplantation. Cubina and co-authors (83) used intravesical morphine administered by a catheter placed at the time of open ureteral reimplantation surgery to manage postoperative discomfort and bladder spasms. The analgesic results appeared to be secondary to direct action on local receptors, because no serum morphine levels could be detected.

Other Transmitters

Evidence exists to support a role for histamine and serotonin in bladder smooth muscle contractile function. Contractile H_1 receptors have been documented in rabbit bladder, and the response to histamine is blocked partially by atropine. This has led some to speculate that muscarinic receptors may be partly involved in this pathway. When applied directly to the bladder, serotonin (5-hydroxytryptamine) produces a biphasic contraction. The initial phase is thought to be a result of stimulation of autonomic ganglia, and the prolonged plateau is caused by a direct effect on the smooth muscle (61). It is beginning to appear more likely that serotonin exerts its major effects within the CNS (99). Other transmitters receiving increasing attention include the excitatory amino acids and γ-aminobutyric acid (GABA); these are discussed in ensuing sections on the role of CNS modulation of the lower urinary tract. However, Maggi and co-workers (232,233) have shown that GABA may enhance neurotransmission in the bladder body. Furthermore, receptors for GABA have been detected in the bladder.

CENTRAL NERVOUS SYSTEM REGULATION OF THE LOWER URINARY TRACT

Neural Pathways

In the mature individual, the ultimate control of micturition resides in the CNS and is under cortical control (88). With maturity, cortical input then serves to remove any inhibitions over the micturition center, which in turn removes any descending inhibitory influences. It is the removal of this supraspinal influence that allows for micturition to proceed. Upon completion of micturition, the spinal pathways are shifted back into an inhibitory mode. Much has been learned about where these voiding pathways reside within the CNS. Early studies consisted of neural injury models, but the current literature contains neurophysiology studies of increasing sophistication. As a result of the tremendous growth in neuroscience research, an increasing number of inhibitors of CNS neurotransmission are now available to help sort out the role played by various transmitters such as GABA (88). This section begins with a review of basic neuroanatomy, followed by a discussion of some of the newer advances in neurochemistry and neurophysiology.

Tracing Studies

The neural circuits that control lower urinary tract function have been delineated over many years with studies that grow increasingly more sophisticated. It is worth giving a brief overview of how these pathways came to be identified. Intravesical administration of WGA coupled to horseradish-peroxidase resulted in staining of those spinal segments involved with bladder function. Subsequent viral tracing studies have been conducted in animal models in which the pseudorabies virus particles are administered intravesically. This neurotropic virus is then taken up by the afferent nerves within the bladder wall, and transported in a retrograde fashion by axonal transport. Furthermore, the pseudorabies virus crosses synapses, resulting in viral expression in a second-order neuron. The neurons that have been labeled with the pseudorabies virus are then identified by immunohistochemical staining (Fig. 26A.20). In this manner, those segments within the spinal column, brainstem, and cortex that play a role in the micturition process have been identified. These studies give an anatomic picture or circuit diagram, but do not offer insight about how these circuits interact. A second kind of tracing study can not only label the affected spinal column segments, but also begin to assess function. Following chemical or infectious irritation of the rat urinary bladder, it was demonstrated that increased c-fos gene expression over controls was seen in very specific segments of the spinal cord (Fig. 26A.20) (349).

In Vivo and *In Vitro* Physiology Studies

Although the traditional studies (270) to assess neural pathways called upon the use of a controlled surgical injury and assessment of the subsequent change in function, there has been an increasing ability to conduct detailed electrophysiology studies. These are accomplished by stimulating the afferent or efferent nerves and monitoring the resulting changes in bladder pressure or action potentials in the efferent neurons. It also has proven possible in a rat model to remove the bladder, pelvic sidewall, and sacrum, with an intact spinal cord and brainstem and place this preparation in an organ bath (324). This allows for the application of electrical stimulation at various spots along the spinal column, while simultaneously measuring bladder pressures (Fig. 26A.30). This system also allows for the application of receptor agonists or antagonists to sort out which neurotransmitters are active during the voiding cycle. An alternative model that allows for study of the sacral reflex arc is the spinal slice preparation. In this system, the nerves are stained *in vivo* to identify the afferent and efferent limbs, and a thin slice of a sacral level of interest is harvested and maintained in physiologic buffer (Fig. 26A.31). This allows investigators to stimulate the afferent nerves while simultaneously measuring the action potentials in the interneuron and the efferent limb of the circuit (98).

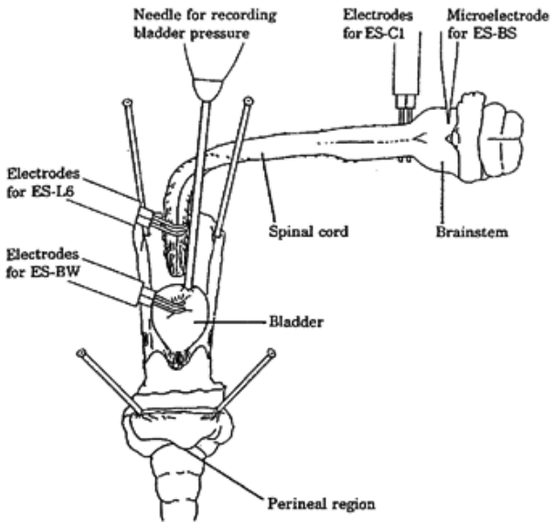

FIGURE 26A.30. The *in vitro* brainstem–spinal cord–bladder preparation. In this preparation, stimulation of neural pathways at various points can trigger a bladder contraction. (From Sugaya K, deGroat WC. Micturition reflexes in the in vitro neonatal rat brain stem–spinal cord–bladder preparation. *Am J Physiol* 1994;266:R658, with permission.)

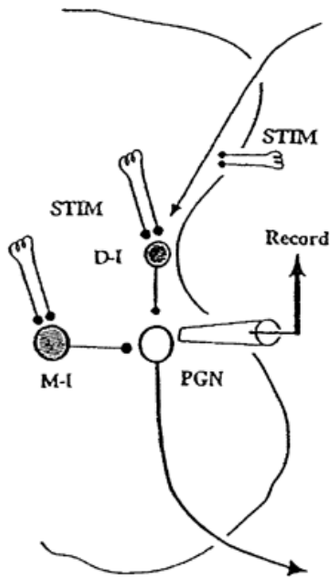

FIGURE 26A.31. The spinal slice preparation in which neurons are labeled *in vivo* with a fluorescent marker administered intravesically, allowing for their identification later *in vitro*. Stimulation of the afferent neurons is carried out with an electrode, and the ensuing postsynaptic currents are measured. PGN, parasympathetic preganglion neurons; STIM, stimulating electrode. (From deGroat WC, Araki I. Maturation of bladder reflex pathways during postnatal development. In: Baskin LS, Hayward SW, eds. *Advances in bladder research. Advances in experimental medicine and biology,* vol. 462. 1999:253, with permission.)

Clinical Findings

In the course of assessing voiding dysfunction in a variety of settings, clinicians have a growing opportunity to understand what role each part of the CNS plays in bladder function. Carefully documenting the voiding history, performing a careful neurologic examination, and tabulating the urodynamic findings now can be correlated with new imaging technologies such as MRI or positron emission tomography (PET) (36) scanning. However as with any clinical study, patients present with a variety of possible explanations for their voiding dysfunction. An elderly patient with lower urinary symptoms and Parkinson's disease may have voiding dysfunction on the basis of structural anatomic findings such as BPH. This heterogeneity in patient population is minimized in animal models where the examiner has more control over the variables. This points out the importance that animal models have had in arriving at the current understanding of how the CNS controls bladder function.

Spinal Cord and Brainstem

Spinal cord segments S-2 to S-4 are responsible for the process of micturition, with the major focus of activity at S-3 (32,90,99,302). These nerve fibers exit the cord at the vertebral T-12 to L-1 level and pass down to the respective vertebral foramen, through which they exit. The interior zones of the spinal cord are composed of gray matter in which groups of neurons that carry out similar functions are bundled together; they are called *nuclei*. The parasympathetic neurons originate from nuclei in the intermediolateral zones of the gray column (Fig. 26A.32). As these tracts descend through the sacral segments, the nuclei controlling the rectal and bladder function become separated, with bladder neurons remaining at the lateral aspect of the gray matter. Some interneurons are thought to connect the nuclei serving the rectum and bladder. Onuf's nucleus is a series of neurons clustered in the midventral spinal gray matter at human levels of S-2 and S-3. It supplies the innervation to the external striated urethral sphincter, the anal sphincter, and most pelvic floor muscles with classic somatic fibers.

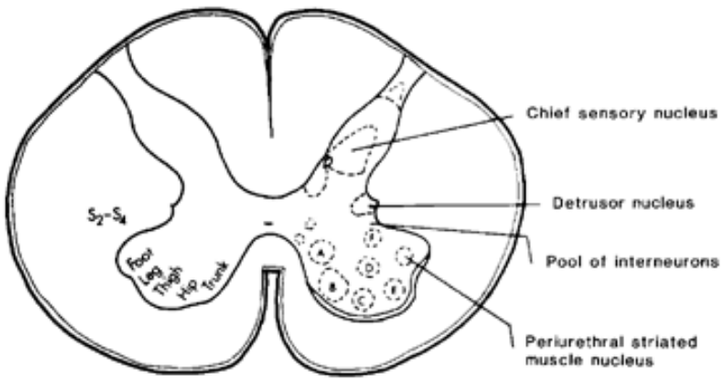

FIGURE 26A.32. Spinal cord at level S-2–S-4. Location of detrusor and pudendal motor nuclei. Bilateral representation, though not pictured, exists. (From Hald T, Bradley W. *The urinary bladder: neurology and dynamics*. Baltimore: Williams & Wilkins, 1982:5, with permission.)

Within the brainstem's anterior pontine region lies a group of neurons called *Barrington's nucleus,* which are still believed today to be the origin of impulses for bladder control (20,87,98). Destruction of this center or any areas below it will introduce permanent voiding dysfunction (43,99). Transection above this pontine center results in detrusor hyperactivity, a phenomenon well known to clinicians evaluating incontinence after strokes. Neurons modulating the pontine micturition center come from the cerebellum, basal ganglia, thalamus, hypothalamus, and cerebral cortex (Fig. 26A.33). Experimental electrical stimulation of Barrington's center caused detrusor contraction and a simultaneous decrease in EMG activity in the external striated sphincter (63,324).

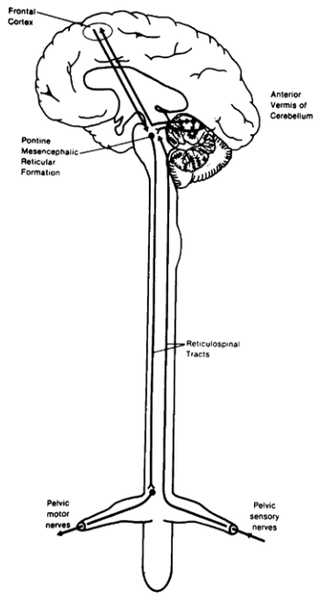

FIGURE 26A.33. The pontine voiding center and its connections with the cerebral cortex, cerebellum, and spinal cord. Sensory stimuli are also integrated in the pontine region before being conveyed to the cortex by the spinothalamic tracts. (From Bhatia NN, Bradley WE. Neuroanatomy and physiology: innervation of the urinary tract. In: Raz S, ed. *Female urology*. Philadelphia: WB Saunders, 1983:12, with permission.)

Sensory stimuli from the lower genitourinary tract must allow the distinction between pain, temperature, touch, stretch, and fullness. These differing sensory functions are handled in different segments of the spinal cord. Sensations of stretch or fullness are carried to the posterior columns of the cord and conveyed to the pons (i.e., the nucleus tegmentalis dorsalis) (32). From there, spinothalamic tracts carry these signals to the cortex (Fig. 26A.33).

Cerebellum

The cerebellum serves to modulate motor activity initiated in other parts of the CNS. It receives sensory input from the bladder and pelvic floor muscles. Its efferent role is to maintain tone and coordination in the pelvic floor striated muscles, and it also has an influence in coordinating relaxation of the pelvic floor with detrusor contraction. Electrical stimulation of the cerebellar fastigial nucleus suppresses the detrusor reflex by inhibiting the pontine micturition center. In a clinical correlate, Leach and colleagues (195) reported on urodynamic findings in 15 patients with cerebellar ataxia. Detrusor hyperreflexia was seen in 60%, and an acontractile bladder was noted in 30% of the patients in this series.

Basal Ganglia, Thalamic Nuclei, and Limbic System

The nuclei of the basal ganglia, located below the cortex and adjacent to the thalamus, consist of the caudate and red nuclei putamen, globus pallidus, and cells of the substantia nigra. Evidence supports the theory that these structures have an inhibitory role on the pontine micturition center (32). The clinical correlate is in patients with Parkinson's disease who have lost their dopaminergic neurons within the substantia nigra, and who have hyperactive detrusors. The thalamic nuclei relay sensory information upward to the cerebral cortex (44,144). It has been shown that bladder distention does cause neuronal activity to increase in these regions. The limbic system comprises areas located primarily in the temporal lobe, and is thought to include the amygdala, hippocampal formation, and cingulate gyrus. Electrical stimulation of these areas produces variable results. Depending on the zones chosen, bladder activity may be facilitated or depressed. There is no obvious clinical pattern for voiding dysfunction following damage to these zones.

Cerebral Cortex

The supermedial portion of the frontal lobes and the genu of the corpus callosum (Fig. 26A.34) are responsible for lower urinary tract control (32,144). Depending on where electrodes are placed, cortical stimulation may either facilitate or inhibit detrusor contractility. However, transection data all suggest that the result is an inhibition of the pontine micturition center (190,262). Following stroke, the most common urodynamic finding is uninhibited detrusor contractions. When voiding occurs, it is with synergistic relaxation of the external sphincter. The areas of the cortex concerned with innervation of the striated sphincter are located on the medial aspect of the cortex within the central sulcus. Axons originating in this region pass caudally through the internal capsule into the lateral columns of the spinal cord. The axons serving the detrusor arise in the frontal lobe and traverse the basal ganglia to synapse with the pontine micturition center. The use of sophisticated imaging modalities such as PET (36) or single-photon emission computed tomography (SPECT) scanning (143) will help to further localize those portions of the cerebral cortex that influence lower urinary tract function (128).

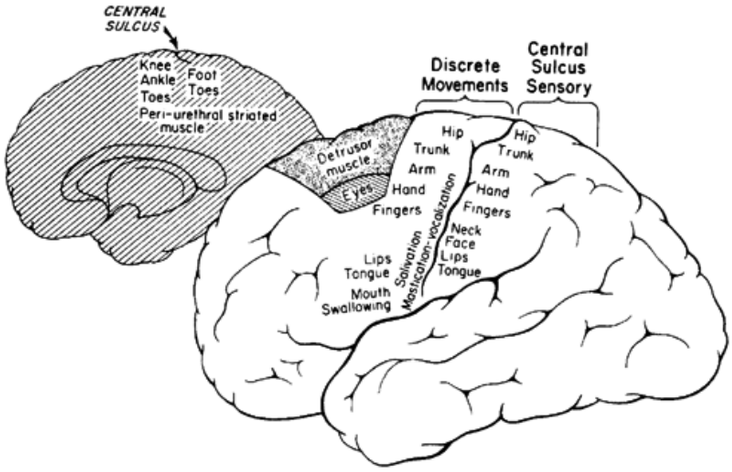

FIGURE 26A.34. Areas in the cerebral hemispheres concerned with innervation of the bladder (lateral surface) and periurethral striated muscle (medial surface). (From Bhatia NN, Bradley WE. Neuroanatomy and physiology: innervation of the urinary tract. In: Raz S, ed. *Female urology.* Philadelphia: WB Saunders, 1983:12, with permission.)

Central Transmitters

The potential transmitters of the CNS governing micturition have been reviewed by deGroat and associates (87,98,99). Both GABA and glycine have been shown to function as inhibitory neurotransmitters within the cord.

In addition, there is modulation by the enkephalins, and evidence of facilitation by dopamine. A current view of the factors influencing the pontine micturition center is shown in Fig. 26A.35 . Acetylcholine also is a CNS neurotransmitter; muscarinic receptors predominate in the brain, whereas nicotinic receptors populate the spinal cord. Acetylcholine effects at the pontine center may to be facilitative (325) or inhibitory (296).

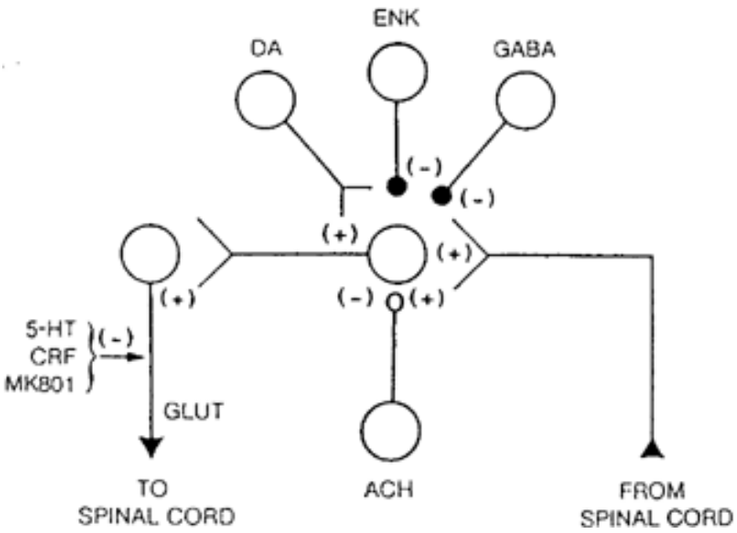

FIGURE 26A.35. A diagram showing the multiple influences demonstrated thus far on neurotransmission in the pontine micturition center, and in the descending tracts of the micturition reflex pathways. ACH, acetylcholine; CRF, corticotropin-releasing factor; DA, dopamine; ENK, enkephalins; GABA, γ-aminobutyric acid; GLUT, glutamic acid; 5-HT, 5-hydroxytryptamine; MK801, a noncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist; (+), excitatory synapse *(open circle);* (-), inhibitory synapse *(closed circle)*. The pontine voiding center may be activated or depressed by acetylcholine. The descending tracts may be inhibited by 5-HT agonists, CRF, and MK801. (From deGroat WC, Booth AM, Yoshimura N. Neurophysiology of micturition and its modification in animal models of human disease. In: Maggi CA, ed. *The autonomic nervous system, nervous control of the urogenital system,* vol. 3. London: Harwood Academic Publishers, 1993, with permission.)

Ample evidence confirms that GABA functions within the spinal cord as a tonic inhibitor of the parasympathetic nuclei in the sacral cord. Using the isolated brainstem–spinal cord–bladder preparation (Fig. 26A.30), Sugaya and deGroat (324) demonstrated that the amplitude of bladder contractions elicited by electrical stimulation of the medullary voiding center was increased when the GABA-receptor antagonist, BCMI, was added to the bath. They also demonstrated that the increases in amplitude and frequency of spontaneous contractions were more prominent in the 1- to 3-day-old rats than in the 7-day-old group. These data suggest that the GABA-mediated inhibitory actions of the pontine micturition center played a more central role in the neonatal group of rats.

Strong evidence also supports a role for the enkephalins in the central nervous component of the micturition pathways (38,92,99). In cats, the systemic addition of naloxone, an opiate antagonist, increased the frequency and amplitude of spontaneous contractions, diminished bladder capacity, and improved bladder emptying capability. The actions of opiates may occur at central sites such as the pontine micturition center, the sacral cord, or the peripheral bladder ganglia. Staining has identified enkephalin-containing nerve terminals in each of these sites, and at each site the local administration of opioids has produced inhibition of the micturition reflex (38).

These inhibitory actions are mediated by three types of opiate receptors: μ, δ, and κ. In the cat spinal cord, the κ receptors primarily are responsible for the inhibitory effects, whereas in the brain, the μ and δ receptors predominate. deGroat and associates (92) proposed that the enkephalins act at δ receptors to depress acetylcholine release from the bladder's preganglionic neurons. They felt that the μ receptors in the brainstem are concerned primarily with modulating bladder capacity, and the δ receptors in the cord are concerned primarily with modulating the magnitude and duration of the bladder contraction. Motor neurons in the nucleus of Onuf (which supplies the striated external sphincter) have been shown to have a strong enkephalinergic innervation, suggesting a possible role for the enkephalins in relaxing the sphincter in conjunction with micturition. The role of enkephalins has been reviewed by deGroat (99), and it is apparent that these mechanisms may influence bladder tone and capacity. The regulatory mechanisms are complex, and the wide range of receptors involved in these responses opens up the possibility for future pharmacologic manipulation of the lower urinary tract using these pathways.

Central Pathways

In an initial formulation, deGroat and Ryall (95) proposed a straightforward system in which sensory data entered the dorsal columns with a synapse impinging on the motor nucleus of the pelvic nerve. A descending neuron acted to modify this simple reflex arc. The reflex neurogenic bladder that develops after spinal cord transection would be explained by the loss of these inhibitory influences. Over the past 30 years, deGroat and co-workers have continued to provide growing evidence for the concept of a supraspinal regulatory pathway of micturition. The experimental evidence in support of this concept is reviewed in the final paragraphs of this section.

The concept that bladder control is mediated by the spinal cord is shown by classic spinal cord transection experiments. In such studies, cord injury results in an initial phase in which the bladder is rendered acontractile. This is followed by the emergence of bladder overactivity. Bladder overactivity also is noted in the presence of hexamethonium (a ganglionic blocker) and tetrodotoxin (which abolishes all neural activity). A model of bladder instability has been developed by Sethia in which bladder transection was used to disrupt the neural fibers within the bladder wall. In this

setting, the bladder developed uninhibited contractions that could not be ablated by hexamethonium nor tetrodotoxin. This would imply that there is also a myogenic component to the uninhibited bladder contractions seen after spinal cord injury. These studies all suggest that bladder compliance is very dependent on modulation of the bladder smooth muscle tone by descending influences transmitted by the central and peripheral nervous systems.

A number of important functional studies have accumulated to support the notion of a pontine micturition center. Using the *in vitro* brainstem–spinal cord–bladder preparation, Sugaya and deGroat (324) demonstrated that electrical stimulation of a collection of neurons within the pons produced a rise in bladder pressure. In these experiments, they also demonstrated that this rise in bladder pressure was blocked by the addition of either (a) hexamethonium or (b) glutamatergic-receptor antagonists. In these preparations, tactile stimulation of the perineum also produced a rise in bladder pressure that could be inhibited by these same blocking agents as well. Furthermore, transection of the spinal cord above the lumbar segments enhanced the reflex contractions in response to tactile stimulation of the perineum. These data again would imply that the spinal reflex arc mediated within the sacral segments is modulated by influences descending from the brainstem.

Growing evidence also suggests that the function of the sacral reflex arc is age dependent, and that with maturation there is greater influence from the pontine micturition center over the voiding cycle. Evidence comes from experiments performed using the spinal slice preparation. In these experiments, fluorescence labeling allowed for identification of the parasympathetic preganglionic neurons, which were studied with whole-cell recording methods to determine the nerve conductance (14,15,87). Electrical stimulation of interneurons (located within a 100-μm radius of the labeled neurons) produced a postsynaptic current in the parasympathetic neurons that could be measured (Fig. 26A.31). High-efficiency transmission was noted in neonates with a gradual loss taking place in excitatory transmission at 3 weeks of age (Fig. 26A.36). This loss of transmission efficiency was blocked when the animal was spinalized.

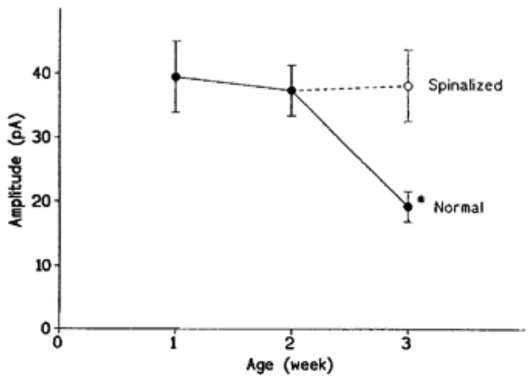

FIGURE 26A.36. There is a developmental shift in excitatory transmission as measured by current amplitude at interneuronal synapses giving rise to parasympathetic preganglionic (motor efferent) fibers. This diagram shows the currents measured in the motor fibers following stimulation of afferent neurons (see experimental design in Fig. 26A.31). With normal development there is a decline in synaptic efficiency and a drop in current amplitude produced by standard presynaptic stimulation. This drop in synaptic efficiency seen with normal development is blocked by spinal cord injury. These data imply that the developmental shift in synaptic transmission at the sacral level is modulated by supraspinal influences. (From deGroat WC, Araki I. Maturation of bladder reflex pathways during postnatal development. In: Baskin LS, Hayward SW, eds. *Advances in bladder research. Advances in experimental medicine and biology,* vol. 462. 1999:253, with permission.)

Summary of Central Nervous System Control Over Micturition

deGroat's current (87,98) concept of this neural axis reflects that two forms of bladder-to-bladder reflexes exist. One is mediated at the sacral level of the cord and is activated by nonmyelinated afferent C fibers; these neurons are blocked by capsaicin. The second reflex arc is called *supraspinal;* it is mediated by myelinated afferent A fibers that enter the dorsal columns and travel upward to the pontine micturition center. At this point, the signals are made available for the cortex to assess the sensory input. If the situation is deemed appropriate, influences descend from the cortex to the pontine micturition center that will either facilitate or inhibit this cluster of neurons (Fig. 26A.37). One point that deGroat has emphasized strongly is the role of the sympathetic system in facilitating the storage of urine (Fig. 26A.37). This diagram emphasizes the detrusor sphincter reflexes and the role of the sympathetic fibers in maintaining tone at the bladder neck in response to filling, as well as an inhibition of the detrusor. However, once micturition is initiated, the adrenergic system plays some role in relaxing the bladder outlet and releasing its inhibition of detrusor function to allow for the parasympathetic system to generate effective voiding pressures. deGroat (99) also believes that the NO pathway plays a critical role in relaxation of the bladder neck in response to the appropriate neuronal signal. The pudendal nerve, which is activated during filling to enhance storage of urine, is inhibited by supraspinal influences during micturition, thereby causing the striated external sphincter to relax.

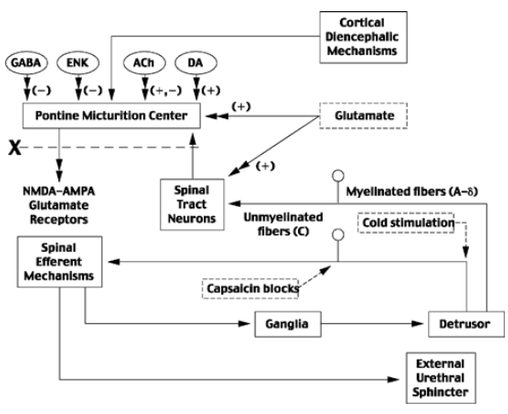

FIGURE 26A.37. Central micturition reflex pathways in the cat. With an intact neural axis, micturition is initiated by a supraspinal reflex pathway centered in the pontine-mesencephalic reticular formation. The reflex is triggered by myelinated afferents (A-δ) subserving tension receptors in the bladder wall. In animals with chronic spinal injury, micturition is blocked initially as connections between the brainstem and sacral cord are interrupted. A spinal reflex emerges that is triggered by unmyelinated C-fiber vesical afferents. This reflex is usually weak or undetectable in animals with an intact neural axis. [From deGroat WC. A neurologic basis for the overactive bladder. *Urology* 1997;50(6A):36, with permission.]

The aforementioned distinction between A and C fibers is not merely of academic interest. Under normal circumstances, sensory signals from the bladder wall are transmitted by the myelinated A fibers only. However, in response to spinal cord injury, C-fiber afferents become active, and the clinical relevance of this is the potential role for the use of capsaicin as a therapeutic modality under these circumstances (236,349). These fibers also are mediators of the

cold water reflex–stimulation test, which is seen in infants and following spinal cord injury. Sorting out which pathways are activated in various types of bladder injuries will be critical to applying capsaicin or newer analogs thereof in the medical management of patients. Resiniferatoxin, a vanilloid capsaicin analog, is 1,000 times more potent but has less initial neural depolarization, which should minimize the pain experienced with intravesical administration. These recent advances in C-fiber inhibitors and their potential application have been well reviewed (72,104).

IMPORTANT QUESTIONS ABOUT BLADDER FUNCTION

In the final pages of this chapter, the goal is to present some of the key features of bladder function and to use the preceding information to explain the observations made during the storage and emptying phases of the micturition cycle. The goal is to put the science that has been reviewed to work by tying together some of the major concepts about bladder function in a normal setting. This will serve as a stepping stone to the next chapter, in which the clinical aspects of voiding function will be discussed. Every effort has been made to present a balanced viewpoint, and the literature cited, for the most part, has already been presented. Some of the viewpoints expressed represent the authors' thoughts about bladder function; these are based on their own collective experimental and clinical work.

What Bladder Wall Properties Determine Normal Compliance?

All investigators agree that a unique feature of the urinary bladder is its remarkable compliance, whereby large volumes of urine produce exceptionally low intravesical pressures. All agree that the bladder has notable viscoelastic “passive” properties (79,142,373). The methods may vary, but these clinical and experimental observations demonstrate that the bladder may be filled to a substantial degree before a significant rise in pressure occurs. In assessing the early phases of the CMG curve, one might argue that the bladder merely is “unfolding,” and the smooth muscle simply is undergoing an anatomic realignment from an empty tubular

structure to a more spheric configuration. Once this has occurred, the next phase of compliance is a relaxation of the smooth muscle elements to allow the cells to elongate at the expense of becoming thinner. The role of the extracellular matrix is crucial in this phase, because without it, the smooth muscle cells would not be capable of acting in unison. However, this phase of the CMG is going to be more sensitive to pharmacologic manipulation.

What really determines the compliance of the urinary bladder? As shown in Fig. 26A.38, the middle portion of the fetal bovine CMG curve is exquisitely sensitive to the effects of calcium depletion in the buffer and exhibits a significant shift to the right (increased compliance). This also was demonstrated in the rabbit whole bladder model (205), fetal bovine muscle strips (368), and the murine whole bladder (157). Pharmacologic manipulations to affect smooth muscle tone produce a marked increase in bladder capacity in the midportion of the CMG curve. Coplen and associates (80) used the larger size of the bovine bladder to their advantage by repeating sequential CMGs after calcium depletion and after peeling away the muscle layer, leaving only the lamina propria and mucosa. In Fig. 26A.38, these two CMGs are presented and compared with the baseline study. A significant increase in compliance is seen following calcium depletion, and an even greater increase following the myomectomy. Clinically, this compliance of the mucosa and lamina propria was used by Cartwright and Snow (64) as they developed the concept of autoaugmentation for the neurogenic bladder. By peeling away the constricting and fibrotic smooth muscle, a template was left that ballooned out to create a large diverticulum. Smooth muscle and urothelium reappeared onto this “scaffold,” demonstrated on histologic examination in a canine model (65).

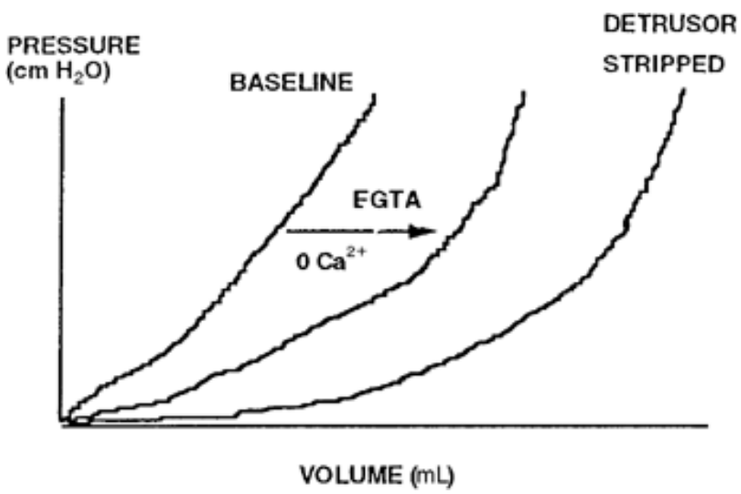

FIGURE 26A.38. The *in vitro* whole bladder model was applied to the fetal bovine bladder in this series of experiments. Each bladder was mounted as an intact organ in an isolated bath containing 300 mL of oxygenated Tyrode's solution at 37°C. The bladder was filled at 1 mL/minute with a pump, and the intravesical pressure was monitored continually with a pressure transducer and recorded on a polygraph. After a baseline cystometrogram (CMG) was obtained, the bladder was emptied and rested for 1 hour. Then the buffer was changed over to a system with 0 calcium and 2 mM EGTA (a powerful calcium-chelating agent), and field-stimulated to deplete intracellular calcium reserves. After 1 hour, the CMG was repeated; as shown there was a significant shift to the right, with some increase in total capacity. The bladder was again emptied and rested for 1 hour. Then the muscle layer was peeled away, and the CMG was repeated. Following detrusor stripping, a remarkable increase in bladder capacity and compliance was noted. (From Coplen D, Macarak E, Levin RM. Developmental changes in normal fetal bovine whole bladder physiology. *J Urol* 1994;151:1391, with permission.)

Ewalt and co-workers (127) proposed that the lamina propria layer might be responsible for bladder compliance. The experimental evidence in normal fetal and adult bovine bladders (80) supports that the lamina propria and mucosal layers are the most compliant layers of the bladder wall. Ewalt's findings require further explanation—this was an immunohistochemical study in which noncompliant bladders from myelomeningocele patients were compared with control bladders obtained at the time of reimplant surgery. Frozen sections were cut and stained for collagen types 1 and 3 and fibronectin. The results were striking, with a dramatic increase in the deposition of collagen, especially within the lamina propria layer. Furthermore, the collagens that were deposited appeared to have an increased quantity of type 3 (although both types were increased) and of fibronectin. An interesting histologic observation was the deposition of collagen fibers in between the muscle bundles, which possibly could act to restrict the cells. Although Coplen and colleagues' data suggested that the lamina propria layer was the most compliant of the bladder wall components, these data were obtained in normal tissue (80). In the presence of obstructive pathology, it is entirely possible that the dense deposition of matrix elements in the lamina propria will serve to diminish bladder compliance. These observations also might help explain why, despite the logic underlying its development, autoaugmentation has failed to work in every case.

The association of increases in type 3 collagen with noncompliant bladders was strengthened by the work of Baskin and colleagues (21,22,25) in a fetal bovine system. They demonstrated that bladders from the first trimester were the least compliant, with a gradual gain in compliance in the second trimester. The third-trimester bladders were the most compliant. Similar findings were seen in a fetal bovine model using an entirely different experimental methodology (196). Baskin and co-workers (21,22,25) demonstrated that the type 3 collagen fraction was highest in the first-trimester bladders, and then diminished with each trimester in parallel with the increases in compliance. Coplen and co-authors' data (80) pointed out the major contributing role of tone in these measurements of compliance, because these bladders all became more compliant in the absence of calcium. Upon depleting the intracellular calcium reservoirs, Dean and Cargill (101) found that fetal bovine compliance diminished with normal aging, which is contrary to Baskin's original report. Considered together, these data would suggest that compliance is a complex

property that is the sum interaction of many variables and is unlikely to be attributable to any one bladder wall component alone.

Experimentally, *in vitro* evidence exists for a loss of bladder compliance following obstruction or ischemia (168,218). Given the collagen deposition in these obstructed bladders, one might make the logical assumption that the deposition of extracellular matrix is responsible for this shift to a less compliant state. However, in a rat model (273) and a murine model (199) of bladder outlet obstruction with *in situ* cystometry performed in a sedated animal, no loss of bladder compliance could be demonstrated. In a detailed videourodynamic analysis of bladder outlet obstruction in the awake rabbit free of sedation, Stein and colleagues (320) demonstrated that bladder compliance remained unchanged. This lack of change in bladder compliance was seen despite the impressive accumulation of extracellular matrix. These findings in the *in vivo* animals free of sedation or anesthesia contrast sharply with observations made in the *in vitro* whole bladder system.

Clinically, many bladders such as those seen in patients with outlet obstruction or spina bifida end up as tiny, fibrotic, and noncompliant. How can these clinical observations be reconciled with the experimental findings of unchanged compliance? In the clinical setting, infection may be superimposed, or additional inflammation secondary to a chronic indwelling catheter may be present. Furthermore, the patient with an outlet obstruction usually is decompressed before any surgical intervention. Regardless of its pathogenesis, all would agree that the end-stage bladder characterized by poor compliance and associated with massive deposition of extracellular matrix responds poorly to medical management. In the future, major emphasis must be placed on interrupting the sequence of molecular events that lead to the end-stage bladder. Intervening to enhance bladder performance will require a multidisciplinary team approach to gain a better understanding of how the muscle, matrix, and nervous system interact during normal development and in response to outlet obstruction.

The response of the bladder to pressure work in terms of collagen expression has been well established; what remains is a more detailed assessment of how the stimulus of mechanical stretch or distention is converted into a signal that triggers collagen synthesis (225,227). Whereas one approach might be to inhibit collagen production, another might be to accelerate its degradation, hence the importance of the work of Peters and co-workers (286) in assessing the role of the collagenases and the TIMP system following outlet obstruction in the fetal lamb. Such observations are important in terms of defining potential pathways to be targeted with pharmacologic intervention.

It also appears that the bladder will respond differently to pressure work than to volume work. Longhurst and associates (223) have shown that, although the collagen content of a bladder doing volume work rises in a diabetic rat model (116) or a tight-skin mouse model (223), the cystometric curves are shifted to the right. That is to say, despite evidence of increased collagen deposition based on hydroxyproline assays, the bladders doing volume work are more compliant. This work must be put in perspective by noting that the collagen determinations were by hydroxyproline assay (hence the types of collagen are not known), and there is controversy over how to express such findings relative to other cell contents. With the advent of transgenic technology, the impact that single gene overexpression may have on the phenotype may be better understood. Lemack and associates (198) demonstrated that transgenic overexpression of the rat elastin gene produced a more compliant murine bladder.

It is interesting to consider the effects of urinary diversion on bladder function. Chun and colleagues (75) reported on dogs who underwent urinary diversion by intestinal conduits. The bladders experienced a loss of compliance when studied in a whole bladder model using a low-filling-rate CMG technique. In addition, the responses to cholinergic agonists were diminished, and this correlated with a drop in muscarinic-receptor density. These changes proved reversible once the ureters were reimplanted. Therefore it would appear that the bladder, like any other muscle system, must perform a certain amount of work to maintain optimal performance.

How Does the Nervous System Contribute to Bladder Capacity?

It is clear, at least in animals, that a spinal sympathetic reflex that has two components exists, which is evoked during bladder filling. One series of neurons delivers adrenergic stimuli to β-receptors located in the bladder body, which serve to diminish muscle tone. In humans, evidence that this component is significant is sparse. A second set of neurons delivers α-adrenergic influence to the bladder neck and proximal urethra, resulting in an increased resistance that improves storage capacity. In addition, evidence shows that adrenergic stimuli are transmitted to parasympathetic ganglia, where they provide an inhibitory influence over these cholinergic neurons. The pudendal nerve also is activated to provide somatic excitatory stimuli to the striated sphincter during filling. This innervation contributes to compliance, as noted by experimental work in which the administration of α-blockers produces a bladder with reduced compliance. Administration of naloxone has been shown to diminish bladder capacity and increase the pressures generated by spontaneous contractions. Either systemic or direct injections of morphine into the CNS produce enhanced bladder capacity and a decrease in the magnitude of spontaneous contractions (308). These observations argue for a role of the enkephalins in regulating bladder tone.

The presence of spontaneous activity during filling has been studied experimentally. Most smooth muscle strip preparations exhibit a certain degree of rhythmic contractions *in vitro* independent of any stimulation, but a correlation of this with *in vivo* activity is difficult. It also depends on the type of *in vitro* model used. Levin and colleagues (203) observed that, although spontaneous activity is seen in isolated strips, it is not observed in the whole bladder preparation. This implied that the contractions seen in strips are a myogenic response to stretch that is applied incrementally. This has been studied *in vivo* as well. For example, in the anesthetized cat, Klevmark (179) reported that slow-fill cystometry produced rhythmic contractions that were not seen in the awake animal. Furthermore, these contractions were unchanged by cord transection above T-10, and their pattern changed or they were abolished by partial or complete peripheral denervation. These experiments support the notion that bladder contractions are inhibited during filling by neural input from the sacral cord. In a rat model, Sugaya and deGroat (324) have shown that supraspinal neural input helps maintain this state of minimal bladder activity via a pathway with GABA as the main transmitter. Some authors (41,324) have summarized three major experimental findings in support of the notion that neural output from the cord tonically inhibits the bladder. Spontaneous bladder activity was increased by (a) removing the lumbosacral cord, (b) blocking ganglionic function, and (c) abolishing all neural activity with tetrodotoxin.

How do these experimental findings relate to humans? Most contemporary descriptions of urodynamics maintain that any phasic increases in bladder pressure that occur in response to filling are abnormal (1,348). However, it is important to keep in mind that artifact may be introduced into a urodynamic study if the filling rate is not set correctly. It certainly is possible to induce apparent uninhibited contractions at a fast nonphysiologic filling rate, and such contractions will not be reproduced when the filling is accomplished at slower rates. This explains the interest in Holter-type monitoring systems for assessing bladder function in the ambulatory patient.

What Determines Outlet Response During Filling?

Most investigators agree that urethral resistance is increased during filling. This measurement is made using a pressure transducer that is withdrawn across the urethra to produce the urethral pressure profile, a graph of pressure versus urethral distance. This is a difficult measurement to standardize both in clinical practice and experimentally. At least three components contribute to urethral pressure: (a) a thick and soft mucosa that coapts, (b) a smooth muscle layer invested in matrix, and (c) an outer striated muscle layer. Some believe that it is virtually impossible to separate these various components from one another, nor is it possible to separate the striated and smooth muscle components on a pharmacologic basis.

The neurophysiology data suggest increased activity in the pudendal and hypogastric nerves during bladder filling (89,99). This correlates with the clinical urodynamic picture of increasing pelvic floor EMG activity as the bladder progressively fills. This pelvic floor activity is transmitted by the pudendal nerve, which also innervates the striated sphincter. It still is not certain what role pelvic-nerve activity may have in modulating the striated sphincter. How to separate these two muscle components is experimentally difficult. However, it seems logical to assume—based on physiology, morphology, and pharmacology—that the urethral smooth muscle does play a role in increasing urethral resistance. To rigorously prove this either clinically or experimentally is difficult, and much of the evidence is indirect. Not all experimenters report equivalent findings regarding urethral pressures in response to bladder filling. Abdel-Rahman reported no change in urethral pressures while filling a cat bladder. Yet, Bridgewater and co-authors (48) reported an increase in urethral pressure in a pig bladder during filling, and a drop in pressure during micturition. This drop in pressure was inhibited by blockers of NO synthesis, leading these authors to attribute urethral relaxation to neuronal-mediated NO release. This concept is receiving growing support from multiple research groups.

Perhaps the current view of the urethra and bladder neck is best summarized as follows: evidence of a rich sympathetic innervation of the bladder neck and urethra exists, and strong evidence suggests that as bladder filling occurs, the neuronal output to these muscle groups is increased. Given the anatomic arrangement of the base and urethra, this tension results in a closing of the shutter mechanism. Furthermore, evidence shows that some of the bladder base musculature extends into the urethra. With micturition, there is a tightening of some of these muscle fibers so that the angle of the vesicourethral junction changes into a more funneled configuration, in conjunction with a NO-mediated relaxation of parts of the bladder neck and urethra, all of which allow for egress of urine at low pressure.

The passive properties of the urethral wall also contribute to resistance and hence to continence, albeit the extent to which this is feasible may be debated. Some authors have claimed it may contribute 20% to 40% of the resistance accounting for continence. It is important to be aware of the original observations that this mucosa is resting on a rich vascular bed that also is rich in collagen and elastin (372,373). This “mucosal seal mechanism” (60) is important to keep in mind for several reasons when considering the therapy of urinary incontinence (Fig. 26A.2). First, in postmenopausal females, it is a layer that is amenable to hormonal replacement, and this can explain the small number of women whose mild incontinence may be managed by

estrogen replacement. Second, it is important in knowing where to place endoscopically injected collagen or autologous fat.

Why Is Continence Preserved During Increases in Intraabdominal Pressure?

Clearly, the forces that maintain outlet resistance are complex. The dynamics of opening the bladder neck and urethra are even more complex, given that the baseline state of affairs is a closed bladder outlet. This is important because egress of urine requires two key features: a sustained detrusor contraction of appropriate magnitude, and an open and funneled bladder neck. Only if these two conditions are met will micturition occur at low pressures. A cough or Valsalva maneuver will result in increased intravesical pressure, as will the administration of subcutaneous bethanechol. However, these maneuvers will not result in urinary leakage in the normal individual because, although these two maneuvers increase intravesical pressure, that is all they accomplish. They do not cause or contribute to a “coordinated” bladder contraction. Because the bladder neck is closed, the pressure is distributed evenly within the bladder.

In addition, some anatomic factors should be taken into account. It is agreed that increases in intraabdominal pressure are transmitted to that portion of the urethra (proximal) that is located within the abdominal cavity, a mechanism first proposed by Enhorning (126). Enhorning speculated that with stress urinary incontinence, the urethra descended out of the abdominal cavity and into the pelvis, where increases in intraperitoneal pressure could not provide additional urethral compression. This view was countered by Tanagho (332), who demonstrated that the urethra was gaining inherent tone from the constriction of sphincteric muscle groups (striated, smooth, or both).

As simple and appealing as these views might be, those who operate frequently in the female pelvis point out that the boundary separating the urethra into “abdominal” and “extraabdominal” zones is not so distinct (102). Based on studies in human cadavers, DeLancey (103) has proposed the hammock hypothesis, in which the urethra lies on a supportive layer composed of the endopelvic fascia and the anterior vaginal wall. If this layer is anchored properly to the arcus tendineus fascia and the levator ani muscles, the result is a urethra that is suspended in a hammock and compressed against the pubis. As long as this hammock is intact, even a cystocele will not affect the urethral pressure profile. But if the hammock is loosened, the urethra falls away from the pubis, and the compressive effect is lost, allowing for egress of urine into the urethra (Fig. 26A.39). An example of just how this hammock may be interrupted is offered by ectopic ureteroceles that, if large enough, can distort the bladder neck and extend down the posterior aspect of the urethra. In doing so, a large ureterocele may create a large cystic cavity posterior to the urethra, and when the ureterocele is deflated by either endoscopic incision or upper-pole partial heminephrectomy, the result is a bladder neck and urethra that may not function normally. It is noteworthy that following upper pole heminephrectomy only, 10% of the patients developed stress urinary incontinence (154).

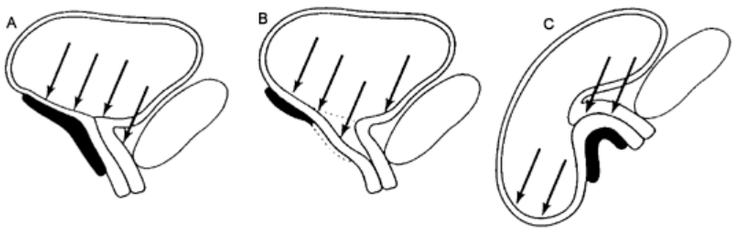

FIGURE 26A.39. The hammock hypothesis is illustrated in these diagrams. **A:** The investing layer of pelvic fascia and anterior vaginal wall, which compose the hammock *(shown in black),* serve to compress the urethra, which feels the effects of the abdominal pressure; this results in elevated urethral resistance. Loss of this sling effect *(dotted line)* produces a zone of low resistance in which increases in abdominal pressure produce egress of urine into the posterior urethra, **(B)** thereby initiating stress incontinence. The presence of a cystourethrocele alone may not produce stress incontinence if there is an adequate sling to counteract the effects of increased abdominal pressure by increasing urethral resistance **(C).** (From DeLancey JOL. Structural support of the urethra as it relates to stress urinary incontinence: the hammock hypothesis. *Am J Obstet Gynecol* 1994;170:1713, with permission.)

Although controversy about the exact details may exist, most authors agree that the evidence favors some kind of compressive force that augments the urethral resistance during periods of elevated abdominal pressure. It still is uncertain why a suspension procedure corrects genuine stress incontinence. Whether this is by increasing direct pressure transmission to the urethra, or by locating the urethra closer to the pubis, which can act as a “backboard,” remains controversial. To summarize this section, the following three reasons why normal rises in intraabdominal

pressure do not result in urinary incontinence are presented.

1. An increase in total bladder pressure is not the same as a coordinated bladder contraction (with a coordinated contraction there also must be an opening of the bladder neck).
2. A striated sphincter reflex increases tone in the striated external sphincter with cough, strain, or any other rises in abdominal pressure.
3. Anatomic factors such as the cradling of the urethra against the pubic bone by the hammock increase resistance to egress of urine into the urethra. These concepts will be better understood by functional MRI studies of continent and incontinent patients.

Normal Lower Urinary Tract Function: Unifying Concepts

In any scientific review of a process as complex as micturition, there is bound to be ample controversy. Differences in species, methods, models, and investigators combine to create a diversity of opinions in the literature. When searching for ever finer details, these differences become more apparent. Although this is a source of great challenge to the scientist, it is a source of confusion for the clinician struggling to develop a rational strategy for management of voiding dysfunction. In these final paragraphs, the core concepts with which most (99%) scientists and clinicians would agree are summarized.

The bladder must be capable of performing two separate functions—storing and emptying. The bladder is one of the most compliant organs in the body, enabling its volume to expand dramatically without any significant increases in pressure until a critical point is reached. The bladder is composed of mucosa, lamina propria, smooth muscle cells, nerve endings, fibroblasts, and extracellular matrix (perhaps up to 50% of the total cross-sectional area). It is this dynamic combination of elements interacting together that allows low-pressure filling. Once a critical pressure is reached, the autonomic and somatic nervous systems are put into action. Through the pudendal nerve, somatic fibers activate the striated sphincter. An additional spinal sympathetic reflex is evoked, and its efferent fibers are carried via the hypogastric nerve. The activation of this circuit produces three primary effects: inhibition of detrusor contractility (ß effect), activation of the bladder base and urethra (α effect), and inhibition of parasympathetic transmission through the ganglia. There appears to be strong support for a role for endogenous opioids and GABA in suppressing spontaneous contractions and enhancing bladder volume on the basis of CNS mechanisms.

Storage is further aided by the anatomic location of the urethra, with intraabdominal pressures being transmitted to it to enhance its resistance. This helps maintain the necessary relationship for continence: urethral pressure must always exceed intravesical pressure. When intravesical pressure exceeds urethral pressure, leakage will result regardless of the anatomy.

Once maturation has occurred, the process of micturition involves a sensation of fullness perceived by the frontal lobes of the cerebral cortex. These sensory signals are conveyed from stretch sensors by myelinated afferents, which pass superiorly to the cortex via the dorsal columns of the spinal cord. If the social setting is deemed appropriate, signals travel from the frontal cortex back down to the pons, where the micturition or voiding center is located. These circuits may offer a stimulatory or inhibitory signal to the pontine voiding center. Endogenous opioids and GABA act as inhibitors of this nucleus, whereas dopamine stimulates these neurons. Once the pontine micturition center has been stimulated, signals are sent down the cord to the intermediolateral zones of the gray matter at the S-2 to S-3 segments, which is where Onuf's nucleus exists. This nucleus contains the motor neurons of the parasympathetic system that, when activated, initiate detrusor contraction.

The supraspinal stimulation of the parasympathetic neurons initiates detrusor contraction and also triggers the inhibition of the sympathetic system and the pudendal nerve reflex. The stimulation of the parasympathetic system via the pelvic nerve results in a sustained bladder contraction of adequate magnitude. This is timed to occur synergistically with a relaxation of the bladder outlet combined with a dilation of the urethra to produce a funneled configuration with low resistance to flow. It is now known from *in vitro* and *in vivo* experiments that NO is a major neurotransmitter involved in the relaxation of the bladder neck and urethra. In addition, the sympathetic and pudendal reflexes are inhibited, resulting in diminished stimulation of the α-receptors of the base and urethra, and producing diminished tone and EMG activity of the striated sphincter. In addition to these “simple” circuits are superimposed influences from the cerebellum, thalamus, basal ganglia, and other supraspinal influences yet to be fully elucidated.

No matter what controversies exist, the experts agree on several major points. The micturition cycle involves two relatively discrete phases: bladder filling and urine storage, and bladder emptying. For these two components of bladder function to occur normally, the following concepts must apply.

Bladder Filling and Urine Storage

1. Increasing urinary volumes at low pressures must be accommodated with appropriate sensation.
2. The bladder outlet must be closed at rest and remain so during increases in intraabdominal pressure.
3. Involuntary bladder contractions must not be present.

Bladder Emptying

1. There must be a coordinated contraction of the detrusor smooth muscle that is sustained and of adequate magnitude.
2. There must be a concomitant relaxation of the bladder neck and lowering of urethral resistance at the level of the smooth and striated sphincter.
3. There must be no anatomic obstruction.

With this background review of the basic science of micturition, and the preceding summary, the authors hope that the reader is now prepared for a discussion of the clinical aspects of voiding dysfunction. In our view, it is extremely important for the clinician to appreciate that no matter how sophisticated the science, two basic phases are involved in maintaining continence: storage and emptying. This provides an excellent means of categorizing voiding dysfunction, because most causes will fall into either of these two main categories. There are, of course, subdivisions within each main category, and some disorders represent combinations of failure to store and empty. Creating these categories also facilitates the conceptualization, choice, and interpretation of urodynamic studies. Most important of all, abnormalities of these categories and subdivisions have differing treatment options, and by classifying the clinical problem in this way, one can choose the most optimal therapy from treatment menus. These clinical considerations will be expanded upon fully in Chapter 26B .

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26B VOIDING DYSFUNCTION: DIAGNOSIS, CLASSIFICATION, AND MANAGEMENT

William D. Steers

David M. Barrett

Alan J. Wein

Part of "26 - VOIDING FUNCTION AND DYSFUNCTION "

W.D. Steers: Department of Urology, University of Virginia, Charlottesville, VA 22908.

D.M. Barrett: Department of Urology, Tufts University School of Medicine, Boston, MA 02111; Lahey Clinic, Burlington, MA 01805.

A.J. Wein: Division of Urology, University of Pennsylvania, Philadelphia, PA 19104.

OVERVIEW

Voiding dysfunction results from an abnormality affecting urine storage or release. A division into causes related to the bladder and etiologies involving its outlet allows all voiding dysfunction to be categorized as disorders related primarily to (a) bladder filling or urine storage, (b) emptying, or (c) a combination of filling or storage and emptying disorders. Within this scheme, combined disorders become understandable, and a therapeutic rationale is evident. Throughout this review of various types of lower urinary tract dysfunction, this classification of the clinical pathophysiology is maintained to provide a coherent description for the explanation of symptoms, urodynamic findings, and therapy. Although urodynamic and other classification schemes are useful, it is simplest to relate each diagnostic term to urine storage or release.

This chapter begins with a brief consideration of the pathophysiology and symptomatology and ends with a general outline of treatment for disorders that are categorized as “failure to empty” or “failure of filling or storage.” All aspects of neurourologic evaluation and integration of data are related within various classification systems for both neurogenic and nonneurogenic voiding dysfunction. This discussion is followed by a review of treatments for all types of voiding dysfunction. Specific voiding dysfunctions associated with neurologic disease are considered along with other disturbances in micturition.

Failure to Empty

Under normal circumstances, the urinary bladder empties completely. Failure to evacuate urine results from reduced smooth muscle content, decreased smooth muscle contractility, loss of proper neural input, excessive bladder outlet resistance, or any combination of the these conditions. Absolute or relative failure of the detrusor to contract may derive from a temporary or permanent alteration in the neuromuscular mechanisms necessary for initiating and maintaining a detrusor contraction. This includes not only loss of communication between a nerve terminal and muscle cell but also communication between muscle cells. Inhibition of the micturition reflex in a neurologically intact individual may occur by means of a reflex mechanism—for example, due to a painful stimulus, generated in the pelvis and perineum. Nonneurogenic causes include impairment of bladder smooth muscle contractility such as may occur following ischemia and metabolic disturbance, severe infection, or fibrosis. Increased outlet resistance can result from anatomic obstruction or failure of coordination of the smooth or striated sphincters during a bladder contraction. Treatments for failure to empty incorporate attempts to increase intravesical pressure, facilitate the micturition reflex, or decrease outlet resistance.

Failure to Store

Within the appropriate social constraints and normal fluid intake and renal function, adult humans urinate up to nine times a day and once or never during 8 hours of sleep. However, as with most human behaviors there is a distribution of these values, and the definition of *normal* is difficult. The function of the bladder for greater than 99% of a 24-hour period is urine storage under low pressure (less than 10 cm H_2O). Because failure to evacuate urine can cause hydronephrosis, renal failure, and eventually death, it is teleologically logical that the default for micturition mechanisms is to empty the bladder in response to stress, disease, injury, and so on. Thus it is not surprising that one of the most common bladder disorders is urinary incontinence.

Failure of the bladder to fill at low pressure and store urine may be related to the bladder, the outlet (bladder neck, urethra, and external urethral sphincter), or both. The terminology to describe problems with urine storage is confusing. *Overactivity of the bladder* has been recently defined as an inappropriate increase in urinary frequency with or without urgency or urge urinary incontinence (66). It is a useful term that is recognized by patients. Some experts prefer terms such as *lower urinary tract symptoms* (LUTS), the *unstable detrusor*, or *irritative voiding* to describe this problem with urine storage not associated with urine leakage with provocative maneuvers and an abnormality of the bladder outlet. At the extreme end of what may be a spectrum, if pain or discomfort is also present patients are often diagnosed with interstitial cystitis, abacterial prostatitis or prostatodynia, male pelvic floor disorder, or nonbacterial urethritis in the absence of an identifiable cause.

Bladder overactivity can result from increased sensory or motor mechanisms. Moreover, increased excitability of detrusor smooth muscle enhanced excitatory neural mechanisms or reduced inhibitory mechanisms can underlie sensory and motor overactivity. Motor overactivity of the bladder during filling can be associated with identifiable involuntary contractions, or as low compliance (change in pressure divided by change in volume) without a discrete detrusor contraction. Sensory overactivity is characterized by a reduced threshold for first sensation during filling with or without discomfort. Involuntary contractions can occur with aging, neurologic disease, injury, inflammatory or irritative processes in the bladder, and outlet obstruction. Most involuntary contractions are idiopathic. In dementias and aging, changes in blood flow within white matter of the prefrontal cortex, demonstrated by positron emission tomography and single-photon emission computed tomography scanning, correlate with involuntary contractions (224). Ultrastructural changes in the bladder in elderly patients with detrusor hyperreflexia and impaired contractility (DHIC) imply significant changes in the bladder itself during aging (152). Thus both myogenic and neurogenic abnormalities contribute to the increasing complaint of bladder overactivity often with involuntary bladder contractions. The ability to inhibit these contractions in a laboratory or clinical environment yet not during normal routines has been demonstrated using ambulatory urodynamics (23). Thus the absence of involuntary detrusor contractions during urodynamic evaluation fails to exclude motor overactivity as a cause of symptoms. Reduced compliance during filling may be secondary to injury or disease, but it may also result from any process that alters the viscoelastic properties of the bladder wall. Decreased outlet resistance may also develop from structural or biochemical abnormalities of urethral smooth muscle or the striated urethral sphincter, as well as from changes in innervation due to neurologic, autoimmune, and metabolic diseases or injury.

Disorders of the bladder outlet are often responsible for urine loss. It has been thought that stress urinary incontinence in women is caused by a failure of the transmission of

intraabdominal pressures to the bladder neck and proximal urethra with straining. This concept has been challenged by microtip transducer measurements within and outside the urethra during provocative maneuvers (446). Intraurethral pressures rise before extraurethral pressures, suggesting an active neural component to continence. A change in the anatomic position of the vesicourethral junction and proximal urethra during elevated intraabdominal pressure may prevent the roof of the vagina from acting as a support for the bladder neck and urethra (129). Magnetic resonance imaging (MRI) during straining demonstrates abnormalities in the pelvic anatomy in women with stress incontinence (394). In men, stress urinary incontinence is rare. When it does occur, it arises from changes in neural function or is the result of trauma following transurethral or pelvic surgery, such as radical prostatectomy. In the latter condition, stress incontinence has been associated with a loss of urethral compliance, possibly as a result of ischemia. Loss of urethral compliance is also caused by radiation or fibrosis from an indwelling catheter. The treatment of abnormalities related to the filling or storage phase of micturition can be directed toward inhibiting bladder contractility, decreasing sensory input during filling, or increasing outlet resistance, either continuously or during abdominal straining.

EVALUATION OF VOIDING COMPLAINTS

A concise, thorough, yet cost-effective approach to the workup of a patient with voiding dysfunction is outlined in Table 26B.1 . In most instances, one should initially proceed with the simplest, least invasive, most inexpensive methods, because these will often yield adequate data to support a reasonable therapeutic trial, especially of reversible therapy. The evaluation should provide insight into etiology or guide therapeutic strategy.

History	Intravenous urogram/ renal sonography
Voiding log	Voiding cystourethrogram
Physical examination including neurologic	Endoscopy
Urinalysis/culture	Urodynamics
Renal function assessment (radionuclide, creatinine)	

TABLE 26B.1. NEUROUROLOGIC EVALUATION

History

A detailed history is the most important element of the evaluation. The lack of specificity and sensitivity for many urodynamic tests heightens the reliance on history to differentiate disorders, determine etiology, and plan therapy. The clinical history of individuals with voiding dysfunction should query for neurologic disease, trauma, surgery, and medications. Drugs can be the sole reason for a change in voiding habits. Symptoms related to other organs that receive similar somatic and autonomic innervation are especially important. A temporal correlation between the triad of bladder, bowel, and sexual dysfunction should alert the clinician to the possibility of a neurogenic etiology. Simultaneous fecal incontinence, constipation, lower abdominal distention, or cramping suggests a neurologic disorder affecting intestinal or rectal sphincteric function. Changes in sexual function, such as reduced frequency, duration, and ability to obtain or maintain erections or a decrease in the volume of semen and force of ejaculation in men, could indicate a neural pathology. Likewise, a history of difficulty with vaginal relaxation or lubrication in women may indicate a neural problem. Questions relating to global neurologic status, such as orthostasis, double vision, loss of coordination, paresis, or paresthesias, should be asked.

The clinician should ascertain two things when obtaining a history. First, what is bothering the patient or most affecting quality of life? Second, what is the basis for the symptom, and does this influence therapy or prognosis? The first issue is important because many mixed symptoms require therapy that may be effective for one symptom yet worsens another. The functional classification of voiding dysfunction, as failure to empty or failure to store, can provide a basis for collecting historical data from the patient. A “wet” patient with an empty bladder is most characteristic of a storage failure, whereas a “dry” patient with a bladder that cannot be emptied is typical of evacuation failure. Primary symptoms such as these are a useful guide to a diagnosis. However, development of secondary symptoms or a combination of complaints confuses the picture. Implementation of therapeutic measures based on historical factors alone can be ineffective due to the lack of specificity of complaints. This is not to say that empiric therapy based solely on symptoms is not a pragmatic or cost-effective approach. Failure of conservative treatments or contemplation of invasive procedures warrants evaluation beyond mere history and physical examination.

Urinary incontinence (failure to store) is the involuntary, socially unacceptable, loss of urine. Incontinence arises from ureteral ectopy, congenital or acquired fistula, neuromuscular dysfunction of the detrusor or urethral sphincter, or abnormalities of the pelvic floor.

Patients with wetness from ureteral ectopy or congenital fistula are almost always females who are seen after failed toilet training. The classic presentation of a female with continuous daytime and nighttime incontinence can sometimes be difficult to obtain. Ureteral ectopy is often associated with other abnormalities of the ureteral bud or urogenital sinus, and urologic imaging should be undertaken. Formerly, an intravenous pyelogram was recommended, but recent evidence suggests that MRI with gadolinium is

the most sensitive imaging modality. Administration of indigo carmine with cystoscopy and vaginoscopy is often useful.

Deficiencies in the smooth or striated muscle or fibroelastic tissue that makes up the bladder neck and proximal urethra and surrounding tissues give rise to varying degrees of urinary incontinence. Differing in severity, leakage may occur only with associated increases in intraabdominal pressure, and thus is classified as stress or exertional urinary incontinence. Yet urinary incontinence associated with provocative maneuvers is not always due to an anatomic or functional defect of the outlet. Involuntary contractions can be triggered by rises in intraabdominal pressure. A careful history may uncover a pattern of massive urine loss with minor straining or leakage beyond the straining, or the feeling that the entire bladder is emptying—all suggestive of an involuntary contraction. A scarred, fibrotic, or noncompliant urethra and bladder neck, following trauma, multiple surgical procedures, instrumentation, or radiation therapy, may lead to incontinence. In this latter case, a constant dribbling or urine loss with minimal exertion occurs. Incontinence may also result from involuntary (unstable) detrusor contractions. This type of incontinence is associated with neurologic disease and is characterized by precipitous and episodic leakage with or without urgency. Involuntary contractions in the absence of sensation can occur. Loss of urine at night should prompt a different line of questioning. Involuntary contractions are often the cause. However, severe stress incontinence could contribute to leakage with movement or on getting out of bed. Enuresis can be classified by etiology. Total incontinence implies that voluntary voiding is prevented by continuous urine loss through an incompetent bladder outlet or decompensation from urinary retention.

Urine loss is not universally a symptom of storage failure. Overflow incontinence may manifest in a patient with detrusor decompensation or dysfunction with failure to empty. The leakage can be continuous if associated with minimal increases in intraabdominal pressure, thereby masquerading as an intrinsic sphincter deficiency or ureteral ectopy if in a child. Alternatively, incontinence may result from involuntary contractions caused by outlet obstruction and failure to empty. In this case, the precise cause of altered detrusor contractility remains unclear, but incontinence is often the resultant symptom.

Urgency is the extreme desire to void either because of discomfort or a fear of leaking. The urgency that is associated with discomfort can be due to inflammatory disease of the lower urinary tract. Urodynamic studies may be normal except for lowered threshold for first sensation and pain (idiopathic). The urgency that is associated with a fear of leaking, or a history of doing so, is usually associated with an involuntary bladder contraction, categorized as detrusor instability (nonneurogenic) or hyperreflexia (neurogenic). Thus urgency may be either a symptom of a primary failure to fill or store, or a manifestation of the detrusor hyperreflexia that develops secondary to bladder outlet obstruction. If associated with urinary frequency greater than eight times in 24 hours, the term *overactive bladder* has been used.

Daytime urinary frequency may be psychogenic. This is easily explained on the basis of multiple interactions between those central nervous system (CNS) centers (limbic, hypothalamic) associated with emotions and autonomic function. However, such an increase may represent a genuine need to void and may indicate inflammation or pain on low-volume bladder distention or detrusor overactivity. Increased frequency of urination may arise from a failure to empty completely, either because of a decreased functional bladder capacity (e.g., residual urine volume), or in association with outlet obstruction–induced detrusor overactivity.

Nocturia can accompany nonpsychogenic urinary frequency and indicate a failure of adequate urine storage or incomplete emptying of the bladder. Patients with nocturnal enuresis may have detrusor hyperreflexia (22). Enuresis may be seen in patients who exhibit a primary failure of storage or in patients who have developed detrusor overactivity because of a failure to empty secondary to outlet obstruction.

The symptom of “pressure” does not equate with the urge to void characterized by a feeling that the bladder is full or that the urge to void will soon occur. Often, no discernible voiding dysfunction is discovered in patients with a pressure symptom. This symptom could represent a resetting of the threshold for visceral afferents supplying the bladder, or it may reflect an intravesical pressure during filling that is pathologically elevated, yet below the level necessary to elicit the sensation of distention or urgency. Pressure also may be representative of the patient's accurate perception of the fact that the bladder does not empty completely and that residual urine exists. Sensation of suprapubic pressure or discomfort is mediated by afferents in the hypogastric nerve. Perineal or penile discomfort suggests mediation by afferents in the pelvic nerve.

Hesitancy and straining to void, when associated with true voiding dysfunction, often reflect a failure to empty. Hesitancy and difficulty initiating a urinary stream is not diagnostic of obstruction. Rather, increased outlet resistance or detrusor hypocontractility can give rise to these complaints.

The lack of specificity of these symptoms, especially in males, has led to an attempt to standardize terminology. The International Continence Society (ICS) and World Health Organization (WHO) have proposed the nomenclature outlined in Table 26B.2 . The terms *prostatism, irritative voiding symptoms,* and *obstructive voiding symptoms* should be abandoned because of lack of clarity. The term *lower urinary tract symptoms* collectively encompasses all symptoms. *Storage symptoms* refer to frequency, nocturia, urgency, incontinence, and pain. *Voiding symptoms* refer to slow stream, hesitancy, intermittency, straining, dysuria,

hematuria, and terminal dribble. *Postvoid symptoms* include postvoid dribble and the feeling of incomplete emptying. *Prostatic enlargement* describes the increase in prostate size on physical examination or imaging. *Bladder outlet obstruction* is a urodynamic diagnosis defined only by an increase in voiding pressure and simultaneous decrease in flow rate measured during urodynamics. *Benign prostatic hyperplasia* (BPH; not hypertrophy) is reserved exclusively as a histologic diagnosis.

Lower urinary tract symptoms (LUTS)	A collective term to encompass all LUTS
Storage symptoms	Frequency, nocturia, urgency, incontinence (all types), pain
Voiding symptoms	Slow stream, hesitancy, intermittency, straining, dysuria (urethral pain during voiding), hematuria, terminal dribble
Postvoid symptoms	Postmicturition dribble, feeling of incomplete emptying
Prostatic enlargement	Increase in prostate size felt digitally or detected by imaging
Bladder outlet obstruction	Characterized by an increase in voiding pressure ($p_{det}Q_{max}$) and a decrease in urine flow rate (Q_{max}) measured during urodynamic studies
Benign prostatic hyperplasia	As a term, would be reserved exclusively as a descriptive histologic term

TABLE 26B.2. INTERNATIONAL CONTINENCE SOCIETY (ICS) AND WORLD HEALTH ORGANIZATION (WHO) PROPOSED NOMENCLATURE

Any combination of symptoms and abnormalities can occur, such as coexistent failure to store and failure to empty. Outlet obstruction may exist in combination with detrusor overactivity. This combination of pathology may give rise to hesitancy, straining to void, frequency, nocturia, and urgency with urge incontinence. Likewise, elements of both sphincteric and detrusor incontinence can exist in a woman who complains of stress incontinence that is accompanied by frequency, nocturia, and urge incontinence. A thorough review of the temporal aspects of these symptoms enhances the clinician's ability to tailor subsequent tests to confirm any diagnoses.

A voiding log or diary provides objective documentation of symptoms. A diary can assess daytime urinary frequency, incontinence, and voided volumes. A voiding log is especially valuable to monitor therapy. Often, patients report that urinary frequency or incontinent episodes have decreased, but inspection of the written record reveals otherwise. Pad weighing and administration of oral dyes excreted in the urine are useful adjuncts to monitor failure to store. Whether a 2-hour log is as representative as a 24-hour log or a 48-hour record is as accurate as a 5-day record is debatable (564). Practically, few patients can record diaries at their place of employment or school.

Physical Examination

In addition to symptoms, physical examination provides visual confirmation of the presence and degree of urinary incontinence and may suggest an etiology. For example, a distended bladder suggests a failure to empty. Cutaneous scars provide evidence of relevant neurosurgical, orthopedic, or pelvic surgical procedures.

A careful neurologic examination is mandatory because it may uncover evidence of a neurologic lesion or disease along with symptoms of voiding dysfunction. The examination should encompass inspection of the skull and vertebral column, assessment of mentation, and evaluation of sensory and motor function. Concentrating on the pelvis, evaluation of rectal sphincter tone and the bulbocavernosus reflex is essential to assess the integrity of sacral reflex arcs. Global assessment of autonomic function can be accomplished in the office with an upright and supine blood pressure. Acknowledgment of the presence of one or another type of neurologic disease may considerably alter further testing and treatment.

Pelvic Floor Abnormalities

A variety of methods have been used to assess the degree of pelvic floor dysfunction in women. A Q-Tip test has been used to determine the degree of urethral hypermobility (Fig. 26B.1). With a moistened Q-Tip in the urethral meatus, the patient is asked to strain. Angulation of the Q-Tip greater than 35 degrees is thought to indicate urethral hypermobility. Unfortunately, variability and lack of correlation with stress incontinence has limited the usefulness of this test. Its diagnostic and prognostic significance is debatable. Nevertheless, this simple test provides comparative data for outcome analysis.

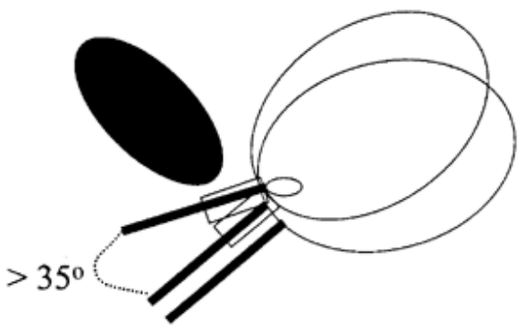

FIGURE 26B.1. Assessment of urethral hypermobility with Q-Tip test. The Q-Tip is placed into the urethra. The patient coughs and strains. A goniometer is used to measure the angle of descent from a horizontal axis. A greater than 35-degree change is considered significant.

Complaints of low back or sacral pain with or without vaginal pressure or overt bulging of a mass from the urethra should raise suspicion for pelvic floor prolapse. Assessing the degree of prolapse is problematic and lacks standardization. One scheme for classifying prolapse is based on physical examination. Physical examination should be initially performed with the patient relaxed in the lithotomy position. Failure to duplicate the symptom of prolapse or stress urinary incontinence warrants instructing the patient to

stand and place one foot on a stepping stool. One blade of the speculum or a Sims' speculum is used to inspect the vagina. A clear plastic speculum, especially if transilluminated with a fiberoptic light, is very useful, especially if a fistula is suspected. Prior filling of the bladder with water or methylene blue aids in identification of a vesicovaginal fistula. The patient is asked to gently bear down several times and cough. Some women fail to adequately strain and must be prompted. If a very distal anterior vaginal wall bulge is observed, the differential includes vaginal inclusion cyst, urethral diverticulum, ureterocele, Gartner's duct cyst (off midline), tumor, or urethrocele. Beyond the urethral meatus and distal urethra, a bulge most likely represents the bladder. Determining whether the bladder herniates in the midline or laterally (paravaginal defect) can be difficult. Pelvic MRI in women has clarified many of the potential defects leading to these deformities. One of the most popular and easiest staging schemes to learn for pelvic prolapse is the Baden system. The Baden system is easy to apply based on the hymen as a reference point, but it is difficult to reproduce. In general, no prolapse is grade 0. A prolapse of the bladder on straining in the supine and upright positions is a grade I cystocele. A cystocele at the introitus is categorized as grade II. One that protrudes halfway beyond the introitus is a grade III cystocele. Complete eversion represents a grade IV cystocele. If this degree of cystocele is associated with an everted vaginal cuff or cervix, this has been termed *procidentia* or *complete pelvic floor prolapse*. Grade IV prolapse can cause ureteral obstruction, and upper tract imaging may be useful to determine if hydronephrosis exits. A pelvic floor prolapse staging system has also been developed by the ICS pelvic organ prolapse quantification (POPQ). This system measures, in centimeters, nine sites of the vagina and perineal body in relation to the hymen. It has fairly good intraobserver and interobserver reliabilities (67) (Fig. 26B.2). The nine sites are as follows:

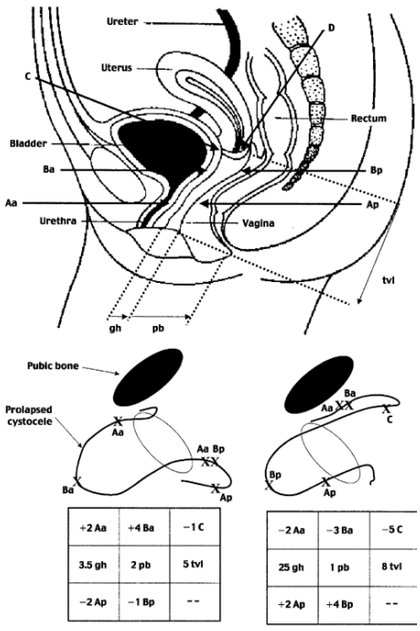

FIGURE 26B.2. Diagrams of anterior and posterior support defects based on POPQ evaluation. Leading point of prolapse is Ba (anterior) on left and Bp (posterior) on right. Numbers are measurements in centimeters for precise quantification. Severity is normalized to total vaginal length (tvl). Pb, perineal body.

1. Aa, located 3 cm proximal to the urethral meatus on the anterior vaginal wall
2. Ba, the most distal portion of the upper anterior wall
3. C, the most distal edge of the cervix or vaginal cuff
4. D, the posterior vaginal fornix
5. Ap, located 3 cm proximal to the hymen on the posterior vaginal wall
6. Bp, the most distal portion of the upper portion of the posterior vaginal wall
7. gh, the diameter of the genital hiatus
8. TVL, the total vaginal length
9. Pb, thickness of the perineal body

What this system gains in accuracy is lost in its cumbersome nature to learn and its complexity to communicate until it becomes second nature to remember during the examination.

If a bulging mass seems to originate more proximally in the vagina, one should suspect an enterocele, especially if a previous hysterectomy has been performed. Rectoceles are identified by digital rectal examination and subjectively graded small, medium, and large. Patients often complain of difficulty evacuating stool, requiring vaginal manipulation. The degree of anal tone is assessed as well. Only with a complete rectovaginal examination can appropriate therapy be formulated.

Urinalysis

Studies of abnormal renal function may uncover an unsuspected failure of emptying, or reflex intrinsic renal disease. Urinalysis and bacteriologic studies are needed because a urinary tract infection can evoke or worsen all of the symptoms of a failure to store and may result from causes of storage failure. Pyuria or persistent or recurrent infection may indicate inadequate emptying with persistent residual urine. Hematuria may be due to a malignant, traumatic, or inflammatory process. An unexplained abnormal urinalysis prompts further diagnostic tests. Recurrent unexplained dysuria, especially in older individuals with a history of smoking, warrants urine cytology to exclude carcinoma *in situ* even if a urinalysis is normal.

Imaging

Routine upper tract imaging is unnecessary in many patients with lower tract dysfunction. Retrospective data suggest that a significant abnormality is detected in only a small percentage of patients studied. However, selective imaging is warranted. Results of a urodynamic evaluation, such as reduced bladder compliance, may serve as useful indicators to select patients who warrant upper tract imaging. Upper tract deterioration can suggest emptying failure that has occurred on the basis of bladder distention, pathologically elevated voiding pressures, or both. In addition, urography is useful in assessing the upper urinary tracts before the institution of any urinary diversion to assess ureteral anatomy. In the absence of hematuria, renal sonography is the

most cost-effective tool to screen for hydronephrosis, assess renal parenchyma, and measure bladder wall thickness, as well as measure residual urine. Patients with known neurogenic bladders probably require annual ultrasounds because silent deterioration of the upper tracts can develop with stable neurologic disease or after surgical or pharmacologic therapy designed to decrease bladder contractility (augmentation) or increase outlet resistance (fascial sling, artificial urinary sphincter). It is often useful to have a baseline imaging test for later comparison.

Cystography and voiding cystourethrography provide direct confirmation of leakage with stress, relevant details of bladder and urethral configuration, and documentation of ureterovesical reflex. A straining cystogram has been used to classify the type of anatomic stress incontinence. Type 0 stress incontinence occurs when the bladder neck and proximal urethra are closed at rest and no urine loss is detected. Voluntary contraction of the outlet may explain this finding, although a phenazopyridine (Pyridium) pad test is needed to document that urinary incontinence really exists. In young women, excess vaginal secretions can occasionally be interpreted as incontinence. Type I stress incontinence is characterized by urine loss with the bladder and proximal urethra positioned above the inferior margin of the symphysis. Type IIA occurs when the bladder neck and proximal urethra descend below the symphysis, as opposed to Type IIB, in which these structures reside below the symphysis at rest. Type III stress incontinence is characterized by an open bladder neck at rest and correlates with intrinsic sphincter insufficiency. An open bladder neck at rest should prompt further evaluation to exclude neurologic disease, although in women this is not the rule. Urethral hypermobility (type II) in the absence of a low abdominal (Valsalva) leak-point pressure indicates that vaginal suspension can be considered.

Real-time voiding cystourethrography can be used to diagnose loss of coordination of the bladder with its outlet (failure to empty). Rarely, unsuspected lesions, such as a urethral diverticulum, can be diagnosed as a cause of postvoid dribbling or prolapsed ureterocele as a cause of intermittent obstruction. Even leakage secondary to an involuntary detrusor contraction can be detected by an astute examiner without the aid of differential bladder and abdominal pressures. An abnormality of emptying might be suggested by secondary signs of outlet obstruction, such as trabeculation, cellules, diverticula, or vesicoureteral reflux. If obstruction has been documented, voiding cystourethrography carefully done during bladder contraction can generally localize the site. For example, it is often useful to have radiographic confirmation of detrusor-sphincter dyssynergia. An open bladder neck can be seen on a cystogram in normal women. However, in individuals with signs or symptoms of neurologic disease, an open bladder neck may signify dysfunction of the thoracolumbar cord or its neural output.

Endoscopic evaluation may be helpful in detecting or suggesting previously unknown inflammatory or neoplastic disease or outlet obstruction. Patients with neurogenic bladders, chronic infections, bowel augmentation, or indwelling foreign bodies (i.e., catheters) for more than 7 to 10 years should be periodically assessed with cystoscopy because of the 0.4% risk of malignancy (402,611). A bloody urethral discharge should prompt immediate evaluation. Cystourethroscopy can also help guide which type of intervention is feasible, such as transurethral prostatectomy versus prostatic incision or thermotherapies for obstruction from BPH. Although conservative management of obstructive symptoms without cystoscopy is the standard of care, missed pathology such as a urethral stricture is possible. Therefore refractory symptoms warrant videourodynamics, retrograde urethrography, or cystoscopy to exclude anatomic defects.

URODYNAMICS

Urodynamics denotes a variety of diagnostic tools for the identification and measurement of physiologic and pathologic parameters involved in the storage, transportation, and evacuation of urine. The goal of urodynamic testing is to identify and quantitate the causative factors that contribute to voiding dysfunction. Because symptoms are nonspecific, the need for urodynamic testing arises when conservative measures fail or symptoms worsen. This is particularly important before advocating invasive therapy. A number of studies have documented the poor correlation between a patient's symptoms and the findings of urodynamic testing. This is true both for patients without neurologic disorders (132,170,450) and those with neurourologic disorders (56). In a study done in patients with multiple sclerosis, it was found that when treatment was instituted on the basis of symptoms and signs, it was effective in only 27% of patients. When treatment was based on urodynamic testing, efficacy rose to 83% (56). However, it is not known under what circumstances empirical treatment based solely on symptoms and examination represents a more cost-effective approach than proceeding with formal urodynamic evaluation. For example, for symptoms of precipitous involuntary loss of urine associated with urgency, does documentation of involuntary contraction on a cystometrogram really influence a trial of anticholinergic medication? How often does urodynamics per se reflect neurologic disease or poor bladder compliance and accurately indicate prognosis?

Urodynamic tests have limitations and present the potential for misinterpretation. Ideally, the symptoms should be reproduced during the urodynamic testing. Failure to elicit the symptom during routine testing suggests that the study must be repeated in as close an approximation as possible to the situation in which the patient's symptoms actually occur, be it rising, standing, coughing, laughing, or

jogging. Ambulatory urodynamics has been very useful in this regard. However, evidence for whether ambulatory urodynamics makes any difference in outcome is lacking. Moreover, ambulatory urodynamics is plagued with artifacts. Patients should be asked to assess the similarity of their usual voiding to the voiding sequence evaluated urodynamically. This helps validate urodynamic data. However, the number of indeterminate tests may be high. In one study, reliable pressure/flow data used to diagnose obstruction was obtained in only one-third of patients (133). Details on how the test is performed and how data are generated is critical for accurate interpretation. Even when performed correctly, experts may disagree on interpretation as evidenced by a recent report of pressure/flow studies (290). The intraobserver differences on calculation of an Abrams Griffiths number were substantial. Conversely, there may be certain symptoms elicited during evaluation that have urodynamic correlates, yet do not correspond to the patient's original complaints. These findings may represent artifact or may be early subclinical abnormalities not manifested during normal voiding but revealed by the provocative nature of urodynamic testing. For example, involuntary contractions can be elicited in up to 20% of normal, asymptomatic subjects in the urodynamic laboratory.

Interpreting sensory data during urodynamic testing is obviously subjective. This is unfortunate because many patients with voiding dysfunction have only sensory abnormalities. It is relatively easy to assess whether the sensation of bladder filling is normal, decreased, or absent. However, a number of sensations that may arise during filling are difficult to classify. The most troublesome of these is the symptom of urgency. Although this can correlate with involuntary bladder contractions or detrusor hyperreflexia, it is not uncommon to reproduce this symptom during testing without urodynamic abnormality. The explanation is the lack of sensitivity to record the subtle changes that develop in the bladder or outlet, or the central inhibition that occurs during urodynamic testing. Methods have been developed to more objectively quantify sensory thresholds in the bladder (622,628).

Urodynamics is an operator-dependent and interactive study best performed with physician participation. Basic urodynamic modalities include cystometry with residual volume determination, uroflowmetry (voiding flow rate), leak-pressure evaluation (abdominal and detrusor), urethral pressure profilometry (static and dynamic), and combined studies (with or without fluoroscopy). The type of these tests and sequence in which they are administered is dependent on the presenting symptoms, associated findings, and presumptive diagnosis based on other neurourologic tests. Table 26B.3 lists the urodynamic modalities as they relate to evaluation of the bladder or bladder outlet. In general, the simplest and least invasive modality should be performed first. A detailed outline of the neurourologic assessment has been standardized by the ICS (548).

	Bladder	Outlet	Bld + Out
Fill/store	$P_{det(fill\ CMG)}$ $\Delta P/\Delta V$	$P_{urethra}$ ALPP	DLPP
Empty	$P_{det(void)}$	$P_{urethra}$ EMG	VFR res vol

ALPP, abdominal leak point P; DLPP, detrusor leak point P; EMG, electromyography; res vol, residual urine volume; VFR, voiding flow rate.

TABLE 26B.3. URODYNAMIC ASSESSMENT

Cystometry

Cystometry measures changes in intravesical pressure with progressive increases in bladder volume. A cystometrogram (CMG) evaluates the filling or storage phases of detrusor function. The presence or absence of a detrusor contraction, although an important observation, is not the only important information from this test.

Schematically, a normal CMG may be divided into four phases (Fig. 26B.3). There is an initial rise in pressure to achieve resting bladder pressure (phase I). The second phase—the tonus limb—is thought to reflect the viscoelastic properties of the smooth muscle, collagen, elastin, and mucopolysaccharides of the bladder wall. Distention may also release autocrinelike factors that influence contractility [e.g., parathyroid hormone–related protein, prostaglandin, peptides, and nitric oxide (NO)]. During the filling or storage phase, bladder pressure should rise very little because the normal bladder is designed to accommodate increasing urine volumes at low pressure. Normal adult bladder capacity averages 400 to 750 mL. Within this capacity, bladder pressure should not exceed 15 cm H_2O; the mean rise in normal bladders is 6 cm H_2O. Rapid filling may generate a steeper tonus limb (phase II). Bladder wall fibrosis due to infection, radiation, and detrusor hypertrophy may also reduce accommodation and produce a steeper tonus limb. At peak capacity, the detrusor muscle and other elastic tissues achieve maximal elongation, and any additional increase in volume will be accompanied by a rise in intravesical

pressure. During this third stage (phase III), the patient should still be able to suppress involuntary voiding contractions. Ruch and Tang (481) believed that the characteristic shape of the cystometry curve is independent of neural control and is an inherent property of the structural elements of the bladder wall. More recent data with lesioning in animals or after intrathecal drugs in humans contradicts this notion, because acute changes in the tonus limb can occur with alterations in neural input (539).

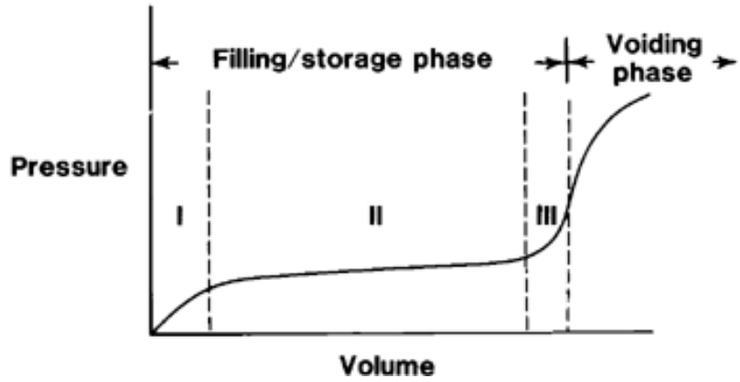

FIGURE 26B.3. Characteristics of normal cystometrogram.

The fourth phase of the normal CMG is the generation of a voluntary voiding that is dependent on smooth muscle and intact neural pathways to the micturition center located in the brainstem. A normal patient should be able to suppress voiding even at capacity. In at least 20% of CMG studies, the patient is unable to generate a micturition reflex on command. This has been attributed to psychologic supraspinal inhibition resulting from the unnatural circumstances of the study. Performance of this phase of the cystometrogram with the male patient in an erect posture and the female patient seated on a commode may facilitate a micturition reflex. Some patients with spinal cord injuries report that reflex voiding occurs only in certain positions. Formerly, urologists thought that compression of the urethra caused such difficulty. It is more likely that stimulation of sacral dermatomes reflexly inhibits micturition. Thus patients can void in the decubitus position but not in the seated position.

In the absence of detrusor contraction, diagnoses such as obstruction cannot be made urodynamically. This accounts for the observation that patients in retention, who are not shown to be obstructed because of the lack of a possible detrusor contraction, may still benefit from surgical intervention. Telemetry has been a valuable addition to urodynamic testing in which documentation of a detrusor contraction is warranted. Ambulatory urodynamics allows as close to normal an environment as possible to avoid profound supraspinal inhibition of micturition.

Both liquid (H_2O, saline) and gas (CO_2) have been used for cystometry. Although CO_2 avoids an air embolus, is clean and portable, allows a rapid rate of bladder filling, and is quick to perform, it introduces sufficient artifact as to be totally unreliable and its use should be abandoned (548). Rapid filling required for CO_2 cystometry causes a nonphysiologic appearance of the tonus limb that can be misinterpreted as reduced compliance, accommodation, and low values for total capacity. CO_2 is irritating to the urothelium, and some patients complain of discomfort and dysuria. Because gas is compressible, phasic bladder contractions of small amplitude may not be detected, and high-pressure contractions may appear to be of low amplitude. Gas may also escape around the catheter unnoticed, particularly if outflow resistance is low. CO_2 cannot be used for pressure/flow studies. Thus CO_2 cystometry cannot assess compliance, obstruction, or incontinence.

The cystometric variables that may be observed during a study are those of compliance, contractility, sensation, and capacity. A stable bladder should remain so even at an unphysiologic rate of filling of 100 mL per minute or with changes in temperatures of filling. Certain patients require a slower rate of bladder filling, including patients with a known neurologic condition, those suspected of having a hyperreflexic bladder, those with bladders with decreased compliance, and children. In adults, slow filling (physiologic filling) is up to 10 mL per minute. Medium filling is defined as 10 to 100 mL per minute. Rapid filling is any value exceeding 100 mL per minute (548). In small-capacity or poorly compliant bladders, rates of 25 to 50 mL per minute are used. During filling, the bladder volumes are recorded at (a) first sensation of filling, (b) sensation of urgency to void, and (c) sensation of maximum capacity. During the filling, provocative measures such as coughing and the Valsalva maneuver should be used to uncover involuntary contractions. The total pressure (P_{ves}) measured within the bladder is intravesical pressure, which is the sum of the pressure induced by the detrusor (P_{det}) and by intraabdominal pressure (P_{abd}). Therefore a rise in intravesical pressure recorded on a simple cystometrogram may at least partially reflect intraabdominal pressure. To eliminate such artifacts, it may be necessary to measure intraabdominal pressure simultaneously by means of a rectal catheter. Cystometers are readily available that electronically subtract the rectal pressure from the total bladder pressure, thus giving the subtracted bladder pressure, which is detrusor pressure. This measurement is crucial for provocative cystometry and for voiding studies to determine the efficiency of the voiding contraction. Subtracted pressures are the standard for measuring intravesical pressures. In this regard, care must be taken to accurately zero the pressures at the beginning of a study. The use of microtip transducers has led to misinterpretation because these devices are difficult to accurately zero. If not properly calibrated and zeroed, cystometry combined with flow rates will provide inaccurate information concerning obstruction, detrusor compliance, and detrusor leak pressures. In essence, the test results are only as valuable as the operator.

Ambulatory Cystometry

Recognition that laboratory urodynamics produces significant artifacts and may fail to evoke symptoms has led to the development of ambulatory urodynamics. Advances in telemetry, microtip pressure transducers, and computer technology allow recording of urodynamic data for delayed playback. The most common finding from ambulatory studies is the detection of involuntary contractions associated with symptoms that have not been seen in the office. However, care must be taken to avoid overdiagnosis of abnormal detrusor activity. Combining ambulatory studies

with voiding and symptom diaries and a rectal pressure probe reduces the number of abnormal contractions by 5% and 19%, respectively. This improved sensitivity rarely changes clinical decision making or therapy but can be extraordinarily useful for clinical trials. Gorton and Stanton (219) demonstrated that ambulatory urodynamics did detect detrusor instability in a greater number of patients but failed to improve outcomes. Vereecken and Vannuland (582) found that filling pressures and volumes are lower, whereas voiding pressures are higher during ambulatory urodynamics compared with standard studies. Finally, the ability to diagnosis obstruction is relatively equivalent whether one uses ambulatory urodynamics or conventional studies (474).

Abnormal Cystometric Patterns

Abnormalities of bladder function that may be detected by cystometry include altered sensation, changes in detrusor compliance, disorders of detrusor contractility, and presence of involuntary detrusor contraction or detrusor areflexia.

Bladder compliance refers to the ratio of the change in bladder volume to pressure that occurs during filling. Normally, filling pressures average 6 cm H_2O and should not exceed 15 cm H_2O. A bladder with decreased compliance is one in which the pressure rises steeply with filling (Fig. 26B.4). Technical variables affecting the absolute value for compliance include method of calculation (Fig. 26B.5) and rate of filling. Some authors refer to initial and terminal compliance, based on the portion of the filling urine from which the measurements are calculated (202). Reduced compliance may result from detrusor hypertrophy, fibrotic changes in the bladder wall, bladder wall inflammation, and possibly neurologic lesions.

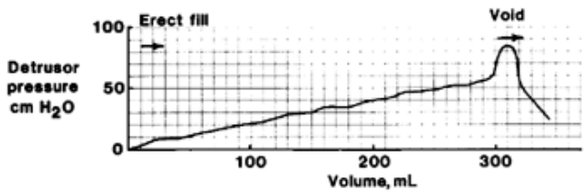

FIGURE 26B.4. Cystometrogram showing decreased detrusor compliance.

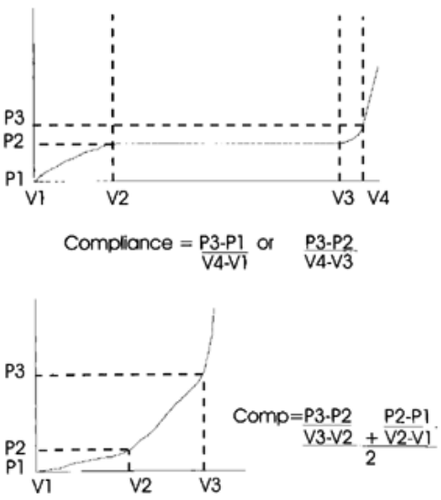

FIGURE 26B.5. Calculated bladder compliance by two different methods.

Involuntary detrusor contraction refers to a phasic rise in bladder pressure. This may occur in response to provocation such as a cough, stress, or postural change, or it may occur spontaneously (Fig. 26B.6). States of increased detrusor contractility have been referred to as *detrusor instability* or *detrusor hyperreflexia*. In general, *detrusor hyperreflexia* refers to an involuntary bladder contraction that is a direct result of associated neurologic disease, whereas *detrusor instability* is seen in the absence of neurologic disease (234). Detrusor hyperreflexia commonly occurs as a result of suprapontine cerebral disorders, such as cerebrovascular accidents or parkinsonism. This may also occur in patients with suprasacral spinal cord disease processes, such as multiple sclerosis, or trauma with or without concomitant detrusor-sphincter dyssynergia.

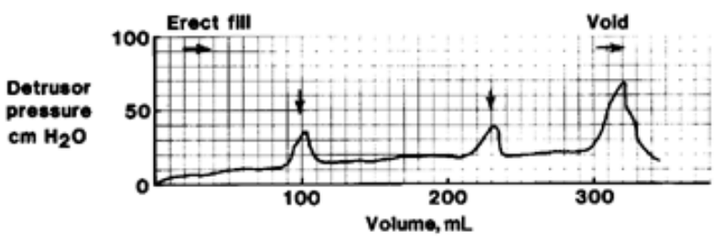

FIGURE 26B.6. Cystometrogram showing increased detrusor contractility.

With marked detrusor instability (or hyperreflexia), the compliance may also be reduced, probably secondary to detrusor muscle hypertrophy, and alterations in extracellular matrix such as collagen subtype (164) (Fig. 26B.7).

At the most severe end of the spectrum is the noncompliant bladder with reduced capacity (Fig. 26B.8). Steepness of the curve can be the result of muscle contraction and reduced compliance or severe fibrosis. This may be from a neurogenic cause, although it may be seen in patients with severe outlet obstruction or inflammation. An involuntary contraction can also be masked within the rising slope of the filling curve.

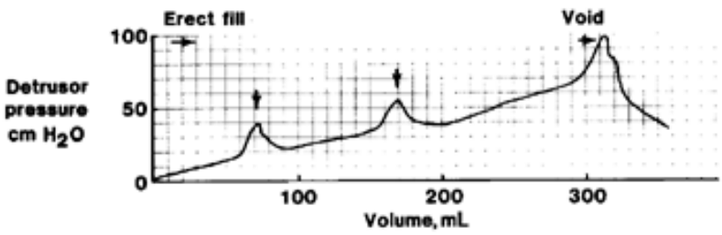

FIGURE 26B.7. Cystometrogram showing decreased compliance and increased detrusor contractility.

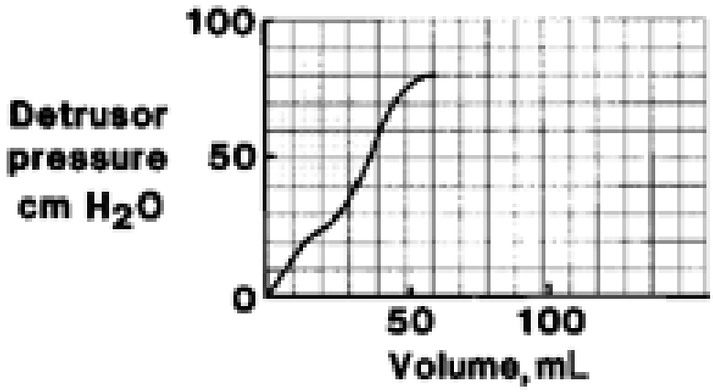

FIGURE 26B.8. A cystometrogram showing noncompliant bladder.

A capacious bladder of normal or increased compliance (Fig. 26B.9) may result from chronic overdistention caused by decreased sensation. This sensory abnormality can occur in the diabetic patient or from chronic outlet obstruction. It may also be a behavioral phenomenon in patients who voluntarily inhibit micturition for long periods. Weir and Jaques (609) found that 30% of patients with bladder capacities in excess of 800 mL were urodynamically normal. Therefore increased bladder capacity alone is not necessarily an indication of disease, especially in patients who can generate a normal detrusor contraction and empty completely.

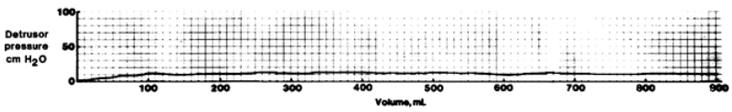

FIGURE 26B.9. Cystometrogram showing increased detrusor compliance.

Decreased bladder capacity may be purely sensory in origin (normal compliance and stability), and it is commonly seen with an idiopathic frequency syndrome and in those with an inflamed bladder. These patients are usually able to produce a voluntary detrusor contraction on ambulatory urodynamics (Fig. 26B.10).

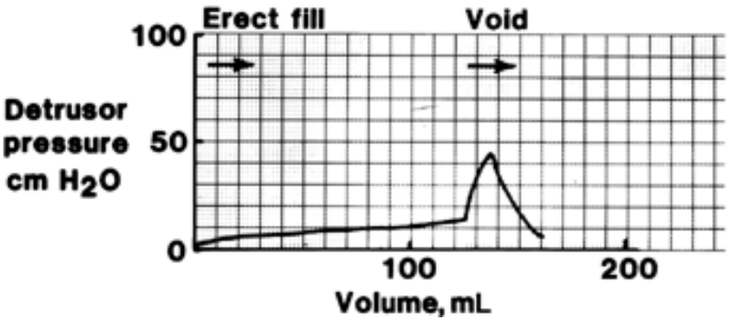

FIGURE 26B.10. Cystometrogram showing normal compliance and contractility, but small capacity.

Reduced or low bladder compliance ($\Delta V/\Delta P$) is 20 mL/cm H_2O (548). Compliance is determined from the reference value of pressure when the bladder is empty until maximum cystometric capacity or the initiation of a detrusor contraction. A minimal ΔP of 1 cm H_2O is used. Therefore the maximal potential value for compliance equals the volume range over which it is calculated.

Ice Water Test

The ice water test was introduced in the 1950s to assess micturition reflexes in patients with spinal cord injury and neurogenic bladders (71). The basis for this test is a cold thermoreceptive (cooling) reflex generated by unmyelinated C-fiber bladder afferents. In neurologically intact adults, voiding results from activation of myelinated Aδ afferents. In neonates, spinal cord–injured patients, and those with suprasacral injuries, a spinal C-fiber reflex can often be elicited (197). Intravesical administration of C-fiber neurotoxins such as capsaicin and resiniferatoxin can eliminate this reflex (98). Some authors believe the temperature (0°C), rate of filling (300 mL per minute), volume (100 mL), and pressures of the abnormal detrusor activity (greater than 15 cm H_2O) are critical to the definition of a positive test (197). However, these parameters lack a scientific basis and merely reflect thresholds at which abnormal activity appeared during some studies. Slightly slower rates, contractions of lower amplitude, and higher volumes may lead to higher false-positive results (specificity) but increased sensitivity. Therefore using more rigid criteria seems to increase specificity for neurologic disease, but provoking activity with slower rates and including lower pressure contractions increases the likelihood of detecting this C-fiber reflex. It would be interesting to correlate methodology with response to vanilloid neurotoxins (capsaicin, resiniferatoxin) to ascertain the degree specificity with different methods. If patients demonstrate detrusor instability, performing the test as initially defined is problematic.

Initially, the ice water test was thought to be specific only for a “neurogenic” bladder. Subsequently, animal data

suggested that spinal cord injury, inflammation, or obstruction of the bladder may also lead to neuroplasticity with the development of a C-fiber–mediated spinal reflex (121,535,566). From 47% to 71% of patients with obstruction but not idiopathic instability exhibit this reflex (89,220). In one study, 15% of patients without neurologic disease and detrusor instability had a positive ice water test (445). Proponents of using this test to diagnose neurologic disease claim that all clinically active patients will eventually manifest neurologic disease.

Bethanechol Supersensitivity Test

Similar to the ice water test, the bethanechol supersensitivity test was thought to be diagnostic of neuropathology—namely, denervation of the bladder. The basis for this assumption is the pharmacologic principal of denervation supersensitivity known as Cannon's law. Cannon's law of denervation states that when a tissue is deprived of its nerve supply, it will develop hypersensitivity to its own neurotransmitter(s). Bethanechol chloride is a cholinergic agonist that exhibits a relatively selective action on the urinary bladder and gut, with little or no effect at therapeutic dosages on ganglia or the cardiovascular system (287,573). It is cholinesterase resistant and causes a contraction *in vitro* of detrusor smooth muscle from both body and base of the bladder (455). Bethanechol has a minimal effect on the normal bladder, decreasing the capacity slightly, increasing detrusor tone, and increasing the maximum voluntary micturition pressure. It will not cause the normal bladder to become unstable.

Lapides and colleagues (306) argued that this test is accurate in patients with a “denervated” bladder. One major limitation is reports of false-positive bethanechol supersensitivity tests in patients with only detrusor hypertrophy and instability. Furthermore, obstruction of the bladder causes patchy denervation. Thus this test has limited value in diagnosing “neurogenic” pathology. Others have found significant rates of false-negative and false-positive responses (64).

To perform a bethanechol supersensitivity test, subcutaneous injection of 0.035 mg/kg of bethanechol chloride is followed in 15 to 30 minutes by repeated cystometric examination (Fig. 26B.11). Oral bethanechol does not have a significant effect on the bladder. In patients with an areflexic bladder, a neurogenic cause may produce a rise in pressures of at least 15 cm H_2O at 100 mL filling, in excess of the pretreated cystometric pressure. If detrusor hypocontractility exists, a false negative may result.

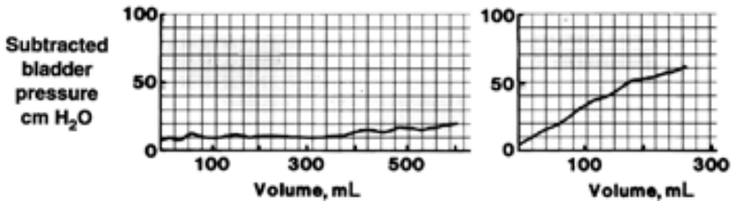

FIGURE 26B.11. Cystometrogram with positive bethanechol stimulation test.

The use of bethanechol is contraindicated in patients with bronchial asthma, peptic ulcer, hyperthyroidism, enteritis, bowel obstruction, bladder outlet obstruction, cardiac disease, or a history of recent gastrointestinal surgery (597,598).

Uroflowmetry

The use of urine flow rates alone has diminished in recent years. Problems with reproducibility and specificity have caused this test to fall out of favor, especially in the evaluation of BPH. However, for following patients sequentially after therapy (e.g., urethroplasty) this test remains valuable. *Flow rate* is the volume of fluid expelled from the urethra per unit time. It is expressed in milliliters per second. Flowmeters record overall rate and flow pattern (Fig. 26B.12). Both parameters provide useful information regarding lower urinary tract function. Urine flow rate is an expression of the combined activity of the detrusor and urethra. A normal flow rate will usually indicate a good function of both organs. Conversely, a low flow rate can result from poor detrusor contractility or outlet obstruction. Thus specificity is limited. Moreover, straining can result in artificial elevations in flow rates.

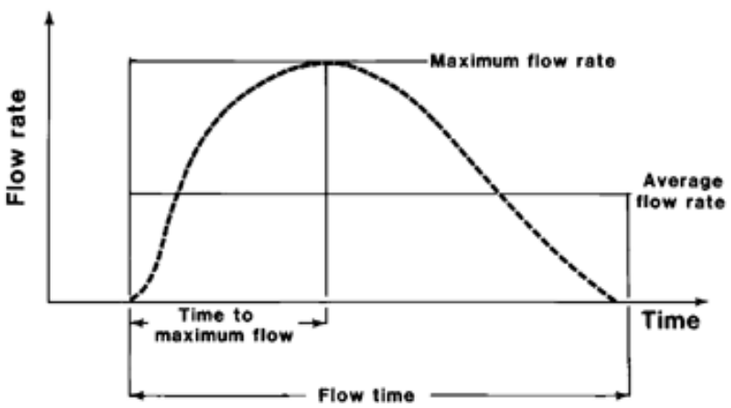

FIGURE 26B.12. Characteristics of normal uroflow.

Obstruction of the urethra (due to benign prostatic hyperplasia or urethral stricture) may be overcome by a more forceful detrusor contraction. Higher bladder pressures during micturition may result in a normal peak flow rate during the early stages of the obstruction, but a reduced average flow (high pressure, normal flow obstruction). Initially, the detrusor may be able to overcome increased outlet resistance, resulting in a normal flow rate. This scenario may be particularly operative in young women and men. This situation demonstrates that a normal flow rate fails to rule out obstruction. For a full definition of lower tract function, simultaneous pressure (cystometry) and flow studies during

voiding are usually indicated. However, a urine flow study even by itself has some value as a screening test for other types of lower urinary tract dysfunction, such as dyssynergia; for preoperative and postoperative assessment of lower urinary tract surgery; and to study the effects of pharmacologic agents on urethral resistance and voiding efficiency.

To a clinician, urine flow rate variables (Table 26B.4) of most importance are the maximum flow rate, voided volume, and flow pattern. The patient should be asked whether the flow rate obtained represents the usual force. Ideally, urine flow interpretation should be for volumes of at least 10 mL. Interpretation of flow rates with smaller voided volumes can be misleading. Volumes of more than 500 mL are also accompanied by reduced flow rates, perhaps because of overstretching the detrusor fibers. Flow rates, however, are also related to the sex and age of the patient. Most data in the literature relate to measurements of flow in men younger than 55 years of age and cite norms of 15 and 25 mL per second for mean and maximum rates. Flow rates in women may also be influenced by hormones. A recent study showed that instrumentation lowered flow rates and progesterone levels influenced micturition times (583).

TABLE 26B.4. URINE FLOW RATE MEASUREMENTS

1. *Flow time:* time over which measurable flow occurs
2. *Time to maximum flow:* time elapsed from the onset of flow to maximum rate
3. *Maximum flow rate:* maximum rate of flow
4. *Voided volume:* total volume expelled by way of the urethra
5. *Average flow rate:* voided volume divided by flow time
6. *Voiding time:* total duration of micturition, including interruptions
7. *Flow pattern:* may be continuous, interrupted, or specifically described

In one of the largest community-based studies of urinary flow rates, Girman and co-workers (209) analyzed data from 2,000 men 40 to 70 years old. Based on this large number of older men, data showed that peak flow rate and voided volume decrease with each decade after age 40. Peak flow decreased from 20.3 mL per second for ages 40 to 44 to 11.5 mL per second for men 75 to 79 years old. Whereas only 6% of men in the former age group had peak flow rates less than 10 mL per second, 35% of the older group had markedly diminished flow. This difference may be attributed to altered contractility or obstruction. Because of a learning effect and patient variability, several flow rate measurements are more useful than a single test. Females have significantly higher flow rates than males matched for age and voided volumes. The values presented in Table 26B.5 are quoted from Abrams (2) and represent the minimum flow rate for a given sex, age, and voided volume. In children, sex differences exist. However, in one study of 180 children ages 7 to 10 years, no age difference was found for maximum and mean flow rates (360).

TABLE 26B.5. MINIMUM ACCEPTABLE URINE FLOW RATES

Age (yr)	Minimum Voided Volume (mL)	Flow Rates (mL/sec)	
		Males	Females
4–7	100	10	10
8–13	100	12	15
14–45	200	21	18
46–55	200	22	15
56–80	100	9	10

From Abrams P. The practice of urodynamics. In: Mundy AR, Stephenson TP, Wein AJ, eds. *Urodynamics, principles, practice and application,* Edinburg: Churchill-Livingstone, 1984, with permission.

If abdominal straining is used to augment voiding, the stream appears interrupted (Fig. 26B.13). Other causes of an interrupted stream may be striated sphincter contraction during voiding by a patient with detrusor-sphincter dyssynergia, or more commonly, by an anxious child; and artifactual recording, most commonly seen when a male patient directs the urinary stream across the collecting funnel (Fig. 26B.14).

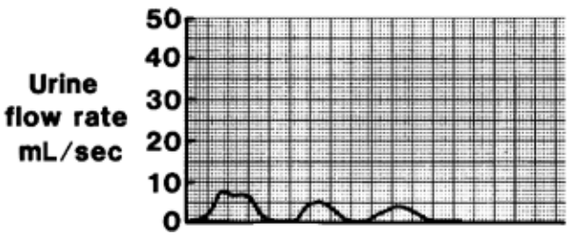

FIGURE 26B.13. Uroflow with interrupted stream during straining to void.

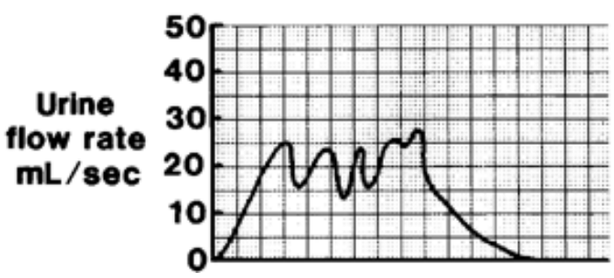

FIGURE 26B.14. Uroflow with interrupted pattern resulting from intermittent sphincter activity.

In outlet obstruction, a flat, elongated curve with a low maximum flow rate is reached in the initial part of the record (Fig. 26B.15). In patients with detrusor hypocontractility, the flow pattern can be persistent, flat, or intermittent if abdominal muscles are recruited to augment voiding. The urine flow rate is reduced, and the maximum flow rate corresponds to the middle portion of the tracing. Despite the suggestion of obstruction that can be based

on uroflow, Chancellor and colleagues (94) and others have established that uroflowmetry alone cannot distinguish between outlet obstruction and impaired detrusor contractility.

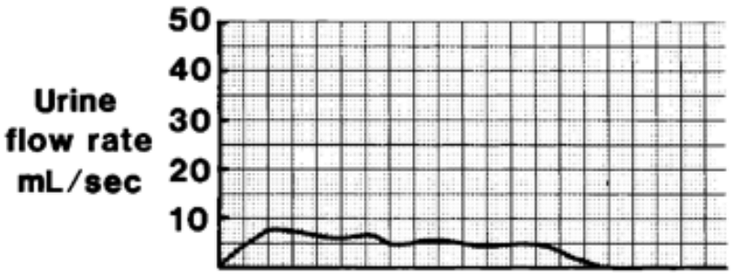

FIGURE 26B.15. Uroflow with abnormal flow rate characteristic of detrusor outlet obstruction.

Residual Urine Volume

Residual urine volume also reflects the activity of the bladder and outlet during the emptying phase of micturition. A consistently increased residual urine volume indicates increased outlet resistance, decreased bladder contractility, or both.

Although the bladder should empty completely, residual urine consistently greater than 150 mL is often deemed clinically significant. Residual urine can be measured in a variety of ways. A postvoid residual is usually measured using ultrasonography or catheterization. Detection following intravenous urography fails to provide volumetric data. More recently, portable bladder scans have been used by health care professionals and patients to detect bladder capacity and retained urine after voiding or instrumentation.

The greater the residual urine, the more likely that detrusor hypocontractility exists (201). Absent residual urine is compatible with normal lower urinary tract function during emptying, but it does not exclude significant disorders of filling or storage (incontinence) and problems with emptying in which the intravesical pressure is still sufficient to overcome increases in outlet resistance. Typical of this latter situation is the patient with outlet obstruction as a result of benign prostatic obstruction. Initially, despite significant obstruction, the detrusor empties the bladder by contracting with a greater force, manifested as hypertrophy and increased intravesical pressure. Yet with time, the detrusor will decompensate, leading to elevated residual volumes and reduced intravesical pressures produced during voiding. Ghoniem (201) and others have suggested that as residual urine volume becomes a greater percentage (greater than 30%) of bladder capacity, the likelihood of impaired contractility, rather than obstruction, increases. This exemplifies the fact that it is rare to reach a diagnosis on the basis of any single urodynamic study. Results of all studies must be coherent, and ultimately they must be compatible with the symptoms and with the results of the remaining neurourologic evaluation.

Electromyography

Electromyography (EMG) is the measurement of bioelectric potentials generated by depolarization of muscle. Smooth muscle potentials are notoriously difficult to measure. Results of bladder or urethral smooth muscle potential determinations using catheter electrodes are still experimental and often not validated. Even with somatic muscle EMG, most of the activity detected using patch electrodes is noise rather than true neurogenic activity.

Striated muscle is innervated by motoneurons whose cell bodies lie in the anterior horn of the spinal cord. The anterior horn cell in the gray matter of the spinal cord, its axon, and all of the muscle fibers that it innervates is called a *motor unit*. An excitatory impulse from an anterior horn cell causes contraction of all the muscle fibers in that motor unit. The electrical discharge produced by contraction of the muscle fibers of the motor unit by their depolarization is called *motor unit action potential*. This may be detected by electrodes and displayed on an oscilloscope screen, computer monitor, or strip chart. Even more helpful, it may be converted to an audible sound. Individually recorded on an oscilloscope, the motor unit action potentials may exhibit biphasic, triphasic, or rarely, polyphasic configurations. In the relaxed state, the normal striated muscle is almost electrically quiescent, and only infrequent action potentials are recorded. However, with progressive muscle contraction, increasing numbers of motor units are recruited, and each motor unit fires at a more rapid rate. These firings can be individually recorded electromyographically, and the configuration of the action potentials aids diagnosis. At the point of maximum contraction, motor unit action potentials are so frequent that total overlap occurs and EMG separation cannot be achieved, resulting in an interference pattern. It takes considerable experience to interpret the various parameters recorded on an oscilloscope during sphincter EMG. Movement artifacts can often be confused with action potentials. Identification of variations is important in making an accurate neurologic diagnosis. Individual motor unit action potentials may be detected by needle electrodes placed directly into or near the muscle to be studied. When surface electrodes are used, individual motor unit action potentials are not visualized; rather, an overall global recording of the activity of the muscle is detected (field potentials) (32). If one is not interested in individual motor unit action potentials—for example, if one wishes only to document dyssynergia—surface electrodes are adequate. They detect whether the pelvic floor muscles are contracting or relaxing at any given instant. However, because they are unable to detect individual motor unit action potentials, surface electrodes cannot help in assessing the integrity of these muscles and their nerve supply.

During cystometric bladder filling, there should be incremental increase in EMG activity as more motor units are recruited. This has been referred to as the guarding reflex. This activity will reach a maximum near peak bladder capacity, and at the command to void, there should be sudden and persistent cessation of sphincter activity throughout voiding (59). On completion of bladder emptying, resumption of baseline sphincter activity occurs. To assess external sphincter activity, the examiner should ask the patient to interrupt voiding in the middle of the stream, at which point there should be an abrupt increase in sphincter activity that should be sufficient to stop the flow. Resumption of voiding should subsequently occur. If the holding pattern is maintained, the detrusor reflex should ideally be lost in approximately 10 seconds (595). This inhibition of detrusor activity with external sphincter contraction is due to somatic afferent input to the spinal cord, which can inhibit autonomic outflow to the bladder.

Abnormal EMG patterns may be detected in a number of situations. Detrusor-sphincter dyssynergia describes sphincter activity that is inappropriate to the activity of the detrusor. Three varieties of such incoordination (Fig. 26B.16) have been described (365). One pattern involves an appropriate increase in EMG activity with bladder filling, which is followed by inappropriate involuntary increase in activity at the onset of detrusor contraction. Thus the detrusor contracts against a closed sphincter.

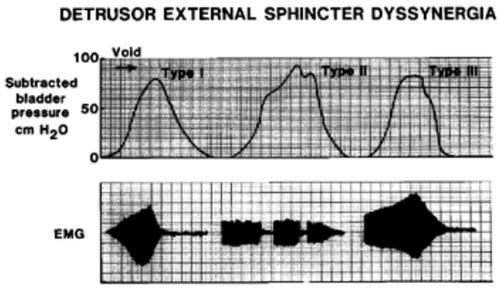

FIGURE 26B.16. Varieties of external sphincter discoordination. EMG, electromyograph. (Adapted from McGuire EJ. Electromyographic evaluation of sphincter function and dysfunction. *Urol Clin North Am* 1979;6:121, with permission.)

A second type of incoordination involves failure to develop an adequate reflex detrusor contraction because of increased EMG activity during voiding, which inhibits the detrusor motor nucleus in the sacral spinal cord, with resultant loss of detrusor contraction. This type of incoordination may be seen in patients with suprasacral spinal cord injury.

The third type involves contraction and relaxation of the sphincter during bladder filling. This amounts to periods of uninhibited sphincter relaxation, which is associated with reflex detrusor contraction leading to urgency and urge incontinence.

Simultaneous EMG activity with an increase in intravesical pressure does not uniformly indicate sphincter dyssynergia. Detrusor striated-sphincter dyssynergia is the most difficult and overdiagnosed entity in the field of voiding dysfunction. Patients suspected of having this diagnosis should always be further investigated with urodynamic or radiologic evaluation to study activity of the bladder and the outlet during the emptying phase of micturition and the spinal cord to exclude neurologic disease. True detrusor striated-sphincter dyssynergia should exist only in patients who have an abnormality in pathways between the sacral spinal cord and brain, usually due to neurologic disease or injury. Such a diagnosis in a patient without such pathology deserves exhaustive study to exclude a neural diagnosis. The exception to this rule appears to be in infants, who occasionally demonstrate apparent detrusor-sphincter dyssynergia without clinical or radiographic evidence of neurologic pathology (37), known as *nonneurogenic dysfunctional voiding* (345). In general, dyssynergia cannot occur unless a lesion resides between the pons and sacral spinal cord.

Interpretation is clouded by a voluntary contraction of the pelvic floor that occurs with a Valsalva maneuver and by voluntary contraction of the striated urethral sphincter as a method to abort urgency, both examples of so-called pseudodyssynergia. Rudy and Woodside (484) have suggested that inspection of the early segment of the CMG-EMG will help distinguish pseudodyssynergia from true dyssynergia (Fig. 26B.17). If EMG activity is recorded after a rise in detrusor pressure, true detrusor-sphincter dyssynergia exists.

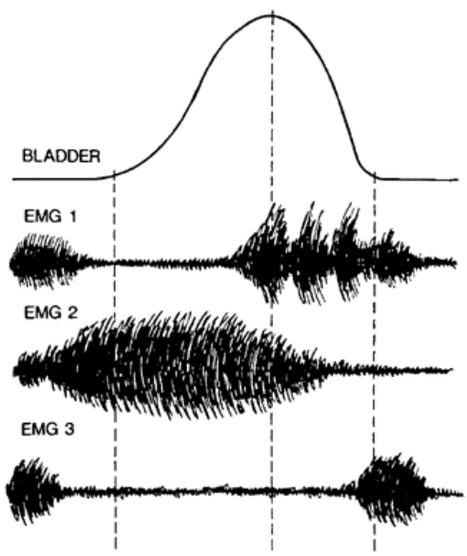

FIGURE 26B.17. Schematic diagram of cystometrogram.EMG. Bladder-intravesical pressure trace. *EMG 1:* Pattern seen in nonneurogenic neurogenic bladder. EMG activity quiets before and with positive *dP/dt*, and augments with negative *dP/dt*. *EMG 2:* Pattern seen in true external sphincter. Dyssynergia EMG activity augments before and with positive *dP/dt*, and quiets with negative *dP/dt*. *EMG 3:* Pattern seen in normal voiding. EMG quiets before and during detrusor contraction. (From Rudy D, Woodside J. Non-neurogenic neurogenic bladder: the relationship between intravesical pressure and the external sphincter electromyogram. *Neurourol Urodyn* 1991;10:169, with permission.)

Learned dysfunctional sphincter habits may be responsible for voiding abnormalities, with resultant recurrent urinary infections, influx, and upper tract deterioration. An attempt has been made to retrain these patients by the application of biofeedback techniques using sphincter EMG during voiding (346). The patient can discern from an EMG audio monitor whether sphincter relaxation is being accomplished; hence positive reinforcement may correct the problem.

Evoked Responses

The value of evoked responses is extremely limited, and these tests are rarely performed. Problems with specificity, sensitivity, and noise, as well as poorly controlled variables, influence evoked potentials and hamper the utility of this method of investigation. Thresholds and latencies tend to be highly laboratory dependent. Evoked responses are potential changes in neural tissue, recorded with averaging techniques, resulting from distant stimulation, usually electrical (257). Evoked responses may be used to test the integrity of peripheral, spinal, and CNS pathways. As with nerve conduction studies, the conduction time (latency)

may be measured. In addition, information may be gained from the amplitude and configuration of these responses.

An example of such procedures is the sacral evoked response, which is measured by the latency of the bulbocavernosus reflex (53,63,410). The bulbocavernosus reflex arc is mediated by afferent and efferent pudendal nerve fibers. The reflex is polysynaptic, traversing at least several spinal cord segments. Clinically, the bulbocavernosus reflex is elicited by briskly squeezing the glans penis and observing or feeling a reflex contractility response of the external anal sphincter or bulbocavernosus muscle. Alternatively, the reflex may be stimulated by pulling the balloon of a Foley catheter against the bladder neck. The bulbocavernosus reflex is present in almost all normal men and in approximately 70% of normal women. This reflex is often preserved after complete spinal cord transection. If lost, it is one of the first reflexes to return after recovery from spinal shock. Following spinal cord injury, reflexes return in a caudal to rostral progression. Absence of this reflex in a man is strongly suggestive of a sacral neurologic lesion, but it is preserved in approximately 5% to 10% of patients with an incomplete lower motor neuron lesion.

Probably the best use of this reflex is not as a quantitative assessment, but as an all-or-none test in sequentially following a patient. An absent reflex clinically can occur in a normal subject. However, the loss of the bulbocavernosus reflex after spinal surgery is an ominous sign and could indicate a cauda equina syndrome. The urologist is often the one to alert the orthopedic surgeon or neurosurgeon of this finding in a patient with persistent urinary retention after laminectomy. Because it is difficult to grade the reflex clinically, measurement of the bulbocavernosus reflex latency offers a more sensitive quantitative means of evaluating the sacral reflex arcs. When one side of the penis is stimulated electrically, as by a surface-stimulating electrode, there is a bilateral contractile response in the bulbocavernosus muscle that may be detected by electrodes placed bilaterally into this muscle (63,296). Considerable EMG expertise is required to determine the onset of the evoked response because of the possibility of interference from units that are firing randomly or as a result of the patient's anxiety. Although some authors have recommended that evoked responses of 20 to 30 stimulations be electronically averaged to determine the latency, Blaivas (53) claims that the shortest latency rather than the average is a more reliable means of evaluating the sacral segments, because the bulbocavernosus reflex is polysynaptic.

The bulbocavernosus reflex is a crossed response, and it is therefore possible to stimulate on one side and record from both sides the ipsilateral and contralateral bulbocavernosus muscles. This is useful in detecting subtle abnormalities that affect only a single afferent or efferent pathway. It is possible to evaluate the right and left afferent and efferent pathways individually. The normal bulbocavernosus reflex latency varies from approximately 30 to 40 ms, but the exact values vary slightly from one laboratory to another and with age, sex, and bodily habitus. Any neurologic process that interferes with the integrity of the reflex arc will result in a prolonged latency. Common disorders that result in prolonged latencies include diabetes mellitus, alcoholic neuropathy, and prolapsed discs. Less commonly, a prolonged latency may be an early manifestation of a spinal cord tumor or multiple sclerosis. The indications for such evoked testing are unclear.

Many believe that the clinical neurologic examination is just as sensitive as evoked potential testing as a means of detecting neurologic disease. Conversely, if the clinical assessment is completely normal, an evoked potential study never yields valuable insight. In a consensus statement from the World Health Organization (584), experts concluded that “opinion at this point cannot recommend them [concentric needle electromyography with dorsal nerve of the penis/clitoris stimulation] for clinical practice and classifies them as investigational.” Moreover, a word of caution is warranted in interpretation of the results of sacral evoked responses. This test merely quantitates the integrity of innervation of the striated pelvic floor and perineal muscles

and the supraspinal neurologic pathways involved in lower urinary tract function. It does not give information concerning the status of the smooth muscle of the detrusor, bladder neck, and proximal urethra. Although, in general, it is reasonable to assume that when a neurologic lesion affects the striated perineal floor muscles, it is likely that the same process also involves the detrusor, because the pudendal and parasympathetic nuclei in the sacral spinal cord are practically adjacent to one another. Nevertheless, certain neurologic disorders (e.g., amyotrophic lateral sclerosis, Shy-Drager syndrome) may involve one portion of the nervous system and spare another. The value of sphincter electromyography is most appreciated in the differentiation of Parkinson's disease from olivopontocerebellar degeneration (multisystem atrophy). In this case, the detection of denervation potentials in the sphincter EMG will occur only in multisystem atrophy (428).

Leak-point Pressure

Abdominal Leak-point Pressures

Leak pressure terminology is confusing. Detrusor leak pressures are not equivalent to Valsalva leak pressures. Valsalva leak pressures measure the same function as abdominal leak pressures. However, the absolute values may vary depending on whether a slow strain, rapid Valsalva, or cough is used to test the integrating of the continence mechanisms of the bladder outlet. The most commonly performed leak pressure is the abdominal or Valsalva leak-point pressure (ALPP). This is a direct measurement of the abdominal pressure required to overcome urethral resistance. This urethral resistance is known as the urethral opening pressure. The abdominal leak pressure indirectly measures closure forces on the urethra or bladder outlet during straining and represents a simple test to classify urinary incontinence. The abdominal leak-point pressure is used in women to estimate to what degree stress urinary incontinence is due to anatomic displacement of the pelvic floor and bladder or intrinsic sphincter dysfunction. The lower the abdominal leak pressure, the greater the degree of intrinsic sphincter deficiency.

The test is performed with the patient supine or seated. Straining is done at 100, 200, and 250 mL bladder volumes using a 6- or 7-Fr urethral catheter. A smaller catheter is best to avoid artifact or lessen obstruction if a narrow noncoagulant urethra is evaluated. If urethral narrowing is present, a false-negative test can occur. Leakage is documented fluoroscopically or visually. McGuire and associates (371) studied women with urinary incontinence using fluoroscopy and monitoring detrusor and intraabdominal pressures. At a bladder volume of 200 mL, patients increased abdominal pressures by incremental straining. The pressure at which leakage occurred was then recorded. The pressure when fluoroscopic or actual leakage occurred defined the ALPP. Patients with an ALPP of less than 60 cm H_2O were defined as having intrinsic sphincter deficiency (type 3 urinary incontinence) (Fig. 26B.18). Urethral hypermobility (type 2 incontinence) as a cause of stress urinary incontinence was associated with pressure greater than 90 cm H_2O. A gray zone between 60 and 90 cm H_2O exists. In reality, a spectrum of insufficiency probably exists. As with all urodynamic tests, the pressure methodology used to perform the test should be presented in all reports.

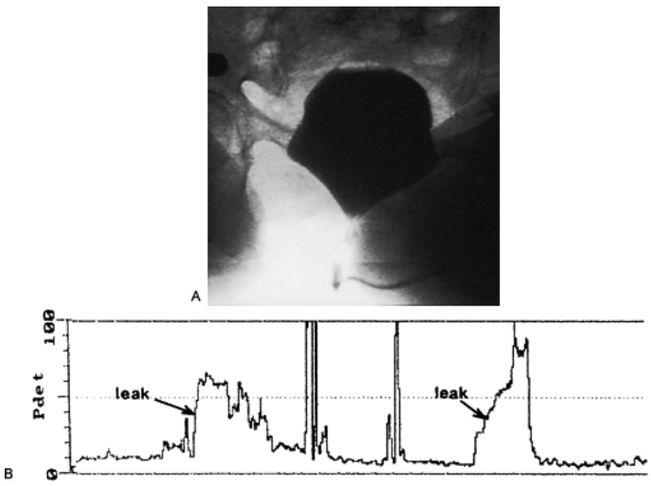

FIGURE 26B.18. Video image **(A)** and pressure recording **(B)** from bladder during straining as part of an abdominal leak-point pressure study in 40-year-old woman with stress incontinence leakage at 37 cm H_2O, indicating intrinsic sphincter deficiency.

Patients with cystoceles may have elevated ALPPs as a result of pressure transmission to the prolapsed bladder. Therefore an abdominal leak-point pressure should be obtained in all women before repair of prolapse even in the absence of complaints of incontinence. Historically, 60% of women develop stress incontinence after repair of vaginal prolapse. The leak pressure test may help preselect those women needing an additional incontinence procedure. Performing the test after reduction of a significant cystocele with a pessary or similar device is necessary to obtain an accurate ALPP. If an involuntary detrusor contraction occurs, neural relaxation of the outlet will cause a falsely low ALPP. Many reports uncover intrinsic deficiency after reduction of prolapse and use sling surgery to prevent stress incontinence. However, no prospective study exists in which patients discovered to develop intrinsic sphincter deficiency (ISD) after reduction of a cystocele do not receive antiincontinence surgery. ALPP provides valuable information regarding function of the bladder neck and proximal urethra. Although valuable, fluoroscopy is not essential to differentiate anatomic incontinence from urethral dysfunction. An ALPP can also be estimated by measuring the rectal pressure with straining and observing urine leakage. The optimal bladder volume at which to perform this test is debated. One report has suggested that a volume of 1,000 mL identifies more patients with intrinsic sphincter deficiency, probably because of alteration in urethral angle if a large cystocele is present.

Detrusor Leak-point Pressures

Detrusor leak-point pressure (DLPP) is very different from ALPP. It is especially useful in the evaluation of patients with decreased compliance and incontinence. DLPP represents the pressure in the bladder at rest when urine leaks from the urethra. Whereas urine loss should never occur during abdominal straining even at high pressures, urine exits the urethra at relatively low bladder pressures during voiding. This measurement can be difficult to accurately assess if an intrinsic sphincter deficiency or vesicoureteral reflux exists.

A DLPP greater than 40 cm H_2O is predictive of upper tract deterioration, especially in patients with spinal cord injury and in children with myelodysplasia. The results of this test are not 100% predictive. Slower physiologic filling probably accounts for some differences. Yet, in general, the DLPP provides prognostic information regarding future upper tract changes. DLPP is measured by recording detrusor

pressure with a 7-Fr urethral catheter or a suprapubic tube. Catheter size can influence the accuracy of the test (117). The pressure at which urine exits the urethra without straining represents the DLPP. The DLLP plus an estimate of bladder compliance provides the best prognostic information as to the risk of upper tract deterioration. The ALPP is a provocative dynamic test that mimics circumstances that may cause leakage. In contrast, the DLPP, along with compliance, assesses pressures detrimental to renal function. Each procedure tests a different aspect of lower urinary tract storage.

Urethral Pressure Profile

Urethral pressure profiles are less commonly performed by urologists. Noteworthy exceptions include research studies on urethral function or assessment of functional urethral length before sphincterotomy, and determination of functional integrity of an artificial urinary sphincter. A urethral pressure profile (UPP) is a recording of the pressure within the urethra at each point along its length. In 1969, Brown and Wickham (77) described a technique that is the basis for perfusion urethral profilometry. They used a specially designed catheter with multiple side holes and an occluded tip. Fluid infused along the catheter escaped through the side holes, and the UPP measured the resistance of the urethral walls to distention by this escaping fluid. This resistance is expressed in terms of the pressure necessary to maintain a steady flow of fluid through the catheter system. The UPP recording commences in the bladder, and constant withdrawal of the catheter is accomplished through the entire length of the urethra.

Being a measure of the urethra's response to distention, various factors affecting urethral compliance will alter the appearance of the profile curve. Contributing to normal urethral compliance are smooth muscle activity, striated muscle activity, fibroelastic component of the urethral wall, vascular tension resulting from the rich spongy network around the urethra, and an extrinsic compression component of varying degrees. Obviously, alteration of any of these variables may significantly alter the appearance of the curve. A high pressure point may be caused by poor compliance or obstruction. For these reasons, perfusion profilometry is often replaced by the use of catheter microtip transducers that record pressure directly. Despite methodology, the diagnostic value of the static UPP is limited because it is a

study that is performed neither during filling or storage nor during emptying. A narrow, poorly compliant yet incompetent urethra may result in a falsely elevated urethral pressure.

Static infusion profilometry does have value in evaluating artificial sphincter function or a potential site of obstruction. Alterations in the static profile correlate in a general way with some disease entities, such as stress incontinence, an enlarged prostate, and striated-sphincter dyssynergia. When obstruction (e.g., detrusor-sphincter dyssynergia) has been diagnosed by other methods (pressure/flow), the UPP may be used to direct the site and length of transurethral incision or laser vaporization. Overlap between normal and abnormal values is large. Thus the utility of infusion profilometry as a specific diagnostic study is limited. Some urodynamic experts question whether this test has a role in evaluating any voiding disorder. More recently, other methods of UPP measurement have been developed.

Static Urethral Pressure Profile

Although the static UPP technique may be modified by altering the position of the patient and the degree of bladder filling, the static UPP measures urethral pressure with the patient lying down, the bladder empty or at half capacity, and the urethra closed. Although perfusion profilometry has historically been the method most commonly used, two techniques have gained popularity to measure static UPP: the balloon catheter technique and the catheter tip transducer.

Perfusion Urethral Pressure Profile

The perfusion UPP technique uses a catheter with side holes through which saline solution or gas is perfused (1 mL per minute) with a motorized syringe pump. The pressure is measured by means of a side arm from the catheter. The pressure registered by the transducer represents the resistance to flow from the catheter side hole, as previously mentioned. Consequently, when the catheter is in the bladder, only bladder pressure opposes the outflow of saline solution, and the measured pressure is low. The catheter is then withdrawn at a constant rate (0.5 to 1.0 mm per second) through the entire length of the urethra. The initial pressure recorded on the chart strip recording is the intravesical pressure, followed by a positive deflection at the bladder neck and progressive increase in urethral pressure to the middle portion of the urethra in the female (Fig. 26B.19) and to the membranous urethra in the male (Fig. 26B.20). Beyond this point, pressure progressively decreases again until the external meatus is reached. Recommended nomenclature for UPP has been proposed by the International Continence Society. The most frequently measured parameters are as follows:

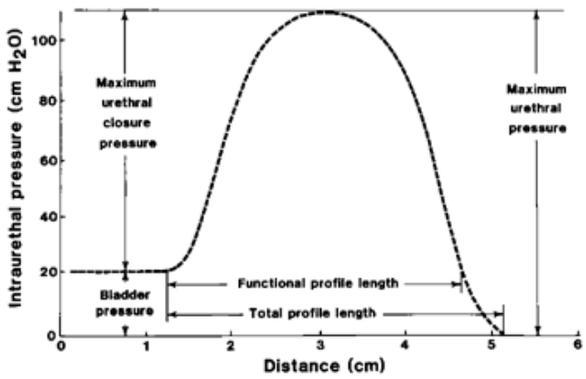

FIGURE 26B.19. Normal perfusion urethral pressure profile in a woman.

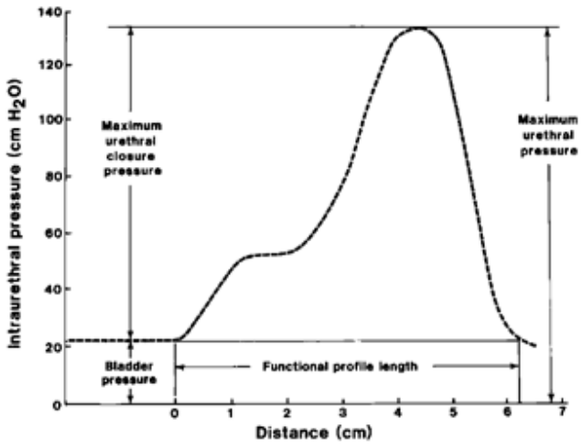

FIGURE 26B.20. Normal perfusion urethral pressure profile in a man.

1. Maximum urethral pressure, which is the maximum pressure of the profile
2. Maximum urethral closing pressure, which is the difference between the maximum urethral pressure and bladder pressure
3. Functional profile length, which is the length of the urethra along which the pressure exceeds bladder pressure

It is probably essential to simultaneously record external sphincter activity during the UPP. This will ensure that unintentional external sphincter contraction does not cause artifactual increase in maximum closing pressure. Many patients find it impossible to inhibit the external sphincter during the perfusion withdrawal process, and this is even more true of those with hypersensitive urethras and neurogenic bladder dysfunction. Simultaneous measurement of rectal pressure is advocated as a means to identify unintentional abdominal straining, which might also alter the normal profile curve.

In normal female patients, there is a gradual tendency for the maximum urethral pressure to decrease with age. This occurs mainly after menopause. The shape of the UPP curve is symmetric. In male patients, there is no

decrease in maximum urethral pressure with age. In defunctionalized bladder or prolonged anuria, an extraordinarily high (greater than 100 cm) maximum urethral pressure is seen (537). However, there is a tendency for the length of the prostatic urethra to increase, particularly after age 45. The shape of the UPP curve in the male is asymmetric. In the proximal part of the profile, there is a variable plateau corresponding to the bladder neck and prostatic tissues. A high pressure with significant plateau depending on withdrawal rate may signify bladder neck obstruction. In the distal part of the profile, there is a variable plateau because of the bladder neck and prostatic tissues. In the distal part of the profile, the pressure recorded is higher than from the distal female urethra because of the length and configuration of the male urethra. The highest pressure is generally recorded at the site of maximal concentration of periurethral striated musculature. Maximum urethral pressures of 20 cm H_2O or less generally correlate with intrinsic sphincter deficiency. The distal urethra is rarely of clinical significance, except on the rare occasion when the profile is recorded in a patient with a urethral stricture.

Balloon Catheter System

With the balloon catheter system, the eyeholes of the catheter are covered by a fine plastic balloon. This technique relies on a closed system that must be free of all bubbles or leaks. Although accurate, frequent calibration and replacement of balloon catheters is required as a result of a gradual change in compliance of the thin-walled balloons. This system is relegated to rectal pressure measurements. Care must be taken to barely distend this balloon to obtain a pressure reading without distending the rectum. Rectal distention similar to fecal impaction inhibits the micturition reflex.

Catheter Tip Transducer

The catheter tip transducer technique uses a catheter on which one or two transducers are mounted. The transducer is at the site of recording and obviates the problems inherent in recording at a distance from the organ being monitored. It allows for urethral pressure measurement during voiding. Double–transducer tip catheters allow for the simultaneous measurement of intravesical and urethral pressure. Small catheters are available that allow CMG and UPP testing during cystoscopy (38). The disadvantages of transducer catheters are their fragility, expense, and limited life span. The most problematic aspect of microtip transducers is the difficulty in zeroing and calibration. Many experts avoid these catheters.

Stress Urethral Pressure Profile

Stress urinary incontinence in women is the main indication for stress UPP, a test usually performed by urogynecologists. The stress UPP is best performed with a dual-sensor catheter tip transducer. The sensors should be separated by a 5- to 10-cm interval. The catheter is introduced into the bladder and then slowly withdrawn through the urethra while the patient is asked to cough at regular intervals. For coughs to be recorded for each 0.2 cm of urethral length, a slow withdrawal speed of 0.1 cm per second is used (2).

In normal patients, the increased pressure seen during coughing on the intravesical pressure trace is also seen superimposed on the urethral pressure trace. In normal patients, the raised intraabdominal pressure is transmitted to the proximal two-thirds of the female urethra. In patients with genuine stress incontinence, there is a failure of pressure transmission. However, the ease, lower cost, and ability of the ALPP to distinguish types of stress urinary incontinence (intrinsic sphincter deficiency) has supplanted urethral pressure profilometry at many institutions.

Static and *dynamic* refer to whether the test is performed with the patient at rest or voiding, respectively. The dynamic pressure profile is intended to show variation in sphincteric closure pressure under various physiologic events, as well as under different maneuvers. Unlike the static UPP, this method supplies information on the outlet during voiding. This dynamic pressure profile is obtained easily by the membrane catheter or microtransducer technique, but it is practically impossible to obtain by perfusion techniques (558). Normally, the pressure profile rises when the bladder is filled. In addition, postural change affects the urethral pressure. The lowest pressure is recorded when the patient is in the supine position. Sitting up increases urethral pressure, functional length, and magnitude of closing pressure. A precipitous rise in intraabdominal pressure, as caused by coughing, or a low sustained increase in intraabdominal pressure, as caused from bearing down, should simultaneously raise urethral pressure, which is normally much higher than the increase in intraabdominal pressure. An elevated pressure that falls off abruptly at some point between the bladder neck and the bulbomembranous urethral junction is sufficient to diagnose proximal sphincter dyssynergia (368). A key observation is a discrete fall in pressure distal to the site of obstruction.

A drop in total urethral pressure occurs just before voiding (556). When fluoroscopic evaluation is unavailable, dynamic profilometry may be applied to diagnose such uncommon causes of obstruction as proximal sphincter dyssynergia. A pressure gradient in an area of the urethra that is normally wide open with a detrusor contraction establishes the diagnosis of obstruction.

Multifunction Studies

In most clinical settings, it is usually practical and more cost-effective to screen patients by performing stopwatch uroflowmetry, ultrasonographic measurement of postvoid residual volume, and eyeball cystometry using a catheter-tip syringe (54). Although some experienced urodynamicists

disagree, one or more of these simple tests will help the clinician understand the patient's symptoms in most cases. Limited resources, a capitated health care system, generalist medicine, and the trend toward cost-effectiveness will demand justification for all clinical tests. However, in some instances of voiding dysfunction, a more sophisticated study is indicated. Criteria for such a study include the following (62):

1. When simple diagnostic procedures are inconclusive
2. When the patient has persistent symptoms despite what appears to be appropriate treatment
3. When the patient has a preexisting condition known to be associated with complex urodynamic abnormalities
4. When history and physical examination suggest neurologic disease
5. When morbidity of an invasive procedure is deemed excessive
6. When therapy relies on precise diagnosing to determine whether bladder suspension versus periurethral injections is needed

Ideally, abdominal pressure should be measured so that subtracted bladder pressure can be monitored during voiding studies. This is particularly important when the detrusor contractions are of small magnitude and when voiding is accompanied by abdominal straining.

Simultaneous Pressure/Flow Study

Although pressure/flow studies are considered the most accurate tool to define obstruction, their use has been hindered by a lack of consensus on the absolute values diagnostic for obstruction, the invasiveness of the procedure, and the inability to obtain reliable data in patients without a detrusor contraction or with impaired contractility. Outlet obstruction (Fig. 26B.21) can be diagnosed only by simultaneous pressure/flow determination or voiding urethral pressures. Detrusor pressure is measured with a catheter in the bladder while the flow rate is recorded (Fig. 26B.22). Obstruction is a voiding pressure of greater than 100 cm H_2O. A urethral resistance factor $R = P/Q_{max}^2$ with a value greater than 0.6 reflects obstruction. Because the urethra is not a rigid tube, as assumed in Griffith's equation, in 1988 the ICS recommended pressure/flow diagrams to determine obstruction. A 1994 report revealed that only one-third of pressure/flow studies yielded an uninterpretable result (133). Unfortunately, although pressure/flow studies document obstruction better than other methods, they may still fail to predict symptomatic outcomes of therapy. Furthermore, their invasiveness, cost, and time-consuming nature appear to limit their routine use.

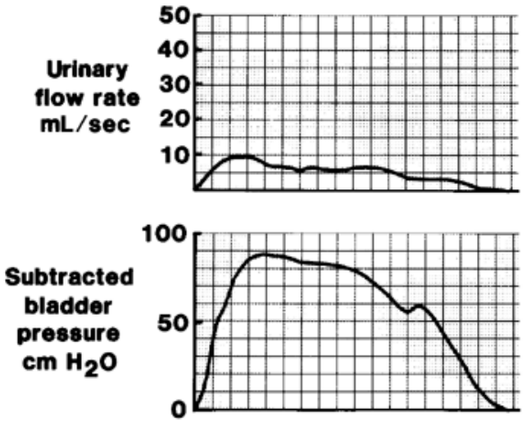

FIGURE 26B.21. Abnormal uroflow consistent with outlet obstruction.

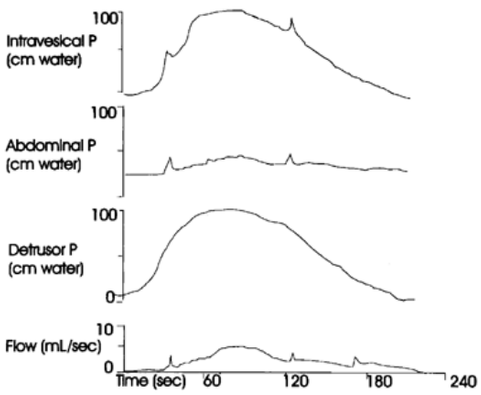

FIGURE 26B.22. Simultaneous combined pressure/flow urodynamic study in 55-year-old man with irritative and obstructive voiding symptoms. Detrusor pressure represents total intravesical pressure minus abdominal pressure. Note elevated detrusor pressure over 90 cm H_2O with low maximum (less than 5 cm H_2O) flow rate consistent with bladder outlet obstruction.

In general, patients identified by pressure/flow studies as being obstructed have better results after surgery. Abrams (2) used pressure/flow studies to select prostatism patients for surgery and achieved an 80% success rate of relieving obstruction in obstructed patients with high voiding pressures. Schaefer and associates (496) developed a computer program analysis of pressure/flow to determine obstruction. They found that 25% of those undergoing transurethral resection of the prostate (TURP) were not obstructed. In addition, patients classified by their program to be severely obstructed did best. Similarly, Rollema and Van Mastrigt (476) created a computer program referred to as CLIM, which uses two parameters to assess obstruction: the maximum extrapolated rate of increase of isometric pressure and the intersection of the quadratic urethral resistance relation. Similar to other reports, 25% of those undergoing TURP

were not obstructed using the CLIM program, and men with obstruction had better outcomes. The continuing debate on testing for BPH has highlighted the shortcomings of any single portion of the neurourologic examination for providing useful prognostic information.

Synchronous cystometry and sphincter EMG is a useful urodynamic combination for assessing spinal cord function (54,59). This test examines the relationship between the striated external urethral sphincter and the detrusor during the storage and voiding phases of micturition.

The disorder diagnosed by simultaneous cystometry and EMG is detrusor external-sphincter dyssynergia (DSD). In normal patients, or in those with detrusor instability or detrusor hyperreflexia resulting from neurologic lesions above the pons, the external urethral sphincter relaxes completely immediately before onset of the rise in detrusor pressure. Detrusor-sphincter dyssynergia is an abnormal reflex that occurs only when the neural pathways between the pons and sacral spinal cord are interrupted. In the absence of such a neurologic lesion, extreme caution should be exercised in diagnosing DSD. Conversely, if DSD is diagnosed, the clinician is obligated to search for such a lesion. The relaxation continues throughout the detrusor contraction unless the patient voluntarily attempts to interrupt micturition.

Detrusor external-sphincter dyssynergia is characterized by an involuntary contraction of the external sphincter coincident with or immediately preceding the rise in detrusor pressure. Blaivas and colleagues (62) have noted three patterns of DSD (Fig. 26B.16). Type 1 is characterized by an abrupt increase in EMG activity whose onset coincides with the beginning of the detrusor contraction. At the peak of the detrusor contraction, there is a sudden complete decrease in EMG activity as detrusor pressures fall. In type 2, there is intermittent EMG activity throughout the detrusor contraction. Type 3 is characterized by a crescendo-decrescendo pattern of external sphincter activity that parallels the detrusor contraction.

Pseudodyssynergia is a behavioral abnormality in which the patient subconsciously or consciously attempts to inhibit micturition (601). This results in “voluntary” contraction of the external sphincter during the detrusor contraction. These pseudodyssynergic syndromes are commonly encountered in children with persistent voiding symptoms, in men with prostatitis, and in women with the urethral syndrome.

It is impossible to distinguish between true dyssynergia and pseudodyssynergia by simultaneous cystometry and EMG unless intraabdominal pressure is measured concurrently. In pseudodyssynergia, there is usually some elevation of intraabdominal pressure as the patient tightens the abdominal and pelvic floor musculature.

Another and possibly simpler way to screen for DSD is by performing the combined uroflow and EMG (33). When uroflow is accompanied by absent external sphincter activity, dyssynergia may be excluded.

Videourodynamics

Videourodynamics is a technique using synchronously recorded urodynamic studies and cystourethrography for the evaluation of complex lower urinary tract problems. It encompasses pressure/flow external-sphincter EMG studies during filling, storage, and voiding phases of the micturition cycle, together with periodic screening of the synchronous cystourethrographic appearances of the bladder and its outlet.

Radiographic contrast material is infused for cystometry, permitting fluoroscopic visualization of the lower urinary tract. Urodynamic parameters are recorded and displayed on a storage oscilloscope or computer monitor. The fluoroscopic image of the bladder and urethra is electronically mixed with that of the urodynamic data and displayed on the same monitor. The advantage of these studies is that they combine the objectivity of urodynamics with the visual radiographic image of the part being studied, resulting in far more logical interpretation of results. The test also provides a permanent record and excellent tool for teaching. Alternatively, transrectal or transvaginal sonography can be used to image the bladder neck or urethra (50).

Videourodynamics has proved particularly valuable in the identification of complex bladder outlet obstruction problems and in the identification of the precise etiologies of incontinence. If bladder outlet obstruction has been diagnosed or is suspected, but the site of obstruction is not clear, a micturitional static urethral pressure profile determination can provide useful diagnostic criteria (62). Demonstration of a drop in pressure during voiding beyond the suspected site of obstruction, at which time the bladder and proximal urethra are normally isobaric, establishes the diagnosis of an obstruction between the bladder and the site of the decreased pressure. Fluoroscopy also allows visualization of the dilation proximal to site of obstruction (626).

Detrusor external-sphincter dyssynergia is characterized by involuntary contraction of the external sphincter during detrusor contractions (Fig. 26B.23). This is verified by fluoroscopy during voiding. If a patient was treated by external sphincterotomy and a question arises as to the efficacy of surgery, this may be best evaluated by images and urethral pressures during a videourodynamic study.

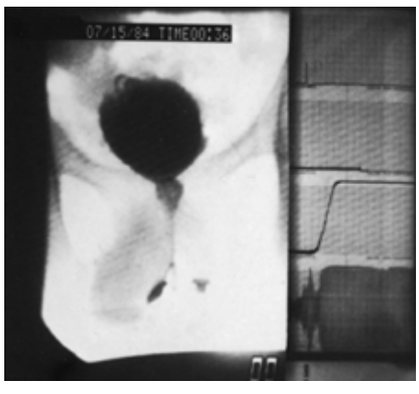

FIGURE 26B.23. Videourodynamic study in a 15-year-old paraplegic (T-5) boy who had high residual urine volumes and recurrent urinary infection. Intravesical pressure exceeded 100 cm H_2O (scale, 0 to 100 cm H_2O), and electromyographic activity was excessive during the detrusor contraction. Although the bladder neck opened, the prostatic urethra was dilated to the level of the external sphincter. There was no urinary flow *(top strip recording)* or increase in abdominal pressure *(second strip recording from the top)*. This is classic detrusor external-sphincter dyssynergia.

CLASSIFICATION OF VOIDING DYSFUNCTION

A clinical classification system should clarify principals and management. A good classification system can distill the essence of a clinical situation into a few key words or phrases. An ideal classification system for voiding dysfunction is challenging in that it must integrate data from many sources regarding diurese pathologies. Voiding symptoms should be linked with urodynamic data to provide a pathology and suggest management based on the category of

dysfunction. Although many systems of classification for voiding dysfunction were formulated primarily to describe dysfunction secondary to neurologic disease or injury, contemporary tests often cannot distinguish among myogenic, neurogenic, or psychiatric pathologies. The ideal classification system should be applicable to all types and causes of voiding dysfunction. Thus, in addition to the primarily neurologic systems, urodynamic and functional classification schemes also exist.

Lapides Classification

Lapides (302,303) contributed substantially to the classification and care of patients with neuropathic voiding dysfunction and popularized a modification of a scheme originally proposed by McLellan in 1939 (377). The systems are virtually identical except that Lapides further divided McLellan's category of autonomic bladder into motor neurogenic and sensory neurogenic bladder. The Lapides classification is the scheme most familiar to urologists and describes the clinical and cystometric conditions in most types of neurogenic voiding dysfunction. In the uninhibited neurogenic bladder and reflex neurogenic bladder groups, the exact categorization further implies whether the striated sphincter is dyssynergic (reflex neurogenic bladder) or synergic (uninhibited neurogenic bladder) during bladder contraction. This scheme is attractive for didactic purposes but is of little prognostic or therapeutic value.

A *sensory neurogenic bladder* results from any disease that selectively interrupts the afferents between the bladder and spinal cord or the afferent tracts to the brain. Whether lightly myelinated (Aδ) or unmyelinated fibers transmit sensation and pressure in humans is unclear. The distinction may become important as therapies are developed. Ice water tests and electrosensory threshold data indicate that more than one functional type of bladder afferent probably exists in humans. Classically, a sensory bladder is seen with long-standing diabetes mellitus, tabes dorsalis, and pernicious anemia. The first clinical changes consist only of impaired sensation of bladder distention. Unless voiding is initiated out of habit or on a timed basis, varying degrees of bladder overdistention are thought to lead to hypocontractility. With bladder decompensation, significant amounts of residual urine usually are found, and the cystometric curve many times demonstrates a large bladder capacity with a flat, low-pressure filling curve (high compliance). It was thought that the bethanechol supersensitivity test was positive in the early stages, but later negative as decompensation of the bladder smooth muscle occurred. The neurobiologic basis for this scheme has been shown to be conceptually flawed. Sensory nerves—or, more appropriately, afferents—from the bladder contain neuropeptides, including substance P, calcitonin gene-related peptide (CGRP), and vasoactive intestinal polypeptide (VIP). If Canon's laws of denervation hold, loss of these peptides should not cause hypersensitivity to the cholinergic agent bethanechol.

A *motor paralytic bladder* results from disease processes that destroy the parasympathetic motor innervation of the bladder. Extensive pelvic surgery or trauma can produce a motor paralytic bladder. Interestingly, herpes viruses affect dorsal root ganglia (afferents), and their destruction may abolish afferent input necessary for reflex micturition. Theoretically, if myelinated (Aδ) afferents mediating reflex micturition are destroyed, unmyelinated axons may still mediate sensation, but a distention-evoked reflex is abolished. This condition would appear to be a paralytic bladder; thus older schemes may list herpetic bladder disorders as motor paralytic. Consistent with this notion, early symptoms may vary from painful urinary retention to a relative inability to initiate and maintain normal micturition. In early stages, the filling limb of the cystometrogram is normal with normal sensation, but without a voluntary bladder contraction at bladder capacity. Later, chronic overdistention and bladder decompensation may occur, and a large-capacity bladder with a flat low-pressure filling limb and generally large residual urine volume will result. Again, the bethanechol test is reported to be positive despite, in some instances, a lack of anatomic and pharmacologic evidence for true afferent denervation.

The *uninhibited neurogenic bladder* is the most common manifestation of neurogenic pathology. A destructive lesion in many regions of the neuraxis can result in facilitation of the micturition reflex. Cerebrovascular accident, brain or spinal cord tumor, Parkinson's disease, and demyelinating

disease are the most common causes of this type of lesion. These diseases generally result in a voiding dysfunction characterized clinically by frequency, urgency, and incontinence, and cystometrically by normal sensation with an involuntary detrusor contraction at low filling volumes. Nerve irritation or early degeneration, such as with neuropathies and herniated discs, can also elicit involuntary detrusor contraction. Residual urine is characteristically small or absent unless anatomic outlet obstruction or true involuntary smooth or striated sphincter dyssynergia occurs. The patient can initiate a bladder contraction voluntarily but is often unable to do so during cystometry because of insufficient urine storage before onset of detrusor hyperreflexia.

The term *reflex neurogenic bladder* describes the post–spinal shock condition after complete interruption of the sensory and motor pathways between the sacral spinal cord and the pontine micturition center. This develops in traumatic spinal cord injury and transverse myelitis and may occur with extensive demyelinating disease, tumor, or ischemia injury. Typically, the patient has absent bladder sensation and is unable to voluntarily initiate micturition. Incontinence ensues because of low-volume detrusor hyperreflexia, which coincides with striated-sphincter dyssynergia. This type of lesion is equivalent to a complete upper motor neuron lesion in the Bors-Comarr system.

An *autonomous neurogenic bladder* denotes a complete motor and sensory separation of the bladder from the sacral spinal cord. Any disease process that destroys the sacral spinal cord or causes extensive damage to the sacral roots or pelvic nerves may result in this condition. The patient is unable to void voluntarily. Cystometry reveals detrusor areflexia and absent bladder sensation. This type of bladder is equivalent to the complete lower motor neuron lesion in the Bors-Comarr system and represents parasympathetic decentralization. This is also the type of dysfunction seen in patients with spinal shock until a spinal reflex develops to initiate micturition weeks to months later. The characteristic cystometric pattern is initially similar to the late stages of the motor or sensory paralytic bladder, with a marked shift to the right of the filling curve and a large bladder capacity at low intravesical pressure. However, secondary changes in the filling limb may occur that cause an increase in slope (decreased compliance). This may be secondary to chronic inflammatory change or to the effects of the denervation, with secondary neuromorphologic and neuropharmacologic changes, especially in regulation of α-adrenergic receptors or reorganization of sympathetic pathways. Emptying in an autonomous neurogenic bladder may vary from none to a large percentage of bladder capacity, depending on the resistance offered by the bladder outlet.

Urodynamic Classification

Evolution of this type of classification system has paralleled urodynamic expertise and, in the United States, has been pioneered by Krane and Siroky (294,297). When exact urodynamic classification is possible, this system provides a precise description of the particular voiding dysfunction. If a normal or hyperreflexic detrusor exists with coordinated smooth and striated sphincters and without anatomic obstruction, the bladder should empty completely. Striated-sphincter dyssynergia is most commonly seen in patients with a complete suprasacral spinal cord injury after the period of spinal shock has passed. Smooth-sphincter dyssynergia is seen most in autonomic dysreflexia when it is characteristically associated with detrusor hyperreflexia and striated-sphincter dyssynergia. Detrusor hyperreflexia can occur in nearly all neurologic lesions above the sacral spinal cord, may be associated with inflammatory or infectious disease, or may be idiopathic. Detrusor areflexia may be secondary to bladder muscle decompensation or to various other conditions that produce inhibition at either the level of the brainstem micturition center, sacral spinal cord, bladder ganglia, or bladder smooth muscle. Areflexia also ensues if the sacral autonomic nucleus is destroyed. Patients with a voiding dysfunction that falls into this category often attempt bladder emptying by abdominal straining or a Credé maneuver. Their continence status and the efficiency of their emptying efforts are determined by the status of the smooth and striated sphincters of the outlet.

This classification system is best applied when detrusor hyperreflexia or normoreflexia exists, because urodynamic techniques exist to describe the activity of the smooth and striated sphincters during bladder contraction. Thus a typical T-10 paraplegic patient exhibits detrusor hyperreflexia, smooth-sphincter synergia, and striated-sphincter dyssynergia. When a voluntary or hyperreflexic bladder contraction cannot be elicited, this system is inadequate because it is not appropriate to speak of true dyssynergia in the absence of an opposing bladder contraction.

Rare and difficult to diagnose is smooth muscle or internal-sphincter dyssynergia. Although it often occurs with thoracic spinal cord lesions associated with detrusor hyperreflexia and external-sphincter dyssynergia, isolated pathology may exist. A young, anxious male with functional obstruction isolated to the bladder neck and proximal urethra may represent a spectrum of this disorder. A high urethral pressure at the bladder neck, and a fall in pressure over this region during voiding or fluoroscopic lack of opening during bladder contraction, help diagnose the pathology. Smooth muscle dyssynergia or nonrelaxation of the bladder neck probably results from overactivity of adrenergic nerves. Therefore lesions of the thoracolumbar spinal cord, where sympathetic outflow originates, have also been reported to cause this disorder.

Functional System

Classification of voiding dysfunction can also be formulated on a functional basis, describing the dysfunction simply in

terms of whether the deficit produced is primarily one of the filling or storage phase of micturition or of the emptying phase (599,604) (Table 26B.6). This type of classification system is an excellent alternative when a particular dysfunction does not lend itself to an agreed-on classification in one of the other systems. This sytem has been promoted primarily because of dissatisfaction with attempts to exactly classify voiding dysfunction based solely on urodynamics or neurologic lesion.

TABLE 26B.6. FUNCTION CLASSIFICATION

Failure to store	Failure to empty
Because of the bladder	Because of the bladder
Because of the outlet	Because of the outlet

This simple scheme is based on agreement on principles governing micturition. Bladder filling and urine storage require accommodation of increasing volumes of urine at a low intravesical pressure and with normal and appropriate sensation; absence of involuntary bladder contractions; and a bladder outlet that is closed at rest and remains so with stress. Storage failure can then result because of problems related to bladder hyperreflexia or low compliance and because of a permanent or intermittent decrease in outlet resistance. Bladder emptying requires a coordinated bladder contraction of adequate magnitude and lack of anatomic obstruction and concomitant lowering of resistance at the level of the smooth and striated sphincter. Failure to empty can then result from inadequate bladder contractility or increased outlet resistance. Failure in either category generally is not absolute but is more often relative.

Such a system can easily accommodate causative or urodynamic connotations (Table 26B.7). However, it avoids argument in those complex situations where the exact cause or urodynamic mechanism of a voiding dysfunction is unclear. A logical extension of this system functions especially well as a “menu” for the treatment of voiding dysfunction (Table 26B.8, Table 26B.9, Table 26B.10, Table 26B.11 and Table 26B.12).

TABLE 26B.7. EXPANDED FUNCTIONAL CLASSIFICATION

- Failure to store
  - Because of the bladder
    - Detrusor hyperactivity
      - Involuntary contractions
        - Suprasacral neurologic disease
        - Bladder outlet obstruction
        - Idiopathic
      - Decreased compliance
        - Fibrosis
        - Idiopathic
      - Sensory urgency
        - Inflammatory
        - Infectious
        - Neurologic
        - Psychologic
        - Idiopathic
  - Because of the outlet
    - Stress incontinence
    - Nonfunctional bladder neck/proximal urethra
- Failure to empty
  - Because of the bladder
    - Neurologic
    - Myogenic
    - Psychogenic
    - Idiopathic
  - Because of the outlet
    - Anatomic
      - Prostatic obstruction
      - Bladder neck contracture obstruction
      - Urethral stricture
    - Functional
      - Smooth-sphincter dyssynergia
      - Striated-sphincter dyssynergia

TABLE 26B.8. THERAPY TO FACILITATE BLADDER EMPTYING

- Increasing intravesical pressure/bladder contractility
  - External compression, Valsalva
  - Promotion or initiation of reflex contractions
    - Trigger zones or maneuvers
    - Bladder training, tidal drainage
  - Pharmacologic therapy
    - Parasympathomimetic agents
    - Prostaglandins
    - Blockers of inhibition
      - α-Adrenergic antagonists
      - Opioid antagonists
  - Electrical stimulation
    - Directly to the bladder
    - To the spinal cord or nerve roots
  - Reduction cystoplasty
- Decreasing outlet resistance
  - At a site of anatomic obstruction
    - Prostatectomy
    - Urethral stricture repair/dilation
  - At the level of the smooth sphincter
    - Transurethral resection or incision of the bladder neck
    - Y-V plasty of the bladder neck
    - Pharmacologic therapy
      - α-Adrenergic antagonists
      - β-Adrenergic agonists
  - At the level of the striated sphincter
    - External sphincterotomy
    - Urethral overdilation
    - Pudendal nerve block or interruption
    - Pharmacologic therapy
      - Skeletal muscle relaxants
        - Centrally acting relaxants
        - Dantrolene
        - Baclofen
      - α-Adrenergic antagonists
  - Biofeedback, psychotherapy
- Circumventing problems
  - Intermittent catheterization
  - Continuous catheterization
  - Urinary diversion

TABLE 26B.9. THERAPY TO FACILITATE URINE STORAGE

Inhibiting bladder contractility/decreasing sensory input/ increasing bladder capacity
Timed bladder emptying
Pharmacologic therapy
Anticholinergic agents
Musculotropic relaxants
Polysynaptic inhibitors
Calcium antagonists
β-Adrenergic agonists
β-Adrenergic antagonists
Prostaglandin inhibitors
Tricyclic antidepressants
Dimethyl sulfoxide
Bromocriptine
Biofeedback, bladder retraining
Bladder overdistention
Electrical stimulation (reflex inhibition)
Interruption of innervation
Central (subarachnoid block)
Peripheral (sacral rhizotomy, selective sacral rhizotomy)
Perivesical (peripheral bladder denervation)
Augmentation cystoplasty
Increasing outlet resistance
Physiotherapy
Electrical stimulation of the pelvic floor
Pharmacologic therapy
α-Adrenergic agonists
Tricyclic antidepressants
β-Adrenergic antagonists
Estrogen
Vesicourethral suspension
Bladder outlet reconstruction
Surgical mechanical compression
Nonsurgical mechanical compression
Circumventing problem
Antidiuretic hormone–like agents
External collecting device
Intermittent catheterization
Continuous catheterization
Urinary diversion

TABLE 26B.10. VOIDING DYSFUNCTION: GOALS OF MANAGEMENT

Upper urinary tract preservation or improvement	Adequate control
Absence or control of infection	No catheter or stoma
Adequate storage at low intravesical pressure	Social acceptability/ adaptability
Adequate emptying at low intravesical pressure	Vocational acceptability/ adaptability

TABLE 26B.11. PATIENT FACTORS TO CONSIDER IN CHOOSING THERAPY

Prognosis of underyling disease, especially if progressive or malignant disease	Desire to avoid surgery
Limiting factors: inability to perform certain tasks (hand dexterity, ability to transfer)	Sexual activity status
Mental status	Reliability
Motivation	Educability
Desire to remain catheter or appliance free	Psychosocial environment: interest, reliability, and cooperation of family
	Economic resources
	Age

TABLE 26B.12. REASONS TO CHANGE OR AUGMENT A GIVEN REGIMEN

Upper urinary tract deterioration	Inadequate emptying
Recurrent sepsis or fever of urinary tract origin	Inadequate control
Lower urinary tract deterioration	Unacceptable side effects
Inadequate storage	Skin changes secondary to incontinence of collecting device

Use of this system for a given voiding dysfunction requires a reasonably accurate notion of urodynamic findings. However, an exact diagnosis is not required for treatment. Some patients just do not have a discrete storage or emptying failure, and the existence of combination deficits must be recognized to properly use this system of classification. For example, T-10 paraplegic patients generally exhibit a relative failure to empty because of striated-sphincter dyssynergia. In such a combination deficit, to use this classification system, one must assume that either one deficit is primary and that significant improvement will result from its treatment alone, or that the voiding dysfunction can be converted primarily to a disorder of storage or emptying by surgical or pharmacologic therapy. The resulting deficit can then either be treated or circumvented. With the same example, the combined deficit in a T-10 paraplegic patient can be converted primarily to a failure to store using surgical procedures (e.g., external sphincterotomy) directed at the dyssynergic striated sphincter, and the resultant incontinence (secondary to detrusor hyperreflexia) can be circumvented (in a male) with an external collecting device. Alternatively, the deficit could be converted primarily to a failure to empty using surgical or pharmacologic measures designed to abolish or reduce the detrusor hyperreflexia, and the resultant failure to empty can be circumvented with clean intermittent catheterization. Other examples of combination deficits include impaired bladder contractility with sphincter dysfunction, bladder outlet obstruction with detrusor hyperactivity, and bladder outlet obstruction with sphincter malfunction.

The major limitation of this functional classification is that not every voiding dysfunction can be reduced or converted primarily to a failure of storage or emptying. In addition, although the functional classification of therapy that is a correlate of this scheme seems logical, there is a danger of pursuing therapy and overlooking a correctable or serious abnormality. Nonneurogenic voiding dysfunction

can also be classified within this system, with the possible exception of sensory disorders. Unfortunately, these disorders are virtually ignored by all classification systems.

International Continence Society Classification

The ICS has proposed a classification based on the functional state of the bladder and urethra (256). It has been revised over the years and updated to include incontinence, pressure/flow studies, patients with neurogenic bladders, and ambulatory urodynamics (548,579). An active detrusor function is indicated when, during the filling phase, there are involuntary detrusor contractions that the patient cannot suppress. Involuntary bladder contractions associated with known neurologic disease fall under the category of detrusor hyperreflexia, whereas the term *unstable detrusor* or *bladder instability* is applied to such activities that occur in a patient without known neurologic disease. *Compliance* refers to the volume–pressure relationship in a bladder, and *low compliance* represents another form of detrusor overactivity. The underactive detrusor may be described as *noncontractile* (no contraction under any circumstances), *hypocontractile* (impaired contractility), or *areflexic*. A patient with an underactive detrusor may be described as having a *high-compliance bladder* (a capacious bladder that shows little change in pressure in response to a given volume increment). An overactive urethral closure mechanism contracts involuntarily against the detrusor contraction (dyssynergia) or fails to relax during attempted micturition. An incompetent urethral closure mechanism allows urinary incontinence. This may occur only during a rise in intraabdominal pressure (stress incontinence), or it may be persistent, in which case continuous leakage will occur. It may also be caused by an involuntary decrease in urethral pressure in the absence of detrusor activity (the unstable urethra, or urethral instability).

Urethral instability probably represents the normal neurogenic relaxation of the bladder outlet during voiding. In the absence of the detrusor contraction due to neurogenic or myogenic areflexia, the fall in urethral pressure can be easily observed (364). The patient typically complains of stress urinary incontinence (failure to store) and obstructed symptoms (failure to empty) with residual urine and normal sensation.

Within the ICS system, a T-10 paraplegic patient would be classified as follows: overactive detrusor, overactive urethra, hyposensitive. The condition of a stroke patient with urgency incontinence would most likely be classified as follows: overactive detrusor, normal urethra, normal sensation. The condition of a patient with stress incontinence would be classified as follows: normal detrusor, incompetent urethra, and normal sensation.

TREATMENT OF VOIDING DYSFUNCTION

Therapies available for managing voiding dysfunction are easily categorized on a functional basis according to their effects on the bladder or on the outlet (Table 26B.8 and Table 26B.9). This functional outline is followed in discussing each therapy. Some of the surgical therapies are discussed elsewhere in this text. Surgery for incontinence and neurogenic voiding dysfunction are primarily discussed.

The choice of a surgical versus a nonsurgical mode of management is based on many factors (Table 26B.10). One of the most important concepts to be put forth in recent years is a urodynamic clarification of “adequate storage at low intravesical pressure.” McGuire (367) and McGuire and co-workers (374,376) have clearly shown that upper tract deterioration is apt to occur when storage, even though adequate in terms of continence, occurs at sustained intravesical pressures of greater than 40 cm H_2O. This value corresponds to that obtained in experimental studies in which intravesical pressure was raised until urine did not fully flow in the bladder. Application of this approach to patients with storage problems because of decreased bladder compliance has resulted in the concept of the “detrusor leak-point.” Patients with leakage pressures less than 40 cm H_2O will not experience upper tract deterioration in the absence of other complicating factors, such as significant vesicoureteral reflux with urinary tract infection. Poor bladder compliance (less than 20 cm H_2O) plus an elevated detrusor leak-point pressure places the patient at very high risk for upper tract deterioration.

When treating patients with voiding dysfunction, a perfect result is rarely achieved, and a flexible approach to therapy must be adopted. Any decision must take into account the wishes of an informed patient and the practicality of each proposed solution, especially in those patients with neurologic disease (Table 26B.11). Whether initial therapy is to be surgical or nonsurgical is a decision best made with the patient and family. In every case, the patient and family must be informed of all methods of management, reversibility, side effects, results, and frequency and extent of follow-up and costs. The simplest, least destructive, and most reversible form of therapy that can satisfy the goals of treatment usually should be tried first. A combination

of therapeutic maneuvers, drugs, and surgery can sometimes be used, especially if they act through different mechanisms and their side effects are not synergistic.

Absolute or relative indications for changing or augmenting a particular regimen exist. These are generally agreed on, although the relative importance of an indication for change might be disputed (Table 26B.12).

Therapy to Facilitate Bladder Emptying

Increasing Intravesical Pressure or Bladder Contractility

Credé Maneuver

External compression and Valsalva manual compression of the bladder (Credé maneuver) can be effective in patients with decreased bladder tonicity who can generate a pressure greater than 50 cm H_2O with this maneuver, and whose outlet resistance is low (211,604). The technique of voiding by the open-hand Credé method involves placement of the thumb of each hand over the area of the left and right anterior superior iliac spine and of the digits over the suprapubic area, with slight overlap at the fingertips. The slightly overlapped digits are then pressed into the abdomen, and when they have gotten behind the symphysis, pressed downward to compress the fundus of the bladder. Both hands are then pressed as deeply as possible downward into the real pelvic cavity. At times, compression of the bladder can be accomplished more efficiently by using the fist of one hand (closed-hand method) or a rolled-up towel.

A similar increase in intravesical pressure may be achieved by abdominal straining. This method of voiding is particularly useful in patients with orthotopic neobladders. In both men and women, the technique of straining (Valsalva) involves sitting and resting the abdomen forward on the thighs. During straining in this position, hugging of the knees and legs may be advantageous to prevent bulging of the abdomen. To increase intravesical pressure in this manner requires voluntary control of the abdominal wall and diaphragmatic muscles, or in the case of the Credé maneuver, adequate hand control. Straining at the time the Credé maneuver is applied should be avoided, because this increases intraabdominal pressure and causes bulging of the abdominal wall, which then tends to lift the compressing hands off the fundus of the bladder. The Credé maneuver is much easier in a patient with a lax, lean abdominal wall than with a taut or obese one, and it is more readily performed on the abdominal bladder of a child than on the pelvic bladder of an adult. This straining maneuver is not without complications. Pelvic prolapse in women and hemorrhoids in both sexes can occur. Credé maneuver is not to be recommended after augmentation because of the risk of rupture.

Voiding by these maneuvers is unphysiologic and is resisted by the same forces that prevent stress urinary incontinence. Reflex funneling of the bladder neck and proximal urethra does not generally occur with external compression maneuvers. In contrast, in patients with intact pelvic floor striated muscle reflexes, outlet resistance may increase. If adequate emptying is not achieved, other therapies to decrease outlet resistance may be considered, but these may adversely affect continence. Vesicoureteral reflux is another relative contraindication to Credé or Valsalva maneuvers, especially in patients who are capable of generating a high intravesical pressure. The greatest likelihood of success with this therapy is in patients with an areflexic and hypotonic or atonic bladder and some outlet denervation (striated or smooth sphincter or both). Not uncommonly, the patient also exhibits stress incontinence. The continued use of external compression or the Valsalva maneuver implies that the intravesical pressure between attempted voidings is consistently below that necessary to cause upper tract deterioration. This may be an erroneous assumption, and close follow-up is necessary to avoid this complication in patients with normal outlet resistance. The most flagrant misuse of this form of management is in patients with a decentralized or denervated bladder in whom decreased compliance during filling has developed. Such patients may silently develop upper tract deterioration with minimum filling.

Bladder Latissimus Myoplasty with Electrical Stimulation

For patients with detrusor areflexia or hypocontractility who exhibit low outlet resistance, a technique similar to cardiac assist myoplasty has been pioneered by Stenzl and colleagues to facilitate emptying (543). Latissimus free flap transfer with microsurgical neural and vascular anastomoses is a complex surgery requiring a team of urologists and plastic surgeons. Operating times exceed 12 hours. Care must be taken to appropriately position the latissimus muscle around the bladder and secure it to pelvic structures so it can generate appropriate force to expel urine. An implantable neurostimulator is controlled using an external wand to activate the nerves supplying this flap. Patient selection is key. Women with sacral lesions causing detrusor areflexia and low outlet resistance are able to empty the bladder completely at low pressures. Although the number of patients eligible for this technique may be limited, early results are encouraging.

Promotion or Initiation of Reflex Contraction

In spinal cord injury or disease characterized by detrusor hyperreflexia, manual stimulation of areas within the sacral and lumbar dermatomes may sometimes provoke a reflex bladder contraction (71,204). Pulling the skin or hair of the pubis, scrotum, or thigh; squeezing the clitoris; and digital rectal stimulation are examples of the type of activity that sometimes induces “trigger voiding” in these patients. According to Glahn (211), the most effective method of

inducing such a contraction is rhythmic suprapubic manual pressure (seven or eight pushes every 3 seconds). This is thought to produce a summation effect on the tension receptors in the bladder wall, resulting in an afferent neural discharge, which activates the bladder reflex arc. Recent experimental data show that following complete spinal cord transection, somatic (cutaneous and visceral; i.e., vaginal, rectal) afferents can activate a transient spinal micturition reflex. In neurologically intact individuals, these somatic afferents inhibit micturition through spinal mechanism. The same mechanisms are exploited for use with cutaneous electrical stimulation in the treatment of detrusor hyperactivity. Patients who are potentially able to induce bladder contractions by such a maneuver should be encouraged to find their own optimal "trigger points" and position for urination. Manual dexterity, and the ability to transfer to a commode or use of an external collecting device, is required. Unfortunately, this type of patient often suffers from sphincter dyssynergia, and such maneuvers may have to be combined with measures to decrease outlet resistance at the level of the striated or smooth sphincter.

No objective data support the notion that a rhythmic pattern of bladder filling and emptying by maintaining a copious fluid intake, and by periodically clamping and unclamping an indwelling catheter or with intermittent catheterization, can "condition" or "train" the micturition reflex.

Pharmacologic Manipulation

Parasympathomimetic Agents

The final common pathway for a physiologic bladder contraction is stimulation of the muscarinic cholinergic receptors on bladder smooth muscle. Cholinergic nerves supplying the bladder release acetylcholine, which acts primarily on muscarinic receptors of the M_3 subtype to evoke a detrusor contraction and voiding (18). In addition, activation of M_2 receptors on smooth muscle inhibits bladder relaxation by blocking signal transduction pathways that raise cyclic adenosine monophosphate (cAMP) (242). Following injury or denervation, an upregulation of M_2 receptors occurs. Hence, direct activation of muscarinic receptors should enhance detrusor contractility. Agents that imitate the actions of acetylcholine might be expected to be useful in the management of patients who cannot empty because of inadequate bladder contractility. Many acetylcholine-like drugs exist. However, only bethanechol chloride exhibits a relatively selective action on the urinary bladder and gut, with minimal action at ganglia or on the cardiovascular system (573). It is cholinesterase resistant and causes a contraction *in vitro* of smooth muscle from all areas of the bladder (455).

Bethanechol has been recommended for the treatment of postoperative or postpartum urinary retention in a subcutaneous dose of 5 to 10 mg. For more than 40 years, it has been used in the treatment of the atonic or hypotonic bladder (315), and it has been reported to be effective in achieving "rehabilitation" of the chronically atonic or hypotonic detrusor (135,301,522). However, few clinicians would consider this regimen to make a major difference in emptying the bladder. In uncontrolled reports where this drug is effective, it cannot be excluded that retention was psychogenic or that reflex micturition would have returned spontaneously.

Bethanechol has also been used to stimulate or facilitate the development of reflex bladder contractions in patients with suprasacral spinal cord injury (437). Twiddy and associates (572) have concluded that, at least in spinal cats, intact pelvic reflex pathways are required for bethanechol to produce what they described as a brisk and sustained increase in intravesical pressure during bladder filling. However, in hyperreflexic patients with poor bladder compliance, bethanechol may cause upper tract deterioration by raising intravesical pressure.

Although anecdotal success in selected patients has been described, attempts to facilitate bladder emptying in series in which bethanechol was the only variable have been dismal. A pharmacologically active subcutaneous dose (5 mg) did not demonstrate significant changes in flow parameters or residual urine volume in women with a residual urine volume equal to or greater than 20% of bladder capacity and no evidence of neurologic disease or outlet obstruction, or in a group of 27 "normal" women of approximately the same age (603). A similar dose likewise failed to produce urodynamic evidence of improved emptying in patients with a positive bethanechol supersensitivity test (605). Yet this dosage elevates intravesical pressure throughout the filling limb of the cystometrogram while reducing bladder capacity (307,522). Bethanechol is capable of eliciting an increase in tension in bladder smooth muscle such as would be expected from *in vitro* studies, but its ability to stimulate or facilitate a physiologic-like bladder contraction in patients with voiding dysfunction has been unimpressive. Similar sentiments with respect to its use in neuropathic dysfunction, have been expressed by Gibbon (205), Light and Scott (328), Merrill and Rotta (379), and Yalla and colleagues (623). In fact, it is difficult to find reproducible urodynamic data that support recommendations for the usage of bethanechol in any patients. Its use should be abandoned.

No agreement exists as to whether cholinergic stimulation produces an increase in urethral resistance (605). It appears that pharmacologically active doses increase urethral closure pressure in patients with neurogenic bladder dysfunction with detrusor hyperreflexia (526). If so, a reasonable question is whether cholinergic agonists could be combined with agents that decrease outlet resistance to facilitate emptying. Khanna (276) reported that a combination of a total daily oral dose of bethanechol of 50 to 100 mg with 20 to 30 mg of oral phenoxybenzamine produced

satisfactory results in a group of patients with an atonic bladder and functional outlet obstruction. Personal experience with such therapy, using even 200 mg of oral bethanechol daily, has been extremely disappointing. Most clinicians would agree that a daily dose of 50 to 100 mg rarely affects any urodynamic parameter. Moreover, some spinal cord–injured patients develop hydronephrosis on this drug, possibly due to elevated intravesical pressures (personal observation). This is further evidence that bethanechol's use should be abandoned.

Acetylcholinesterase drugs such as physostigmine and neostigmine have been administered to humans. Because these agents prevent the breakdown of acetylcholine, they may facilitate emptying. Neostigmine increases intravesical pressures and elicits detrusor contractions; however, its utility in emptying the bladder is unproven, and its side effects are prohibitive.

Activation of certain receptors enhances release of acetylcholine from nerve terminals in the bladder. In this regard, activation of serotonergic (5-HT_3) receptors has been proposed, but trials demonstrating the clinical usefulness of this approach are lacking.

Prostaglandins

It has been hypothesized that prostaglandins influence bladder contractile activity. With this rationale, Bultitude and associates (78) reported that instillation of 0.5 mg of prostaglandin E_2 (PGE_2) into the bladders of females with varying degrees of urinary retention resulted in short-term emptying and improvement of long-term emptying in two-thirds of the patients studied. Desmond and colleagues (130) also reported results with intravesical use of this agent in patients whose bladders had absent or impaired contractile activity. A total of 20 of 36 patients showed a strongly positive and 6 showed a weakly positive immediate response. Fourteen patients were reported to show prolonged beneficial effects, all but one of whom had shown a strongly positive immediate response. Further analysis revealed that an intact sacral reflex arc was a prerequisite for any positive response. The authors also noted that the effects of PGE_2 appeared to be additive or synergistic with cholinergic stimulation in some patients. Vaidyanathan and colleagues (577) reported that intravesical instillation of 7.5 mg of 15(S)-15-methyl PGF_2 produced reflex voiding in some patients with incomplete suprasacral spinal cord lesions. The favorable response to a single dose of drug when present lasted from 1.0 to 2.5 months. Other investigators, including Delaere and colleagues (126), have failed to show success with this type of treatment. Prostaglandins have a relatively short half-life, and it is difficult to envision a durable response. Hypotension, tachycardia, cardiac arrhythmia, convulsions, hypocalcemia, and diarrhea can occur. The absence of any recent reports on efficacy seems to indicate lack of support for or interest in this approach.

Blockers of Inhibition

Sympathetic reflexes promote urine storage by exerting an inhibitory effect on pelvic parasympathetic ganglionic transmission, increasing outlet resistance, and possibly relaxing the bladder body. Activation of α-adrenergic receptors inhibits ganglion transmission. Some have suggested on this basis that α-adrenergic blockade, in addition to decreasing outlet resistance, may facilitate transmission through these ganglia and thereby enhance bladder contractility. Methyldopa had been tried with this rationale with at least some good initial results (458). More reports advocate a trial of an α-adrenergic blocking agent for the initial treatment of postoperative or psychogenic urinary retention that is due to BPH.

Recent understanding of the roles of neuropeptides has also provided new insights into lower urinary tract function and its pharmacologic alteration. Endogenous enkephalins, serotonin, and gamma-aminobutyric acid (GABA) are thought to exert a tonic inhibitory effect on the micturition reflex, and agents such as narcotic antagonists and serotonin or GABA antagonists offer new possibilities for enhancing reflex bladder activity (348,533,576). In spinal cord–injured animals and one human trial, the opiate antagonist naloxone facilitated bladder emptying (612).

Electrical Stimulation

Clinical trials of direct electrical stimulation to completely empty the bladder have met with partial success and periodic enthusiasm. Direct electrical stimulation has been attempted in patients with hypotonic and areflexic bladders. Initial success, defined as a low postvoid residual with sterile urine, was achieved in only 50% to 60% of patients, and secondary failure, usually related to equipment malfunction, often supervened. The spread of current to other pelvic structures whose stimulus thresholds were lower than that of the bladder often resulted in abdominal, pelvic, and perineal pain; a desire to defecate; contraction of the pelvic and leg muscles; and erection and ejaculation in males. It was also noted that the increase in intravesical pressure generally was not coordinated with bladder neck opening or pelvic floor relaxation and that other measures to accomplish these ends might be necessary. Grimes and colleagues (225,226) applied electrical stimulation directly to the sacral spinal cord, attempting to take advantage of the remaining intact motor pathways to initiate micturition. Although some short-term success was noted, many of the side effects seen with direct bladder stimulation occurred because the stimulus, so applied, was also unphysiologic.

To overcome stimulation-induced detrusor-sphincter dyssynergia, a variety of methods have been used. Tanagho and colleagues (559) and Schmidt (499), among others, have pursued neurostimulation for both emptying and storage problems. They found that it was not possible at the spinal cord level to separate a bladder center from a striated-sphincter center. However, they have pursued with

some success stimulation of individual sacral nerve roots. The commercially available Finetech-Brindley implantable stimulator uses poststimulus voiding. Poststimulus voiding relies on differences in relaxation times between the detrusor and external urethral sphincter. It evokes voiding in spurts at supraphysiologic pressures. Lower limb movement is not uncommon. Other techniques rely on surgical interruption of pudendal fibers, blockade of somatic transmission, fatiguing of the external urethral sphincter, and activation of small fibers. The latter methodology has been exploited by Rijkhoff and colleagues (470). Small fiber activation requires a tripolar electrode that activates both large-diameter (somatic to external sphincter) and small-diameter (autonomic to bladder and urethra) fibers. The lower current needed to activate large fibers allows a differential activation. Blockade distal to the stimulating cathode using an anode will selectively cancel out the action potential in the large but not small fibers. This is termed *anode blockade*. Although acute experiments in humans are encouraging, problems remain with chronic stimulation because small changes in current alter parameters. Too small a current is insufficient to activate the bladder, and too large a current blocks small-diameter fibers to the bladder. Moreover, charge-balanced biphasic currents are needed to prevent nerve damage. Alternatively, some investigators have explored the use of "cold block" of pudendal nerves (501). These techniques assume that detrusor contractility is preserved. This is rarely the case. Loss of neural input, at least experimentally, alters detrusor contractility and may even lead to apoptosis and fibrosis in the long term. For the outcomes of electrostimulation to surpass those of intermittent self-catheterization, minimal morbidity and nearly complete emptying must be achieved.

Reduction Cystoplasty

On the surface, a reduction cystoplasty seems to be an attractive alternative for patients with chronic urinary retention who have large decompensated bladders. Reduction cystoplasty has been advocated for patients with megacystis due to prune-belly syndrome. In 11 boys with prune-belly syndrome followed for an average of 8 years, reduction cystoplasty allowed only a 50-mL residual urine after double or triple voiding. With techniques of reduction cystoplasty involving either fundus invagination or detrusor duplication (but not simple excision of bladder tissue only), symptomatic successes with lower bladder capacity and lower residual urine volumes have been achieved (237,283,473). However, it is puzzling that despite such improvement, Roberts and colleagues (473) and Kinn (283) reported absolutely no change in bladder or sphincter activity. In patients with contractile bladders, flow rates seem to change only when outlet reduction is also performed.

Decreasing Outlet Resistance at a Site of Anatomic Obstruction

Prostatic enlargement and urethral stricture are two of the more common causes of bladder outlet obstruction in males. The pathophysiology of their development and their surgical and nonsurgical correction are dealt with elsewhere in this volume.

Decreasing Outlet Resistance at the Level of the Smooth Sphincter

Transurethral Resection of Incision of the Bladder Neck

Emmett (156) performed the first transurethral bladder neck resection in a patient with neurogenic bladder dysfunction in 1937, and for years this procedure represented the initial approach in cases of poorly balanced bladder function. Originally, the operation was performed primarily in two groups of patients: those with weak or absent detrusor contractions and those with anatomic or functional obstruction at the level of the bladder neck and proximal urethra, which prevents emptying even with a sustained detrusor contraction (79,206,604). Some urologists still prefer to resect the bladder neck whenever there is significant residual urine or signs of outlet obstruction associated with a neuropathic bladder, and treat other areas of outlet resistance later (203,204,211). However, obstruction is rarely documented. Instead, symptoms and flow rates alone have been used.

More refined urodynamic techniques have resulted in the realization that dyssynergia at the level of the bladder neck or proximal urethra is relatively common in cases of complete paraplegia above T-12 and quadriplegia (502), but uncommon in other neurologic disorders, or in patients with obstruction but without neurologic disease. Kaplan and associates (270) have proven urodynamically that some men diagnosed as having chronic prostatitis actually are obstructed and benefit from bladder neck incision. The prime indication for bladder neck incision is failure of medical therapy (e.g., α-blocker) in a patient with obstruction at the bladder neck or proximal urethra level, diagnosed by combined detrusor pressure/flow studies with either fluoroscopic demonstration of a failure of opening of the smooth-sphincter area, or a micturitional urethral profile showing that the bladder pressure falls off sharply at some point between the bladder neck and the area of the striated sphincter. In the past, it was believed that another category of patient for whom this procedure would be useful was one with a sacral spinal cord lesion and an areflexic bladder who could achieve a measurable increase in intravesical pressure by straining or use of the Credé maneuver, but who could not empty the bladder adequately by these methods (604). The procedure simply creates a form of "graded" stress incontinence in these patients and demonstrates that other

alternatives for adequate emptying should be sought first. Although documented instances of bladder neck obstruction in women have been reported (134), extreme caution must be exercised in surgically treating this entity in females because of the risk of incontinence.

Techniques of resection include the following:

1. A thorough circumferential resection of all tissue between the internal orifice and the verumontanum (in males)
2. A limited resection of dorsal tissue from the 3 o'clock through the 9 o'clock position
3. A resection further limited to the posterior lip
4. Transurethral incision of the bladder neck at the 5 o'clock and/or 7 o'clock position, or both

A 12 o'clock incision is used extending from the bladder base down to the level of the verumontanum because most of the striated muscle is located anteriorly and the vessels are lateral. The issue of preservation of fertility and use of electroejaculation has influenced the technique somewhat in that some urologists no longer routinely incise the bladder neck. Hemostasis is achieved by electrocoagulation with the flat surface of the knife electrode. Ability to empty the bladder varies from the 16% of Moisey and colleagues (389) to 50% by Blaivas and Norlen (61). Whether laser incision produces similar results with less morbidity is unknown (439). Complications of sphincterotomies include hemorrhage, incontinence, urethral stricture, and erectile dysfunction. Whether urethral stents are effective in nondyssynergic patients with primary bladder neck obstruction or reduced bladder contractility has not been assessed.

Y-V Plasty of the Bladder Neck

A simple Y-V plasty of the bladder neck can accomplish the same effect as a transurethral resection or incision. However, urinary incontinence can result in females. This procedure is recommended only when an open surgical procedure is already required to correct a concomitant disorder. When outlet reduction is required to render a refractory, poorly emptying bladder totally incontinent before inserting an artificial sphincter, an open Y-V plasty—although originally mentioned as a possibility (505)—makes subsequent placement of a bladder neck cuff extremely difficult. The artificial urethral sphincter in women has been abandoned with newer therapies such as periurethral bulking agents that will probably eliminate the need for this procedure. Faced with a frustrated patient with an acontractile or hypocontractile bladder who refuses intermittent self-catheterization, some urologists may resort to incision and Y-V plasties of the bladder neck, with anecdotal success.

Pharmacologic Therapy

Krane and Olsson (292,293) endorsed the concept of a physiologic internal sphincter partially controlled by tonic sympathetic stimulation of contractile α-adrenergic receptors in the smooth musculature of the bladder neck and proximal urethra. Neurally evoked contraction of the proximal urethra is the result of activation of α-adrenergic receptors (298,615). Some obstructions that occur at this level are a result of inadequate opening of the bladder neck or inadequate decrease in resistance in the area of the proximal urethra. Krane and Olsson presented evidence that α-adrenergic blockade could be useful in promoting bladder emptying in patients with an adequate detrusor contraction but without anatomic obstruction or detrusor striated-sphincter dyssynergia. Abel and colleagues (1) called attention to the fact that functional obstruction mediated by the sympathetic nervous system could occur solely in the urethra rather than at the bladder neck, and they coined the term *neuropathic urethra*.

The implication that α-adrenergic blockade could be useful in certain patients with a failure to empty despite adequate intravesical pressure has been confirmed by many reports (265,547,614). Successful results—usually defined as an increase in flow rate, a decrease in residual urine, and improvement in a dilated upper tract—could often be correlated with an objective decrease in urethral profile closure pressures. One would expect success with such therapy to be most evident in patients without DSD, as reported by Hachen (230); however, Mobley (386) reported a startling 86% success rate in 21 patients with a reflex neurogenic bladder, with a corresponding success rate of 66% in what was called flaccid and 57% in what was called autonomous neurogenic bladder dysfunction. Success in those cases was defined as postvoid residual urine volume consistently less than 100 mL. Such effects could be explained by a decrease in perineal striated muscle activity induced by α-adrenergic blockade (193). This effect is probably mediated by a central mechanism. Evidence of adrenergic innervation of the human striated sphincter is controversial (479,602). Scott and Morrow (506) noted excellent results with phenoxybenzamine therapy in 9 of 10 patients with a hypocontractile bladder and a flaccid external sphincter, in a single patient with an upper motor neuron bladder with intact sympathetic innervation, but in only 8 of 21 patients with hyperreflexia and autonomic dysreflexia and 0 of 6 patients with an upper motor neuron bladder and sympathetic denervation (lesion between T-10 and L-2). Terazosin has been shown to facilitate emptying in patients with detrusor-sphincter dyssynergia. However, in the group of 28 men, blood pressure fell and only 42% of patients had a significant drop in voiding pressures (440). In contrast, Swierzewski and co-workers (552) noted improvement in bladder compliance in all 12 patients provided.

There is also a rationale for the addition of α-adrenolytic therapy in patients with inadequate emptying secondary to neuropathic voiding dysfunction after conventional pharmacologic treatment has failed. Parasympathetic decentralization

has been reported to increase the adrenergic innervation of the bladder, with a resultant conversion of the usual ß (relaxant) effect of the bladder body in response to sympathetic stimulation to an α (contractile) effect (120,413,551). Although the alterations in innervation have been disputed (409), the alteration in receptor function has not. Koyanagi (291) showed supersensitivity of the urethra to α-adrenergic stimulation in a group of patients with autonomous neurogenic bladders. Experimental work by de Groat and Kawatani (120) suggests that sympathetic preganglionics sprout and innervate parasympathetic neurons in the pelvic ganglia after decentralization. This implies that a similar change in adrenergic receptor function may develop in the urethra after parasympathetic decentralization. Nordling and colleagues (411) described a similar phenomenon in females after radical hysterectomy and attributed this change to damage to the sympathetic innervation of the lower urinary tract. Despite these observations, Mattiasson and co-workers (356) found that maximal urethral pressure at rest was lower, not greater as would be predicted, in patients with parasympathetic decentralization, as compared with normals.

Prazosin hydrochloride, doxazosin, terazosin, and alfuzosin are antihypertensive agents with an affinity for postsynaptic α_1-adrenergic receptors, in contrast to other α-adrenergic blockers such as phentolamine and phenoxybenzamine, which agonize both α_1- and α_2-receptor sites. These α_1-receptor antagonists relax the smooth muscle of human urethra and lower outlet resistance (17).

The potential side effects of nonselective α_1-adrenergic blockers include dizziness, asthenia, and orthostatic hypotension. The incidence of these phenomena was thought to be minimized by administering them at bedtime. However, subsequent studies have shown that dizziness is unrelated to postural hypotension and occurs regardless of time of dosing (321). Patient compliance has been enhanced and side effects reduced with the development of α-adrenergic blockers with long half-lives (12 hours). Terazosin and doxazosin are currently used to facilitate urine release by reducing bladder outlet resistance. Both drugs are administered at bedtime. Terazosin is initiated at a 1-mg dose and usually achieves optimal effects at 5 mg. However, doses up to 10 mg have been used with only a slightly increased incidence of side effects (319).

Clonidine is another antihypertensive agent that can reduce sympathetic tone, reflected in the urinary tract by a decrease in the urethral closure pressure profile (410). As an α_2-adrenergic agonist, the drug inhibits noradrenergic release and thus indirectly behaves as an α_1-adrenergic blocker. Other commonly used pharmacologic agents with significant α-adrenergic blocking properties include chlorpromazine and haloperidol (607).

These and other agents with α-adrenergic blocking properties that act at various urinary and neuraxis levels have been used for voiding disorders. A trial of such agents to treat failure to empty may be worthwhile, because their efficacy will become obvious within days and the side effects are reversible. Unfortunately, such therapy in some groups has been considerably less spectacular than reported.

ß-Adrenergic stimulation has been shown experimentally to decrease the UPP and urethral resistance (565). Similarly, Vaidyanathan and colleagues (575) reported a decrease in urethral closure pressure after administration of terbutaline, a relatively specific $ß_2$-adrenergic agonist. However, acute ß-blockade has no effect on resting urethral pressure (565). Thus ß-adrenergic agonists and antagonists have not proven useful to facilitate bladder emptying by decreasing outlet resistance.

During voiding, active urethral relaxation occurs through the release of NO from parasympathetic nerves supplying the urethra (16). NO activates guanylate cyclase in urethral smooth muscle, causing a rise in cyclic guanosine monophosphate (cGMP) and a fall in urethral pressure (195). Therefore NO donors or agents that prevent its degradation may be of benefit in functional obstruction of the urethra. Type 5 phosphodiesterase (PDE-5) is responsible for the breakdown of cGMP. Thus agents that prevent the breakdown of cGMP can lower outlet resistance. The PDE-5 inhibitor sildenafil relaxes human urethral smooth muscle (99a). Anecdotally, men report improved voiding symptoms the morning after an evening ingestion of sildenafil. Trials are currently underway examining PDE-5 inhibitors for obstructive disorders. Combination pharmacotherapy, or fusion drugs that contract the bladder yet reduce outlet resistance, merits scrutiny.

Central Activation of Micturition Reflex

Neuropharmacologic experiments suggest that several excitatory central transmitters participate in micturition. Most notably, glutamate (NMDA and AMPA receptors) and dopamine (D_1 and D_2 receptor) agonists, when administered in the pontine micturition center or intrathecally, trigger micturition (348). In parkinsonian patients, subcutaneous apomorphine, a dopamine D_1 and D_2 agonist, can elicit voiding (104). Similarly, the dopamine agonist pergolide (Permax) has been shown to facilitate voiding in Parkinson's patients (627). Recently, it has been shown that sublingual apomorphine triggers a voiding reflex in spinal cord–injured patients (536). With advances in localized drug administration, such as with intrathecal pumps, it is theoretically possibly to devise a pharmacologic cocktail that activates micturition pathways and inhibits storage pathways. Potential side effects of these intrathecal drugs include orthostatic hypotension, reflex tachycardia, nasal congestion, diarrhea, miosis, sedation, and edema. Ejaculatory failure occurs, caused by lack of seminal emission and not by

retrograde ejaculation, but without any adverse effect on erection.

Decreasing Outlet Resistance at the Level of the Striated Sphincter

External Sphincterotomy

Therapeutic destruction of the external urethral sphincter was first performed by Watkins (592) in a patient with nonspastic obstruction. The first large clinical series was reported in 1958 by Ross and colleagues (477). The primary indication for this procedure is failure of the bladder to empty in a male patient with a suprasacral lesion when other types of management have been unsuccessful or impossible. An adequate involuntary detrusor contraction is necessary.

A substantial improvement in bladder emptying occurs in 70% to 90% of cases (604). Upper tract deterioration is rare after successful sphincterotomy, and any vesicoureteral reflux often disappears because of lower bladder pressures and the maintenance of sterile urine in a patient with a low residual urine volume and without an indwelling catheter. An external collecting device is generally worn postoperatively.

External spincterotomy can be performed using incisions at the 5 and 7 o'clock positions; at the 3 and 9 o'clock positions; at the 2, 4, 8, and 10 o'clock positions; and at the 11 and 1 o'clock positions (604). However, the 12 o'clock position, originally proposed by Madersbacher and Scott, is preferred (229,342,343,624). The anatomy of the striated sphincter is such that its main bulk is anterior and lateral. Postoperative erectile dysfunction in those individuals who have erections varies from 5% to 30%, but it is less common (approximately 5%) with incision in the anteromedial position (342). Complications of external sphincterotomy include hemorrhage, erectile dysfunction, and urinary extravasation. Urethral stricture rarely occurs at the site of sphincterotomy.

External sphincterotomy can be performed with a knife electrode, and resection can be performed with a loop electrode or laser vaporization. The incision must extend from the level of the verumontanum at least to the bulbomembranous junction. A gradually deepening incision allows good visual control and minimizes the chances of significant hemorrhage and extravasation. In an effort to reduce hemorrhage after sphincterotomy, a contact sapphire laser has been used (438). The incidence of hemorrhage after laser sphincterotomy has been reported to be significantly lower than with electrocautery (438).

Acute sphincterotomy failure generally indicates an inadequate incision or resection of tissue. Failure may also be caused by the presence of another unsuspected obstruction (e.g., at the bladder neck) or by inadequate bladder contractions, either those of insufficient magnitude or those that are poorly sustained. In fact, sphincterotomy may contribute to the development of poorly sustained detrusor contractions. Residual urine does not always indicate failure, because low pressure but incomplete emptying in an individual may be acceptable.

Regardless of the method chosen, why do sphincterotomies fail to provide complete emptying of the bladder? Theoretically, dyssynergia may help increase the duration of a spinal micturition reflex by boosting afferent firing from the bladder. Eliminating the outlet resistance may decrease intravesical pressure, resulting in poorly sustained reflex-evoked contractions. Alternatively, Light and colleagues (326,327) provide electrophysiologic evidence for subtle sacral cord pathology in spinal cord– injured patients with increased residual urine after sphincterotomy.

The use of sphincterotomy to manage spinal cord–injured patients has waned with realization that long-term management is plagued with problems and with the advent of new, less invasive therapies, such as α_1-adrenoceptor antagonists. Vapnek and associates (580) followed spinal cord–injured patients up to 18 years after sphincterotomy and found that less than 50% were still managed with a condom catheter. The remaining patients required conversion to suprapubic cystotomy tubes because of condom catheter problems, decreased bladder compliance, persistent postvoid residual urine, and renal deterioration. The use of sphincterotomy has greatly diminished because of side effects and questionable long-term efficacy. Urinary diversion is an alternative.

Indwelling Urethral Stents

Because of long-term dissatisfaction with sphincterotomy to completely empty the bladder, and to prevent renal deterioration or infections, new therapies are being investigated. In a multicenter trial of urethral stents for the management of detrusor-sphincter dyssynergia, stents decreased voiding pressures and residual urine (96). However, nearly 30% of patients required two stents to bridge the region of high urethral pressure. Furthermore, 8% of patients needed another procedure for secondary bladder neck obstruction. Long-term follow-up is necessary to determine whether stents are more effective and less morbid than laser or electrocautery sphincterotomy. Side effects of stents include recurrent infection, stenosis, migration, discomfort, and erosion. Removal, if necessary, is often difficult.

Pudendal Nerve Block or Interruption

Relief of obstruction at the level of the striated sphincter has been attained by a pudendal neurectomy, which was first described in 1899 by Rocket (528). Historically, this method enjoyed the same popularity in patients with fixed

neurologic lesions and striated-sphincter dyssynergia, but it is seldom used today (604). Assessment of the results using a pudendal block should precede the formal procedure. Neurectomy should be performed only unilaterally because bilateral sectioning results in a high rate of erectile dysfunction and may result in fecal and severe stress urinary incontinence.

Pharmacologic Therapy

There is no class of oral pharmacologic agents that will selectively relax the striated musculature of the pelvic floor. Chlordiazepoxide, methocarbamol, orphenadrine, and diazepam belong to a group of agents classified as centrally acting muscle relaxants (49). The primary side effect of all members of this group is sedation. The recommended oral doses are not effective in controlling striated-sphincter dyssynergia seen secondary to neurologic disease. Centrally acting GABA agonists inhibit motor outflow, but usually at oral doses are associated with profound sedation. The theoretic rationale with GABA agonists is either relaxation of the pelvic floor striated musculature during bladder contraction or such relaxation removing a stimulus that is inhibitory to bladder activity.

Dantrolene sodium is a skeletal muscle relaxant that dissociates excitation–contraction coupling at a site distal to the neuromuscular endplate in the sarcoplasmic reticulum (49). The drug has been used in patients with classical detrusor striated-sphincter dyssynergia and was initially reported as being successful in improving voiding (400). Therapy in adults is begun at a dose of 25 mg twice daily, increasing the dose weekly in 50- to 100-mg increments up to a recommended daily maximum of 400 mg given in divided dosages. Hackler and associates (231) achieved improvement in voiding function in approximately half of their patients treated with dantrolene but found that such improvement required doses of 600 mg per day. Although the drug has no autonomic side effects, like all CNS depressants, it may induce a generalized weakness severe enough to compromise its therapeutic benefits, especially in doses associated with sphincter relaxation. Other potential side effects include euphoria, dizziness, diarrhea, and hepatotoxicity. Toxicity to the liver is thought to be related to high-dose, long-term use and has resulted in some fatalities.

Another approach may be to inhibit neural input to the external urethral sphincter, thereby diminishing bladder outlet resistance. α_2-Adrenergic agonists such as clonidine prevent urethral smooth muscle contraction by inhibiting release of norepinephrine from noradrenergic nerves (17). In addition, clonidine and other α_2-adrenergic agonists are postulated to modulate afferent input from striated muscles. The α_2-adrenergic agonist tizanidine (Zanaflex) is a centrally acting skeletal muscle relaxant (587). Tizanidine is undergoing clinical evaluation in multiple sclerosis patients to determine whether this drug can facilitate bladder emptying by reducing loss of coordination between the bladder and its outlet and detrusor-sphincter dyssynergia due to suppressed neural pathology. Another muscle relaxant that can inhibit the external urethral sphincter is inaperisone, which, in addition to possessing central muscle relaxant properties, is a nicotinic receptor antagonist. Inaperisone is undergoing clinical trials to reduce pelvic floor spasticity and thereby facilitate bladder emptying.

A more commonly used centrally acting agent that relaxes the external urethral sphincter is the GABA agonist baclofen. Baclofen is thought to inhibit primary afferent fiber terminals in the spinal cord, thereby abolishing monosynaptic or polysynaptic spinal reflex activity. It has been found to be useful in the treatment of mild skeletal spasticity resulting from a variety of causes. Treatment is started at an initial dosage of 5 mg three times daily, and the dosage is doubled every 3 days until a daily total dosage level of 60 mg is reached. The manufacturer recommends that the total daily dosage not exceed 20 mg four times daily. Furthermore, a patient should be gradually weaned off baclofen to prevent seizures. Florante and colleagues (175) reported that 73% of their patients with voiding dysfunction secondary to acute and chronic spinal cord injury showed lower striated-sphincter responses and decreased residual urine volume after treatment, but only with an average daily oral dose of 120 mg. Nanninga (401) and Steers and associates (539) have found that intrathecal baclofen is often effective at inhibiting the striated urethral sphincter while circumventing the problems with sedation. Similarly, it can completely abolish hyperreflexia and nocturia and increase compliance, first sensation, and bladder capacity. However, in quadriplegics, care must be taken not to eliminate the micturition reflex necessary for trigger voiding. Side effects include lower-extremity flaccidity at doses necessary to affect the bladder, as well as respiration depression, erectile dysfunction, and constipation. Other potential side effects of baclofen include drowsiness, insomnia, rash, pruritus, dizziness, and weakness. Hallucinations or seizures may sometimes occur after abrupt withdrawal. The use of an intrathecal delivery system offers many potential advantages, and in the future it may be used for other drugs to elicit or inhibit micturition or pain. The latest development relies on the use of injections of botulinum toxin A (Botox) into the external urethral sphincter. This compound blocks the nicotinic neuromuscular function. Clinical trials indicate reduction in residual urine (average 125 mL), urethral pressures, and voiding pressures (148,503).

Biofeedback and Psychotherapy

Biofeedback is a useful adjunct to improve voluntary control of neural, visceral, and skeletal responses (383,384). Biofeedback, behavioral training. and psychotherapy are used to treat disorders of both urine release and storage. These regimens encompass a wide range of maneuvers and are discussed in more detail under therapies for urine storage. In children with difficulty evacuating urine due to nonneurogenic

causes, biofeedback has been very successful for problems with urination and defecation. The data used in biofeedback may be as sophisticated as visual or auditory information produced by modern electronic equipment that is monitoring a physiologic process, or as simple as a self-kept record of symptoms and biologic events (such as a chart for recording the time and volume of voiding and the presence of urgency and incontinence). The list of physiologic processes subject to some self-control includes blood pressure, heart rate, blood flow, sweat gland activity, skin temperature, body temperature, respiratory function, genital responses, bowel and bladder motility, and skeletal muscle control.

Hinman (248) and Allen (6) were perhaps the first to recognize that nonneurogenic striated-sphincter dyssynergia (or a disorder qualitatively similar to it) can occur on a psychogenic basis and cause gross upper tract damage. Each used a combination of psychologic retraining, suggestion, medication, and parental cooperation in a treatment program. Wear and colleagues (593) described the use of a urodynamic display of external-sphincter EMG activity to facilitate this type of treatment. They reported significant clinical improvement in four of eight patients so treated. Maizels and co-workers (346) further simplified this technique by using anal skin electrodes for the repeated display of striated-sphincter activity without pain or significant inconvenience to the patient. In one of the largest series reported, Rapariz Gonzales (456) described outcomes in 50 consecutive patients (82% female, 18% male) with uncoordinated voiding syndrome (Hinman's syndrome, nonneurogenic neurogenic bladder). The mean age was 12 years. Using flow rates and sphincter EMG for follow-up at 12 months, a reeducation program was curative in 42% of children; 22% were improved, 2% relapsed, and 14% had no response. Successful therapy in this type of situation requires a strongly motivated patient who is capable of understanding the instructions for biofeedback training.

Circumventing Problems

Intermittent Catheterization

Intermittent catheterization is the most effective means of attaining a catheter-free state in patients with acute spinal cord lesions (187). It is also an extremely effective method of treating an adult or child whose bladder fails to empty, especially when efforts to increase intravesical pressure or decrease outlet resistance have been unsuccessful. In patients with inadequate urine storage because of involuntary bladder contractions, decreased compliance, or stress incontinence with adequate or inadequate emptying, it may also be used if the dysfunction can be converted solely or primarily to one of emptying by pharmacologic or surgical means (604). Lapides and associates (305) deserve enormous credit for first applying the concept of intermittent self-catheterization to large groups of outpatients with voiding dysfunction. Subsequently, Lapides and co-workers and many others have demonstrated the long-term efficacy and safety of such a regimen. Requirements for intermittent catheterization include a cooperative, well-motivated patient or family, adequate hand control (or a family member willing to catheterize), and sufficient urethral exposure. Teaching intermittent self-catheterization requires an approach that communicates acceptance of the procedure by the instructor. It is advantageous to have a special urologic nurse who instructs the patients or families in the regimen; provides them with understandable written instructions to refresh their memories regarding technique, precautions, and danger signals; and provides continuing support for patients who call with questions or problems about their regimen.

For adult male patients, 14- or 16-Fr stiff or flexible catheters are generally used. In some cases (e.g., in patients with impaired fine motor skills), stiffer plastic catheters may be easier for the patient to insert. These are also commercially available in a disposable form. A notable advantage to red rubber catheters is their longevity and overall low cost. However, for catheterizing Mitrofanoff stomas, they lack sufficient stiffness. They can be reused indefinitely and boiled for sterilization if desired. Shorter, disposable plastic female catheters, now manufactured by several companies, are recommended for female patients. They are inexpensive and convenient. These 14-Fr, 6-inch catheters are easy to handle. Female patients may catheterize themselves on the toilet without a mirror, making intermittent catheterization less confusing, cleaner, and quicker. Red rubber or Robinson catheters may also be used for female patients if desired. For the patient's convenience, liquid cleansing agents are usually easier to handle in the form of cotton balls soaked in the agent. These can be easily carried in a small jar. Any water-soluble lubricant is suitable for lubricating the catheter before insertion.

Several studies examining urinary tract infections and upper tracts with management by clean intermittent catheterization deserve mention. McGuire and associates (375) advocated intermittent self-catheterization in spinal cord–injured patients as a method to preserve good bladder compliance. They found that urine cultures in roughly one-third of patients remain sterile, one-third have bacteriemia, and one-third suffer recurrent urinary tract infections. Perkash and Giroux (439) followed the upper tracts and urine cultures in 50 spinal cord–injured patients on intermittent catheterization and found that 86% of patients developed positive urine cultures (greater than 10^4 cfu/mL) and 42% had genitourinary complications. However, upper tract deterioration did not occur if adequate bladder compliance and low intravesical pressures were maintained. These latter two goals, rather than self-catheterization per se, may be more important determinants in the preservation of renal function.

Continuous Catheterization

Indwelling urethral catheters are best for short-term bladder drainage, and careful use of a small-bore catheter fails to adversely affect the ultimate outcome. Occasionally, an indwelling catheter is a last resort for long-term bladder drainage. After 72 hours, virtually all patients with an indwelling urethral catheter have bacteriuria. A contracted, fibrotic bladder can result from chronic inflammation. Encrustations may form on the catheter or on the retention balloon. Urethral complications are relatively uncommon in females, but bladder spasm may occur, producing urinary incontinence. The temptation to use a large retention balloon should be resisted, because the continuous use of such a balloon combined with some pressure on the catheter may cause erosion of the bladder neck. A suprapubic trochar catheter may be initially more comfortable than a urethral catheter, and it obviates urethral fistulae and strictures in the male over longer periods. Bladder spasm with incontinence may, however, be more of a problem, and when blockage occurs, nursing personnel are more reluctant to change this type of catheter without physician assistance.

Dolin and associates (139), in examining women who died of bladder cancer, found that the incidence of squamous cell carcinoma was especially high in paraplegic women. Jacobs and Kaufman (259a) reported development of squamous cell carcinoma of the bladder in 6 of 59 patients with spinal cord injuries who had long-term indwelling catheters. Four of these patients had no obvious tumor visible on endoscopy, and the diagnosis was made by bladder biopsy. Five of these patients also had transitional cell elements in their tumor. Broecker and associates (76) surveyed 81 consecutive spinal cord–injured patients with indwelling urinary catheters for more than 10 years, and although they did not find carcinoma, they discovered squamous metaplasia of the bladder in 11 patients and leukoplakia in one patient.

The long-term morbidity of chronic indwelling catheters is recognized, but often other reasonable alternatives are nonexistent. Bennett (40) has suggested that in quadriplegic women, urinary diversion is preferable to indwelling catheters, based on follow-up over 20 years. However, a cohort group of diverted patients was not used to reach this conclusion.

Alternatively, Dewire and co-workers (131) suggest that use of chronic indwelling catheters is not associated with any greater incidence of calculi, pyelonephritis, hematuria, urosepsis, or erosion compared with a retrospective cohort of patients managed with either condom catheters or urinary diversion. Chai and colleagues (88) also reported no significant differences in cord-injured patients managed with indwelling catheters versus those with reflex voiding. However, Chai's group uncovered a greater incidence of renal scarring and caliectasis in the catheterized patients. Age of injury and level of injury help predict upper tract deterioration in spinal cord–injured patients. Management with an indwelling catheter is a risk factor for renal deterioration. Overall, indwelling catheters are to be avoided for long-term usage. In males, suprapubic tubes are preferred. In females, eventual dilation of the urethra limits their use. However, for short-term use proper positioning of a urethral catheter can reduce the likelihood of bulbar urethral erosion (Fig. 26B.24).

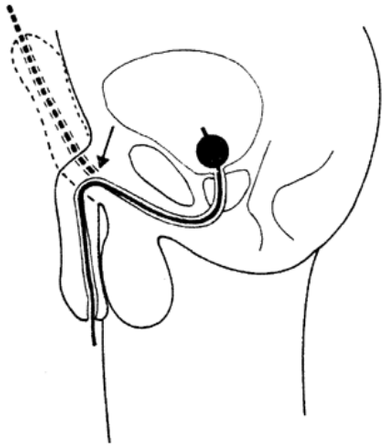

FIGURE 26B.24. In neuropathic patients an indwelling catheter may cause a urethral decubitus at the penoscrotal angle with possible fistula formation *(arrow)*. Therefore the penis must be placed to the lower abdomen *(dotted line)*.

Ileocystostomy

In patients with competent outlets, adequate bladder capacity, good bladder compliance, and optimal body habitus, the feasibility of ileocystostomy has been suggested (96). Likened to a chimney, this method of bladder drainage avoids ureteral reimplantation and relies on the intrinsic vesicoureteral mechanism to prevent reflux. However, if the patient is not properly selected, residual urine or incontinence can occur, necessitating what would be a more difficult urinary diversion (Fig. 26B.25). Key selection criteria include a small contracted bladder and a thin body habitus. Otherwise, incomplete drainage occurs.

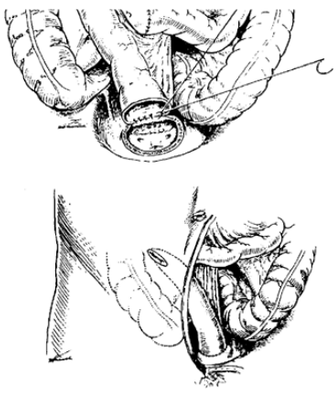

FIGURE 26B.25. Ileocystostomy. (From Cordonnier JJ. Ileocystomy for neurogenic bladder. *J Urol* 1957;78:606, with permission.)

Urinary Diversion

Supravesical Diversion

Supravesical diversion is undergoing a resurgence due to improved techniques, especially continent diversion and

popularity of bladder reconstructive techniques. Indications for performing supravesical diversion may include the following:

1. Progressive hydronephrosis and intractable upper urinary tract dilation (which may be caused by blockage of the ureterovesical junction resulting from a trabeculated, thick bladder or from vesicoureteral reflux that does not respond to conservative measures)
2. Recurrent upper urinary tract infections
3. Difficulty performing or inability to perform urethral catheterization, especially in children

Although the various techniques of supravesical urinary diversion are covered in other chapters of this book, it is important to note that urinary diversion cannot always prevent upper urinary tract deterioration. The initial results of the ileal conduit seemed encouraging in terms of upper tract preservation (73). Unfortunately, long-term results have been disappointing (147,424,447,504). The colonic conduit, which allows a reflux-preventing implantation of the ureters, was expected to produce better long-term results. Although earlier reports seemed to support this supposition (8,9,387), long-term results seem to be equally disappointing (153).

Continent forms of diversion that may be applicable to patients with voiding dysfunction involve the application of a continent abdominal wall stoma (Indiana pouch, ileocecal reservoir, or gastroileal pouch) (215). Obesity, severe scoliosis, and kyphosis are relative contraindications to conduit stomal diversion because of difficulty in fitting a stomal bag. A novel approach in obese patients is to perform liposuction around the stoma to ensure a better fit. Obviously, such a problem does not exist with continent stomal diversion (24). On the other hand, continent stomal diversion requires that the patient be able to perform intermittent catheterization or that dependable assistance be available for catheterizing the stoma. Angulation of the intestinal segment in the abdominal wall can create problems with catheterization. Even preferable to continent diversions is orthotopic bladder replacement, especially in men. Preservation of the distal sphincter mechanism helps preserve continence. Nocturia enuresis is common. The Studer ileal neobladder is becoming a popular method of replacement (430). Voiding dysfunction in orthotopic neobladders includes retention and incontinence, especially enuresis. Risk factors for failure to empty neobladders include increasing age and excessive length of intestine required to fashion the neobladder. A conscious reduction in length and anterior fixation of the neobladder to prevent posterior prolapse have been used to reduce retention rates. A review of voiding dysfunction with neobladders has recently been published (531). Long-term results in patients with these forms of continent diversion may be no better than the traditional ileal conduit, although early operative complications are probably greater (19,618). Bladder reconstruction and substitution are covered more completely elsewhere in this book.

Therapy to Facilitate Urine Storage

Treatments to facilitate urine storage can be applied to patients with urinary incontinence and overactive bladder. The overactive bladder is characterized by urinary frequency, urgency, and nocturia with or without urge incontinence.

Inhibiting Bladder Contractility, Decreasing Sensory Input, and Increasing Bladder Capacity

Timed Bladder Emptying

Timed bladder emptying is actually a form of behavioral therapy (166), although it is not a sophisticated concept. The idea is to completely or partially empty the bladder on a frequent enough schedule to keep the intravesical volume below that at which storage failure results. This may involve nothing more than frequent voiding with a limited fluid intake in patients with detrusor hyperactivity. It may involve a more complicated coordination of an intermittent catheterization schedule with bladder volume in patients with detrusor hyperreflexia and sphincter dyssynergia whose status has been converted to that of relative emptying failure, but only if the bladder is emptied periodically (before the threshold is reached for hyperreflexia or decreased

compliance causing storage failure or upper tract damage). Formal behavioral programs have gained acceptance in first-line management of failure to store (80,81,84,166). Timed voiding should be a key component of any pharmacologic regimen.

Pharmacologic Therapy

Anticholinergic Agents

Because acetylcholine is the principal neurotransmitter responsible for contraction of the detrusor, anticholinergics are the first-line therapy for the overactive bladder (18). Clinically available anticholinergics are mixed muscarinic antagonists that bind to the M_2 and M_3 muscarinic receptor subtypes (18). The nonselective muscarinic antagonist oxybutynin and its major metabolite directly relax smooth muscle *in vitro* as well (17). It is doubtful whether this is clinically relevant. Several M_3-selective muscarinic antagonists are currently under investigation for the treatment of the overactive bladder and urge incontinence. These M_3-selective antagonists include Darifenacin and YM905 (588). A clever strategy might be to use M_2- or M_3-selective antagonists that possess agonist properties at M_1 or M_4 receptors. Drugs exhibiting this profile may be particularly useful in the elderly, in whom blockade of M_1 receptors may promote confusion or exacerbate various dementias, including Alzheimer's disease. One mixed M_2-M_3 antagonist/M_1 agonist undergoing clinical trials for overactive bladder is LU25109. Experimentally, mixed M_3 antagonist/M_1 agonists exhibit both anticholinergic and antinociceptive properties (509). Therefore an M_3 antagonist/M_1 agonist such as LY297802 could be promising for the treatment of overactive bladders with associated discomfort, such as interstitial cystitis. This drug could provide the added benefit of reduced CNS side effects mediated by M_1 receptors.

Anticholinergic drugs are a logical choice for problems with failure to store urine (35). In the human detrusor, all currently available antagonists bind to virtually all muscarinic subtypes with equal effectiveness (406). Atropine and atropine-like agents are often effective against detrusor hyperactivity (60,263). In such patients, the volume of the first involuntary contraction is generally increased, the amplitude of the contractions is decreased, and the total bladder capacity is increased, with a proportionate reduction in symptoms. Thus, to be most effective, these agents are best given with advice for timed voiding. Interestingly, bladder compliance in normal individuals and in those with detrusor hyperreflexia, where the initial slope of the filling curve on cystometry is normal before the involuntary contraction, may not be significantly altered (263). The effect of these agents on intravesical pressure during filling in those patients who exhibit only decreased compliance has not been well studied. Despite this lack of data, anticholinergics continue to be recommended in combination with intermittent catheterization for decreased compliance (370). These agents may help prevent loss of compliance (more than they reduce filling pressures) due to changes in extracellular matrix. Although significant clinical improvement may be achieved in patients with detrusor hyperreflexia, only partial inhibition generally results, postulated to be due to afferent hyperactivity, noncholinergic contractile activity, or altered extracellular matrix, among other reasons. Most of the drugs discussed under the heading of inhibiting bladder contractility are agents that inhibit muscarinic cholinergic receptors. These agents, although helpful, leave much to be desired in terms of efficacy. For example, controlled studies on the use of anticholinergics for urinary incontinence report only a 5% to 44% cure rate (361). In one report, the cure rate for oxybutynin was only 5%, and nearly 80% of patients discontinued medication use because of side effects (273).

In a randomized, prospective study comparing propantheline to the anticholinergic and antispasmodic drug oxybutynin (Ditropan), the latter drug was significantly more effective in relieving urgency and increasing bladder capacity (567). Hyoscyamine (Levsinex) is popular as an anticholinergic because it can be administered on a twice-daily regimen (Table 26B.13). Efforts to reduce side effects have been disappointing because of inability to identify either a muscarinic receptor subtype unique to the bladder or drugs selective only for the detrusor smooth muscle. In an effort to minimize the side effects of dry mouth, tolterodine has been developed. This agent, given at 2 mg twice daily, causes less dry mouth than oxybutynin given at 5 mg three times daily. Statistically, tolterodine reduces the number of incontinent episodes and urinary frequency (99). In an analysis of more than 1,200 subjects randomized to oxybutynin 5 mg three times daily or tolterodine 1 or 2 mg twice daily, reduction in micturitions by 20% over 24 hours was reported. A 40% to 60% reduction in incontinence episodes was observed. Dry mouth was seen in 78% of the oxybutynin group but only 24% to 40% of the tolterodine group. It is unclear whether administering oxybutynin at 2.5 mg twice daily would have a similar profile.

Tolterodine 2–4 mg b.i.d.
Oxybutynin 2.5–5 mg t.i.d.
Oxybutynin 5, 10, or 15 mg q.d. × 2
Propantheline 15–45 mg q.i.d.
Hyoscyamine 1 mg b.i.d.

TABLE 26B.13. COMMON ANTICHOLINERGICS FOR STORAGE FAILURE

Despite new formulations, the potential side effects of all antimuscarinic agents remain and include inhibition of salivary secretion (dry mouth), blockade of the iris sphincter muscle (papillary dilation), blockade of the ciliary muscle of the lens to cholinergic stimulation (blurred vision for near objects), tachycardia, drowsiness, and inhibition of gut motility (606). Greater appreciation of central effects of some anticholinergics has been gained from reports of

confusion in the elderly and restlessness in children on these drugs. Moreover, severe problems with dental disease, especially in the elderly, have been attributed to drugs causing dry mouth. Antimuscarinic agents are generally contraindicated in patients with narrow-angle glaucoma and should be used with caution in patients with significant bladder outlet obstruction, because complete urinary retention may be precipitated.

Purinergic and Indirect Anticholinergic Agents

Atropine only partially antagonizes the bladder response in animals to either pelvic nerve stimulation or direct electrical stimulation. However, atropine completely inhibits the response of the human bladder smooth muscle to exogenously administered acetylcholine and electrical stimulation of the pelvic nerve. At present, there is no completely accepted explanation for this relative atropine resistance, but the most attractive theory is that a major portion of the neurotransmission after injury or with disease, mediated by parasympathetic (pelvic) nerve stimulation, is secondary to release of a transmitter other than acetylcholine or norepinephrine. Candidates include substance P or neurokinin A, released from afferents, and adenosine triphosphate (ATP), found in efferents, In certain disease states, noncholinergic and nonadrenergic neurotransmission may provide excitatory input to the bladder and contribute to involuntary bladder contractions. This finding could explain the inability of anticholinergics to control symptoms in many patients. Experimental evidence in animals and some human data suggest that purinergic transmission provides excitatory input to the diseased bladder in patients with denervation, obstruction, or idiopathic urge incontinence (517). The predominant purinergic receptor expressed by human bladder smooth muscle is of the P_{2X1} subtype, whereas P_{2X3} receptors are expressed by afferent terminals in the human bladder (423). Thus P_{2X} antagonists could offer a combined afferent/efferent approach for the management of the overactive bladder. Unfortunately, agents that block purines (ATP) are not yet clinically available. Suramin, an antipurinergic drug, is an antihelminthic used to treat nematode diseases. It antagonizes the P_2 receptor, but it has not been clinically evaluated for bladder dysfunction. Moreover, this agent blocks the enzyme that degrades ATP, known as ATPase, thus negating some of its effect. Suramin is also highly toxic.

An unexplored approach to combat the overactive bladder may be to inhibit acetylcholine release from cholinergic nerves in the bladder. M_4 agonists inhibit acetylcholine release (112). Galanin and protein kinase C inhibitors also prevent acetylcholine release (17). No trials are underway using these agents for the overactive bladder.

Musculotropic Relaxants (Antispasmodics)

Musculotropic relaxants are direct-acting smooth muscle depressants whose antispasmodic-activity effect on smooth muscle contractility is separate from the cholinergic receptor mechanism (171). Although all agents that relax detrusor smooth muscle *in vitro* also reduce intracellular calcium, many possess variable antimuscarinic and local anesthetic properties. There is still a question as to how much of their clinical efficacy is caused simply by their atropine-like effect. If any of these agents do exert a clinically significant inhibitory effect that is independent of an antimuscarinic action, there exists a therapeutic rationale for combining their use with that of a relatively pure antimuscarinic agent.

Oxybutynin chloride is a moderately potent anticholinergic agent with a strong independent musculotropic relaxant activity and local anesthetic activity (171,567). This agent has been used successfully to depress detrusor hyperreflexia in patients with neurogenic bladder dysfunction. A randomized, double-blind control study in 30 patients with detrusor instability that compared oxybutynin at 5 mg three times daily with a placebo was performed by Moisey and colleagues (388). More recently, a 3-mg dose given three times a day was shown to be as effective in treatment of women (n = 53) with detrusor instability (392). Of 23 patients who completed the study with oxybutynin, 17 had symptomatic improvement and 9 had evidence of urodynamic improvement, mainly an increase in bladder volume at first contraction and an increase in total bladder capacity. In elderly subjects, oxybutynin is tolerated and effective for treatment of detrusor hyperactivity (634). The recommended adult dosage of oxybutynin is 5 mg three or four times daily, although single doses as larger as 10 mg or as small as 3 mg are also used.

The use of osmotic mini-pumps has allowed many formulations to be given once daily. Ditropan XL (oxybutynin) exploits this principal to allow once-daily administration of this anticholinergic. By reducing the peak levels of this drug, fewer side effects are reported (18,213). There is no difference in therapeutic efficacy between controlled-release and immediate-release Ditropan. Dry mouth was reported in 67% and 87% of subjects, respectively, at the dosages necessary to achieve maximal therapeutic effects.

In an effort to improve efficacy and reduce or eliminate side effects, oxybutynin has been administered intravesically (72,222,271). In adults and children, the regimen (5 mg in 20 to 30 mL of saline two or three times daily) has been shown to increase capacity and compliance and reduce urge incontinence of involuntary detrusor contractions. Side effects, although somewhat reduced, are still common because of systemic absorption from the bladder.

Dicyclomine hydrochloride is also reported to possess a direct relaxant effect on smooth muscle, in addition to an antimuscarinic action (143,278). An oral dose of 20 mg three times daily in adults has been reported to increase bladder capacity in patients with detrusor hyperreflexia (173), and the dose can be raised to at least 30 mg to achieve a clinical effect. The potential side effects are antimuscarinic ones.

Flavoxate hydrochloride is another compound that has been reported to have a direct inhibitory action on smooth muscle, in addition to anticholinergic and local analgesic properties (288). Briggs and associates (74) reported essentially no effect of this agent on detrusor hyperreflexia in an elderly population. Similarly, in a placebo-controlled trial, Chapple and co-workers (101) found flavoxate not to be beneficial in management of detrusor instability. This experience coincides with the subjective impression of limited clinical efficacy in situations in which other anticholinergics have failed (43). The recommended adult dosage is 100 to 200 mg three to four times daily. Reported side effects are rare and are primarily antimuscarinic in nature.

Polysynaptic Inhibitors

Baclofen has been discussed previously in the section on agents that decrease outlet resistance secondary to striated-sphincter dyssynergia. It has also been shown to depress detrusor hyperreflexia secondary to a spinal cord lesion (280,480). In a double-blind crossover study, Taylor and Bates (562) reported baclofen to be effective also in decreasing daytime and nighttime urinary frequency and incontinence in patients with idiopathic detrusor hyperreflexia. By blocking afferent transmission in the sacral spinal cord, or through a GABA-like effect in the pons, this agent may inhibit reflex micturition. However, the systemic doses required to consistently achieve a desired effect on micturition globally depress CNS function. Intrathecal administration can bypass some of the dose-limiting side effects.

Calcium Antagonists

The rationale underlying the potential use of calcium antagonists for the inhibition of bladder contractility relies on the pivotal nature of cytosolic calcium in smooth muscle contraction (532). The calcium antagonist nifedipine has been shown to inhibit contraction induced by several mechanisms in human and guinea pig bladder muscle (179,516). It is also capable of completely blocking the noncholinergic portion of the contraction produced by electrical field stimulation in rabbit bladder (255). Nifedipine more effectively inhibited potassium-induced than carbachol-induced contractions in bladder strips, whereas terodiline, an agent with both calcium-antagonistic and anticholinergic properties, had the opposite effect (255). This agent in low concentrations seemed to have mainly an antimuscarinic action, whereas at higher concentrations it was a calcium antagonist. *In vitro* experiments appeared to show that these two effects are at least additive with regard to bladder contractility. Whether the calcium antagonistic properties of terodiline contributed to its clinical effectiveness *in vivo* is unclear. Rud and colleagues (483) reported that in oral dosages of 12.5 mg two or three times daily, terodiline produced a marked decrease in the number of hyperreflexic contractions in a group of seven women with urgency incontinence and two with nocturnal enuresis. Bladder capacity was approximately doubled, and the amplitude of the contractions was decreased. In a double-blind crossover study in 12 women with motor urge incontinence, Ekman and colleagues (150) reported an increase in bladder capacity, and in the volume at which the sensation of urgency was experienced, in all but one of the patients treated with terodiline, whereas placebo treatment had no effect on either objective or subjective parameters. Unfortunately, deaths occurred on this drug due to cardiac arrhythmias, and it was removed from the market. Clinical trials for the overactive bladder are under way investigating temiverine and its active metabolite RCC36, which inhibit L-type voltage-gated Ca^{2+} channels and muscarinic receptors (106). Like terodiline, temiverine has a dual site of action, and it may have greater efficacy than a pure anticholinergic agent. Cardiac arrhythmias similar to the mixed Ca^{2+} channel blocker–anticholinergic terodiline are unlikely because temiverine does not influence the delayed or inward rectifier K^+ currents.

Palmer and associates (429) reported a double-blind placebo trial with a single 20-mg daily dose of flunarizine in 14 females with urinary frequency, incontinence, and urodynamically proven detrusor instability. A statistically significant decrease in urgency was produced in the flunarizine-treated group, but there was no change in the frequency of micturition. Although there was a trend toward improvement of cystometric parameters, this was not statistically significant (p =.05). Similarly, Mattiasson and associates (357) demonstrated that intravesical verapamil increases compliance and capacity, as well as decreasing bladder hyperactivity, in patients with nonneurogenic rather than neurogenic causes of involuntary contractions. However, verapamil's clinical usefulness appears to be limited.

The reported side effects produced in patients treated with calcium antagonists for voiding dysfunction are few. Potential adverse effects include hypotension, facial flushing, headache, dizziness, abdominal discomfort, constipation, nausea, rash, weakness, and palpitations. With intravesical administration, hypotension can be profound. Urine must be acidic to prevent precipitation of the drug after intravesical instillation.

Potassium Channel Openers

The use of K^+ channel openers has been championed for the treatment of overactive bladder. Opening K^+ channels hyperpolarizes smooth muscle cells, thereby preventing the influx of Ca^{2+} and subsequent refilling of intracellular stores (17). A variety of potassium channel openers relax the detrusor *in vitro,* including minoxidil, glipizide, and pinacidil. The heterogeneity of potassium receptors that can relax smooth muscle raises the possibility of selectivity for the bladder and efficacy in disorders of urine storage. Orally, these agents can trigger profound hypotension, hyperglycemia, and increased hair growth. It has been postulated that intravesical administration of potassium channel openers

can increase bladder compliance and capacity, yet reduce side effects. Experimentally, the K^+-ATP channel opener ZD6169 relaxes bladder smooth muscle *in vivo* and *in vitro* (106). Preclinical trials are underway with oral ZD0947, another K^+-ATP channel opener. If hypotension is avoided, the use of K^+-ATP channel blockers may offer a useful strategy.

ß-Adrenergic Agonists

Direct relaxation of the bladder occurs in response to norepinephrine released by sympathetic noradrenergic nerves through the activation of ß-adrenergic receptors (17). Based on data showing insensitivity of the detrusor to $ß_1$- and $ß_2$-adrenoceptor antagonists, the predominant ß-adrenoceptor subtype expressed by the human bladder is probably $ß_3$ (333). The presence of ß-adrenergic receptors in human bladder muscle has prompted attempts to expand bladder capacity with ß-adrenergic stimulation. Such stimulation can create significant increases in the capacity of animal bladders, which contain a moderate density of ß-adrenergic receptors (308). *In vitro* studies show a strong dose-related relaxant effect of $ß_2$-adrenergic agonists on the bladder body of rabbits, but little effect on the bladder base or proximal urethra (277). In men, ß-adrenergic agonists appear to slightly increase bladder capacity, but effects on involuntary contractions and urge incontinence are variable. The $ß_2$-adrenergic agonist terbutaline (Bricanyl) at oral dosages of 5 mg three times daily has been reported to have a "good clinical effect" in some patients with urgency and urge incontinence, but no significant effect on the bladders of neurologically normal humans without voiding difficulty (414). Lindholm and Lose (331), in an uncontrolled trial, found terbutaline useful in 80% of women. Castleden and Morgan (87), in the elderly, and others in children, found that the ß-adrenergic agonists did not affect urodynamic parameters or improve urge incontinence. The inability of ß-adrenergic agonists to consistently abolish hyperreflexia, increase compliance, or relax the bladder outlet has prevented their widespread use. This lack of efficacy could be due to lack of action at the $ß_3$-adrenergic receptor. There are now several $ß_3$-adrenoceptor agonists in various stages of investigation for nonurologic disorders. These include SK37344, SR59230A, and BRL35135, which is slightly less potent in human bladder tissue than SK37344. *In vitro* SR59230 is less potent than BRL35135 in relaxing human bladder smooth muscle.

a-Adrenergic Antagonists (Table 26B.14)

Phenoxybenzamine 10–20 mg b.i.d. to t.i.d.
Terazosin 3–10 mg q.d.
Doxazosin 4–18 mg q.d.
Tamsulosin 0.4–0.8 mg q.d.
Clonidine 0.1 mg q.d. to b.i.d.

TABLE 26B.14. COMMON α-ADRENERGIC DRUGS FOR FAILURE TO EMPTY OR AUTONOMIC DYSREFLEXIA

There are a variety of reasons to suspect that $α_1$-adrenergic blockers could be useful in the management of overactive bladder. Jensen (262) reported an increased α-adrenergic tone in patients with "uninhibited" bladders. Short- and long-term administration of prazosin was reported by him to increase bladder capacity and decrease the amplitude of contractions in this category of patients (262,264). Rohner and colleagues (475) reported conversion of the normal ß-adrenergic response of canine bladder body to an α-adrenergic response after bladder outlet obstruction. Perlberg and Caine (441) studied the *in vitro* response of bladder dome muscle from patients with obstructive prostatic hypertrophy and found an α-adrenergic response to noradrenaline (instead of the usual ß-adrenergic response) in 23% of 47 patients. They speculated as to a potential relationship between irritative symptoms in these patients that altered adrenergic response. Lepor and associates (319) have reported on the long-acting α-adrenergic blocker terazosin in placebo-controlled multicenter trials for obstruction from BPH. Randomized to placebo or 2.5 or 10 mg of terazosin, patients demonstrated significant increases in maximum urine flow and reduction of irritative and obstructive symptoms. Similar results have been reported for doxazosin (396). Shapiro and colleagues (510) have shown that symptomatic (obstructive) and flow rate responses in BPH patients correlate with the percent density of smooth muscle in the adenoma.

The predominant $α_1$-adrenoceptor subtype mRNA in the prostatic stroma and urethra is $α_{1A}$, comprising 70% of the total $α_1$-mRNA (453). The vasculature expresses all three $α_1$-receptor subtypes. Regardless of effects on obstruction, $α_{1A}$-receptor antagonists have been developed for BPH to enhance efficacy while ameliorating side effects. The $α_1$-adrenoceptor blocker tamsulosin is somewhat more selective for $α_{1A}$ than $α_{1B}$ and $α_{1D}$ receptors (468). This is not the same as "uroselectivity." Not surprisingly, a variety of highly selective $α_{1A}$-adrenoceptor antagonists are undergoing preclinical or clinical trials for the treatment of symptoms due to BPH. These $α_{1A}$-adrenoceptor antagonists include RS17053, SB216469, REC 15-2739, KMD 3213, and L-771,688,SNAP6383 (353). Although these agents reduce outlet resistance and raise maximal flow rates, there is concern that the relief of symptoms of urinary urgency, frequency, and nocturia may be less than anticipated. Following obstruction, the mRNA for the $α_{1D}$ receptor is upregulated in the bladder (349). Therefore whether $α_{1A}$ and $α_{1D}$ are nonselective, $α_1$-adrenoceptor antagonists for BPH symptoms requires further study.

The less-than-anticipated efficacy of highly selective $α_1$-adrenoceptor antagonists in reducing urgency, frequency, and nocturia may be due to the action of $α_1$-adrenergic antagonists on sites other than the prostate or urethra (123).

For example, intrathecal doxazosin, a nonselective α_1-adrenoceptor antagonist, reduces bladder hyperactivity in obstructed animals (259). It is interesting to note that in animals, α-adrenergic blockers given at the time of fixed urethral obstruction also prevent bladder hyperactivity, raising the possibility of another site of action, possibly the spinal cord (540). Others theorize that at least some of the symptomatic improvement in irritative symptoms seen in patients with BPH who are treated with α-adrenergic blocking agents may be caused by a direct effect of these agents on bladder muscle, rather than their effect on overflow resistance. Likewise, in spinal cord–injured patients, terazosin facilitates bladder emptying and may increase compliance (552).

A dual site of action (prostate and CNS) may also explain the lack of correlation between increased flow rates after α_1-adrenoceptor blockade and relief of irritative symptoms (320,321). The nonselective α_1-adrenergic antagonist alfuzosin has been approved for use in BPH in Europe. Alfuzosin, although a nonselective α_1-adrenergic antagonist, fails to penetrate the CNS. Nevertheless, it is unclear whether this agent is less effective for urgency, frequency, and nocturia than other α_1-adrenoceptor blockers that reach high levels in the cerebrospinal fluid. On the other hand, alfuzosin may have fewer side effects such as asthenia or dizziness.

Phosphodiesterase Inhibitors

Exploitation of signal-transduction pathways in bladder smooth muscle also has potential benefit for the management of failure to store urine or the overactive bladder. A rise in cAMP due to activation of adenylate cyclase causes smooth muscle relaxation. Forskolin, which activates adenylate cyclase, could be clinically useful to treat increased bladder contractility and detrusor overactivity. Endogenous smooth muscle relaxants are also found in the bladder. For example, bladder smooth muscle synthesizes parathyroid hormone–related peptide (PTHrP), which relaxes bladder smooth muscle through the activation of adenylate cyclase (541). Potentially, PTHrP and its analogs could be useful in treating detrusor instability or poor bladder compliance.

Similarly, phosphodiesterase (PDE) inhibitors could have a role in the treatment of urge incontinence. Most notably, PDE_1 inhibitors elicit greater relaxation of the human bladder smooth muscle than PDE_3 or PDE_5 inhibitors in response to activation of adenylate or guanylate cyclase (546). Unfortunately, PDE inhibitors are much less potent at relaxing the human bladder than even oxybutynin. Therefore therapeutic efficacy greater than current anticholinergics is unlikely unless other mechanisms of actions are operative. The use of combination therapy using PDE inhibitors and anticholinergics merits investigation.

Prostaglandin Inhibitors

Prostaglandins could have an important role in modulating contractility of lower urinary tract tissues either through a direct action of smooth muscle or by an influence on afferent or efferent neurotransmitter release. Thus there exist multiple mechanisms whereby inhibitors of prostaglandin synthesis might decrease bladder contractility.

Cardozo and colleagues (84) reported such effects in a double-blind placebo study of 30 women with detrusor instability, in whom they used the prostaglandin-synthesis inhibitor flurbiprofen at a dosage of 50 mg three times daily. Abnormal bladder activity was not abolished in significantly more drug-treated than placebo-treated patients, and bladder capacity did not change. It was concluded that the drug failed to abolish detrusor hyperreflexia, but it delayed the intravesical pressure rise to a greater level of distention. Forty-three percent of the patients experienced side effects from the drug, primarily nausea, vomiting, headache, indigestion, gastric distress, constipation, and rash. Cardozo and Stanton (83) reported symptomatic improvement in patients with detrusor instability who were given indomethacin, another prostaglandin-synthesis inhibitor, at dosages of 50 to 200 mg per day. This was a short-term study with no cystometric data, and the drug was compared only with bromocriptine. The incidence of side effects was high, although no patient had to abandon treatment because of them.

Tricyclic Antidepressants (Table 26B.15)

Imipramine	25 mg q.h.s. to 50 mg t.i.d. 10 mg q.d. elderly
Doxepin	25–50 mg q.h.s.
Amitriptyline	50 mg q.h.s. to 75 mg t.i.d.
Comipramine	25 g q.h.s. to t.i.d.

TABLE 26B.15. TRICYCLICS FOR TREATMENT OF FAILURE TO STORE

Tricyclic antidepressants, particularly imipramine hydrochloride, are useful for facilitating urinary storage (86,385,444). All of these agents possess varying degrees of at least three major pharmacologic actions. First, they have central and peripheral anticholinergic actions at some, but not all, sites. Second, they block the active transport system in the presynaptic nerve ending that is responsible for the reuptake of the released amine neurotransmitters serotonin and noradrenaline. Third, drugs such as imipramine bind to glutamate receptors in the CNS (NMDA) and could influence excitatory neurotransmission in micturition reflex pathways. Serotonin is released from terminals in the spinal cord, and some serotonin agonists inhibit bladder activity. Therefore blocking serotonin uptake would potentially inhibit micturition (533). This would be especially true during rapid eye movement (REM) sleep, during which serotonergic transmission, and thus inhibition of autonomic outflow, are low. Paradoxically, tricyclics also block both adrenergic and serotonin receptors.

Tricyclics are useful in treating chronic pain. This action has been attributed to the ability of these agents to modulate nonadrenergic and serotonergic influences on afferent input to the spinal cord. The efficacy of tricyclics in bladder hyperactivity in patients in whom anticholinergic drugs have failed argues for a noncholinergic mechanism of action on micturition.

Imipramine has prominent systemic anticholinergic effects. However, it appears to have only a weak antimuscarinic effect on bladder smooth muscle (325,421). A direct inhibitory effect on bladder smooth muscle is neither anticholinergic nor adrenergic (43,421). Effects include a local anesthetic–like action at the nerve terminals in the adjacent effector membrane, an effect that occurs in cardiac muscle (51), or an inhibition of the participation of calcium in the excitation–contraction coupling process (421). Clinically, the drug decreases bladder contractility and increases outlet resistance (86,344). In trying to correlate the mechanism of action with the clinical effect, one might postulate that the increase in outlet resistance is caused by a peripheral blockade of noradrenaline reuptake, which would tend to produce or enhance an α-adrenergic tone in the smooth muscle of the bladder base and proximal urethra. Such combined pharmacologic actions would make tricyclics useful in treating hypersensitivity disorders, urge incontinence, and mixed stress-urge incontinence. However, dose-limiting side effects, especially in the elderly, are often prohibitive, although the drug can be effective. All patients should be warned of drowsiness, confusion, palpitations, and feeding disturbances.

Castleden and associates (86) began therapy in elderly patients who had detrusor instability with a single 25-mg nighttime dose of imipramine, which was increased every third day by 25 mg until the patient was continent or had side effects, or a dose of 150 mg was reached. Of 10 patients, 6 became continent, and in those who underwent repeated cystometry, bladder capacity increased by a mean of 105 mL, and bladder pressure at capacity decreased by a mean of 18 cm H_2O. Maximum urethral pressure increased by a mean of 30 cm H_2O. Although our subjective impression was that such effects became evident only after many days of treatment, some patients in this series became continent after only 3 to 5 days of treatment. This implies that the mechanism for treatment of depression differs from that for the overactive bladder.

Afferent-based Drug Therapy

A variety of disease states are associated with upregulation and activation of unmyelinated C-fiber afferent reflex pathways supplying the lower urinary tract (122). These conditions include spinal cord injury, bladder inflammation, and urethral obstruction. Thus mechanisms associated with the development of C-fiber reflexes could be fruitful targets for drugs to treat the overactive bladder or pain. In this regard, the vanilloid agonists capsaicin and resiniferatoxin have shown promise. Because capsaicin activates afferents, causing dumping of vasoactive calcitonin gene-related peptide (CGRP) and nociceptive peptides (substance P, neurokinins), its use has been abandoned in favor of resiniferatoxin. This agent is several orders of magnitude more potent than capsaicin. In early trials, resiniferatoxin improved or eradicated the overactive bladder and urge incontinence in up to 50% of patients (99).

In neuropathic or inflammatory pain models, expression of tetrodotoxin-resistant sodium channels (TTX-R) occurs in C-fibers (418). Expression of TTX-R receptors is associated with continuous or spontaneous burst firing of C-fiber afferents. It is tempting to postulate that upregulation of TTX-R receptors may contribute to the overactive bladder. By inference, TTX-R antagonists may be useful in the treatment of bladder overactivity or urge incontinence. The experimental drug 403W02 ameliorates neuropathic pain in experimental models (569). It would be of interest to investigate whether this agent also inhibits bladder activity.

Dimethyl Sulfoxide

Dimethyl sulfoxide (DMSO) is a naturally occurring organic compound that has been used as an industrial solvent. Among its properties is its ability to penetrate the intact skin, transporting chemicals along with it for absorption into the bloodstream. It has multiple pharmacologic actions (membrane penetrant, antiinflammatory, local analgesic, bacteriostatic, diuretic, cholinesterase inhibitor, collagen solvent, vasodilatory) and is used for the treatment of arthritis and other musculoskeletal disorders (110). The only formulation approved for use on the human bladder is a 50% solution; a 70% solution is generally used topically for musculoskeletal disorders.

Stewart and Shirley (545) reported symptomatic improvement in 75% of patients with interstitial cystitis after a course of treatment with this agent and an improvement in bladder capacity in 80% of these patients. Generally, one 50-mL intravesical instillation is performed every other week for a total of six treatments. The solution is allowed to remain in the bladder for 15 minutes, after which it is expelled by spontaneous voiding. Fowler (186) reported results with DMSO in 20 patients with early interstitial cystitis; 3 complete and 16 partial symptomatic remissions were achieved. However, functional bladder capacity measured at the termination of therapy in 18 cases was observed to increase by more than 25% in only 4 patients. In 10 patients with severe detrusor hyperreflexia, Andersen and colleagues (14) were not able to demonstrate any subjective or objective effects of the drug. The unpleasant garliclike odor after systemic DMSO is its primary side effect and makes double-blind placebo studies impossible. Cataracts have been reported in experimental animals; thus ophthalmologic evaluation is recommended with long-term therapy. As a last resort, this drug has been used by some clinicians in the frustrating patient with the urgency-frequency syndrome but without objective evidence of true interstitial cystitis or detrusor hyperreflexia. Although anecdotal improvement is sometimes reported, few if any formal

reports of the results of such therapy exist. Currently, DMSO is approved for the treatment of interstitial cystitis.

Behavioral Therapy, Biofeedback, Pelvic Floor Exercises, and Pelvic Floor Muscle Training

This group of nonpharmacologic modalities to treat disorders of urine storage and overactive bladder has long been used in nursing and urogynecology and is now gaining popularity in urologic practices (81,84,166). Bladder training programs generally consist of three components: education, scheduled voiding, and positive reinforcement. Biofeedback uses electronic or mechanical instruments to provide information to patients about the status of the pelvic floor. Studies on the application of behavioral and biofeedback methods report a 54% to 95% improvement in incontinence across diverse populations with varying degrees and causes of failure to store urine. Cardozo and associates (84) reported that 27 of 32 female patients completed the study. According to subjective data, 11 were cured, 11 improved, and 5 were considered failures of therapy. Objectively, the corresponding numbers were 12, 4, and 11. In this series, treatment was most effective in patients with mild to moderate detrusor instability and was not helpful in severe cases, defined as a large detrusor contraction simultaneous with the first sensation of the desire to void.

Frewen (189) used “bladder drill retraining” in patients with cystometrically documented idiopathic detrusor instability and urge incontinence. Each patient was given a detailed explanation of the presumed causation of the symptoms along with a written description. A micturition chart, on which patients recorded the times of and intervals between urination, the volume produced, and the degree of incontinence, served as the biofeedback data. In this study, 75% of the patients were hospitalized for an average stay of 10 days. Supportive therapy with sedatives and anticholinergics was used in all patients. The objective cure rate was 82.5%. In a later study, 30 consecutive patients with urgency, frequency, or both, 10 of whom had urge incontinence, were treated on an outpatient basis. Provocative cystometry was performed in 22 of these patients, only 8 of whom showed detrusor instability. At the conclusion of 12 weeks of treatment, 24 of the 30 patients were subjectively free of urinary symptoms. However, of the 8 patients with bladder instability, only 3 showed objective disappearance of detrusor hyperreflexia. The lack of validated outcome instruments, nontherapeutic controls, and long-term data is a serious shortcoming of behavioral trials.

Elder and Stephenson (154) reported the results of a Frewen-type regimen in the treatment of 21 of 27 patients who completed their study. All patients initially had symptoms of increased frequency, urgency, and urge incontinence. Cystometric studies showed that 7 had detrusor instability, 11 had “reduced compliance,” and 3 had normal filling curves. In addition to the bladder training program, 18 of 21 patients were admitted to the hospital for their initial therapy, which in all cases included an anticholinergic (emperonium bromide) and a tricyclic antidepressant (a combination of nortriptyline and fluphenazine). Of the 3 patients with normal cystometric filling curves, 2 were symptomatically cured and 1 was improved. In 5 of the 11 patients with reduced compliance, there was a reversion of the cystometrogram to normal; all 5 of these women were symptomatically cured. In 6 patients, the filling curve was unchanged; symptomatically, 2 of these were cured, 3 were improved, and 1 was unchanged. None of the 7 patients with detrusor instability showed any change in the bladder filling curves. However, symptomatically, 3 were cured, and 2 were improved. In a group of older women (older than age 55) with either urodynamically proven urethral sphincter incompetence (n = 88) or detrusor instability (n = 35), bladder training reduced incontinent episodes by 57% with patients having detrusor instability (166). Not surprisingly, nocturnal enuresis was not improved.

Recently, the American Urological Association in communication with the American Urogynecologic Society convened a consensus committee to review the world literature on this topic and peripheral nerve stimulation. The consensus was that biofeedback, behavioral therapies, and exercises were useful to treat bladder dysfunction. There is much confusion regarding the term *biofeedback*. Nevertheless, these regimens appear to be useful for both stress and urge urinary incontinence using weekly sessions and no more than ten per year. Hospitalization is no longer done. Biofeedback-assisted pelvic floor muscle training therapy is especially useful in homebound older adults. A recent study by McDowell and colleagues (362) demonstrated a 75% reduction in urinary accidents in 85 of 105 subjects enrolled. A meta-analysis of biofeedback and pelvic muscle exercises revealed a trend toward improvement (594). Although it is difficult to isolate the various factors in each of these studies, the value of some type of behavioral training and biofeedback as noninvasive therapy for disorders of urine storage is evident. Wyman and co-workers (621) conclude that the specific regimen may not be as important as the structured intervention with education, counseling, and frequent patient contact. This therapy, alone or in combination with pharmacologic therapy, seems justified.

Bladder Overdistention

Cystodistention involves prolonged stretching of the bladder wall with a hydrostatic pressure equal to systolic blood pressure. Smith (520) summarized the experience at his center and detailed the technique used. The procedure is a modification of the original cystodistention procedure described by Helmstein. The bladder is distended to systolic blood pressure for four successive periods of 30 minutes. After each distention, the bladder is emptied and its capacity measured. An indwelling catheter is left overnight. For repeat distentions, longer periods are used. Few, if anyone,

still perform such vigorous distention with its inherent risks of bladder ischemia. Distention is usually performed under continuous regional (epidural) anesthesia. Wolk and Bishop (619) also report success with hydrodistention for irritative symptoms. Improvement, when it occurs, is generally attributable to ischemic changes in the nerve endings or terminals in the bladder wall (508). Thus the procedure can be grouped under the general heading of those procedures designed to produce bladder denervation. Interestingly, recent experiments evidenced implications of ischemia in the pathogenesis of detrusor instability with obstruction and aging. Potential complications include bladder rupture (5% to 10%), hematuria, and retention. We have been unimpressed with the results of this procedure in patients with storage failure secondary to neuropathic detrusor hyperactivity. Pengelly and associates (435) studied patients with urinary symptoms associated with detrusor hyperreflexia and came to similar conclusions. A retrospective review based on patient recall of therapies for interstitial cystitis performed by the Interstitial Cystitis Database group sponsored by the National Institutes of Health revealed that hydrodistention of the bladder was the only therapy reported to consistently work, but only for weeks (454). No long-term success was achieved.

Electrical Stimulation

Peripheral Stimulation.

Electrical stimulation of somatic (skin, striated muscles), visceral (cervix, vagina), and mixed (spinal roots) nerves can inhibit the micturition reflex and forms the basis of therapy for detrusor hyperreflexia (165,499). The neurophysiologic mechanisms for this inhibition are poorly defined, but retrograde axonal tracing and electrophysiologic studies on animals demonstrate a convergence of somatic and visceral afferents on a common population of spinal interneurons. These interneurons may release transmitters, such as NO, endogenous opiates, or VIP, which inhibit micturition (120). In addition, activation of inhibitory sympathetic pathways to the bladder has been demonstrated with some electrostimulation methods (332).

Intermittent or continuous electrical stimulation can be performed using implantable or nonimplantable devices. Implantable devices involve placement of electrodes on the bladder, urethra, pelvic striated musculature, and spinal nerves or roots. Nonimplantable devices include rectal, vaginal, and transcutaneous stimulators.

Bladder inhibition with implantable devices is optimized when stimulation intensities evoked contractions of the striated urethral sphincter or pelvic floor musculature, resulting in a reflex afferent discharge back to the spinal cord (581). However, this stimulation can be associated with a variety of unwanted side effects. Patients with an intact spinal cord may have pain when spinal nerves rather than anterior roots are stimulated (554). Autonomic dysreflexia can be seen during spinal nerve stimulation in patients with high spinal cord injuries. Koldewijn and associates (289) reported on 17 patients in whom compliance was increased 1 year after S-2 to S-5 posterior root sectioning and electrostimulation. Similarly, Gasparini and colleagues (196) reported good results in 24 patients with up to 4 years of follow-up.

Results with spinal nerve or root stimulation for detrusor hyperreflexia in highly selected patients are encouraging, with up to 90% cure or improvement (289,499). The stimulation parameters, however, may have to be altered over time to maintain maximal results.

A variety of nonimplantable anal or vaginal stimulators differing in design and stimulation parameters are available. Eriksen and Mjolernod (160) reported a 71% cure rate for stress, urge, or mixed incontinence with anal electrostimulation. Bent and colleagues (44), while noting that patients reported a 70% improvement with transvaginal stimulators, were unable to document any objective improvement in leak episodes or pad weighing. A technique known as acute maximal functional electrical stimulation requires stimulation of the vagina, perineum, or anus on a monthly outpatient basis to achieve long-term bladder inhibition (448). Early data on acute maximal functional electrical stimulation indicates a 20% to 80% cure or improvement rate in selected patients. However, the inability to predict those patients that will respond to therapy, combined with poor patient compliance, has prevented the widespread use of nonimplantable stimulators. There is no shortage of short-term, uncontrolled, invalidated studies supporting dramatic successes with peripheral electrostimulation. Yet few clinicians embrace this approach, and most question outcomes.

In an effort to improve comfort or compliance, transcutaneous posterior tibial nerve stimulators have been used clinically to inhibit bladder activity and improve urinary continence (374). Several new techniques based on the acupuncture site for the bladder and posterior tibial nerve stimulation have shown promise. In a report of preliminary subcutaneous nerve stimulation (SANS; urosurge), 75% of patients with bladder overactivity and documented detrusor instability reported improvement (334). Despite these abundant reports of success in the literature, a consensus panel from the American Urological Association charged with reviewing behavioral regimens concluded that peripheral nerve stimulation could not be recommended as routine therapy based on the equivocal data. In some patients, electrostimulation may help them identify or improve pelvic floor contractions.

Sacral Root Stimulation.

Beginning with the pioneering work by Tanagho and Schmidt, the use of implantable sacral nerve stimulation for bladder overactivity has gained acceptance (559). The precise physiologic basis of this therapy is unclear, but it most likely works through stimulation of somatic and visceral afferents (directly and by reflex stimulation of pelvic floor muscles), which in turn inhibit pain and micturition pathways in the spinal cord. This is

analogous to the gate theory of pain. Although it is recognized that the Medtronic Interstim can result in cure or improvement in symptoms of urgency, frequency, and urge incontinence, the use of sacral nerve root stimulation must be viewed realistically (Fig. 26B.26). If one reviews the literature with over a dozen clinical trials, the following observations can be made. First, a home trial of percutaneous stimulation of the sacral roots is needed to select patients who are refractory to conventional drug therapies who might respond to neuromodulation. Second, the definition of success varies, but more than a 90% improvement in symptoms and dry rates can be achieved. Third, the cost is high, both financial and in terms of manpower. Fourth, a significant reoperation rate and learning curve is reported. Of all subjects with overactive bladders or incontinence having failed pharmacologic therapy, roughly 50% respond during the trial period. Of these, only 50% achieve a greater than 90% improvement, at a cost of $20,000 and with up to a 35% reoperation rate. The cost-benefit ratio of this modality must be carefully weighed, but if appropriately selected, this device can achieve a significant improvement or cure in a very difficult patient. Chai and colleagues (90) also report success in controlling urinary frequency and pain in women with interstitial cystitis. Reports of long-term durability with a low dropout rate are now appearing. However, as with most implantable biomechanical devices, eventual reoperation is likely.

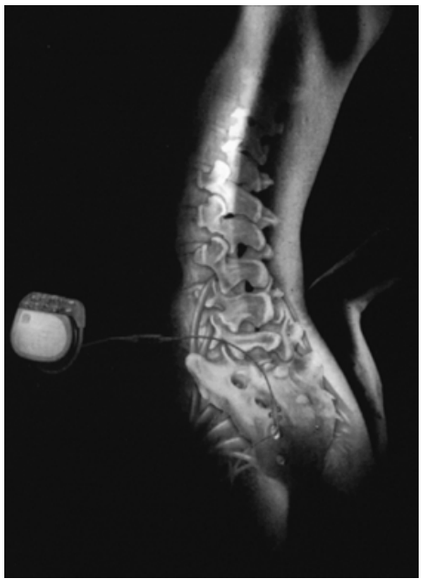

FIGURE 26B.26. Interstim sacral nerve root stimulation for overactive bladder.

Denervation Techniques

Denervation techniques have been used to disrupt the sensory or motor pathways to the bladder in the hope of eliminating the micturition reflex and, thereby, the uninhibited bladder contractions associated with urge incontinence. This assumes that all urge incontinence and overactive bladder is due to an unstable bladder. Moreover, it assumes instability due to reflex contractions generated by nerves.

Denervation can be accomplished by selective blockade with local anesthetics, alcohol, or phenol; or by surgical transection, which has been performed at different sites in the nervous pathways to the bladder (Fig. 26B.27). Denervation at the level of the bladder by prolonged hydrodistention, bladder transection, or myotomy has had initial encouraging results, with a 65% to 75% cure rate (188,619). However, long-term failures are common.

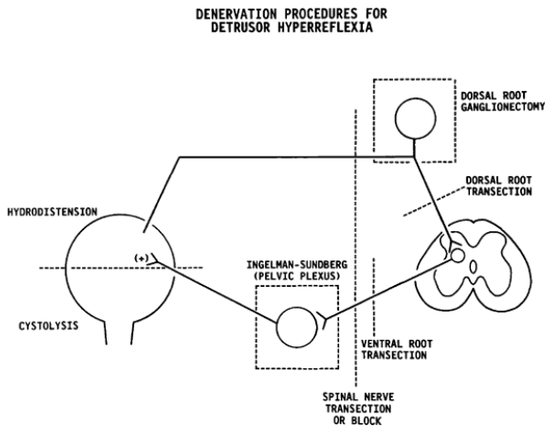

FIGURE 26B.27. Methods of bladder denervation. (From Steers WD. Mechanisms and management of detrusor hyperreflexia with spastic disorder. *State of Art Reviews in Neurosurgery* 1989;4:333, with permission.)

Sectioning the pelvic nerve or subtrigonal plexus is possible (Ingleman-Sundberg procedure) but technically difficult in men due to the relative inaccessibility of these nerves. Furthermore, bowel and sexual dysfunction are often produced by pelvic neurectomies. Subtrigonal injections of alcohol or phenol have been used (239), but a 30% fistula rate has been reported. A simple subtrigonal neurolysis has also been used to treat refractory detrusor instability in women. Anecdotally, many clinicians cannot document efficacy for this technique.

The sacral nerves or roots are relatively accessible and are the most easily identified site for transection. The sacral nerves can be electrically stimulated with bipolar electrodes while monitoring bladder and rectal pressures, as well as striated urethral EMG activity (499,554). Therefore it is useful to intraoperatively identify motor pathways to the lower urinary tract before nerve sectioning to identify the major bladder pathways. Therapy for detrusor hyperreflexia has been especially successful with superselective sectioning of the spinal roots—especially the S-3 anterior spinal root—while lessening the chances of unwanted side effects (339,567). Early cure or improvement rates have been reported in 30% to 100% of patients, and satisfactory long-term results have been achieved in up to 50% of patients. Differences in cure rates and duration of response have been attributed to variations in surgical techniques.

Another surgical procedure used to abolish detrusor hyperreflexia has been dorsal root ganglionectomy (372). In a study comparing dorsal root ganglionectomy with selective spinal nerve sectioning, only ganglionectomy consistently produced low-pressure bladder and urinary continence. Care must be taken before embracing denervation techniques. Nearly all experimental studies reveal devastating effects of depriving muscle of its innervation. The

propensity of the nervous system to adapt and provide alternative routes of neural input bears remembering.

Augmentation Cystoplasty

Enterocystoplasty has been reported to be beneficial for the treatment of storage failure secondary to bladder dysfunction. The procedure was initially used for bladder contracture secondary to tuberculosis. Some patients with neurogenic bladder dysfunction who had failed more conservative management benefited from this therapy (330).

Although controversy exists regarding the optimal method of bladder reconstruction and amount of bladder to be removed, successful results have been reported by a number of clinicians, as long as the technique used avoids making a diverticulum and achieves detubularization of the augmenting bowel patch (399). Goldwasser and Webster (216) reviewed the subject and categorized success rates by cause of dysfunction. Initial positive results have been obtained in 80% to 90% of patients with tuberculous cystitis, interstitial cystitis, and neurogenic bladder dysfunction. The success rate in a small number of patients with radiation injury to the bladder has been in the neighborhood of 50%. Long-term results with interstitial cystitis, however, have been disappointing.

Luanghot and associates (338) reported on 21 incontinent adults with refractory detrusor hyperreflexia secondary to neurologic disorders. Using tubularized ileocecal patch, 95% of patients were dry and not on anticholinergics at a mean follow-up of 3 years. For small, poorly compliant neurogenic bladder, augmentation seems reasonable. For idiopathic instability, less encouraging results are commonplace. More recently, autoaugmentation has been achieved by merely stripping off muscle fibers and leaving mucosa to create, in effect, a wide-mouthed diverticulum (550) (Fig. 26B.28). Many of these patients experience emptying failure afterward, although in most of these, preoperative prediction of this phenomenon is possible by careful urodynamic evaluation. Sphincter weakening procedures may then be used, or intermittent catheterization may be used to obviate this problem. Storage failure secondary to bladder dysfunction and a significant sphincter component may be safely managed with augmentation cystoplasty in combination with the use of an artificial urinary sphincter or periurethral bulking agent. Intermittent catheterization can even be performed safely under these circumstances per urethra or via Mitrofanoff mechanism using appendix or ureter. An algorithm for managing patients with poor bladder compliance, with or without detrusor-sphincter dyssynergia, culminating in augmentation cystoplasty is shown in Fig. 26B.29 . Contraindications for augmentation cystoplasty include renal insufficiency, bowel disease, and inability to perform intermittent catheterization. Patients should be

warned of the rare but possible problem of increased rate of malignancy. Spontaneous rupture can also occur, especially in children. In this regard, it is important to realize that radiographic evidence of rupture using a fluoroscopic or computed tomography cystogram may be lacking. Finally, if any reservoir or augmentation is performed, the patient or caregiver must irrigate at least three times per week to lessen the chances of stone formation.

FIGURE 26B.28. Autoaugmentation technique (From Cartwright PC, Snow BW. Bladder augmentation: partial detrusor excision to augment the bladder without use of bowel. *J Urol* 1989;142:1050, with permission.)

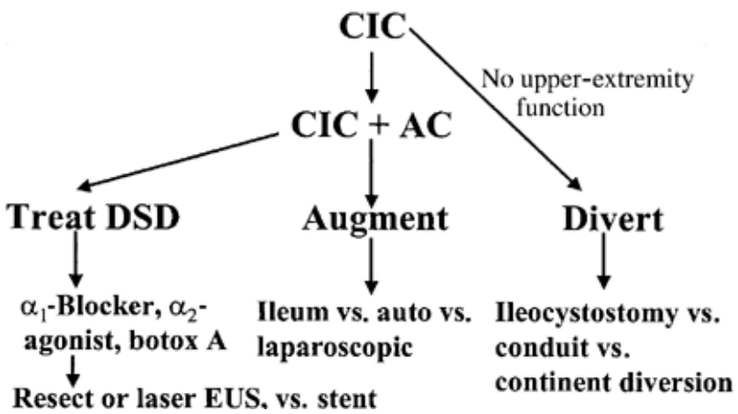

FIGURE 26B.29. Algorithm for management of residual urine and poor bladder compliance with upper tract changes in patients with neurogenic bladder. DSD, detrusor external-sphincter dyssynergia.

Increasing Outlet Resistance

Physiotherapy

By periodically performing various pelvic floor exercises for several months, it is possible for females, at least, to increase pelvic striated muscle tone and to control minor degrees of prolapse and sphincteric incontinence (81). Kegel's exercises are designed to improve the functioning of the pubococcygeal muscles. These exercises involve voluntary tensing of the perineal muscles approximately 20 times in the morning, afternoon, and evening to strengthen the perineal muscular, fascial, and elastic tissues. Patients are instructed to contract their perineal muscles as though interrupting the flow of urine and to squeeze the vaginal muscles while drawing up the perineum and rectum as though interrupting a bowel movement. Every effort should be made to motivate the patient to learn the exercise routine correctly and to practice it conscientiously on a daily basis. In uncomplicated urinary stress incontinence, consistent exercise is said to bring symptomatic improvement within 6 weeks, although several months are required to bring all supportive and sphincteric structures to optimal capacity. Only minor degrees of sphincteric incontinence can be significantly improved in this fashion.

Electrical Stimulation

Intravaginal and anal electrical stimulation have been used to treat storage failure by increasing outlet resistance and decreasing bladder contractility (160). The mechanism involves indirect stimulation of the striated pelvic floor musculature through branches of the pudendal nerve (165). In cats, additional urethral closure is provided by a pudendal to hypogastric reflex that stimulates the smooth muscle of the bladder neck and proximal urethra by means of an α-adrenergic effect. In properly selected cases, initial cure or improvement rates range as high as 50% to 80%, figures that many have not been able to reproduce. One must remember to select the proper unit, because parameters for this type of stimulation differ from those used to inhibit bladder contractility. Overall, electrostimulation appears to be more effective for urge than stress incontinence except in those patients unable to contract their pelvic floor voluntarily.

Pharmacologic Therapy

α-Adrenergic Agonists (Table 26B.16)

Ephedrine	25–50 mg q.i.d.
Pseudoephedrine	30–60 mg q.i.d.
Phenylpropanolamine	50 mg t.i.d.
Phenylpropanolamine SR	5 mg b.i.d.

TABLE 26B.16. α-AGONISTS FOR FAILURE TO STORE

The bladder neck and proximal urethra contain a preponderance of α-adrenergic receptor sites that, when stimulated, produce smooth muscle contraction. Such stimulation alters the urethral pressure profile by increasing maximum urethral pressure (MUP) and maximum urethral closure pressure (MUCP) (149). Various orally administered pharmacologic agents are available to produce α-adrenergic stimulation with relatively mild side effects. Potential side effects of all the agents that produce a peripheral α-adrenergic sympathetic effect include blood pressure elevation, anxiety, and insomnia caused by central nervous system stimulation. They may also cause headache, tremor, weakness, dizziness, respiratory difficulties, palpitations, and cardiac arrhythmias. All of these agents should be used with caution in patients with hypertension, cardiovascular disease, or hyperthyroidism (606).

Ephedrine is a noncatecholamine sympathomimetic agent that owes part of its peripheral action to the release of norepinephrine but that also directly stimulates both α- and ß-adrenergic receptors (607). The oral adult dosage is 25 to 50 mg four times daily. Some tachyphylaxis develops in response to its peripheral actions, probably as a result of depletion of norepinephrine stores. Pseudoephedrine is a stereoisomer of ephedrine that is used for similar indications with similar precautions (600). The adult dosage is 30 to 60 mg four times daily, and the 30-mg dosage form is available in the United States without a prescription. Norephedrine chloride in a dosage of 75 to 100 mg was shown to increase short-term MUP and MUCP in women with urinary stress incontinence (149). At a 300-mL bladder volume, MUP rose from 82 to 100 cm H_2O, and MUCP rose from 63 to 95 cm H_2O. The functional profile length did not change significantly. A 14-day double-blind crossover study comparing the effects of norephedrine to placebo showed that reduction of urinary leakage with the drug as compared with placebo occurred in 12 of 22 patients. Diokno and Taub (136) reported a good to excellent response in 27 of 38 patients with sphincteric incontinence treated with ephedrine sulfate. They noted that beneficial effects were most often achieved in those with minimum to moderate wetting and that little benefit was achieved in patients with severe stress incontinence. Obrink and Bunne (415) noted that 100 mg of norephedrine chloride twice daily did not improve severe stress incontinence sufficiently to offer an alternative to surgical treatment. They further noted that in their group of ten such patients, MUCP was not influenced at rest or with stress at low or moderate bladder volumes.

Phenylpropanolamine hydrochloride shares the pharmacologic properties of ephedrine and is approximately equal in peripheral potency, while causing less central stimulation (608). With dosages of 50 mg three times daily, Awad and colleagues (25) found that after 4 weeks of therapy, 11 of 13 females and 6 of 7 males with stress incontinence (severity not noted) were significantly improved. MUCP was increased from a mean of 47 to 72 cm H_2O in the empty bladder and from 43 to 58 cm H_2O with a full bladder. Fifty milligrams of phenylpropanolamine was combined with 8 mg of chlorpheniramine (an antihistamine) and 2.5 mg of isopropamide (an antimuscarinic) as a sustained-release capsule (Ornade) used primarily for relief of symptoms of allergic rhinitis. Stewart and colleagues (544) prescribed one capsule twice daily and found that of 77 women with urinary stress incontinence, 18 were completely cured, 28 were much better, 6 were slightly better, and 25 were no better. In 11 men with postprostatectomy stress incontinence, the numbers in the corresponding categories were 1, 2, 1, and 7. Subsequently, Montague and Stewart (390) performed urethral profilometry in 12 women with moderate to marked stress incontinence and six women with no history of incontinence. MUP increased more than 20% in 11 of the incontinent women and in only 1 of the continent group. Rees and Ransley (463) reported on the use of Ornade in 83 children with daytime wetting from a variety of causes. Of 24 children with bladder neck incompetence, 41% were cured, 29% had minimum symptoms, and 12% were improved. Interestingly, of 31 patients with bladder instability, the corresponding improved percentages were 24%, 24%, and 20%. The latter beneficial effect may have been caused by the anticholinergic agent in the preparation. Treatment had to be discontinued in 8 children because of side effects; 23 other children had mild and transient side

effects. Major surgery was avoided by drug treatment in four children. The formulation of Ornade has now been changed so that each capsule contains only 75 mg of phenylpropanolamine and 12 mg of chlorpheniramine. It is also available as a liquid.

In a rare placebo-controlled study of sustained-release phenylpropanolamine (5 mg twice daily) on 24 women with stress incontinence evaluated subjectively and with a voiding log and urodynamics, maximum urethral closure pressure increased by 12% over placebo, and episodes of incontinence decreased by nearly 50% (108). Scrutiny of all controlled data on the use of α-adrenergic agonists for all types of stress urinary incontinence reveals an overall cure rate of 0% to 14% and a 19% to 60% rate of improvement. No studies have stratified patients on the basis of hypermobility (type II) or intrinsic sphincter deficiency (type III), although mild, moderate, or severe categories are mentioned.

Phenylpropanolamine is no longer a drug that can be obtained only by prescription in the United States. It is readily available as a component of many appetite suppressants, and patients can be instructed to obtain an inexpensive brand that contains 50 to 75 mg of phenylpropanolamine with no caffeine and a minimum of extra ingredients.

Recent concern by the U.S. Food and Drug Administration has arisen over health concerns with α_1-adrenergic agonists. More specifically, cardiac arrhythmias and associated deaths from nonprescription drugs demand advising the patient of risks and side effects.

In an effort to reduce side effects and increase efficacy, selective α_{1A}-adrenoceptor agonists are being investigated. A-204176 contracts urethral tissues *in vitro* and raises urethral pressure in humans *in vivo* (75). Unfortunately, it also raises blood pressure, which is the first proof that α_{1A}-adrenergic receptors are expressed by the human vasculature and have a physiologic effect.

ß-Adrenergic Antagonists

Theoretically, ß-adrenergic blocking agents might be expected to "unmask" or potentiate an α-adrenergic effect, thereby increasing outlet resistance. In one of the only studies of ß-blockers for voiding dysfunction, Gleason and colleagues (212) reported success in treating certain patients who had stress urinary incontinence with propranolol, a ß-adrenergic blocking agent, using oral dosages of 10 mg four times daily. The beneficial effect, however, became manifest only after 4 to 10 weeks of treatment, a difficult fact to explain on an acute pharmacologic basis. Although such treatment has been suggested as an alternative method of drug therapy in patients with hypertension and sphincteric incontinence, few if any subsequent reports of such efficacy have appeared, and others have reported no significant changes in UPPs in normal women after ß-adrenergic blockade (140). Although 10 mg four times a day is a relatively small dosage of propranolol, it should be recalled that the major potential side effects of the drug are related to its therapeutic ß-blocking effects. Heart failure may develop, as well as an increase in airway resistance, and asthma is a contraindication to its use.

Estrogen

Estrogens may act through several mechanisms to improve stress incontinence. Salmon and colleagues (493a) first reported the use of estrogen in the treatment of stress urinary incontinence in 1941. Raz and colleagues (457) found that a daily dose of 2.5 mg of conjugated estrogens (Premarin) improved stress incontinence and increased urethral pressures in postmenopausal patients, effects that they attributed to mucosal proliferation, with a consequently improved "mucosal seal effect." A beneficial effect was also attributed to enhancement of the α-adrenergic contractile response of urethral smooth musculature to endogenous catecholamines. Schreiter and colleagues (500) reported similar benefits after 10 days of treatment with daily divided doses of 6 mg of estriol. They showed also that the effects of estrogen and exogenous α-adrenergic stimulation were additive. Hodgson and associates (249) reported that the sensitivity of the rabbit urethra to α-adrenergic stimulation was estrogen dependent, because castration caused a decreased sensitivity, and treatment with low levels of estrogen reversed the defect. Ekstrom and co-workers (151) substantiated both acute and chronic effects of estrogens on α-adrenergic receptors in the bladder outlet.

Despite experimental enthusiasm, urodynamic evidence for estrogen effects on bladder and urethral function is not convincing. Rud (482) studied the effects of 4-mg daily doses of estradiol and 8-mg daily doses of estriol on 30 women with an average age of 61 years, 24 of whom had stress urinary incontinence. Small but statistically significant changes occurred in MUP (59 to 63 cm H_2O), functional urethral length (25 to 28 mm), and actual urethral length (33 to 37 mm). No statistically significant change occurred in urethral closure pressure (37 to 39 cm H_2O). Eight of the 24 incontinence patients experienced subjective and objective improvement, nine experienced subjective improvement only, and seven experienced neither subjective nor objective improvement. There was no correlation between subjective or objective improvement and the previously mentioned urodynamic measurements. However, in 18 patients, pressure transmission to the urethra was recorded during cough, and in 7 of these patients this condition improved. All of these patients had subjective improvement, and 5 were shown to be objectively dry. Rud (482) pointed out that it is hard to believe that the small changes in urodynamic measurements, even though statistically significant, were directly related to resumption of continence. He noted also that the increased pressure transmission ratio might have been caused by factors outside the urethra—either in the striated musculature of the pelvic floor or in the periurethral vasculature or supporting tissues. Interestingly,

he found no changes in urodynamic measurements in five continent and three stress-incontinent females who had cystic glandular hyperplasia treated with a single injection of 1,000 mg of intramuscular progesterone, except that the pressure transmission ratio was lower in the three patients in whom this was measured.

Levin and colleagues (322) have shown that parenteral administration of estrogen can change the α-adrenergic receptor content and the autonomic innervation of the lower urinary tract of immature female rabbits. Whether these experiments have any clinical significance is unknown. Estrogen therapy seems capable of facilitating urinary storage in some women by increasing outlet resistance, and there is evidence of an augmentative or perhaps additive effect with α-adrenergic therapy in this regard. Whether the levels achieved by commonly used oral or parenteral estrogen preparations or by estrogen vaginal creams actually increase the α-adrenergic receptor content of the smooth muscle of the bladder outlet or the "mucosal seal effect" is unproven. Bhatia and coworkers (48) showed that 6 weeks of conjugated vaginal estrogen cured or significantly improved 54% of women with stress incontinence. Women who failed to respond did not demonstrate an increased functional length or maximum closure pressure. In a 3-month prospective study of postmenopausal women with stress incontinence who received piperazine estrogen for 3 weeks and were assessed with a voiding diary, no statistically significant improvement was noted over placebo (617). Results of combined α-agonist and estrogen therapy may be somewhat better, with cures up to 23% and reduction in episodes 38% at most (247,589). Some clinicians have the impression that intravaginal conjugated estrogen for 2 to 3 months is more effective than oral agents. Cardozo and associates (85) performed a meta-analysis on 77 studies of estrogen for symptoms related to atrophic vaginitis and concluded that estrogens are efficacious in this group of women. A reduction in irritative voiding and recurrent urinary tract infections has been most notable. An estrogen-impregnated ring (Estring) has also been evaluated. A reduction in symptoms of urge and stress incontinence occurred in 48% and 50% of women, respectively, compared with 11% of controls (161). The potential long-term effects of such treatment must be carefully considered, however, in light of the current controversy over whether estrogen therapy predisposes the patient to the development of endometrial carcinoma. Furthermore, all women placed on estrogens should be advised of the need for an annual mammogram.

Vesicourethral Suspension

Fixation of the vesicourethral junction in a physiologic position was initially reported to correct genuine stress urinary incontinence in females in 85% to 90% of cases (Table 26B.17). A review of the world literature reveals that significant overlap exists in improvement and cure rates for stress incontinence. Most data show that the Marshall-Marchetti-Krantz procedure provides the most durable results. However, it also has significant morbidity. Innumerable modifications of the Marshall-Marchetti-Krantz procedure, and other procedures designed to fix the vesicourethral junction in a physiologic position, have been described. In general, there is not one dominant procedure for correcting genuine stress urinary incontinence. Whether genuine stress urinary incontinence is due to hypermobility or arises from intrinsic sphincter deficiency will influence the success of surgery.

	Subjective Response		Objective Response	
Procedure	No. of Patients	% Success	No. of Patients	% Success
MMK	6,827	93	443	89
Burch	1,726	90	2,300	84
Needle suspension	1,888	78	446	70
Pubovag sling	1,712	82	720	85
Periurethral injections	319	56	133	60

From Jarvis G. *Br J Obstet Gynaecol* 1994:101:371.

TABLE 26B.17. SURGERY FOR STRESS INCONTINENCE

Choice of a specific procedure is based on experience; type of stress incontinence; presence of pressure of pelvic floor deformities such as cystocele, enterocele, or rectocele; previous procedures; concomitant surgery; patient preference; and medical condition. All effective operations restore the physiologic position of the bladder neck–proximal urethral area. More important, they anchor the vagina and urethra, preventing hypermobility and allowing transmission of intraabdominal pressure to the urethral and bladder neck.

The Marshall-Marchetti-Krantz (MMK) operation (Fig. 26B.30) approximates the periurethral and vaginal fascia to the posterior surface of the cartilaginous portion of the pubic symphysis. If we envision the suspension of the vagina and urethra as a bridge, a cable of fascia (pubocervical) extends from the pubis or either side to the ischial tuberosity. The pubocervical fascia is strung from this fascial cable and fixed to the vagina, cervix, and urethra. Any

condition that lengthens or attenuates (aging, vaginal childbirth), weakens (collagen disorder), or destroys (trauma) these tissues can produce hypermobility and stress incontinence.

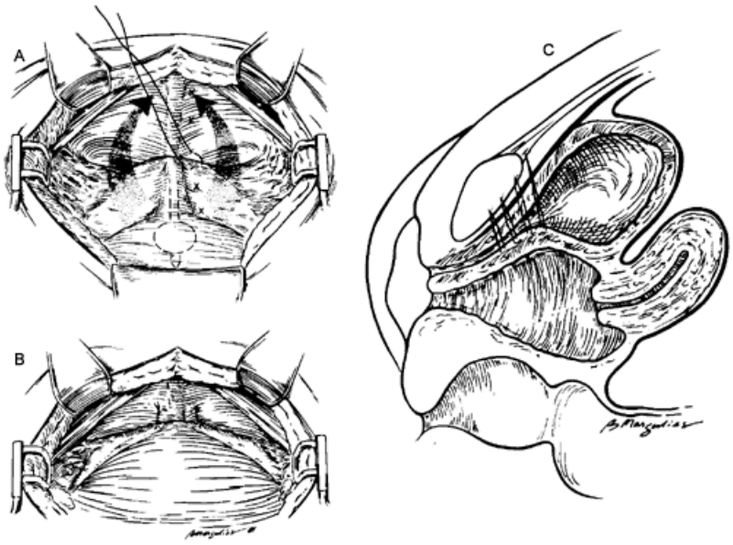

FIGURE 26B.30. Marshall-Marchetti-Krantz procedure. This procedure corrects stress urinary incontinence by approximating the periurethral and vaginal fascia to the underside of the pubis symphysis with three or four pairs of sutures. **A:** The placement of the sutures in the periurethral and vaginal fascia and at the level of the vesicourethral junction. The *large, stippled upward curved arrows* point out the sites of suture attachment on the underside of the pubic symphysis. The orientation of this view is retropubic, as the surgeon would see it. Accurate placement of the sutures is important to achieve satisfactory suspension, and to ensure good fixation it is helpful to take a double bite through the periurethral fascia and anterior vaginal wall, taking care not to put the suture through the vaginal mucosa. Insertion of the sutures is facilitated by elevation of the anterior vaginal wall. It is usually helpful for the surgeon to use the left hand to do this while placing the sutures with the right hand. **B:** Retropubic view after the sutures have been tied individually, commencing with the more distal pair. While the surgeon is tying the sutures, it is useful to have the assistant elevate the vaginal wall. The most proximal suture may need to be passed through the insertion of the rectus abdominus muscle. **C:** Lateral view showing correction of the anatomic abnormality contributing to stress urinary incontinence by the Marshall-Marchetti-Krantz procedure. Here the most proximal sutures are shown passing through the insertion of the rectus abdominus muscle. (From Webster GD. The urethra. In: Paulson DF, ed. *Genitourinary surgery*. New York: Churchill Livingstone, 1984, with permission.)

Although the original procedure was done through a horizontal suprapubic incision, a vertical incision may yield better exposure in patients who represent failures of previous pelvic surgical procedures. The original procedure (354) involved mobilization of the urethra to within 1 cm of the meatus, and it used three no. 1 doubled chromic sutures inserted equidistantly from each other on either side of the urethra, the sutures catching the deep vaginal wall and the lateral wall of the urethra. A similar suture was placed lateral to the vesicourethral junction, and additional sutures were placed in the vaginal wall to bolster the repair. Sutures were also placed between the musculature of the lower and lateral bladder and the posterior rectus sheath to further close the space of Retzius. Most surgeons who perform this operation use absorbable sutures. Some surgeons prefer to open the bladder to facilitate suture placement; some use nonabsorbable sutures; and others, who consider urethral lengthening to be the primary therapeutic goal, place sutures only between the bladder and rectus fascia (304). In an attempt to prevent sutures from detaching from the pubis, some surgeons anchor sutures using drills to secure fixation. The downside of the MMK procedure is the development of osteitis pubis, occasional urinary retention due to obstruction, and the need for open pelvic surgery.

Retropubic colposuspension (vaginal suspension), first described by Burch in 1961, fixes the vesicourethral junction without retaining sutures in the pubis (Fig. 26B.31). The suture placement generally commences distally at the level of the vesicourethral junction, although some surgeons prefer a midurethral level. Fixation is to Cooper's ligament.

One concern, however, is that aggressive elevation of perivesical tissues can kink the ureters, causing bilateral ureteral obstruction. Some believe that this operation gives broader support to the urethra and bladder base and avoids the risk of urethral compression and obstruction. Potential enteroceles in Douglas's pouch must be obliterated by successive purse-string sutures in this area (527). A modification of the Burch technique with placement of sutures through the vaginal wall has been reported, with a success rate of 92% as a first procedure, and 89% cure rate for recurrent stress incontinence (281). Numerous studies have now appeared confirming durability of response for the Burch procedure, with dry rates between 65% and 75% after 5 to 10 years (10,113,312). The overall complication rate is as high as 41% (113). Infections, obstruction of the bladder outlet and ureters, and need for open surgery are potential complications of the Burch colposuspension. This procedure may not correct urinary incontinence due to

intrinsic sphincter deficiency. Failures of the Burch procedure are noted to possess intrinsic sphincter deficiency. A pubovaginal sling procedure can “rescue” these patients. However, a prospective study examining the response of patients with documented ISD has yet to be performed to settle this controversy.

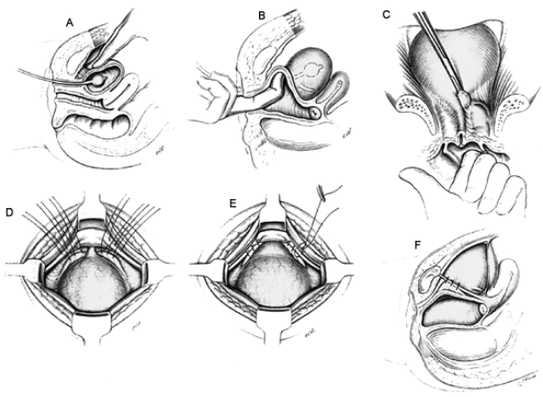

FIGURE 26B.31. Burch colposuspension. **A:** Sagittal section showing blunt finger dissection in the retropubic space of Retzius, between symphysis pubis and anterior surface of bladder and urethra. **B:** Sagittal section showing upward pressure in the lateral vaginal fornix to aid the surgeon in the abdominal section. **C:** Retropubic view from area of pubis but with the pubis removed. With the operator's finger still in the vagina and elevating the lateral vaginal fornix, the bladder base is dissected medially off the paravaginal fascia. **D:** Retropubic view, as seen by surgeon, showing three pairs of sutures in place but not tied. Some surgeons use heavy absorbably sutures, whereas others use nonabsorbable sutures. The sutures are inserted into the paravaginal fascia and then to the nearest point on the ipsilateral iliopectineal ligament. The most distal (caudal) sutures are inserted opposite the bladder neck and not lower. The next two sutures are inserted more proximally (cephalad) alongside the bladder base. The lateral vaginal fornix should be elevated toward the iliopectineal ligament as the corresponding suture is being placed through the ligament so as to position the suture accurately. **E:** The tying of the sutures, showing approximation of the paravaginal tissue to the iliopectineal ligaments. **F:** Sagittal section showing elevation of the bladder neck and bladder base on a shelf of paravaginal fascia, sutured to the iliopectineal ligament. (From Stanton SL. Colposuspension. In: Stanton SL, Tanagho EA, eds. *Surgery of female incontinence*. Berlin: Springer-Verlag, 1986, with permission.)

The needle suspension procedure was first introduced by Pereyra in 1959. Numerous modifications of this procedure have evolved, and currently there are several in use that involve endoscopic control to make sure that the suspending sutures are not passed through the lumen of the bladder or urethra. The Stamey procedure uses the intact tissues lateral to the vesicourethral junction as the primary source of support for suspension of the bladder neck. As initially described, the surgeon was to watch the bladder neck close with tightening of the suprapubic sutures. This is now recognized as too tight. The Raz needle suspension perforates the retropubic space between the pubic bone and the endopelvic fascia, freeing the endopelvic fascia from its lateral pubic attachments. The suspension sutures are placed through the edge of the lateral vaginal wall, incorporating the endopelvic fascia in this area (233). Several modifications of the Raz technique have been made over the years. In a long-term follow-up of over 200 patients, Raz and co-workers (460) reported a durable cure or only rare incontinence in 90% of these individuals. Others report failure at 7 years as high as 40% (109). A modification of the Raz technique to correct small to moderate (grade I to II) cystoceles includes the four-corner (461) suspension.

The Gittes technique (210) relies on a helical suture through the vaginal mucosa and submucosa. A Stamey or Raz needle is passed from two small suprapubic incisions. The technique has been successful in 97% of women with grade I (leakage only with severe abdominal straining) stress incontinence, but only 42% effective with grade III (total, possibly intrinsic sphincter deficiency) (299). The Gittes procedure can be accomplished on an outpatient basis under local anesthesia (210). Thus this technique can be performed on patients categorized as high operative risk.

Each of these modified Pereyra procedures had a large number of ardent supporters. Although the results in the treatment of stress incontinence, when performed by experienced operators, seemed to approach the best results achieved by modifications of the Marshall-Marchetti-Krantz or the Burch procedures, long-term data reveal an alarmingly high failure rate. Needle procedures have largely been abandoned because of long-term data revealing poor durability of this surgery. Only 30% to 40% of women remain dry with needle suspensions after 48 months (312).

Interest in laparoscopic surgery has led to evaluation of this technique to suspend the urethrovesical junction using a Burch technique, in an effort to decrease patient discomfort and allow earlier return to full activity. Initial reports suggested that a laparoscopic Burch technique is feasible, with results approaching the open abdominal procedure (300,561). Operative times vary with experience of the laparoscopist, and success depends on type of suture material or staples, experience, and whether previous abdominal or suprapubic surgery has been attempted. Long-term results in prospective trials are needed to assess the durability of this procedure for treating urethral hypermobility. However, long-term durability remains of concern. McDougall and colleagues (361a) compared the laparoscopic Burch procedure with a transvaginal suspension in 100 patients. Only 15 of 50 patients (30%) remained completely continent after laparoscopic Burch colposuspension.

Bladder Outlet Reconstruction

Reconstruction of the bladder neck is one method of restoring sphincteric continence in patients with a fixed, open bladder outlet. Other alternatives involve mechanical compression of the bladder outlet and include sling procedures, submucosa urethral tunneling, periurethral bulking agents, and the use of an artificial sphincter. Bladder neck reconstruction for the treatment of urinary incontinence was introduced by Young in 1907 and subsequently modified by Dees (119) and Leadbetter (313). Procedures using the Young-Dees principle involve reconstruction of a neourethra from the posterior surface of the bladder wall and trigone. In the male, the prostatic urethra affords additional substance for closure and for increase in outlet resistance. The Leadbetter modification involves proximal reimplantation of the ureters to allow more extensive tubulization of the trigone. Long-term success rates of between 60% and 70% have been achieved (314). Tanagho (557) and Tanagho and co-workers (560) described a procedure based on a similar concept, but using the anterior bladder neck to create a functioning neourethra sphincter. A success rate of 70% was reported. Despite these encouraging reports, others have had difficulty reproducing these dramatic successes.

Surgical Mechanical Compression

Submucosal Tunnel

In cases of sphincter incompetence, Nill and associates (405) described a technique of creating a bladder tube and reimplanting it submucosally to achieve continence (Fig. 26B.32). Of 38 patients (mean age of 10 years, range of 6 months to 46 years) with neurogenic intrinsic sphincter deficiency, all were dry. Difficulties with catheterization or stricture represent the major morbidities.

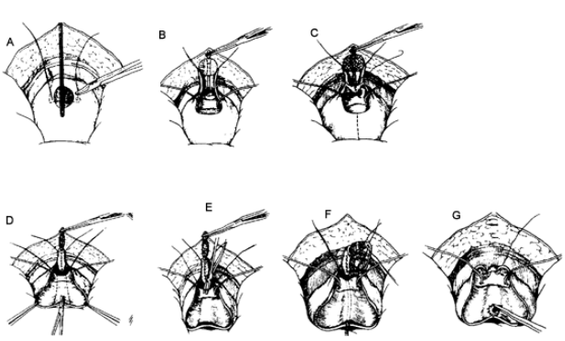

FIGURE 26B.32. Kropp technique for submucosal tunnel. **A:** Bladder strip harvested. **B:** Ureteral orifices identified. **C:** Tubularization begun at bladder neck. **D:** Bladder is bivalved to help create submucosal tunnel. **E:** Tunnels are connected. **F:** Red rubber catheter used to pull urethral tube through tunnel. **G:** Bladder neck and wall closure are then performed. (From Kropp K. Suburethral tunnel for correction of urinary incontinence. *R Surg Tech Urol* 1991;4:1, with permission.)

Gracilis Myoplasty

A novel approach to urethral compression has been the experimental surgery involving intact gracilis muscle transposition with electrostimulation using intramuscular electrodes (97).

Early results appear to be promising, but long-term follow-up is needed.

Periurethral Injections

The injection of Polytef paste periurethrally to increase urethral resistance has been developed and promoted primarily by Politano and protégés (449,585). Most clinicians inject the Polytef paste transurethrally, and an ingrowth of fibroblasts is stimulated, which produces a bolstering effect but does not stricture the urethra. Good results were reported by Politano's group in up to 70% of patients. Deane and associates (115) described four cures and two improvements in 6 females with genuine stress incontinence and five cures and size improvements in 22 females with bladder neck incompetence at rest. They were able to achieve only one improvement in 8 males with postprostatectomy incontinence. Malizia and colleagues (347) expressed concern regarding the potential of distal embolization of the Polytef particles, which they observed in laboratory animals and humans. Migration of Polytef to skin in a woman treated for incontinence has also been reported. Reference is also made to blood-vessel, pulmonary, and lymph nodes after vocal cord injections of Polytef.

To improve efficacy through reduced viscosity, and to reduce potential morbidity of Teflon migration or malignancy, other agents have been used to increase bladder leak-point pressure and treat intrinsic sphincter deficiency. These agents include glutaraldehyde cross-linked (GAX) collagen, fat, and silicone. Fat, readily accessible and without cost, is initially successful in 82% of patients (494). However, a high failure rate in the long term, due to autolysis, is thought to occur.

Periurethral GAX collagen has been reported to cure 88% of women and children with stress incontinence due to intrinsic sphincter deficiency (279,549,591) (Fig. 26B.33). Results are much more disappointing in men after radical prostatectomy, with cure rates as low as 20% (245). At 2 years, up to 20% of patients may require a repeat injection. Long-term data indicate durable cure rates in 12% to 20% of men and 40% to 50% of women. Resorption or extrusion of the material is problematic.

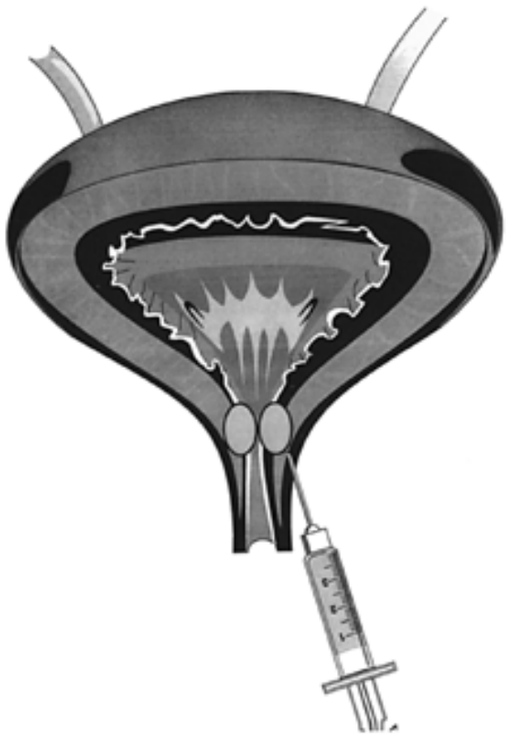

FIGURE 26B.33. Periurethral bulking agent.

To improve durability yet avoid the mechanical properties of a thick paste, three new materials have appeared. Autologous chondrocytes and myoblasts have been injected periurethrally and are undergoing clinical trials. A carbon slurry (Durasphere) has been approved for use as an injectable agent for incontinence. Published clinical trials with adequate follow-up are lacking.

Pubovaginal Sling

Since 1907, a considerable number of procedures utilizing a suburethral sling technique have been described, using either autologous or alloplastic material. A Dacron, Marlex, collagen-coated woven polyester (ProteGen) or fascial (autologous versus cadaveric donor) sling is placed underneath the proximal urethra under no tension and secured to or over the rectus fascia. Alternatively, the use of bone anchors has been advocated. Slings are effective following failed retropubic suspensions, suggesting a different pathology and mechanism of action for this procedure. Dry or dramatic

improvement in incontinence at before 2 years with fascial slings is more than 90%, and 60% to 80% after 2 to 7 years has been reported (91,111,312). The advantages of fascial slings include avoiding erosion, pain, fistulae, and irritation (286). Cadaveric (allograft) fascial slings avoid the discomfort of autologous harvesting. Tensile strengths of certain cadaveric materials are comparable to autologous fascia (316). A recent report of human DNA on the cadaveric fascia raises the theoretic possibility of disease transmission (e.g., prions) (103). The risk of HIV transmission from properly screened tissue donors is 1 in 667,600, which is lower than with transplantation. There are six suppliers of fascia lata allograft in the United States. Costs range from $60 to $1,200 for varying sizes. However, several studies reveal a reduction in operating time and hospital staff (512).

These procedures have been used for patients with all types of stress incontinence and have been very effective in patients with recurrent stress incontinence, obesity, and pelvic floor weakness, and especially after repeated unsuccessful surgeries. The fascial sling suspension is ideal for women with a combination of urethral hypermobility and intrinsic sphincter deficiency. The technique elevates and fixes the urethra in a normal retropubic position. However, the noncircumferential compression afforded by the sling is optimal treatment for patients with little urethral closing function and those with poor urethral smooth muscle function resulting in intrinsic sphincter deficiency (58,369,553). Although originally described through a retropubic approach, a combined vaginal and abdominal approach (Fig. 26B.34) often facilitates the procedure. The vaginal access to and dissection of the retropubic space for sling placement is similar to that provided by the Raz-type suspension procedure. In general, urge incontinence can be corrected in more than one-fourth of patients following the sling procedure. However, the biggest drawback to pubovaginal slings is the reported *de novo* detrusor instability of 10% to 20%. Pain from the sutures is seen early and occurs in roughly 15% of women. Urinary retention is uncommon, occurring only 5% of the time.

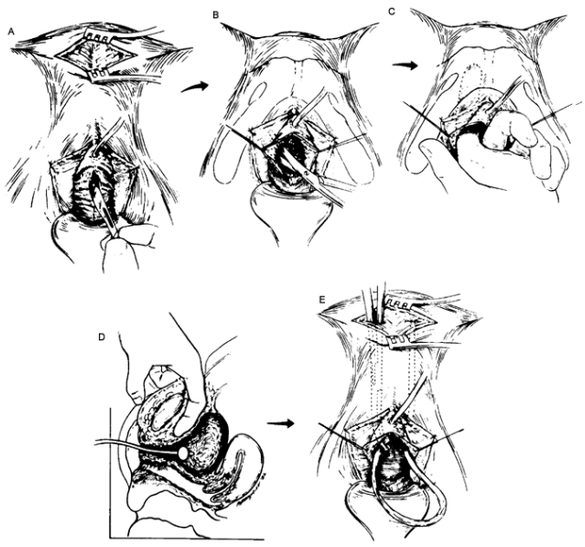

FIGURE 26B.34. Fascial sling procedure. **A:** In this variation, a combined vaginal and abdominal approach is used. **B:** After reflecting the vaginal wall from the urethra, the paraurethral musculofascial tissue is dissected into the retropubic space at the level of the bladder neck. The approach is similar to that used in the Raz suspension procedure. **C:** This space is further digitally dissected, as in the Raz procedure. **D:** Rarely, a retropubic dissection is also necessary, as pictured. **E:** The fascial sling, which may be obtained from rectus or external oblique fascia, or fascia lata, is looped around the urethrovesical junction and fixed to the rectus fascia suprapubically. The tension of the sling must be carefully adjusted to provide the minimum necessary to achieve the desired goal of elevation or compression. (From Webster GD. The urethra. In: Paulson DF, ed. *Genitourinary surgery*. New York: Churchill Livingstone, 1984, with permission.)

The use of bone anchors for suspensions, slings, and laparoscopic surgeries raises several issues. First, efficacy does not appear to be enhanced. Suspension surgeries usually do not fail because the sutures pull out from above. Second, these devices add cost to the procedure without proven increased efficacy. Third, morbidity is increased. Despite arguments that orthopedic appliances are readily tolerated, few metallic devices are placed into bone via the vagina. Pain is an increasingly common complaint following bone anchors, and reports of osteomyelitis are now appearing (159).

In an effort to avoid prosthetic slings or harvesting of fascia, Raz and co-workers (461) have used a buried vaginal wall sling. Most patients have difficulty resuming volitional voiding immediately after surgery. Rarely, permanent self-intermittent catheterization may be required after any compressive sling procedure. More commonly, detrusor instability occurs in up to 25% of women after the procedure or may be exacerbated if it already exists. Adjustment of proper sling tension requires considerable operator experience. Prosthetic materials such as Marlex are to be avoided because of the significant incidence of erosion. An increase in urethral pressure in the area of the urethra adjacent to the sling of 10 cm H_2O has given consistently good postoperative results.

In an effort to further reduce morbidity and discomfort, a tension-free vaginal tape procedure has been developed (Fig. 26B.35). Three-year data from more than 100 women reveal a dry rate of 86% to 90% (420). Anecdotal reports of bladder perforation, hemorrhage, and even one death in Europe will be clarified once long-term prospective studies are performed.

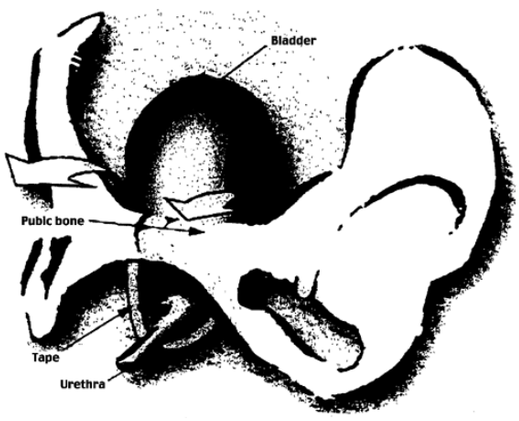

FIGURE 26B.35. Placement of Prolene tape. Observe that the tape is loosely located around the midurethra. (From Ulmsten U, Johnson P, Rezapour M. A three year follow up of tension free tape for the surgical treatment of female stress urinary incontinence. *Br J Obstet Gynecol* 1999;106:345, with permission.)

Artificial Urinary Sphincter

Control of sphincteric urinary incontinence with implantable prosthetic devices has improved. The most significant contribution was the introduction in 1973 of a totally implantable artificial sphincter mechanism that could be used in adults and children of both sexes (505). Through biomechanical evolution, improvements have led to the currently used device, which is composed of an inflatable

snap-on cuff, a pressure–balloon reservoir, and a control assembly (Fig. 26B.36). Constructed of silicone rubber, this hydraulic device is filled with normal saline or an iso-osmotic contrast medium. Cuff closing pressure is regulated by the elasticity in the wall of the balloon and is partially dependent on the volume of fluid within the balloon. Fluid flow through the system is mediated by the pump and a series of unidirectional valves within the control assembly. On the side of the control assembly is a small button that allows manual activation and deactivation of the sphincter mechanism. Balloon pressures are manufactured that, under normal clinical situations, provide enough cuff closing pressure to ensure urinary continence, but do not damage the underlying tissue of the urethra or bladder neck.

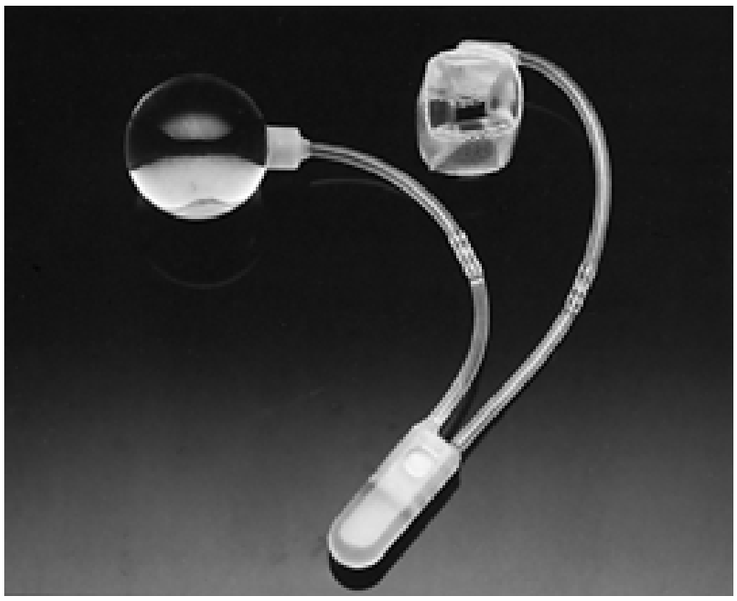

FIGURE 26B.36. AS 800 artifical sphincter mechanism.

Excessive pressure produces tissue ischemia and ultimately pressure necrosis, with erosion of the cuff into the lumen of the underlying urethra or bladder neck. This

generally is manifested by recurrent incontinence and concurrent infection around the implanted sphincter. Device removal is required for adequate healing; however, another device may be implanted later.

Identification of candidates for artificial sphincter implantation requires a thorough neurourologic workup to properly establish the unique aspects of the patient's incontinence. Specific criteria for implantation have been established (214,352), with most patients having intrinsic sphincter deficiency with normal detrusor contractility and compliance. Usual candidates are men with incontinence related to radical prostatectomy or transurethral resection of the prostate, and neurogenic causes such as myelomeningocele or previous pelvic trauma; and females.

Surgical implantation of the device involves implantation of the cuff around the bulbous urethra of adult males (Fig. 26B.37). Bladder neck cuff placement may be technically challenging in patients with previous bladder neck or pelvic surgery. The pressure-balloon reservoir is placed in a pocket underneath the fascia of the anterior abdominal wall, or in the peritoneal cavity if extensive scarring is present. The pump control assembly is positioned in a convenient location in the subcutaneous tissues of the scrotum or labia.

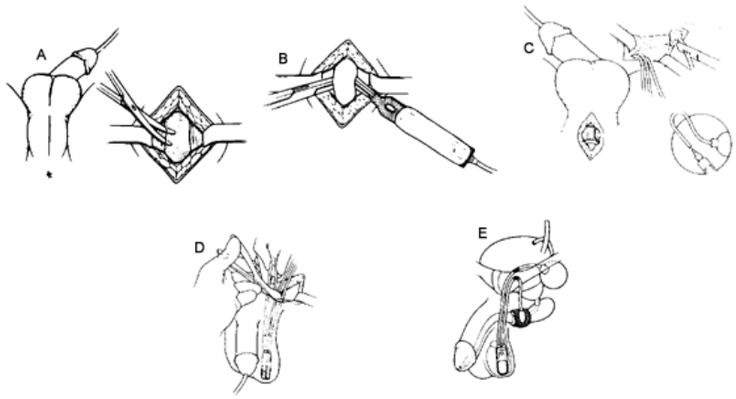

FIGURE 26B.37. A–E: Implantation of the artificial sphincter cuff around the bulbous urethra.

The device remains in a deactivated configuration for 6 to 8 weeks to allow complete healing around the pump and cuff. Device activation is performed manually by merely compressing the pump chamber firmly. The device may be deactivated by pressing the button on the side of the control assembly.

Results of implantation on 221 patients with the AS-800 device who had follow-up for up to 3 years indicated that 95% of the patients were socially dry. The patient must have

realistic expectations of this device. Significant rises in intraabdominal pressure will trigger leakage during vigorous exercise or lifting. The more incontinent the patient, the more satisfactory the outcome. Mechanical reliability based on life-table analysis projects a 97% survivorship at 3 years. Although initial results appear reasonable, long-term results will help establish more accurately the exact role of the artificial sphincter in treating severe incontinence. An algorithm for testing a nonfunctioning artificial sphincter is presented in Fig. 26B.38 . Overall, reoperation rate approaches 30%. Placement of a more distal second cuff may be needed if incontinence recurs. In the long term, problems with fibrosis underneath the cuff causing a recurrence in incontinence have necessitated double cuff revisions in some patients. If the patient lives long enough, the device will undoubtedly have to be replaced some years after implantation.

Use of the artificial urinary sphincter (AUS) following external beam radiotherapy is associated with a high reoperation rate approaching 55%.

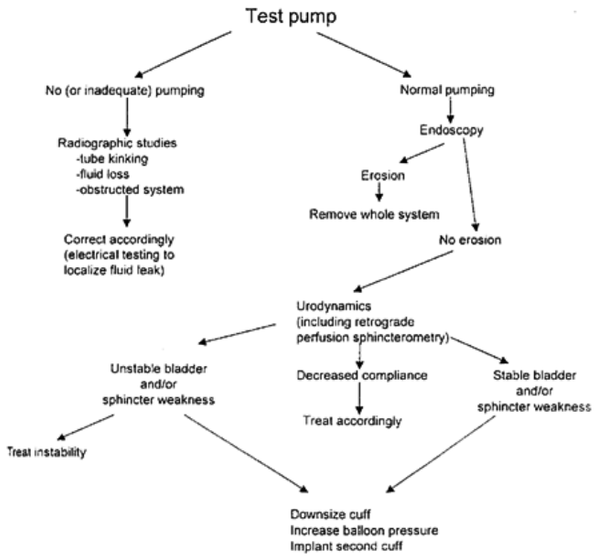

FIGURE 26B.38. Algorithm for the investigation and treatment of problems with the AUS. Evaluation starts with testing the pump. (Courtesy of Dr. Erik Schick.)

Nonsurgical occlusive devices for the male are external and compress the penile urethra by squeezing the penis from two sides. Their main disadvantages include bulk, discomfort (in those with sensation), and potentially, pressure necrosis of the urethra, especially in those patients with impaired sensation.

Urethral compression is feasible only in patients with low-pressure bladders. Although any pressure system can theoretically be occluded, continued obstruction of a high-pressure system can result in disastrous lower and upper urinary tract sequelae.

Antidiuretic Hormone–like Agents

A novel approach to the treatment of urinary frequency occurring within a specific period of time has been the use of synthetic antidiuretic hormone (vasopressin) analogues. Desmopressin acetate (DDAVP) has been used effectively in patients with central diabetes insipidus. For diabetes insipidus, the usual adult dosage is 2 to 4 μmg subcutaneously daily as a single or divided dose. For children, the usual dosage range is from 0.5 to 3.0 μmg daily. Large doses may cause transient headaches, nausea, and a slight increase in blood pressure. Fluid intake should be adjusted during this therapy to avoid hyponatremia and water intoxication.

The drug has been used to decrease the frequency of nocturnal enuresis (Table 26B.18). Hilton and Stanton (246) used a nighttime dose of 20 μmg intranasally in a double-blind placebo study of 25 women with nocturnal urinary frequency. The number of mean episodes per night decreased from 3.17 in the pretreatment group to 1.94 in the group treated with active drug, compared with 2.61 in the placebo-treated group. The nocturnal urinary output, as expected, also decreased significantly in the drug-treated group. One patient already receiving treatment for hypertension with a diuretic became hypertensive, with a diastolic pressure of 110 mm Hg (entrance pressure was 80 mm Hg). The authors emphasize that hypertension, ischemic heart disease, and congestive failure should all be considered contraindications to the use of this type of medication. A double-blind, placebo-controlled study was also performed in a group of 21 males with benign prostatic hypertrophy and significant nocturia (350). Active treatment consisted of 20 mg of drug administered intranasally. This produced a mean decrease in nocturia from 2.60 episodes during the control period to 1.93, statistically significantly better than the response to placebo (2.31) but hardly a significant clinical change.

TABLE 26B.18. DESMOPRESSIN FOR NOCTURNAL ENURESIS

Author	No. of Patients	Age (yr)	Dose DDVAP (μg)	Success
Tuvemo	18	6–12	20	89
Delaere	23	7–43	20	68
Terho	52	5–13	20	67
Miller	55	6–17	40	65
Ramsden	21	18–older	20	76

Rittig and associates (471) and Djurhuus and co-workers (138) demonstrated an abnormal diurnal variation of vasopressin and suggest this mechanism as a cause for enuresis. Although it explains increased nightly output, this hypothesis fails to explain why individuals with enuresis fail to awaken and void. A large number of placebo-controlled clinical trials using desmopressin have been reported (Table 26B.18). Success rates range from 68% to 89% in a usual daily dose of 20 μmg. An oral preparation of DDAVP has been released. Efficacy is only slightly lower due to somewhat reduced bioavailability. These studies are remarkable for the lack of adverse effects reported. The major limitation is the cost of the desmopressin regimen. However, care must be taken in the elderly, who are prone to hyponatremia and confusion. If hyponatremia is to occur, it appears very soon after initiation of therapy. Thus serum sodiums are recommended 24 hours after the first dose, several days later, and then at 2 weeks. If used for nocturia, an attempt should be made to determine the cause before initiation of drug therapy. Medications, sleep apnea, and fluid consumption are common culprits (267). Desmopressin has even been evaluated in men with symptoms of BPH (350).

Vasopressin has also been successful in treating urgency and incontinence in patients with multiple sclerosis (284). Overall results with this type of agent in patients other than those with central diabetes insipidus enuresis and detrusor hyperreflexia seem more statistically than clinically significant. However, this class of treatment may prove to be useful on a long-term basis in the occasional case of nocturia or enuresis that has proved refractory to all other forms of therapy, or in short-term situations in which a decrease in intravesical volume and consequent urinary frequency is desired for a limited period of time.

External Collection Devices

No satisfactory external collecting device has been devised for the female because of the difficulties of fixation and leakproof collection. Absorptive padding, a collection device of sorts, is a last resort for many patients. The ideal substance is one that is highly permeable and absorbent. Immediately next to the patient is generally a layer of hydrophobic material.

External collecting devices for the male (Texas or condom catheter) are generally successful insofar as urine collection is concerned, but are unacceptable to many patients because of the visible equipment required, the incontinence,

and the “leaks” of often foul-smelling urine that can result. Some of these leaks can be prevented by using self-ventilating systems that prevent siphoning (124). Compressive collective devices can also cause severe pressure necrosis of the penis and urethrocutaneous fistula, especially in patients with impaired sensation (217). For this reason, a collecting device without a single discrete roller band or application ring would seem to offer at least a theoretic advantage. Newer silicone devices with better seals and internal tissue adhesive are available that are better tolerated.

Assessing Outcomes

One of the greatest difficulties in the management of patients with voiding dysfunction is comparing treatments and assessing outcomes. In this regard, experts have proposed various parameters to measure and report when evaluating treatment modalities based on disorder, sex, and age of the patient (177,336,359,412). Measurements should include symptom scores, diaries, pads, urodynamic tests, and quality-of-life instruments. If experts could validate and combine questionnaires, diary forms, and quality-of-life assessments for neurogenic bladder patients, men and women with voiding complaints, incontinent patients of both sexes, children, and the elderly, better studies of therapeutic efficacy with cross comparisons could be designed.

VOIDING DYSFUNCTION AND NEUROLOGIC DISEASE

The bladder is the only visceral organ that requires central neural input for total function and survival of the individual. Thus it is not surprising that many neurologic lesions generally affect bladder filling, urine storage, and bladder emptying in a relatively consistent fashion, dependent on the area affected (Table 26B.19). Neurologic lesions anywhere along the neuraxis can result in involuntary bladder contractions, with changes in the smooth-sphincter and striated-sphincter areas analogous to those that occur in normal micturition (185). Patients with complete lesions of the spinal cord above spinal cord level S-2, after they recover from spinal shock, generally exhibit involuntary bladder contraction with smooth-sphincter synergia but striated-sphincter dyssynergia. Patients with spinal cord trauma caudal to that level generally do not manifest involuntary bladder contractions per se. Detrusor areflexia is the rule initially, and depending on the extent of neurologic injury, various forms of decreased compliance during filling may occur. Damage to the neurologic outflow from the lower thoracic and upper lumbar levels may result in an open smooth-sphincter area, whereas the area of the striated sphincter generally retains a residual resting sphincter tone but is not under voluntary control. Discrete lesions of the spinal cord often elicit involuntary bladder contractions with variable degrees of striated-sphincter dyssynergia or synergia, depending on the severity of the disease and the intactness of the cortical and pontine-mesencephalic regulatory tracts (Fig. 26B.39). In this section, the most common types of voiding dysfunction that occur with specific neurologic diseases or trauma are discussed. Throughout this discussion, it becomes apparent that the lower urinary tract can serve as a window to the nervous system.

TABLE 26B.19. URODYNAMIC FINDINGS WITH SELECTED NEUROLOGIC DISORDERS

Disorder	Common Urodynamic Diagnosis
Suprapontine Lesions	
Cerebral aneurysm	DH
Brain abscess	DH
Olivopontocerebellar degeneration	DH
Multiple system atrophy	DH, DA, ISD
Parkinson's disease (striatonigral form of multiple system atrophy)	DHIC
Senile dementias	DH
Cerebral palsy	DH
Cerebrovascular disease	DH, DA
Cerebellar ataxia	DH
Bilateral lesions of putamen	DH, DA
Normal pressure hydrocephalus	DH, DA
Huntington's chorea	DH
Hereditary ataxias	DH
Shy-Drager (also spinal)	DA, ISD
Spinal Lesions	
Multiple sclerosis	DH, DA, DSD
Syringomyelia	DH, DSD
Herniated disc (cervical, thoracic)	DH, DSD
Herniated disc (lumbosacral)	DA, DH
Hereditary spastic paraparesis	DH
Tropical spastic paraparesis	DH
Myelomeningocele	DA, DH, DSD, ISD
Anterior spinal artery syndrome	DH, DA with nl sensation
Sacral agenesis	DA, ISD
Tethered cord syndrome	DH, DA
Transverse myelitis	DH, DA, DSD
Mucopolysaccharidoses (including Hunter's syndrome)	DH
Lyme disease	DH
Congenital sensory neuropathy	DA without sensation
Neurosyphylis	DA without sensation
Guillain Barré syndrome	DA, DH, ± sensation
Poliomyelitis	DA, DHIC
Tumor	DH, DA
AIDS	DH
Cauda Equina/Peripheral Neuropathies	
Sacrococcygeal teratoma	
Caudal regression syndromes	DH, DA
Imperforate anus	DA, ISD
Diabetic neuropathy	DH (early), DA without sensation (late)
Alcoholic neuropathy	DH, DA ± sensation
Uremic neuropathy	DH
Polyarteritis nodosa	DH
Porphyria	DH
Vital neuropathies (herpes zoster, simplex, Epstein-Barr, adenovirus, coxsackie)	DA ± sensation
Vitamin B_{12} deficiency	DA without sensation
Systemic lupus erythematosus	DH

DA, detrusor areflexia; DH, detrusor hyperreflexia; DSD, detrusor-sphincter dyssynergia; ISD, intrinsic sphincter deficiency.

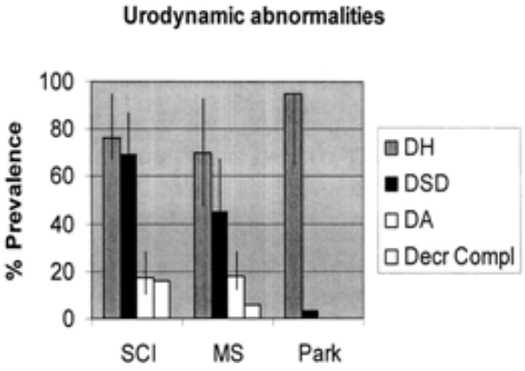

FIGURE 26B.39. Examples of urodynamic abnormalities and prevalence among selected groups of neurogenic bladder patients based on several recent urodynamic reports. DA, detrusor areflexia; DH, detrusor hyperreflexia; DSD, detrusor-sphincter dyssynergia; MS, multiple sclerosis; PARK, Parkinson's disease; SCI, spinal cord injury.

At or Above the Brainstem (Supraspinal)

Cerebrovascular Disease

Transient ischemia associated with cerebrovascular disease has not been associated with any particular type of bladder dysfunction, but after an occlusive or a hemorrhagic episode of a cerebral vessel, focal neurologic deficits often occur, and voiding dysfunction of a particular type may result (571,631). Bladder symptoms are present during the acute phase in 70% of individuals, but are persistent in only 10% of victims. During the first weeks and months, the symptoms of bladder dysfunction may become apparent. The most common long-term expression of lower urinary tract dysfunction after cerebrovascular accident is detrusor hyperreflexia. Sensation is variable but generally intact, and thus the patient has urgency. An ice water test is positive in 63% of patients (258). The appropriate response is to try to inhibit the involuntary bladder contraction by forceful contraction of the striated sphincter. Gelker and associates (198) evaluated 51 patients undergoing rehabilitation after a stroke and found that 37% had urinary incontinence. Urodynamics evaluation revealed that 37% had detrusor hyperreflexia and 21% had areflexia. Incontinence in these stroke victims correlated with large infarcts, aphasia, cognitive impairment, and functional disability, not with age or site of lesion.

Sakakibara and co-workers (490) reported on 72 stroke victims assessed at 3 months. Fifty-three percent had urinary symptoms, most notably nocturia (36%), urge incontinence (29%), and hesitancy (25%). Six percent presented following stroke in urinary retention. Voiding dysfunction correlated with hemiparesis but not hemianopia. Sixty-eight percent of symptomatic victims exhibited detrusor hyperreflexia on urodynamics, and 14% had detrusor-sphincter dyssynergia.

Concussion

Generally, when voiding dysfunction occurs after a closed head injury or spinal cord contusion, there is an initial period of detrusor areflexia followed by recovery of unstable reflex detrusor dysfunction. This is not a common sequela of cerebral concussion, but when it occurs, the same considerations apply as for voiding dysfunction secondary to cerebrovascular disease.

Brain Tumor

Both primary and metastatic brain tumors have been reported to be associated with disturbed bladder function. The most commonly involved area that results in bladder dysfunction is the superior aspect of the frontal lobe (55). Resultant voiding dysfunction consists of detrusor hyperreflexia and urinary incontinence without dyssynergia.

Parkinson's Disease

Parkinson's disease primarily affects the pigmented neurons of the substantia nigra. This results in a relative dopamine deficiency and a predominance of cholinergic activity in the corpus striatum. Dopaminergic projections to the prefrontal cortex synapse may inhibit micturition. The net result of loss of dopaminergic input is tremor in motor systems and detrusor hyperreflexia expressed by the bladder. Classic neurologic symptoms include bradykinesia, tremor, and skeletal rigidity. Voiding dysfunction occurs in 25% to 75% of patients, but as with cerebrovascular disease, there may be preexisting detrusor or outlet abnormalities, and the symptoms may be affected by the various treatments that are instituted (578).

Symptoms generally consist of urgency, frequency, nocturia, and urge incontinence. The most common urodynamic correlate is detrusor hyperreflexia (46,434). Dopamine agonists (L-dopa and apomorphine) improved voiding by reducing detrusor hyperreflexia (21). In primates with experimental parkinsonian condition, dopamine agonists similarly increased volume of the micturition and reduced hyperactive voiding (630). True striated-sphincter dyssynergia with detrusor hyperreflexia does not occur, but it is less clear whether these patients retain voluntary striated-sphincter control (55,523) (Fig. 26B.40). Slow relaxation of the striated sphincter may occur (bradykinesia). Araki and Kuno (20) found that symptoms in 203 Parkinson's patients correlated with disease severity rather than disease duration. Their incidence of symptoms based on questionnaires in a neurology clinic was 27%, substantially lower than previous reports from urology clinics. The IPSS in patients correlated with a Hoehr and Yahr staging of Parkinson's disease severity. Urinary symptoms rose and quality of life fell with a score of 3 or higher. No correlation was observed between symptoms and whether patients were receiving anticholinergics and dopamine receptor agonists.

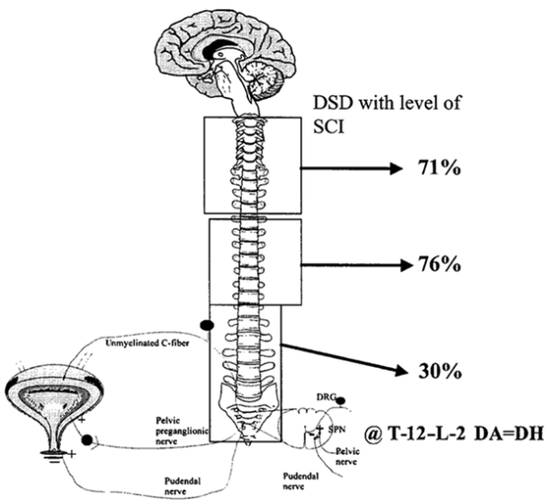

FIGURE 26B.40. The prevalence of detrusor-sphincter dyssynergia *(DSD)* with level of injury in spinal cord injury *(SCI)*. DA, detrusor areflexia; DH, detrusor hyperreflexia.

One dilemma in dealing with parkinsonian men is deciding if they have outlet obstruction secondary to prostatic enlargement, and whether prostatectomy is indicated. Men with Parkinson's disease and symptoms, and urodynamic findings identical to those with BPH, do not respond to prostatectomy. Even combined pressure/flow studies are not predictive of outcome after surgery in these patients. Poorly sustained bladder contractions, sometimes with slow sphincter relaxation, may occur as a result of the neurologic disease, and in these individuals prostatectomy may result in no change or even worsening of the voiding symptoms. Thus many experts wonder whether any men with Parkinson's disease should ever undergo surgery for obstruction. Acontractile bladders are unusual in Parkinson's disease and are generally seen only in women, in which case the situation is probably representative of a preexistent problem and unrelated to the Parkinson's disease per se.

Shy-Drager Syndrome

Shy-Drager syndrome is an uncommon degenerative disorder that results in atrophy of areas in the cerebellum, brainstem, peripheral autonomic ganglia, and thoracolumbar preganglionic sympathetic neurons (46,55). Patients generally have parkinsonian symptoms coupled with orthostatic hypotension and anhidrosis. Voiding dysfunction similar to Parkinson's disease consists of detrusor hyperreflexia (67%). Unlike with Parkinson's disease, a bladder neck that is open at rest (100%) and denervation of the striated sphincter (61%) also occur. Areflexia or poorly sustained bladder contractions may develop, however. Combined with diminished smooth- and striated-sphincter tone, management of the voiding dysfunction may be quite difficult.

Spinal Cord Lesions

Suprasacral Spinal Cord Lesions

Only recently have bladder overactivity and pyramidal signs been reported with cervical myelopathy (486,487). Syringomyelia, a benign condition once causing neurologic symptoms, is associated with voiding difficulties, especially retention (489).

Traumatic spinal cord injury results from a high-velocity missile, from fracture or fracture dislocation of the spinal column, or after sudden or severe hyperextension. Spinal cord bony segments are numbered by the vertebral level, and these have a differing relation to spinal cord segmental level at various locations. The sacral spinal cord begins at about the spinal column level of T-12 to L-1. The spinal cord terminates in the cauda equina at the spinal column level of approximately L-2. In addition to trauma, spinal cord damage may be produced by vascular disease, arteriovenous malformations, myelopathy, arachnoiditis, or myelitis.

Over the past 30 years, the survival of patients with spinal cord injuries has dramatically improved. This has resulted from the development of specialized centers for the care of such patients, resulting in a decreased number of potentially significant complications of all types. Urologic care and urologic surveillance have undergone decided improvements. Renal failure has been replaced by pulmonary problems as the most common late causes of death, at least in male patients. Amyloid disease of the kidneys may cause death, and bladder and outlet dysfunction and urinary tract infection with urosepsis are still substantial problems. Controlled and coordinated bladder emptying depends on an intact neural axis. Bladder contractility and the occurrence of reflex bladder contractions depend on an intact conus medullaris (sacral spinal cord segments) and its afferent and efferent connections. Complete lesions above this area but below the area of the sympathetic outflow generally result in detrusor hyperreflexia, absent sensation below the level of the lesion, smooth-sphincter synergia, and striated-sphincter dyssynergia. Lesions above the spinal column level of T-6 (spinal cord level of T-7 or T-8) may result in smooth sphincter dyssynergia as well. After a significant spinal cord injury, “spinal shock” occurs. This refers to a decreased excitability of spinal cord segments below the level of the lesion (235,367). This is synonymous with absent somatic reflex activity and a state of flaccid muscle paralysis below this level. Although classic teaching refers to generalized areflexia, most peripheral somatic reflexes of the sacral cord segments (the anal and bulbocavernosus reflexes) may never disappear or, if they do, return within minutes or hours of the injury. Spinal shock includes a suppression of autonomic activity, and the bladder is acontractile and areflexic. The smooth-sphincter mechanism generally functions, however, and EMG activity can generally be recorded from the striated sphincter (269). Because sphincter tone exists, urinary incontinence does not result, urinary retention is the rule, and intermittent catheterization (or continuous catheterization in some instances) is necessary to circumvent this problem. If the distal spinal cord is intact but simply isolated from higher centers, there will eventually be a return of detrusor contractility. At first, such reflex

activity is poorly sustained and produces only low-pressure changes, but the strength and duration of such involuntary contractions increases, producing involuntary voiding, usually with incomplete bladder emptying. The return of reflex bladder activity in such patients is generally manifested by involuntary voiding between intermittent catheterizations, and occurs along with recovery of lower-extremity deep tendon reflexes. In evolving lesions, every attempt should be made to preserve bladder pressure storage as low as possible, often by the combination of intermittent self-catheterization and anticholinergic therapy (375). Any measures that might impair this, such as indwelling catheter drainage, are to be avoided. Surgery designed to decrease outlet resistance can be useful.

The urodynamic picture that results when a patient has a complete lesion above the sacral spinal cord is detrusor hyperreflexia, smooth-sphincter synergia (with lesions below T-6), and striated-sphincter dyssynergia. Neurologic examination shows spasticity of skeletal muscle distal to the lesion, hyperreflexic deep tendon reflexes, and extensor plantar responses. There is impairment of superficial and deep sensation. Incomplete bladder emptying generally results, usually because of striated-sphincter dyssynergia. The neurologic center responsible for coordinating bladder and striated-sphincter activity is in the pontine-mesencephalic formation (68,69,121,223,490,491). Any lesion between this area and the sacral spinal cord can interfere with this coordination. True dyssynergia, either continuous or intermittent, often develops, but in some instances there is simply a failure of relaxation without an increase in sphincter activity over baseline. In one study, only 6% (*n* = 34) of spinal cord–injured patients did not have dyssynergia.

Occasionally, incomplete bladder emptying may result from poorly sustained detrusor contractions. This seems to occur more commonly in lesions close to the conus medullaris than with more rostral lesions (235). Poorly sustained contractions may also be caused by locally functioning reflex arcs, which result in detrusor inhibition from strong striated pelvic floor muscle contractions, or result from a loss of higher center–mediated detrusor facilitation, which normally occurs after the initial increase in intravesical pressure during a bladder contraction.

Sacral Spinal Cord Lesions

After recovery from spinal shock, there is usually a depression of deep tendon reflexes below the level of the lesion, with varying degrees of flaccid paralysis. Sensation is absent below the level of the lesion. Detrusor areflexia is common initially and accompanied by a competent but nonrelaxing smooth sphincter. The striated sphincter retains some tone, although it is not under voluntary control. Absent or diminished EMG activity is seen. The bulbocavernosus reflex may be retained and is the first reflex to return with recovery from spinal shock (221,232,269,326). Although the classic description of this problem is that of an adequate-capacity bladder with high compliance, in many instances decreased compliance develops. As with other neurologic lesions distal to the sacral spinal cord (200,232), this represents a response to decentralization. At a point at which bladder pressure becomes greater than urethral pressure, leakage results, and if this leak-point (detrusor leak-point pressure) is high enough, upper tract deterioration may occur. It is not uncommon for incomplete lesions to result at this level or for various degrees of reorganization to develop. Thus varying degrees of bladder and sphincter dysfunctions or combinations thereof are seen.

Attempts to correlate completeness of lesion or level with upper tract deterioration are contradictory. Hackler and colleagues (232) found that patients with lower motor lesion were more likely to have poorly compliant bladders. Conversely, Gerridzen and associates (200) found that quadriplegics were more likely to have upper tract deterioration. Kaplan and associates (269) have warned that neurologic findings do not uniformly correlate with deteriorating renal function. Grainger and co-workers (221) found that women with spinal cord injury rarely had upper tract deterioration without infection. They also found that more of the women developed autonomic dysreflexia. Weld and co-workers (610), using a logistic regression analysis on 316 spinal cord–injured patients, found that incomplete and sacral lesions were associated with poor bladder compliance, which in turn correlated with reflux, pyelonephritis, and calculi. Older age at injury and use of a Foley catheter also correlated with poor compliance. Therefore neurourologic evaluation should help characterize each of these patients, and management modalities must be consistent with the goals and practicalities previously mentioned. Assigning risk of hydronephrosis merely to physical examination, level of lesion, or urodynamics exclusively cannot be done consistently. Thus vigilant follow-up is mandatory.

Multiple Sclerosis

Multiple sclerosis is one of the most common neurologic diseases causing voiding dysfunction (47,56,184,356,398,513). The disease is caused by focal neural demyelination, which impairs nerve conduction. It affects the spinal cord in nearly 75% of patients (Fig. 26B.41). The demyelinating process characteristically involves the posterior and lateral columns of the cervical spinal cord, which is the site of pathways that subserve bladder and outlet function. From 50% to 88% of patients with this disease complain of voiding symptoms at some time (39). Bladder involvement is part of the presenting symptom complex in approximately 10% of patients and may constitute the sole initial complaint, either in the form of acute urinary retention of an unknown cause, or in the acute onset of involuntary bladder contractions with urgency and frequency. Detrusor hyperreflexia

is the most common urodynamic abnormality detected and occurs in 50% to 90% of cases (39,47,56,513). Of patients with detrusor hyperreflexia, 30% to 65% also have striated-sphincter dyssynergia. Bladder areflexia may also occur and has been reported in 1% to 40% of cases, but of these, a substantial proportion progress to detrusor hyperreflexia. Smooth-sphincter synergia is the rule.

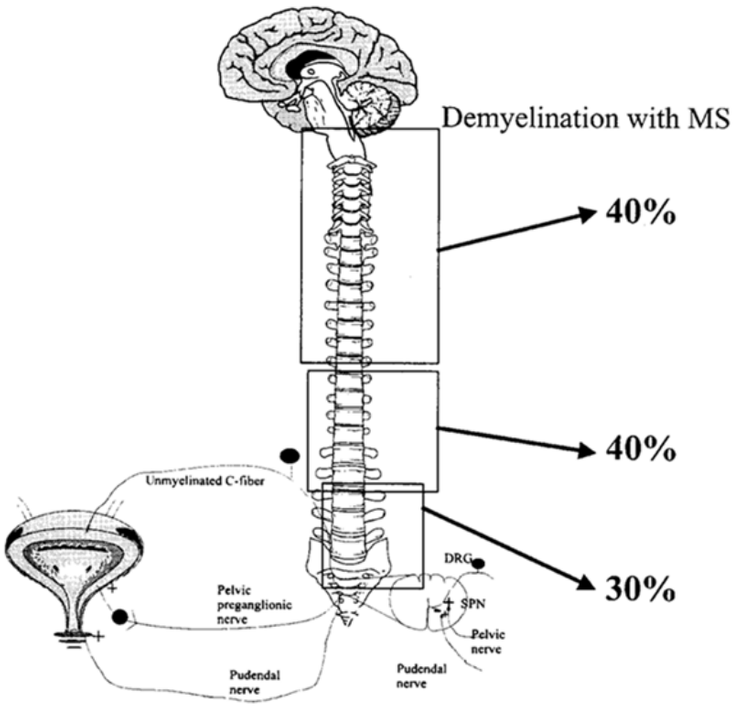

FIGURE 26B.41. Level of spinal involvement with multiple sclerosis *(MS)*.

Blaivas and Barbalias (57) have identified certain risk factors for voiding dysfunction in patients with multiple sclerosis. These include an indwelling catheter, detrusor striated-sphincter dyssynergia in men, and decreased compliance, resulting in sustained intravesical pressures greater than 40 cm H_2O. Betts and co-workers (47) found that severity of voiding complaints correlated with exacerbation of neurologic symptoms. Because sensation is frequently intact, one must be careful to separate pseudodyssynergia from true striated-sphincter dyssynergia. Also, there are some varieties of striated-sphincter dyssynergia that are more worrisome than others (65). For example, sustained DSD results in high bladder pressures of long duration that are most associated with urologic complications. Betts and colleagues (47) found that only men with multiple sclerosis and chronic paraplegic men (longer than 5 years) developed dyssynergia and upper tract changes. Sirls and associates (513) noted that medical management alone is nearly always effective in preventing upper tract deterioration. Fortunately, unlike spinal cord injury, progressive neurologic conditions such as multiple sclerosis rarely cause renal deterioration due to detrusor-sphincter dyssynergia unless an indwelling catheter is used in management. The reason for this disparity is unknown.

Peripheral Nerve Lesions

Diabetes Mellitus

Peripheral and autonomic neuropathies are common in diabetes. Diabetic neuropathy has been attributed to segmental demyelinization and impairment of nerve conduction (269). Neuropathy tends to develop in middle-aged and elderly patients with long-standing or poorly controlled diabetes (478). Surprisingly, few large, well-documented studies of voiding dysfunction in diabetics have been published. The exact incidence of diabetic cytopathy is uncertain, because unselected patients generally do not complain of bladder symptoms. If specifically questioned, 5% to 50% report symptoms of voiding dysfunction. Frimodt-Moller (190,191) coined the term *diabetic cystopathy* to refer to involvement of the lower urinary tract in this disease. The insidious onset of impaired bladder sensation can be the first manifestation of such involvement. Likewise, in early diabetic neuropathy, detrusor hyperreflexia can develop (7). A gradual increase in the time interval between voiding then develops, which may progress to a point at which the patient urinates only once or twice a day without ever sensing any urgency. Ultimately, bladder decompensation may occur

due to impaired detrusor contractility, which necessitates abdominal straining to initiate and maintain the voided stream, the strength and force of which are impaired.

Typical urodynamic findings include impaired bladder sensation, increased cystometric capacity, decreased bladder contractility, impaired uroflow, and residual urine (41). Yet these findings are surprisingly uncommon even in patients undergoing renal or pancreatic transplantation (41,537). Norden and co-workers (408) found that of 27 patients with diabetic nephropathy who were followed for over 30 months, only 7% had residual urine. Furthermore, presumed diabetic autonomic dysfunction failed to correlate with progression of renal insufficiency. Interestingly, diabetic men tend not to undergo as many prostatectomies for BPH, possibly because of impaired sensation, and in turn, lack of irritative voiding symptoms (511). The main differential diagnosis is outlet obstruction, because both conditions can produce a low flow rate. The flow pattern in diabetics reflects abdominal straining. Pressure/flow studies are easily able to differentiate the two conditions. The secondary manifestations of resultant bladder decompensation are seen and may be prevented by early awareness of the problem and the institution of strictly timed voiding.

Guillain-Barré Syndrome

Guillain-Barré syndrome is an immune-mediated peripheral neuropathy. It elicits voiding difficulties—both detrusor hyperreflexia and areflexia—in nearly one-fourth of patients (492). Bladder symptoms appear after the weakness is established.

Tabes Dorsalis (Neurosyphilis)

Luetic involvement of the posterior sacral roots and the dorsal columns of the spinal cord may result in the loss of bladder sensation and resultant voiding dysfunction (162). Although rare in the postpenicillin era, tertiary syphilis is classically associated with detrusor areflexia with decreased or absent bladder sensation. Garber and associates (194) have demonstrated not only detrusor hyperreflexia, but detrusor-sphincter dyssynergia that was attributed to suprasacral involvement with neurosyphilis. Pernicious anemia (vitamin B_{12} deficiency) may also result in a similar type of "sensory neurogenic bladder" (251).

Viral Infections

An assortment of viral disorders can trigger voiding dysfunction, including herpes simplex genitalia (469), herpes zoster (261), herpes varicella (404), Epstein-Barr virus (524), cytomegalovirus (381), human T-lymphotropic virus (HTLV-1) (590), and HIV (275). Bladder symptoms appear days to weeks after the primary viral manifestations of flulike symptoms, arthralgia, fever, and cutaneous lesions. Herpes infections, when associated with cutaneous lesions in the sacral dermatomes, are most commonly found with urinary retention secondary to detrusor areflexia from involvement of sacral dorsal root ganglia. These viruses appear in the urine and can be taken up by nerves in the bladder wall and anterogradely transported to the sacral cord.

Transverse myelitis, even causing quadriplegia, is often associated with complete neurologic recovery; yet urinary symptoms may be the only residual sequelae (488).

Endoscopic examination in a patient with herpes zoster may reveal a similar type of vesicles within the bladder mucosa. This condition is usually self-limited and resolves spontaneously within a month or two. Tropical spastic paraparesis (HTLV-1) represents a somewhat unique viral cause of neurogenic bladder in which most patients have detrusor-sphincter dyssynergia (590). Dasgupta and colleagues (114) found thickening of nerves in the lamina propria of the bladder in this disease. Nearly 60% of patients with this rare disorder have urinary complaints.

Disc Disease

Most disc protrusions compress the spinal roots in the L-4 to L-5 or L-5 to S-1 disc interspaces. Voiding dysfunction due to a prolapsed or herniated disc correlates with the usual clinical manifestations of low back pain radiating in a girdlelike fashion along the involved spinal root areas (244,363). The most consistent urodynamic finding is detrusor areflexia. However, a herniated disc may initially irritate nerve roots and cause detrusor hyperreflexia. The striated sphincter may be normal or show evidence of denervation. In patients with cervical myelopathy due to disc disease or spondylosis, detrusor-sphincter dyssynergia has been reported (241). Patients with voiding dysfunction from a disc typically have difficulty urinating, straining, or urinary retention. Laminectomy may not improve bladder function, and it may be difficult to separate causation as a result of the disc sequelae from changes secondary to the surgery. In a prospective assessment of bladder function after lumbar decompressive laminectomy for disc or spinal stenosis in an elderly group of 20 patients, Deen and co-workers (118) reported improved bladder function in 60% by 1 year. In experimental work in animals, Delamarter and colleagues (127) found that a 75% constriction of the cauda equina was required before a flaccid neurogenic bladder developed.

Pelvic Surgery

Voiding dysfunction is relatively common after pelvic plexus injury. This often arises after abdominoperineal resection and radical hysterectomy (167,192,514). Neurologic dysfunction after these procedures is reported in 10% to 60% of patients, and voiding dysfunction is permanent in 15% to 20% (363,366). The type of voiding dysfunction

that occurs is dependent on the specific nerves involved, degree of injury, and the pattern of reinnervation or altered innervation that results over time. Urinary retention, with varying degrees of sensory preservation, is generally the initial manifestation of such voiding dysfunction. The permanent pattern is generally a failure of voluntary bladder contraction, or impaired bladder contractility, with obstruction by residual striated-sphincteric tone, which is not subject to voluntarily induced relaxation. Often, the smooth-sphincter area is open and nonfunctional, attributed to destruction of the terminal sympathetic nerve supply to this area. Alternatively, such an appearance in a patient whose bladder neck has not been operated on may result from increased intravesical pressure and obstruction at the level of the striated sphincter. Decreased compliance is common, and with the obstruction caused by fixed residual striated-sphincter tone is the paradoxic occurrence of both storage and emptying failure. These patients often leak across the distal sphincter area and, in addition, are unable to empty their bladder because, although they have increased intravesical pressure, they have nothing that approximates a true bladder contraction. Thus they represent a combined problem of filling or storage and emptying. They often have urinary incontinence with increases in intraabdominal pressure. This is usually most obvious in females, because the prostatic bulk in males often masks a deficit in urethral closure function. Alternatively, patients may have variable degrees of urinary retention. Urodynamic studies may show decreased compliance, poor proximal urethral closure function, loss of voluntary control of the striated sphincter, and a positive bethanechol supersensitivity test (514). Upper tract risk factors are related to the leak-point, and the therapeutic goal is low-pressure bladder storage with periodic emptying. A prostatectomy should not be performed unless a clear demonstration of outlet obstruction is possible (363). Prostatectomy will often simply decrease urethral sphincteric function and thereby result in occurrence or worsening of stress urinary incontinence.

OTHER NEUROLOGIC CAUSES OF VOIDING DYSFUNCTION

A wide array of central and peripheral neurologic disorders have been associated with failure to store or empty urine. Many supraspinal disorders, including normal pressure hydrocephalus (4) and cerebellar ataxia (311), can cause detrusor hyperreflexia and urge incontinence. Similarly, urodynamic evaluations in other neurodegenerative disorders and para-autonomic failure have revealed detrusor hyperreflexia or, rarely, areflexia (243,493).

Inherited disorders such as familial spastic paraparesis and congenital type II neuropathy cause voiding dysfunction. The disorder is associated with inability to relax the external urethral sphincter and detrusor hyperreflexia (82). The latter is associated with loss of bladder sensation (29). Of interest, the receptor for nerve growth factor is abnormal, resulting in loss of sensory nerves.

Disorders causing vasculitis or inflammation of the bladder or its innervation can also disturb micturition. Lyme disease (95), periarteritis nodosa (10), systemic lupus erythematosus (586), Rocky Mountain spotted fever (252), and porphyria (462) have been linked with either hyperactive voiding (detrusor instability) or urinary retention (detrusor areflexia). In these instances, it is difficult to distinguish bladder symptoms resulting from vasculitis or neural involvement. The paucity of reports of voiding problems, and rather circumstantial evidence for autonomic involvement, suggest that these associations are probably rare.

Myotonic dystrophy does not affect the external sphincter. Yet detrusor hypocontractility is common, suggesting involvement of bladder smooth muscle or autonomic nerves (419,486,487).

Bladder Outlet Obstruction

General Pathophysiology

Bladder outlet obstruction remains one of the most commonly encountered but overdiagnosed disorders in urology. Surgical treatment of benign enlargement of the prostate once constituted the most frequently performed operative procedure within the specialty. With the advent of medication (α-adrenergic blockers, 5α-reductase inhibitors) and less invasive surgical procedures (e.g., laser, hyperthermia, stent), transurethral resection of the prostate is no longer performed as frequently. Bladder outlet obstruction can be divided into fixed anatomic or functional causes. Functional in this case does not mean psychogenic, but simply indicates increased urethral resistance to the forces of bladder emptying by neuromuscular phenomena, which may be involuntary or voluntary. Anatomic causes of bladder outlet obstruction include prostatic enlargement (benign or malignant), bladder neck contracture, urethral stricture, and meatal stricture. Functional causes of bladder outlet obstruction include dyssynergia and loss of relaxation at the level of the smooth sphincter and at the level of the striated sphincter.

Bladder Response to Obstruction

The bladder responds unpredictably to obstruction, producing hyperactivity or impaired contractility. Whether these sequelae take place along a continuum or are independent is unclear. Abrams (3) summarizes data that strongly suggest that outlet obstruction causes detrusor instability. Consistent with this notion, bladder suspension surgery in women that obstructs the outlet (proven on urodynamics) produces detrusor instability. Abrams (3) cites evidence that the incidence of detrusor instability in patients with outlet

obstruction secondary to prostatism ranges from 53% to 80%, with a mean of 62%. Postoperatively, the incidence ranged from 0% to 55% in these same series, with a mean of 24%. The fact that outlet obstruction in the form of prostatic enlargement is a major cause of bladder instability in males is supported by the high rate of preoperative instability (50% to 75%) in such patients and the high reversal rate of this phenomenon after prostatectomy (70%). Although the proof of cause and effect consists of retrospective correlation of the disappearance of this phenomenon after the relief of outlet obstruction, this nevertheless seems to be a reasonable argument. Disappearance of irritative voiding and instability takes between 1 and 6 months. Reversion to a normal cystometric accommodation limb and disappearance of all irritative symptoms may take as long as 12 months. When the involuntary contractions seem to result from outlet obstruction, the pathophysiology has been attributed to myogenic changes, denervation supersensitivity, or neurogenic causes (323). Abrams (3) has pointed out that no series has demonstrated an association between the incidence of instability and the severity of obstruction. He also noted an increasing incidence of detrusor instability in asymptomatic elderly men. Chalfin and Bradley (92) have presented evidence that there may be a change in sensory input that triggers detrusor reflex activity in the area of obstruction. Moore and colleagues (391) report an increase in presumptive sensory nerves in patients with detrusor instability. However, Chapple and co-workers (100) found evidence of decreased sensory neuropeptides in the bladder in men with detrusor instability, due to obstruction from BPH. In contrast, Harrison and associates (240) and Mattiason and colleagues (358) demonstrated an increase in total sensory neuropeptides in obstructed animals. Steers and colleagues (534,538) found that anatomic changes in sensory nerves correlate with levels of nerve growth factor (NGF) in the bladder. NGF is known to sensitize afferents and reduce their threshold for firing and could theoretically play a role in irritative sensory symptoms. Perhaps the tension receptors in the bladder wall have a reduced threshold for firing when the bladder wall is under stress. Blockade of NGF receptors in animals prevents changes in afferents and bladder hyperactivity. Prostatic enlargement could distort or compress the abundant nerve endings in its capsule. Reversion to normal voiding after prostatectomy could thus be explained by a decompression phenomenon or by decreased NGF and subsequent reversal of neural change. However, local anesthesia of the prostatic urethra in men with detrusor instability fails to abolish irritative symptoms, although bladder capacity increases (629). Furthermore, Tammela and colleagues (555) could not find that the temperature threshold decreased in men with detrusor instability due to BPH. These involuntary contractions may also occur on an irritative or a neurologic basis.

Although detrusor instability can occur in response to outlet obstruction alone, its etiology is probably multifactorial, a response to a combination of aging, neurologic, architectural, and strictly urodynamic factors related to pressure or volume changes within the bladder. This must be true because age-matched women and elderly men with obstruction often have the same degree of irritative symptoms (88). The phenomenon is much less common in response to urethral stricture disease, although it may be manifested in the presence of smooth- or striated-sphincter dyssynergia. Recently, it has been recognized that patchy denervation occurs in bladder from obstructed men. Animal models reveal that obstruction and aging are associated with ischemia (27,485). Thus ischemic mechanisms may play a role in neural and myogenic processes.

Decreased bladder compliance during filling without discrete involuntary contractions is another interesting phenomenon that can likewise be caused by or coexist with outlet obstruction. The possible relationship of this phenomenon to outlet obstruction has been the subject of much investigation. Benson and colleagues (42) showed that increasing the degree of stretch on muscle strips from the bladder body changed the response to norepinephrine from the usual ß (relaxation) response to an α (contractile) one. Rohner and colleagues (475) recorded the same type of change of response to adrenergic stimulation after producing chronic bladder outlet obstruction in dogs. Perlberg and Caine (441) showed that muscle strips from the bladder dome of 23% of patients with prostatic enlargement requiring surgery showed an α-adrenergic response instead of the normal ß-adrenergic response. Therefore it is not surprising that α-adrenergic blockers increase urine flow and decrease obstructive symptoms (318,319). It is less clear how irritative symptoms are reduced. Shapiro and co-workers (510) were able to correlate the effect of α-adrenergic blockers with the amount of smooth muscle in the prostate. The clinical significance of all these forms of detrusor hyperactivity that occur in response to outlet obstruction is that they—and not the simple phenomenon of residual urine with a decreased functional bladder capacity—are often responsible for the clinical correlates of frequency, nocturia, urgency, and urge incontinence.

Detrusor hypocontractility, as opposed to hyperactivity, may also occur in response to significant infravesical obstruction. The finding of residual urine is more a sign of detrusor decompensation than of the outlet obstruction that caused it. For this reason, the relief of outlet obstruction more commonly leads to satisfactory urodynamic resolution in patients with a low—as opposed to a large—residual urine volume (201).

Morphologically detectable changes to bladder outlet obstruction include bladder muscle hypertrophy followed by connective tissue replacement with increased collagen deposits within the bladder wall (208). Smooth muscle hypertrophy and hyperplasia develop in response to outlet obstruction, along with collagen deposition. Although the

absolute amount of collagen increases, the collagen concentration decreases (574). What regulates the degree of cellular hypertrophy in response to obstruction is unknown, but Gilpin and associates (208) reported that the largest increases in cell size were observed only in patients with concomitant connective tissue infiltration. Whether the endoscopic appearance of trabeculation is more related to collagen deposition or muscular hypertrophy is a matter of discussion. Regardless, trabeculation does not correlate with symptoms or presence of detrusor instability (12,13). Experimental models of bladder outlet obstruction vary with respect to the species used and the degree or duration of the obstruction. Even so, general response patterns exist.

Outlet Obstruction in the Male

Prostatic obstruction may be caused by hyperplasia, carcinoma, or inflammation. Obstruction is defined by an elevated intravesical pressure and a subnormal flow rate during voiding. Many asymptomatic elderly males satisfy this definition but without the usual symptom complex known as “prostatism” (88). When symptoms are associated with prostatic obstruction, they fall into two general categories: obstructive and irritative. The obstructive symptoms consist of hesitancy, a slow stream, prolonged urination, and a feeling of incomplete emptying. They are clearly distinct from the irritative symptoms, which consist of frequency, nocturia, urgency, and urge incontinence. These findings are statistically related to detrusor hyperactivity. Frequency and nocturia can also occur on the basis of a substantial residual urine volume, with a resultant decrease in functional bladder capacity. Bladder trabeculation develops in response to either detrusor hyperactivity or obstruction without such hyperactivity (12,13).

The optimal neurourologic evaluation for patients with suspected outlet obstruction secondary to prostatic enlargement differs markedly from center to center, and it may vary from a history, physical examination, and endoscopic examination to sophisticated combined pressure/flow studies. Despite this lack of consensus, a national guideline has been developed that outlines the minimum evaluation necessary and absolute indication for treatment and offers an alternative approach for BPH. Flow rates alone are insufficient to screen for obstruction. Significant outlet obstruction can exist in the presence of relatively normal flow rates, and diagnoses can be made in this subgroup of patients only by pressure/flow studies that show grossly elevated intravesical pressures (497) (Fig. 26B.42).

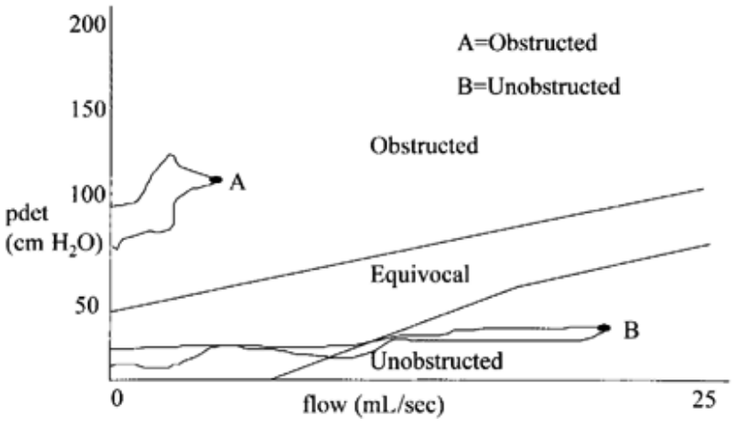

FIGURE 26B.42. Pressure/flow nomogram after Abrams.Griffith. Patient A is clearly obstructed based on peak micturition pressure and flow rate. Patient B is not obstructed.

Other anatomic causes of bladder outlet obstruction in the male include sclerosis or fibrosis of the bladder neck, urethral stricture disease, and urethral valves. Neurologic causes of sphincter dyssynergia have already been discussed. Functional causes of outlet obstruction in the male include smooth-sphincter dyssynergia (sometimes called *bladder neck dyssynergia* or *dyskinesia*) and striated-sphincter dyssynergia. Each of these can be secondary to neurologic or nonneurologic causes. The former syndrome characteristically occurs in males between ages 30 and 55 years who complain of long-standing obstructive and irritative symptoms. Many of these patients have seen several urologists and have been diagnosed as having psychogenic voiding dysfunction because of a normal prostate on rectal examination, a negligible residual urine volume, and a normal endoscopic bladder appearance. In this group of patients, objective evidence of outlet obstruction is easily obtainable by pressure/flow studies (Fig. 26B.43). Secondary bladder changes may occur, manifested by detrusor hyperactivity or decompensation with residual urine volumes. Once obstruction is diagnosed, it is localized at the level of the bladder neck in these individuals by micturitional urethral profilometry, formal videourodynamic study, or cystourethrography during a bladder contraction that shows obstruction at the level of the bladder neck, prostatic enlargement having already been excluded endoscopically. The diagnosis may also be made indirectly in such a patient by

the finding of outlet obstruction in the absence of a distal urethral stricture, prostatic enlargement, or evidence of striated-sphincter dyssynergia. The cause of this problem is unknown. Its occurrence in young, anxious, high-strung individuals and its partial relief by α-adrenergic blocking agents have prompted some to speculate that it may in some way be related to sympathetic hyperactivity (295). This theory is unproven. Exacerbation of these symptoms occurs during a relatively short and early period of prostatic enlargement, and marked relief in these cases is generally effected by a small prostatic resection. Interestingly, the spontaneously hypertensive rat exhibits urinary frequency and unstable bladder contractions, suggesting either a genetic component or a heightened sympathetic nervous system (107).

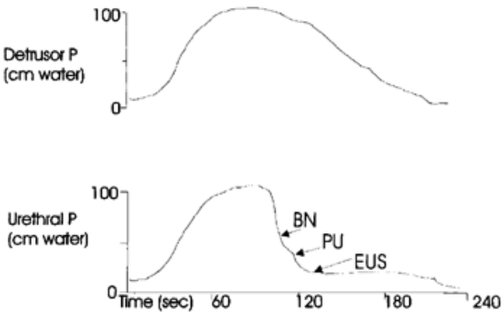

FIGURE 26B.43. A 25-year-old white male diagnosed with obstruction on a combined pressure/flow study has a 70 cm H_2O pressure drop across the bladder neck during a static urethral pressure profile, indicating site of functional obstruction.

Functional obstruction at the level of the striated sphincter in males and females occurs most commonly in association with neurologic disease; such dysfunction has been discussed previously. It is easy to produce obstruction voluntarily in this area and to stop voiding on command. This is one form of pseudodyssynergia (601), which must be distinguished from true involuntary functional obstruction at this level. Many believe that true detrusor striated-sphincter dyssynergia, implying involuntary contraction of the striated sphincter during the emptying phase of micturition, occurs only in patients with neurologic disease. The existence of this entity in individuals without neurologic disease seems to be reported most commonly in children, but it is reported in some adults as well, in whom the entity has been postulated to cause problems ranging from obstructive or irritative symptoms of an obscure cause to recurrent urinary tract infection. It is difficult to prove urodynamically. Unequivocal demonstration of this entity, in our opinion, requires pressure/flow EMG evidence of bladder emptying occurring simultaneously with involuntary striated-sphincter contraction in the absence of any element of an abdominal straining component, either in an attempt to augment bladder contraction, or as a response to discomfort during urination. Such reports do exist (266) and seem to confirm the existence of the syndrome. The cause is uncertain; it may represent a persistent transitional phase in the development of micturitional control, or persistence of a reaction response to the stimulus of urethral pain during voiding long after the problem has disappeared (266).

Outlet Obstruction in the Female

The most common cause of outlet obstruction in women is probably bladder neck suspension surgery. The frequency of infravesical obstruction in nonoperated females is rare when compared with incidence in males. Farrar (168) cites a figure of 10% of females referred to urodynamic centers as having outlet obstruction. He reports that the most common site of urodynamically proven outlet obstruction in these women is in the distal urethra and that this condition usually results from a failure of this area to fully attain its potential caliber during voiding. Groutz and associates (227) evaluated 587 consecutive women and found that 6.5% were obstructed using pressure/flow studies. Half of these women had antiincontinence surgery. Stricture occurred in 13%, primary bladder neck obstruction occurred in 85%, 5% had a learned disorder, and 5% exhibited detrusor-sphincter dyssynergia. Other causes of outlet obstruction include benign and malignant urethral masses, severe bladder prolapse, and rarely, uterine pathology such as large fibroids (Fig. 26B.44).

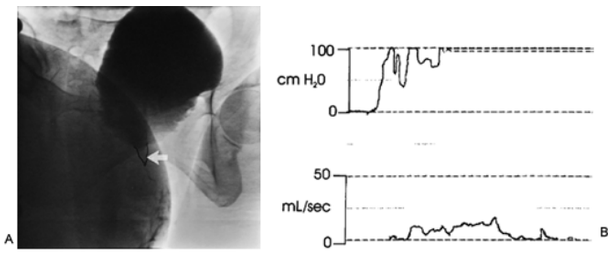

FIGURE 26B.44. A: Bimanual examination and fluoroscopy of a 40-year-old woman detects a large uterine fibroid displacing and compressing the bladder outlet *(arrow)* on anteroposterior view. **B:** A urinary retention pressure/flow study documents elevated voiding pressure (greater than 100 cm H_2O) with low to normal flow.

Bladder neck obstruction in females remains rare except after surgeries for stress incontinence. Diokno and colleagues (134) have clearly defined this entity in a small number of patients without a history of surgery, on the basis of urodynamic video pressure/flow criteria. They point out that the diagnosis of obstruction in this situation must be based on the demonstration of a relation between pressure and flow, and it should not be made on the basis of a single isolated parameter or any study that does not include simultaneous measurements of such parameters (Fig. 26B.45). Furthermore, following suspension surgery, urodynamics can often be equivocal. Awad and colleagues (26) and Nitti and Raz (407) have clearly shown that suspension procedures can cause obstruction with low flow rates, detrusor instability, or retention. Once the diagnosis of obstruction has been made (only equivocally one-third of the time), the site of obstruction can be localized further, either by simultaneous periurethral EMG recording and fluoroscopic monitoring during flow or by micturitional urethral pressure profilometry.

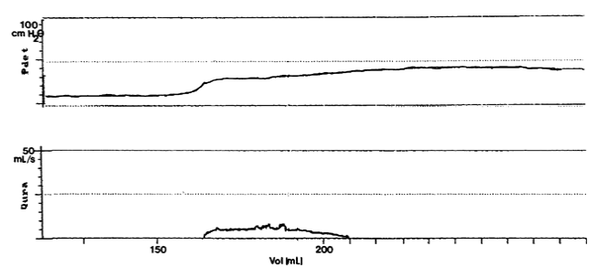

FIGURE 26B.45. A 45-year-old woman 1 year after Marshall-Marchetti-Krantz (MMK) bladder suspension. Severe urge incontinence and straining to void developed immediately after surgery. A combined pressure/flow study shows normal voiding pressure for female with low flow rate. Relief of symptoms and residual urine occurred after urethrolysis.

Treatment of obstruction after suspension surgeries requires urethrolysis. The most common preoperative complaint is urge incontinence; 13% are in retention and 51% possess residual urine (111). Resolution of urge incontinence and complete emptying varies from 65% to 93%.

Urinary Incontinence

Definitions

The ICS has defined *urinary incontinence* as involuntary loss of urine, which is a social or hygienic problem that is objectively demonstrable (256). Loss of urine can occur through the urethra and other routes. The terminology used to describe various types of urethral urinary incontinence is somewhat confusing because symptoms, signs, physical conditions, urodynamic findings, and anatomic factors are sometimes mixed together. The International Continence Society's Committee on the Standardization of Terminology is responsible for most of these definitions, and this committee now has input from the American-based Society for Urodynamics and Female Urology (SUFU), formerly known as the Urodynamics Society. Clinical practice guidelines have also been presented by the Agency for Health Care Policy and Research (361). In addition, SUFU is developing its own incontinence guidelines.

Stress incontinence can denote a symptom, a sign, or a condition. The symptom of *stress incontinence* indicates the patient's statement of involuntary loss of urine when exercising

physically. The sign denotes the observation of involuntary loss of urine from the urethra immediately on an increase in abdominal pressure. *Genuine stress incontinence* denotes involuntary loss of urine when the total intravesical pressure exceeds the maximum urethral pressure in the absence of detrusor activity. *Urge incontinence* refers to the involuntary loss of urine associated with a strong desire to void. Urge incontinence may be subdivided into motor urge incontinence, which is associated with involuntary bladder contractions, and sensory urge incontinence, which is not associated with involuntary bladder hyperactivity. *Reflex incontinence* applies to the involuntary loss of urine resulting from abnormal reflex activity in the spinal cord in the absence of sensation. Overflow incontinence is the involuntary loss of urine when intravesical pressure exceeds the maximum urethral pressure, caused by an elevation of intravesical pressure associated with distention of the bladder in the absence of detrusor activity. The term *total or continuous incontinence* is descriptive and can be associated with any combination of the aforementioned conditions.

Epidemiology

True prevalence figures for urinary incontinence vary widely. Based on a survey in England, the prevalence of urinary incontinence ranges from 2.5% to 5% in men and 10% to 25% in women. Burgio and associates (80) found a disturbingly high prevalence of incontinence, approaching 31% of healthy middle-aged women. As many as 58% of women have had urinary incontinence at some time. In the elderly (defined as over age 60), 15% to 30% are incontinent (132). Elderly women are twice as likely as men to be incontinent. The average period before patients seek treatment has been reported to be as long as 8 years. In nursing homes, the problem of incontinence exceeds 50% (361). After radical prostatectomy, the prevalence of urinary incontinence varies with surgical technique, documentation, age of patient, preexisting bladder dysfunction, and extent of disease. Incontinence after radical prostatectomy ranges from 5% to 80% given these variables. The cost of caring for patients with incontinence in the United States is $7 billion in the community and $3.3 billion in nursing homes (1987 dollars) (253). Thus few urologic conditions affect so many lives socially and financially.

Pathophysiology

Discounting individuals with cerebral disease and dementia, who do not recognize a need to urinate in a socially acceptable manner or place, the pathophysiology of urinary incontinence involves the bladder, the outlet, or both. Bladder hyperactivity may be manifested either as discrete involuntary contractions or as a more tonic decrease in the volume–pressure curve during filling (decreased compliance). Bladder-related incontinence may also occur in an individual without hyperactivity, but with such hypersensitivity on filling that urinary incontinence results from an uncontrollable need to rid oneself of a painful bladder sensation that has occurred in response to filling. Incontinence primarily related to the outlet most commonly results from intermittent decreases in urethral pressure below that of bladder pressure, which occur during abdominal straining and are unrelated to bladder hyperactivity. Rarely, episodic decreases in outlet pressure without a bladder contraction may also be responsible for urinary incontinence (urethral instability). Finally, the bladder outlet may simply have lost its closure potential and be nonfunctional, defined as *intrinsic sphincter deficiency*. Virtually any combination of bladder- and urethra-related causes may exist, compounding the complexity of finding an adequate solution and necessitating a diagnostic evaluation.

Outlet-related Incontinence in the Female

Under this category, we consider genuine stress incontinence, the nonfunctional bladder neck and proximal urethra (ISD), and urethral instability. Delancey (128) and Raz and Smith (459) have eloquently reviewed the structural basis for stress incontinence due to urethral hypermobility. *Urethral instability* refers to a seemingly reflex-caused total loss of urethral closure pressure provoked by bladder filling without a corresponding increase in intravesical pressure (364). This term is probably a misnomer, because the drop in urethral pressure probably represents a component of a normal voiding reflex in which afferent input from the bladder triggers urethral relaxation just before micturition. In the absence of a detrusor contraction, because of myogenic or motor-neuron disease, this fall in urethral pressure is expressed as stress incontinence. This is an entity that cannot be diagnosed by conventional urodynamic study but requires sophisticated urethral pressure recordings. In addition, there have been no systematic investigations regarding the treatment of this entity, but conceptually it would seem to make sense to try to raise the urethral pressure well above the threshold at which a precipitous decrease results from whatever stimulus is involved. Treatment remains problematic. Pharmacologically blocking the neural-evoked relaxation would be ideal. The transmitter is unknown, although NO has been implicated (431,442). Therefore current theory relies on pharmacologically (α-adrenergic agonists) or surgically increasing outlet resistance.

Factors related to maintaining outlet continence fall under three general categories: those related to urethral closure pressure, those related to urethral length, and those related to support of the urethral trigonal anatomy. Urethral length has been considered an important factor by some in the prevention of stress urinary incontinence. Lapides (303) considered the normal functional urethral length in the female to be 3.0 to 4.5 cm and believed that stress incontinence occurred when and because the functional length of

the urethra was less than 3.0 cm in the erect position. Although this may be correct much of the time, there is considerable disagreement about whether there is more than a minimum change in the resting UPP and functional urethral length after surgical correction of stress urinary incontinence. Also, there seems to be a minimum change in functional urethral length in the elderly between those patients who have stress urinary incontinence and age-matched control subjects. Factors such as these have led most people to believe that reduction of urethral length alone is rarely a factor in promoting stress urinary incontinence. Even in men after radical prostatectomy, continence cannot be entirely correlated with anatomic urethral length as measured radiographically (416). Urethral closure pressure contributes to a cough-competent outlet; and any decreases in factors that contribute to urethral closure pressure, although they may not cause stress incontinence by themselves, in combination can either result in stress incontinence or make a preexisting problem much worse. Alternatively, augmenting these factors may result in enough of an increase in urethral closure pressure to significantly ameliorate the problem.

The smooth muscle of the outlet is estimated to account for 30% to 50% of urethral closure pressure. The smooth muscle has inherent tonus and is responsive to pharmacologic stimulation, particularly α-adrenergic stimulation. Factors that decrease smooth muscle tone and responsiveness include overstretching, trauma, α-adrenergic blockade, ß-adrenergic stimulation, progesterone administration, and age. Factors that increase smooth muscle tone and responsiveness include stretch (up to a certain point), α-adrenergic stimulation, ß-adrenergic blockade, and estrogen administration.

The striated muscle of the outlet likewise has been estimated to account for 30% to 50% of urethral closure pressure. This striated muscle effect is not confined to the urethra in the area of the urogenital diaphragm, because the striated muscle extends along the urethra from this level for a variable distance to the bladder neck. Striated muscle also possesses an inherent tonus and is capable of voluntary or reflex activity. The factors that decrease striated muscle tone and responsiveness include a section of the pudendal nerve (and perhaps the pelvic nerve), skeletal muscle blockade, age, trauma, and overstretching. Factors that increase striated muscle tone and responsiveness include pudendal nerve stimulation and perhaps pelvic nerve stimulation.

The vascular cushion effect refers to the turgor of the blood vessels in the urethral submucosa and is estimated by Raz and colleagues (457) to account for 20% to 30% of urethral closure pressure, although others think its contribution is minor. Factors that decrease this effect include estrogen deficiency, trauma, and age. Factors that increase this effect include estrogen administration. This “inner urethral softness” (632) acts as a framework of spongy tissue that supplements the pliability and elasticity of the urethral mucosa. The “mucosal seal effect” is caused by the infolding of the urethral epithelium surfaces and complete apposition of the surface folds for which mucous secretion is necessary. Although the exact contribution of this mucosal seal effect to urethral closure pressure is unknown, the lack of it increases the amount of compression pressure required to form a complete seal. Factors that decrease this effect include estrogen deficiency, trauma, and age. Factors that increase this effect include estrogen administration in an estrogen-deficient female.

Several groups (128,393,529) have concisely summarized current concepts of the anatomic support and configuration of the urethral trigonal region. Pelvic support of the vesicourethral segment is contributed mostly by the pubourethral ligaments, which are condensations of the endopelvic fascia (128). The main support is from the posterior pubourethral ligaments, which extend from the inferior portion of the pubis to the midurethra. These prevent downward and posterior rotational displacement of the urethra. A “hammock” of levator ani muscle, covered by endopelvic fascia, supports the bladder and urethra in their intraabdominal position. The pubourethralis, a division of this muscle, forms a sling around the proximal urethra as it passes through the pelvic diaphragm and aids in preventing posterior displacement of the proximal urethra and bladder neck. The perineal musculature and fasciae provide additional inferior support, especially during abdominal straining. The fascia of the bladder and anterior vaginal wall fuse to form the pubocervical fascia. At the level of the bladder neck and proximal urethra, and at the level of the bladder and the fascial ring of the cervix, these two fasciae are densely adherent. Along the base of the bladder, the vesicovaginal space can be developed between these two fascial planes. The pubocervical fascia prevents herniation of the bladder and urethra into the vagina. The vagina provides a potential space for both anterior and posterior vaginal prolapse. Anterior vaginal prolapse may occur through the upper (cystocele), middle (trigonocele), or lower (urethrocele) third of the pubocervical fascia. The sacrouterine and cardinal ligaments support the uterus and cervix laterally and posteriorly, respectively, and provide direct and indirect supports to the bladder and urethra through these attachments. The primary function of these suspensory mechanisms is to support the upper urethra and urethrovesical junction and to provide a stabilizing effect to check the descent of these areas, which might otherwise be produced by an increase in intraabdominal pressure.

The one factor that seemed to be common to patients with genuine stress urinary incontinence was a failure of transmission of intraabdominal pressure increases so that these increases did not act to occlude the proximal urethra. Enhorning (158) was the first to urodynamically demonstrate this failure of abdominal pressure transfer to the upper

urethra. The concept has been refuted by using microtip transducers in the urethra and extravesical space. The rise is greater and occurs in the urethra (446). Anatomically, the pathophysiology seems to involve downward and posterior rotational movement of the bladder neck and proximal urethra during intraabdominal straining so that the bladder neck and proximal urethra descend to a position in which concomitant transmission of intraabdominal pressure to these areas does not occur. The urethra is in a dependent position with respect to the bladder base, and the tensile forces of the full bladder open the bladder neck with stress and permit flow into the proximal urethra (529). Whatever other factors contribute to decreases in urethral closure pressure, this abnormal descent of the bladder base and proximal urethra remains the only factor regarding which a consensus has been reached as a cause common to all patients with genuine stress incontinence. All effective vesicourethral suspension procedures correct this problem by anchoring the vesicourethral junction in a physiologic position and preventing its descent during abdominal straining.

The pathophysiology of classical stress urinary incontinence is corrected by any of the standard vesicourethral suspension procedures, all of which restore the anatomic and physiologic position of the proximal urethra in such a fashion as to allow transmission of intraabdominal pressure so that urethral closure pressure is enhanced to a similar and sometimes greater degree. In doing so, proper support is provided to prevent rotational descent of the bladder neck and proximal urethra. Such correction assumes that the factors responsible for urethral closure pressure in the first place are physiologically intact and capable of translating these intraabdominal pressure increases into increased urethral resistance.

Some patients have gross incontinence during abdominal straining; in such cases, a vesicourethral suspension may not be effective for correction. These patients, classified by McGuire and colleagues (371) as having type 3 (intrinsic sphincter deficiency) stress incontinence, have a nonfunctional bladder neck and proximal urethra. There is no pressure or poor closure pressure in this area. On an x-ray film with the patient erect and the bladder full, this area can appear fixed in an open or relatively open position. Alternatively, a small (less than 60 cm H_2O) increase in abdominal pressure forces urine through this region. The incontinence that is seen in patients with this finding is generally quite severe, although they often complain primarily of stress incontinence. Patients may state that they “leak” constantly or with any slight increase in intravesical pressure. Their abdominal leak pressures are uniformly less than 60 cm H_2O. Often, they complain particularly of gravitational incontinence that occurs simply on assuming the erect position. They often have a history of previous pelvic surgery, and the characteristic history includes three or more failed procedures for what was diagnosed as genuine stress incontinence. These patients have a particularly low urethral closure pressure in the first 1 to 2 cm distal to the bladder neck, and radiographically they exhibit a bladder neck and proximal urethra that never quite closes in the erect position with the bladder full. However, such patients do not exhibit an increase in subtracted bladder pressure. Treatment relies on increasing abnormal leak pressure with a periurethral bulking agent or pubofascial sling. Hypermobility of the vesicourethral segment is often not a problem in these patients, if this segment is fixed because of previous scarring and fibrosis. Likewise, combined hypermobility and intrinsic sphincter deficiency can coexist, requiring fixation using a pubofascial sling. Some authors advocate a pubovaginal fascial sling for all types of stress incontinence, quoting cure and improvement rates of 92% (91) with a mean follow-up of 3 years.

Bladder-related Incontinence in the Female

Bladder related incontinence in the female may be related to phasic rises in detrusor pressure, either of neurologic (detrusor hyperreflexia) or nonneurologic (detrusor instability) causation. Such incontinence may also be related to an abnormal tonic rise in intravesical pressure (decreased compliance). The neurologic causes of involuntary bladder contraction have already been reviewed. The cause of detrusor instability is obscure, especially in women, in whom outlet obstruction is uncommon (397,399). Some work has begun to elucidate neurophysiologic and neuromorphologic differences in detrusor muscle and micturition pathways between patients with bladder instability and normals; however, the cause of this troublesome and common clinical problem remains obscure.

One subject that should be mentioned is the simultaneous occurrence of bladder instability and stress urinary incontinence. Detrusor instability per se is a common cause of urinary incontinence in females. Instability has been cited as one of the most common causes of failure of a suspension operation for stress urinary incontinence (26). Whether preoperative urodynamic findings indicate that such an operation is likely to fail is an important question. A careful urodynamic evaluation in all such patients might well decrease the enthusiasm for corrective surgery in patients who also have genuine stress incontinence. Many have noted the occurrence of detrusor instability in patients with stress incontinence but have repaired the stress incontinence anyway, ideally to ameliorate the involuntary bladder contraction component of the incontinence by nonsurgical means. More often than not, however, this does not constitute a problem. McGuire and Savastano (373) have documented their long-stated position that only a small number of women with a combination of stress incontinence still have symptomatic urinary loss as a result of persistent detrusor abnormalities at 8 weeks after corrective surgery for the stress incontinence. They reviewed 603 women with

urodynamically and radiographically diagnosed stress incontinence; 180 had associated detrusor instability or urge incontinence or both. The overall incidence of detrusor instability was 30%. By 8 weeks after surgery, only 25 patients (4%) of the entire group, and only 14 of those with detrusor instability or urge incontinence at any time, were still troubled with incontinence resulting from that condition. Thus, in McGuire's experience, women with both stress incontinence and detrusor instability fare worse after surgery than those with only stress incontinence, with respect to total freedom from incontinence. However, 90% of women with stress incontinence and detrusor instability or urge incontinence were totally relieved of urinary incontinence at 6 months by an operation designed to treat only the stress incontinence. These data also suggest that, at least in some patients, stress incontinence and detrusor instability are causally related. Patients with stress incontinence who also have bladder-related incontinence because of decreased compliance do not seem to fare so well after surgery to correct just the stress incontinence. Finally, the *de novo* development of stress urge incontinence due to instability should raise suspicion concerning bladder outlet obstruction.

Urgency-frequency Incontinence in the Female Without Detrusor Hyperactivity or Outlet Incompetence

There are patients who have symptoms that suggest involuntary bladder contractions, yet have no consistent cystometrically demonstrable rise in pressure during the filling phase of micturition. Most of these patients report symptoms of urgency, frequency, dysuria, pressure, and incontinence in varying proportions. The treatment of this symptom complex is, initially at least, usually empiric, and consists of one or a combination of the agents to decrease detrusor hyperactivity (598). The fact that most of these patients do not have involuntary contractions most likely accounts for the generally less than optimal results achieved only with this type of treatment (464). Urodynamic evaluation of these patients may be entirely normal, may show hypersensitivity only during filling, or may show variations in urethral pressures. Fossberg and colleagues (181) reported successful subjective results in 22 of 34 female patients with sensory urge incontinence, many of whom had wide urethral pressure variations during filling, using phenylpropanolamine 50 mg twice daily. The ideal pharmacologic treatment for at least the urgency, frequency, and dysuria component of this symptom complex, which seems to be more sensory than motor in origin, would be an agent that produces topical anesthesia or hypoesthesia of the bladder and urethral mucosa. Although there are agents that are reported to have this action as their primary effect, the clinical results that have been obtained with such compounds in these circumstances have been poor, at least in our experience. MacCaulay and colleagues (341) report that, compared to women with stress incontinence, those with sensory urgency scored higher on anxiety and hysteria scales. There is no doubt that in at least some of these patients the symptoms are psychosomatic. However, poor treatment results in this group probably reflect that state-of-the-art techniques and practices fail to detect pathophysiology from the myriad possibilities (Table 26B.20), and optimal treatment for some of these has not yet been defined.

Lower urinary tract or genital infection, bacterial or nonbacterial	Bladder carcinoma or carcinoma in situ
Meatal obstruction	Bladder stone
Bladder outlet or urethral obstruction	Estrogen deficiency
Detrusor hyperactivity	Interstitial cystitis
Smooth-sphincter dyssynergia	Radiation cystitis
Striated-sphincter dyssynergia	Tuberculous cystitis
Urethral diverticulum	Emotional factors
Urethral caruncle	Decreased central or peripheral opioid/ peptide influence
Urethral carcinoma	Nonlaminar turbulent distal urethral flow

TABLE 26B.20. POSSIBLE CAUSES OF URGENCY-FREQUENCY-INCONTINENCE SYNDROME

Bladder-related Incontinence in the Male

Detrusor hyperreflexia and instability in the male have been discussed, especially as they pertain to outlet obstruction secondary to prostatic enlargement. Likewise, decreased compliance as a cause of urinary incontinence in the male has been covered. Overflow incontinence represents another form of bladder-related incontinence that seems to be more common in males than in females, although it occurs in both. The primary pathophysiology is actually a failure of emptying, leading to urinary retention with “overflow” incontinence, which results from either continuous or episodic elevation of intravesical pressure over urethral pressure. Overflow incontinence results from outlet obstruction or detrusor inactivity, either neurologic or pharmacologic in origin, or secondary to inadvertent overdistention of the bladder. Our subjective impression is that it develops in patients whose bladder neck and proximal urethral resistance is decreased, or in whom the detrusor is not totally decompensated. Treatment is directed at the primary cause of the failure to empty, or at circumvention if correction of the primary cause is not possible, or if irreversible bladder decompensation has occurred.

Outlet-related Incontinence in the Male

In theory at least, categories of outlet-related incontinence that are similar to those in the female should exist in the

male; that is, urethral instability, stress urinary incontinence, and a nonfunctional bladder neck and proximal urethra. In reality, there is little, if any, information regarding the topic of urethral instability in the male, possibly because conditions that cause stress incontinence in the male must affect the distal sphincteric mechanism and are universally associated with damage to urethral nerves. Stress-related incontinence exists after neurologic injury (this is discussed in the section on voiding dysfunction after radical pelvic surgery and in the section on myelodysplasia).

The most common type of outlet-related incontinence in the male is postprostatectomy incontinence. However, postprostatectomy incontinence is not caused solely by outlet-related reasons. Twenty-five percent of these patients have bladder dysfunction (hyperactivity) that accounts for all or part of their symptoms (Fig. 26B.38). The incidence of bladder hyperactivity in patients with postprostatectomy incontinence has been variously reported (178,311,452,625). Although many of these patients had not been studied urodynamically before surgery, it can be assumed that—because of the high incidence of bladder instability secondary to outlet obstruction in the male—a substantial proportion of them actually had detrusor hyperactivity preoperatively. Thus, in most cases, it did not develop in response to the prostatectomy. Recognition of the abnormal bladder function is of utmost importance in the management of these patients, because satisfactory continence may most often be obtained with pharmacologic therapy alone when the patient has only a minimum amount or no element of sphincteric insufficiency.

Postprostatectomy incontinence is one of the most devastating complications that can befall the patient and urologist. The continence zone after a radical prostatectomy is located between the verumontanum and urogenital diaphragm. One can characterize the various types of prostatectomies, including radical prostatectomy, as to the potential antiincontinence mechanisms left intact, and therefore as to the probability of urinary incontinence (related to the outlet) after prostatectomy. All types of prostatectomies essentially ablate the proximal sphincter mechanism, consisting of the smooth muscle of the bladder neck and proximal prostatic urethra, as well as the nonmuscular elements of the wall of these structures. These surgeries ideally leave intact enough of the distal sphincter mechanism (the smooth muscle of the urethra from the level of the verumontanum to the urogenital diaphragm; the striated muscle between the leaves of the urogenital diaphragm; the striated muscle that is applied along the outer wall of the urethra for a variable distance from the urogenital diaphragm to and beyond the apex of the prostate; and the nonmuscular elements of the urethral wall in that area) to produce continence in the absence of bladder hyperactivity and sensory urgency. Radical prostatectomy has the greatest potential for significant distal sphincter mechanism destruction, whereas transurethral prostatectomy is less likely to disturb this mechanism. The primary pathology seems to be noncompliance of the urethra. This may result from ischemia rather than direct injury. If one considers the potential damage to proximal or distal sphincter mechanisms or their innervation with various types of prostatectomy, a correlation with the commonly quoted figures for severe incontinence after different types of prostatectomy is evident (Fig. 26B.46):

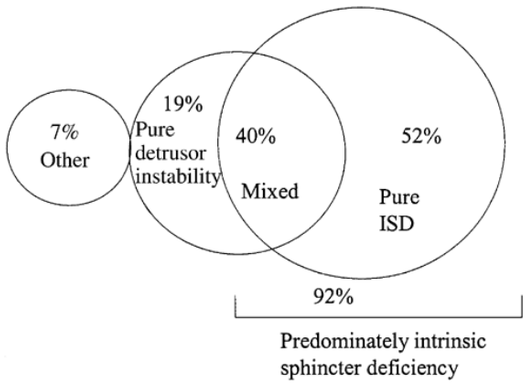

FIGURE 26B.46. Pathogenesis of urinary incontinence following radical retropubic prostatectomy. The pooling of urodynamic data from several recent large series reveals that intrinsic sphincter deficiency *(ISD)* is the most common cause. Other causes include reduced bladder compliance. Older series reporting predominant detrusor instability included obstructed patients.

Transurethral prostatectomy for benign prostatic hypertrophy, 0.2% to 1.4%

Transurethral prostatectomy for carcinoma, 10% to 20% (presumably because the distal sphincter mechanism is in some cases compromised by the carcinoma)

Suprapubic prostatectomy, 1% to 6%

Nonradical retropubic prostatectomy, 0.2% to 2.6%

Radical retropubic prostatectomy, 1% to 87% (depending on the definition of incontinence)

Simple perineal prostatectomy, 1.9% to 10.5%

Radical perineal prostatectomy, 2% to 15%

Given the evidence that postprostatectomy incontinence is related to age, coincident bladder or outlet dysfunction, site of surgery, and presence of stricture formation, one can postulate several mechanisms for postprostatectomy incontinence, including one or more of the following: (a) destruction of smooth muscle in the distal sphincter, (b) injury to nerves supplying the distal sphincter, and (c) ischemia with loss of muscle and neural function.

In a prospective comparison of perineal and retropubic prostatectomy, Doublet and co-workers (142) found that incontinence was more prevalent with the perineal approach, although not statistically different from the abdominal procedure. Attempts to preserve the bladder neck or create a neourethra have been advocated to help preserve continence (542). Although such techniques may help preserve continence, they could also facilitate future periurethral injection therapy if it should become necessary in the future.

Incontinence associated with detrusor hyperactivity or sensory urgency can resolve within months. Incontinence without urgency is more worrisome and less apt to dissipate spontaneously. Thus a urodynamic evaluation of patients with these problems is necessary to ascertain the exact contribution of outlet and bladder-related factors. Often, this evaluation is delayed for at least a year after surgery and just before institution of therapy.

Any patient whose proximal or distal sphincteric mechanism is already compromised is at greater risk from incontinence when another procedure in the area of the bladder neck and anterior urethra is performed. Postprostatectomy bladder neck contracture can also prevent closure of the outlet and produce incontinence. Any neuromuscular disease affecting the tone of the smooth or striated muscle of the distal sphincteric mechanism will predispose an

individual patient to a greater chance of urinary incontinence after even a well-done transurethral resection. This may include any neuromuscular disease, myasthenia gravis, Parkinson's disease, diabetic neuropathy, or alcoholic neuropathy. Moreover, a patient who has had a membranous urethroplasty or an abdominoperineal resection, or who has a rigid urethral stricture in this area, is at significant risk for urinary incontinence after a prostatectomy.

Incontinence in the Elderly

Incontinence in the elderly is a pervasive and distressing problem for patients, their families and friends, and health professionals. This subject is also of immense social and economic importance (427,466,467). Studies in Great Britain and Europe have fixed the prevalence of urinary incontinence in the hospitalized elderly at between 18% and 40% in men and between 24% and 46% in women. In community-dwelling elderly, the corresponding figures are 5% to 25% in men and 7% to 42% in women. In the United States, it is estimated that 28% to 50% of elderly nursing-home patients are incontinent of urine. It is estimated that over $3.3 billion per year in additional care is required for the 15% of incontinent elderly who are institutionalized (253).

The pathogenesis of incontinence in the elderly is multifactorial. Ischemia to areas of the prefrontal cortex has been demonstrated by Griffiths (224). Ischemia of the bladder may also occur. Elbadawi and co-workers (152) stress the importance of changes in the bladder in the development of detrusor instability.

The subject of incontinence in the elderly requires different considerations than incontinence in other age groups (467). First, there is a large segment of the elderly with transient incontinence. Transient incontinence is most often associated with acute medical conditions, psychologic responses, or iatrogenic factors, particularly associated with the administration of various types of pharmacologic agents. Restricted mobility and impaction of stool are also common causes of transient incontinence (Table 26B.21). Appropriate early management can often prevent this type of incontinence from becoming an established pattern. Transient cause for incontinence may contribute to 50% of the total number of cases of incontinence in the elderly.

Delirium
Infection
Atrophic urethritis/vaginitis
Pharmaceuticals
Psychologic, especially depression
Excessive urine output (cardiac, DM)
Restricted mobility
Stool impaction

After Resnick NM, Yalla SV, Laurino E. The pathophysiology of urinary incontinence among institutionalized elderly persons. *N Engl J Med* 1989;320:1.

TABLE 26B.21. DIAPPERS MNEMONIC FOR TRANSIENT INCONTINENCE

Another type of problem, not specific to the elderly but more characteristic of this group, is functional incontinence. This refers to the inability of a normally continent person to reach the toilet in time to avoid an accident. The reason may

be an illness—commonly a musculoskeletal limitation—that prevents an appropriately quick response to a need to void, or it may be a failure—on an organic, cerebral, or psychologic basis—of the individual to appreciate the social necessity of voiding in the right place at the right time; or it may represent spiteful behavior associated with depression, suppressed hostility, or anger (426). Bladder hyperactivity, usually with sensation (urge incontinence), is the most common of urodynamically definable conditions contributing to incontinence in the elderly and is estimated to occur in between 40% and 70% of incontinent elderly patients. Involuntary voiding without stress or sensation (reflex incontinence) may occur as well, either because of interruption of sensory pathways, spinal cord disease, or cortical damage that can cause detrusor hyperreflexia and also diminish the awareness of bladder filling. Stress incontinence in the elderly is much more common in females than in males who have not undergone prostatectomy. Nonsurgical management is often beneficial and appropriate. Overflow incontinence represents an easily diagnosable problem in these patients. If this is secondary to outlet obstruction with an intact detrusor, surgical treatment is often successful. If the detrusor is decompensated, intermittent catheterization, if practical or available, will totally obviate the problem.

Painful Bladder and Urethra

Evaluation and management of patients afflicted with purely sensory disorders of the lower urinary tract is frustrating and challenging. These patients often complain bitterly of symptoms suggestive of lower urinary tract dysfunction, without an obvious infectious cause or urodynamic correlate, but occasionally with endoscopic abnormalities. However, cystoscopic abnormalities are not constant or diagnostic (199). Recognition that disorders of sensory nerves can occur is limited by inability to objectively measure responses.

Interstitial Cystitis and the Urethral Syndrome in the Female

Hunner (254) first described a painful bladder condition manifested by frequency, nocturia, urgency, and suprapubic pain in a group of young women whose endoscopic examination revealed ulcers on the vesical mucosa. Subsequently, it has become evident that the classical finding of a scarred, contracted bladder that splits and bleeds on distention is present only in approximately 10% of cases of interstitial cystitis (IC). The onset of the disease is commonly subacute, and full development of the symptom complex takes place over a relatively short time (236). Many women can pinpoint the onset of symptoms. Often, the symptoms initially seem to be similar to those of urinary tract infection, of which many of these women have a repeated history. Positive urine culture report is more difficult to verify. The symptom complex, however, although initially thought to be simply caused by another infection, “never disappears.” The most common symptoms of the patient with classic interstitial cystitis are pain, frequency, nocturia, and urgency because of suprapubic discomfort. In most cases, voiding relieves the pain somewhat, but the pain recurs with bladder filling. The patients are usually women between ages 30 and 70 years, although men and children of either sex constitute approximately 10% of cases (236). Abacterial prostatitis or prostatodynia may correspond to the male counterpart. Oravisto (422) found the occurrence of IC in Helsinki to be 18 per 100,000 women. Kinder and Smith (282) found only 27 cases in more than 17,000 urologic registrations in London.

One of the problems in gathering data about this disease entity is the total lack of an objective and agreed-on definition. The National Institutes of Health (NIH) has developed guideline criteria for inclusion and exclusion in NIH-supported clinical trials on IC (Table 26B.22) (207). Although originally meant to be criteria for entry into research protocols on IC, they have become the de facto definition. Some patients with IC clearly fall outside of these guidelines. In effect, this entity is a disorder of exclusion. The symptom complex is not specific. Urodynamic investigation is unrevealing except for the presence of hypersensitivity during filling. A potassium test has been advocated but merely demonstrates hypersensitivity (93). Its sensitivity is 69%,

but specificity is only 50%. Occasionally, patients exhibit decreased compliance during filling; in our experience, these are usually chronic cases, with a long duration of disease, and with fibrosis of the bladder wall. Many of these changes may result from previous therapy or the response to minimal distention, similar to a defunctionalized bladder. Endoscopic findings vary widely. Classical Hunner's ulcers are rarely seen, but bleeding on refilling the bladder after cystoscopic distention is common. The bleeding may result from petechial hemorrhage, ecchymoses, or free bleeding from vessels, and is estimated by Hald and Holm-Bentzen (236) to occur in up to 90% of patients. Messing and Stamey (380) described the appearance of glomerulations (discrete rounded petechial mucosal hemorrhage) in response to cystoscopic hydrodistention and emptying as a manifestation of early interstitial cystitis. Such endoscopic findings are nonspecific and can be seen after filling and emptying of the bladder in patients with other inflammatory bladder conditions, including patients undergoing endoscopic examination for periodic surveillance (e.g., for bladder tumors) without either definable disease or symptoms. Conversely, the inability to demonstrate these findings does not exclude the diagnosis. A recent report demonstrating glomerulations in normal women before laparoscopic surgery and in men with prostatitis dispels the notion that cystoscopic changes are pathognomonic of IC (45).

Automatic Exclusion
Less than 18 years old
Bladder tumor
Radiation cystitis
Tuberculous cystitis
Uterine, cervical, vaginal, or urethral malignancy
Bacterial or fungal cystitis or prostatitis within 3 months
Vaginitis
Cyclophosphamide or other chemical cystitis
Urethral diverticulum
Active herpetic infection
Bladder or ureteral calculi
Waking urinary frequency <8 times
Absence of nocturia
Symptoms unrelieved by antibiotics, urinary antiseptics, and analgesics or anticholinergics
Duration less than 9 months
Involuntary bladder contractions on cystometry
Capacity greater than 350 mL on cystometry in a conscious patient
Lack of intense urgency at 100 mL volume (gas) on 150 mL liquid cystometry at full rate of 30–100 mL/min
Required for Inclusion
1. Presence on cystoscopy of either glomerulations after distension or Hunner's ulcer
2. One of the following subjective symptoms: pain in bladder or urinary urgency

TABLE 26B.22. NIDDK-NIH CRITERIA FOR INTERSTITIAL CYSTITIS

The IC database initiated by the National Institutes of Health has been revealing (454). More than 90% of patients are Caucasian with a mean age of 43 years. Using pain-urgency-frequency scoring, 7% have mild, 44% have moderate, and 49% have severe symptoms. Severe urgency and frequency (more than 15 urinations per 24 hours) are seen more than severe pain (Likert score greater than 7) (29%). Although symptoms fluctuate, no indication of worsening over time has been seen.

The cause of the disease has variously been considered to be infectious (bacterial and nonbacterial), traumatic, autoimmune, and neural. Dixon and Hald (137) nicely summarized the varied pathologic findings and also attempted to implicate a defective bladder urothelium in the pathogenesis of this disease, an idea originally suggested by Gordon and colleagues (218). They summarized the available pathologic evidence, which suggests that the disease is associated with a pancystitis. The bladder wall is frequently thickened, and the perivesical tissues are infiltrated. There is frequent thinning of the mucosal lining, and in some areas the mucosa may be denuded. The areas of ulceration are frequently covered by a layer of fibrin. An intense reaction occurs in the subepithelial connective tissue beneath the areas of mucosal thinning. The lamina propria is edematous and congested and contains dilated capillaries and perivascular hemorrhages. A diffuse cellular infiltration of all areas of the bladder wall by lymphocytes exists, but this is most evident in the lamina propria. Mast cell infiltration in the muscle coat ("detrusor mastocytosis") has been proposed as a diagnostic feature by Larsen and colleagues (309). This observation or measurement of mast cell products in the urine, such as histamine and its metabolites, has been adopted by some as a diagnostic feature. However, there is no agreement as to this criterion among many other clinicians (380).

Parsons and associates (433) have proposed a theory of pathophysiology involving a defect in the protective layer of glycosaminoglycans lining the mucosa of the urinary bladder, allowing a marked increase in bladder urothelial permeability, which in turn allows "leakage of urine" into the bladder wall, thereby inducing a local inflammatory response. Dixon and Hald (137) could not support such a theory implicating a defective glycocalyx, because they detected no structural differences in the glycosaminoglycans layer between patients with interstitial cystitis and control subjects. However, they mention the possibility that abnormalities of bladder urothelial permeability may occur because of other reasons, perhaps defective "urothelial tight junctions," with resultant urine leakage into the bladder wall.

Circumstantial evidence suggests that remodeling of sensory pathways occurs in patients with IC. Immunohistochemical data reveal that patients with IC have more nerves in the submucosa and muscle of the bladder (105,250,340). Lundeberg and associates (340) postulate that the number of mast cells depends on innervation. Chemically induced bladder inflammation in animals has been shown to reduce the threshold of mechanoreceptive afferents (228) and to alter the micturition reflex (52). Therefore it is reasonable to suggest that, in IC, sensory remodeling (pain begets pain) could develop in the spinal nociceptive pathways from the bladder in response to irritative stimuli in the bladder, reinforcing or reflecting the proliferation of axons in the bladder. Sensory neuroplasticity or chronic pain has been documented in models using the endotoxin component (lipopolysaccharides) of gram-negative bacterial cell walls. Thus one or more minor urinary tract infections in women or men could give rise to a neuropathic condition and chronic pain. Similar irritative hypotheses have been put forth to explain irritable bowel syndrome and pain with rheumatoid arthritis. Lending credence to the neurogenic pathogenesis in response to irritation, infection, or injury is the finding of elevated NGF in the urine and bladder tissue from IC patients (337,417). IC patients also express greater levels of mRNA for a substance P receptor (351).

Consistent with altered sensory nerve function in IC is effectiveness of intravesical anesthetics such as lidocaine and DMSO; the sensory neurotoxin capsaicin (436); electrical stimulation of sacral nerve roots (165); or denervation by cystolysis (620), hydrodistention (146), or sacral rhizotomy (382). Intravesical vanilloids that diminish afferent activity have also been used. Intravesical capsaicin and resiniferatoxin show only moderate success, suggesting that pain

pathways rostral to the bladder in the spinal cord and brain are activated. All therapies have partial and often only temporary success. Insight into the possible explanation for failure of the therapies derives from the experience of patients undergoing radical cystectomy or partial cystectomy with bladder augmentation. Even in these cases, surgical removal of the bladder does not uniformly abolish the sensation of bladder pain (596). This phenomenon is similar to the phantom limb syndrome experienced by patients after amputation of an extremity. These findings also suggest that mechanisms central to peripheral bladder sensory nerves play a role in chronic dysesthesias and pain.

Attempts to formulate any sort of a meaningful review of this disease are hampered by the fact that there is absolutely no agreement on a definition of the disease, or any way to grade its severity. The disease is often defined on the basis of symptoms alone without endoscopic or pathologic findings. It may be defined on the basis of symptoms with endoscopic findings but without specific pathology, or on the basis of pathologic findings with symptoms but with or without typical endoscopic findings. It has been suggested that ulcerative and nonulcerative interstitial cystitis are two different pathologic and clinical entities. Responses to treatment differ among patients in these various categories, probably accounting for the wide variations and disagreements regarding successful results with hydrodistention, intravesical instillations of DMSO, sodium oxychlorosene (Clorpactin) or doxorubicin, surgically or laser-induced "denervation," synthetic glycosaminoglycan therapy, and biofeedback. Often, the most effective therapies are those used for any chronic pain disorder. These include biofeedback, transcutaneous electrical nerve stimulation, and tricyclic antidepressants. Reports of long-acting calcium channel and α-adrenergic blockers appear promising (174,238). The use of intravesical agents such as bacille Calmette-Guérin has shown some promise (443). With a mean follow-up of 27 months, patients have shown a 60% response rate compared with 27% for placebo. Responses have also correlated with changes in cytokines in the urine that suggest an immune mechanism of action.

The urethral syndrome in the female is another imprecisely defined entity that, to most urologists, is a diagnosis of exclusion for these patients with frequency, urgency, or dysuria without evidence of any disease process in the urinary or genital tract. George (199) summarized the clinical features. Frequency by day is the primary complaint of most patients, who describe a constant, unpleasant sensation in the area of the urethra that is only temporarily relieved by voiding. Nocturia is generally of mild degree and never reaches the levels experienced by most patients with true interstitial cystitis. Patients complain that their voiding is typically slow and hesitant, and in fact, the measured flow rate, even with adequate volume, may be low.

A diagnosis of obstruction cannot be made on the basis of flowmetry, but must rely on pressure/flow documentation. Any positive finding uncovered during a search for infectious, inflammatory, or urodynamically definable pathologic characteristics should be treated specifically. Unfortunately, this leaves a large number of patients who must be treated either by biofeedback, reassurance and encouragement (really a form of biofeedback, but simply practiced by the urologist during office hours), empiric pharmacologic therapy, and a host of other treatments, generally directed toward the urethra or the surrounding structures. Schmidt (498) and Tanagho and colleagues (559) have come up with an interesting theory of striated-sphincter dysfunction as a cause of the urethral syndrome. Treatment of such dysfunctional striated-sphincter activity in their hands has been successful in ameliorating the clinical condition, and such treatment has ranged from simple reeducation—with or without pharmacologic therapy—to various forms of neurostimulation to fatigue the presumed erratic behavior of the striated sphincter.

Prostatodynia/Prostatitis/Male Pelvic Floor Dysfunction

The terms *prostatodynia* and *abacterial prostatitis* describe a syndrome in the male that is somewhat similar to the urethral syndrome in the female (144) and may represent the male counterpart to interstitial cystitis. Likewise, recent reports of lack of inflammation on biopsy of these patients have led to reassessment of our beliefs (570). Similar to IC, glomerulations can be seen, NGF levels are elevated, and relative ischemia may be present (102). Classically, the patient has an ill-defined discomfort in the prostatic area, but with no evidence of true acute or chronic prostatitis and no evidence of infectious or inflammatory findings in the expressed prostatic secretions. The National Institutes of Health has recently proposed criteria for the diagnosis of prostatitis (335,403) This syndrome of chronic genital discomfort, which often includes symptoms of irritative voiding dysfunction, typically occurs in tense and anxious persons (425). In a series of 37 such patients in whom the diagnosis had been established by clinical, bacteriologic, and urodynamic screening (with no identifiable disease), Osborn (425) reported the somatic symptoms as consisting of perineal pain (76%), pain after ejaculation (56%), suprapubic discomfort (55%), penile pain (44%), orchialgia (35%), and loin pain (17%). Orchialgia may arise from the close proximity of testicular nerves to the prostate capsule. Zorn and associates (633) noted that injection of this region with local anesthetic transiently abolished testis pain. Voiding symptoms consisted of postmicturition dribble (35%), hesitancy (26%), persistent nagging urethral sensation (23%), and necessity of straining to void (17%). The pathophysiology is obscure, and causative considerations have ranged from undiagnosed bacterial, trichomonal, or chlamydial infections, to what is described as tension myalgia of the pelvic floor striated musculature, or increased adrenergic

tone, occurring primarily in persons with a tendency to a tense, neurotic personality (507). In patients without an identifiable cause—unfortunately, quite a large number—long-term therapy is frequently used to either decrease bladder contractility or decrease outlet resistance. As with interstitial cystitis, tricyclics and α-adrenergic blockers can be effective (238).

Enuresis

Enuresis is the nocturnal or diurnal incontinence of urine in a child older than age 4 years. Primary enuresis is present from birth, and secondary enuresis is preceded by a dry interval of 6 to 12 months. The incidence of enuresis has been estimated at 12% of children ages 4 to 5 years (180), and it is known to have a familial predisposition (613). Theories regarding the cause of enuresis include such factors as delayed central nervous system maturation, psychogenic and behavioral components, environmental influences, deep sleep, allergies, small bladder capacity, uninhibited neurogenic bladder, structural abnormalities of the urinary tract, and lack of diurnal variation in vasopressin (138,172,272,317,355). The incidence of underlying organic problems is higher in the older patient population. A history of enuresis is a risk factor for urge incontinence and detrusor instability in adult women (176,392). This discussion focuses on children with enuresis without neurologic or urologic disorders.

The extent of the urologic evaluation of enuretic children has recently undergone reevaluation. In the past, most children underwent intravenous urography, voiding cystourethrography, and endoscopy. However, current recommendations are for a much more selective and minimal evaluation, because organic pathology is rare. The importance of history, physical examination, and results of urinalysis and urine culture in this evaluation are paramount. One should determine the pattern of incontinence, whether nocturnal, diurnal, or both; associated urinary frequency or urgency; fecal soiling or constipation; and a history of urinary tract infection and obstructive voiding symptoms. Careful examination of the spine, abdomen, and genitalia, and neurologic evaluation of sacral spinal cord segments, is necessary. The voided stream should be observed. A urinalysis and urine culture, if indicated, are performed. A history or laboratory findings suggestive of urinary tract infection, or evidence suggestive of a hyperactive external urethral sphincter, urinary tract obstruction, or neurologic problem, mandate further evaluation. Determination of the uroflow rate, possibly combined with surface perineal EMG, may be indicated (32).

Many investigators have performed urodynamic evaluations of enuretic children in an attempt to identify any specific abnormality of vesicourethral function responsible for their incontinence. Overall, urodynamic abnormalities alone in children with nocturnal enuresis are unusual. Whiteside and Arnold (613) studied 50 patients who had normal urinary flow rates and complete bladder emptying. In 13 patients with nocturnal enuresis only, 15% had detrusor instability approaching what may be seen in a normal population. In contrast, 97% of 37 patients with both diurnal and nocturnal enuresis had detrusor instability. Blaivas and associates (59) evaluated 13 children with diurnal and nocturnal enuresis and found two with neurogenic bladder dysfunction. Seven of the remaining 11 patients had decreased bladder capacity. Firlit and associates (172) performed pressure, flow, and EMG urodynamic studies on 34 children with diurnal and nocturnal enuresis and found 13 patients with uninhibited bladders, 17 with hyperactive external sphincters, and 4 with normal results. Kass and associates (272) urodynamically evaluated 65 children with primary enuresis. Forty-two of these patients had either a history or evidence of a urinary tract infection. Among these, 30 had uninhibited detrusor contractions, 10 were normal, and 2 had mixed types of neurogenic bladder dysfunction. Of the remaining 23 patients, 5 had uninhibited detrusor contractions, and 18 were normal. Smey and colleagues (518) reported a subgroup of enuretic children who had hyperactive external urethral sphincters as a contributing factor to incontinence. Diurnal enuresis, urinary frequency and urgency, urinary tract infection, and fecal soiling or constipation appear to correlate with the presence of uninhibited detrusor contractions, hyperactive external urethral sphincters, or both.

Various treatments have been used for enuretic children, including reassurance, psychotherapy, alarm conditioning, behavior modification, hypnotherapy, pharmacologic manipulation, and various surgical techniques. The preponderance of evidence currently suggests that the history, physical examination, and basic laboratory findings will indicate the appropriate extent of evaluation and initial management of most nocturnal enuretic children. Children with past or present urinary tract infection, evidence of lower urinary tract obstruction, or abnormalities on physical or neurologic examination should undergo thorough urologic evaluation, including imaging, followed by appropriate treatment. Meatotomy may be helpful in the male child with documented meatal stenosis (overdiagnosed), but may be associated with a high relapse rate. The routine use of meatotomy or urethral dilations is to be condemned. Children with none of the aforementioned findings, or those who have had a negative urologic evaluation, may be managed in a more conservative manner.

When deciding whether to initiate therapy, it is important to assess the effect of the problem on the patient and the family as a whole. When some parents and children are informed that no significant organic or psychologic problem is causing enuresis, reassurance and fluid restriction before bedtime may be the only treatment required. Many are quite willing to wait for the spontaneous resolution of enuresis that occurs at a rate of 15% per year in patients

between ages 5 and 19 years (180). If treatment is desired, a conditioning device such as a pad-and-bell bed alarm is successful in up to 60% of patients, and behavior modification therapy, aimed at making the patient responsible for changing his or her behavior, and complemented by positive reinforcement, is helpful in up to 70% of patients (355).

For patients who are unable to accept or who fail these approaches, pharmacologic therapy may be effective. The results of the thorough study by Kass and associates (272) suggest that successful empiric pharmacologic treatment of these patients can be instituted on the basis of historical information, physical examination, and urinalysis. Eighty-five percent of patients with nocturnal enuresis and daytime urgency and frequency respond well to anticholinergic medication. Seventy percent of patients with nocturnal enuresis only are successfully treated with imipramine hydrochloride. Nortriptyline hydrochloride may be efficacious in those patients who do not respond to imipramine hydrochloride. Tricyclics in these circumstances probably work by increasing spinal levels of monoamines during sleep, which inhibit micturition. Imipramine has the additional benefit of a more rapid onset of action and shortened half-life if undesirable side effects are encountered, such as hyperactivity or lethargy. Tricyclics are contraindicated in children with a seizure disorder.

Some reports indicate that desmopressin 20 μmg intranasally is effective in decreasing or eliminating enuresis in children and adults who have failed behavioral and pharmacologic therapies (138,260). The primary limitation of this treatment is cost. Side effects include weight gain, headache, stomachache, and rarely, epistaxis. A high relapse rate can be expected if drug therapy is withdrawn early, particularly in younger children. Pharmacologic therapy is more effective if it is suggested in a positive manner and combined with a program of behavior modification and positive reinforcement techniques.

Myelodysplasia

Myelodysplasia (spinal dysraphism) is a congenital anomaly occurring in 1 to 2 per 1,000 births in the United States. Multifactorial genetic and environmental influences are thought to be responsible for the unfused neural arches and associated spinal cord defects (155). Prenatal screening involving ultrasound or amniocentesis can be used to identify these patients. Although early neurosurgical intervention has decreased the incidence of meningitis and hydrocephalus in infancy (310), urologic complications resulting from neurogenic vesical dysfunction (NGVD) remain the leading cause of morbidity and death in survivors (519). For most, urinary incontinence is a formidable social handicap; and, in some, vesicoureteral reflux, hydroureteronephrosis, chronic pyelonephritis, and urolithiasis ultimately result in renal failure (329). In recent years, sophisticated urodynamic evaluation of these children has permitted more precise and rational treatment. In a study by Roach and associates (472), initial urodynamics were predictive of future clinical course in 55% of children. Conversely, the bladder may change over time and necessitate close follow-up. Teichman and colleagues (563) reported that urodynamics did not predict renal deterioration in many myelodysplastic children and argued for an early aggressive approach based on number of urinary infections and presence of vesicoureteral reflux. During the first 3 years of life, changes in the external sphincter may lead to upper tract deterioration (525). Pharmacologic therapy—often in conjunction with intermittent catheterization—and application of new surgical techniques have rendered many of these patients continent and promoted the preservation of renal function. Other children require bladder reconstruction with continent stoma or periurethral injections to achieve continence.

Spinal dysraphism encompasses a spectrum of anomalies, from the more occult dermal sinus, lipoma of the spinal cord, aberrant roots or fibrous traction bands, and abnormal filum terminale, to the more apparent and generally more serious lesions of the meningocele and myelomeningocele (15). Although the occult forms may be associated with significant NGVD, this discussion is concerned primarily with the more common form encountered by the urologist, which is myelomeningocele. The location of myelomeningoceles is most commonly lumbosacral (42%), thoracolumbar (27%), and sacral (21%); only 10% are in a thoracic or cervical location (268). Some investigators maintain that the level of vertebral defect largely determines the degree of neurologic damage (34), but most studies suggest no correlation between vertebral level and the NGVD. Significant NGVD has been associated with minimum bony defects (15). These disparities can be explained by the various possible neuropathologic lesions, or reorganization of pathways of the spinal cord, which include hydromyelia, syringomyelia, failure of upward migration or tethering of the cord, and dysplasia of the cord. Further, these changes may extend several segments above and below the site of the myelomeningocele. The importance of urodynamic evaluation to determine the precise vesicourethral dysfunction present in an individual patient is apparent.

Caudal Regression Syndrome

The syndrome of caudal regression was described by Duhamel (145) and is currently referred to as VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, and limbs). In VACTERL syndrome, sacral agenesis, imperforate anus, fusion of the lower extremities, and absence of the genitourinary tract except for the gonads can occur. The disordered embryogenesis appears to occur at the fourth to fifth week of fetal life, when the lumbosacral spine and nephrogenic masses are forming, and the cloacal septum is separating the genitourinary sinus from the rectum. Fortunately, the most

severe form is rare, but imperforate anus and sacral agenesis are relatively common. Nearly 73% of children with caudal regression syndrome have neurogenic bladder-sphincter dysfunction of sacral agenesis (70). The combination of sacral agenesis and imperforate anus is highly associated with voiding dysfunction.

Imperforate Anus

Several classifications of imperforate anus have been proposed, and that of Santulli and colleagues (495) remains widely used. They classified imperforate anus into four major groups based on the level of the imperforation in relation to the puborectalis muscle or the pelvic floor: low or translevator lesions, intermediate lesions (which are uncommon), high or supralevator lesions, and miscellaneous lesions. In nearly all males with supralevator lesions, a fistulous communication exists between the prostatic urethra and the blind end of the rectal pouch; in females, a rectovaginal fistula is common. Patients with translevator lesions do not have fistulae between the intestinal and urinary tracts; rather, the rectal fistula opens near the posterior scrotal raphe in males and the distal vagina or posterior fourchette in females. Combined openings of the urinary and gastrointestinal tracts also occur.

Patients with supralevator lesions are managed with a diverting colostomy shortly after birth, with the definitive rectal pull-through and repair of rectourethral fistula performed when the child has grown to approximately 25 pounds. Those who have infralevator lesions are treated with a primary anoplasty. All patients should have uroradiographic studies to detect associated genitourinary anomalies. Patients with supralevator lesions have a 52% to 67% incidence of genitourinary anomalies, but those with infralevator lesions have a 16% to 18% incidence (432).

Sacrococcygeal Teratoma

Sacrococcygeal teratoma is the most common germ cell tumor of infancy. It is associated with vesicoureteral reflux, obstruction of the bladder, and neurovesical dysfunctions. In one series, 12% of children had a neurogenic bladder (465). Nearly 81% of children with presacral involvement have urologic complications. Urodynamics should be performed in all children at presentation to compare with postresection findings because a high incidence of neurovesical dysfunction after surgery has been noted (465). Treatment is based on previous strategies for failure to store or empty.

Cerebral Palsy

For many years, it was believed that cerebral palsy per se did not cause neurovesical dysfunction. However, McNeal and associates (378) and later Decter and colleagues (116) found that up to one-third of children have voiding dysfunction. Urodynamic findings correlated somewhat to neurologic findings, with involuntary bladder contraction being the most common finding. Treatment has been based on symptoms and urodynamic findings. Occult spinal cord pathology has been suggested in the basis of detrusor-sphincter dyssynergia in a few patients. However, this finding may be artifact. Anticholingeric drugs are commonly used, but problems with constipation are especially prevalent. Intermittent catheterization is used for failure to empty.

Nonneurogenic Voiding Dysfunction

A major challenge to the pediatric neurourologist is determining the cause of vesicourethral dysfunction in the child who has no neurologic deficits. These children are seen by the clinician only after voiding difficulties have led to either urinary tract infection or significant social disability. The spectrum of voiding abnormalities is not unlike that of patients with true neurologic disease (5). Thus to label this type of vesicourethral dysfunction as nonneurogenic speaks only to the general neurologic state of the child and not to the problem of vesicourethral dysfunction. Because these patients have no outward indicators for the potential of underlying vesicourethral problems, it becomes important for all clinicians to assess carefully the subtle changes in voiding mentioned by the child or the parents. When in doubt as to the significance of a particular symptom, a simple noninvasive test such as uroflowmetry may better define its importance.

When voiding dysfunction is identified without outward neurologic disease or evidence of spinal dysraphism, confusion abounds as to its cause. Some investigators have suggested an underlying psychologic defect, and others emphasize an occult neuropathy (265,616). Lack of progression and absence of any other neurologic involvement argue against neurologic pathology. Regardless of origin, many of the voiding abnormalities are thought to be related to a disorder of coordination between the detrusor contraction and external sphincter relaxation. Support for a nonneurologic acquired abnormality comes from Bauer and associates (36), who failed to show denervation potentials on raw EMG data obtained from the external sphincter in such children. In addition, many such voiding abnormalities are associated with acquired bowel defects such as encopresis. Also supporting an acquired cause is the fact that many such voiding abnormalities can be corrected by a period of bladder retraining, which may include biofeedback. The full spectrum of voiding dysfunction may be seen, and the diagnostic characteristics are the same as those seen with true neurologic disease (599). Many such patients have subtle but sustained irreversible damage to the detrusor, resulting in myogenic decompensation. In others, vesicoureteral reflux may have developed, and surgical repair will be necessary to ensure adequate bladder emptying (521). In all such patients, therapy should be designed to promote adequate bladder emptying and an acceptably low voiding pressure to protect the upper urinary tracts.

Those with urgency, frequency, and wetting related to vesicourethral incoordination are ideally suited to bladder retraining with the biofeedback methods. However, those with significant failure-to-empty defects may be better managed with conventional techniques of intermittent catheterization, with or without the use of adjunctive pharmacologic agents. The length of therapy in both categories of patients is dependent on the degree of detrusor decompensation, upper tract disease, and the likelihood of relapse into a vesicourethral incoordination state. Regular follow-up is necessary in these patients to ensure that relapse has not occurred and that the upper tracts are being protected.

Psychogenic Voiding Dysfunction

Voiding dysfunction in the absence of organic disease has been classified as psychogenic (294,295). All types of voiding problems are associated with psychologic manifestations. However, which came first—the voiding dysfunction or the psychologic problem—is not always clear. Voiding abnormalities are obviously organic, psychogenic, or indeterminate. Voiding symptoms related to psychologic disturbances range from urinary retention to marked urgency, frequency, and enuresis (341).

Psychogenic Retention

For those patients with defects related to a “failure to empty,” the symptoms may range from acute retention to those suggesting a more chronic course, such as urinary infection or overflow-type incontinence (28,30,141,451). Acute retention is often temporally related to some catastrophic psychologic stress in the patient's life. These patients are often young or middle-aged women. However, some males and children may also demonstrate this phenomenon (274). Such patients may exhibit a propensity for repeated episodes of acute retention with essentially normal voiding in between. In a prospective study from Denmark, the annual incidence of retention in women was estimated to be 7 in 100,000 (285). Only 2 of 18 patients had obstruction, and 9 of 18 had hypocontractility. The cause was indeterminate and possibly psychogenic.

Fowler and co-workers (182) described a syndrome of urinary retention in exclusively premenopausal women, often with polycystic ovaries and urinary retention. EMG recordings from the external sphincter resembled myotomia. Impaired sphincter relaxation has been shown (125). Fowler (185) postulates a local, hormone-dependent channelopathy.

Patients with a chronic pattern continuously maintain considerable residual volumes. A propensity toward urinary infection may be seen, and depending on the degree of retention and presence of incontinence, upper tract disease may develop. The patient may give a history of having been toilet trained at an early age and may exhibit excellent urinary control. Many will be lifelong infrequent voiders and require voiding only one to four times daily. Micturition in such patients may require straining, pushing, or a Credé maneuver to augment emptying. The sensation to void becomes impaired, and the desire to void is noticed only when large volumes occupy the bladder. Periodic “treatments,” such as urethral dilation or internal urethrotomy, may transiently benefit the patient; however, excessive residual urine generally returns.

The pathophysiology of psychogenic retention is open to controversy, but it is much easier to accept in patients with acute retention. It is important to exclude other causes; often viral illnesses are overlooked (451). Theoretically, excessive stimuli, either excitatory or inhibitory, originate in centers above the brainstem and influence coordinated micturition. Speculation exists as to the point at which impairment leading to retention occurs in the cascade of events that takes place during normal micturition. The two most plausible explanations are as follows:

1. Excessive stimulation of the centers of the pyramidal tracts that directly innervate the skeletal muscle urethral sphincter, resulting in a failure of the sphincter to relax in preparation for voiding
2. Inhibition of the autonomic motor nucleus in the brainstem that innervates the bladder body, resulting in decreased detrusor contractility

Urodynamic parameters in patients with acute urinary retention generally reflect decreased detrusor contractility, normal compliance, and slightly elevated urethral closing pressure. After the acute phase resolves, the parameters, including uroflow rate, may be normal. Those with a long-term history of urinary retention will have decreased detrusor contractility, increased compliance, increased intraabdominal pressure during voiding, and reduced average flow rate.

The diagnosis of psychogenically induced urinary retention is one of exclusion, and subtle neurologic or metabolic disease must be excluded (31). It becomes the responsibility of the urologist to coordinate this evaluation and exclude other pathologies. Also, management of the voiding problem must be undertaken along the lines outlined earlier for patients with failure to empty. Psychologic consultation is required when patients have overt psychologic disease or when they fail to understand the potential for a psychologic disturbance as a cause of voiding abnormalities.

Uroradiography, endoscopy, and urodynamics are normal in most of these patients. In a select few, however, micturition may be impaired by functional outflow obstruction (169). Cystometry reflects normal compliance but a decreased functional capacity (464). Occasionally, detrusor instability is seen. Uroflow reflects a small voided volume, and the average rate is decreased. Combined studies including fluoroscopy are best for detecting the functional outlet obstruction syndrome. Voiding pressure is high and flow

rate decreased. There is little if any bladder neck funneling during the detrusor contraction. Thus the condition suggests dyssynergia of the bladder neck and proximal urethra.

It is unclear whether this extreme version of the urgency-frequency syndrome is truly psychogenic, but the lack of associated neurologic disease in most of these patients makes the diagnosis plausible (395). Even in females with detrusor instability, at least one-third of patients who failed to respond to any treatment demonstrate psychoneuroticism on psychiatric evaluation (392). Many of these patients respond, at least temporarily, to measures designed to reduce outflow resistance (459). Internal urethrotomy or bladder neck resection is a last resort and should be performed only in the presence of data substantiating outlet obstruction (157). Even then, results tend to be poor. Botulinum toxin injections into the external urethral sphincter and NO cream have been used without success (183). Results with sacral nerve stimulators have met with some success (163). The goal of such therapy is to reduce voiding pressures and reverse the stimulus that provokes the sensation of urgency. The psychodynamics of the psychogenic urgency-frequency abnormality are similar to the retention syndrome, in that inhibitory or excitatory stimuli from the central nervous system above the brainstem alter the micturition sequence in such a way that either sensation or contraction is impaired.

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27

SPINAL CORD INJURY

Wade Bushman

W. Bushman: Department of Urology, Northwestern University Medical School; Rehabilitation Institute of Chicago, Chicago, IL 60611.

Contents

UROLOGIC MANIFESTATIONS OF SPINAL CORD INJURY

Part of "27 - SPINAL CORD INJURY "

Due to recent improvements in medical care, the outlook for patients with spinal cord injury (SCI) has undergone a transformation. Complete cervical myelopathy was described in the 5,000-year-old Edwin Smith Surgical Papyrus as an “ailment not to be treated” (170). Even at the beginning of the twentieth century, the 2-year mortality rate was 80%. However, the current 12-year survival rate is 85%, a figure that approaches the noninjured survival rate (87). Better urologic care, achieved by improved diagnostic capabilities and better management strategies, has been a major factor in the improved survival. As significant progress has been made in urinary tract management, sexual function and fertility have become prominent concerns (Table 27.1).

TABLE 27.1. PERCENTAGE OF SPINAL CORD–INJURED PATIENTS INDICATING GREAT INTEREST IN AN EDUCATIONAL TOPIC

Topic	%
Medical Topic Area	
Testing of nerve and muscle function	51.4
Bladder or kidney problems	51.1
Pain	42.7
Spasticity	38.1
Bowel program management	35.3
Pressure ulcers	35.0
Increasing tiredness or fatigue	34.8
Medications	34.1
Contractures	23.1
Autonomic dysreflexia	23.0
Sexuality Topic Area	
Sexuality issues	39.8
Fertility	23.8
Wellness Topic Area	
Exercise programs	53.1
Stress reduction	38.1
Nutrition	36.0
Weight control	34.8
Smoking cessation	14.9
Alcohol or drug abuse	11.1

From Hart KA, Rintala DH, Fuhrer MJ. Educational interests of individuals with spinal cord injury living in the community: medical, sexuality, and wellness topics. *Rehabil Nurs* 1996;21:82, with permission.

This chapter begins with a brief overview of SCI, reviews the acute and chronic phases of injury, and introduces the options for management of the neurogenic bladder. The role of urodynamic testing in SCI is then discussed, followed by sections that comprehensively discuss each major method of bladder management. The succeeding sections address the common urologic complications of SCI. The concluding sections address the subjects of sexual dysfunction and infertility in SCI.

Epidemiology of Spinal Cord Injury

Spinal cord injury is surprisingly common, with approximately 10,000 new cases annually. Patients are more often male (82%) and young (59% between 16 and 30 years). The most common causes are motor vehicle accidents (45%), falls (22%), violence (16%), and sports injuries (13%). Midcervical and thoracolumbar injuries are the most common (48).

Level of Injury

The level of SCI is usually described by the neurologic level of injury and the degree of functional impairment. By

convention, the neurologic level of injury is the most caudal spinal cord segment with good motor and sensory function (Table 27.2). *Complete* injury exists if there is absent function below the level of injury or only partial preservation of neurologic function no more than three segments below the level of injury. Injury is considered *incomplete* if nonreflex neurologic function is preserved more than three segments below the level of injury. Overall, approximately 50% of spinal cord injuries are complete, and approximately 25% of all patients with SCI fall into each of the following categories: incomplete quadriplegic, incomplete paraplegic, complete quadriplegic, and complete paraplegic. Two classification schemes are commonly used to describe neurologic impairment: the Frankel system and the American Spinal Injury Association (ASIA) Impairment Scale (Table 27.3). Motor strength is usually graded on a five-point scale (Table 27.4). The level of injury is the major determinant of functional capability and independence (Table 27.5).

TABLE 27.2. KEY MUSCLES DETERMINING MOTOR LEVEL AND KEY AREAS DETERMINING SENSORY LEVEL

Key Muscles Determining Motor Level	
C-5	Elbow flexors (biceps, brachialis)
C-6	Wrist extensors (extensor carpi radialis longus and brevis)
C-7	Elbow extensors (triceps)
C-8	Finger flexors (flexor digitorum profundus) to the middle finger
T-1	Small finger abductors (abductor digiti minimi)
L-2	Hip flexors (iliopsoas)
L-3	Knee extensors (quadriceps)
L-4	Ankle dorsiflexors (tibialis anterior)
L-5	Long toe extensors (extensor hallucis longus)
S-1	Ankle plantar flexors (gastrocnemius, soleus)
Key Areas Determining Sensory Level	
C-2	Occipital protuberance
C-3	Supraclavicular fossa
C-4	Top of the acromioclavicular joint
C-5	Lateral side of the antecubital fossa
C-6	Thumb
C-7	Middle finger
C-8	Little finger
T-1	Medial (ulnar) side of the antecubital fossa
T-2	Apex of the axilla
T-3	Third intercostal space (IS)
T-4	Fourth IS (nipple line)
T-5	Fifth IS (midway between T-4 and T-6)
T-6	Sixth IS (level of xiphisternum)
T-7	Seventh IS (midway between T-6 and T-8)
T-8	Eighth IS (midway between T-6 and T-10)
T-9	Ninth IS (midway between T-8 and T-10)
T-10	Tenth IS (umbilicus)
T-11	Eleventh IS (midway between T-10 and T-12)
T-12	Inguinal ligament at midpoint
L-1	Half the distance between T-12 and L-2
L-2	Midanterior thigh
L-3	Medial femoral condyle
L-4	Medial malleolus
L-5	Dorsum of the food at the third metatarsophalangeal joint
S-1	Lateral heel
S-2	Popliteal fossa in the midline
S-3	Ischial tuberosity
S-4–5	Perianal area (taken as one level)

From Maynard PM, ed. *International standards for neurological and functional classification of spinal cord injury.* Chicago: American Spinal Injury Association, 1996, with permission.

TABLE 27.3. TWO COMMONLY USED CLASSIFICATION SCHEMES FOR SPINAL CORD INJURY

Frankel System (classifies injury by level of function below the neurologic level of injury)

A. Complete
B. Preserved sensation
C. Preserved but useless voluntary motor function
D. Preserved, useful voluntary motor function
E. Normal sensory and motor function

American Spinal Injury Association (ASIA) Impairment Scale

A. Complete: no sensory or motor function preserved in sacral segments S-4 and S-5
B. Incomplete: sensory but not motor function preserved below neurologic level, extending through sacral segments S-4 and S-5
C. Incomplete: motor function preserved below neurologic level and muscle grade less than 3 in majority of key muscle groups below neurologic level
D. Incomplete: motor function preserved below neurologic level and muscle grade 3 or greater in majority of key muscle groups below neurologic level
E. Normal: normal sensory and motor function

From Maynard FM, ed. *International standards for neurological and functional classification of spinal cord injury,* rev. Chicago: American Spinal Injury Association, 1996, with permission.

TABLE 27.4. GRADING SCALE FOR MUSCLE POWER

0—No movement
1—Trace movement
2—Movement through full range with gravity eliminated
3—Movement through full range against gravity
4—Movement through full range against some resistance
5—Normal power

From Gutierrez PA, Young RR, Vulpe M. Spinal cord injury. An overview. *Urol Clin North Am* 1993;20:373, with permission.

TABLE 27.5. EXPECTED LEVEL OF FUNCTIONING ACCORDING TO THE NEUROLOGIC LEVEL OF INJURY[a]

Level of Injury	Self-care	Transfers Between Bed and Wheelchair	Mobility
C-1–C-4 (high tetraplegia)	Dependent on others	Dependent on others	In a manual wheelchair, dependent on others; independent in a motorized wheelchair
C-5–C-8 (low tetraplegia)	Partially independent with adaptive equipment or totally independent	Dependent on one person with a transfer board or totally independent	Independent in a manual wheelchair either for short distances only or for longer distances outdoors; able to drive an automobile with adaptive equipment
T-1–T-10 (high paraplegia)	Totally independent	Totally independent	Independent in a manual wheelchair; ambulatory with knee-ankle-foot orthoses, walker, and assistance, for exercise only
T-11–L-5 (low paraplegia)	Totally independent	Totally independent	Ambulatory for short distances only with knee-ankle-foot orthoses and a walker, or ambulatory for longer distances outdoors with ankle-foot orthoses and canes

[a]The level of injury refers to the last normal root above the injured portion of the spinal cord. Self-care refers to feeding, dressing, and bathing.
From Ditunno JF Jr, Formal CS. Chronic spinal cord injury. *N Engl J Med* 1994;330:550, with permission.

Spinal Cord Syndromes

Several syndromes exist with unique and characteristic features. *Central cord syndrome* results from hemorrhagic necrosis of central gray matter and medial white matter with relative preservation of laterally located distal tracts. This produces sacral sensory sparing and motor weakness that is typically greater in the upper extremities—sometimes called *upside-down quadriplegia*. It is seen with cervical extension injuries, particularly in the elderly, and in patients with cervical stenosis. *Brown-Séquard syndrome* results from asymmetric lesions and produces contralateral defects in pain and temperature sensation and motor weakness. *Anterior cord syndrome* results from a lesion in the region supplied by the anterior spinal artery. This can be seen in flexion injuries, acute central herniations of the nucleus pulposus, and vascular insults. Sparing of the posterior columns and dorsal horns produces weakness and loss of pain and temperature sensation below the level of injury.

Cauda equina–conus medullaris syndrome results from injuries below the thoracolumbar junction. It involves injury to the sacral cord (conus) and lumbosacral roots and produces flaccid weakness due to lower motor neuron dysfunction. Sacral reflexes are lost (63).

ACUTE PHASE

Part of "27 - SPINAL CORD INJURY "

Acute spinal cord injury is followed by a period of spinal shock lasting 2 to 12 weeks. During this period, patients exhibit detrusor areflexia. Most patients are initially managed by urethral catheter drainage. Once the patient is stabilized, alternative forms of management may be initiated. In the 1980s, there was a period of enthusiasm for early placement of a suprapubic (SP) tube (111), but this is no longer a common practice. One study suggests that short-term management choice during the recovery period produces no real difference in the long term (91), but most think that clean intermittent catheterization is preferable. Intermittent catheterization is usually done every 4 hours with the goal of maintaining maximum bladder volumes less than 500 mL (167). As the spinal shock phase resolves, patients usually display an evolving pattern of bladder dysfunction. Significant changes may continue to occur up to 6 months after injury. Because of recent trends toward shorter hospitalization, the challenge of accommodating the changing pattern of function often extends past the time of discharge (49).

CHRONIC PHASE

Part of "27 - SPINAL CORD INJURY "

The upper motor neuron (UMN) lesion produces an initial flaccid paralysis of the bladder and lack of reflex activity below the level of the lesion. Some sphincter activity appears

to persist throughout the acute period, accounting for the maintenance of resting urethral sphincter pressure and continence (125). Recovery of detrusor function usually follows return of the bulbocavernosus reflex and deep tendon reflexes below the level of injury. During the recovery phase, detrusor reflex activity manifests as poorly sustained low-pressure contractions. Depending on the integrity of the sphincter, contractions of increasing pressure may or may not cause leakage between catheterizations. Over time, the pattern of reflex activity may progress to higher-pressure contractions and the patient may begin to void (174). Some patients with incomplete SCI recover the ability to void voluntarily. However, in the absence of perineal pinprick sensation and position sense of the great toe, recovery of voluntary bladder control is unlikely (165). Loss of pons-mediated coordination between the detrusor and sphincter can produce functional obstruction with diminished and interrupted urine flow and incomplete emptying (16,112,167,171).

The appearance of reflex detrusor activity appears to involve a complex reorganization of the micturition reflex. In the neurologically intact individual, A-delta fibers are the afferent pathway activated by bladder distention. C-fiber afferents exist and are activated by cold or chemical irritation; however, they are normally quiescent (43). Following SCI, there is hypertrophy of the C-fibers and emergence of a short-latency, C-fiber–mediated reflex contraction of the detrusor in response to bladder filling. The emergence of the C-fiber afferents appears to be a major factor in development of reflex detrusor activity and is probably the reason that ice water instillation can trigger detrusor contraction in the chronic SCI bladder and why capsaicin, a neurotoxin specific for the C-fiber afferents, can inhibit this reflex detrusor activity (174).

The lower motor neuron (LMN) lesion also produces initial areflexia. In contrast to the upper motor neuron lesion, areflexia typically persists even after the resolution of spinal shock. This may be complicated by sphincteric deficiency or the development of diminished compliance (64,99,162).

The chronic phase of SCI is not necessarily a static phase. Over time, there may be a continued evolution of bladder dysfunction. The marked thickening and trabeculation of the bladder that occurs in a patient with uncontrolled detrusor activity is a finding familiar to all urologists. An emerging concept is that changes in the end-organ function may influence the neural regulation of the bladder (Fig. 27.1). This provocative concept suggests that uninhibited detrusor activity, functional obstruction or loss of compliance, and elevated bladder pressures may contribute—by a mechanism of neural plasticity—to progressively worsening hyperreflexia and loss of compliance. Both UMN and LMN lesions can produce an evolving pattern of bladder dysfunction, and for this reason all patients with SCI require lifelong urologic follow-up. Patients should be seen at least annually for the first several years after injury. Those who are considered at low risk for upper tract deterioration and are stable over the first several years may be followed biannually. Those who are at higher risk of upper tract complications because of a high-pressure bladder or indwelling catheter, those who exhibit progressive changes in the pattern of bladder dysfunction on annual cystometry, and those with new bladder symptoms or symptomatic infection require more frequent evaluation. The annual evaluation should include an upper tract study (ultrasound), urinalysis, urine culture if a urea-splitting bacterial infection is suspected on the basis of an alkaline urine pH, and appropriate urodynamic testing.

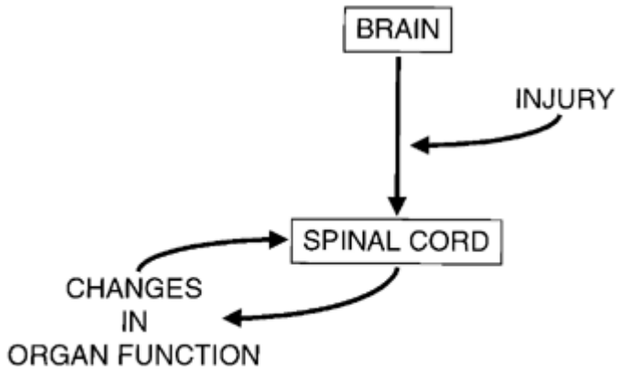

FIGURE 27.1. Reciprocal influences between the bladder and spinal cord below the level of injury contribute to reorganization of the spinal reflex circuitry following spinal cord injury. (From deGroat WC. Anatomy and physiology of the lower urinary tract. *Urol Clin North Am* 1993;20:383, with permission.)

OPTIONS FOR BLADDER MANAGEMENT: AN OVERVIEW

Part of "27 - SPINAL CORD INJURY "

Many SCI patients are managed by an indwelling urethral catheter. Others elect to have a suprapubic catheter placed, some wear external catheters, and others perform clean intermittent catheterization. Sekar and colleagues (132) reported the method of management at discharge in 913 patients: indwelling catheter (20%), condom catheter (31%), Credé (5%), intermittent catheterization (33%), and normal voiding (12%). Usually, the method of management is determined by the motivation and functional limitations of the patient, the availability of caregivers, and the counseling provided by the rehabilitation team (Table 27.6). The management options and important ancillary measures for patients with UMN and LMN bladder dysfunction are summarized in Table 27.7 . Men and women with neurologic impairment face different challenges in the selection of long-term management strategies and therefore are discussed separately. The details of each management strategy, associated issues, and potential complications are discussed later in this chapter.

TABLE 27.6. CONSIDERATIONS IN SELECTING METHOD OF BLADDER MANAGEMENT: PATIENT FACTORS AFFECTING OUTCOME

Physical limitations (e.g., use of hands, mobility)	Intelligence, education, educability
Motivation	Psychosocial environment
Reliability	Economic resources
	Long-term facilities

From O'Donnell WF. Urological management in the patient with acute spinal cord injury. *Crit Care Clin* 1987;3:599, with permission.

TABLE 27.7. OPTIONS FOR LONG-TERM BLADDER MANAGEMENT[a]

Men	Women
Upper Motor Neuron Lesion	
Reflex/balanced voiding	**Reflex/balanced voiding**
Sphincterotomy	Neurostimulator
Sphincteric stent	
Botulinum toxin	
Neurostimulator	
Intermittent catheterization	**Intermittent catheterization**
Anticholinergic medication	Anticholinergic medication
Bladder augmentation	Bladder augmentation
	Catheterizable stoma
Indwelling catheter	**Indwelling catheter**
Suprapubic cystostomy	Suprapubic cystostomy
Incontinent diversion	**Incontinent diversion**
Ileal conduit	Ileal conduit
Ileocystostomy	Ileocystostomy
Lower Motor Neuron Lesion	
Valsalva/Credé voiding	**Valsalva/Credé voiding**
Sphincterotomy	
Sphincteric stent	
Botulinum toxin	
Intermittent catheterization	**Intermittent catheterization**
Anticholinergic medication	Anticholinergic medication
α-Adrenergic blockers	α-Adrenergic blockers
Bladder augmentation	Bladder augmentation
Indwelling catheter	**Indwelling catheter**
Suprapubic cystostomy	Suprapubic cystostomy
Incontinent diversion	**Incontinent diversion**
Ileal conduit	Ileal conduit
Ileocystostomy	Ileocystostomy

[a]Major management options for men and women with typical UMN and LMN lesions are shown in **boldface**. Below each option are listed the ancillary measures or surgical interventions commonly used for that method of management.

Men

In the 1970s and 1980s, it was said that the “ultimate goal of bladder management in the SCI patient is the resumption of a balanced bladder” (112). The so-called balanced bladder was one defined as having low voiding pressures, no outlet obstruction, and low residual volume (less than 100 mL). This was considered an achievable goal in 80% of SCI patients (112). Patients were usually managed by intermittent catheterization until spontaneous voiding returned and balanced bladder function was achieved. Men managed this way usually wear a condom catheter. Others transfer to toilet and either initiate a voiding reflex with suprapubic tapping (UMN injury) or, because of detrusor areflexia and diminished sphincter tone (LMN injury), empty by Valsalva or Credé maneuver (62,101). Despite the observation that a catheter-free state was associated with a lower rate of urologic complications than with indwelling catheter or diversion (113,127), enthusiasm for the balanced bladder diminished because of frequent problems with incomplete emptying, infection, vesicoureteral reflux, and hydronephrosis. Intermittent catheterization has become the strongly preferred long-term management option for patients who can perform intermittent catheterization independently or who have a dedicated caregiver available and willing to perform catheterization. This preference is based on the finding that well-managed patients performing intermittent catheterization have a higher quality of life and lower incidence of serious urologic complications than patients managed by other methods. The indwelling Foley catheter or suprapubic tube is often a last resort for patients with high spinal cord lesions who are unable to perform intermittent catheterization or wear an external catheter. The potential complications associated with a permanent indwelling catheter are myriad. A suprapubic tube offers selective advantages in minimizing risks of urethral injury, recurrent epididymitis, and prostatitis, but it does not reduce the incidence of symptomatic urinary tract infection (UTI), stones, or bladder cancer. For properly selected patients, urinary diversion by ileocystostomy (bladder chimney) is a superior option.

Women

Women with SCI pose a particular challenge because of the relative inaccessibility of the urethra and the lack of external collecting devices. Spontaneous voiding is used by some women despite the lack of a usable external collection device (21). Some patients are able to transfer to the toilet and void by induced reflex, Credé maneuver, or straining or with the use of an implantable neurostimulator. Patients who either cannot transfer or who cannot establish a predictable voiding schedule elect to wear absorbant pads. This clearly has drawbacks, including chronic wetness, *Candida* rashes, and risk of skin breakdown. Intermittent catheterization is the preferred option, but many patients need to transfer in order to perform urethral catheterization. Construction of a continent abdominal stoma makes intermittent catheterization an option for many patients for whom it would not otherwise be possible (8,98,135). Use of an indwelling urethral catheter in women is associated with the same risks and

complications as in men. In addition, urethral erosion and loss of sphincter function occurs frequently and results in chronic leakage around the catheter (8,98,135). Suprapubic cystostomy may offer an advantage in avoiding this specific complication. In several reported series, the percentage of patients managed by the different methods varied significantly: reflex voiding (39%); intermittent catheterization (10% to 65%); and indwelling catheter (31% to 48%) (98,135).

Urodynamics

Why Test?

Urodynamic testing is the basis for understanding and managing neurogenic bladder dysfunction. The insights it has provided have led to revolutionary changes in bladder management over the past several decades. In current clinical practice, the use of information provided by urodynamic testing to optimize bladder management is the primary means to eliminate leakage, reduce the incidence of symptomatic UTI, and avoid upper tract deterioration. This section presents the rationale for routine urodynamic testing, reviews the important methodologies, identifies the risk factors for upper tract deterioration, and describes the role of urodynamic testing in patient management.

Most patients with SCI are attended primarily by physicians specialized in physical medicine and rehabilitation. In many centers, urologic consultation and urodynamic testing are not routine elements of the rehabilitation program. Patients are managed empirically. In patients managed with a condom catheter, bladder emptying is assessed by either bladder scanning or catheterization. In patients managed with intermittent catheterization, symptoms such as autonomic dysreflexia or leakage between catheterizations often prompt treatment for a presumed UTI and empiric anticholinergic therapy. Urologic consultation and urodynamic testing are reserved for patients who continue to have problems with leakage, recurrent symptomatic infections, worsening spasms or autonomic dysreflexia, or hydronephrosis. Although this approach works reasonably well for many patients, there is a compelling argument that *proactive* bladder management guided by urodynamic testing maximizes quality of life, preserves bladder function, and reduces long-term risks. This argument is based on three principles.

1. The first principle is that bladder behavior cannot be accurately predicted from the level of injury. The spinal cord micturition center is located between S-2 and S-4 and is focused primarily at S-3. This is generally located anatomically at vertebral level L-1, although there is some individual variation in the correlation of cord level to vertebral column anatomy. In general, complete suprasacral cord injury results in detrusor hyperreflexia (DH). This is often accompanied by striated-sphincter dyssynergia [detrusor external-sphincter dyssynergia (DESD)]. Smooth muscle sphincter dyssynergia [detrusor bladder-neck dyssynergia (DBND)] may also occur. Complete sacral spinal cord injury below the micturition center usually produces detrusor areflexia (DA), a competent but nonrelaxing smooth muscle sphincter, and a striated sphincter that may retain tone but is not under voluntary control (Fig. 27.2). However, these generalizations cannot be relied on for individual patient management (16,75,164). Among 284 patients with spinal cord lesions, 15% of patients with cervical lesions had detrusor areflexia and 24% of patients with sacral cord lesions had detrusor hyperreflexia (Table 27.8). The proposed reasons for the lack of correlation include individual anatomic variation, the presence of incomplete lesions, and the presence of occult secondary cord lesions.

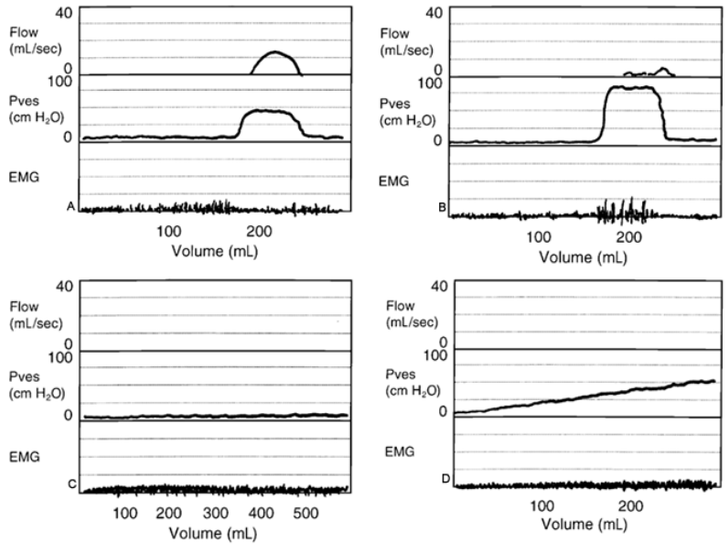

FIGURE 27.2. Major forms of neurogenic bladder dysfunction. **A:** Detrusor hyperreflexia (DH). Uninhibited detrusor contractions during bladder filling or uninhibited voiding reflex with synergistic relaxation of the external sphincter during voiding. **B:** Detrusor hyperreflexia with detrusor external-sphincter dyssynergia (DH/DESD). Uninhibited detrusor contractions during bladder filling or uninhibited voiding reflex with dyssynergic behavior of the external sphincter. This is seen in most patients with cervical and thoracic spinal cord injury. DESD may coexist with dyssynergia of the internal sphincter (bladder neck). **C:** Detrusor areflexia (DA) occurs most often in those with lumbar and sacral-level injuries. **D:** Diminished compliance may occur in combination with either DH or DA. It is most common in patients with thoracolumbar injuries.

TABLE 27.8. URODYNAMIC FINDINGS IN 284 SPINAL CORD–INJURED PATIENTS

Spinal Cord	Normal (%)	Detrusor Hyperreflexia with Detrusor External-sphincter Dyssynergia (%)	Detrusor Hyperreflexia Without Detrusor External-sphincter Dyssynergia (%)	Detrusor Areflexia (%)
Cervical (n = 104)	0	55	30	15
Thoracic (n = 87)	0	90	10	0
Lumbar (n = 61)	0	30	30	40
Sacral (n = 32)	12	12	12	64

From Watanabe T, Rivas DA, Chancellor MB. Urodynamics of spinal cord injury. *Urol Clin North Am* 1996;23:459, with permission.

2. The second principle is that “the bladder is an unreliable witness” (15). The gross clinical measures of bladder function—voided volume, postvoid residual, and continence—are not reliable indicators for detecting serious underlying problems. Diminished compliance, for example, may be completely asymptomatic yet cause hydronephrosis and irreversible renal insufficiency. Low compliance has been estimated to occur in as many as 17% of patients and is more common in patients with thoracolumbar injuries (65). Similarly, elevated voiding pressures may also be relatively asymptomatic and yet predispose a patient to upper tract changes, infection, and reflux. Reliance on clinical impression can be particularly misleading in patients with thoracolumbar injuries where diminished compliance and significant voiding dysfunction may exist with minimal neurologic deficit (160,161).
3. The third principle is that urodynamic testing can identify patients with increased storage pressures or increased outlet resistance for whom early intervention will avert upper tract complications and prevent a progressive deterioration in bladder function. In patients who void involuntarily or by reflex voiding (e.g., suprapubic tapping), the key goals are to maintain low storage pressure (less than 40 cm H_2O) at capacity, low voiding pressures, and acceptable bladder emptying (100). Urodynamic testing identifies potential risk factors and allows tailored intervention (e.g., sphincterotomy) to optimize bladder function. In patients performing intermittent catheterization, urodynamic testing identifies those with dangerously high storage pressures (greater than 40 cm H_2O at capacity), as well as those with more modest degrees of diminished compliance or significant uninhibited detrusor activity. Early intervention to address these problems may prevent progressive hypertrophy, bladder wall fibrosis, gradual loss of functional capacity, and worsening compliance.

When to Test

Urodynamic testing has little practical value during the acute and recovery phases of SCI. The initial selection of a long-term management strategy is generally made according

to the patient's preference, neurologic level of function, and level of support at home. Because significant changes in bladder function may occur between 3 and 6 months after injury (125), testing is reasonably deferred until 6 months after injury.

How to Test

Urodynamic testing is an invasive test that should be done only in the absence of bacteriuria. For patients who are chronically colonized, pretreatment with antibiotics is necessary to clear bacteriuria before testing. This is ideally based on culture and sensitivity obtained before testing. When this is not feasible, the patient may be treated for 2 days before testing with a fluoroquinolone antibiotic and the urine examined before testing (41).

The nature of the urodynamic testing performed will depend on the equipment available (160). Cystometry performed with water is the single most useful test, allowing evaluation of compliance and capacity. When combined with electromyographic (EMG) monitoring, DESD can usually be identified as well. Fluoroscopy is a valuable adjunct that permits the examiner to make an unequivocal diagnosis of DESD by narrowing of the membranous urethra and dilation of the prostatic urethra (Fig. 27.3), to rule out bladder neck obstruction, identify bladder diverticula, and demonstrate vesicoureteral reflux. Transrectal ultrasound imaging of the bladder outflow tract has been used in lieu of fluoroscopic imaging to identify DESD but has not achieved great popularity (13). Rectal pressure monitoring is useful in patients who void voluntarily to evaluate the component of straining, but it is not required for most patients with SCI. Similarly, urethral pressure profilometry is generally unnecessary. Endoscopic evaluation is not a routine component of urodynamic evaluation but is sometimes required for evaluation of hematuria, stricture, or false passage or to rule out bladder stone. It may be performed at the same visit. In men, both cystometry and flexible cystoscopy can be performed with the patient seated in a wheelchair (7,53,121). It is important to recognize the potential for autonomic dysreflexia to occur in patients with high SCI, to appropriately monitor for this and to stop testing and decompress the bladder if signs or symptoms of dysreflexia occur.

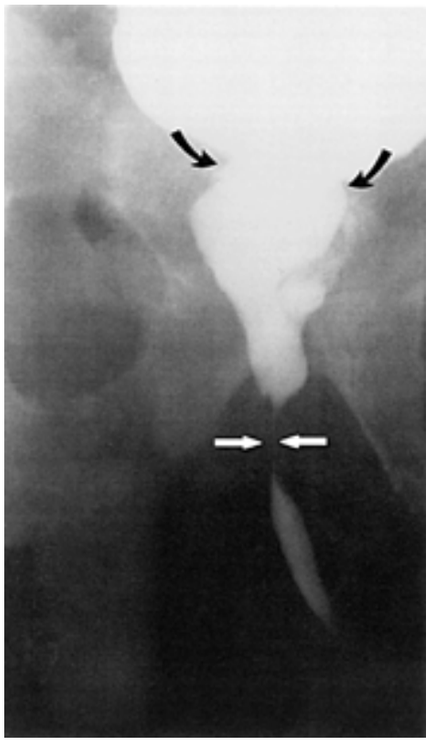

FIGURE 27.3. Detrusor external sphincter dyssynergia. Voiding cystourethrogram demonstrating detrusor external-sphincter dyssynergia (DESD) without bladder neck obstruction. *Straight arrows* denote the narrowed external sphincter. *Curved arrows* point to the open bladder neck. (From Chancellor MB, Rivas DA, Abdill CK, et al. Prospective comparison of external sphincter balloon dilatation and prosthesis placement with external sphincterotomy in spinal cord injured men. *Arch Phys Med Rehabil* 1994;75:297, with permission.)

Filling cystometry is used to determine sensation to bladder filling, compliance, and capacity. A gradual but progressive increase in intravesical pressure indicates significantly diminished compliance. For patients with diminished compliance, intravesical pressure may rise gradually and progressively to the point where leakage occurs (i.e., where detrusor pressure exceeds sphincteric resistance). The detrusor pressure at which leakage occurs is termed the *detrusor leak-point pressure* (DLPP). If detrusor contractions occur during filling, the pressure and duration of the contractions, the volume at which these occur, and the presence or absence of associated urine flow are noted. Patient perceptions (urge, symptoms of dysreflexia, or lower extremity spasm) should be recorded. If a patient voids reflexively, filling is continued until voiding occurs and voiding pressure, flow rate, and postvoid residual (PVR) are noted. EMG or fluoroscopy can be used to identify sphincter dyssynergy. The urodynamic evaluation is often tailored to address a patient's specific clinical issues. If the patient experiences leakage between catheterizations, the integrity of the sphincter may be assessed by determining the Valsalva leak-point pressure (VLPP) at 150 to 200 mL of filling. This may be done by having the patient cough, perform the Valsalva maneuver, or lift up as during self-transfer. For patients with cervical or upper thoracic injuries who cannot cough or perform the Valsalva maneuver adequately, the examiner may apply direct pressure over the bladder and determine the Credé-induced leak-point pressure. Leakage during these provocative maneuvers usually indicates sphincteric deficiency, and by a series of graded efforts, the VLPP can be estimated.

Risk Factors for Upper Tract Deterioration

Upper tract deterioration occurs in 9% to 40% of patients with SCI (90). This usually occurs from obstruction at the

ureterovesical junction (UVJ). Increased resistance at the UVJ from muscular hypertrophy or fibrosis is uncommon, and it can be distinguished by resolution of the hydroureteronephrosis with stenting and catheter drainage but not catheter drainage alone. More commonly, obstruction at the UVJ results from increased bladder pressure. An intravesical pressure of approximately 40 cm H_2O impairs upper tract emptying. Hydronephrosis develops when intravesical pressure exceeds this threshold for significant periods of time either as a result of diminished compliance or from sustained, high-pressure detrusor contractions (Fig. 27.4). Wyndaele (170) suggested that maximum detrusor pressures of 70 cm H_2O or greater caused upper tract damage. Gerridzen and colleagues (58) found that among patients with areflexia, those showing upper tract changes had an average maximum detrusor pressure of 58 cm H_2O compared with 24 cm H_2O in those without changes. They also found that among patients with hyperreflexia, elevated voiding pressures were associated with upper tract changes (115 versus 72 cm H_2O). Linsenmeyer and colleagues (90) reviewed 84 consecutive patients managed by reflex voiding and found that a longer duration of detrusor contraction was significantly correlated with upper tract stasis.

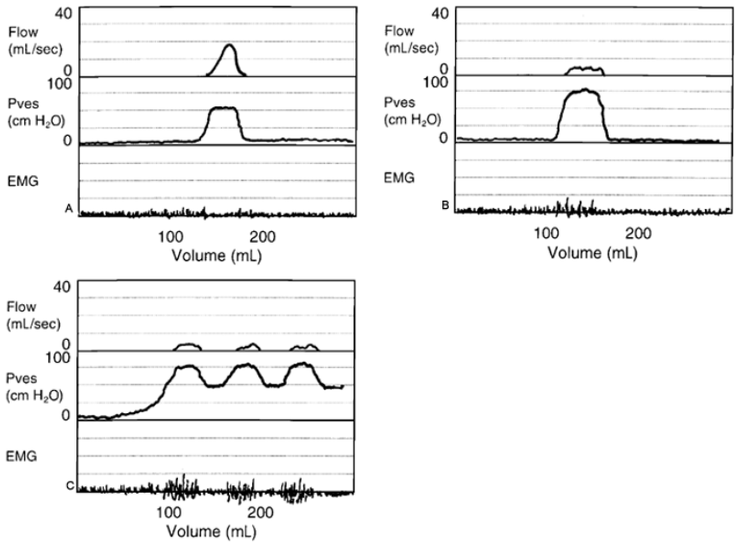

FIGURE 27.4. Cystometry reveals relative risk for upper tract deterioration. Three voiding patterns are observed during cystometry. **A:** Patient 1 exhibits detrusor hyperreflexia (DH) with voiding at modest pressures. **B:** Patient 2 exhibits DH with detrusor external-sphincter dyssynergia (DESD): Voiding occurs at high detrusor pressure. **C:** Patient 3 exhibits DH with DESD in combination with diminished compliance. Patient 3 is at greatly increased risk for upper tract deterioration because poor emptying (due to DESD) combined with diminished compliance results in persistently elevated storage pressures.

The reported incidence of vesicoureteral reflux in the SCI population ranges from 13% to 25% (90). Reflux is often attributed to increased intravesical pressure, but anatomic predisposition may be a critical factor. Linsenmeyer and colleagues (90) found no difference in any urodynamic parameter between four patients who voided reflexively with reflux as compared with patients who did not reflux. Three of the four were considered to have abnormal-appearing ureteral orifices on cystoscopy. Anatomic predisposition to reflux may be either congenital or acquired as a result of chronic inflammation, infection, bladder hypertrophy and fibrosis, or denervation of bladder and ureter. From these observations, it may be inferred that some patients have reflux that will resolve with lowering of bladder pressures, and others have reflux that may persist even at low intravesical pressures.

Role of Testing in Patient Management

The purpose of urodynamic testing is to identify patients at risk for upper tract deterioration and to optimize bladder management. Among patients with so-called balanced bladder managed by spontaneous voiding, urodynamic evaluation will identify patients with diminished compliance, elevated DLPP (greater than 40 cm H_2O), or incomplete bladder emptying. These findings may be used to direct pharmacologic or surgical intervention to moderate uninhibited detrusor activity, eliminate high-pressure storage, and improve bladder emptying (Table 27.9).

Compliance	Detrusor Leak-point Pressure (DLPP)	Postvoid Residual	Risk of Hydronephrosis
Normal	Low (<40 cm H_2O)	Low	–
Normal	Low	High	+
Normal	High (>40 cm H_2O)	Low	+
Normal	High	High	++
Low	Low (<40 cm H_2O)	Low	+
Low	High (>40 cm H_2O)	Low	+++
Low	High	High	++++

In patients with *normal* compliance, the risk of hydronephrosis is greater with the combination of high DLPP and incomplete emptying. This combination can result in frequent, high-pressure contractions that produce chronically elevated intravesical pressures. In patients with *low* compliance, the risk of hydronephrosis is substantial whenever sphincteric resistance (DLPP) exceeds 40 cm H_2O. The risk is greatest when patients do not void the bladder by discrete detrusor contractions but simply "overflow" at the DLPP.

TABLE 27.9. IMPLICATIONS OF URODYNAMIC FINDINGS FOR BALANCED BLADDER/REFLEX VOIDING

Among patients managed by intermittent catheterization, cystometry will identify patients at risk for upper tract deterioration because of diminished compliance, a competent sphincter (DLPP greater than 40 cm H_2O), or sustained high-pressure detrusor contractions during filling. Urodynamic evaluation can direct intervention to prevent leakage between catheterization. Cystometry may identify uninhibited detrusor activity amenable to pharmacologic treatment (e.g., anticholinergic). In other patients, cystometry may reveal diminished compliance as a major factor and direct alternative pharmacotherapy (e.g., α-adrenergic blocker) or surgical intervention (augmentation cystoplasty). In still others, testing will identify sphincteric weakness as the cause of leakage (Table 27.10).

Compliance	Detrusor Hyperreflexia	Detrusor Leak-point Pressure (DLPP)	Risk of Hydronephrosis	Risk of Incontinence
Normal	No	High (>40 cm H_2O)	–	–
Normal	Yes	High	+	++
Normal	No	Low (<40 cm H_2O)	–	+++
Normal	Yes	Low	–	++++
Low	No	High (>40 cm H_2O)	++++	+
Low	Yes	High	++++	++
Low	No	Low (<40 cm H_2O)	+	+++
Low	Yes	Low	+	++++

In patients with *normal* compliance, the risk of upper tract deterioration is generally low. Reflux or upper tract changes may occur in patients with sustained, high-pressure detrusor contractions and a competent sphincter (high DLPP). Incontinence results either from uninhibited detrusor contractions or from sphincteric deficiency (low DLPP).
In patients with *low* compliance, the risk of hydronephrosis is substantial when the sphincteric resistance (DLPP) exceeds 40 cm H_2O. Low sphincteric resistance protects against hydronephrosis but results in greater incontinence.

TABLE 27.10. IMPLICATIONS OF URODYNAMIC FINDINGS FOR INTERMITTENT CATHETERIZATION

I am not aware of any published data showing a value of routine urodynamic studies in patients with an indwelling catheter. Many patients with a long-term catheter show diminished compliance or capacity. One study suggested a benefit of anticholinergic medication in maintaining more favorable urodynamic characteristics (increased compliance, lower leak-point pressure) (78). Cystography can identify patients with reflux, a finding that may be relevant in patients with repeated febrile UTI, but there are few published data to support surgical correction of reflux in this situation.

METHODS OF BLADDER MANAGEMENT

This section discusses the major forms of bladder management, including reflex or balanced voiding, intermittent catheterization, indwelling catheter drainage, and continent and incontinent urinary diversion. Each section provides detailed information on management issues, common complications, and strategies to reduce patient risk.

Balanced Voiding

Reflex or induced voiding remains a widely used method of bladder management. It is most appropriate for men with reflex voiding who are able to wear a condom catheter and for both men and women who can transfer to toilet and initiate a voiding reflex by suprapubic tapping (101). It may also be used in selected patients with detrusor areflexia and diminished sphincter tone who can empty by Valsalva or Credé maneuvers (62). However, reflex voiding as a method of bladder management is associated with a number of problems. Bacteriuria is common, especially in men using a condom catheter. In one study, a catheterized specimen revealed bacteriuria in 53% of patients. One-third of those with positive cultures grew multiple isolates (110). Incomplete emptying combined with bacteriuria creates the potential for symptomatic UTI and stone formation. There is a 3% to 30% incidence of cutaneous complications, including redness, excoriation, swelling, and ulceration of the penile skin. The frequency of condom change (daily versus alternate day) does not appear to affect the incidence of cutaneous or urologic complications (140). There are often problems keeping a condom catheter in place. Some men develop a retracted penis or a protruding suprapubic fat pad. Placement of a semirigid penile prosthesis can help, but this increases the risk of complications due to patients' limited mobility and impaired sensation (155). Women who use pads as a means of urine collection are at risk for skin breakdown and decubitus ulceration (8). In one study, more than 10% of patients managed by reflex voiding developed severe hydronephrosis or reflux (152). This occurs because of diminished compliance or from a combination of detrusor hyperreflexia and DESD. If patients void by Credé or Valsalva maneuver, intravesical pressures during voiding must exceed the resistance of the bladder outlet, which may increase paradoxically (4). Voiding pressures can be very high (95 to 160 cm H_2O) in patients with a functional continence mechanism and can produce vesicoureteral reflux and hydronephrosis (62).

Patients managed with balanced bladder function require diligent annual follow-up. Patients who have detrusor hyperreflexia without DESD, low-pressure voiding, and low residual are at low risk for complications. Patients who have detrusor hyperreflexia with DESD or low compliance are at higher risk for upper tract complications or poor bladder emptying (Table 27.9). All patients should be followed annually with urinalysis, renal ultrasound, and postvoid residual urine measurement. Annual urodynamic evaluation is recommended for all patients, but it is particularly critical for those at higher risk. In cases of high-pressure storage or voiding, early intervention to reduce storage or voiding pressures should be considered (137).

In summary, this is a convenient and workable option for the patient who maintains low intravesical pressure during urine storage and empties well. However, enthusiasm for this form of management has to be tempered. Over the long term, many patients develop problems with incomplete emptying and elevated intravesical pressures that cause recurrent UTI, vesicoureteral reflux, and hydronephrosis. External sphincterotomy has traditionally been used to correct this, but the long-term success rate of sphincterotomy is disappointing. Many patients continue to empty poorly after sphincterotomy or require repeat sphincterotomy, and many patients abandon condom catheter drainage on long-term follow-up.

A number of topics relevant to balanced or reflex voiding are addressed in the following sections. These include external sphincter and bladder neck dyssynergy; treatment of dyssynergia by sphincterotomy, sphincteric stenting, and botulinum toxin injection; and the use of an implantable anterior root neurostimulator in combination with posterior rhizotomy to restore volitional voiding.

Sphincter Dyssynergy

In patients with SCI, discoordination between the sacral and pontine mesencephalic micturition centers can produce dyssynergia between the bladder and sphincter. Early testing of patients after suprasacral SCI reveals that sphincter muscle activity is present very early after injury but shows an evolving pattern of interaction with the detrusor over the first several months after injury. Voiding efficiency is maximal at 12 weeks and diminishes thereafter (125). DESD has been termed an *abnormal continence reflex,* a variant of the normal increase in sphincter activity that accompanies bladder filling (125). Blaivas and colleagues (17) postulated that DESD results when the increase in intravesical pressure that accompanies a detrusor contraction increases firing of the pelvic nerve afferents and triggers contraction of the external sphincter. Electromyographic recordings from patients with DESD confirm that increased sphincter EMG activity occurs with an increase in intravesical pressure and abates during the negative slope (decrescendo) phase of the detrusor contraction (125). Clinically, three major patterns of DESD are recognized (Fig. 27.5). DESD can produce high-pressure voiding and incomplete emptying. DESD associated with elevated maximum detrusor pressure has been associated with at least a 50% incidence of urologic complications, including sepsis, hydronephrosis, reflux, stones, and renal insufficiency (29).

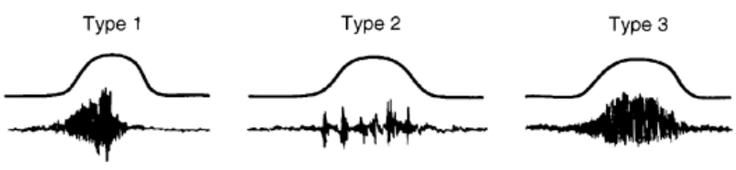

FIGURE 27.5. Three types of detrusor external-sphincter dyssynergia. Type 1 dyssynergia is characterized by a crescendo increase in electromyographic activity that reaches its maximum at the peak of the detrusor contraction. As the detrusor pressure began its decline, there was sudden complete external-sphincter relaxation. Voiding occurs only during the downslope of the detrusor pressure curve. Type 2 dyssynergia is characterized by clonic contractions of the external urethral sphincter interspersed throughout the detrusor contraction. These patients usually void with an interrupted, spurting stream. In type 3 dyssynergia, the external urethral sphincter contraction persisted throughout the entire detrusor contraction. These patients void with an obstructive flow or do not void at all. (From Blaivas JG, Sinha HP, Zayed AAH, et al. Detrusor external sphincter dyssynergia: a detailed electromyographic study. *J Urol* 1981;125:545, with permission.)

DBND may coexist with DESD. Schurch and colleagues (129)

evaluated 34 patients with upper motor neuron lesions and found that 32 had DESD and 25 had DBND. DBND coexisted with DESD in all cases but persisted even when DESD was abolished by pudendal nerve block. It is usually stated that DBND occurs only with complete suprasacral cord injury above T-6; however, Schurch and colleagues (129) found that DBND was not confined to patients with lesions above T-6. They found a high incidence among patients with cervical lesions, but also observed it in patients with both upper and lower thoracic lesions. In a study of 43 patients, Krongrad and colleagues (82) found a higher incidence of DBND in both high and low thoracic lesions (approximately 25% each) than in cervical lesions (7%).

Role of Sphincterotomy

Transurethral procedures to relieve functional outlet obstruction in SCI were introduced over 50 years ago (39,52,124). Currently, DESD is surgically treated by transurethral sphincterotomy (Fig. 27.6). This is usually performed by a single incision completely transecting the

sphincter muscle at 12 o'clock (79). This requires an incision at least 2 cm long and 6 mm deep (155). The 12 o'clock position has been found to be associated with fewer complications of hemorrhage and impotence. Completeness of the sphincterotomy may be assessed intraoperatively by performing the bulbocavernosus reflex and demonstrating loss of the sphincter contraction. Because DBND and DESD may coexist, some have recommended empiric transurethral resection or incision of the bladder neck in combination with external sphincterotomy (1), but this is controversial. Most reserve treatment of the bladder neck for patients who are diagnosed with bladder neck obstruction on videourodynamic study either initially or following a previous external sphincterotomy. Although Schurch and colleagues (129) found that DBND always coexists with DESD, Al-Ali and Haddad (1) reported good results when bladder neck resection was performed without external sphincterotomy in patients with incomplete, low thoracic lesions.

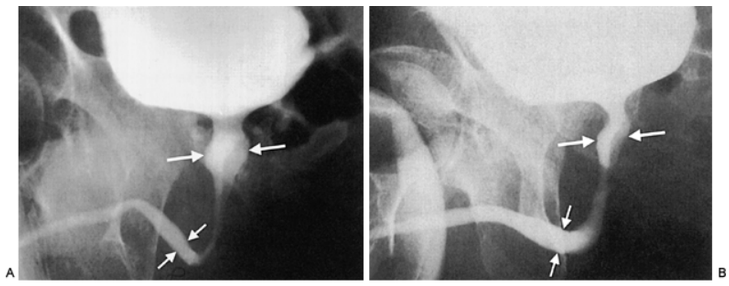

FIGURE 27.6. Effect of sphincterotomy. Comparison of voiding cystourethrogram before **(A)** and after **(B)** transurethral external sphincterotomy. Postoperatively, there is an increase in urethral diameter in the region of the external sphincter. Also note the decrease in dilation of prostatic urethra *(large arrows)* and slight increase in diameter of the infrasphincteric bulbous urethra *(small arrows)* following surgical ablation of the external sphincter. (From Fontaine E, Hajri M, Rhein F, et al. Reappraisal of endoscopic sphincterotomy for post-traumatic neurogenic bladder: a prospective study [see comments]. *J Urol* 1996;155:277, with permission.)

There has been considerable debate over the indications for sphincterotomy and the appropriate measure(s) for judging the success of the procedure. Many have used a high PVR as an indication for surgery and judged success or failure by the change in PVR (155). Others have argued that febrile infections and upper tract complications are more likely related to high intravesical pressures and pointed out that sphincterotomy may be successful in reducing high intravesical pressures without necessarily decreasing the PVR (155). Several authors have found an increased rate of complications in patients with DLPP greater than 40 cm H_2O, suggesting that the primary goal of sphincterotomy should be to reduce outlet resistance to less than 40 cm H_2O (74,79). Regardless of which measure is used, most patients show improvement after sphincterotomy. In a prospective study of 92 patients with a 20-month mean follow-up, Fontaine and colleagues (55) reported an overall 84% objective improvement after sphincterotomy. Mean voiding pressure decreased from 82 to 41 cm H_2O, and mean PVR decreased from 210 to 101 mL.

Some patients fail to improve after sphincterotomy, and others show only temporary improvement. Early failure is most often due to poor detrusor contractility. In a review of 60 patients who underwent sphincterotomy, Lockhart and colleagues (93) reported 15 failures. Detrusor acontractility or hypocontractility was the cause of failure in 11 of the 15 patients. Urodynamic testing can identify some patients with areflexia or detrusor hypocontractility preoperatively; however, some patients appear to develop hypocontractility or acontractility *de novo* after sphincterotomy (93). Yang and Mayo (173) reported that 3 of 37 patients with detrusor contraction greater than 30 cm H_2O preoperatively developed *de novo* hypocontractility after spincterotomy. The loss of contractility after sphincterotomy has been attributed to the loss of Barrington's urethrovesical reflex (106). Light and colleagues (86) noted that detrusor hypocontractility after sphincterotomy appeared to result from afferent dysfunction of the lumbosacral cord and postulated that the presence of obstruction is necessary to maintain a positive feedback mechanism for the detrusor contraction. Although the mechanism is still debated, the consensus is that some patients will unpredictably lose detrusor contractility after sphincterotomy. With respect to this issue, paraplegics may be at an advantage because they can assist emptying if necessary by Valsalva or Credé maneuver. Other causes of immediate failure include persistent high outlet resistance due to DBND and recurrent or persistent DESD. This was reported as the reason for failure in 2 of 15 patients by Lockhart and colleagues (93) and 6 of 18 patients by Yang and Mayo (173). The mechanism for DESD after sphincterotomy may be incomplete surgical division of the sphincter or scarring and contracture of the divided muscle. Whatever the mechanism, the incidence of repeat operation ranges between 15% and 50% (79). In a 10-year retrospective analysis, Santiago (126) reported that 9 of 25 patients required repeat sphincterotomy and also noted a relatively high failure rate for repeat procedures. Laser sphincterotomy has been proposed to reduce the need for repeat procedures, but Perkash (115) reported that 7 of 76 patients with laser sphincterotomy required repeat within 1 year. Similarly, Rivas and colleagues (122) observed recurrent obstruction within 1 year in 3 of 22 patients.

Contrasting with the generally good success rate of spincterotomy in the short term are disturbing reports of high long-term failure rates. In their review of 37 patients (1987 to 1993) all with detrusor contraction greater than 30 cm H_2O preoperatively, Yang and Mayo (173) reported 18 failures. The shorter mean follow-up in patients considered to be successful as compared with patients deemed to be failures (26 versus 49 months) suggests increasing failure with time. Reporting on 16 patients with median 39 months of follow-up after sphincterotomy, Vapnek and colleagues (155) found only 8 still using condom catheter drainage. Because of a risk of initial failure, a frequent need for repeat sphincterotomy, and the long-term failure rate, patients should be counseled about the possibility of failure and subsequent need for an alternative form of bladder management. Sphincterotomy irreversibly destroys sphincteric competence and creates dribbling incontinence even if it fails to improve emptying. This obviates other options, such as intermittent catheterization, that require a competent sphincter. For this reason, sphincterotomy has been considered a last resort in the patient who could perform intermittent catheterization (71).

Sphincteric Stent

Placement of a wire mesh stent across the external sphincter has proven to be an effective method to relieve functional obstruction by DESD. The indications for stenting are the same as for sphincterotomy. The advantages of the stent are

reduced risk of hemorrhage or adverse impact on potency and the possibility of reversing the procedure. Generally, a 3-cm stent is used and is placed with the proximal end at the verumontanum (Fig. 27.7). In a prospective randomized trial, patients undergoing standard external sphincterotomy were compared over a 2-year follow-up with patients treated by stent placement. Both treatments yielded comparable decreases in maximum detrusor pressure. More than half of the patients in both groups reported resolution of autonomic dysreflexia (29a). Follow-up studies showed that urodynamic improvement is maintained. The stent becomes epithelialized after insertion, with greater than 90% coverage in most patients within 6 months. Even so, stent removal is possible without significant long-term complications, and sphincter behavior reverts to prestent condition (31,32). Stent removal is required in approximately 15% of patients, most commonly for migration. Stones, encrustation, and obstruction by fibrosis or hyperplasia are relatively uncommon problems (32).

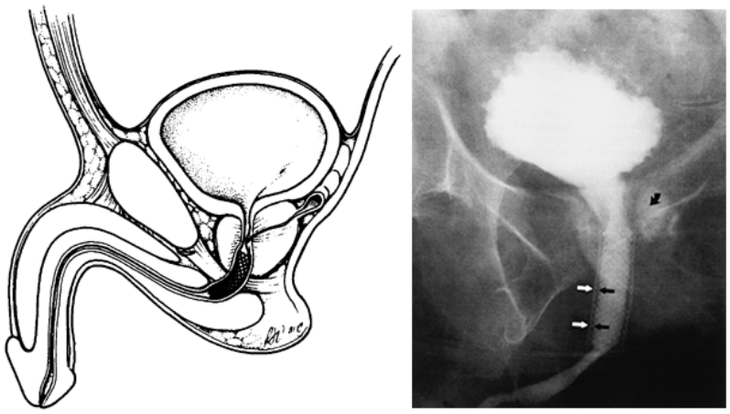

FIGURE 27.7. A: Treatment of detrusor external-sphincter dyssynergia (DESD) by stenting. Diagram of a wire mesh stent placed across the region of the external sphincter. (From Chancellor MB. Urinary sphincter prosthesis. In: Olsson CA, ed. *Current surgical techniques in urology.* Wilmington, DE: Medical Publishers, 1991, with permission.) **B:** Voiding cystourethrogram 12 months after stent placement demonstrating widely open external sphincter. Mild urothelial hyperplasia and intraprostatic reflux are noted (*small* and *curved arrows,* respectively). (From Chancellor MB, Rivas DA, Abdill CK, et al. Prospective comparison of external sphincter balloon dilatation and prosthesis placement with external sphincterotomy in spinal cord injured men. *Arch Phys Med Rehabil* 1994;75:297, with permission.)

Botulinum Toxin

Botulinum toxin, injected transurethrally or transperineally into the region of the external sphincter, has been used to weaken the effect of sphincter dyssynergy (51,128). The effect on maximum detrusor pressure is more modest than either sphincterotomy or stent and is temporary (3 to 9 months), necessitating repeat injection. Medical therapy for DESD has been disappointing. Continuous intrathecal baclofen decreases dyssynergia in up to 40% of patients (138), but oral baclofen has not proven effective. Centrally acting muscle relaxants such as diazepam cause sedation and have not proven useful. Clonidine was reported to inhibit vesicosphincter reflexes in patients with SCI (70), but this was only a preliminary study. α_1-Adrenergic antagonists such as terazosin have no demonstrable effect on the external sphincter, but they decrease resistance at the bladder neck and can be used both diagnostically and therapeutically in patients with persistent voiding difficulty following external sphincterotomy (30).

Neuromodulation

In an attempt to restore normal voiding in the SCI patient, investigators have explored the feasibility of electrical stimulation of the detrusor muscle, the conus medullaris, and the anterior sacral nerve roots. The best results have been obtained by combining sacral posterior root rhizotomy with implantation of an externally controllable anterior sacral root stimulator (Fig. 27.8). Posterior rhizotomy is done to increase bladder capacity and compliance. Anterior sacral root stimulation produces simultaneous detrusor contraction

and external sphincter activation; however, the timing of stimulation is adjusted so that the peaks of detrusor contraction and sphincter activation are out of phase and micturition occurs between bursts of stimulation (38). There is a large collective experience with the anterior root stimulator, accrued even as the technique of sacral rhizotomy was being refined. Brindley (20) reported the mean 4-year follow-up of his first 500 patients. He reported that 86% of surviving patients continued to use the device for micturition and that upper tract deterioration occurred in only 2 of 365 patients who had undergone complete posterior rhizotomy (20). In a subgroup analysis of 184 patients in that same cohort, Van Kerrebroeck and colleagues (153) reported that 156 of 184 patients (69 males, 87 females) used the stimulator alone for micturition. In a more recent series of 52 patients, Van Kerrebroeck and colleagues (154) reported complete continence in 73%. Although suitable for both male and female paraplegics and tetraplegics, the ideal candidate for the implantable neurostimulator is a patient with complete thoracic SCI who can transfer to the toilet and either cannot or prefers not to perform intermittent catheterization. Possible complications of the procedure include device-related complications, new or worsened SCI, loss of erectile function, and altered bowel function or continence.

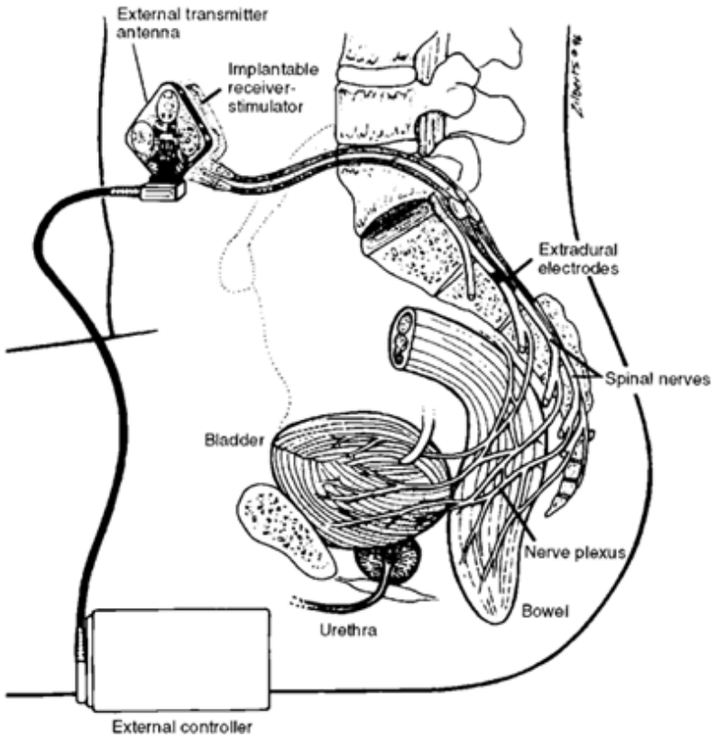

FIGURE 27.8. Restoration of voiding by posterior rhizotomy and neurostimulation. In select patients, voiding function may be restored by use of an implantable neurostimulator. A complete posterior rhizotomy is performed to provide sufficient bladder capacity. A surgically implanted neurostimulator is connected to the anterior sacral roots through extradural electrodes. Voiding is accomplished by activation of neurostimulation using a handheld external control device.

Intermittent Catheterization

Intermittent catheterization is the preferred long-term management option for most patients. The standard guidelines are a daily fluid intake of 1800 mL and catheterization every 5 to 6 hours for volumes of approximately 300 mL (87). Of course, there is considerable individualization in patterns of fluid intake and catheterization. Most patients use a clean rather than sterile method of self-catheterization (Table 27.11). One prospective study demonstrated a high rate of bacteriuria with intermittent catheterization by either method and suggested that the incidence of symptomatic UTI was the same (80). The key variables determining

patient acceptance of intermittent catheterization are functional capability and continence (117). Functional capability, broadly defined, includes the patient's intrinsic capabilities or the presence of a dedicated caregiver who can perform catheterization. Frequently, an occupational therapist can offer patients with cervical injury and limited hand function splints and practical modifications that facilitate self-catheterization. Women tetraplegics present a difficult challenge because of their inability to transfer and access the urethra. In selected patients, a continent abdominal stoma can make intermittent catheterization a realistic option. Incontinence—leakage between catheterizations—is the number one reason that patients discontinue intermittent catheterization (148). Sometimes this is related to sphincteric weakness, but usually it is related to uninhibited detrusor activity. With aggressive management to achieve complete continence, excellent long-term compliance with intermittent catheterization is obtained. In a series of 89 patients initially managed by intermittent catheterization with a mean follow-up of 6 years, Chai and colleagues (27) found that 71% continued to be managed by intermittent catheterization. In their mean 5-year follow-up of 40 patients on intermittent catheterization at the time of discharge, Maynard and Glass (96) found that 80% continued to perform intermittent catheterization.

TABLE 27.11. CLEAN INTERMITTENT SELF-CATHETERIZATION

Supplies Needed

Catheter—size 14 Fr (clear plastic, rubber, or silicone)
Container such as sandwich-size plastic bag with a Ziploc or twist-tie closure
Water-soluble lubricant such as K-Y Jelly (not Vaseline)

Catheterization Procedure

Wash hands with soap and water or a towelette.
Lubricate 2 inches of the catheter, beginning at the tip with a water-soluble lubricant.
Men: Retract the foreskin if uncircumcised. Hold the penis erect, stretching it taut. Insert the lubricated catheter, using firm but gentle pressure. After urine starts to flow, insert the catheter about 2 more inches.
Women: If you are right-handed, use the second and fourth fingers of your left hand to hold your labia apart. Locate the urethral orifice (opening) with the third finger of your left hand. With your right hand, hold catheter about 1 inch from the tip. Direct catheter slightly upward. Insert catheter gently until urine begins to flow.
Allow urine to drain until urine flow stops. Remove the catheter slowly, stopping whenever urine flows, and allow it to drain. Then continue to remove the catheter.
Pinch the catheter just before removing completely to avoid soiling yourself with urine.
Wash the catheter with a mild facial soap and rinse it with water. Replace the catheter in its container. Wash your hands.

Catheter Care

The catheter should be cleansed daily with a solution of vinegar and water. Use 1 part vinegar to 4 parts water. Then rinse with plain water.
Alternatively, you also soak the catheter in hydrogen peroxide for 30 minutes and then rinse with water.

Helpful Hints

Carry antiseptic towelettes to cleanse your hands in case water is unavailable.
If you have difficulty placing the catheter and you become nervous, stop, take a deep breath, and then start over. Do not force the catheter at any time.
The catheter can be used until it is no longer flexible or it becomes brittle.

Adapted from self-catheterization educational handout provided by Northwestern Memorial Hospital, developed by Urology Nursing Staff, Department of Nursing, and Department of Urology.

The assertion that intermittent catheterization is a superior method of bladder management has not gone unchallenged. One study that is often cited as evidence that a catheter-free state confers no advantage in terms of long-term complications is the retrospective study of 57 patients in a Veterans Administration Medical Center (47). With a mean follow-up of 12 years, the authors found no difference in renal or bladder calculi, pyelonephritis or urosepsis, gross hematuria, urethral or penile erosion, or urethral stricture in patients managed with or without a chronic indwelling catheter. However, the 25 catheter-free patients in this study included only 11 patients managed by intermittent catheterization. Thirteen were managed by spontaneous voiding or condom catheter, and one was status post urinary diversion. Because no subgroup analysis was done, this study does not allow a valid comparison of intermittent catheterization to management by an indwelling catheter.

The preponderance of evidence indicates that intermittent catheterization, particularly when combined with diligent efforts to control bladder pressure, affords a much lower rate of urologic complications than is usually associated with either an indwelling catheter or reflex voiding. In comparing the complication rate in 22 women managed by intermittent catheterization with those in 13 managed by urethral catheter drainage, McGuire and Savastano (98) reported a much lower complication rate with intermittent catheterization. Advantages were realized in the incidence of intravenous pyelogram (IVP) changes (0% versus 54%), autonomic dysreflexia (0% versus 54%), stone recurrence (0% versus 100%), nonfunctional urethra or urethral erosion (0% versus 54% and 46%, respectively), urine leakage (27% versus 92%), and febrile UTI (32% versus 92%). This study is noteworthy for the authors' stated efforts to maintain bladder storage pressures less than 30 cm H_2O. Bennett and colleagues (8) also reported a significantly lower incidence of complications in women managed by intermittent catheterization as compared with either catheter drainage or spontaneous voiding with use of incontinence padding. A number of other studies have demonstrated very low complication rates on long-term follow-up of patients managed by intermittent catheterization (27,83). Chai and colleagues (27) attributed the low complication rates in their series to their efforts to maintain low-pressure storage. The low complication rates observed in series like these are clearly superior to the complication rates that attend chronic indwelling catheter drainage (Table 27.12). Likewise, patients managed by intermittent catheterization had lower incidence of hydronephrosis, reflux, and kidney stones than patients managed by either reflex voiding or Credé maneuver (59).

TABLE 27.12. COMPLICATION RATES WITH INTERMITTENT CATHETERIZATION VERSUS INDWELLING CATHETER

Complications	Intermittent Catheterization (n = 31; mean follow-up, 5.9 years)[a]	Indwelling Catheter (n = 32; mean follow-up, 12 years)[b]
Renal stones	3%	25%
Bladder stones	16%	41%
Pyelonephritis	0%	25%
Gross hematuria	3%	6%
Urethral erosions	0%	12.5%
Urosepsis	0%	6%
Urethral stricture	0%	9%
Epididymitis	6%	6%
Difficulty catheterizing/ false passage	3%	0%

[a]Data from Chai T, Chung AK, Belville WD, et al. Compliance and complications of clean intermittent catheterization in the spinal cord injured patient. *Paraplegia* 1995;33:161.
[b]Data from Dewire DM, Owens RS, Anderson GA, et al. A comparison of the urological complications associated with long-term management of quadriplegics with and without chronic indwelling urinary catheters. *J Urol* 1992;147:1069.

Patients managed by intermittent catheterization should undergo routine urodynamic monitoring with intervention as necessary to maintain continence between catheterization and keep storage pressures below 40 cm H_2O (27). Leakage between catheterization is most often due to uninhibited detrusor activity and low bladder capacity. Some patients eliminate leakage by restricting fluid intake and increasing the frequency of catheterization, and others may wear a

condom catheter to manage leakage between catheterizations, but these are awkward and tedious solutions (117). Medication to increase bladder capacity and decrease the amplitude of uninhibited detrusor contractions provides continence to most patients (50). Useful medications include anticholinergics, tricyclic antidepressants, and occasionally α-adrenergic blockers (27). It has been postulated that muscular hypertrophy, diminished compliance, and increased intravesical bladder pressures may develop over time and that pharmacologic intervention to suppress uninhibited detrusor activity diagnosed by urodynamic testing may help prevent this progression. In patients in whom diminished compliance exists despite maximal anticholinergic therapy, α-adrenergic blockers such as terazosin have been shown to improve compliance (146). Less commonly used measures to treat uninhibited detrusor activity include intravesical instillation of oxybutynin (114,163) and intravesical instillation of capsaicin (42,46,169). For patients with incontinence between catheterization and high-pressure uninhibited detrusor contractions, some have advocated sphincterotomy to reduce the elevated bladder pressures (116), but this commits the patient to both intermittent catheterization and a condom catheter—a condition that does not promote long-term compliance. If intravesical pressures remain elevated despite maximum tolerable medical therapy, surgical intervention is appropriate. Surgical augmentation of the bladder can provide a large-capacity, low-pressure bladder (54,94,134,158). In general, bowel augmentations such as ileocystoplasty have yielded larger increases in bladder capacity than detrusor myomectomy (autoaugment) (142). Rhizotomy as an isolated procedure to increase bladder capacity was done more frequently in the past than currently (57,100).

Some patients experience nocturnal enuresis related to excessive urine output at night. This has recently been shown to occur in patients with SCI because of the absence of normal diurnal pattern of antidiuretic hormone secretion (77). DDAVP has been used successfully in selected patients (33). Sphincteric weakness is the problem in some patients. Penile clamps are rarely used because of risk of injury, but implantation of an artificial urinary sphincter is a well-defined remedy (131,170). Collagen injection has also been used with some success (10).

Among men performing intermittent catheterization, urethral strictures can occur from repeated instrumentation. The reported incidence ranges from 3% to 19% of patients managed by intermittent catheterization for more than 5 years (27,117). Low-friction hydrophilic catheters might decrease stricture occurrence, but this has yet to be demonstrated (157). Occasionally, patients do not have a true stricture but experience episodic difficulty passing the catheter through the sphincter. If a gentle pressure of the catheter tip against the sphincter is maintained, the sphincter will usually relax and permit catheter passage. If not, a gloved finger in the anus may induce relaxation of the sphincter and facilitate passage of the catheter. Some patients develop hypertrophy of the smooth muscle at the bladder neck that creates a ledge, which can interfere with catheterization (116). Passage may be facilitated either by using a coudé catheter or administering α-adrenergic blockers to decrease bladder neck tone (71).

Indwelling Catheter

A chronic indwelling catheter is an option of last resort, and the complications associated with it are well documented. Jacobs and Kaufman (73) reported on 19 veterans with SCI managed by an indwelling catheter for a mean of 21 years. Abnormal upper tracts on IVP (hydronephrosis, stones, pyelonephritic scarring, or absent kidney due to nephrectomy) were found in 76%. Major complications requiring hospitalization (pyelonephritis, stones, need for nephrectomy, hemorrhagic cystitis, bladder cancer, and serious urethral complications) occurred in 96%. The rate of major complications was 0.25 per year. Other series have shown similar complications. Chao and colleagues (34) provided data on patients managed by an indwelling catheter for 20 years or more. Among 32 patients, there was a high incidence of renal stones (8 patients), bladder stones (7 patients), upper tract scarring and caliectasis (14 patients). Three patients developed carcinoma of the bladder, including squamous cell carcinoma (one patient), transitional cell carcinoma (one patient), and adenocarcinoma (one patient). Dewire and colleagues (47) reported a comparably high incidence of complications (Table 27.12). It has been reported that regular use of oxybutynin in patients with an indwelling catheter may preserve bladder compliance and reduce the incidence of hydronephrosis (78). Similarly, some authors have recommended daily clamping of the catheter for 2 hours to maintain bladder capacity (133). However, neither measure has been validated by prospective studies.

Despite the many urologic complications associated with chronic catheterization, renal function is usually preserved. Sekar and colleagues (132) found no significant influence of the method of bladder management on preservation of renal function. A total of 1,114 patients with SCI were followed annually with effective renal plasma flow determined by renal scan. Twenty percent of the patients had been followed for at least 10 years; 40% had been followed at least 5 years. Changes in renal function were compared among patients managed by indwelling Foley catheter, condom catheter, intermittent catheterization, and suprapubic catheter. No significant deterioration in renal plasma flow was seen with any method of bladder management, and no differences could be demonstrated. This observational study is not without methodologic weaknesses, but it is an important study showing that long-term management with an indwelling catheter is not generally associated with an inexorable decline in renal function.

Indwelling urethral catheters are particularly problematic in women because of urethral complications (150). In a series of 13 women managed by chronic Foley drainage for a mean of 7 years, McGuire and Savastano (98) reported development of a nonfunctional urethra in 54% and urethral erosion in 46%. This was in addition to other complications, including IVP changes (54%), autonomic dysreflexia (54%), stone recurrence (100%), urine leakage (92%), and febrile UTI (92%). In a series of 22 patients with catheter drainage for a mean of almost 17 years, Bennett and colleagues (8) found a similarly high incidence of urethral incompetence (9 patients), as well as other complications, including hydronephrosis (6 patients), reflux (10 patients), and bladder stones (16 patients). When severe urethral incompetence occurs in a woman with an indwelling urethral catheter, surgical intervention is usually required to provide effective drainage and eliminate leakage. In many cases, a pubovaginal sling tied with moderate tension will suffice and can be combined with suprapubic catheter placement. In other cases, surgical closure of the bladder neck may be necessary.

Foley Versus Suprapubic Tube

Long-term suprapubic catheterization as an alternative method of bladder drainage has been viewed with varying enthusiasm. Some older series (65) suggested a much higher incidence of serious complications with a suprapubic tube than with a urethral catheter. Recent series are more encouraging. In 185 patients managed by suprapubic catheterization for a mean of 2 years, the most common problems were catheter blockage (18%), leakage (8%), and recurrent symptomatic UTI (4%). Bladder stones requiring intervention were present in nearly half of those patients experiencing these problems (133). MacDiarmid and colleagues (95) reviewed 44 patients in whom a suprapubic catheter was used with a mean follow-up of nearly 5 years. No patient experienced renal deterioration. Incontinence occurred in 11%, most often in women with urethral incompetence due to long-term use of a urethral catheter. Symptomatic infections were common (52%) as were bladder stones (41%) and catheter blockage (36%). This experience suggests that suprapubic catheterizations is an acceptable alternative to chronic urethral catheterization. In women, it may avoid the urethral complications associated with Foley catheters (148).

Catheter blockage occurs frequently with both urethral and suprapubic catheters. The occluding sediment is usually calcium and magnesium phosphate, a composition similar to that of infection stones. Bacterial urease activity and urinary calcium concentration are considered the most important factors (23). Treatment to eradicate urea-splitting organisms, avoiding drug- or diet-induced increases in pH or urinary calcium, and maintaining adequate hydration and generous urine output are measures that may reduce the incidence of catheter blockage.

Indwelling catheters are associated with metaplastic and neoplastic changes in the bladder urothelium, particularly squamous metaplasia and squamous cell carcinoma. The risk is greater with an indwelling catheter than with intermittent catheterization, suggesting that chronic irritation plays a causal role (166). Nitrosamines produced by infecting bacteria may also contribute to neoplastic transformation (141). Bejany and colleagues (6) reported a 2.3% incidence of tumors among their patients. Squamous cell carcinoma predominated (9 of 11 patients). One patient had transitional cell carcinoma and one had mixed transitional and squamous cell carcinoma. Locke and colleagues (92) prospectively screened 25 patients catheterized for a minimum of 10 years by urine cytology and bladder biopsy. Two cases of squamous cell carcinoma of the bladder were identified (92). Trop and Bennett (150) reported that screening biopsy of 32 patients managed with an indwelling catheter for 4 to 36 years showed squamous metaplasia in 27 patients, transitional cell carcinoma in three patients, and squamous cell carcinoma in two patients.

Although some have argued against routine screening (172), screening for bladder cancer in high-risk patients has been recommended because tumors identified by screening are usually lower stage and have better survival rates than those that cause symptoms (108). Various screening protocols have been suggested. MacDiarmid and colleagues (95) recommended routine cystoscopic screening of patients with an indwelling catheter for more than 5 years. However, patients with indwelling catheters often have chronic inflammatory changes in the bladder mucosa that make the cystoscopic appearance nonspecific. Cytology may be a useful adjunct (143). Although it may be sufficient to perform annual screening with cystoscopy and cytology, and to biopsy only those patients with suspicious findings, some have recommended routine cystoscopy, cytology, and random biopsy in all patients who have had an indwelling catheter for 10 years (73).

Incontinent Urinary Diversion

Ileal conduit urinary diversion was a popular management strategy in the past, but the complications associated with long-term reflux of chronically colonized urine have diminished enthusiasm for its use (102). Ileocystostomy (Fig. 27.9), or “bladder chimney,” is currently the preferred method of incontinent urinary diversion because reflux is prevented by the integrity of the native ureterovesical junction (105,123,130). This reconstruction is suitable for the patient who has not done well with catheter drainage and in whom no management strategy, other than incontinent urinary diversion, is a realistic option. Proper patient selection is essential to avoid postoperative issues of incontinence

due to sphincteric deficiency or large-volume “residuals” with stasis and sediment or stone formation. In female patients in whom sphincteric incompetence exists due to long-term Foley catheter drainage, a pubovaginal sling may be performed simultaneously to eliminate leakage from below (123).

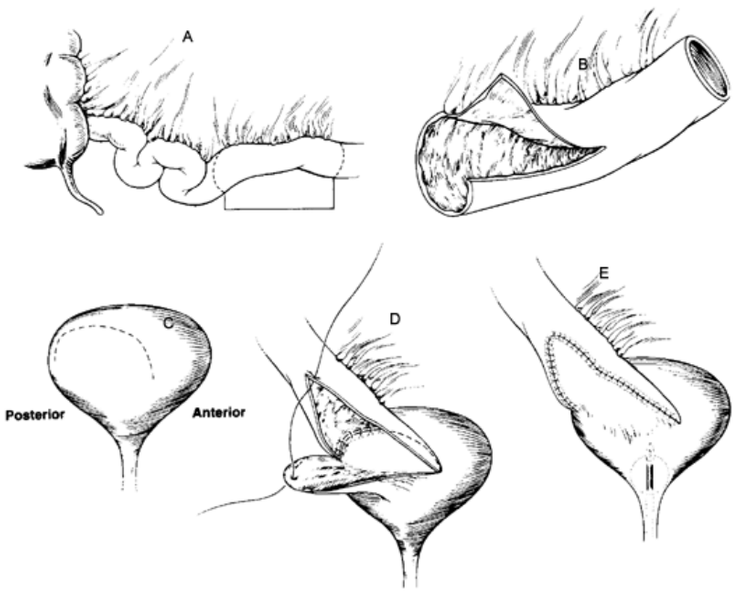

FIGURE 27.9. A–E: Incontinent ileovesicostomy. A segment of ileum long enough to reach without redundancy from the bladder to a predetermined stoma site is isolated, spatulated, and anastomosed to the bladder. (From Schwartz SL, Kennelly MJ, McGuire EJ, et al. Incontinent ileo-vesicostomy urinary diversion in the treatment of lower urinary tract dysfunction. *J Urol* 1994;152:99, with permission.)

Continent Urinary Diversion

A continent stoma can facilitate intermittent catheterization in patients with an inaccessible or damaged urethra. Usually, this is combined with creation of a large-capacity, low-pressure reservoir (139). This type of reconstruction can be used even by patients with limited hand function and has a substantial positive impact on quality of life and sexuality (104,161). Reconstruction may involve cystectomy performed for erosion, fistulization, or tumor, with creation of continent urinary diversion. More commonly, augmentation of the existing bladder is combined with creation of a catheterizable stoma. A variety of reconstructions have been used with good success and excellent continence rates. The recently described Monti procedure combined with ileocystoplasty provides the advantages of bladder augmentation using small bowel with a narrow-caliber catheterizable channel of generous length (Fig. 27.10) (26,103). If urethral incompetence exists, it may be addressed by either pubovaginal sling or formal bladder neck closure (11,35,69,85,104,119,139,145,147,110).

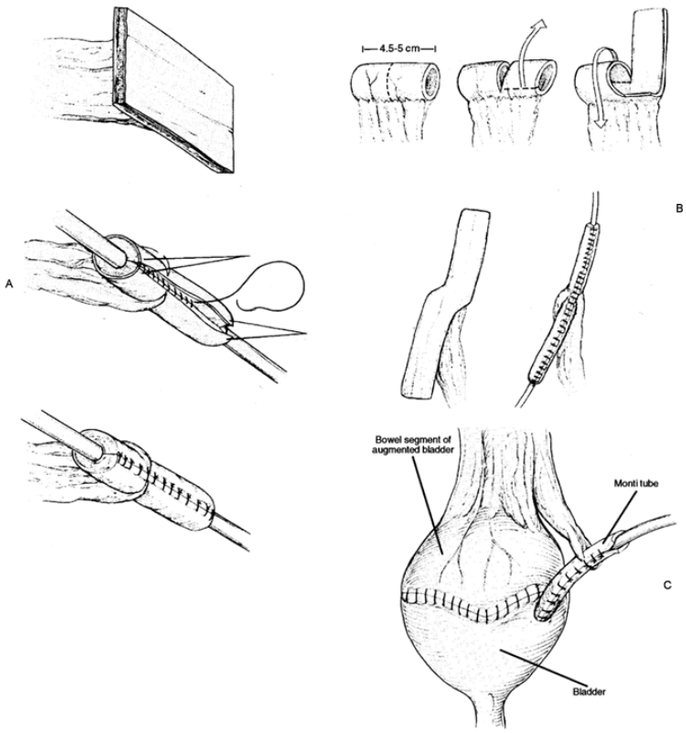

FIGURE 27.10. Monti procedure. **A:** A catheterizable tube is created from a 2- to 3-cm segment of ileum opened longitudinally and then tubularized along the perpendicular axis. **B:** If a longer catheterizable channel is required, a double Monti tube can be created. **C:** Implantation of the catheterizable channel into the bladder to provide a continent stoma can be combined with simultaneous ileocystoplasty to provide a large-capacity bladder. (From Labbi A, Gosalbez R, Lince LF. Monti procedure: refashioned short bowel segments for construction of catheterization channels. *Curr Surg Tech Urol* 2000;13:1, with permission.)

UROLOGIC COMPLICATIONS OF SPINAL CORD INJURY

Part of "27 - SPINAL CORD INJURY "

Urinary Tract Infection

UTIs and stones are the most common urologic complications of spinal cord injury. Although the overall incidence of UTI is not known, one prospective study of patients managed by either intermittent catheterization or condom catheter showed an incidence of significant bacteriuria associated with fever and chills of 1.82 episodes per person per year (156). Another retrospective study reported an annual incidence of UTI in spinal cord patients of 20% (168). The increased incidence of UTI in the spinal cord population results from a number of factors: elevated intravesical pressures, bladder overdistention, vesicoureteral reflux, outlet obstruction, large postvoid residuals, instrumentation, and urinary tract stones. Other influences may include pattern

of fluid intake, reduced host defenses due to chronic illness, local tissue trauma, and personal hygiene (156).

The relative risk of UTI with different methods of bladder management has not been subject to rigorous controlled studies; however, there is a general consensus that patients with an indwelling catheter are at greatest risk for developing UTI. Patients with an indwelling catheter are almost uniformly bacteriuric. The daily incidence of bacteriuria accrues at the rate of 5% to 10% per day, and the vast majority of patients with a catheter in place for more than 30 days are bacteriuric (56,159). The infection rate with suprapubic tubes and Foley catheters is equivalent (109). Bacteriuria is common in men managed with a condom catheter. The incidence of bacteriuria has been found to be greater than 50% in one study (110). Factors that predispose to bacteriuria are kinking of the catheter and colonization of the urine from skin flora (24). Occasional catheterization may also serve as an inoculating event. Sphincterotomy may reduce the incidence of symptomatic UTI by reducing outlet resistance and decreasing intravesical pressures (25). Intermittent catheterization may reduce the incidence of symptomatic UTI as compared with an indwelling catheter, but most patients maintained on intermittent catheterization are also bacteriuric. Studies comparing sterile versus nonsterile methods of catheterization are inconclusive. Some studies have shown a significant effect on the rate of UTI, but others have not (120). Bacterial colonization of the perineal skin and distal urethra is thought to be an important source of urinary pathogens (60). A sterile method of intermittent catheterization has been developed that uses an introducer tip to bypass the distal 1.5 cm of the urethra. A prospective study of spinal cord–injured patients performing intermittent catheterization with or without the introducer tip showed significant decrease in UTI with the use of the urethral introducer tip (9).

The criteria for diagnosis of significant bacteriuria and distinguishing colonization from infection are issues of clinical importance. The National Institute on Disability and Rehabilitation Research (NIDRR) Consensus Statement recommended the following criteria, based on colony-forming units (cfu) per milliliter of urine, for the diagnosis of bacteriuria in patients with spinal cord injury (107). For patients on intermittent catheterization, 10^2 cfu/mL or greater was considered significant. A value of greater than 10^4 cfu/mL was considered significant for clean void specimens from catheter-free males using collecting devices. Any detectable trace of uropathogens from indwelling catheters or suprapubic aspirates was considered significant, because the vast majority of patients with an indwelling catheter and low-level bacteriuria showed an increase to greater than 10^5 cfu/mL within a short period of time (24). Asymptomatic bacteriuria is generally not treated. Occasionally, individuals in an immunocompromised state or with vesicoureteral reflux may be considered for treatment or prophylaxis. Patients with alkaline urine due to otherwise asymptomatic infection with urea-splitting organisms such as *Proteus mirabilis* are a special case because of the potential for stone formation. In these patients, the bacteriuria should be treated with appropriate antibiotics based on culture and sensitivity testing and follow-up cultures obtained to ensure eradication of the urea-splitting organism.

The significance of pyuria remains controversial. Pyuria is commonly observed in patients with SCI in the absence of overt symptoms. In some patients, this may occur from irritative effects of the catheter on the bladder wall. In others, it may be related to the bacteriuria. One small study suggested that more than 50 leukocytes per high-power field predicted a higher likelihood of developing symptoms related to UTI (118). On the other hand, a small prospective study failed to confirm the predictive value of pyuria. Although mean level of pyuria was almost tenfold higher in symptomatic versus asymptomatic infection, changes in level of pyuria did not predict progression to symptoms (40). The significance of pyuria in patients with spinal cord injury remains to be clarified by further research.

The issue of prophylaxis to prevent UTI has been exhaustively examined. Antibiotic prophylaxis will decrease the incidence of bacteriuria and UTI in the short term, but a long-term benefit is doubtful. Because of the potential for antibiotic prophylaxis to elicit antimicrobial resistance, it is not generally recommended. However, prophylaxis might be considered for selected patients. This may include patients in whom symptomatic infection recurs with the same organism despite proper treatment and in whom thorough evaluation reveals no specific nidus for bacterial persistence. This may occur more commonly than generally acknowledged. In one study, two-thirds of patients treated for UTI showed the same organism to be present days to weeks after the completion of the antibiotic course (40). In men, this may be related to prostatic colonization (76).

A number of studies have suggested that bladder irrigation with antimicrobial agents may reduce bacteriuria; however, the use of such agents has been limited because of allergic reactions and hematuria (24). Methenamine is a well-tolerated oral medication that is converted to formaldehyde in nonalkaline urine. It shows no effect on gastrointestinal flora, has minimal side effects, is inexpensive, and does not produce resistant organisms (3). Several studies have suggested that methenamine may decrease the incidence of bacteriuria and UTIs in patients managed by intermittent catheterization (3,81,144). However, the long-term efficacy of methenamine in reducing UTI has not been convincingly demonstrated. It is important to note that methenamine is not active in alkaline urine, a condition that is associated with urea-splitting organisms.

UTI is the most common cause of fever in the spinal cord–injured patient (12). Because of loss of sensation, many patients do not experience frequency, urgency, or dysuria. More commonly they report abdominal or back discomfort,

leakage between catheterizations, increased spasticity, autonomic dysreflexia, malaise, lethargy, and cloudy or malodorous urine. The most common uropathogens in catheter-associated UTIs are *Escherichia coli, Proteus* species, *Klebsiella* species, *Pseudomonas* species, *Serratia* species, *Providencia* species, enterococci, and staphylococci, including methicillin-resistant species. Infection with multiple organisms is common. When possible, a urine culture should be obtained before empiric treatment is initiated. A broad-spectrum antibiotic such as a fluoroquinolone is the agent of choice for empiric therapy (24). Amoxicillin, nitrofurantoin, and trimethoprim-sulfamethoxazole are generally not recommended because of high prevalence of resistance to these agents in the SCI population. Patients with fever or hemodynamic changes are generally hospitalized and treated with empiric broad-spectrum therapy such as aminoglycoside and ampicillin or a penicillin derivative (24). Patients treated with antibiotic to which the urine cultures demonstrates sensitivity should show a response within 24 to 48 hours. If not, repeat urine culture should be obtained and imaging studies performed to rule out obstruction. Invasive procedures such as cystograms or urodynamic studies are delayed until the acute infection is resolved. The duration of therapy in spinal cord–injured patients has not been established. Treatment for 7 to 14 days is usually recommended; however, shorter regimens of 4 to 5 days are probably effective in the mildly symptomatic patient (24). The role of a follow-up culture is unclear because asymptomatic bacteriuria may not be a cause for treatment. However, in a patient with recurrent UTIs, follow-up culture may be appropriate to rule out bacterial persistence, which would trigger urologic investigation. Likewise, a patient treated for infection with a urea-splitting organism should have a follow-up culture to ensure its eradication.

Patients with recurrent, symptomatic UTI should undergo urinary tract imaging and review of their bladder management program, with particular attention to their frequency of intermittent catheterization or voiding schedule, the use of recommended drugs, and catheterization techniques (24). Recurrent symptomatic infection may be related to high storage pressures and should prompt urodynamic evaluation. Intervention to decrease storage pressures will usually decrease the incidence of symptomatic infection.

Stones

Kidney and bladder stones occur in the SCI population with a reported incidence of 7% to 32% (66). In a study of 898 SCI patients, there was a 14.8% incidence of renal stones and a 29% incidence of bladder stones requiring cystolitholapaxy (66). Chronic UTI and hypercalciuria associated with immobilization are the primary etiologic factors (22). The presence of a chronic indwelling catheter is associated with a much higher rate of stone formation. In the study by Hall and colleagues (66), the risk of stone was 57% among patients with an indwelling catheter versus 28% in those without. The presence of vesicoureteral reflux was associated with a much higher rate of kidney stone formation (38% versus 11%).

Autonomic Dysreflexia

Autonomic dysreflexia is an acute syndrome of massive reflex sympathetic discharge in response to noxious stimuli. It occurs in patients with SCI at or above the T-6 level (37,149). Bladder distention is the most common cause of autonomic dysreflexia. Other causes include bowel distention or any of a range of intense (e.g., sexual activity) or noxious stimuli (149). These stimuli elicit a cord-mediated sympathetic response that is isolated from supraspinal inhibition and results in generalized sympathetic activity below the level of injury. Hypertension resulting from this response elicits a limited parasympathetic response, including reflex bradycardia and vasodilation above the level of injury (Fig. 27.11).

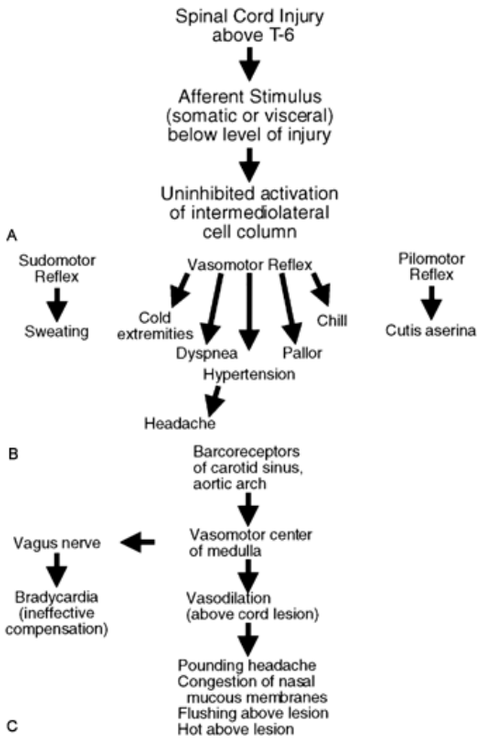

FIGURE 27.11. Pathophysiology of autonomic dysreflexia. **A:** Mechanism of reflex induction. **B:** The autonomic reflex. **C:** The inhibitory response to the reflex. (From Trop CS, Bennett CJ. Autonomic dysreflexia and its urological implications: a review. *J Urol* 1991;146:1461, with permission.)

Patients may complain of headache, shortness of breath, blurred vision, anxiety, agitation, chest pain, and nausea. Pallor, piloerection, somatic and visceral muscle contraction, and spasticity are observed below the level of the lesion, and flushing and intense sweating are seen above. Systemic changes include hypertension and bradycardia or sometimes tachycardia. Uncorrected, autonomic dysreflexia can produce life-threatening complications. The first order of treatment is to remove the initiating stimulus, if possible. When necessary, nifedipine can be administered sublingually to treat the acute episode (2). Terazosin has been recognized as an effective prophylactic therapy for patients with recurrent symptoms of autonomic dysreflexia (151). Some patients with reflex voiding experience dysreflexia related to increases in bladder pressure during voiding. In selected patients, sphincterotomy or stenting may decrease voiding pressures and ameliorate the symptoms of dysreflexia (5,29,32,115).

Anesthetic Risks

Patients with SCI present a unique anesthetic challenge. Perioperative issues include autonomic dysreflexia, bradycardia, hypotension, respiratory inadequacy, and muscle spasms. Patients with low, complete lesions and no history of dysreflexia undergoing surgery below the level of the lesion may not need anesthesia for pain control but should have anesthetic monitoring. In patients with higher lesions, autonomic dysreflexia may be precipitated by bladder distention, as well as other surgical maneuvers. General anesthesia can be used; however, spinal anesthesia is being increasingly recognized as a safer and more effective method of anesthesia that effectively protects against autonomic dysreflexia (67). Respiratory function is often a major perioperative

concern in patients with high SCI. Lesions above C-6 may affect diaphragmatic function. Abdominal and intercostal muscle function may be severely compromised by high thoracic lesions, making effective coughing impossible without assistance (2).

SEXUAL DYSFUNCTION

Part of "27 - SPINAL CORD INJURY "

Sexual function is an important concern for both male and female SCI patients and their partners (14,36,44). In one study of women with SCI, 69% were satisfied with their postinjury sexual experiences but considered self-confidence, spasticity, and lack of spontaneity to be significant issues (36). Sexual function in men with SCI is generally more problematic and includes issues of impotence, ejaculatory dysfunction, and failure to achieve orgasm. Following recovery from spinal shock, men may display reflexogenic erections or psychogenic erections (14). Reflexogenic erections are typically brief erections induced by stimulation below the level of the lesion and require an intact sacral (S-2 to S-4) reflex arc. If the lesion is above T-11, complete rigidity of the penis can be obtained, but if the lesion is below that level, erection will involve the corpora cavernosa while the spongiosum remains nontumescent. Psychogenic erections induced by cortical outflow involve discharge from the sympathetic center (T-11 to L-2) and are observed in patients with lesions below L-2. Erections occur in more than half of SCI patients, but the frequency of successful coitus is less. Reports of successful coitus range from 5% to 75% (19). Erectile dysfunction has been successfully treated in men with SCI with a range of options, including use of an elastic band to maintain a spontaneous erection, vacuum devices, intracavernous injection of papaverine or prostaglandin, and penile prostheses (14,72). Recently, sildenafil has been shown to be an effective and well-tolerated treatment option for erectile dysfunction in SCI (45,61,97).

INFERTILITY

Part of "27 - SPINAL CORD INJURY "

Women with SCI may experience amenorrhea that lasts for 6 to 12 months after injury. Subsequently, most women with SCI are able to conceive. Pregnancy may be complicated by issues of impaired sensation, autonomic dysreflexia, and increased risk of premature labor and low birth weight, but most patients are able to successfully bear children (19). Fertility in men is more seriously compromised. The estimated incidence of successful pregnancy achieved through intercourse by men with SCI ranges from 1% to 10%. Pregnancy rates of 1% and 6% have been observed in men with complete and incomplete upper motor neuron lesions, respectively. The comparable rates in lower motor neuron lesions are 5% and 10% (88). The causes of infertility include both erectile and ejaculatory dysfunction and poor semen quality.

Hypothalamic neural output travels in the anterolateral columns to terminate in the intermediolateral columns between T-10 and L-3. Sympathetic outflow regulates seminal emission and mediates bladder neck closure during ejaculation. The S-2 to S-4 cord segments provide genital afferent innervation and somatic motor innervation of the striated sphincter and perineal musculature. Bors and Comarr (18) reported that ejaculation occurs in 5% and 32% of men with complete and incomplete UMN lesions, respectively. The rates in complete and incomplete LMN lesions were higher—18% and 70%, respectively. Many patients exhibit a diminished, dribbling ejaculation. In addition to the neurologic dysfunction caused by SCI, confounding influences may exist such as external sphincterotomy and the use of α-adrenergic blockers, which may

cause retrograde ejaculation and impaired vasal and seminal vesical peristalsis (88).

Methods of assisted ejaculation have been used to obtain semen for insemination. These include administration of anticholinesterases, vibratory stimulation, and electroejaculation. Intrathecal prostigmine, which was reported to produce erections and ejaculations, was associated with severe side effects (89). Vibratory stimulation is delivered by placement of a vibrator on the base or glans of the penis and administering stimulation until ejaculation occurs. This technique is most successful in men with incomplete lesions or lesions above T-10. Electroejaculation, achieved by using a rectal probe, is the most popular method of assisted ejaculation because of a high success rate and low incidence of significant side effects. It has been reported to be successful in obtaining semen in 85% to 100% of men with SCI (136). In the event of retrograde ejaculation, the sperm can be retrieved by catheterization and centrifugation. In men who do not ejaculate even with stimulation, sperm can be retrieved by direct aspiration of vasal fluid (89).

Poor semen quality is the rule in men with SCI. One review reported that only 13% of men with SCI had a sperm concentration exceeding the lower limit of normal (20 million/mL) and less than 1% had motility greater than 40%. The average motility of semen obtained by electroejaculation has been reported to be 25%. Lumbar injuries are associated with the lowest motility (89). Factors that have been considered as possible contributors to poor semen quality include UTI, method of bladder management, stasis of prostatic fluid, testicular hyperthermia, abnormal testicular histology, changes in the hypothalamic-pituitary-testicular axis, antisperm antibodies, and side effects of chronic medications (89). A simple and comprehensive, yet nonspecific, explanation put forth by Brackett and colleagues (19) is that poor semen quality in patients with SCI results from a disturbance of the autonomic nervous system. Even though sperm quality may be preserved during the acute phase of injury, most men cannot ejaculate during the acute phase even with vibratory stimulation or electrostimulation, and sperm banking is not generally recommended or attempted (88). Despite all of these issues, fatherhood is possible for many SCI patients through assisted reproductive techniques (19). Techniques of assisted reproduction may include techniques such as artificial insemination or *in vitro* fertilization, and Brackett and colleagues (19) reported over a 50% pregnancy rate in couples who wished to pursue parenthood.

SUMMARY

Part of "27 - SPINAL CORD INJURY "

Over the past century, patients with spinal cord injury have been a driving force in the development of sophisticated urodynamic testing and novel strategies for lower urinary tract management. The impact on the prognosis and quality of life of patients with neurogenic bladder dysfunction has been profound. The investigative techniques, insights, and strategies developed for treatment of these patients have had added value for their general relevance to the evaluation and treatment of nonneurogenic voiding dysfunction in the pediatric and adult population. Basic and clinical research continue to keep spinal cord injury at the forefront of advances in the understanding of bladder function and the neurophysiology of micturition, the development of new drug therapies for bladder dysfunction, and the possible role of the central nervous system in spermatogenesis and fertility.

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28

INFLAMMATORY DISEASES OF THE BLADDER

Grannum R. Sant

G.R. Sant: Department of Urology, Tufts University School of Medicine, New England Medical Center, Boston, MA 02111.

Contents

Inflammatory diseases of the bladder result from specific infectious causes or chemical, radiation, or unknown factors. Uncomplicated urinary tract infections (UTIs) typically occur in young women with normal urinary tracts. Thirty-five percent of women 20 to 40 years of age experience at least one UTI, and acute cystitis affects 4 to 6 million women, resulting in more than 7 million office visits and more than 100,000 hospitalizations annually in the United States (164,165). Cystitis is rare in males, except in uncircumcised boys and adult homosexual men (97).

Complicated UTIs occur in persons with congenital anatomic genitourinary (GU) abnormalities, in those with urologic conditions such as “infection” stones or obstruction, or following urologic surgery and/or urinary catheterization. Bacterial drug resistance is common in complicated UTIs, as are Gram-positive and polymicrobial bacteriuria (147). Complicated UTIs require extended courses of treatment, and recur unless underlying anatomic or functional defects are corrected.

Although *Escherichia coli* is the most common organism in UTIs, complicated UTIs are frequently caused by Enterobacteriaceae such as *Proteus*, *Providencia, Klebsiella, Serratia, Pseudomonas,* and *Enterococcus* species (147). The treatment of complicated UTIs has improved with the

introduction of the fluoroquinolones. These drugs have broad-spectrum antimicrobial activity, achieve high urinary levels following oral administration, and have long half-lives and a low incidence of side effects and bacterial drug resistance (74).

EPIDEMIOLOGY OF URINARY TRACT INFECTIONS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

The prevalence of UTIs varies according to age and gender (Table 28.1). Boys have a higher rate of neonatal UTIs than girls (8). Following the neonatal period, the proportion of females to males with UTIs increases to approximately 25:1, and this female preponderance continues into adulthood (166). In the elderly and institutionalized, the prevalence in both sexes is nearly equal (146).

TABLE 28.1. PREVALENCE OF URINARY TRACT INFECTIONS

Age Group	%	Ratio (Male:Female)
Neonatal	1	1.5:1
Preschool	2–3	1:10
School-age	1–2	1:30
Reproductive age	2–5	1:50
Elderly	20–30	1:5–10

Congenital GU tract disorders, such as vesicoureteral reflux or posterior urethral valves, occur in approximately 40% of male bacteriuric infants—a rate two times higher than that in bacteriuric girls (8). Uncircumcised boys are 10 to 40 times more likely than their circumcised counterparts to develop UTIs in the first year of life because of bacterial colonization of the prepuce (97,161). Bacteriuria in men is rare until the fourth to fifth decades when prostatic diseases and lower urinary tract instrumentation increase the risk. The 5% prevalence rate of bacteriuria in women of childbearing age is due to bacterial colonization of the vaginal introitus and distal urethra (48,165). Three percent of women experience more than one UTI per year, with the majority having a fairly constant rate of infection, averaging three UTIs annually (165).

Relapse of a UTI (Table 28.2) with the isolation of the original bacteria following antimicrobial therapy occurs within weeks of completion of therapy and is due to bacterial persistence or unresolved bacteriuria (165). The latter results from bacterial resistance from prior antibiotic therapy or R-factor mediated resistance, poor antibiotic delivery, azotemia or medullary concentrating defects, or a large bacterial "inoculum." Bacterial persistence occurs with "infected" renal calculi (both sexes) and chronic bacterial prostatitis (men) (97,147). These conditions are the only urologically correctable causes of recurrent UTIs, and patients with bacterial persistence require a complete urologic evaluation.

TABLE 28.2. BACTERIAL PERSISTENCE VERSUS REINFECTION

	Bacterial Persistence	Bacterial Reinfection
Time interval	Weeks	Months–years
Bacterial species	Same	Different
Source of bacteria	GU tract	Outside GU tract
Frequency	Uncommon	Common
Evaluation	All patients	Men, children
Causes	Chronic bacterial prostatitis, Infected calculi (renal, prostatic)	Bacterial adherence (introitus, prepuce)
Surgically correctable	Often	No

GU, genitourinary.

The most common cause of recurrent UTIs is reinfection—isolation of a new bacterial strain following eradication of the original infecting bacteria (Table 28.2). Such infections recur at longer time intervals compared with bacterial persistence, and the bacteria arise from outside of the GU tract, that is, the perineum and vagina in women (48,153) or the colonized prepuce in uncircumcised boys (161).

PATHOGENESIS OF URINARY TRACT INFECTIONS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

A critical balance exists between bacterial virulence factors and host defense mechanisms (Table 28.3 and Table 28.4). Virulence factors are important in patients with normal (anatomic, functional) urinary tracts, whereas altered host defenses are more important in complicated UTIs. The short length of the female urethra and its frequent bacterial colonization contribute to the high frequency of UTIs in women. In men, the longer urethra and the antibacterial activity of prostatic fluid blunt bacterial urethral ascent and reduce the risk of UTIs (97,162).

TABLE 28.3. BACTERIAL VIRULENCE FACTORS

Bacterial adherence	Aerobactin production
Bacterial adhesions	Capsular K antigen
Uroepithelial cell receptors	Bacterial lipopolysaccharide (O antigen)
Bacterial biofilm	
Hemolysin production	

TABLE 28.4. HOST DEFENSES

Mechanical effects of voiding	Antiadherence mechanisms
Bacterial inhibitory properties of urine	Bacterial interference
Immune mechanisms	Uromucoid (Tamm-Horsfall Protein)
Ureteral peristalsis	Mucosal glycosaminoglycans (GAGs)
	Secretory IgA (SIgA)

Bacterial adherence is mediated by fimbriae or pili (typically 150 to 200 per cell), proteinaceous cell surface appendages that attach to disaccharide moieties on epithelial cells (167,171). Type 1 mannose-sensitive fimbriae are expressed by bacteria colonizing the vaginal introitus and lower urinary tract, whereas bacteria associated with pyelonephritis, bacteremia, and urosepsis more frequently express P (mannose-resistant) and other (e.g., X, S, G, M) fimbriae (153). Increased vaginal cell receptivity occurs in women

during and between episodes of recurrent UTIs and is paralleled in buccal mucosal cells, suggesting a genetic predisposition (153). Genetic factors associated with an increased risk of UTIs include the P1 blood group, with an increased risk of pyelonephritis in children, and blood group (e.g., Lewis) nonsecretors, with an increased risk of recurrent cystitis in women (155).

Other virulence factors contribute to the pathogenesis of UTIs (Table 28.3). Bacterial strains causing acute pyelonephritis are more likely to produce hemolysin, aerobactin, express O and K antigens, and show increased adherence to uroepithelial cells compared with strains causing simple uncomplicated cystitis (114). Certain bacterial species, such as *Pseudomonas,* produce a bacterial biofilm on mucosal or foreign body (catheter, prostheses) surfaces. This biofilm is derived from bacterial expolysaccharide and host extracellular matrix proteins (139). Bacteria growing within the biofilm (sessile bacteria) are protected from the effects of antibiotics (139), which may explain the difficulty in eradicating infections associated with indwelling catheters and GU prostheses.

Host defense mechanisms counteract the propensity of uropathogenic bacteria to cause UTIs (Table 28.4). High postvoid residual urine volumes favor bacterial growth and proliferation in patients with bladder outlet obstruction and neuropathic bladder dysfunction (22,171). Tamm-Horsfall protein (uromucoid), produced in the ascending limb of the loop of Henle, helps to bind *E. coli* to uromucoid, and elimination of the latter during voiding is an efficient antibacterial defense (114,167). Emptying mechanically interferes with bacterial adherence because of the shearing forces associated with voiding. Normal urine inhibits bacterial growth and is bactericidal against small numbers (inocula) of uropathogens (114). Factors contributing to this inhibitory defense mechanism are high osmolality, high urea concentration, low urinary pH, and the high organic acid content of urine (171).

Commensal lactobacilli adhere to vaginal epithelial cells and competitively prevent adherence of pathogenic bacteria (167). The glycosaminoglycan (GAG) moiety of the mucopolysaccharide lining of the bladder wall discourages bacterial adherence (114).

Urinary IgA and IgG antibodies exert a protective effect by coating infecting bacteria and interfering with urothelial attachment. Children susceptible to recurrent bacteriuria have lower baseline levels of urinary IgA. Bladder immunoglobulin levels can be increased experimentally by immunization, leading to faster clearance of infection (181).

UNCOMPLICATED CYSTITIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

E. coli is responsible for most community-acquired UTIs. *Staphylococcus saprophyticus,* a Gram-positive, coagulase-negative, novobiocin-resistant, nonhemolytic coccus, accounts for 10% to 20% of UTIs in sexually active women (165). Other aerobic, Gram-negative bacteria causing cystitis include *Klebsiella* species, *Enterococcus, Proteus mirabilis,* and *Pseudomonas.* Less common infecting organisms include *Staphylococcus epidermidis,* fungi, *Gardnerella vaginalis, Lactobacillus,* and *Ureaplasma urealyticum.*

Diagnosis of a UTI is based on the presence of symptoms and confirmation of the infection. Dysuria is the main symptom associated with frequency, urgency, nocturia, pain, and voiding in small amounts. Acute pyelonephritis causes flank, back, and abdominal pain, and systemic symptoms, such as fever, malaise, nausea, vomiting, and sweats. Upper tract UTIs are more difficult to treat, have higher complication rates, and require prolonged treatment and frequent hospitalization. Clinical evaluation cannot reliably delineate lower from upper tract infections (9). Many patients (10% to 50%) with cystitis have subclinical pyelonephritis, as shown by sophisticated localization culture techniques. Definitive techniques to localize infections such as ureteral catheterization (Stamey test) and the bladder washout (Fairley test), are invasive and not commonly used.

Pyuria, greater than 10 white blood cells (WBCs) per high-power field (HPF) is a sensitive indicator of infection. Pyuria also can be detected by dipstick chemical detection of leukocyte esterases or a hemocytometer cell counting chamber (52). Bladder urine is normally sterile, but voided urine can be contaminated by distal urethral and perineal organisms. Following its initial description in acute pyelonephritis, significant bacteriuria has been defined as greater than 10^5 bacteria per milliliter of urine (83). However, recent studies in acutely dysuric women with symptoms of cystitis show that one-third have colony counts of 102 to 104 colony-forming units (CFU) per milliliter of urine (164). Significant bacteriuria is now defined as greater than 102 colonies of bacteria per milliliter in a symptomatic patient. Reasons for low counts include urinary frequency, diuresis, fastidious organisms, and slow-growing bacteria (165).

Direct microscopic examination of a Gram-stained, uncentrifuged urine showing one bacterial organism per oil-immersion field or an unstained centrifuged urine showing any bacteria correlates with a colony count of greater than or equal to 105 CFU/mL of urine. The bacterial enzyme, nitrate reductase, produces nitrite from urinary nitrates and is the basis of a quick dipstick test for bacteriuria. These rapid methods for the detection of bacteriuria are specific but not very sensitive.

In sexually active young women, symptoms of cystitis can be mimicked by sexually transmitted diseases (STDs) or vaginitis. Vaginitis can be caused by candidal fungal species, trichomonas, genital mycoplasmas, or *Gardnerella vaginalis* (175). The common STD pathogens are *Neisseria gonorrhea, Chlamydia trachomatis,* and herpes simplex viruses. In the past, symptomatic women with "low count" bacteriuria and urethritis were diagnosed as having the "urethral syndrome" (164).

Chronic bladder inflammation may lead to cystitis cystica, which is characterized microscopically by lymphoid follicles or cysts (Fig. 28.1). Cystitis cystica, cystitis glandularis, and Brunn's nests are related conditions, commonly seen in chronic inflammation. Brunn's nests are invaginations of transitional cell epithelium that grow down from the bladder surface and become separated. Central cavitation of the infolded mucosa results in cystitis cystica. The cysts in cystitis cystica are lined by low cuboidal cells, which may differentiate into columnar epithelium and formation of cystitis glandularis. These lesions are not associated with neoplasia, although they suggest mucosal instability.

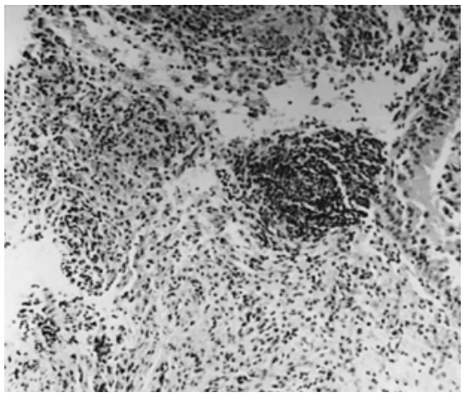

FIGURE 28.1. Cystic follicularis. Bladder biopsy in a 67-year-old woman with recurrent cystitis and the cystoscopic appearance of cystitis cystica. Sections of a trigonal biopsy show inflammation, fibrosis, and lymphoid follicles in the lamina propria.

The bladder trigone in women frequently reveals whitish patches that show squamous metaplasia on biopsy. The term "pseudomembranous trigonitis" is mistakenly used to describe this squamous metaplasia. Leukoplakia is also a whitish patch that infrequently involves the trigone. Lesions suspicious for leukoplakia should be biopsied because squamous cell develops in approximately 25% of cases of leukoplakia (137).

Cystitis associated with pneumaturia suggests bowel fistulization into the bladder. Enterovesical fistulae appear as reddened edematous areas in the posterior bladder wall. A shaggy necrotic center may be visualized, with bowel contents emanating into the bladder. Sigmoid diverticulitis is the most common cause of enterovesical fistulae (96). A computed tomography (CT) scan is recommended in all cases of suspected enterovesical fistulae. Vesicovaginal fistulae occur primarily after gynecologic surgery and vesicouterine fistulae after cesarean section (126).

Uncomplicated cystitis is treated with antibacterial agents that achieve high urinary concentrations. Conventional 7- to 10-day treatment with trimethoprim-sulfamethoxazole (TMP-SMX), amoxicillin, and nitrofurantoin is safe and effective (165). In enterococcal UTIs, *in vitro* TMP-SMX sensitivities are misleading because *in vivo* the organisms can incorporate exogenous folates and escape the antibacterial action of TMP-SMX (55). Uncomplicated UTIs, especially in women, are often treated with single-dose or short-course (3 to 5 days) therapy (113). This results in better patient compliance, less cost, fewer side effects, and less chance of bacterial resistance (165). The widespread use of TMP-SMX and ampicillin has led to the development of chromosomally and plasmid-mediated bacterial resistance (140,163,188).

COMPLICATED URINARY TRACT INFECTIONS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Recurrent Urinary Tract Infections in Women

Simple cystitis responds to antimicrobial therapy in more than 90% of cases. However, 20% of women develop recurrent cystitis as a result of reinfection by bacteria from the colonized perineum or introitus (165). GU tract abnormalities are not a significant factor in causation of these UTIs. A genetic predisposition to increased bacterial adherence to urothelial cells is linked to HLA phenotypes (HLA-A3) and blood group nonsecretor status (Lewis and ABO groups) (Table 28.5) (155).

Inherited	Acquired
Blood group nonsecretors	Sexual activity
HLA-3 phenotype	Diaphragm usage
	Spermicidal use

TABLE 28.5. RISK FACTORS FOR URINARY TRACT INFECTIONS IN WOMEN

Acquired risk factors include sexual activity and the use of the diaphragm and spermicidals (Table 28.5) (45,75). Bacterial colonization of the vagina is more notable in women using spermicidal foams and diaphragms. Nonoxynol-9, an active ingredient in spermicides, has significant antimicrobial activity against sexually transmitted bacteria and lactobacilli but little activity against *Enterococcus, Klebsiella,* and *E. coli* (75). Diaphragms may partially

obstruct the urethra, interfere with normal voiding, and increase the risk of urinary stasis and infection (45).

Treatment of recurrent cystitis includes postintercourse voiding and long-term, low-dose or postcoital oral antimicrobial prophylaxis. Continuous, low-dose antibiotic prophylaxis for 3 to 12 months reduces infection rates from 2 to 3 to less than or equal to 0.15 infections per patient year (164,165). Prophylactic antibiotics need to be safe and inexpensive, and they should not select resistant bacteria from the bowel flora. Common antimicrobial regimens used for prophylaxis are nitrofurantoin (100 mg daily), TMP-SMX (one-half double-strength tablet daily), or trimethoprim (100 mg daily) (135). With TMP-SMX, bacterial resistance, enterococcal superinfections, and yeast vaginitis are problematic (165). Norfloxacin also has been used for prophylaxis (116). However, the fluoroquinolones are not the drugs of choice for prophylaxis, unless the bacteria are resistant to the commonly used antibiotics. The cost of quinolones makes them less attractive for long-term prophylaxis compared with nitrofurantoin, TMP-SMX, or trimethoprim.

Antibiotic prophylaxis is recommended for patients with more than three UTIs per year. If the infections are temporally related to sexual intercourse, postcoital prophylaxis can be used. Temporary discontinuation of diaphragms and/or spermicidals may be needed in some women to break the vicious cycle of recurrent UTIs (45). In postmenopausal women, intravaginal estrogen reduces the frequency of recurrent UTIs by altering the vaginal flora and pH (138). Intravaginal lactobacilli instillation has been used to prevent recurrent UTIs. Lactobacilli increase vaginal acidity, produce hydrogen peroxide (some species), and interfere with attachment of uropathogenetic bacteria. Cranberry juice also may play a role in reducing pyuria and recurrent cystitis (79). Bacterial immunization protocols also have been used to reduce the chance of recurrent UTIs.

Urinary Tract Infections in Pregnancy

Asymptomatic bacteriuria occurs in 5% of pregnant women—a rate similar to that in nonpregnant women (21,147). Asymptomatic bacteriuria predisposes to pyelonephritis. The hormonal and mechanical changes that occur in pregnancy increase the risk of pyelonephritis (147). Hyperestrogenism causes “hydroureter of pregnancy” by the eighth week of gestation, with greater frequency on the right side because of mechanical factors (e.g., right-sided placenta). Ureteral peristalsis is reduced, and bladder capacity increases as the bladder moves out of the pelvis into the abdomen. Urinary stasis, reduced renal concentrating ability, aminoaciduria, and gestational glycosuria increase the risk of pyelonephritis, especially in the third trimester.

Thirty percent of women with asymptomatic bacteriuria develop acute pyelonephritis later in pregnancy and pyelonephritis is the most common (1% to 2%) medical complication in pregnant women (172). Pyelonephritis is associated with maternal and fetal risks (198). Premature labor is more common because of bacterial liberation of prostaglandins from phospholipids in the amniotic and chorionic membranes. Treatment of asymptomatic bacteriuria prevents the development of acute pyelonephritis in more than 90% of patients. Women should be screened at their first prenatal visit, and bacteriurics should be treated to reduce the risks of prematurity, premature labor, low birth weight, and other fetal complications. Penicillin and ampicillin are relatively safe for both the mother and the developing fetus (17). Despite many years of clinical use, these drugs are still classified as class B in the U.S. FDA safety rating for drugs used in pregnancy. Nitrofurantoin, although classified as a class C drug, is generally regarded as safe in all trimesters of pregnancy as are the cephalosporins (186). The use of quinolones in children and pregnant or nursing women is not recommended (74).

Recurrence or persistence of infection following antibiotic treatment suggests the presence of anatomic abnormalities, bacterial persistence, stones, or renal parenchymal infection and should lead to a full urologic evaluation following parturition. Up to 20% of patients so evaluated will have structural abnormalities of the kidney, ureter, or bladder (147).

Urinary Tract Infections in the Elderly

By the sixth decade of life, bacteriuria is present in 20% of women and 10% of men (41). The prevalence is higher for patients in nursing homes, extended care facilities, and hospitals. Although *E. coli* is the most common infecting organism, there is an increased rate of infection with *Proteus, Klebsiella, Enterobacter, Serratia, Pseudomonas,* and *Enterococcus.* Elderly men have a high frequency of Gram-positive bacteriuria (40% to 50% of all UTIs) related to the more frequent use of urethral catheterization, cystoscopy, and antimicrobial usage (163). Infections are frequently polymicrobial in hospitalized or institutionalized patients.

Numerous factors contribute to the high rate of bacteriuria in the elderly (Table 28.6). Micturition is impaired as a result of prostatic enlargement in men or bladder prolapse in women and levels of prostatic antibacterial factor (PAF) decrease with age. Perineal soiling from fecal incontinence, reduced host defense mechanisms (e.g., T-H protein), and indwelling and condom catheters all predispose to bacteriuria.

Urine cultures in the elderly with symptomatic UTIs do not always show greater than or equal to 105 bacteria per milliliter of urine—a situation similar to that in sexually active women. Pyuria is not as significant a marker for bacteriuria in the elderly as it is in the young.

TABLE 28.6. URINARY TRACT INFECTIONS IN THE ELDERLY

Prevalence: 20%–50%
Female to male ratio: 2:1–3:1

Risk Factors
Immobilization, instrumentation
Hospitalization, age, systemic disease
Fecal incontinence, neurogenic bladder dysfunction
Catheters (Foley, condom)

Men
Benign prostatic hyperplasia
Prostate cancer
Loss of prostatic antibacterial factor

Women
Bacterial colonization introitus, perineum; pH changes

Bacteriology
Polymicrobial; intermittent bacteriuria
More noncoliform infections
Gram-positive infections in men

Asymptomatic bacteriuria in the elderly does not contribute to excess mortality or morbidity (41,146). Because of the risks of adverse drug reactions and bacterial resistance, routine antibiotic treatment of asymptomatic bacteriuria is unwarranted. Treatment should be started if patients become symptomatic, in immunosuppressed/neutropenic patients, or when urease-producing bacteria cause the infection.

Aging affects the pharmacokinetic disposition of drugs in the elderly because of changes in body composition and diminished function of organs, such as the kidney and the liver. The risk of drug interaction is greater because the elderly use multiple concurrent drugs more frequently than their younger counterparts. The fluoroquinolones generally are tolerated well by elderly patients, and the indications for their use parallel those in younger patients (74,130). Because of the high tissue levels obtained after oral administration, the fluoroquinolones are attractive for the treatment of tissue (e.g., kidney, prostate) infections in the elderly. Judicious use of these agents can reduce the need for hospitalization in patients with pyelonephritis and allows earlier hospital discharge (158).

Catheter-associated Urinary Tract Infections

Catheter-associated UTIs account for 40% of hospital-acquired (nosocomial) infections (Table 28.7). Catheterization (indwelling or in and out) and lower tract instrumentation account for 80% of these infections (163). Between 15% and 20% of all hospitalized patients undergo catheterization, and 1% to 3% develop bacteriuria with a mortality rate of approximately 10% (188). The incidence of bacteriuria with indwelling catheters averages 5% per day and bacteriuria is universally present in all catheterized patients after 3 to 4 weeks.

TABLE 28.7. CATHETER-ASSOCIATED URINARY TRACT INFECTIONS (UTIs)

Catheter-associated UTIs account for 40% of all nosocomial infections.

Significant Causes
Periurethral migration
Bacterial biofilm
Altered bladder defenses (e.g., glycosaminoglycans)

Less Significant Causes
Retrograde spread from distal urethra
Drainage bag contamination
Break in closed drainage system

Because bacteria colonize the distal urethra, catheter insertion results in bacteriuria in 1% of ambulatory patients and 20% of hospitalized patients. Intraluminal contamination may occur by ascending infection from the drainage bag or by breaks in the system of closed drainage. However, the main route of infection is the extraluminal periurethral space (173). Once bacteria reach the bladder, their persistence and proliferation depend on factors, such as bacterial adherence, the antibacterial effect of surface glycosaminoglycans, and the development of “bacterial biofilms” on the catheter surface (115). Poorly fitted condom catheters cause urethral obstruction and impaired bladder emptying (81) and bacteria from the perineum and scrotum may colonize the condom portion of the catheter and act as a reservoir for infection.

Risk factors for bacteriuria in catheterized patients include duration of catheterization, inadequate care of the drainage bag and closed drainage system, female gender, diabetes mellitus, renal failure, and systemic immunosuppression (163). Certain bacteria, such as *Providencia stuartii* and *S. epidermidis,* readily adhere to catheter surfaces and are frequent causes of catheter-associated bacteriuria. Urease-producing bacteria, such as *Proteus* species, hydrolyze urea to ammonia, increase urinary pH, and predispose to the formation of struvite and apatite stones.

Catheter-associated UTIs can be reduced by limiting the duration of catheterization and by using alternative methods of drainage, such as intermittent catheterization (clean or sterile), or suprapubic tubes (147). Instillation of antibacterial agents into the bladder or urinary drainage bag and rigorous meatal cleansing are of little benefit in reducing the risk of catheter-associated UTIs (145). Use of catheters coated with silver alloy may reduce the risk, as does short-term

systemic oral antibiotic therapy for up to 14 days especially in patients undergoing transurethral surgery or renal transplantation.

Catheter-associated UTIs are a major reservoir of antibiotic-resistant organisms in the hospital, but they are rarely symptomatic (approximately 10%), and infrequently cause bloodstream infection (174). Symptoms referable to the urinary tract, fever or peripheral leukocytosis have little predictive value for the diagnosis of catheter-associated UTI (174). The fluoroquinolones are excellent for treatment of catheter-associated UTIs because of their activity against the *Enterobacteriaceae* and *Pseudomonas* sp. It is extremely rare for *E. coli* to develop resistance but *Pseudomonas* resistance has been reported in 5% to 27% of patients treated with the fluoroquinolones (74).

TUBERCULOSIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

GU tuberculosis occurs as a result of hematogenous spread from pulmonary tuberculosis. Over the last few years, the prevalence of tuberculosis has increased in the Western world as a result of changing immigration patterns and the “epidemic” of HIV infections with associated immunosuppression (25). Urologists should consider the diagnosis of GU tuberculosis in patients with irritative voiding symptoms of unclear etiology and sterile pyuria.

Bladder tuberculosis results from downward seeding from a renal focus, and symptoms follow at varying time intervals after the onset of pulmonary or renal tuberculosis (56). Women and children may present earlier with frequency, dysuria, and hematuria—characteristics of bladder implantation of tubercle bacilli. Men more commonly present with epididymitis (134). Men predominate over women (2:1 ratio) and the common age group is 20 to 40 years. Bacterial cystitis is superimposed on bladder tuberculosis in approximately 20% of patients. However, the majority of patients have sterile pyuria (57).

Cystoscopically, tuberculosis appears as patchy erythematous ulcerations with exudates. These lesions mimic transitional cell carcinoma or carcinoma *in situ* (CIS) and biopsy. The ureteral orifices and bladder base are most inflamed in the acute phase. In untreated cases, fibrosis and contracture may occur. Because the trigone contracts less, the ureteral orifices may assume a position in the angle at the top of the bladder making ureteral catheterization difficult if it becomes necessary to evaluate or treat (stent) the hydronephrosis associated with healing tuberculous ureteritis (26).

For diagnosis, at least three consecutive early-morning urine specimens should be cultured, each on two types of media, plain Lowenstein-Jensen medium for *Mycobacterium tuberculosis* and a pyruvic egg medium containing penicillin for *Mycobacterium bovis* (57). Routine guinea pig inoculations are no longer required. Drug sensitivity should be checked whenever mycobacteria are cultured (124). Recently, rapid diagnosis of GU tuberculosis using the polymerase chain reaction (PCR) and DNA hybridization has shown high sensitivity and specificity as well as the capacity for rapid detection using urine samples (110).

Treatment of tuberculous cystitis is based on the premise that pulmonary and renal involvement also is present. Most patients can be treated on an ambulatory basis if their chemotherapy is closely supervised (56). Multidrug oral therapy is currently preferred. Short-course therapy prevents the emergence of resistant organisms because of the rapid bactericidal and sterilizing properties of the drugs used (57). The main antituberculous drugs currently in use are isoniazid, rifampin, streptomycin, pyrazinamide, and ethambutol. Isoniazid (10 to 30 mg/kg per day) is the most effective and important antituberculous agent, and its use requires pyridoxine supplementation. The introduction of rifampin (10 to 20 mg/kg per day), an oral drug, has eliminated the need for parenteral therapy and significantly shortened the course of therapy from the previously accepted 2 years to 4 to 9 months (57).

Short-course, multidrug chemotherapy is based on the following principles: (a) Rifampin and pyrazinamide are potent sterilizing agents, (b) isoniazid and pyrazinamide or isoniazid and rifampin are excellent sterilizing combinations, and (c) streptomycin or ethambutol adds little to the sterilizing ability of the previous combinations. Ethambutol (15 to 20 mg/kg per day) has largely replaced the use of paraaminosalicylic acid, but it is not recommended for children because of the risk of optic neuritis. Patients receiving ethambutol should have monthly visual examinations. Streptomycin and other drugs are needed occasionally when the patient has problems with the preferred drugs or in treating drug-resistant cases.

The most used combination is pyrazinamide, isoniazid, and rifampin administered daily (usually in one dose at night) (191). Streptomycin is added if the infection is severe or the patient is highly symptomatic. Steroids are indicated in patients with severe tuberculosis cystitis or lower ureteral strictures. The main adverse drug reactions are hypersensitivity (usually with streptomycin and rifampin) and hepatotoxicity (isoniazid and rifampin), with jaundice and elevated serum transaminase and alkaline phosphatase levels. Two years of therapy is still recommended by some authorities, although 9-month therapy is less costly and equally effective (56). Bladder fibrosis and contracture are generally preventable by medical therapy. Bladder augmentation or urinary diversion seldom is necessary (57).

VIRAL CYSTITIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Viral cystitis causes irritative voiding symptoms and hematuria. The usual causative viruses are adenovirus types 11, 21, and 35, papovavirus, and influenza A (89,156). Children and immunocompromised adults typically are affected (111).

Cytomegalovirus cystitis has been reported to occur in AIDS.

Viral cultures are not generally available, and diagnosis is usually made clinically. Definitive diagnosis requires viral isolation from acute phase urine cultures and serum antibody titers (complement-fixing and specific-neutralizing antibodies). Ultrasound examination of the bladder may document the characteristic thickening and irregularity of the bladder wall in viral cystitis. The symptoms and the hematuria typically resolve in 2 to 3 weeks. If the ultrasound changes resolve, diagnostic cystoscopy, usually employed for the evaluation of hematuria, may be omitted selectively. If the symptoms and ultrasound changes persist or if there is a palpable bladder mass on rectal or abdominal examination, further evaluation with cystoscopy is warranted. There also may be transient vesicoureteral reflux (107). Because viral cystitis is usually hematogenous in origin, a diagnostic evaluation for obstruction or other anatomic abnormalities is usually not indicated.

Acute viral hemorrhagic cystitis may occur after renal and bone marrow transplantation (197). The disease is usually self-limiting, although serious complications such as pneumonia can occur in immunosuppressed individuals. Patients can be managed successfully without the need to reduce immunosuppressive drug dosing. Intravenous ribavirin and ganciclovir have been used to treat acute adenovirus-associated hemorrhagic cystitis (15).

FUNGAL INFECTIONS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Fungal inflammations of the GU tract are becoming more prevalent because of increased broad-spectrum antibiotic use and the increasing number of patients receiving immunosuppressive drugs and chemotherapy (194). GU fungal infections are commonly caused by *Candida albicans,* but also may be due to *Aspergillus fumigatus, Cryptococcus neoformans, C. glabrata,* and others (159). Symptoms vary widely from the asymptomatic patient with a fungus-colonized bladder catheter to the patient with severe urgency, frequency, and dysuria. *Candida* is a saprophyte in the urinary tract, vagina, external genitalia, or perineum. Antibiotics suppress normal bacterial flora (aerobic, anaerobic, Gram-negative, and Gram-positive bacteria) and encourage colonization and infection with fungal species (141). *Candida* is usually an opportunistic pathogen associated with diabetes mellitus, obstructive uropathy, neuropathic bladder dysfunction, neoplasia, systemic antibiotic/steroid/immunosuppressive therapy, and indwelling urinary catheters.

Most candidal UTIs represent candiduria—lower tract colonization (159). Risk factors for the development of candiduria include female gender and ICU location. Patients receiving oral fluconazole and quinolones are at increased risk of developing *C. glabrata* candiduria (67). Invasion of the bladder wall may lead to candidal cystitis, disseminated candidal infection, and candidemia. Differentiation of colonization from infection relies on the use of urinalysis, urine culture, blood culture, and appropriate serologic and imaging studies. Budding forms and pseudohyphae are seen on careful urinalysis. Blood cultures are positive in only 50% of patients with invasive or renal candidiasis. Serologic testing for the antibody response to candidal antigen is useful for diagnosing serious infection (159).

Candidal species (except *C. glabrata*) form fungus balls or bezors that can obstruct the urinary tract. CT of the bladder may delineate filling defects and bladder wall thickening (Fig. 28.2). Ultrasonography is useful for demonstrating fungus balls (Fig. 28.3). The number of organisms required to constitute a “significant infection” is different for fungal cystitis as compared with bacterial cystitis. In patients without indwelling catheters, colony counts of 10,000 to 15,000/mL of urine on a clean-voided or straight-catheterized specimen are significant and require further investigation (194).

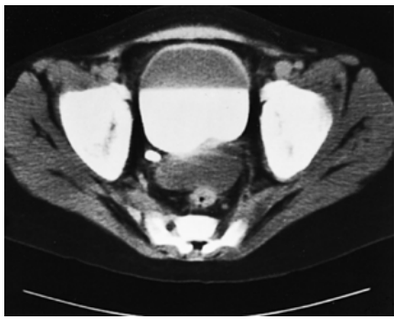

FIGURE 28.2. Computed tomography scan of the bladder in a 15-year-old girl with a fungus ball on the posterior wall of the bladder and severe fungal cystitis.

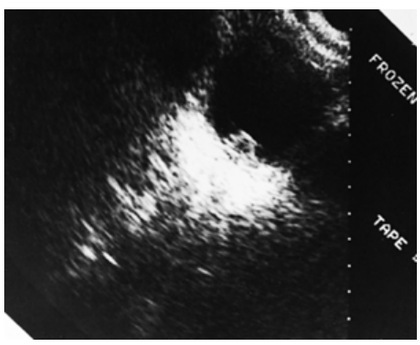

FIGURE 28.3. Same adolescent as in Fig. 28.2. Fungus ball and posterior bladder wall thickening and inflammation as seen on ultrasound of the bladder.

In candidal cystitis, the bladder mucosa is hemorrhagic and covered by a whitish pseudomembrane or elevated white plaques similar to those seen in fungal stomatitis. Fungus balls appear as gray, shaggy aggregations in the bladder that may be adherent to the bladder wall.

The most common clinical scenario in urologic practice is persistent candiduria in patients with indwelling urinary catheters. Therapy is based on laboratory sensitivity tests. Treatment of fungal cystitis with intravesical irrigations of amphotericin B is preferable to systemic therapy, if renal or systemic involvement is absent (196). Irrigation for 5 days with a solution of 50 mg amphotericin B suspended in 1 L of sterile water eradicates candiduria in 90% of patients.

Ambulatory patients with chronic candiduria can be treated with daily bladder instillations of amphotericin B or miconazole (194). Improvement in host defenses (e.g., better nutritional status) and correction of predisposing factors (e.g., discontinuation of broad-spectrum antibiotics or removal of indwelling catheter) are also important.

Systemic candidiasis requires parenteral therapy with amphotericin B, flucytosine (5-FC) or the imidazoles (e.g., miconazole, ketoconazole, fluconazole) (195). Parenteral administration of amphotericin B requires attention to prescribing guidelines because of its nephrotoxicity. 5-FC is not available for parenteral administration but reaches high urinary levels after oral administration (150 mg/kg/ per day in divided dosages with reduced dosages for patients with reduced renal function). Oral fluconazole is safe and effective for short-term (up to 2 weeks) eradication of candiduria, especially following catheter removal (157).

MALACOPLAKIA

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Malacoplakia is an uncommon, benign granulomatous disease of the GU tract. It commonly involves the bladder (i.e., 40% of reported cases), although the kidney can be involved (40,99). Malacoplakia causes severe irritative voiding symptoms and hematuria and needs to be distinguished by biopsy from other benign and malignant bladder conditions. The term derives from the Greek “malakos” (soft) and “plakas” (plaque). Cystoscopically, malacoplakia consists of yellow-brown, soft plaques with a smooth surface and raised margins surrounded by peripheral hyperemia.

Microscopically, malacoplakia consists of infiltrates of large macrophages mixed with lymphocytes and plasma cells. Large, eosinophilic histiocytes contain abundant PAS-positive Michaelis-Gutmann bodies—rounded intracytoplasmic inclusions with a concentric “owl-eye” or “birds-eye” appearance, containing incompletely digested mineralized bacterial components (99) (Fig. 28.4). Normal lysosomal phagocytosis and digestion relies on the integrity of intracellular microtubules that are under the control of intracellular cyclic nucleotides (cGMP/cAMP ratio). Abnormally low levels of cyclic 3′,5′-guanosine monophosphate (cGMP) have been demonstrated in patients with malacoplakia (99). Bethanechol raises intracellular cGMP levels, and ascorbic acid reduces cAMP levels (199). The association of malacoplakia with recurrent UTI suggests an immunologic deficiency.

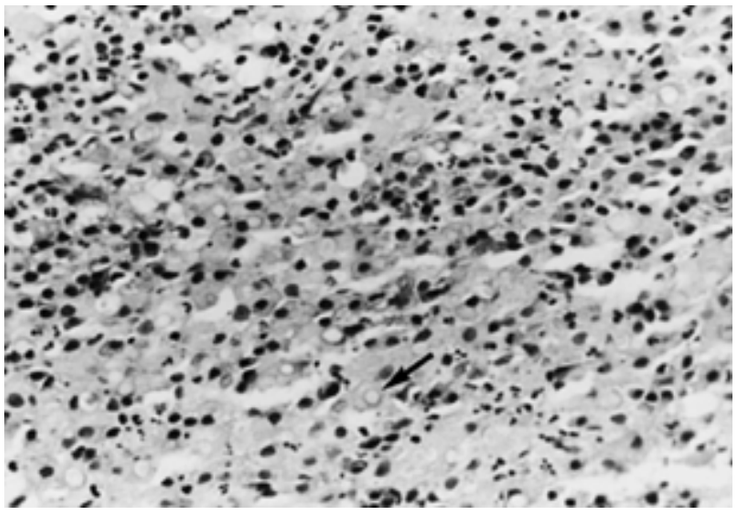

FIGURE 28.4. Malacoplakia of the bladder. Bladder biopsy in a 2½-year-old boy with an *Escherichia coli* urinary tract infection and hematuria; inflammatory reaction with Michaelis-Gutmann body *(arrow)* seen in lamina propria. (From Witherington R, Brannan WJ, Wray BB, et al. Malacoplakia associated with vesicoureteral reflux and selective immunoglobulin: a deficiency. *J Urol* 1984;132:975, with permission.)

Malacoplakia commonly presents with chronic UTIs and is associated with a 40% incidence of systemic diseases such as carcinoma, immunodeficiency, and autoimmune disease (27). The female-to-male ratio is 2:1 to 4:1. After renal transplantation, malacoplakia has particularly serious implications and may be associated with graft loss and mortality. It may be necessary to stop azathioprine in cases of bladder involvement after transplantation and to consider early transplant nephrectomy in cases of renal parenchymal (transplant) involvement (170).

Treatment of malacoplakia is based on the current theories of pathogenesis. Medical treatment consists of bethanechol, ascorbic acid, and antibiotics such as TMP-SMX, rifampicin, or the fluoroquinolones (185). Because of the effective medical regimens, total endoscopic removal of the bladder lesions of malacoplakia may not be necessary (99). If bladder lesions persist despite medical therapy, transurethral or (rarely) open excision may be indicated. Prolonged antibiotic treatment and close follow-up are needed. Long-term antibiotic treatment of the associated UTI is a cornerstone

of therapy (23). TMP-SMX may play a special role because of its lipophilic quality, postulated cell-membrane binding, and cell-entry capacity, all of which facilitate macrophage phagocytosis.

CYCLOPHOSPHAMIDE CYSTITIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

The oxazaphosphorine alkylating agents, cyclophosphamide and isophosphamide, are widely used to treat lymphoproliferative disorders, solid tumors, certain nonmalignant diseases, and as conditioners before bone marrow transplantation (143). Urologic side effects include frequency, dysuria, urgency, suprapubic discomfort, and both microscopic and hematuria. Rarely, mucosal necrosis, bladder fibrosis, contracture, vesicoureteral reflux, and tumor formation occur. The incidence of GU side effects ranges from 2% to 40% in patients on long-term, cyclophosphamide therapy (95). The risk of hemorrhagic cystitis is dose related. Patients who are dehydrated or receiving intravenous rather than oral treatment are at increased risk.

The urotoxicity of these alkylating agents is due to acrolein, a liver metabolite of the oxazaphosphorines (143). The bladder is most affected because of its reservoir function, which allows prolonged contact (dwell times) between acrolein and the bladder mucosa (95). Cystoscopically, the bladder initially appears edematous with multiple punctate hemorrhages. Later, diffuse telangiectasia, reduced capacity, and trabeculation occur. Histologically, the early lesion is that of edema, ulceration, and hemorrhage heading to chronic inflammation and fibrosis.

Therapeutic approaches to the prevention of cyclophosphamide-induced hemorrhagic cystitis are aimed at neutralization or detoxification of acrolein (169). Hydration combined with frequent voiding or indwelling bladder catheterization reduces the urotoxicity of acrolein. Two drugs, *N*-acetyl cysteine (Mucomyst) and 2-mercaptoethane sulfonate (Mesna), form nonurotoxic stable thioesters by binding to the carbon-to-carbon double bonds of acrolein. *N*-acetyl cysteine can be administered orally, parenterally, or intravesically (143). However, it reduces the antineoplastic and immunosuppressive effects of cyclophosphamide when given systemically and is cumbersome and expensive to use as a bladder irrigant. Mesna binds specifically to acrolein without affecting the therapeutic effects of the oxazaphosphorine alkylating drugs (35). It is oxidized to a stable inactive disulfide within minutes of parenteral administration and becomes activated when excreted in the urine. Excretion is rapid with a half-life of 1.5 hours. Mesna also enhances renal excretion of cysteine, thereby increasing the number of sulfhydryl groups available for attachment to acrolein. Routine prophylactic administration of Mesna with cyclophosphamide has been recommended (127). An oral form of Mesna has been developed. Once the bladder complications have occurred and bladder hemorrhage is present, the cyclophosphamide should be stopped if possible because this allows the toxic cystitis and hematuria to subside in most cases. Bladder cancer has been reported to occur with a higher incidence after cyclophosphamide therapy (127). The management of cyclophosphamide-induced hemorrhagic cystitis is described later.

RADIATION CYSTITIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Approximately 20% of patients who receive pelvic irradiation suffer bladder complications, half of these being hemorrhagic cystitis (29,143). Hemorrhagic cystitis secondary to radiation therapy occurs after treatment of prostate, bladder, and cervical cancers. Hematuria may be acute or chronic and is accompanied by urgency, frequency, and dysuria. Hematuria may develop acutely during radiation therapy or occur months to years later.

Pathologically, radiation injury to the bladder involves progressive obliterative endarteritis with resulting telangiectasia, submucosal hemorrhage, and smooth muscle and interstitial fibrosis. Mucosal ischemia results from the endarteritis, causing hypoxic surface damage, ulceration, and bleeding. Acute radiation cystitis occurs either during or shortly after the radiation therapy has been given. Histologically, edema and inflammation of the mucosa and lamina propria characterize it. Most cases of acute radiation cystitis subside spontaneously during the 12 to 18 months after completion of therapy. Late sequelae occur up to 8 to 10 years after radiation and result from endarteritis, which leads to inflammatory cell infiltrates, fibrosis throughout the bladder wall, and increased mucosal vascularity. Factors that contribute to radiation cystitis are bladder outlet obstruction, infection, previous radiation or surgery, and excessive radiation dosage (29).

Unlike cyclophosphamide cystitis, there are no effective preventive measures for radiation-induced hemorrhagic cystitis, although sodium pentosan polysulfate (PPS), a semisynthetic heparin-like compound, may be uroprotective (61). This drug is not yet approved for clinical use in the United States. Reports on the use of hyperbaric oxygen for established, clinically significant radiation cystitis are encouraging (11,29). Hyperoxia reverses the radiation-induced tissue damage by promoting neovascularization, healthy granulation tissue, and generalized vasoconstriction. Hyperbaric oxygen therapy may be the preferred treatment for radiation-induced hemorrhagic cystitis because cessation of hematuria is achieved in 90% of patients (11). Conjugated estrogen (either parenteral or oral) recently has been shown to be effective treatment in a small number of patients with cyclophosphamide or radiation-induced hemorrhagic cystitis (98).

There is little reason to cystoscopically document early, acute radiation cystitis. Treatment is directed at prevention of infection and control of bladder spasms. In chronic and

severe cases, cystoscopy shows diffuse telangiectasia and reduced bladder capacity. Symptomatic treatment of radiation cystitis consists of anticholinergic and antispasmodic agents for frequency and urgency. As in the case of troublesome bleeding from cyclophosphamide, a progressive treatment sequence may be needed (143).

TREATMENT OF HEMORRHAGIC CYSTITIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Most cases of hemorrhagic cystitis are due to chemotherapeutic agents or pelvic irradiation. Uncommon causes include viral, bacterial, fungal or parasitic infections, drugs (e.g., the penicillins, danazol), and chemical toxins (e.g., busulfan, aniline, toluidine derivatives and ether). The best treatment of hemorrhagic cystitis is prevention, especially for cyclophosphamide-induced cystitis. However, once hemorrhagic cystitis is established, treatment is the same irrespective of the cause (Table 28.8).

General Measures	**Specific Measures *(continued)***
Hydration	Prostaglandin irrigation
Continuous bladder irrigation	Conjugated estrogens
Clot irrigation	Hyperbaric oxygen
Cystoscopy	Sodium pentosan polysulfate (PPS)
Clot evacuation	Arterial embolization
Fulguration bleeding points	**Surgery**
Specific Measures	Arterial ligation
Epsilon aminocaproic acid (Amicar)	Diversion
Alum irrigation	Cystectomy
Silver nitrate	
Phenol instillation	

TABLE 28.8. MANAGEMENT OF SEVERE HEMORRHAGIC CYSTITIS

The mainstay of therapy is clot evacuation. This can be done at the bedside using a multiple hole, wide lumen catheter (Robbins catheter). If this is unsuccessful, cystoscopy with clot evacuation and fulguration of visible bleeding points is necessary. Hydration with or without epsilon aminocaproic acid (Amicar) is the usual next step. Amicar, given orally or parenterally, inhibits clot lysis by urinary urokinase. Amicar may cause existing clots to become dense and adherent, and its use is contraindicated in upper tract bleeding because it may cause renal failure secondary to clot obstruction.

If hematuria continues, bladder irrigation with 1% silver nitrate (an astringent) via a three-way indwelling Foley catheter may be successful. Alum (potassium or ammonium aluminum sulfate) is an astringent that acts by protein precipitation over the bleeding surfaces. Systemic absorption is minimal, and continuous bladder irrigation with a 1% to 2% solution is employed without anesthesia and even in the presence of vesicoureteral reflux. This treatment is painless, nontoxic, and inexpensive. Alum precipitation may cause catheter blockage and dense mucosal precipitates. Encephalopathy and acidosis can occur, especially in patients with renal insufficiency in whom serum aluminum levels should be monitored (95).

Prostaglandins are effective in the treatment of hemorrhagic cystitis. Prostaglandins used include PGE_1, PGE_2, and carboprost tromethamine (prostaglandin F2) (95). Prostaglandins are cytoprotective and have antiinflammatory and vasoconstriction properties. Their advantages include ease of administration (intravesical, parenteral), no anesthesia requirements, lack of a coagulum/precipitate to block catheters, tolerance by very ill patients, and lack of systemic side effects other than bladder spasms. The prostaglandins usually are instilled intravesically. Recently, intravesical epsilon aminocaproic acid has been used to control bladder hemorrhage (93).

For severe, intractable hemorrhage, formalin instillation is an effective treatment (30). It hydrolyzes proteins and coagulates superficial bladder mucosal tissue. The concentration of formalin is the most critical factor relative to effectiveness and complication rate (e.g., perforation, bladder fibrosis) (30). Generally, a 2.5% to 4.0% solution is utilized for 20 to 30 minutes, using passive instillation at a volume of one-half of the bladder capacity, followed by continuous bladder irrigation with normal saline. Instillation is painful and requires general or regional anesthesia. An intraoperative cystogram should be done to exclude vesicoureteral reflux as inadvertent formalin reflux into the upper tracts can lead to fibrosis, obstruction, papillary necrosis, and other complications (152). If reflux is present, occlusive balloon catheters are inserted into the lower ureters and the patient is placed in the reversed Trendelenburg position.

Patients with severe hemorrhagic cystitis refractory to formalin instillation may require selective hypogastric artery embolization, percutaneous nephrostomy drainage, ileal loop diversion, cutaneous ureterostomy, cystectomy, or other procedures. Urinary diversion may become necessary as a lifesaving maneuver (143). Open surgical exposure of the bladder and application of phenol to actively bleeding points has been successful in a child with cyclophosphamide cystitis (32).

EOSINOPHILIC CYSTITIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Eosinophilic cystitis is a rare bladder entity associated with an eosinophilic infiltrate in the lamina propria and muscle layers (184). The presentation of eosinophilic cystitis is nonspecific with the most common symptoms being dysuria, frequency, lower abdominal discomfort, and hematuria. Occasionally, a mass may be palpable and mistakenly suspected as bladder sarcoma in children (180). A history of

allergies and peripheral eosinophilia is common, especially in women and children.

An IgE-mediated allergic cause is suggested by the strong allergic histories of the patients and the bladder histology. The characteristic cystoscopic findings are yellow raised plaques, necrotic ulcerated lesions resembling bladder tumors, and generalized edema and erythema (58). Often, the mucosa overlying the bladder mass may be cystoscopically normal and the diagnosis of eosinophilic cystitis missed, unless deep biopsies are obtained. Because of the clinical presentation and cystoscopic findings, the disease has been confused with malacoplakia, tuberculosis, interstitial cystitis, and bladder neoplasms. The diagnosis is made by bladder biopsy. Bladder ultrasound may show a thickened and irregular bladder wall, and vesicoureteral reflux occurs in approximately 33% of cases.

Treatment of eosinophilic cystitis is nonspecific. Steroids and antihistamines are the mainstays of treatment. Other treatment modalities include intravesical dimethylsulfoxide (DMSO), intravesical steroids, nonsteroidal antiinflammatory drugs (NSAIDs), radiation, and chemotherapy (184). Although it is believed that eosinophilic cystitis is a self-limiting disease in children, relapses and progression are common in adults. The synthesis and secretion of interleukin (IL)-5 might explain the chronicity of the lesions of eosinophilic cystitis by activated eosinophils (31). Because healing may lead to fibrosis with loss of renal function, surveillance for upper tract dilation is important.

Cystectomy and urinary diversion are seldom indicated (184). Hydronephrosis and ureteral dilation occur in approximately 25% of patients. In rare cases of severe bleeding and upper tract dilation, radiation to the bladder, extensive cystoscopic fulguration, and partial or total cystectomy have been utilized.

EMPHYSEMATOUS CYSTITIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Emphysematous cystitis is an uncommon disorder characterized by gas in the bladder wall and surrounding tissues. Its clinical manifestations are protean, ranging from the relatively asymptomatic, predominantly radiologic presentation to life-threatening cystitis associated with significant mortality (76).

There is a female preponderance (female-to-male ratio of 2:1). The glycosuria of diabetes mellitus acts as a fermentation substrate for gas-forming bacteria in patients with emphysematous cystitis, and up to 50% of patients are diabetic. Acute renal infection with *E. coli* or *K. pneumoniae* in patients with diabetes mellitus and/or urinary tract obstruction is the cornerstone for the development of emphysematous pyelonephritis (76). Immunocompromised patients and patients with liver disease are also at increased risk. There are increasing reports of cases caused by anaerobic gas-forming *Clostridium* and *Candida* species, especially in severely ill, immunocompromised, and elderly patients (84).

Patients present with lower abdominal pain, fever, hematuria, and pyuria with a plain abdominal roentgenogram confirming the presence of gas (in a linear distribution or multiple “bubbles”) in the bladder wall. In severe cases, symptoms can be suggestive of acute intraabdominal or pelvic pathology as a result of severe bladder inflammation with mucosal sloughing and gangrene. Such patients have signs and symptoms of systemic sepsis and require urgent antibiotic and surgical treatment. Most patients with emphysematous cystitis have mild forms of the disease that respond to appropriate antibiotic therapy, despite the sometimes alarming radiologic appearance of the bladder.

Plain abdominal roentgenograms are usually diagnostic. CT confirms the diagnosis, localizes the site and extent of the gas collection, and excludes abscess formation or fistulae. Intravenous urography, although not essential for the diagnosis, may demonstrate extension of the gas up the ureters, into the kidney, or around the adrenal gland. Such extension is associated with significant mortality and morbidity. Cystoscopy reveals the characteristic submucosal bubbles and free air within the bladder. However, the risk of cystoscopy in a patient with grossly infected urine limits its usefulness.

Most patients with emphysematous cystitis survive in spite of their usually frail medical status and associated illnesses. Management includes appropriate antibiotics, control of diabetes (if present), and establishment of adequate urinary drainage. The serum creatinine level is a reliable predictor of outcome in patients with emphysematous pyelonephritis, with azotemic patients having an increased risk of morbidity and mortality (187). Surgical exploration with debridement or cystectomy is used only in severely ill patients who are not responding to medical and supportive measures. Antibiotic therapy combined with CT-guided percutaneous drainage is an acceptable alternative in select patients with associated emphysematous pyelonephritis (16).

OTHER INFLAMMATIONS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Trichomonas vaginalis, flagellate protozoa, may cause cystitis but usually presents as urethritis or prostatitis. Because the frequency and urgency may be the same as cystitis, microscopic examination and culture of urine and genital secretions should include this possibility. Similarly, *Chlamydia trachomatis* primarily causes urethritis, epididymitis, and prostatitis. Chlamydial infections are transmitted by sexual exposure. *Ureaplasma urealyticum* is recovered infrequently in patients with UTI but needs to be considered in the differential diagnosis of patients with frequency, dysuria, and negative bacterial urine culture (175).

Parasitic GU tract infections cause intensive bladder inflammation and symptoms. *Schistosoma haematobium* is endemic in Egypt, and in infected patients, the ova enter the bladder wall from pelvic veins (125). This causes an eosinophilic inflammatory response that becomes chronic and eventually results in fibrosis and calcification. As the ova are excreted in the urine, an epithelial reaction occurs with severe mucosal hyperplasia and subsequent dysplasia, bladder stones, and squamous cell carcinoma (51). Children with schistosomal cystitis may have nodular filling defects in the bladder, vesicoureteral reflux, and obstructive uropathy. These all improve significantly with praziquantel therapy (44). *Echinococcus granulosus* infestation of the urinary tract typically causes calcified cysts of the kidney, but it also may infiltrate the bladder and cause hematuria, cystitis, bladder cysts, and hydronephrosis (50).

INTERSTITIAL CYSTITIS

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

Interstitial cystitis (IC) is diagnosed with increasing frequency in modern day urologic practice (24). The “elusive” or Hunner's ulcer (77) is a misnomer that has led to the underdiagnosis of IC because many patients lack ulcers. Messing and Stamey (10) described the “nonulcer” variety of IC in 1978 and emphasized its prevalence, which led to the more frequent diagnosis of IC and the recognition of two subtypes of the disease—Hunner's ulcer and the more common nonulcer type (151).

Epidemiology and Natural History

The reported prevalence data for IC reveal wide variations due to varying assessment methods and diagnostic criteria (24). The prevalence of IC in Finland was estimated to be 18.1 per 100,000 women (120). Held and co-workers (69) estimated the prevalence of IC in the United States to be 30 cases per 100,000 total population, based on a questionnaire survey. Data from the 1989 National Household Interview Survey estimated that IC affects 0.5% of the population after adjustments for age, race, and gender—a prevalence of more than 500 cases per 100,000 total population (82). The Nurses' Health Studies (NHS) I and II conducted in 90,000 female registered nurses estimated the prevalence of IC to 60 per 100,000, equivalent to 750,000 women in the United Sates (24). This study relied on self-reporting of IC but used an additional questionnaire and a medical record check to confirm IC, based on the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK) diagnostic criteria for research studies (53).

Most patients with IC are female and white, with a female-to-male ratio of 9 to 10:1 (92). More than 25% of women are younger than 30 years of age at first diagnosis. In patients with Hunner's ulcers (“classic” IC), only 18% were diagnosed before age 30 years, compared with more than 30% in patients with nonulcer IC. The quality of life of IC patients is poor and compares unfavorably to those with other chronic diseases such as chronic renal failure and arthritis because of pain, suffering, and inability to work (106). The disease affects blacks and other ethnic minorities, as well as children and adolescents (20,148). A history of allergy (drug hypersensitivity, bronchial asthma, allergic rhinitis) is present in up to 25% to 40% of IC patients (92,178).

The natural history of IC is variable. Symptoms tend to develop subacutely, progress to the classic symptom complex over a short period of time, and plateau within approximately 5 years (92). A minority progress to a small, shrunken, “end-stage” bladder. Hunner's ulcers tend to occur in middle-aged or older women with reduced bladder capacities and accounts for 57% of cases in Europe (43). In the United States, the ulcer variety of IC is uncommon, accounting for less than 10% of cases (92). Chronicity is a hallmark of the disease, punctuated by periods of exacerbation (flares) and remission. Spontaneous remissions occur in 10% to 15% of patients, but these figures need cautious interpretation because of the lack of a specific disease marker and the subjective nature of IC symptoms (38).

Underdiagnosis of Interstitial Cystitis

Although current estimates of the prevalence of IC put the number of affected individuals in the United States at approximately 750,000, this is probably a considerable underestimate (64). Factors contributing to the underdiagnosis of IC include the variable urologic and nonurologic symptoms associated with IC; their similarity to symptoms associated with other disorders; and a lack of awareness of IC, especially in men (151). Four main groups of patients with IC are commonly misdiagnosed (151) (Table 28.9). Patients with cystitis that remain symptomatic after two or three courses of antibiotic treatment are likely candidates for IC, as are individuals with symptoms of overactive bladder that do not respond to anticholinergics. Many men diagnosed with chronic pelvic pain or prostatitis also are likely to have IC. Women with chronic pelvic pain, a negative laparoscopy, and concomitant bladder symptoms are also potential IC patients.

Men with nonbacterial prostatitis/prostatodynia (chronic pelvic pain syndrome)
"Overactive bladder" symptoms in both sexes unresponsive to anticholinergics
Women with undiagnosed chronic pelvic pain
Women with "cystitis" unresponsive to antibiotic therapy

TABLE 28.9. UNDERDIAGNOSIS OF INTERSTITIAL CYSTITIS

Population surveys estimate the proportion of male patients with IC at approximately 10% of the total. This is an underestimate. Over an 8-year period, Novicki and others (117) reported that men comprised 21% of newly diagnosed IC patients at their clinic. Common misdiagnoses were prostatitis (48%) and benign prostatic hyperplasia (38%). IC must be considered in the differential diagnosis of irritative voiding symptoms and pelvic pain in men. IC is clearly more prevalent in men than previously accepted.

There are many similarities between the symptoms of nonbacterial prostatitis—irritative voiding, pain, sexual dysfunction, and lack of response to antibiotics—and prostatodynia in men and IC in women. Of 60 men, 35 (58%) with nonbacterial prostatitis/prostatodynia and negative bacterial cultures had moderate to severe petechiae, similar to that seen in women with IC, following cystoscopy and hydrodistention under general or regional anesthesia (4). This strongly suggests that the majority of men with nonbacterial prostatitis and prostatodynia have IC.

In women, IC is also commonly misdiagnosed as gynecologic disorders (149) such as chronic pelvic pain or endometriosis. Idiopathic sensory urgency (the presence of urinary frequency and urgency without obvious cause) presents with similar symptoms to IC. Frazer and associates (49) showed an increase in mast cell density in a subset of women with idiopathic sensory urgency compared with normal. As mast cell levels also are increased in IC, many patients with idiopathic sensory urgency may have early IC.

Although the NIDDK criteria were designed primarily for use as research criteria (53), the lack of a suitable diagnostic paradigm has led to their use for clinical diagnosis. Rigorous application of these guidelines is not suitable for clinical diagnosis of IC because 60% of patients considered clinically to have IC would not be diagnosed (64).

Associated Diseases

Many patients with IC have associated diseases such as allergies, autoimmune diseases, fibromyalgia, other rheumatic diseases, irritable bowel syndrome (IBS), and so on. Urinary frequency/urgency and detrusor instability (urodynamically confirmed) are common in women with irritable bowel syndrome (IBS) compared with controls (109). In a questionnaire survey of patients with temporomandibular joint (TMJ) disorders, 46% reported associated IBS, and 19% IC (90). The overlap between these various conditions suggests a common pathophysiology mediated by immune, endocrine, and neurologic (sensory afferent and autonomic) dysfunction.

IC is an uncommon manifestation of systemic lupus erythematosus (SLE). Patients with IC often have associated allergies. Systemic diseases, such as chronic fatigue syndrome and fibromyalgia, also are linked to IC (19).

Clinical Features

Urinary frequency, urgency, and nocturia are common, and suprapubic or pelvic pain is usually prominent. The pain is usually related to bladder filling and relieved by voiding, although some patients complain of pain at the end of voiding. Dyspareunia is common, whereas dysuria and incontinence are infrequent (151). A typical IC patient has seen many urologists, gynecologists, family practitioners, and internists (usually between three to five) before being diagnosed (69,92).

Gynecologic evaluation, although usually normal, may reveal focal vulvitis, an inflammation of the introital vestibular glands characterized by marked dyspareunia. The coexistence of IC and vulvitis or vulvodynia in some patients suggests a common etiologic mechanism (104). Many IC patients report prior gynecologic surgery (hysterectomy, laparoscopy), and up to 40% experience “perimenstrual” symptom exacerbation, suggesting a pathophysiologic role of the female sex hormones (149).

Patients with “mixed” incontinence (frequency, urgency, pain, incontinence) may have IC and genuine stress incontinence (168). Urodynamic evaluation is an important part of the evaluation in such patients. Patients have been labeled as neurotic or psychotic, and shunted to psychotherapists, pain clinics, and psychiatrists before urologic evaluation and definitive diagnosis (88).

Diagnostic Considerations

In the past, the diagnosis of IC was based on the triad of (a) presence of irritative voiding symptoms and pain, (b) exclusion of known bladder diseases, and (c) the presence of glomerulations or Hunner's ulcers at cystoscopy. The National Institutes of Health consensus research criteria for the diagnosis of IC (53) had become the “*de facto*” clinical diagnostic criteria. Recently, there is an evolving consensus that the diagnosis may be made clinically based on the presence of irritative voiding symptoms and pain and exclusion of known bladder diseases or by the newly described potassium sensitivity test. (Table 28.10).

Clinical diagnosis	Potassium sensitivity test
Exclusion of urinary tract infection and cancer	Cystoscopy and hydrodistention
	Under anaesthesia
Local cystoscopy	Possible biopsy
Cystometrogram	Combinations of above

TABLE 28.10. DIAGNOSTIC CONSIDERATIONS IN INTERSTITIAL CYSTITIS

Approximately 10% of IC patients have greater than 10 WBCs or greater than 5 red blood cells (RBCs) per HPF (105). An uncommon presenting feature of IC is gross, painless hematuria. The diagnosis of IC should not be made in the presence of bacterial cystitis, although a prior history

of UTI does not exclude it. CIS and mucosal dysplasia of the bladder can mimic the irritative voiding symptoms and cystoscopic appearance of IC (182). A negative urine cytology or bladder biopsy is required, particularly in men, before a diagnosis of IC is made.

Patients with significant incontinence, urgency, or the lack of pain benefit from urodynamic evaluation. Radiographic imaging, including ultrasonograms, intravenous urograms, CT scans, and plain radiographs are usually unrevealing and noncontributory. A thorough patient history, physical examination, urine analysis, and urine cytology provide key information for diagnosis of IC. Urodynamics, cystoscopy, and biopsy offer important supportive additional information (177).

Although biopsies are used to rule out CIS and other specific diseases, they do not provide a definitive diagnosis of IC (72,80). Analysis of the tissue samples allows the degree and type of inflammation to be evaluated and the presence of mast cells to be assessed (129,179), which help determine whether antihistamine treatment is appropriate for IC. Staining for the presence of substance P and other mediators of neurogenic inflammation may identify patients who respond to pharmacologic treatment targeted at neurotransmitter blockade.

Hydrodistention and cystoscopy under anesthesia provide useful information regarding prognosis and treatment (Table 28.11). Bladder capacity provides an indication of how well patients are likely to respond to therapy; those with smaller capacity bladders prove harder to treat. Up to 20% to 30% of patients get transient—2 to 3 months—relief of their symptoms following hydrodistention (136). Bladder capacity is determined by *passive gravity filling* of the bladder at a hydrostatic pressure of 70 to 80 cm H_2O for 2 to 3 minutes. Drainage of the bladder following filling results in a terminal blood tinge (terminal hematuria) of the draining fluid in 90% of patients because of bleeding from the areas of glomerulations (Fig. 28.5) (105). In a few patients, distention causes mucosal cracks and fissures (Fig. 28.6). Occasionally, a true Hunner's ulcer is encountered. Urethral calibration usually reveals a urethra of normal size. Most patients have normal or increased bladder capacities under anesthesia, glomerulations, and terminal hematuria, while approximately 10% have shrunken bladders with fissures, scars, or ulcers. The cystoscopic findings are summarized in Table 28.10 .

TABLE 28.11. INTERSTITIAL CYSTITIS: ENDOSCOPIC FEATURES

Normal urethral lumen	Nonulcer disease (90%)
Anesthesia (general, spinal)	Capacity >400 mL
Glomerulations	No ulcers, scars, mucosal cracks
Hematuria (terminal blood tinge)	Classic disease (Hunner's ulcer) (10%)
Biopsy	Capacity <400 mL
Exclusion of specific disease	Ulcers, scars, etc.
Prognosis	

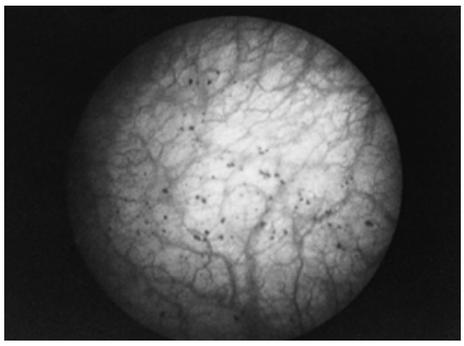

FIGURE 28.5. Cystoscopic view of diffuse “glomerulations” in patient with interstitial cystitis. Note discrete, punctate submucosal capilar tufts following passive bladder hydrodilation.

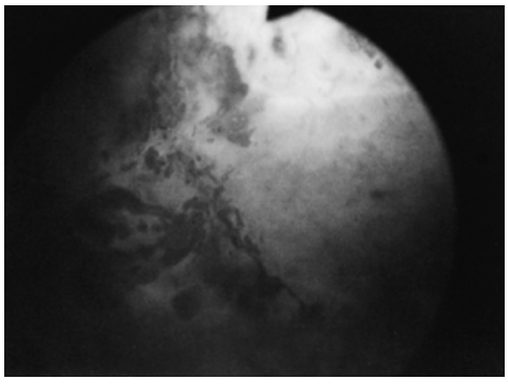

FIGURE 28.6. Interstitial cystitis. Marked mucosal hemorrhage and bleeding following hydrodistention.

Glomerulations are not pathognomonic of IC. Glomerulations may occur in inflammatory bladder conditions caused by radiation, toxic chemicals, and neoplasms. Conversely, some patients show all the symptomatology and urodynamic characteristics associated with IC, but their cystoscopic findings are normal. In a prospective cohort study of 20 urologically asymptomatic women undergoing tubal ligation, glomerulations were present in 40%—a similar incidence to that found in patients with suspected IC (190). This intriguing study needs to be repeated in a larger group of patients with carefully documented voiding logs and gynecologic symptom questionnaires because IC can present with nonurologic symptoms such as chronic pelvic pain, irritable bowel syndrome, and so on (149).

The recently introduced potassium sensitivity test identifies IC patients with bladder-related pain. Approximately 70% of patients with IC experience hypersensitivity to a potassium solution introduced into the bladder (121) because of a bladder epithelial dysfunction that allows potassium ions to diffuse across the epithelium and depolarize sensory nerves and smooth muscle. A positive test helps the physician localize patients' pain to the bladder although a negative test does not reliably exclude IC. Recent therapy for IC, such as hydrodistention, DMSO treatment, and PPS can all significantly reduce the response to potassium.

A recent study (14) has reported a lower correlation between the potassium assay and cystoscopy. In all, 66% of patients with a positive potassium test had IC, based on a positive cystoscopic test, while 46% of patients with a negative potassium test had IC based on a positive cystoscopic test. The potassium sensitivity test may identify patients likely to respond to heparinoid treatments for IC (176). Diagnostic tests for IC under investigation include urinary antiproliferative factor (AFP), bladder surface factors, and proteins such as GP51 (10,86).

Nerve fiber proliferation and expression of substance P and its receptor (Neurokinin 1) have been demonstrated in IC (6,18,103). Changes in the T-cell subpopulations in patients with classic IC indicate a possible role for the immune system in pathogenesis (66,133). Histopathologic typing of the inflammatory infiltrate (e.g., mastocytosis, nerve fiber density) may allow tailored approaches to treatment as the pathogenesis of IC becomes better understood (151).

Etiology and Pathogenesis

Several theories have been proposed regarding IC causation, including infection, vascular obstruction, autoimmunity, lymphatic obstruction, neurogenic and hormonal factors, genetic defects in bladder cytoprotection, toxic urine substances, and even psychiatric causes (Table 28.12). Most certainly, the etiology is multifactorial (38,151), and IC is best regarded as a syndrome of heterogenous causation rather than as a single disease (43).

Infection	Allergic/immune/autoimmune causes
Dysfunctional bladder epithelium	Neurogenic inflammation
Defective glycosamino-glycan cytoprotection	Bladder mastocytosis
Abnormal intercellular junctions	Psychosomatic
Changes in extracellular matrix	Other
Toxic substances in urine	Food intolerance
	Endocrine
	Hormonal
	Genetic

TABLE 28.12. ETIOLOGIES OF INTERSTITIAL CYSTITIS

An infectious (bacteria, mycobacteria, fungi, or viruses) etiology has not been proven (38), although some studies implicate fastidious bacteria such as *Gardnerella vaginalis* and *Lactobacillus* species (193). Studies of *Helicobacter pylori* and *Borrelia burgdorferi* have been negative (37,60). A sensitive PCR assay (2-round amplification using nested primers from a highly conserved region of the bacterial 16s rRNA gene) showed no difference between IC patients and controls with respect to PCR positivity or the type(s) of bacteria present (85). The bacterial flora of the lower urinary tract in IC and the urethral syndrome was found to be considerably different from that of healthy women (59). The significance of these findings is uncertain because it is possible that the inflamed, damaged bladder and urethral mucosa in these conditions can cause increased bacterial adherence and colonization.

Bladder permeability is increased in IC as demonstrated by the intravesical potassium sensitivity test, which is also positive in acute cystitis (100%), detrusor instability (25%), radiation cystitis (100%), IC (75%), and “controls” (4%) (121). A recently described test of bladder epithelial permeability using inert sugars may find application as a less painful method to intravesical potassium in evaluating patients with suspected IC (39). The bladder permeability defect in IC has not been definitively characterized, but it is believed to be multifunctional—surface GAGs, intracellular adhesion molecules, extracellular matrix, and so on (151).

A low-molecular-weight peptide—antiproliferative factor (APF)—identified in the urine of IC patients inhibits *in vitro* proliferation of normal bladder epithelial cells (86). This inhibition of epithelial regeneration following bacterial or chemical damage promotes further assault by microorganisms, urinary antigens, and potassium, and leads to chronic inflammation. Stress and heat-shock proteins are increased in IC suggesting that “toxic” urine upregulates genes involved in stress protein production (160). Triggers for mast cell activation such as stress, infection, and chemicals induce the “stress response” (“heat shock response”) in mammalian cells (129,179).

A sulfonated GAG deficiency has been suggested as a cause of IC (123) and is the rationale for treatment with sodium PPS (Elmiron)—a highly sulfated, exogenous, orally administered glycosaminoglycan (78,112). Altered GAGs are associated with increased bladder surface permeability, the presence of Tamm-Horsfall (T-H) protein in the submucosa, and increased urea absorption (“leaky” urothelium) in IC (38,121). Substances in the urine, such as food, metabolites, food additives, drugs, environmental pollutants, and antibiotics, may leak across the altered bladder mucosal lining and cause bladder inflammation, which can be toxic, allergic, or immunologically mediated (7).

Oral antibiotics have not been convincingly implicated as a cause of IC (94). However, NSAIDs can cause IC (68). The high incidence of IC in women, chronic inflammatory cell infiltrate, response to steroid therapy, and periods of

exacerbation and remissions suggest an autoimmune etiology (183). Circulating autoantibodies directed against bladder tissue lack sensitivity or specificity for IC, suggesting that they are epiphenomena (118).

Potassium diffusion stimulates mast cell activation and causes upregulation of the sensory bladder afferent nerves with neuropeptide (e.g., substance P) release and of neurogenic inflammation, leading to the pain of IC. Increased levels of substance P neurokinin 1 (NK1) receptor has been demonstrated in women with IC (103) and in cats with IC (5,6). The neurokinin-1 receptor is required for mast cell–induced cystitis in experimental models (144). Polymodal, nociceptor activation may cause unmyelinated C fibers in the submucosa of the bladder to release neuropeptides, such as substance P (101), which induce inflammation and degranulate mast cells. Mast cells are intimately related with autonomic nerve fibers (129,179). Neurogenic inflammation probably plays a role, either primary or secondary, in the pathogenesis of IC.

Mastocytosis is present in 30% to 50% of patients, and this represents a subgroup of IC patients (179). The strategic location of mast cells at host-environment interfaces suggests a potential role for bacteria in the pathophysiology of IC (102,179). Mast cells modulate the immune response to infectious agents, and bacteria or bacterial products are known to cause mast cell activation. Increased urinary excretion of mast cell products, such as 1,4-methyl-imidazole-acetic-acid, methylhistamine, tryptase and histamine, has been demonstrated in IC (36,179). Nerve-growth factor (NGF) and neurotrophin-3 (markers of neuronal plasticity and sensory nerve activation) also are increased (119). Estradiol and psychologic stress trigger mast cell activation (179), and stress is a well-known cause of flares in IC patients. Tyrosine hydroxylase immunoreactivity (THIR) in the central nervous system was found to be significantly greater (p <.05) in cats with IC than in healthy cats. These findings point to a role for mast cells, hormones, and the autonomic nervous system in the pathogenesis of IC (5,6).

The p65 subunit of nuclear factor kappa B (NF-KB), a key regulator of genes involved in response to infection, inflammation, and stress, is increased in IC (1). The inflammatory and/or immune response in IC may be exacerbated by the persistent activation of this nuclear factor. The cytokine profile of human uroepithelial cells was assessed in a number of diseases. IL-8 and transforming growth factor-ß (TGF-ß) were constitutively produced in all patients, whereas IL-1ß, IL- 4, IL-6, and interferon (IFN)-γ expression varied according to the disease. IL-1ß and IL-6 staining was detected in IC and cancer, and IFN-γ and IL-4 staining was only observed in IC (62).

An animal model of immediate bladder hypersensitivity/inflammation induced by local application of ovalbumin (OA) in OA-sensitive female Wistar rats was recently described (2). The early inflammatory response and alterations in smooth muscle reactivity to OA challenge in actively sensitized animals are dependent on mast cell degranulation and activation of sensory C-fibres in the bladder.

TREATMENT

Part of "28 - INFLAMMATORY DISEASES OF THE BLADDER "

General Measures

The treatment of IC is largely empirical. The use of many of the common therapies is based on old noncontrolled studies, using clinical and subjective impressions in small groups of patients. Placebo-controlled, blind studies using validated outcomes measures are needed to assess the efficacy and benefits of treatment. The placebo response rate in IC is high because of the intermittency and subjectivity of its symptoms and the chance of spontaneous remission.

Patients can expect symptomatic relief even though treatment is nonspecific and frequently noncurative. They need education and continuing reassurance that IC is not a harbinger of systemic disease or malignancy (192). Acid foods, such as alcohol, citrus juices, and carbonated beverages, and foods rich in tyrosine, tryptophan, and aspartate may cause bladder irritation (54). Patients are advised to identify their dietary provocation factors and to modify their diets accordingly. Behavior modification with increasing intervals between voids is useful in some patients, and referral to a therapist is indicated in depressed or anxious patients. Patients with significant pain that is unresponsive to the usual therapies benefit from referral and management in a multidisciplinary pain clinic.

Rationale for Multimodality Treatment

Our current understanding of the pathogenesis of IC suggests a vicious cycle of changes in the bladder-epithelial membrane barrier, sensory nerve endings, mast cells, and so on and is represented in Figure 28.7 . Epithelial dysfunction due to hereditary or acquired causes (e.g., prior UTI, hormonal changes) means leads to influx of potassium and other urinary constituents into the bladder wall with resultant chemical inflammation, activation and degranulation of mast cells, release of substance P and other tachykinins and neurotransmitters, and neurogenic inflammation (144,151). The latter process is relayed to the dorsal root ganglia in the spinal cord with substance P upregulation in the spinal cord (5,6). This may well contribute to the pelvic pain symptoms, such as irritable bowel syndrome, dyspareunia, pelvic and perineal pain, associated with IC. It also may explain why some IC patients continue to experience pelvic pain even after cystectomy and diversion procedures.

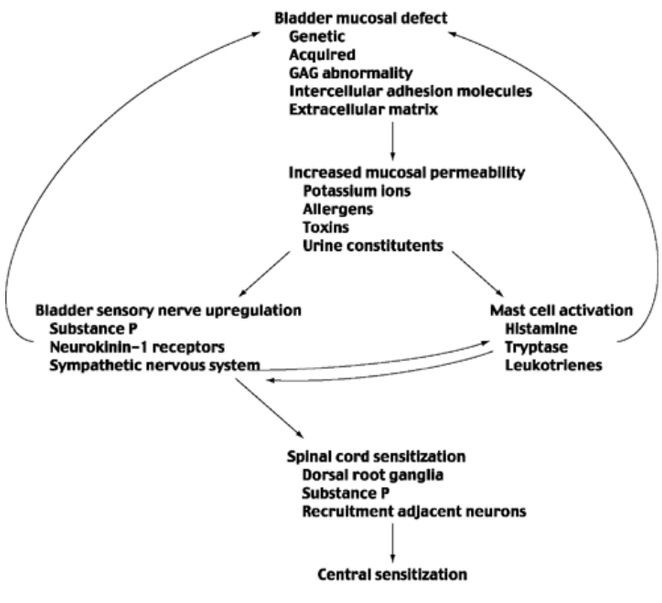

FIGURE 28.7. Postulated pathogenesis of interstitial cystitis. GAG, glycosaminoglycan.

Multimodality treatment aims to target the specific biologic perturbations in IC; for example, the dysfunctional bladder epithelium with sodium PPS, mast cell activation with hydroxyzine, neuropeptide upregulation with antidepressants (tricyclic and serotonin-uptake inhibitors), nerve depolarization with membrane-stabilizers

(gabapentin–neurontin), and detrusor muscle hyperactivity with anticholinergics (e.g., tolterodine, oxybutynin).

Administration of the drugs in combination addresses the multiple pathogenetic biologic factors and allows for smaller doses of individual drugs, shorter time to response, and more acceptable side effect profiles. Common drug combinations include sodium PPS and hydroxyzine, for a patient with a history of allergies and/or mast cell activation on biopsy, and sodium PPS and amitriptyline. Currently the benefits of combination therapy are being investigated in an NIH-sponsored multiinstitutional study, The Interstitial Cystitis Clinical Trials Group (ICCTG), comparing Elmiron versus placebo versus hydroxyzine versus Elmiron with hydroxyzine.

Systemic Therapy

Many of the drugs used to treat IC have been inadequately evaluated in controlled studies, show disappointing results, or have low benefit-to-risk ratios (Table 28.13). H_1-antihistamines (diphenhydramine hydrochloride, dexchlorpheniramine, and hydroxyzine) are effective in some patients, but their sedative effect may limit their use (178). The poor response rate is due to the pharmacokinetic properties of the drug and the effects of absorption, renal excretion, and drug metabolism. Only a small proportion of the active drug or inactive metabolites reaches the inflamed bladder.

Systemic	Intravesical Therapy
Antihistamines	Silver nitrate
Corticosteroids	Heparin
Antiinflammatories (NSAIDs; COX-1 and COX-2)	Oxychlorosene sodium (Clorpactin WCS 90)
Anticholinergics, antispasmodics	Corticosteroids
Immunosuppressives	Sodium bicarbonate
Heterocyclic antidepressants	Doxorubicin
Sodium pentosan polysulfate (PPS; Elmiron)	Elmiron
L-Arginine	Lidocaine/Marcaine
Cimetidine	Disodium cromoglycate
Misoprostol	BCG (bacille Calmette-Guérin)
Heparin	Hyaluronic acid
Calcium channel blockers	? Capsaicin or resineferatoxin (RTX)

NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 28.13. DRUG TREATMENT OF INTERSTITIAL CYSTITIS

Antiprostaglandins (e.g., aspirin) or NSAIDs (e.g., ibuprofen) inhibit prostaglandins (cyclooxygenase pathway) and leukotrienes (lipoxygenase pathway) released by activated mast cells. Antimuscarinic drugs (e.g., probanthine)

and musculotropic relaxants [e.g., oxybutynin (Ditropan), flavoxate (Urispas)] are used for their anticholinergic and antispasmodic properties to reduce frequency and urgency.

The tricyclic antidepressant drugs, such as amitriptyline, nortriptyline, imipramine, desipramine, doxepin, and trazodone, cause meaningful symptomatic responses, especially pain control in approximately half the patients (63). The drug is given at bedtime in gradually increasing doses. The true efficacy of antidepressants in IC has not been studied in placebo-controlled studies.

The use of sodium PPS (Elmiron), a synthetic, highly sulfated polysaccharide similar to heparin but with less anticoagulant activity, is based on the putative deficiency of bladder surface GAGs in IC. Elmiron, one of the few drugs for IC evaluated through prospective, blinded, and randomized studies is the only oral drug approved by the FDA. PPS sodium resulted in overall improvement in approximately 30% of patients who had not responded to intravesical therapy or other oral agents. This rate was approximately twice the placebo response rate (78,112). Mild adverse reactions (e.g., diarrhea, nausea, headache) occur in 6% of patients. The drug is inexpensive; less than 10% of the drug is excreted in the urine, and this accounts for the long time lag (3 months or more) before clinical improvement (73).

A meta-analysis of PPS conclusively demonstrated its efficacy over placebo in controlling pain, frequency, and urgency in IC (78). PPS (100 mg orally three times daily) takes approximately 3 to 6 months to achieve full therapeutic benefit (70) because of the low levels of PPS getting into the bladder. Ongoing dose-escalation studies are under way in the United States to determine whether higher oral dosages result in a shorter time to response without an increased incidence of side effects. Clinical experience that a positive potassium sensitivity test may be a predictor of response to PPS is emerging (176).

Electroanalgesia from transcutaneous electrical nerve stimulation (TENS) is useful to control pain in patients with the ulcer type of IC. Long periods of treatment, usually months, are required before patients show improvement (42). However, TENS is nondestructive and safe and deserves consideration before invasive or surgical therapies. Subcutaneous heparin, a glycosaminoglycan that restores the defective mucous layer of the bladder wall, has been used (100). However, inconvenience, logistical problems associated with administration, and the potential side effects of bleeding (menstrual, ecchymoses) are reflected in the near-universal lack of adoption of this therapeutic approach.

Approximately 40% of IC patients treated with hydroxyzine self-report symptom improvement, and this rate rises to 55% in patients with bladder mastocytosis on biopsy and/or a history of allergies (178). The ability of hydroxyzine to inhibit neurogenic activation of bladder mast cells explains its effectiveness in IC (108).

Immunosuppressive drugs have been used to treat IC. Cyclosporine reduces urinary frequency and bladder pain, but the symptoms recur when treatment is discontinued (47). The therapeutic role of immunosuppressive drugs such as cyclosporine and methotrexate need to be assessed in well-designed prospective, randomized, placebo-controlled studies. Oral steroids and immunosuppressive drugs [azathioprine (Imuran), chloroquine, and oxychloroquine] have not achieved widespread use because of their potential side effects of infection and bone marrow suppression (65).

Misoprostol, an oral prostaglandin analogue, was used to treat IC. In an open label study in 25 patients receiving 600 mg daily for 3 months, 56% had significant symptomatic improvement, although incidence of side effects (64%) was high (87). Calcium channel blocking agents, such as nifedipine, have been reported to be useful in select IC patients (46).

Decreased urine levels of nitric oxide (NO) and high levels of bladder luminal NO have been reported in IC. L-arginine (a nitric oxide donor) was studied in a randomized, double-blind, placebo-controlled study. An “intention to treat” analysis demonstrated no statistical difference between the groups (91). Other studies have confirmed the lack of efficacy of L-arginine in the treatment of IC (12,34). A regimen of sequential antibiotic therapy has been used but does not seem to offer any advance in treatment outcomes (189).

Intravesical Therapy

Intravesical therapy (Table 28.13) is often used in IC treatment (150). Short dwell times in the bladder reduce the chance of systemic absorption and deliver high drug concentrations to the inflamed bladder. DMSO (Rimso 50) is the only intravesical drug approved by the FDA for IC.

Various dosage and treatment schedules of silver nitrate are used, ranging from a dilute 1:5,000 to a 1:100 (1%) concentration administered with local or general anesthesia, with an overall success rate of approximately 50% (65,150). Vesicoureteral reflux needs to be excluded and biopsies should not be performed at the time of treatment because of the risk of silver nitrate extravasation.

DMSO has many pharmacologic properties—antiinflammatory, analgesic, muscle relaxant, and collagen dissolution—that are useful for treatment of IC. The number and timing of instillations are empirical. DMSO usually is given at 1- to 2-week intervals for four to eight treatments. Fifty milliliters of RIMSO-50 are instilled, the catheter is removed, and the patient is instructed to hold the medication in the bladder for 15 minutes before voiding. Patients experience a temporary garliclike breath odor and a similar taste in their mouths for approximately 24 hours. Extensive studies have not demonstrated changes in the ocular refractive index or the development of lens opacities in humans. Individuals can be taught self-intermittent catheterization and instillation of DMSO. Many patients require maintenance therapy for relapsing symptoms, and the timing of treatment is empirical.

Other drugs augment the therapeutic benefit of DMSO therapy (150). Hydrocortisone (100 mg) promotes the antiinflammatory effects of DMSO. Heparin (5,000 units) can be added because of its antiinflammatory and surface-protective action, and sodium bicarbonate enhances steroid activity in the DMSO-steroid mixture. Intravesical heparin (10,000 IU monthly) reduces relapses in patients who respond to DMSO and can be used for maintenance therapy (122).

Oxychlorosene sodium (Clorpactin), a mixture of hypochlorous acid and the sodium salt of dodecylbenzene sulfonic acid, exerts a "detergent" action on the bladder mucosa, and the initial rationale for its use in IC was the similarity between classic IC with small, scarred bladders and tuberculosis of the bladder (150). A 0.4% solution is used for intravesical instillation under general or regional anesthesia because administration is painful. Vesicoureteral reflux is a contraindication to its use because of the risk of ureteral fibrosis. After treatment with oxychlorosene sodium, patients initially require oral narcotics and anticholinergics for control of frequency, pain, and other symptoms. Other intravesical agents include disodium cromoglycate (cromolyn sodium), an inhibitor of mast cell release; intravesical lidocaine (200 mg lidocaine in 40 mL normal saline); intravesical doxorubicin (Adriamycin); and intravesical hyaluronic acid (Cystitat) (38,150).

A single-institution prospective, double-blind, placebo-controlled trial of intravesical Tice strain bacille Calmette-Guérin (BCG) demonstrated a 60% response rate compared with a 27% placebo response in IC (131). BCG is a strong stimulus of the immune system and its efficacy may be due to stimulation of type 1 (TH1) helper cell response (133). Longitudinal follow-up of the BCG responders from that initial study revealed that 8 of 9 (89%) patients maintained symptomatic improvement without long-term adverse events (132). BCG is currently being studied in a multicenter prospective, randomized, placebo-controlled study in the United States. Its role in treatment of IC will depend on the results of this study and the risk-benefit ratio of BCG used for nonmalignant bladder disease.

Electromotive drug administration (EMDA) utilizes the technique of iontophoresis to promote active transport of ionized drugs by application of an electric current. Patients (NIH-NIDDK criteria) treated with intravesical electromotive administration of lidocaine and dexamethasone followed by cystodistention (142) achieve significant symptom relief with increases in bladder capacity. This outpatient treatment approach holds promise as a novel therapy for IC.

Surgery

Surgery is needed in 2% to 3% of patients for control of intractable symptoms or to circumvent the functional effects of a severely limited bladder capacity (Table 28.14). Bladder hydrodistention, an integral part of the diagnostic evaluation, affords transient (3 months) relief of symptoms in approximately 20% of patients (150). A greater degree of distention can be achieved with the Helmstein intravesical balloon (33) in patients with reduced (less than 300 to 400 mL) bladder capacities. The duration of response is usually short, repeat hydrodilations are needed, and the risk of bladder rupture is approximately 8% (150).

Bladder distention	Sacral neuromodulation
Simple hydrodilation	Substitution
Helmstein balloon	enterocystoplasty
Transurethral electrocautery	Cystourethrectomy/urinary
Laser photoirradiation	diversion
(Nd:YAG laser)	

TABLE 28.14. SURGERY FOR INTERSTITIAL CYSTITIS

Transurethral resection (TUR) or fulguration of discrete ulcers controls pain in many patients with classic IC (71). Ulcers and fissures heal within 4 to 6 weeks following laser photoirradiation with the neodymium:yttrium aluminum garnet (Nd:YAG) laser (154), and pain relief is significant. Because of the rarity of Hunner's ulcers and the risk of small bowel perforation, laser treatment has not gained widespread use.

Less than 10% of IC patients require lower urinary tract surgical reconstruction (Table 28.15) for intractable symptoms (e.g., small capacity, pain), failure to respond to medical therapy, or lack of tolerance for standard pharmacotherapy. The outcomes following subtrigonal or supratrigonal cystectomy and orthotopic bladder substitution with an ileocecal pouch (Mainz pouch) were assessed. Both supratrigonal and subtrigonal cystectomy gave similar relief of symptoms (mean follow-up of 31.5 months), although the supratrigonal cystectomy group had better functional bladder rehabilitation (71).

Indications
Intractable symptoms
Failure of nonsurgical treatment
Presence of ulcers
Small bladder capacity (<400 mL)
Required in small number of patients (2%–3%)
Proper patient selection to ensure success
Cystolysis if capacity >350–400 mL
Substitution cystoplasty if capacity <300–350 mL
Cystourethrectomy
For failed cystolysis, enterocystoplasty
Better control of pain symptoms

TABLE 28.15. OPEN SURGERY IN INTERSTITIAL CYSTITIS

Supratrigonal cystectomy with ileocystoplasty resulted in a good clinical outcome in "classic" IC, whereas pain

continued in patients with nonulcer IC. Identification of the IC subtype is crucial in the selection of patients for subtotal cystectomy and ileocystoplasty (128). Anterior vaginal wall hernias may develop in women who undergo simple cystourethrectomy and urinary diversion for intractable IC (3). An extended simple cystectomy, as compared with a radical cystectomy that includes a partial vaginectomy, may well result in weakening of the anterior vaginal wall and resultant anterior enterocele formation.

Another interesting treatment approach is that of sacral neuromodulation using sacral nerve stimulation. A small pilot study showed good responses, and parallel changes decreased levels of urinary antiproliferative factor. This study needs to be validated in a larger multiinstitutional study before it gains widespread acceptance (13). Ongoing studies of neuromodulation using the Stoller afferent nerve stimulator (SANS) and the ANS spinal cord device should shed light on the role of neuromodulation in IC.

Conclusions

Ongoing research into the causes and pathogenesis of IC continues to identify a multiplicity of dynamic pathophysiologic processes involving the various layers and components of the bladder. The initial insult or insults that lead to IC remain unknown. However, an altered bladder epithelial permeability results in a complex cascade of changes and interactions involving urinary cations (e.g., potassium), sensory nerves, activated mast cells, detrusor muscle overactivity, and spinal cord sensitization. The resultant vicious cycle of inflammation and nerve sensitization leads to the chronicity that is the hallmark of IC.

New drug treatments for IC will follow as a result of a better understanding of disease pathogenesis. There is now an emerging consensus favoring multimodality drug treatment for IC. This is based on the roles of the bladder surface urothelium, mast cells, and nerve endings in the pathogenesis of IC. Hopefully these multidrug therapies will lead to better treatment outcomes with patients responding in weeks rather than months.

IC is more prevalent than currently realized. This increasing recognition in men with symptoms of prostatitis and women with chronic pelvic pain has been a notable advance in recent years. Likewise, the recognition that IC patients frequently have a variety of associated diseases lends credence to the hypothesis that a subset of IC patients may have a systemic aberration in their immune, endocrine, or nervous systems.

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29

URINARY FISTULAE

Kevin T. McVary

Fray F. Marshall

K.T. McVary: Department of Urology, Northwestern University Medical School, Chicago, IL 60611.

F.F. Marshall: Department of Urology, Emory University Medical School, Atlanta, GA 30322.

Contents

Descriptions of urinary fistulae in both sexes appear in ancient texts, some of which are attributed to Hippocrates and Rufus. Such fistulae, although seldom life-threatening, can severely compromise the quality of life. Appropriate evaluation and timely correction is paramount. Treatment requires diligence, technical versatility, and supportive handling of the patient, family, and others involved. J. Marion Sims, although not the first to perform a surgical cure for fistula, changed history with the unique observation of vaginal anatomy when he examined patients in the knee–chest position. He described a surgical approach using

three basic principles of urinary fistula repair: (a) excising all scar tissue, (b) obtaining fresh viable margins, and (c) closing the tract without overlying suture lines (60).

In developed countries, urinary fistulae are largely iatrogenic in etiology. Other inciting events or agents include direct invasion by malignancy, radiation therapy, trauma, pelvic inflammatory conditions, infections, granulomatous disease, the presence of foreign bodies, and traumatic delivery. Contributing factors that are critical in the etiology and successful repair of these abnormal communications include poor vascular supply, distal obstruction, poor nutrition, and continued inflammatory or infectious processes. Regardless of the type or location of fistula, the approach to repair should specifically address (a) the extent, number, and location of the fistula(e) and (b) the most likely cause, excluding complicating cofactors such as foreign body, malignancy, inflammatory or infectious conditions (including tuberculosis), and distal obstruction. Consideration of secondary comorbidities such as poor nutrition and previous radiation are critical because they influence the choice of procedure, timing of surgery, and probable outcome. Regardless of the type of fistula, most patients can be managed successfully without permanent supravesical diversion. Some fistulae require innovative techniques. It is crucial for urologists to be versatile and conversant with a broad range of procedures.

The principles of closure include appropriate urinary and fecal diversion. Well-vascularized, healthy tissue should be utilized for repair, and closure should be accomplished without tension and without overlapping suture lines. Infection should be treated adequately before repair. If possible, well-vascularized, noninvolved tissues should be interposed between the suture lines to provide an additional buttress. The operative area should be drained adequately after anatomic reconstruction has been performed.

VESICOVAGINAL FISTULA

Part of "29 - URINARY FISTULAE "

Etiology

In medically underdeveloped countries, obstetric trauma remains the leading cause of vesicovaginal fistulae (15,162) (Table 29.1). In Africa, the common etiologic factors are obstructed labor with pressure necrosis (84%) and “gishiri cutting” (13%), involving an anterior vaginal wall cut to prevent pressure necrosis (31). The prevalence is highest among young primigravida (63%) during unassisted vaginal deliveries (176). The length of labor in these cases ranges from 1 to 6 days (mean 3.9 days). The destruction caused by the long periods of labor extend to the fetus as well because stillbirths are recorded in 93% of cases (76). In countries with more advanced obstetric care, the incidence of childbirth-related vesicovaginal fistulae has declined significantly, for example, from 39% in Judd's series (1920) to fewer than 6%, as reported by Massee and colleagues (105) in 1964 from the same clinic. More current studies from Europe and North America suggest an incidence as low as 0.01% (32,184). In developed countries, the most common cause of vesicovaginal fistula remains iatrogenic injury during gynecologic surgery, usually hysterectomy (27,51,74,178). The pathophysiology of vesicovaginal fistula is thought to be secondary to avascular necrosis of the bladder from suture placement and erosion into the vaginal cuff. A fistula also may follow an uncomplicated operation as the result of a pelvic hematoma that ruptures into the bladder during the postoperative period. Additional mechanisms of iatrogenic fistula include crushing, ligating, cutting, or devascularizing the bladder and vaginal cuff with surgical instruments. A thorough understanding of the relevant anatomy, strict hemostasis, and proper mobilization of tissue planes between bladder and uterus/vagina could minimize these causes. An awareness of predisposing risk factors such as previous radiation, cesarean section, endometriosis, prior pelvic surgery or pelvic inflammatory disease, inflammatory bowel disease, diabetes, concurrent infection, and atherosclerosis also is necessary (71,83,87,152).

Congenital (rare)	Abdominal hysterectomy
Inflammatory	Vaginal surgery
Infection, such as tuberculosis and schistosomiasis	Urologic procedures
	Obstetric trauma
Foreign body in bladder or vagina	Prolonged labor
	High forceps delivery
Prolonged indwelling urethral catheter	Cesarean section
	Direct injury
Endometriosis	Neoplastic
Trauma	Carcinoma of cervix, bladder
Pelvic surgery	Radiation induced

TABLE 29.1. CAUSES OF VESICOVAGINAL FISTULAE

Fortunately, fistulae following aggressive transurethral resection of the bladder neck or transurethral resection of posteriorly based bladder tumors are now rare. Radiation-induced fistulae are commonly associated with carcinoma of the cervix, and several have been reported after radiotherapy of other pelvic malignancies. Fistulae may appear during the course of radiotherapy or after treatment is completed. Those occurring during therapy are probably secondary to necrosis of tumor in the wall of the vagina or bladder. Those that appear later are likely secondary to excessive radiation, which leads to endarteritis obliterans and eventual necrosis of the vesical or vaginal wall. These fistulae usually appear during the first 2 years of treatment and have become less common with improved radiation therapy techniques. Reports of new onset of fistulae secondary to remote irradiation continue to appear suggesting that clinicians should remain diligent in their evaluation of patients whose bladder symptoms evade a clear etiology (111).

Other less common causes of vesicovaginal fistulae are the destruction of tissue by other malignant tumors,

ulceration resulting from a foreign body, (i.e., retained pessary) direct trauma (especially automobile accidents associated with pelvic fractures), tuberculosis, schistosomiasis, calculi, and endometriosis.

Clinical Features

The most common presenting symptom of vesicovaginal fistula is continuous leakage of urine from the vagina. Incontinence developing from operative trauma usually occurs 5 to 14 days postoperatively (74,184). Leakage of urine is directly related to the size and position of the fistula. Patients with small fistulae may void reasonable amounts of urine and notice only slight, position-dependent drainage. Patients with large fistulae have total incontinence and may not void through the urethra at all. Leakage of urine causes irritation of the vagina, vulva, and perineum and usually produces an unpleasant, ammoniacal odor. In neglected cases, phosphatic encrustations may be noted. The posthysterectomy fistula is typically located in the vault of the vagina (164). An obstetric fistula is usually located at a lower level, is larger in size, and is more commonly associated with urethral injury.

Graham (53) described the painful syndrome of postradiation urinary vaginal fistula. He noted that 40% of patients with radiation-induced fistulae developed pain, usually associated with an alkaline urine and deposition of triple-phosphate crystals, which further irritate compromised tissue. Urinary leakage can make the patient a social recluse; disrupt sexual activity; and lead to significant mental depression, insomnia, and low self-esteem (61,74).

Diagnosis

In most patients, the diagnosis is obvious (Table 29.2). However, a complete urologic investigation is mandatory, especially to rule out ureterovaginal fistula. This investigation should include a urinalysis, urine culture, and intravenous urogram. Other tests, such as a retrograde ureteropyelogram, can be performed as necessary. In one series, 12% of patients with vesicovaginal fistulae had associated ureterovaginal fistulae (51). Overlooking additional fistulae continues to perplex even the most experienced urologists (93). Such patients are a continual source of consternation as well as surgical failures.

Urinalysis	Retrograde ureteropyelogram
Urine culture	Cystoscopy and vaginoscopy
High vaginal swab	Computed tomography scan or magnetic resonance imaging
Intravenous urogram	
Dye test	

TABLE 29.2. INVESTIGATIONS FOR URINARY VAGINAL FISTULAE

All patients with fistulae should undergo cystoscopy and vaginoscopy. Every attempt should be made to determine the exact location (in relation to ureteral orifices), size, and underlying cause of the fistula. Successful repair depends on identification of these factors. At examination under anesthesia, it is often possible to palpate the vaginal opening of the fistula. A diligent search should be made for additional communications because many treatment failures have occurred because less obvious fistulae were overlooked. It is also worthwhile to determine the status of the bladder neck and note whether there is any associated loss of urethral tissue. In addition, a careful examination should be done with the patient anesthetized, and a biopsy sample should be obtained from any suspicious lesion to rule out malignancy. In advanced cases with a positive biopsy for carcinoma in the fistula tract, Wein (178) has recommended pelvic exenteration or palliative urinary diversion rather than fistula repair. In equivocal cases, a simple double-dye test can be performed at the bedside (143). The vagina is packed with four sterile, wet gauze pads—one in the left and one in the right vaginal fornix, one at the midvaginal level, and one at the vaginal outlet. The bladder is filled with a 1% carmine solution (red), and 5 minutes later 5 mL of indigo carmine (blue) is injected intravenously. The swabs are removed 10 minutes after the injection. A red stain (carmine) in the midvaginal pack indicates a vesicovaginal fistula, a blue stain on the upper swabs placed in the vaginal fornices indicates a ureterovaginal fistula, and a red stain in the swab at the vaginal outlet indicates leakage through the urethra. Sometimes the findings can be misleading. The amount of indigo carmine excreted depends on renal function, and occasionally, carmine solution can reflux up a ureter and gain entry into the vagina by means of a ureterovaginal fistula, providing a false-positive result for a vesicovaginal fistula. Recently, a simplified double-dye test has been used to diagnose various types of vaginal fistulae with oral phenazopyridine administered until the urine is stained orange. The patient is then instructed to insert a vaginal tampon. The bladder is catheterized, emptied, and filled with saline/methylene blue mixture. After 10 minutes, the bladder is emptied and the tampon removed. An orange stain at the top of the tampon indicates a ureterovaginal fistula, and a blue stain is consistent with a vesicovaginal fistula (124).

The use of computed tomography (CT) scanning with intravaginal contrast has been used in a small number of patients with limited success (60% detection rate). CT findings that suggest fistula include radiation changes, contiguous pelvic mass, and adherent bowel. The use of such imaging techniques may be most beneficial in trying to ascertain the underlying etiology and the extent of prior disease before attempting a surgical repair (82). The use of magnetic resonance imaging (MRI) has been reported largely in the case report format only; thus recommendations are difficult to assess. However, the use of a

T_2-weighted image looking for fluid within the fistula is suggested as a useful characteristic (121). The multiple plane image reconfigurations and tissue characterizations of this technique are also useful (167). In a prospective study of ultrasonographic evaluation of vesicovaginal fistula, Adetiloye and others (1) noted its demonstration in only 29% (7 of 24) compared with examination under anesthesia in 87%. Sonography appears to function as complimentary examination at best. There is no substitute for a diligent search on the part of the clinician to establish the site or sites of fistulae (Table 29.3).

Vesicovaginal fistula	Severe stress or urge incontinence
Ureterovaginal fistula	Vaginitis or enterovaginal fistula

TABLE 29.3. DIFFERENTIAL DIAGNOSIS OF URINARY VAGINAL FISTULAE

Preoperative Care

Medical and psychologic support are necessary in afflicted women. Cystitis, vaginitis, and perineal dermatitis should be treated with appropriate antimicrobials. Local care is important, with meticulous cleansing and frequent pad changes to minimize inflammatory edema and vulvar irritation. Protective creams or ointments are occasionally helpful in reducing vulvovaginitis. Keeping the area as dry as possible, at times by the innovative use of collection or drainage devices, is often helpful. Nutritional supplementation may be of benefit in this group of patients. Video urodynamics is a key diagnostic tool providing information about bladder storage function and urethral continence mechanisms. This issue should be addressed prospectively in fistula at the bladder neck and urethra, irradiated tissue, and in patients with a previous history of or recurrent incontinence (184).

A small fistula may close with catheter drainage alone or after electrocoagulation and catheter drainage (128,130,184). Denuding the fistula tract with a metal screw curettage has resulted in successful healing (8). Nonsurgical treatment of the vesicovaginal fistula has been reported in the past, and reports continue to appear. Davits and Miranda (31) reported their experience with spontaneously healing fistulae with the use of prolonged Foley catheterization. In their four cases, the diagnosis was made easily and prompt conservative treatment was begun. Although this study confirms that this method can be used, the success rate is low. Such techniques require continuous drainage, with some patients on constant suction often for extended periods of hospitalization. The successful closure of small fistula using a fibrin clot following debridement of the tract has been successfully used (64,139). Estrogen replacement also can be used provided there are no medical contraindications in patients who are castrated or postmenopausal. Hyperbaric oxygen treatment also has been used as an adjuvant treatment in radiation-associated fistulae (155). Fistulae associated with the use of adjuvant radiation therapy will not heal spontaneously, and surgical correction is required (144).

Timing of Repair

Controversy remains over the timing of repair. Most surgeons agree that there should be a waiting period of at least 3 to 4 months before surgical repair is performed (27,74,115,178). The rationale for this relates to the acute inflammatory response and edema, which will have a chance to subside. Waiting also allows the tissues to develop an improved blood supply and become more pliable, allowing for greater ease of defect closure without tension. This observation also allows an opportunity to treat any infection that may be present. It should be noted that this sage advice to delay repair is based on the historically more prevalent obstetric fistula, which etiologically and prognostically is different from the more straightforward iatrogenic fistulae seen in the Western world. Several series report excellent results with early operative intervention in patients with vesicovaginal fistula that result from iatrogenic injury (9,14,138,146). Using the transabdominal approach, Blandy reported 100% successful treatments of iatrogenically induced ureteral and vesicovaginal fistulae in 40 patients (14). Ideally, fistula that are to be repaired early should be done within the first 2 weeks before inflammation and fibrosis make reconstruction difficult. Unfortunately, many fistula are not detected until after this period. Regardless, this early aggressive treatment has not received wide acceptance. Wein and associates (178) attributed two of their failures to inadequate delay between the initial surgical procedure and the subsequent attempt at fistula repair. Collins and associates (24) have recommended a 10-day course of cortisone to decrease inflammation, followed by early repair of the vesicovaginal fistula. Because steroids may adversely affect healing, this approach appears hazardous. In their reported series of 38 patients who had repair 4 weeks after diagnosis, a 28% failure was seen.

Every patient should be examined at regular intervals, and treatment decisions should be individualized rather than using arbitrary timelines. The optimal time for repair is when all necrotic tissue has disappeared, tissue pliability is acceptable, inflammatory edema has subsided, the fistula size has stabilized, and all acute inflammatory changes have resolved. In making this judgment, the surgeon should not allow objective judgment to be swayed by a patient's emotions and the referring physician's consternation. There is no question that the planned delay in treatment results in physical discomfort and emotional stress with patients enduring the discomfort and humiliation of having continuous urinary leakage or catheterization for a 3- to 6-month period. Presented with an incontinent and angry patient, one needs to remember the admonition of Dr. V.J. O'Conor, Jr., that “a surgeon must stand firm in his

conviction that an impatient patient is easier to manage than a surgical failure" (126). The failure rate for repair of the fistula will be higher if the tissue is acutely inflamed, edematous, ischemic, or necrotic. Some fistulae recognized in the immediate postoperative period or after trauma with minimum inflammatory changes may lend themselves to early repair. In cases of complex or radiation-induced fistulae, a longer waiting period is usually required to optimize tissue status and assess surgical options.

Operative Management

A vesicovaginal fistula can be repaired through a vaginal, abdominal, or combined approach. The vaginal approach is often used, and a success rate close to 90% is achieved with this technique (27,105,115). Compared with the abdominal approach, the vaginal repair of a fistula is a less extensive procedure, avoids a cystotomy, is associated with less blood loss, results in less discomfort and disability to the patient, and requires a presumed shorter hospital stay (74,115,176). The disadvantage of the transvaginal approach is the relative lack of familiarity with the surgical anatomy by many urologists and the relative lack of versatility in surgical options should the fistula "suddenly" become complex in nature. Furthermore, the abdominal approach often provides better access to the fistula. Improved exposure decreases the likelihood of ureteral injury. If necessary, an omental pedical graft can be interposed between the bladder and vaginal wall (125,128,129,130 and 131,169,178).

Indications for a transabdominal approach include (a) limited access because of a high retracted fistula in a narrow vagina, (b) proximity of the fistula to the ureteral orifices or a need for a ureteral implantation, (c) associated pelvic pathology, (d) complex fistula with multiple fistulous tracts or previous radiation, (e) narrow introitus, (f) poorly estrogenized or scar tissue that does not respond to preoperative estrogen replacement, and (g) morbid obesity. Despite the recent interest in transvesical or transvaginal approaches, the O'Conor technique is time-tested, enjoys a high success rate and is still regarded as the gold standard (122). A combined vaginal and abdominal approach also can be helpful in instances of complicated fistulae with pelvic malignancy or previous radiotherapy (182). This allows for full mobilization of the omentum and its interposition between the vagina and the bladder or urethra (169).

Using a vaginal or abdominal approach to an individual fistula depends on the findings and the surgeon, but the principles of repair are the same. Success is determined by a watertight, multilayered closure without tension and without overlapping suture lines. Maintenance of blood supply, removal of all necrotic tissue, identification and separation of surgical planes (vaginal wall and bladder wall), obliteration of dead space, good bladder drainage, control of infection, and interposition of healthy tissue when appropriate are important technical considerations (115,138). The best chance at closure of the fistula is the first chance. In troublesome incontinence from vesicovaginal fistulae in patients who are not operative candidates secondary to terminal disease, urinary diversion via percutaneous nephrostomy with or without ureteral occlusion can be considered. Occlusion with Gianturco coils and gelatin sponges is safe and reliable in obtaining long-term, if not permanent, supravesical diversion (42).

Vaginal Repair

The inverted lithotomy position provides excellent exposure of the ventral vaginal wall. The bladder is then in a dependent position, and the fistula is more easily dissected. Many surgeons, however, prefer the conventional lithotomy position (74,115,138). A description of how to repair the fistula with the patient in a lithotomy position follows (Fig. 29.1).

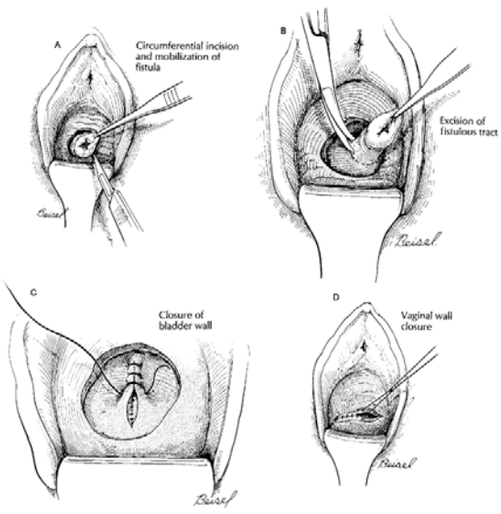

FIGURE 29.1. Schematic representation of a vaginal repair of a vesicovaginal fistula. **A:** Circumferential incision around fistula track with mobilization of the fistula. **B:** Fistula is excised. **C:** Bladder is closed, and then the vagina is closed in multiple separate layers with avoidance of overlying suture lines. **D:** Closure of vagina wall.

After careful evaluation, the ureteral orifice may be catheterized cystoscopically if there is any concern about the ureters. The labia minora are sewn laterally, and a weighted posterior vaginal retractor is placed. Stay sutures are placed in healthy tissue on each side of the fistula because they are helpful in identifying the fistula's opening at a later stage in the operation, when bleeding and excision of tissue may make identification more difficult. Additional Babcock or Allis clamps may bring the fistula tract closer to the surgeon. A Foley or Fogarty catheter also can be placed through the fistula track. This maneuver can greatly aid dissection of a fistula, especially one high in the vagina. If the vagina is small, an incision can be made through the dorsal lateral vaginal wall, similar to an episiotomy incision, to provide better access (52). A circumferential incision is made around the defect, and all scar tissue is excised. Adequate separation of bladder and vaginal wall is attempted to obtain a tension-free closure. In some instances, the separation may be difficult and lead to unnecessary bleeding and devascularization of tissue (115,136). On the other hand, it must be remembered that if basic surgical principles are even slightly compromised in these cases, the failure rate is much higher. Caution is also exercised in the posthysterectomy fistula to avoid opening Douglas's pouch and inadvertently creating a bowel fistula because small bowel may be closely adherent. In high vaginal fistulae, inadvertent injury to the ureters is also possible. After excision of the fistula tract with adequate separation of the bladder and vaginal wall, a three-layer closure is performed (74,131) with absorbable sutures on an atraumatic needle. If there is tension on the closure, relaxing incisions have been recommended, but in such a case, the operation has probably been performed inadequately. A vaginal flap advancement or other maneuver to create a tension-free anastomosis would be a better alternative. Occasionally, bleeding may be profuse, but vaginal packing generally controls it.

One can advance a vaginal flap rather than totally excising the tract, especially in patients with a simple, small fistula. In more difficult cases, the Latzko technique of partial colpocleisis can be performed (86,101,102). This

method involves denudation of an elliptical portion of the vaginal wall surrounding the tract, with the bladder portion left untouched. Partial colpocleisis is performed in three layers, without sutures entering the bladder wall. This enables the posterior vaginal wall to become the posterior bladder wall with eventual reepithelialization with transitional epithelium. The overall success rate of 93% (40 of 43 patients) is comparable to more standardized vaginal approaches (40,164). This method may cause loss of vaginal length and interfere with sexual function but has been particularly effective in patients who have had previous radiation (101,102).

Various flaps have been increasingly utilized in recent years (63,70,103). In patients with a large defect, a pedicle flap enhances the cure rate, presumably because of additional blood supply, improved lymphatic drainage, and better separation of suture lines. With a low or midlevel fistula, the graft of a pedicle flap of labial fibrofatty tissue (103) can easily be performed. The use of this flap is so convenient and well tolerated that its routine use should be encouraged. By careful dissection and preservation of its anterior- or posterior-based blood supply, the labial fat pad can reach high-level fistulae. Conversely, a higher fistula with a large defect may require a buttock flap (66), or

a gracilis muscle or rectus abdominus muscle flap in patients who have undergone radiation (52,53,70,136,154). For fistulae that involve the trigone or lie close to the ureteral orifices, a bladder rotation flap or bladder advancement flap with interposition of omentum often suffices (25,80,142,160). The use of such flaps does not excuse the surgeon from strict adherence to the principles of repair outlined earlier. The use of various tissue interposition maneuvers are discussed later in this chapter. At the end of the operation, the bladder is irrigated and all clots removed. A Foley catheter is left in place, and the vagina is packed with gauze.

Abdominal Approach

The always useful abdominal approach (transperitoneal transvesical) begins by exposing the bladder through a lower midline abdominal incision (Fig. 29.2). The advantage of this incision is that it can be readily extended upward and a pedicle flap of omentum can be mobilized. A limited transvesical approach has been advocated by some for simple vesicovaginal fistula in cases where the vaginal approach is not possible, and the surgeon wishes to avoid the associated morbidity of the traditional transabdominal approach (48,184). In complicated cases, a transperitoneal approach is preferable.

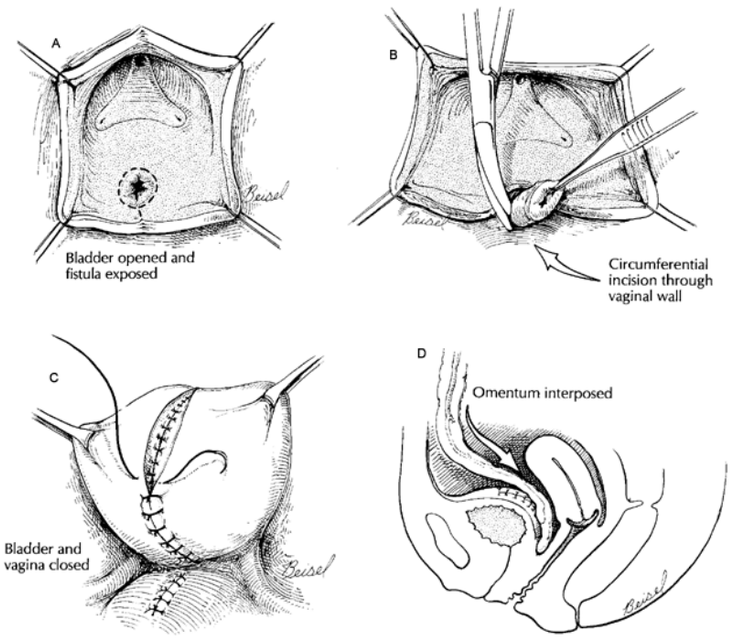

FIGURE 29.2. Abdominal repair of vesicovaginal fistula. **A:** Transabdominal, transperitoneal exposure of fistula track reveals fistula above trigone after the bladder is opened. **B:** Bladder wall is divided and the fistula, including the vaginal wall, is excised transvesically. **C:** Bladder and vagina are closed in multiple separate layers. **D:** Omentum is interposed between bladder and vagina to provide a vascularized pedicle to prevent further fistula formation.

The principles of repair are the same. The peritoneum is opened high above the umbilicus as adhesions are freed and the omentum mobilized for later use. The bladder is opened between Allis clamps, and stay sutures are held with clamps. The bladder incision is extended downward posteriorly, with stay sutures placed on each side. The proposed incision effectively bisects the bladder and extends around the fistula to create a tennis racket appearance. The key is to bisect the

bladder and vagina so that closure can be effected using viable, freely movable flaps that come together easily without tension.

As the fistula is approached, it is often helpful to place a balloon catheter or Young prostatic retractor to elevate the area. A circumferential incision is made through the full bladder wall. All firm scar tissue at the fistula is excised until the edges bleed freely. Once these bladder flaps are developed, the upper vagina is well exposed and hemostasis is excellent. The vaginal part of the fistula is excised and cut back until viable vascular edges are obtained. Any hard, fibrous tissue that does not bleed should be excised. The vagina is closed transversely in two layers, the bladder is closed longitudinally in multiple layers with absorbable sutures, and the omentum is brought down and fixed to the vagina. If adequate omentum is not available, the short gastric arteries are divided, with care taken to preserve arteries from the gastroduodenal source. Although many quote that O'Conor invented the use of omentum for this purpose, it should be emphasized that its use in vesicovaginal fistula repair was initially described by Waltman Walters (175). Closures can be reinforced with a peritoneal flap of the lateral parietal peritoneum (36) if omentum is not available. If the defect cannot be closed without tension, the flap should be used to plug the defect, which can then be used to allow reepithelialization (184). Other alternatives include an advancement flap derived from the posterosuperior wall of the bladder as a means of covering large defects (48). Alternative flaps include the gracilis muscle, island myocutaneous flaps, myofascial flaps, bladder mucosa, appendices epiploicae, and seromuscular intestinal patches (see later for interposition flaps details). A urethral and occasionally a suprapubic catheter ensure continuous drainage.

Recently, surgeons have adopted the use of the versatile bladder mucosa graft in the treatment of vesicovaginal fistula (16,134). This technique consists of a transvesical approach with an incision in the anterior bladder wall above the fistula site. The fistula is removed, including a 3- to 5-mm edge of tissue free of fibrosis. A bladder mucosa graft proportional to the size of the defect is dissected from the muscle. The free graft is positioned so that the submucosal tissue faces the bladder and the mucosa surface faces the vagina. The serosal vaginal surface is sutured through the vesicostomy incision using absorbable sutures. Investigators report a remarkable 96.3% success rate with no late failures (16). It has been proposed that the graft acts as a biologic dressing avoiding scar tissue formation that could result in a new vesicovaginal fistula. A second potential advantage of this procedure is that the suture lines are not directly overlying each other because the graft covers the bladder suture line and produces an extra layer of tissue. The bladder mucosa autograft technique offers a very promising alternative for the treatment of small and well-visualized vesicovaginal fistulae.

The recent reports of a laparoscopic approach to vesicovaginal fistula is not surprising given its application in other areas (114). However, its role as a dependable form of therapy depends on adherence to fistula repair principles and studies that move beyond the case report format.

Postoperative Care

The vaginal pack is removed after 24 to 36 hours. The patient is encouraged to be ambulatory as early as possible to minimize thromboembolic complications, which have been reported in most large series (27). Antimicrobials are used intraoperatively and frequently postoperatively until all tubes are removed. Unobstructed vesical drainage is mandatory for success. Anticholinergics and sedation often reduce bladder spasms. The urethral catheter is removed 7 to 10 days postoperatively, after a cystogram verifies there is no extravasation. It is recommended that the patient abstain from sexual intercourse for at least 6 to 8 weeks postoperatively.

URETHROVAGINAL FISTULA

Part of "29 - URINARY FISTULAE "

Etiology

Urethrovaginal fistula is an uncommon condition that usually results as a complication of such operative procedures as urethral diverticulectomy, anterior colporrhaphy, transurethral resection of the bladder neck, or trauma. In these cases, the most common causes are interference with blood supply leading to tissue slough or nonhealing secondary to infection. In medically deprived countries, obstetric trauma secondary to obstructed labor with pressure necrosis of the anterior vaginal wall is by far the most common cause of urethral destruction. A fistula may result after trauma, especially with pelvic fractures and urethrovaginal lacerations. In addition, vaginal and urethral neoplasms treated with radiotherapy may undergo necrosis and create a fistula. Pressure necrosis also can occur with a prolonged indwelling urethral catheter. Transsexual surgery and drainage of a periurethral abscess are other rare causes of fistulae. Finally, urethrovaginal fistulae can be seen on a congenital basis (101,102).

Clinical Features

Fistulae involving the bladder neck and proximal 2 cm of the urethra may produce continuous incontinence, whereas a fistula distal to the external sphincter may be entirely asymptomatic. A distal fistula also may create a spraying-type split stream. Usually, bothersome urine will drain via the vagina, especially when the patient stands. Of patients, 20% to 40% will have associated stress incontinence. Generally, the defect is obvious on examination, but occasionally, it may be hidden by the rough, irregular vaginal surface.

As many as 19% of patients with this type of fistula may have a secondary communication between the bladder and vagina (92).

Diagnosis

The differential diagnosis includes vesicovaginal fistula, ureterovaginal fistula, severe stress or urgency incontinence, and a copious vaginal discharge. A complete urologic investigation with cystourethroscopy and vaginoscopy reveals the type and size of the defect. In select patients, urodynamic studies, urethral pressure profile, voiding cystourethrogram, and the Bonney test provide additional useful information.

Management

An efficient bladder neck mechanism is critical in females to maintain continence. Studies have shown that the proximal 2 cm of bladder neck and urethra represents the continence zone (85). Unfortunately, as many as 49% of continent postmenopausal women have an incompetent bladder neck mechanism and depend on an intact proximal urethral mechanism to maintain continence (88). The fistula may compromise the urethral closure mechanism, causing the patient to experience stress incontinence in addition to the difficulties from the fistula.

The principles of management are similar to those of vesicovaginal fistula. Treatment depends on symptoms, cause, size, and location of the fistula, as well as other local factors. If stress incontinence is noted, the evaluation should include an assessment for urethral hypermotility, scarring, and fixation. If atrophic tissue is present in the vagina, estrogen replacement may be of benefit provided no medical contraindications are present. For this type of fistula, video urodynamics have an important role in preoperative assessment. In patients with type III stress incontinence, the use of concurrent fascial sling at the time of transvaginal closure warrants serious consideration (13,184). Its role as a reinforcing layer as well as a continence procedure does not preclude alternative interpositions as well (i.e., Martius flap).

In cases of bladder neck destruction, the Young-Dees-Leadbetter (89) repair may be useful in reconstruction. The transpubic approach, as advocated by Waterhouse and colleagues (177), may provide additional exposure, but complication rates are higher. Labial fat pad repair (38,88,103), gracilis muscle flap interposition (70,136), pedicle perineal flap (66), island bulbocavernosus musculocutaneous flap (19), and full-thickness skin graft have been successfully used in reconstruction of the female urethra.

In the small fistula, the Martius procedure, using the fibrofatty labial tissue, may suffice. This tissue is mobilized on a pedicle, preserving its vascular supply on its posterior aspect, and is passed through a subcutaneous tunnel into the vaginal lumen, where it is sutured over the repaired urethra. The ease of usage and other advantages of this flap are so numerous that we recommend it for routine use. The pedicle buttock flap, as described by Hendren (66), however, provides better vascularized tissue and ensures a greater likelihood of success, especially in larger fistulae (Fig. 29.3A and Fig. 29.3B). Success rates of repair vary from 75% to 100%, although some patients require more than a single operation (54,74,136,164). If stress incontinence is associated with a urethrovaginal fistula, a simultaneous continence procedure can be performed once the fistula repair has been completed (88,184). Preoperative planning of urethrovaginal fistula correction must consider bladder neck competency or risk residual stress incontinence as high as 40% (127,136). This issue is critical in those with prior irradiation, bladder fibrosis or multiple previous surgeries. Fistulae induced by irradiation seem to be the most difficult to repair successfully because this group has bladder compliance difficulties in addition to the urethral pathology (38,165). Sophisticated urodynamics are necessary for addressing both bladder and urethral pathology. Tissue interposition is mandatory if a surgical approach is considered. The bladder is then drained suprapubically for several weeks.

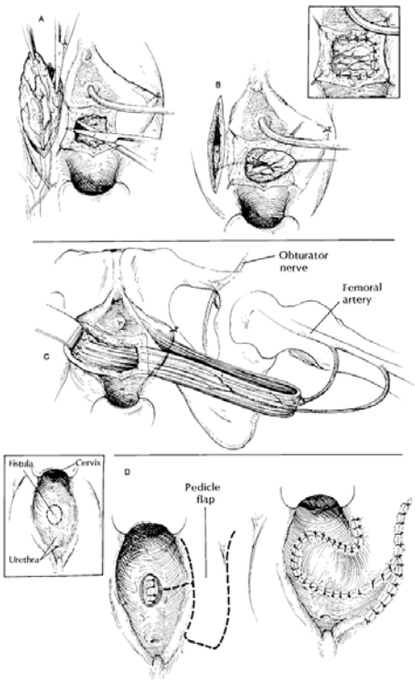

FIGURE 29.3. Alternative flap repair for urethrovaginal and/or vesicovaginal fistula. **A:** Martius interposition: mobilization of the fibrofatty pedicle from the labia. **B:** Tunnel created for a Martius interposition. **C:** Gracilis muscle flap interposition. **D:** After fistula closure a posteriorly based buttock pedicle flap is rotated inward and placed in the vaginal wall with the right labium temporarily displaced and returned. (**A** to **C** from Patil U, Waterhouse K, Laungani G. Management of 18 difficult vesicovaginal and urethrovaginal fistulas with modified Ingelman-Sundberg and Martius operation. *J Urol* 1980;123:653, with permission. **D** from Hendren WH. Construction of female urethra from vaginal wall and a perineal flap. *J Urol* 1980;123:657, with permission.)

URETEROVAGINAL FISTULA

Part of "29 - URINARY FISTULAE "

Etiology

The ureter is especially susceptible to injury during vascular, gynecologic, urologic, and colonic operations. Gynecologic surgery remains the most common cause of ureterovaginal or ureterocutaneous fistulae (91). Total abdominal hysterectomy is the most common operation responsible for ureteral injury (120,174). Endometriosis, obesity, and pelvic inflammatory disease appear to be complicating factors (161). Injuries are more common if the patient has received preoperative radiation. Postoperative radiotherapy does not appear to be associated with an increased incidence of stricture or fistula formation.

Clinical Features

In the postoperative period, a ureteral injury is suggested by the presence of unexplained abdominal pain, flank tenderness, abdominal mass, or fever. Subsequent urinary drainage occurs days or weeks after the injury and is often detected as copious drainage through a postoperative drain site. The patient usually voids normally. However, the presence of associated continuous urinary leakage from the vagina should raise the question of a ureterovaginal fistula. The symptoms are often similar to those in patients with congenital extravesical duplicated ureters.

Diagnosis

An intravenous urogram demonstrates some degree of ureteral obstruction in most cases (9,120,169). Retrograde pyelography usually delineates the nature and extent of the injury. Ureteral catheterization usually reveals obstruction. In equivocal cases, a dye test can be helpful and is quite sensitive (120).

Occasionally, a preexistence abnormal communication may exist between an ectopic ureter and the vagina but may not be demonstrated by the usual tests (90). The upper pole of the kidney may not be visualized on the intravenous pyelogram (IVP) because its function is impaired. Presence of a duplication may be suspected from a “drooping lily” configuration of the lower-pole pelvis. Meticulous cystourethroscopy and careful inspection of the vagina are mandatory because an ectopic orifice can be missed. Occasionally, a mass can be seen in the region of the trigone (15). A mass along the wall of the vagina can be examined by needle puncture and instilled with contrast medium.

Management

The primary goals include renal preservation and prevention of urosepsis. Primary nephrectomy was frequently performed in the past, but Goodwin and Scardino (51) reported a reduced nephrectomy rate of 5%. If a ureteral injury is suspected and diagnosed, the patient will rarely require a nephrectomy for ureterovaginal fistula. However, the management of the ureterovaginal fistula is controversial. Early repair has been advocated to prevent irreversible damage to the kidney. On the other hand, a retrograde catheter or stent can be placed to establish drainage, or a percutaneous nephrostomy also can be placed with a stent (84). The percutaneous nephrostomy is more easily tolerated than a retrograde ureteral catheter and provides better drainage. In select patients, a conservative approach using a ureteral stent and a percutaneous nephrostomy allows the ureter to heal if done in a timely fashion (22). This endourologic management is recommended, particularly if the injuries are recent (less than 3 weeks), if minimal loss of ureteral length (less than 2 cm) is involved, and if some continuity of the ureteral wall remains (26). Several groups of investigators report a 25% to 50% success rate in managing postoperatively discovered ureteral injuries using these techniques (34,37,171). This type of drainage may have a role in preserving renal function even if open surgery is planned.

If urinary extravasation or obstruction persists after removal of the ureteral stent, a formal repair can be performed as soon as the inflammation has subsided and any infection is under control. A psoas hitch ureteral reimplant has been successful for us in these cases. With the sutures placed intravesically, the mobilized bladder can be displaced superiorly and anchored in position, so no dissection is necessary in the scarred pelvis. We insert a finger intravesically to “push” or position the bladder high on one side and then anchor it extravesically. We commonly continue to use intravesical pressure to help introduce and anchor the ureter. Preoperative, purposeful self-distention of the bladder may help secure necessary mobility to reconstruct the urinary tract. The pedicle on one side of the bladder can be sacrificed to gain additional bladder mobility. If a larger segment of ureter has been damaged, Boari flap procedures can be used as well. If these maneuvers fail to surmount the distance needed to reestablish ureteral continuity, then renal descensus, renal autotransplantation, or ileal substitution may be needed. Successful management of ureteral fistula repair using a single, open procedure approximates 100% in select series (99,133). Nephrectomy or renal embolization and percutaneous ureteral occlusion should be used for those who are poor surgical risks (97,148).

ARTERIOURETERAL FISTULA

Part of "29 - URINARY FISTULAE "

Etiology

Fistulae between the urinary system and major arterial vessels (usually iliac) have emerged as a troublesome phenomenon within the last 15 years. Recently, the association between ruptured iliac aneurysms and arteriovesical fistula has been identified (49). Although they were previously considered rare, reports are appearing in the vascular and urologic literature with increasing frequency, presumably secondary to the widespread practice of stenting ureteral pathology (strictures, stones). The mechanism of fistula development has been postulated to require irradiation or previous surgery on the major abdominal vessels, causing injury to the vaso-vasorum (45,46). This phenomenon, combined with the leakage of blood, causes fibrosis and adherence of the ureter to the artery. Once a ureteral stent has been placed, it may create a localized necrosis of the wall (33). The addition of radiation acts as a sclerosing agent and contributes to fibrosis, ureteral obstruction/fixation, and eventual fistulization. This phenomenon is supported by a marked absence of arterioureteral fistula without the presence of ureteral stents. The relationship between arteriourinary fistula following the rejection of pancreas transplants with bladder drainage also has been noted (151). It has been proposed that the inflammatory response in rejection leads to reabsorption of the graft placing the bladder in close proximity with the iliac artery leading to subsequent erosion and fistulization.

Diagnosis

Profuse intermittent hematuria should increase the suspicion of ureteroarterial fistula. The presence of a stented or irradiated ureter or history of previous surgery should suggest a consideration of this condition. The diagnosis is particularly difficult to make at the time of presentation

because the patient is usually critically ill. Imaging studies such as arteriography or CT scanning are rarely helpful but appropriate if time permits. In a recent review, 15 of 22 cases were not diagnosed until the time of surgical exploration (35). Cystoscopy is helpful in lateralizing the side of hemorrhage, and retrograde ureterograms can demonstrate the fistula in a minority of cases (7). The development of hematuria in a patient with a rejected pancreas transplant with bladder drainage should be aggressively evaluated for such a fistula.

Management

Surgical management is the only reasonable alternative for treating these fistulae. Conservative measures are associated with an 83% mortality rate. Goals in the surgical care include (a) control of hemorrhage, (b) maintenance of a vascular continuity, (c) provision of adequate urinary diversion, (d) removal of all infected prosthetic material (graft and stent), and (e) salvage of the kidney if possible. The management of the involved ureter depends on the location and extent of the fistula. Potential urologic maneuvers include ureterectomy, ureteral reimplantation, transureteroureterostomy, cutaneous ureterostomy, and excision of the fistula with primary ureteral repair. Any interposition of healthy tissue that is available (ideally omentum) is advisable. Renal salvage has been successful in 67% of patients (35). Vascular management has required repair of the iliac artery in 48% of patients, all of whom required subsequent bypass procedures (35). Mortality rates before 1980 exceed 50%, but recent reviews report improved postoperative care as the major factor in lowering mortality to 15% (172). Recently, a minimally invasive management of this problem has emerged in which endovascular stent grafting is used (43,58). This promising technique appears to be able to manage the fistula without the need for extracutaneous vascular bypass. This technique obviously requires early recognition, medical stabilization, and angiographic evaluation. Whether this approach becomes a predominant method in treating this potentially fatal problem remains to be demonstrated.

RECTOURETHRAL AND PROSTATIC FISTULA

Part of "29 - URINARY FISTULAE "

Etiology

A rectourethral or prostatic fistula may be congenital or acquired (Table 29.4). The congenital fistula is uncommon and usually occurs in boys in association with congenital anorectal anomalies (28). A rectourethral communication is present in 80% of patients with a high- or intermediate-level imperforate anus. Treatment is usually associated with anorectal pull-through operations.

TABLE 29.4. CAUSES OF RECTOURETHRAL FISTULA

Congenital	Inflammatory
Iatrogenic	Prostatic abscess
Prostatectomy	Urethral stricture
Transurethral resection of prostate	Tuberculosis
Urethral dilation	Crohn's disease of colon
Anorectal surgery	Neoplastic
Direct trauma, especially associated with fractured pelvis	Prostate Urethra Rectum

The acquired fistula is usually a postprostatectomy complication. In the past, perineal prostatectomy was the most common cause. Most patients developed a fistula after a simple prostatectomy or, less frequently, after a radical prostatectomy or an open prostatic biopsy (28,29,78,108,132,173,181,185,187). It also may occur as a complication of suprapubic prostatectomy, retropubic prostatectomy, radical retropubic prostatectomy, radiation therapy of the prostate, or overzealous transurethral resection of the prostate (TURP). Several factors appear to predispose a patient to rectal injury during prostate surgery, including a history of TURP, previous radiation, or rectal surgery (108). Rarely, a prostatic abscess may rupture into the rectum. A rectourethral fistula also has been described in association with Crohn's disease or inflammatory disease of the colon as well as carcinoma of the rectum or prostatic carcinoma (18). Direct trauma also may result in rectourethral fistula, especially in association with a fractured pelvis (168). Rarely, stricture disease or tuberculosis may create a fistula (62).

Clinical Features and Diagnosis

A rectourethral fistula may be strongly suspected from the patient's history. The patient may have pneumaturia or fecaluria with leakage of urine from the rectum during micturition. Urinary drainage via the rectum may lead to diarrhea. Urinary tract infections and epididymitis are common (28), as are urethral stricture and perineal fistula (28,168).

The diagnosis can usually be made by careful inspection of the rectum. Occasionally, the opening can be palpated or visualized directly by proctoscopy. A biopsy is performed when necessary to rule out carcinoma. The fistula also is usually visible on careful cystourethroscopy. Radiographic studies of the bowel and colonoscopy should be performed to verify that no additional colonic disease is present.

Management

The variety of methods recommended for the treatment of rectourethral fistulae bears ample testimony that there is no single accepted method of treatment for this uncommon lesion (Table 29.5).

TABLE 29.5. PRINCIPLES OF URETHRORECTAL FISTULA CLOSURE

Adequate urinary and fecal diversion
Maintenance of infection-free environment
Adequate drainage
Adequate exposure of the operative field
No tension on the suture lines
Transfer of healthy vascular tissue to the site of repair in appropriate cases
Nonapposition of suture lines
Closure of nonedematous, healthy tissue

Rectal injury in association with a surgically or traumatically disrupted lower urinary tract is a serious complication and, if not recognized at the time of surgery, may result in

severe pelvic infection and urosepsis. Diversion of the fecal and urinary stream has been the standard practice in the past. However, several authors describe repair of rectal injury without a diverting colostomy as long as the injury is small, the bowel was prepared preoperatively, and the repair is closed in two layers under good visualization (81,108). Previous pelvic irradiation diminishes the chances of successful primary single-stage repair; thus a suprapubic cystostomy and a diverting colostomy are recommended in this circumstance. After meticulous control of bleeding, the rectum is closed in two layers (the outer layer is closed with silk suture). The urinary tract is reapproximated appropriately for the surgical procedure or injury. Every effort is made to separate the rectal and urinary suture lines. The wound should be irrigated with saline or appropriate antimicrobial solution. Interposition of healthy vascularized tissue between the suture lines is advisable if possible. A Penrose drain is left *in situ* for 5 to 10 days to drain the perirectal tissue.

A proximal colostomy reduces the risk of failure. Allen (4) successfully managed two cases by primary closure supplemented with rectal tube decompression and neomycin irrigation of the bowel. Manual dilation of the anal sphincter should be carried out in an attempt to reduce rectal pressures by temporarily defunctionalizing the sphincter. When in doubt, the clinician should strongly consider a colostomy. Postoperatively, a liquid or low-residue diet should be instituted and maintained for several days. Systemic antibiotics effective against aerobic and anaerobic organisms should be used.

Occasionally, a fistula may occur or first be recognized weeks or months after the original operation. Successful treatment depends on the cause and the general condition of the patient. Controversy remains regarding single-stage and multistage repairs. Wood described a single-stage repair (modified York-Mason) in a series of seven patients with 100% cure and no fecal incontinence (185). All cases were corrected within 2 weeks of the fistula creation. For patients in good general condition a single-stage repair may be effective, but it still carries a higher risk of failure than a multistage repair. For poor-risk patients or patients with major fecal drainage, perineal infection, and inflammation, a multistage procedure is mandatory. Whatever repair is performed, it is imperative that basic surgical principles be rigorously followed (Table 29.5).

In the multistage procedure, a suprapubic cystostomy and a diverting colostomy (29,77,104) are done as the initial procedures. With this therapy alone, approximately one-third of patients may undergo spontaneous resolution of their fistulae (132). Once infection is controlled and the inflammation has subsided, the defect is closed. Adequate bowel preparation is essential for a successful outcome. Intraoperative and postoperative antibiotics are important. Intravenous fluids and an elemental diet are utilized postoperatively. When a postoperative cystogram shows there is no leakage of contrast material, the cystostomy catheter is removed. The colostomy is closed at a later date.

Surgical Techniques

A urethrorectal fistula may be closed by a transrectal, perineal, posterior, or abdominal approach (Table 29.6). Urethral stricture is a common postoperative complication (166). This complication can be avoided by suturing the urethral defect transversely or suturing scrotal skin to the edges of the urethral fistulous opening, as in the Johansson technique (166).

Transrectal approach	Posterior approach
Vose procedure	York-Mason procedure
Parks procedure	Kraske procedure
Perineal approach	Abdominal approach

TABLE 29.6. SURGICAL TECHNIQUES

Transrectal Repair

In 1949, Vose described a simple technique for the closure of urethrorectal fistulae with the transrectal approach. The patient is placed in the lithotomy position. After dilation of the anal sphincter, a bivalve anal speculum is placed to expose the defect. The fistulous track is excised and the defect closed in layers. This procedure is suitable for small fistulae lying close to the anal verge.

A variation of the transrectal approach is the rectal advancement flap popularized by Parks, which is simple and suitable for low fistulae (168). A bivalve anal speculum or a self-retaining anal retractor is inserted, and 1:300,000 epinephrine-in-saline solution is injected beneath the mucosa distal to the fistula. An ellipse of rectal mucosa including the fistula is removed. A full-thickness, inverted U-shaped rectal flap is raised above the fistula, brought down over the fistula, and sutured in two layers to the rectal wall (168).

The transrectal repair is often the only feasible approach in the early postoperative period. Its disadvantage is that it provides limited exposure to the fistula and therefore is reserved for low-lying, small fistulae.

Perineal Repair

In the perineal approach, the patient is placed in the lithotomy position. The fistula is exposed by an inverted U-shaped perineal incision. The fistula is excised, and the dissection is carried well above the fistulous site to obtain good exposure (28,181). The urethra is closed with a single

layer of 4-0 absorbable suture. A urethral catheter is used as a stent for 10 to 14 days. The rectal defect is closed in two layers. The outer layer is closed with silk. Normal vascularized tissue is interposed between the urethra and rectum. The levator ani muscle is readily available and can be approximated in the midline.

For radiation-induced fistulae, the gracilis muscle can be rotated through a subcutaneous tunnel to the perineum and interposed between the urethra and rectum (150). Some surgeons recommend adequate dissection of the rectum and rotating the rectal fistula site away from the midline or bringing the rectal repair to a level lower than the opening in the prostate, but this dissection is difficult because of the extensive scarring present around the fistula. Recently, a useful adjunct to this exposure using a perineal subcutaneous dartos pedicled flap was described for fistula following gunshot or pelvic trauma (188). The advantage of this interposition is the familiarity of scrotal anatomy to urologists (Fig. 29.4). How this method will perform in the face of previous radiation is not known.

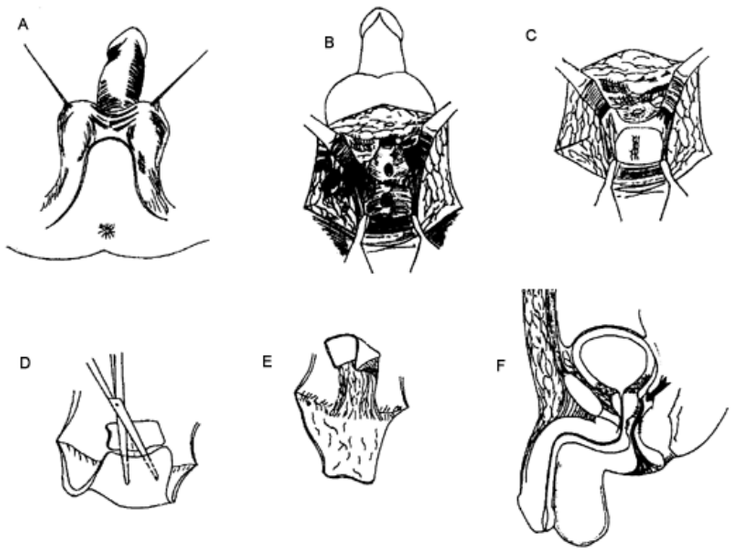

FIGURE 29.4. Creation of a perineal subcutaneous Dartos flap for urethrorectal interposition. **A:** U-shaped perineoscrotal incision is made. **B:** The fistula tract is exposed, and excised, and margins of fistula are freshened. **C:** Rectal wall is repaired in several layers. **D:** Dartos flap is made by incising the apical portion of the perineoscrotal flap and dissecting skin away from Dartos fascia. **E:** The Dartos muscle and fascia flap are mobilized to obtain adequate length. **F:** The Dartos flap is interposed between the rectal repair and the urinary tract.

The Young-Stone technique is a variant of the perineal method (187). The prostatic-rectal fistula is divided, and the entire lower portion of the rectum is mobilized and drawn through the anal sphincter; the redundant rectal wall including the fistulous area is then excised. The resultant cuff of healthy rectal mucosa is anastomosed to the skin edges after the urethral defect is closed in layers. This operation is technically difficult to perform (181), and fecal soiling has been a troublesome complication (94,181).

Posterior Approach

In 1962, Kilpatrick and Thompson described six patients in whom a successful rectourethral repair was performed using the posterior Kraske approach. The Kraske approach involves excision of the coccyx and has been clearly described by Wiseman and Decter (183). York-Mason successfully repaired fistulae in four patients with the posterior transsphincteric approach with no residual incontinence. Beneventi and Cassebaum (10) modified this technique with a rectal flap, thus avoiding neurologic and vascular structures. Recent studies report successful use of this technique in 6 of 7 rectourethral fistulae following radical prostatectomy and cystoprostatectomy (123).

York-Mason Procedure

In the York-Mason procedure, the patient lies in the prone jackknife position (104,185). The incision is begun at the level of the anal margin to the left of the midline and extended upward and laterally to the level of the midsacrum (Fig. 29.5). The mucocutaneous junction is marked with stay sutures. The sphincters are marked with sutures so that they can be easily identified at the end of the operation. The incision is deepened, and the rectal mucosa is divided to expose the defect. The fistulous track is excised. The urethral opening is closed transversely, and the rectal wall is closed in layers. The sphincter muscles are identified and carefully reapproximated. This approach provides excellent exposure, and careful reconstruction of the sphincters has produced complete anal continence (29,71,141,185). Fecal and urinary diversion may induce a spontaneous repair in 46% of posttraumatic, small, less fibrous fistulae not associated with previous radiation or malignancy (2). Combining a Parks anterior wall advancement with a York-Mason transsphincteric approach was utilized successfully in 11 of 11 patients, although urethral stricture developed in 25% (2).

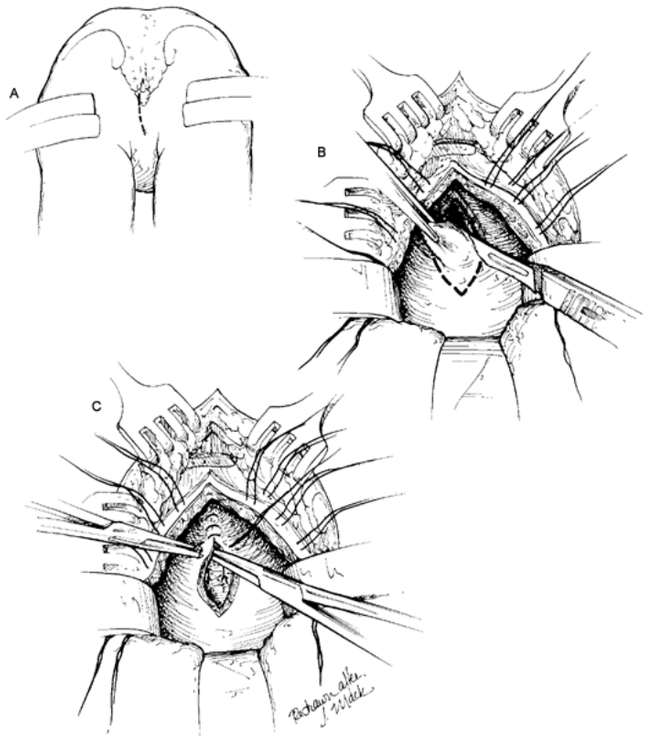

FIGURE 29.5. York-Mason procedure. **A:** Incision to the left of midline. **B:** Transrectal excision of fistula. **C:** Closure of posterior rectal wall after closure of urethra and ventral rectum at fistula site. (From Dahl DS, Howard PM, Middleton RG. The surgical management of recto-urinary fistulas resulting from a prostatic operation: a report of 5 cases. *J Urol* 1974;111:514, with permission.)

Abdominal Approach

Interposition of an omental pedicle graft is indicated for large fistulae, radiation-induced fistulae, and complex fistulae with posterior multifocal strictures (65). The omentum

is freed from the gastric margin, and the highly vascularized omental pedicle is interposed between the rectal and urethral walls. The rectal defect is closed in a single layer, but no attempt is made to close the urethral defect. Neoepithelialization occurs on the interposed omentum.

VESICOENTERIC FISTULA

Part of "29 - URINARY FISTULAE "

The four categories of vesicoenteric fistula—colovesical, rectovesical, ileovesical, and appendicovesical—are grouped together because of the similarities in clinical features and management.

Etiology

An abnormal communication between the bowel and bladder was first described in the second century A.D. by Rufus (116), but the common causes of acquired vesicoenteric fistula have changed from diseases of the past such as typhoid, amebiasis, syphilis, and tuberculosis (73) to diverticulitis, malignancy, Crohn's disease, and trauma (158,170,180) (Table 29.7). Less common causes include ovarian abscess (153), small bowel lymphoma with or without the presence of AIDS (47,37), Meckel's diverticulum (69), pelvic actinomycosis (21), and foreign bodies in the bowel (68). Congenital vesicoenteric fistulae are rare and are often associated with an imperforate anus.

Congenital (rare)	Carcinoma of bladder
Inflammatory	Carcinoma of prostate
Diverticular disease	Radiation enteritis
Crohn's disease	Lymphoma
Tuberculous ileitis	Trauma
Fungal and parasitic disease of colon	Gunshot wounds
Perforated viscus—	Pelvic fractures with bony spicules
duodenal ulcer	Penetrating injuries
Neoplastic	Iatrogenic
Adenocarcinoma of colon and rectum	Foreign bodies in bowel, such as fish and chicken bones
Carcinoma of cervix	

TABLE 29.7. ETIOLOGY OF VESICOENTERIC FISTULA

A colovesical fistula is the most common form of vesicointestinal fistula and is most often associated with diverticular disease of the colon but can result from colorectal carcinoma (73,118,157). It is more common in males, with a ratio of 3:1 (73,157). The lower incidence in women is thought to be due to the interposition of the uterus and adnexa between the urinary bladder and colon (20,79,163,180). Diverticular disease accounts for approximately 50% to 70% of vesicoenteric fistulae (73,140). Malignancy and Crohn's disease account for another 20% and 10%, respectively. Colorectal carcinoma is the most common malignancy associated with a vesicoenteric fistula. Occasionally, carcinoma of the bladder, cervix, prostate, and ovary are implicated (79,140,180). The site of the enteric fistula is influenced by etiology. Colovesical fistula between the sigmoid and dome of the bladder is the most common type of enterovesical fistula (79,140). Ileovesical fistulae are more prevalent in association with cancer and Crohn's disease. Diverticular fistulae are almost entirely colovesical, and rectovesical fistulae result from cancer or trauma (140).

Crohn's disease is the most frequent cause of an ileovesical fistula (55,73,163). The mean duration of Crohn's disease at the time of first symptoms of enterovesical fistula formation is 10 years (55,73), and the average age of the patient is 30 years (73). Ileovesical fistulae develop in 10% of patients with regional ileitis (73). Appendicovesical fistulae are occasionally reported (30,56).

Clinical Features

The presenting symptoms and complications of enterovesical fistula occur primarily in the urinary tract. However, the pathologic process is almost always intestinal (55,73,79,157,163). Suprapubic pain and complaints associated with chronic urinary tract infection are common. Chills, fever, and diarrhea are less common. Patients may notice passage of urine through the rectum or passage of mucus in urine. *Escherichia coli* is the most common offending organism, and nearly one-third of patients have a mixed-organism infection (163).

Pneumaturia and fecaluria may be intermittent and must be sought carefully in the history. Pneumaturia occurs in approximately 60% of patients but is nonspecific because it can occur in infections with gas-forming organisms such as *Clostridia,* fermentation of diabetic urine, or urinary tract instrumentation. Fecaluria is pathognomonic of a fistula and occurs in approximately 40% of cases (140).

Symptoms of the underlying disease causing the fistula may be present, but in about one-third of patients, no symptoms referable to the underlying bowel disease are noted at the time of diagnosis of the fistula (157). Patients with diverticulitis or Crohn's disease are more likely to have pneumaturia than patients with cancer (64% and 57% versus 30%) (140). Abdominal pain is most common in patients with Crohn's disease (50%). These patients also are more likely to have abdominal tenderness or mass (140).

Greenstein and colleagues (55) noted an abdominal mass and abscess more frequently among fistula patients than in a control group of patients with Crohn's disease without a fistula.

Diagnosis

A high index of suspicion is essential for making a diagnosis of vesicoenteric fistula. In most series, patients have been

treated for recurrent urinary tract infections extending 4 to 12 months before a diagnosis of fistula is made. Hafner and colleagues reported that a patient's history is at least as important as any diagnostic test in the diagnosis of ureterovesical fistula (57). Enterovesical fistula is thus a clinical diagnosis, and preoperative studies should be used to delineate the bowel disease and search for malignancy.

Cystoscopy remains the most reliable diagnostic test. The presence of a localized area of edema and congestion is a typical finding in the early stage of a fistula. As the fistula matures, it is surrounded by bullous edema and mucosal papillomatous hyperplasia. Fecal material or mucus may be observed in the bladder. Cystoscopy can be useful in ruling out other causes in the differential diagnosis and permits biopsy of the fistula if one is identified. Charcoal, oral contrast, chromium-151 or indocyanine green Chromagen dye administered by mouth and identified in the urine provides confirmatory evidence of the presence of a fistula (96,159). An attempt can be made to catheterize the suspected tract with a ureteral catheter. Retrograde injection of contrast material can confirm the presence of a fistula. A cystogram may demonstrate contrast outside the bladder at times identified clearly on CT scan. In diverticular disease and Crohn's colitis, the lesion is most commonly on the left posterior wall or the left dome of the bladder, whereas in Crohn's ileitis and in an appendicovesical fistula, the lesion is found in the right posterior wall or right dome of the bladder. A biopsy of the lesion is important to rule out malignancy.

Urinalysis may reveal undigested intestinal food residue. A urine culture may disclose an *E. coli* or mixed-organism infection.

Cystography is the most useful radiologic examination. The “herald” sign, seen best in oblique views, is a crescentic defect on the upper margin of the bladder and represents a perivesical abscess. A “beehive on the bladder” radiographic configuration may be noted (72).

Barium enema, flexible sigmoidoscopy, and colonoscopy rarely reveal the fistula but are useful in delineating diverticular disease from colorectal carcinoma. Radiography of the urinary sediment after a nondiagnostic barium enema may enhance the yield of the test (5). Barium detected in the urine sediment can confirm the presence of a fistula. CT scan often can reveal abnormalities that suggest fistula and can show associated abscesses and tumor masses, but it rarely shows the fistula itself (50). MRI may delineate fistulae better because of its excellent soft tissue contrast and ability to modify the image to ensure visualization of the proper plane of the fistula (135).

Management

A thorough and accurate preoperative evaluation helps in planning the treatment. Both single-stage and multistage procedures have been used in the management of these patients, depending on the underlying disease process and general condition of the patient. A single-stage procedure may be inappropriate in the presence of extensive inflammation, abscess, multiple organ involvement, postradiation changes, or poor-risk patients (79).

In the presence of inflammatory bowel disease, a proximal colostomy does not prevent the development of a fistula (157). Unlike prostatic-rectal fistula, spontaneous closure of vesicoenteric fistula is rare. In conjunction with Crohn's disease, approximately 95% of patients ultimately require surgery (55,109). To prevent recurrence of fistula, excision of the diseased segment of the intestine is essential (6,79).

After adequate bowel preparation, a single-stage procedure is recommended for patients in a good nutritional state in the absence of abscess or severe inflammation and multiorgan involvement (79,152,157). Otherwise, a multistage procedure is appropriate.

In the absence of malignancy, simple closure of the bladder is usually adequate. When possible, omentum is interposed between intestinal and bladder suture lines. A urethral catheter is left *in situ* for 2 weeks. A cystogram is usually performed to verify that the bladder is intact before the catheter is removed. In poor-risk patients and in patients with cancer or complex fistulae, a diverting colostomy affords some palliation. A partial cystectomy may be necessary if a colonic carcinoma is present. If a fistula has developed in this setting, an attempt to resect all carcinoma may be undertaken; however, the prognosis is often poor.

RECTOVAGINAL FISTULAE

Part of "29 - URINARY FISTULAE "

Etiology

Rectovaginal fistulae occur most often after pressure necrosis from obstructed labor (first-degree perineal tears) and are uncommon in this country. Occasionally, rectovaginal fistulae may follow surgical trauma or direct injury to the perineum. Inflammatory fistulae are principally caused by diverticular and Crohn's diseases. Rarely, ulcerative colitis, lymphogranuloma venereum, tuberculosis, or actinomycosis may result in a fistula. Malignant disease and irradiation injury also are rare causes of rectovaginal fistulae.

Diagnosis

Even though the presence of a fecal fistula may be obvious, an evaluation and an examination with the patient anesthetized should be performed in all cases. Barium enema, sigmoidoscopy, and colonoscopy are helpful in evaluating the underlying bowel disease and in determining whether there is stenosis at or below the fistula site. A fistulogram may determine whether a fistula is a simple communication between the vagina and rectum or whether there is an associated abscess cavity. A biopsy specimen of all suspicious lesions should be taken to rule out malignancy. In one large series, a rectovaginal fistula was noted in 18% of patients

who had a vesicovaginal fistula (75). Thus complete evaluation of vaginal comorbidities is worthwhile. Spontaneous closure of small rectovaginal fistulae have been reported in about 10% of cases (75).

Management

The principles of repair are the same as discussed earlier for repair of urinary vaginal fistulae. They include accurate diagnosis, fecal and urinary diversion, adequate operative exposure, excision of the fistula, multilayered closure, maintenance of blood supply, and interposition of such tissues as omentum. High obstetric fistulae are often associated with a urinary fistula. The urinary fistula should be treated first, and the cure rate will be enhanced if fecal diversion is performed before closure of the urinary fistula. A preliminary colostomy is often recommended but is elective during the repair of a straightforward rectovaginal fistula. There is conflicting opinion regarding early versus late repair. Conservative management would suggest an interval of at least 2 to 3 months from causative injury to repair. If the patient has a history of radiotherapy, waiting at least 1 year is advised. There are several approaches through which a fistula can be repaired, including abdominal, vaginal, anal, and transsphincteric. The choice of approach depends on the experience of the surgeon, the site of the fistula, and the condition of the patient.

RENAL AND UPPER URINARY TRACT FISTULAE

Part of "29 - URINARY FISTULAE "

Etiology

Upper tract fistulae constitute a broad group of nonanatomic communications between the upper urinary collecting system and adjacent organs or body surfaces. These fistulae include nephrobronchial, nephrocutaneous, nephroenteric, pyeloenteric, and ureteroenteric. In the past, a tuberculous etiology was the most common cause of renal fistulae. However, the incidence of these infections has decreased, and iatrogenic (percutaneous surgery) and trauma are becoming more common causes (11).

Nephroenteric fistulae originating in the renal pelvis are the most common type and involve the left or right colon and duodenum. Unusual cases involving perforated viscus (i.e., duodenal ulcer) are occasionally reported (186). The nephrocolic fistulae are the most common. Fistulae involving the stomach (41) and jejunum (39) are rare. Although nephroenteric fistulae resulting from trauma, surgery, or malignancy of both intestinal and renal origin are increasingly reported, chronic and acute renal inflammatory disease remains the principal cause (3,59,110,117,149).

It has been noted radiographically that atrophy of the perinephric fat is a prerequisite to fistula formation (113). Bacterial pyelonephritis or pyonephrosis is found in 80% of cases and stones in 65% (11). Ureterointestinal fistulae, generally related to inflammatory bowel disease or diverticulitis, are caused by Hodgkin's disease, colon carcinoma, or xanthogranulomatous processes (145). Chronic inflammatory or infectious disease accompanied by distal stones and obstruction is the most common cause of spontaneous nephrocutaneous fistulae. Xanthogranulomatous disease and actinomycosis are the most common etiologies, and tuberculosis is of historical interest. Kidneys involved in such fistulae are generally associated with calculous disease, pyonephrosis, perirenal abscess, and nonfunction (172).

Clinical Presentation

Symptoms of nephroenteric fistula vary from marked gastrointestinal (GI) complaints (nausea, vomiting, and diarrhea) to recurrent urinary tract infections with flank pain and fever, depending on the location and underlying etiology. Spontaneous drainage of urine from the flank is the classic sign of nephrocutaneous fistula.

Diagnosis

Radiographic studies may not be helpful in making the diagnosis. Barium enema and IVP are reasonable; however, an IVP is likely to be uninformative because approximately 80% of fistulae are associated with a nonfunctioning kidney. A CT scan is helpful in the diagnosis of related renal and GI inflammation or malignancy. Retrograde ureterography is generally needed to illustrate this fistula.

Management

Iatrogenic or traumatic fistula associated with reasonable renal function may be treated conservatively with ureteral stenting and/or percutaneous nephrostomy. Success has been reported in 90% of a selected group of patients (98). The standard treatment for renal units that are diseased is nephrectomy with removal of the fistula tract and bowel resection. Attempts to conserve the kidney when stones and abscess are present lead to persistent morbidity and no improvement in renal function. The treatment of nephrocutaneous fistula is generally nephrectomy because of irreversible nephron loss (172).

FISTULA OF URINARY DIVERSION

Part of "29 - URINARY FISTULAE "

Etiology

The use of a portion of the intestine as a substitute for ureter or bladder has been widely reported and is uniformly regarded as safe and dependable. However, urinary leakage does occur and is one of the most distressing early

complications of diversion. Ureterointestinal leakage may occur as an early or late complication of this surgery. Most fistulae occur within the first 7 to 10 days postoperatively, with a reported incidence of 2% to 9% (95,107). These are considered to be secondary to technical error. Later-occurring fistulae may be related to subsequent necrosis at the anastomosis. Mortality rates from this complication range from 5% to 50% (67,95).

Clinical Features

The patients who have external drainage near the ureterointestinal anastomosis are identified earlier secondary to the increase in drainage output with a corresponding decrease in conduit efflux. If drains are not used, the diagnosis is harder. Classically, such patients will develop an elevated blood urea nitrogen level, signs of sepsis, bowel obstruction, and urine drainage via the incision (67). Diagnosis is generally made by the combination of loopogram, IVP, and significantly increased urea or creatinine levels in the drainage fluid.

Management

If a minor leakage occurs early, it can be safely observed for 2 to 3 days provided drainage has been established and there are no signs of sepsis. Spontaneous closure has been reported in 20% to 60% of patients (95). The use of nutritional support is routine if the leak is major or persists beyond the initial few days. Percutaneous nephrostomy and ureteral stenting across the anastomosis can be used to aid closure of the fistula (22). Because unrecognized stomal stenosis may contribute to fistulization, stomal catheterization with a red rubber catheter allowing conduit decompression should be tried. If conservative therapy fails to cure the fistula, one should consider revision of the ureterointestinal anastomosis with careful attention to the vascular integrity of the ureter using frozen sections to assess the presence of tumor and tissue necrosis. The ureters can be reanastomosed at a different site in the conduit using a Bricker technique. The use of ureteral stents and external drainage is encouraged.

Late-occurring fistulae are treated similarly, with external drainage, proximal urinary diversion with nephrostomy tubes, ample nutritional support, and exact localization of the leakage site. Definitive surgical options include a transverse colon conduit or the addition of a segment of ileum (in series) with the existing conduit. The use of a transverse colon conduit is encouraged in the face of pelvic abscess, extensive loss of ureteral length, previous pelvic irradiation, or previous ileal conduit repair (95). The judicious use of nephrectomy should be considered if the leak is unilateral or if the patient cannot tolerate a major intraabdominal procedure.

MANAGEMENT AND OPERATIVE CARE OF PLANNED INTERPOSITIONS

Part of "29 - URINARY FISTULAE "

Unexpected technical difficulties found during fistula repair should not surprise the urologist who treats these conditions. Because of unforeseen problems or findings, the surgeon must be prepared for alternative maneuvers to ensure operative success. As previously mentioned, the interposition of well-vascularized tissue between suture lines is one key to this success. Complicating factors such as poor tissue quality, prior irradiation, or prior surgery require the urologist to be prepared with a host of additional techniques of tissue interposition to maximize healing and fistula repair. Discussion of tissue interposition is divided anatomically into transabdominal and transvaginal procedures; however, these various procedures often have interchangeable potential applicability.

Transabdominal Repair

Omental Interposition and Substitutes

In any transabdominal fistula repair, the generous use of omentum is recommended. The omentum, with its rich blood supply, (a) offers an excellent vascular bed for proper healing; (b) adequately separates opposing suture lines; and (c) resorbs blood, lymph, and surgical debris. Commonly, the omentum is draped between tissue planes to prevent fistula recurrence. Securing its position with absorbable sutures is important to prevent inadvertent displacement. Occasionally, the omentum has insufficient length to reach the area of need; under these circumstances, mobilization based on the right gastroepiploic artery should be performed. The right artery is used because its consistent vascular supply comes from gastroepiploic arch on the greater curve of the stomach. The right branch is larger and lower, allowing it to reach the pelvis. For proper mobilization, the omentum is first dissected free from the transverse colon. The left gastroepiploic vessels are then divided at their splenic origin, and the short gastric branches are divided if needed. The omental pedicle is then rotated downward and secured between tissue planes. The use of absorbable sutures for mobilization and securing is preferred to prevent precipitation of urinary salts on permanent sutures. Not uncommonly, the omentum is not available because of previous gynecologic surgery; thus the use of pericolonic or mesenteric fat may be necessary. If a radiation field has not altered the peritoneum significantly, creation of a flap of peritoneal membrane from the lateral parietal aspect of the pelvis may be considered (36). Appendices epiploicae of the sigmoid colon have been reported as an acceptable interposition flap (48). One needs to be aware of the potential problems associated with the use of this tissue because insufficient length may cause tension, induce colonic

distention, or promote involvement of future colonic disease.

Rectus Abdominis Flaps

In cases of more extensive fistulae or recurrent fistulae or when omentum and adjacent tissues are not available, use of the more elaborate rectus muscle flap is possible. These can be used for both the vesicovaginal or urethrovaginal fistula provided adequate length is harvested (17,154). This long muscle receives its blood supply from both superior and inferior epigastric arteries. It is mobilized through a careful midline incision by dissection from its anterior and posterior fascia (Fig. 29.6A,Fig. 29.6B and Fig. 29.6C). The inferiorly based muscle is transected at its transverse tendinous intersection and pulled through a peritoneal window. Once the fistula tract is

repaired as previously discussed, the muscle flap is interposed and secured with absorbable sutures (112,156). If being used for a urethrovaginal repair, after muscle flap mobilization, the muscle is passed through the endopelvic fascia and fixed to the opposite tendinous arch or Cooper ligament to support the urethra and bladder neck (Fig. 29.6C).

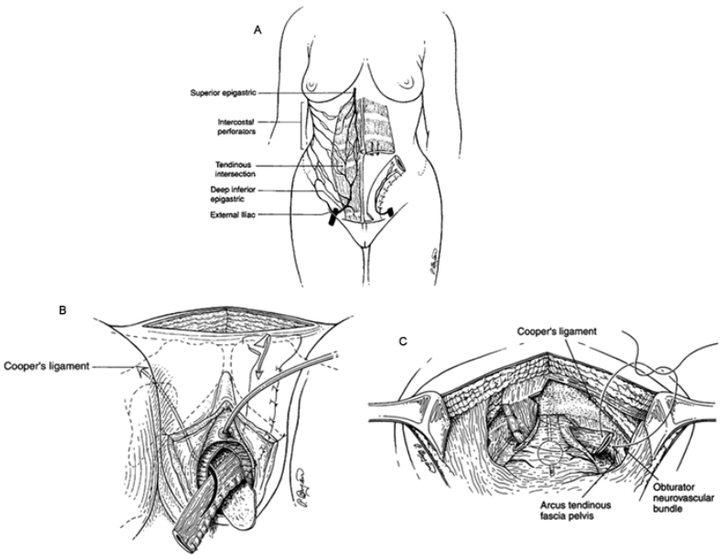

FIGURE 29.6. Rectus abdominis musculoperitoneal flap for closure of bladder or urethral fistula. **A:** Harvest of the rectus abdominis muscle above the first tendinous intersection followed by preservation of the inferior vascular pedicle. The muscle is then tubularized around the inferior epigastric vessels. **B:** The rolled muscle is passed through the endopelvic fascia lateral to the bladder neck to the vaginal exposure site near the previously excised fistula tract and repaired urethra. The flap is interposed and covers the repair site. **C:** The muscle flap is brought back through the contralateral endopelvic fascia site once covering the fistula. This is secured to the contralateral Cooper's ligament or arcus tendinous fascia.

Transvaginal Repair

Gracilis Muscle Flaps

Although it requires additional planning, the gracilis muscle flap interposition has many advantages, including limited exposure to previous irradiation, ease of flap rotation for fistulae below the genitourinary diaphragm, and avoidance of intraabdominal exposure when perineal or vaginal surgery is sufficient. The use of this muscle and its overlying skin (if necessary) is based on (a) its proximal vascular supply from the profunda femoris arteries, (b) the ease of mobilization after transection of its attachment to the proximal skin, (c) its lack of adherence to other muscles of the thigh adductor group, and (d) its minor role in anteromedial adduction of the thigh (Fig. 29.3C). In transabdominal surgery, one can use the gracilis by tunneling the muscle flap via a midthigh plane through a genitourinary diaphragm incision while taking care to avoid pelvic bleeding, sphincter injury, or damage to the ureters (44). This flap can be used successfully with transabdominal or perineal exposures (rectal fistulae) but has bulkiness problems when used with vaginal surgery unless it is swung as a myocutaneous unit. If additional length is needed, the distant two branches may be sacrificed.

Martius Labial Fat Pad Flap

The Martius labial fat pad is an excellent source of interposing tissue for repairing fistulae from the vaginal approach. This tissue has a prominent fibrous component, making it a strong graft that is not nearly as fragile as adipose tissue from other areas. Anatomic studies revealing its ample blood supply from the ventral aspect (external pudendal artery) and dorsal aspect (internal pudendal artery) suggest that it is possible to detach the flap at its superior or inferior end without vascular compromise (38). In most cases, this fat pad does not include the underlying bulbocavernosus muscle. Incorrectly considered synonymous, the labial fat pad interposition and bulbocavernosus flap interposition are two different procedures (19). The use of the Martius flap is recommended routinely but may be applicable only if there is sufficient vaginal epithelium (Fig. 29.3A and Fig. 29.3B). Complications include excessive dissection of the anterior or posterior pedicle or small tunnel aperture causing constriction of the vascular supply. If the vaginal epithelium is insufficient for primary closure of the vaginal defect, the labial flap also may be used to supply skin from the labial majorum. If the flap is not wide enough, the buttock flap based on the cutaneous branches of the inferior rectal artery should be considered (66,176). Use of the buttock flap results in less asymmetry of the anterior vaginal introitus than the use of the Martius flap but runs a risk of impaired blood supply or injury to the anal sphincter (Fig. 29.3C).

A peritoneal flap may be used for smaller fistulae that lie high in the vault and out of reach of the Martius fat pad. Its interposition is created by posterior dissection of the anterior vaginal wall between the vaginal wall and the bladder (147). This exposes the edge of the peritoneum in the pouch of Douglas without the need to enter the abdominal cavity. The edge of the peritoneum mobilized from the posterior wall of the bladder is moved inferiorly and secured over the repaired fistula. One can prevent possible bladder or ureteral injury by avoiding prevesical fascia and remaining just beneath the vaginal wall. Information on the use of intestinal seromuscular flaps is limited (23). This technique has been used in vesicovaginal fistula as well as rectovaginal fistula when omentum is not available. The judicious use of this technique is advised because animal models have developed flap contractions that may compromise any fistula repair (23).

NUTRITION

Part of "29 - URINARY FISTULAE "

The nutritional support of the surgical patient is a commonly overlooked component in urologic care. In the patient with urinary fistula, this aspect is particularly important. The metabolic sequela of a surgical procedure is characterized by hypermetabolism secondary to the response of systemic catecholamines. This results in increased tissue breakdown, decreased body mass, and the loss of essential intracellular components. There is recognition that severe malnutrition can exist in 50% of hospitalized patients, which effects morbidity and mortality and increases the length of hospital stay (12,119,179). Malnutrition also (a) increases the risk for nonhealing of wounds, (b) increases the incidence of respiratory infection, (c) increases the incidence of clean wound infection, (d) decreases immunocompetence, and (e) prolongs the postoperative ileus.

All patients undergoing fistula repair must have their nutritional status assessed because it effects the outcome of the procedure. Important assessments of nutritional status include recent lean body weight loss, reactivity to skin antigen testing, creatinine excretion index, lymphocyte count, serum albumin level, serum transferrin level, and triceps skinfold measurements (106). Once this assessment has been made, the caloric requirements can be calculated and replenished via enteral or parenteral feedings.

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30

CANCER OF THE BLADDER

Donald G. Skinner

John P. Stein

Ronald Ross

Peter Nichols

Bernard Bochner

Derek Raghavan

D.G. Skinner: Department of Urology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA 90033.

J.P. Stein: Department of Urology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA 90033.

R. Ross: Department of Preventive Medicine, University of Southern California, Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA 90033.

P. Nichols: Department of Pathology, University of Southern California School of Medicine, Norris Cancer Hospital, Los Angeles, CA 90033.

B. Bochner: Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.

D. Raghavan: Department of Medical Oncology, University of Southern California, Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA 90033.

Contents

It is estimated that approximately 55,000 new cases of bladder cancer will be diagnosed in 2000 and that approximately 12,500 patients will die from this disease (192). The appropriate management of patients with bladder cancer depends on an appropriate understanding of contributing factors to the etiology of bladder cancer, its natural history, and sound clinical judgment regarding selection of the best therapeutic modality for management of the individual patient. Currently, assessment of the grade and stage of the initial bladder tumor; evidence of multicentricity; and important histologic features, such as the presence or absence of carcinoma *in situ* (CIS), lymphovascular invasion, and an assessment of molecular markers, are important factors that help determine management.

Bladder cancer produces clinical symptoms, the first of which usually remains fixed as a definitive episode in the life of a patient. Urologic consultation is usually sought promptly thereafter. Asymptomatic incidental bladder cancer is rarely encountered either in life or autopsy finding. Only one incidental bladder cancer was found in 2,805 consecutive male autopsied patients, and Kretschmer (180) reported that in none of 902 consecutive patients diagnosed with bladder cancer was a tumor found before symptoms occurred.

It is difficult to determine the relative incidence of various grades and stages of initial bladder tumor in any consecutive series of patients managed by any of the various therapeutic options because of referral patterns. However, it can be inferred that approximately 70% of all new patients with bladder cancer will present with disease that is not deeply invasive. Jewett and Strong's classic article in 1946 (156) described a relationship between the depth of infiltration of the bladder wall and the potential morbidity of bladder cancer. Based on their autopsy study of 107 cases, 100% of patients with superficial tumors confined to the mucosa should be curable; 80% of those whose tumor was confined to the muscularis had localized disease, whereas only 26% of patients whose tumor had penetrated into the intravesical fat were thought to be potentially curable when first evaluated. However, 5-year survival reports for patients with all stages of bladder cancer indicate that the potential curability indicated by Jewett and Strong is seldom realized. In fact, in 1974, Caldwell (43) reported that 50% of patients with invasive bladder cancer die within 18 months of their initial presentation, regardless of therapy. High-grade, invasive bladder cancer is clearly a lethal disease. Prout and Marshall (271) reported that only 15% of 101 untreated patients, who presented with high-grade bladder cancer, survived 2 years regardless of the form of therapy. This clearly underscores the need for the physician to have a good understanding of the pathophysiology of the disease and appropriate knowledge of the treatment schemes.

This chapter summarizes current available knowledge in all areas of bladder cancer, ranging from epidemiology, pathology, staging, management of superficial and invasive disease, and chemotherapy in the management of advanced urothelial cancer. It is hoped that this information will be useful to the clinician in the future management of patients who develop bladder cancer.

EPIDEMIOLOGY AND ETIOLOGY OF BLADDER CANCER

Part of "30 - CANCER OF THE BLADDER "

Bladder cancer does not have the same high profile in terms of either public concern or federal research support as other cancers. Nonetheless, it is an extremely important disease, ranking fourth in incidence among all cancers in the United States in men and ninth in the United States in women. Although no subgroup of the general population is immune to bladder cancer development, the highest-risk demographic subgroup is white, well-to-do males (287). Men have a risk of bladder cancer that is approximately four times higher than that of women. Non-Hispanic white men have a bladder cancer rate that is twice that of any other numerically important racial-ethnic group in the United States. Women show a relatively comparable pattern in terms of race-ethnicity, as do men, albeit at much lower absolute rates. Non-Latino white women have the highest rate among the most common racial-ethnic groups in the United States. There is a clear relationship between bladder cancer incidence and socioeconomic indicators. For example, in Los Angeles, men in the highest quintile of socioeconomic status (based on a combined measure of income and education level) have 1.3 to 1.4 times the rate of bladder cancer compared with men in the lowest quintile (287).

Bladder cancer incidence and mortality rates have shown sustained declines extending over several decades. Declines have been particularly prominent among non-Latino whites. Rates in the middle to late 1990s are roughly 60% of what they were in the late 1970s (287). Despite their much lower absolute rates, both men and women have shown similar patterns of decline. However, other racial-ethnic

groups of either gender generally have not shown declines of similar magnitude (316).

Although bladder cancer typically is believed to be a disease that is well understood epidemiologically, it is troubling that the main demographic risk factors for bladder cancer (high risk in non-Latino white males of high socioeconomic status) are not readily explicable on the basis of the epidemiology of the most prevalent and best-established risk factors. Dozens of epidemiologic studies have established cigarette smoking to be the most important risk factor for bladder cancer around the world (288). Cigarette smoking alone is typically described as explaining perhaps as much as 50% of all male bladder cancer in the United States (i.e., 50% of bladder cancer in men is "caused" by this single exposure). Cigarette smokers, as a group, have two to three times the risk of bladder cancer of nonsmokers. As expected, this risk is substantially higher among long-term heavy smokers compared with short-term, less frequent smokers (48). Risk factors for the former category of smokers may be as much as fivefold to sixfold higher than among otherwise comparable lifelong nonsmokers. Interestingly, smoke-induced bladder cancer is almost exclusively due to cigarette smoking. Pipe smoking and cigar smoking appear to be at most only weakly related to bladder cancer incidence, and smokeless tobacco use appears unrelated to bladder cancer altogether (288). Although bladder cancer risk in ex-smokers probably never reverts back to the rate of lifetime nonsmokers, the risk declines relative to that of active smokers in direct proportion to the time since cessation. Furthermore, inhalation patterns and use of filters have not been shown to substantially modify any smoking-related increase in bladder cancer incidence. Women sustain at least as great an increase in incidence as men for comparable intensity of smoking (48).

The first well-established risk factor for bladder cancer was occupational exposure to a class of chemicals known collectively as the *arylamines.* Epidemiologic "proof" that one particular arylamine, ß-naphthylamine (2-naphthylamine), used in the manufacture of synthetic dyes, caused bladder cancer was established by the early 1950s (46). Much circumstantial data accumulated as early as the late 1800s had already strongly implicated ß-naphthalamine as a bladder carcinogen. Although potent bladder carcinogens, occupational exposure to arylamines is primarily of historical importance (these chemicals have largely been eliminated from industry through government regulation and/or industry initiatives). However, arylamines themselves are not solely of historical importance. Exposure to these chemicals may occur through other environmental sources. In fact, they provide the most likely explanation for the association between cigarette smoking and bladder cancer. Cigarette smoke contains small amounts of a whole series of arylamines, including 2-naphthylamine and aniline (260), another proven bladder carcinogen in occupational settings. Currently, a major focus of bladder cancer epidemiologic research is to better understand the mechanism by which cigarette smoking causes bladder cancer. In particular, there is current interest in examining differences in how individuals metabolize arylamines, which might help further define bladder cancer risk as it relates to cigarette smoking.

It has been hypothesized that genetic differences across racial-ethnic groups might also help explain epidemiologic difference in bladder cancer. It is clear that among various populations across the world, with highly concordant smoking patterns, vastly different underlying rates of bladder cancer exist. This discrepancy even exists among populations living in the same geographic location. In Los Angeles, although African American, Chinese, Japanese, and non-Latino white men have had relatively comparable smoking patterns for many years, bladder cancer rates among these same populations vary by approximately threefold (highest in whites and lowest in the two Asian American populations) (289). Although a number of the enzymes involved in the activation or detoxification of the arylamines present in cigarette smoke have been identified, the precise detailed pathways and the range of genes involved have not been totally elucidated. It is possible that a better understanding of these enzymatic pathways may help explain some of the discrepancies between the epidemiology of cigarette smoking and that of bladder cancer.

Among those enzymatic pathways that have been investigated epidemiologically, the best studied are the *N*-acetyltransferases (NATs), particularly the NAT-2 isozyme, and certain members of the glutathione S-transferase (GST) family of enzymes, especially GSTM1.

NAT-2 is a totally genetically regulated enzyme system, encoded by a single polymorphic gene (26). Aberrant alleles are associated with reduced enzyme activity. Individuals possessing two such "mutant" alleles are phenotypically characterized as "slow" acetylators, meaning they are able to detoxify carcinogenic arylamines through this pathway at a relatively slow rate. The results of a combined analysis of the 12 studies that had evaluated the relationship between NAT-2 slow acetylation and bladder cancer risk have been reported (125). As hypothesized, slow acetylators have an approximately 50% higher risk of bladder cancer than so-called fast acetylators. Furthermore, studies have suggested that smokers, or those occupationally exposed to arylamines, are at particularly high risk of bladder cancer if they have slow acetylator phenotypes (125).

Non-Latino white populations, at particularly high risk for bladder cancer, have the highest prevalence of slow acetylator phenotypes, with African Americans showing an intermediate rate (393). Low-risk Asian populations have a very low prevalence of slow acetylators, approximately one-fourth that of whites.

The GSTs detoxify various toxic chemicals by promoting their conjugation to glutathione, thereby facilitating their excretion. Nearly half of the U.S. white population lacks either copy of the gene-encoding one of these enzymes—GSTM1 (29). Several studies have found that GSTM1-null individuals (i.e., those lacking both gene copies) have between

a 40% and threefold higher risk of bladder cancer than individuals who possess at least one copy of the gene (26,36). Most studies of GSTM1 also note a higher risk in smokers than in nonsmokers.

OTHER RISK FACTORS

Part of "30 - CANCER OF THE BLADDER "

Bladder cancer is a relatively well-studied cancer epidemiologically. A number of potential risk factors have been evaluated and have been eventually dismissed as major contributors to bladder cancer occurrence. Artificial sweeteners, for example, received much attention in epidemiologic studies in the 1970s and 1980s because of their role in experimental bladder cancer development. Currently, there is no clear or consistent evidence that these substances modify bladder cancer risk in humans (288). Coffee consumption has been even more extensively studied as a possible bladder cancer risk factor. With the possible exception of very extreme categories of consumption (approximately 5 to 6 cups per day or more, which may be associated with a modest increase in risk), again no clear pattern of risk has emerged (288).

Analgesics, particularly those with phenacetin as an active ingredient, although other formulations are probable as well, are a recognized cause of upper urinary tract transitional cell cancers (149). Because bladder cancer, like cancer of the renal pelvis, also presents primarily with a transitional cell histology, there is reason for concern that heavy consumption of analgesics might also increase risk of bladder cancer. However, one recent study found that the nonsteroid antiinflammatory drugs (NSAIDs) might actually reduce bladder cancer risk (47), possibly through its ability to inhibit the cyclooxygenase-2 (COX-2) enzyme system (250). Substantial supportive evidence exists for bladder cancer prevention by NSAIDs experimentally (250) and for other cancers (especially colon cancer) in humans (280).

Persistent urinary tract infections also increase the risk of bladder cancer, probably through a mechanism involving chronic inflammation and repair. These bladder cancers are primarily of squamous cell histology (165). The best documented relationship between chronic infection and bladder cancer development occurs in Egypt, where chronic infection with *Schistosoma haematobium* has made squamous cell bladder cancer the principal histologic cell type (353).

Recently, there was epidemiologic confirmation of a longstanding bladder cancer etiologic hypothesis, that is, that frequency of micturition will reduce bladder cancer risk by reducing exposure of bladder mucosa to carcinogenic substances in the urine (256). This interesting study tested this hypothesis indirectly by showing rather convincingly that a surrogate measure of micturition frequency—fluid consumption—was inversely related to bladder cancer risk. This study demonstrated that this relationship was “dose” related and that the inverse association was consistently observed across all major categories of beverages (225). Confirmatory studies performed with equal care are needed to more firmly establish this relationship.

Substantial progress has been made in better understanding the molecular genetic pathways of bladder cancer, leading from normal bladder mucosa to a fully malignant phenotype. It appears that two rather distinct pathways are involved in the development of transitional cell bladder carcinoma. One pathway traverses through CIS to a highly invasive form of the disease, whereas an alternative pathway results in the common low-grade papillary transitional cell malignancy, which uncommonly progresses to a more lethal form (162). Although low-grade papillary transitional cell lesions and the more invasive higher-grade bladder cancers appear to have similar demographic profiles, commonality or differences in environmental risk factors have not been evaluated sufficiently.

Pathobiology

In the United States, it is estimated that approximately 55,000 new bladder carcinomas will be diagnosed in 2000, with transitional cell carcinomas accounting for 90% of all bladder tumors, squamous carcinomas accounting for 7%, and adenocarcinomas accounting for 2% (192). Depending on the population of patients, these proportions can vary. For instance, in regions where *S. haematobium* is a common disease, squamous carcinoma is the most common bladder tumor (76,115). A diverse group of unusual tumors, such as sarcomas and lymphomas, represent less than 1% of newly diagnosed bladder tumors (87,184).

Tumors can metastasize to the bladder but rarely do without evidence of disease elsewhere. The most common mode of spread to the bladder is by direct extension from either the colon, prostate, or cervix. Other tumors that metastasize to the bladder are melanomas and gastric, breast, kidney, lung, renal, and pancreatic carcinomas (317). On the other hand, primary bladder carcinomas spread most commonly to regional lymph nodes, bone, lung, and liver (18,304).

Certain anatomic and histologic findings are important to understand the pathologic aspects of bladder cancer. In the adult, the bladder is located within the pelvis, with the posterior surface or the base lying in a posterior and inferior position. The rectum lies just beyond the soft tissues of the bladder base. In women, these soft tissues contain the cervix and proximal portions of the vagina. In men, these soft tissues between the rectum and posterior bladder are occupied by the seminal vesicles. These relationships are important for two reasons. First, these are the organs most commonly involved by contiguous spread of primary bladder cancers. Second, they explain the pattern of spread of the most common metastatic tumors to the bladder.

Histologically, the bladder mucosa has three layers, including the superficial or umbrella cell layer that is in contact with the urine within the intervesical space. The intermediate cell layer is between the umbrella cells and a

basal layer, which are the cells that are in contact with the basement membrane, and are the apparent germinal cells. The superficial umbrella cells have a unique surface membrane that was named the *asymmetric urothelial membrane* by Koss (177) and now has been shown to be composed of transmembrane proteins called *uroplakins* (231). These proteins appear to be specific to the bladder mucosa and are concentrated in the umbrella cells.

Underlying the basement membrane and separating the transitional mucosa from the muscularis propria is the lamina propria. It is important to recognize that within the lamina propria is a thin band of smooth muscle fibers that is variable in its extent (74,283). This band of muscle is a muscularis mucosa that in a few is complete, but in general is incompletely present. These delicate bands of smooth muscle are easily distinguished from the underlying muscularis propria in sections from cystectomy specimens, by the difference in the extent and size of the muscle fibers, as well as in the presence of prominent thick-walled vessels that course along their path. These same venous channels are not associated with the muscularis propria. On occasion, this thin, delicate muscular layer can be difficult to recognize in biopsies that are involved by invasive carcinoma or are artifactually distorted by the biopsy itself. The remaining tissue in the lamina propria generally is loose connective tissue associated with small, delicate vessels and occasionally inflammatory cells. It also is important to recognize that fat can be found in the lamina propria and muscularis propria, sometimes in significant amounts (30).

The muscularis propria consists of a complex of interlacing smooth muscle bands that, in the area of the bladder neck, can be separated into three layers. The central portion of the muscle wall appears to be circular, and the inner and outer walls appear longitudinal. In other areas, these muscular coats are difficult to separate. Again, fat can be fairly prominent and interlaced throughout this muscular portion of the bladder. In addition, these muscle fibers are separated and supported by connective tissue–containing blood vessels, lymphatics, and delicate nerves. On occasion, paraganglia may also be seen.

The muscularis propria varies in thickness from region to region of the bladder. This recognition becomes important because the T_2 tumors are defined by invasion of this muscular wall. No distinct anatomic structures separate this muscle wall to allow this determination. Therefore, proper orientation of histologic sections is necessary to measure the exact extent of invasion. In addition, bladder diverticula possess a particularly thin and attenuated muscular wall, requiring special consideration in evaluating the depth of invasion.

UROTHELIAL CARCINOMA

Part of "30 - CANCER OF THE BLADDER "

The most common histologic type of carcinoma arising in the bladder is transitional or urothelial carcinoma. This cell type accounts for at least 90% of all bladder cancers in the United States. Transitional cell carcinomas have two basic morphologic expressions: a papillary lesion accounting for 70% to 80% of these tumors and a flat lesion accounting for the other 20% to 30%. Classifications of both papillary and flat carcinomas have broad areas of agreement and understanding, but they also have differences in their definitions, particularly with regard to grade. These differences, although apparently subtle at first look, often can result in difficulty comparing groups of patients from one institution with those of another.

The World Health Organization (WHO)/International Society of Urologic Pathology Consensus Classification published in 1998 (the most recent classification) makes great strides in removing these differences (80). Already, several papers specifically applying this classification's criteria to large patient populations are demonstrating its utility (51,52 and 53).

PAPILLARY NEOPLASMS

Part of "30 - CANCER OF THE BLADDER "

The most common transitional neoplasm is the papillary neoplasm. In the WHO classification (80), these tumors are divided into five categories, including papilloma; inverted papilloma; papillary neoplasm of low malignant potential; papillary carcinoma, low grade; and papillary carcinoma, high grade. Papillary neoplasms are classified on the basis of their architectural and cytologic features. The numbers of categories in this group of papillary tumors is about the same as prior classifications; however, the names are now more reflective of the morphologic appearance and clinical behavior of these lesions.

The papilloma; papillary neoplasm of low malignant potential; and papillary carcinoma, low grade all have good clinical outcomes, but they tend to recur at multiple sites over long periods. It is difficult to separate this group of lesions in a way that all agree upon. On one hand, many argue that the low end of this spectrum should be called *papillomas,* with as many as 20% being classified as such (163). Others point out that when the group is classified in this manner, there is a subpopulation that develops recurrences and may progress to invasive and even fatal carcinomas.

The definition of a papilloma in the WHO classification is that of a discrete papillary growth, surfaced by urothelium of normal thickness, whose cytology is not atypical. The number of cells surfacing the fibrovascular cores is generally of normal number, but exact numbers of cell layers is unnecessary to count. This lesion is believed to be usually small and isolated and occurs most frequently in young patients (Fig. 30.1).

FIGURE 30.1. Low-power view of a urothelial papilloma.

Inverted papilloma is a nodule most often found in the region of the trigone, which, on rare occasions, can have a few papillary structures on the surface but is usually smooth. The tumors grow as nests and trabeculae of epithelium that

cytologically comprise normal transitional epithelial cells (Fig. 30.2). The trabeculae tend to resemble reversed papillary processes, where the small vessels and stroma separate basal layers. The epithelial cells differentiate centrally to create merged, mature surface cords that sometimes contain lumens or even cysts. Both glandular and focal squamous differentiation have been identified in these trabecular layers of transitional epithelium. There can be pleomorphism; however, it should be minimal. Mitoses, although present, are usually uncommon.

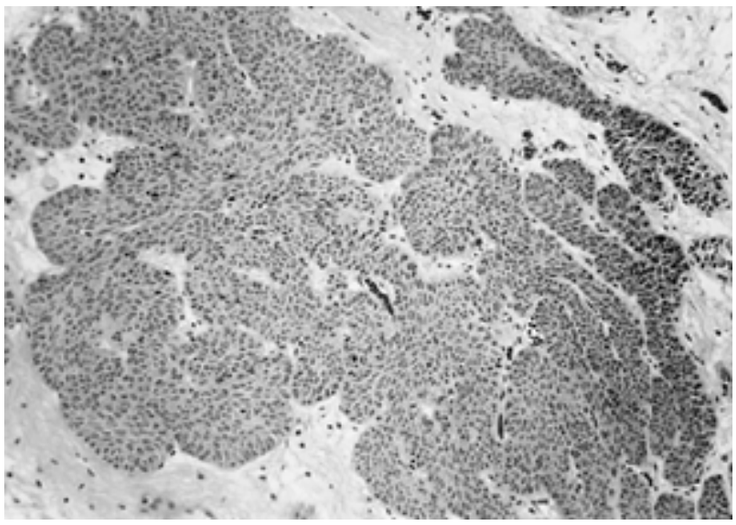

FIGURE 30.2. Inverted urothelial papilloma characterized by anastomosing trabeculae of normal urothelial cells in the lamina propria.

The third category, or papillary neoplasm of low malignant potential, is a papillary tumor in which the papillae are orderly with only slight architectural abnormalities (Fig. 30.3). The surface transitional epithelium is thicker, and a mild degree of nuclear atypia can exist, including nuclear enlargement. Mitoses may be present but are uncommon and usually are found in the basal layers. The main distinction from the papilloma, then, is the increase in cell numbers on the surface and the presence of cytologic atypia. These lesions are found to recur more often and can, on occasion, recur as higher-grade lesions. Some argue that more of these lesions should be in the papilloma group (163), whereas others believe that it is important to delineate this group and ensure that urologists do not minimize its significance. Recurrences of these lesions have occurred many years after the initial removal.

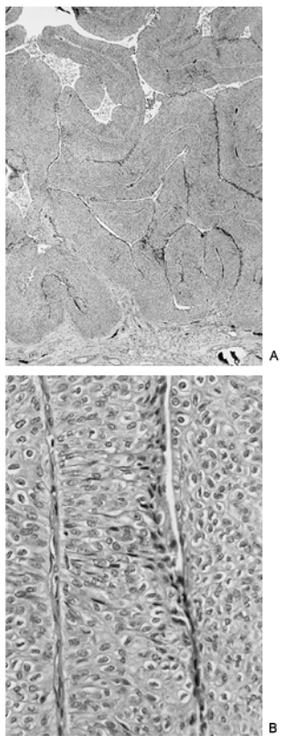

FIGURE 30.3. Papillary urothelial neoplasm of low malignant potential. **A:** Low power. **B:** High power.

Papillary carcinoma, low grade, is a papillary tumor in which there is greater architecture and cytologic variation than the papillary tumor of low malignant potential (Fig. 30.4).

The architectural abnormalities include fused papillary cords and fusion of adjacent papillae. In evaluating fusion of cords, one must examine histologic sections that are cut perpendicularly to the base, as opposed to tangential sectioning. Cytologically, these lesions have variation of polarity and nuclear size, shape, and chromatin texture. Again, mitotic figures are uncommon but can be found throughout all levels of the surface epithelial layer. However, they are usually in the lower half of the epithelial surface. Local areas of neoplastic cells can appear overtly malignant. This is as opposed to papillary tumors of low malignant potential in which the cells should display only nuclear enlargement. These tumors again frequently recur but have a lower risk of progression to an invasive or high-grade carcinoma. The risk of progression is believed to be less than 5%.

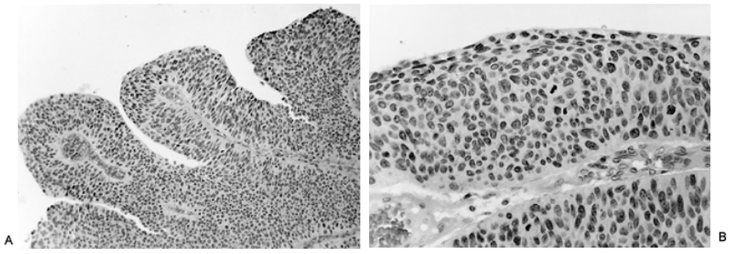

FIGURE 30.4. Papillary carcinoma, low grade. **A:** Low power. **B:** High power.

Last, the papillary carcinoma, high grade, are tumors in which there are distinct architectural and cytologic abnormalities (Fig. 30.5). These tumors have blunted and usually fused papillae, composed of cytologically abnormal cells. The cells are enlarged, and the nuclei are irregular with clumped chromatin and often prominent nucleoli. Mitoses generally are easily identified, occur throughout the urothelium, and are atypical. Clearly, some tumors have both low-grade and high-grade areas, and a clear cutoff has not been defined regarding when to make this distinction. These tumors often are invasive at the time of diagnosis and, if they are not invasive, have a high risk of progression to invasive disease. This group of papillary tumors often has CIS in areas away from its site of involvement.

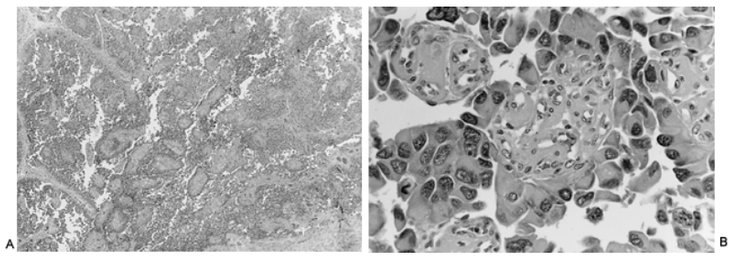

FIGURE 30.5. Papillary carcinoma, high grade. **A:** Low power. **B:** High power.

FLAT LESIONS WITH ATYPIA

Part of "30 - CANCER OF THE BLADDER "

CIS, or high-grade intraepithelial neoplasia, is a rare lesion when occurring alone, but it is relatively common when seen in association with papillary tumors, particularly the papillary carcinoma, high grade (83,84,117,178,222,241). In its most easily recognized or classic form, this tumor is

composed of overtly neoplastic cells throughout the thickness of the mucosa. These cells are generally large, usually have high nuclear-to-cytoplasmic ratios, and have irregular and hyperchromatic nuclei often with nucleoli. Mitotic activity is seen throughout the lesion. Cells comprising this lesion are loosely cohesive, which often leads to a histologic appearance of loosely attached or discohesive cells (Fig. 30.6). There is commonly an increase of small delicate vessels in the lamina propria directly beneath the basement membrane of areas with CIS. Less commonly, carcinomas may demonstrate a pagetoid pattern where the overtly neoplastic cells are scattered throughout the urothelium (361). Occasionally, in areas adjacent to overt CIS, the neoplastic cells can undermine the normal urothelium, creating a layer of CIS beneath a layer of more normal mucosa. On occasion, because of the discohesive properties of the CIS cells, the lesions can be disrupted when viewed microscopically. In these instances, only a few neoplastic cells are left attached to the basement membrane, creating a so-called “clinging” pattern (99).

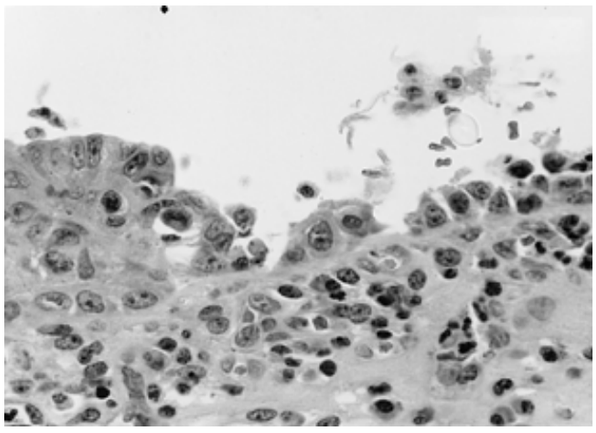

FIGURE 30.6. Carcinoma *in situ* showing discohesion adjacent to full thickness carcinoma *in situ.*

A related group of important lesions are those that are believed to be dysplastic. These lesions have cytologic features that fall short of transitional cell CIS but have some of its features (Fig. 30.7). These lesions can be recognized because they lack the orderly structure of the normal transitional mucosa and they lack the cytologic atypia of CIS. The lack of precise diagnostic criteria makes it difficult to classify this group (309). Biologically, however, this remains an important group because it probably represents a precursor to CIS. An important finding with CIS that may distinguish it from the dysplasias is the finding of small vessels immediately beneath the basement membrane that are associated with CIS.

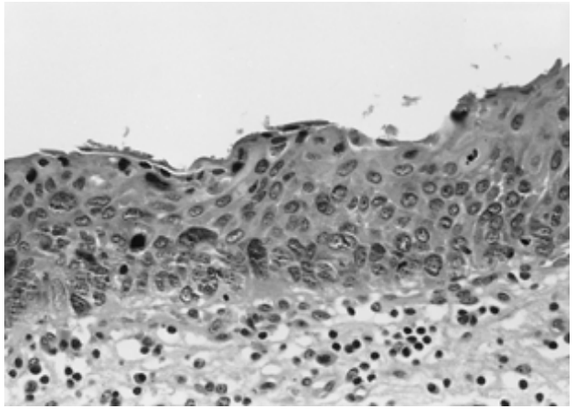

FIGURE 30.7. Dysplastic urothelium showing maturation but also significant cytologic atypia.

Papillary carcinomas, especially high-grade lesions, are often associated with CIS. This observation was first made by Melicow, who noted the presence of CIS between grossly apparent papillary tumors in cystectomy specimens (83,222,223). Eisenberg subsequently demonstrated the increased likelihood of recurrent bladder tumors in patients having papillary carcinoma with CIS. Others have demonstrated the clinical importance of these observations, pointing out that partial cystectomy or segmental resection were contraindicated in surgical management of those patients (321).

INVASIVE UROTHELIAL NEOPLASMS

Part of "30 - CANCER OF THE BLADDER "

Invasive carcinomas usually arise from flat lesions, but papillary neoplasms can become invasive as well (178). Probably the single most important determinant in predicting the behavior of a papillary tumor or flat carcinoma recurrence in this population is the demonstration of tumor invasion. Unfortunately, the diagnosis of early invasion can be difficult to determine (1,205). The first site of invasion is the lamina propria (Fig. 30.8 and Fig. 30.9) (12). The patterns of invasion of papillary tumors and the flat carcinomas often differ. Low-grade papillary tumors tend to have a pushing border without a clear-cut invasive appearance, until a significant degree of invasion is present (Fig. 30.10 and Fig. 30.11) (9,390). These nests should not be confused with von Brunn's nests. Higher-grade papillary tumors and flat carcinomas often invade as single cells or small irregular nests that may elicit a desmoplastic or an inflammatory response. Once invasion is established in the lamina propria, its extent should be evaluated. Established lamina propria invasion usually results in a desmoplastic inflammatory reaction to the tumor. Therefore it is important to distinguish the thin delicate fibers and prominent vascular channels of the muscularis mucosa from the muscularis propria. This distinction is easier when adequately biopsied, in that the muscle fibers of muscularis propria are large and compact. Several groups have demonstrated that substaging these lamina propria invasive tumors has allowed separation into groups with significantly different prognoses (Fig. 30.12) (14,386).

Furthermore, it is important to recognize vascular space invasion within the lamina propria because it may predict a higher likelihood of involvement of paravesical lymph nodes (209).

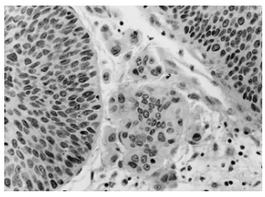

FIGURE 30.8. Microinvasion characterized by small nests of low-grade papillary transitional cell carcinoma just below the basement membrane.

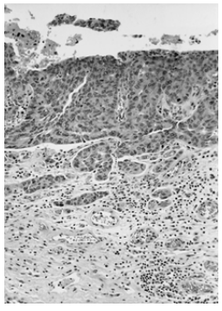

FIGURE 30.9. Early lamina propria invasion of a flat transitional cell carcinoma.

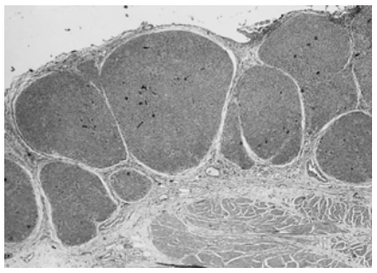

FIGURE 30.10. Endophytic growth pattern of a low-grade transitional cell carcinoma, filling the lamina propria.

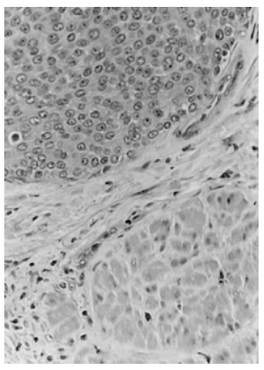

FIGURE 30.11. High-power view of the pushing margin of a low-grade carcinoma.

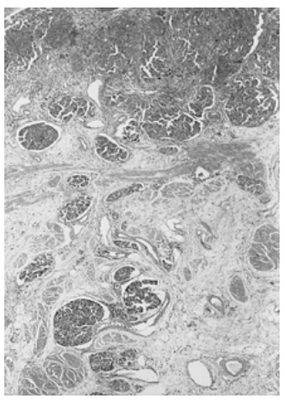

FIGURE 30.12. Significant vascular space invasion associated with a high-grade transitional cell carcinoma.

The papillary and nonpapillary carcinomas of the bladder can also present with a mixed pattern. The mixed pattern is defined as the presence of typical transitional or urothelial carcinomas associated with areas of glandular or squamous differentiation. Some have referred to these areas as *metaplastic;* however, metaplasia by definition refers to replacement of one type of epithelium with another and usually is not applied to malignant tumors. The incidence of squamous or glandular differentiation in transitional cell carcinomas is approximately 10%. There appear to be no prognostic implications to this morphologic finding.

Recently, several groups have described a deeply invasive variant of transitional-cell carcinoma that displays a microcystic pattern (Fig. 30.13 and Fig. 30.14)(261,392). This pattern is usually found in areas of conventional transitional carcinoma but may be found as the dominant pattern as well. These tumors are characterized by small cysts up to 1.2 mm in size. In the lamina propria, they may be morphologically similar to areas of cystitis cystica and cystitis glandularis. These tumors are clinically aggressive. A second bland-appearing

transitional carcinoma has been called the *nested variant* (239,258,352,390). These tumors are also infiltrating but comprised bland nests and tubular formations that resembled von Brunn's nests or cystitis cystica. The bland histologic appearance may be confusing and delayed their correct diagnosis (239,352,390). Morphologically, these tumors can also resemble an inverted papilloma. Importantly, these tumors have a more aggressive course than their bland histology would suggest.

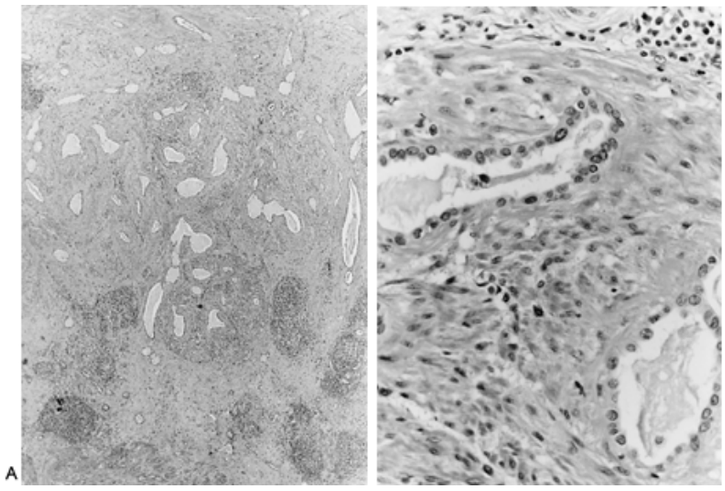

FIGURE 30.13. A: Low-power view of a microcystic variant of transitional cell carcinoma invading deeply into the bladder *(left).* **B:** High-power view of microcystic carcinoma revealing the bland cytologic features of the malignant cells *(right).*

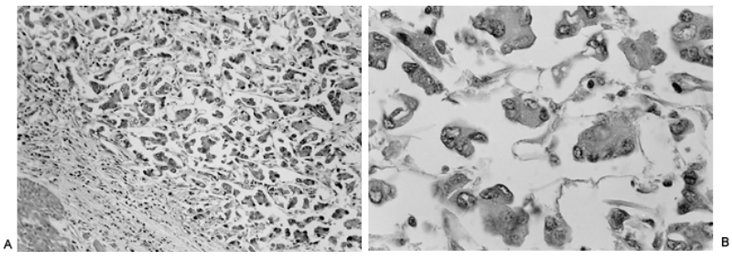

FIGURE 30.14. A: Invasive micropapillary carcinoma composed of small nests of cells with retraction artifact. **B:** High-power view of micropapillary carcinoma, a clinically aggressive variant.

Another clinically aggressive morphologic variant of transitional cell carcinoma is the micropapillary variant (Fig. 30.14). This tumor is described as resembling a papillary serous carcinoma of the ovary. It is composed of slender, delicate, filiform processes or, when invasive, is composed of tight papillary clusters (9). The cases described with this morphologic pattern were almost always found in association with more typical transitional cell carcinoma. This pattern may be associated with noninvasive surface carcinoma, with invasive carcinoma, and in metastatic sites. The presence of this pattern usually suggests muscle invasive disease. This pattern is also commonly associated with vascular space invasion, high stage, and poor clinical outcome.

A number of other malignant tumors have morphologic features that may disguise their urothelial origin (160,305). The most troublesome is the so-called sarcomatoid carcinoma, which has a distinct resemblance to carcinosarcoma. These tumors both occur in the same age range and generally present grossly as large ulcerated, polypoid masses. The major distinction between a carcinosarcoma and sarcomatoid carcinoma is the ability to find an area of urothelial CIS or more clear-cut urothelial carcinoma in sarcomatoid carcinoma. Microscopically, the sarcomatoid carcinoma demonstrates spindled areas that blend imperceptively into the more epithelial areas, as opposed to the distinct separation of epithelial and sarcomatous areas found in carcinosarcoma. Recently, Jones and Young (160) described variants

of sarcomatoid carcinoma that have myxoid and sclerosing features. This tumor has been described by various names, including *spindle cell* and *giant cell carcinoma.*

On occasion, a transitional cell tumor can have areas that resemble a choriocarcinoma, including the production of human chorionic gonadotropin (hCG), as demonstrated by immunohistochemical techniques (Fig. 30.15) (73,148,323). More often, the areas of choriocarcinomatous differentiation are identified focally within urothelial or squamous carcinomas. With these tumors, patients can develop gynecomastia and breast tenderness related to hCG production. The hCG may be elevated in the serum and can be used as a tumor marker to follow patients for recurrent disease.

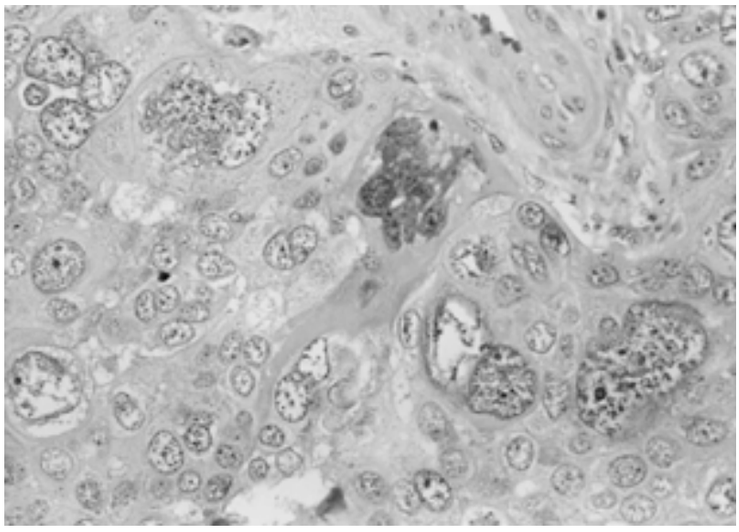

FIGURE 30.15. High-grade transitional cell carcinoma with syncytiotrophoblastic giant cells stained with human chorionic gonadotropin (hCG) by immunohistochemistry.

Transitional cell carcinomas sometimes can mimic lymphoreticular tumors (Fig. 30.16) (398). These tumors may resemble multiple myeloma or lymphoepithelial carcinoma. The recognition of lymphoepithelial carcinoma usually is not difficult if adequate biopsy material is obtained. However, when biopsies are small, the neoplastic epithelial component can be missed or masked by a prominent lymphoid proliferation. Rarely, a carcinoma can appear as a myeloma due to the cytoplasm being filled with intermediate filaments, giving the cells the cytologic appearance of a neoplastic plasma cell (294).

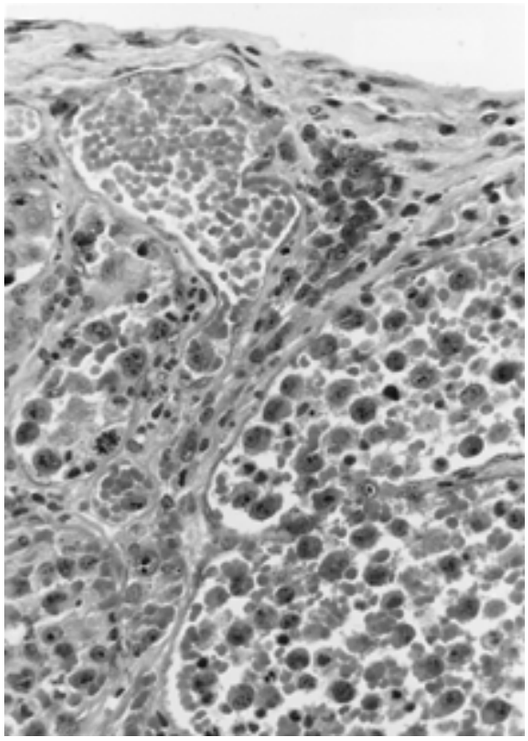

FIGURE 30.16. High-grade T-cell lymphoma characterized by loosely cohesive primitive cells invading the lamina propria of the bladder.

A recent important variant of transitional cell carcinoma is the transitional cell carcinoma with areas of neuroendocrine differentiation (2,28,114,228,255). Morphologically,

these tumors have areas of more distinct transitional cell carcinoma or, rarely, adenocarcinoma or carcinoid tumors in which there is a distinct tumor-component morphologic similarity to an oat cell carcinoma of the lung. These cells have dense core granules by electron microscopy and have immunohistochemical markers of neuroendocrine carcinoma. The group is important to recognize in that these tumors have an aggressive clinical course. These tumors are commonly associated with transitional cell carcinomas, but they also may occur in a pure form.

SQUAMOUS CARCINOMA

Part of "30 - CANCER OF THE BLADDER "

Squamous carcinomas of the bladder are tumors that display squamous differentiation in all areas. Tumors that demonstrate areas of transitional features are placed into the category of mixed transitional cell carcinoma with squamous differentiation. Pure squamous carcinomas are the second most common histologic type, representing between 5% and 7% of bladder carcinomas in the United States and 1% to 3% of bladder carcinomas in the British Isles (292,293). In regions where *S. haematobium* is prevalent, squamous carcinomas represent the most common form of bladder cancer (Fig. 30.17) (76,115). Squamous carcinoma presents as large exophytic masses. They often have a gray-white surface caused by surface keratinization. Squamous metaplasia, especially atypical squamous metaplasia, often is associated with these tumors, and its presence adjacent to less differentiated tumors is a clue about the squamous origin of the tumor.

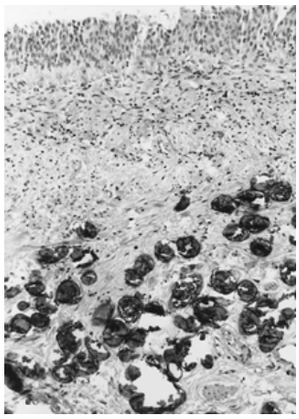

FIGURE 30.17. Calcified ova of *Schistosoma haematobium* within the vessels of the bladder's lamina propria.

Microscopically, squamous carcinomas consist of neoplastic cells with intercellular bridges and keratinization. Areas of keratin pearl formation are common (Fig. 30.18). Cytologically, the cells have abundant amounts of eosinophilic cytoplasm and nuclei, often with prominent nucleoli. These tumors are graded in a different manner than are transitional carcinomas. The degree of keratinization and nuclear pleomorphism are the segregating features. They generally are placed into three categories; well, moderate, and poorly differentiated carcinomas, or grade 1, 2, or 3. Squamous carcinomas associated with schistosomiasis are usually well differentiated. When the tumors are associated with *S. haematobium,* the eggs of the schistosomal organisms can be identified within the vessels or connective tissues of the lamina propria and muscularis propria. Often, these eggs are calcified, making their recognition somewhat difficult.

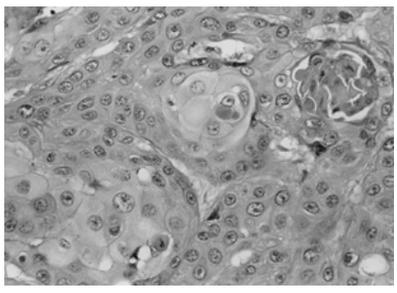

FIGURE 30.18. A squamous pearl within a moderately differentiated squamous carcinoma.

A rare variant of squamous carcinoma, *verrucous carcinoma,* also may occur in the bladder (Fig. 30.19) (383). Grossly, verrucous carcinoma is an exophytic tumor with a warty appearance. When this tumor invades, it has rounded, pushing borders with a slight desmoplastic and inflammatory response. Microscopically, the tumor is composed of papillary structures with acanthotic surfaces. Cytologically, the cells have very little pleomorphism and lack atypia. Although rare in the United States, verrucous carcinoma is found commonly in patients from populations where schistosomiasis is associated with bladder cancer.

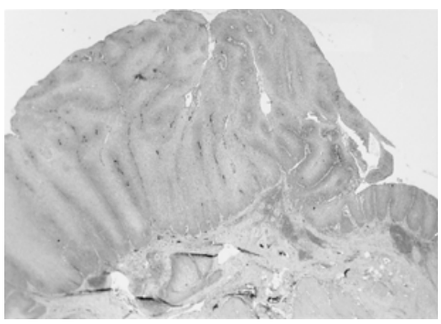

FIGURE 30.19. A verrucous carcinoma, an exophytic neoplasm with a blunt pushing margin.

ADENOCARCINOMA

Part of "30 - CANCER OF THE BLADDER "

Primary adenocarcinoma of the bladder, the third most common epithelial tumor, accounts for 0.5% to 2% of bladder

carcinomas (Fig. 30.20) (13,112,158,237,356,373). Transitional cell carcinomas often demonstrate areas of glandular differentiation and must not be confused with a primary adenocarcinoma. Adenocarcinomas appear to arise from the urachus in approximately one-third of cases and from the bladder mucosa in the remainder (112). Nonurachal adenocarcinomas often are associated with metaplastic enteric bladder mucosa and cystitis glandularis.

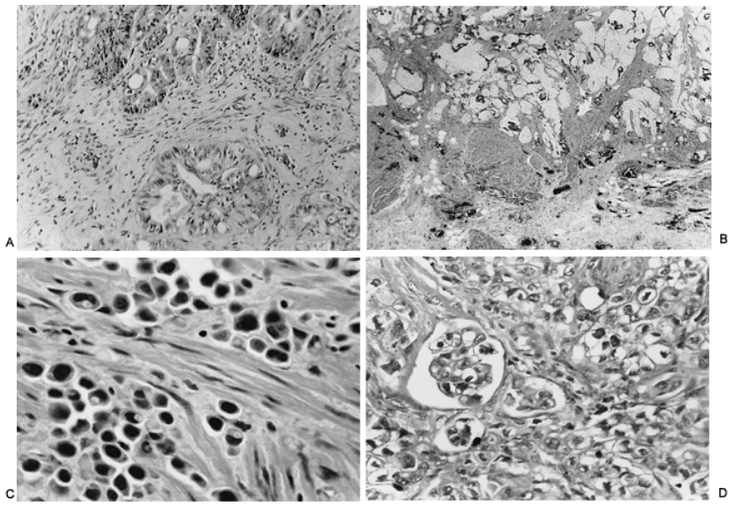

FIGURE 30.20. A: Primary adenocarcinoma of the bladder, enteric type. **B:** Primary mucinous adenocarcinoma of the bladder characterized by small clusters of neoplastic cells in lakes of mucin. **C:** High-power view of a primary signet cell adenocarcinoma of the bladder. **D:** High-power view of a primary clear cell adenocarcinoma of the bladder.

The distinction between urachal and nonurachal tumors often requires clinicopathologic correlation. In 1954, Wheeler and Hill (373) proposed five criteria that identify urachal adenocarcinoma. These criteria include location in the dome of the bladder; absence of cystitis cystica or glandularis; predominant involvement of the muscularis propria rather than the submucosa, with an intact or ulcerated bladder epithelium; demonstration of a urachal remnant connected with the neoplasm; and the presence of a suprapubic mass. Some believe the criteria of Wheeler and Hill are too restrictive (158). It has been suggested that tumors within the dome or anterior wall, tumors in which

there is a clear distinction between the surface mucosa and the underlying adenocarcinoma, and tumors occurring in patients with no evidence of an adenocarcinoma elsewhere (i.e., metastatic) should be considered of urachal origin. Unfortunately, no clear or distinctive microscopic features separate urachal from nonurachal tumors.

For the most part, adenocarcinomas arising within the bladder are indistinguishable microscopically from those arising in the colon. In the largest series of adenocarcinomas (112), these tumors were segregated into five histologic types. In this series, adenocarcinomas not otherwise specified accounted for 27.8% of cases, mucinous 23.6%, enteric 19.4%, signet ring 16.7%, and the mixed type 12.5%. When evaluated from the standpoint of urachal or nonurachal tumors, the majority of the urachal tumors were mucinous (50%), as opposed to 10% of the nonurachal tumors. However, the signet cell carcinomas were largely nonurachal, comprising 23% of this group compared with only 4% of the urachal tumors (112). The behavior of these tumors was different for the sites of origin as well, with the nonurachal tumors having the greatest mortality within the first several years and the urachal tumors having a more gradual mortality spread over 10 years. The stage of the tumors was the best predictor of outcome for both urachal and nonurachal tumors. Grading of the tumors was of little clinical significance. The histologic type was a good predictor only in signet cell–type tumors, which have a poor prognosis.

Histochemical staining for mucin within the cells of these tumors, or their immunohistochemical characterization, was of little help in distinguishing adenocarcinomas arising from the urachus versus those arising elsewhere. Furthermore, these stains were of little help in recognizing adenocarcinomas arising within the bladder from those arising elsewhere and metastasizing to the bladder.

A sixth form of adenocarcinoma arising in the bladder is the clear-cell adenocarcinoma (147,207,391). This type of tumor is rare. Young and Scully (391), in a review of the literature, found that clear-cell adenocarcinomas were most common in women, and of 19 patients having this tumor, 6 tumors were in the bladder and 13 in the urethra. These tumors are similar to clear-cell adenocarcinomas of the female genital system, having a varied appearance including tubular glands, cysts, papillae, and diffuse areas. Hobnail cells almost always are present focally. In the bladder, they generally occur in the area of the trigone or posterior wall. Their importance is distinction from nephrogenic adenomas, metastatic renal cell carcinomas, clear-cell carcinomas arising elsewhere in the female genital tract, and a variety of reactive or inflammatory lesions (147).

MALIGNANT MELANOMA

Part of "30 - CANCER OF THE BLADDER "

Most malignant melanomas identified in the bladder are the result of metastases (3,172,338). In autopsy series of patients dying from melanoma, bladder metastases are common, with as many as 20% of patients having such a metastasis. Primary melanomas arising in the bladder are rare, with no large series and only 11 reported cases. The patients are mostly women ranging in age from 46 to 81 years. When identifying a melanoma within the bladder, it is important to exclude the presence of a cutaneous melanoma, including a regressed cutaneous melanoma or ocular melanoma, because metastasis from these sites is far more common than a primary tumor.

Those cases identified in the bladder resemble melanomas elsewhere. They normally have atypical melanocytes in the mucosa adjacent to the tumor mass. As one would expect, these tumors reveal immunoreactivity with S100 protein and HMB-45. In addition, when evaluated by ultrastructure, they have typical premelanosomes or melanosomes present.

Paraganglioma

Paragangliomas, or pheochromocytomas, typically are distinct, well-circumscribed submucosal or intramural lesions (113). Their size and location are variable. They usually have a lobular growth pattern with a tan to yellow-brown cut surface. Histologically, these tumors grow in nests of cells that are separated by a delicate vascular network, a feature called *zellballen.* The tumor cells generally have moderate to abundant amounts of eosinophilic cytoplasm, ovoid nuclei, and central nucleoli. Nuclei can vary in size, and even though they have atypia, including bizarre forms, this feature is not useful in predicting metastatic potential. Immunohistochemical stains including S100, synaptophysin, and somatostatin have been useful in diagnosing this tumor (238). Studies to identify pathologic predictors of behavior in the bladder paragangliomas have not been fruitful. Predictors of potential metastases include an increase in mitotic figures, necrosis, and vascular invasion. Although these findings are useful in predicting an increased risk of malignancy, the only true predictor is actual metastases.

Unusual Tumors of the Bladder

There is a group of tumors that is uncommon in the bladder, but important because it challenges the clinician and pathologist to ensure their accurate recognition and diagnosis. Benign mesenchymal tumors of the bladder include hemangiomas, lymphangiomas, ganglioneuromas, granular cell tumors, benign fibrous histiocytomas, lipomas, and adenofibromas. Malignant soft tissue tumors that have fewer than ten case reports in the literature include liposarcoma, angiosarcoma, hemangiopericytoma, rhabdoid tumor, malignant fibrous histiocytoma, and both osteosarcoma and chondrosarcoma. Unusual germ cell tumors also reported are yolk sac tumors and dermoid cysts. Choriocarcinomas have been identified; however, these most commonly

are foci of choriocarcinoma associated with transitional cell carcinomas and may be considered a variant of transitional cell carcinoma. Last, carcinoid tumors have presented in the bladder on rare occasions (369).

Primary tumors of the hematopoietic system have been reported in the bladder and usually represent systemic disease at the time of their presentation (350). Less than 50 non-Hodgkin's lymphomas have been described as primary bladder tumors, and they represent the entire morphologic spectrum of the non-Hodgkin's lymphomas (16,91,108,119,266). Hodgkin's disease has been reported in the bladder as primary presentation in only a single case report (213). In autopsy series, the bladder is more frequently involved by non-Hodgkin's lymphomas, with 7% to 19% of cases having bladder involvement. Hodgkin's disease had only a 4% incidence of bladder involvement at autopsy. Multiple myeloma often involves the bladder at some time over its course. This involvement is usually microscopic and rarely important clinically. Plasmacytomas can present in the bladder (385). The importance of this histologic entity is distinguishing it from an unusual and recently described variant of transitional cell carcinoma that has plasma cell features (294). This distinction can be accomplished easily by applying immunohistochemical stains. Last, leukemias can involve the bladder and are often found at autopsy (108). The acute leukemias appear to involve the bladder slightly more frequently than the chronic leukemias.

Neurofibromas are another unusual tumor presenting in the bladder. Almost all cases of neurofibroma in the bladder have been associated with von Recklinghausen's disease. One-third of neurofibromas occur in children. Most neurofibromas have been of the plexiform type and are often in the region of the distal ureters and bladder neck, resulting in ureteral obstruction. Occasionally, these tumors undergo apparent malignant transformation to a neurofibrosarcoma. These tumors usually reveal areas of neurofibroma with focal areas of neurofibrosarcoma.

Soft Tissue Tumors of the Bladder

One of the most common and significant sarcomas presenting in the bladder is the rhabdomyosarcoma. The average age at presentation is 5 years. The tumor is rarely found in adults (126,129,159). Five percent of cases submitted to the Intergroup Rhabdomyosarcoma Study presented within the bladder. These tumors occur slightly more commonly in males (3:2 ratio) and present most commonly in the trigone. Clinically, the patients present with hematuria or bladder neck obstruction. Rhabdomyosarcomas that grossly present as multiple polypoid masses are called the *botryoid type. Botryoid* is derived from a Greek word meaning a “bunch of grapes.” Grossly, the tumors present as multiple polypoid masses or a single large mass replacing the bladder wall and sometimes extending within the bladder lumen. When the tumors are large and bulky, their exact site of origin is difficult to ascertain. Common sites of origin that involve the bladder secondarily are the prostate, vagina, and retroperitoneum.

The usual histologic pattern is that of embryonal rhabdomyosarcoma. This appearance reveals polypoid projections comprising proliferating small cells in an edematous stroma. The characteristic pattern is one in which the collections of small neoplastic cells create a layer immediately beneath the mucosa, which has been likened to the cambium layer of a plant. Because the botryoid pattern is found superficially, it is seen in biopsies from cystoscopy. In these cases, the deeper patterns of tumor often will be spindle cell or alveolar. This tumor has also been reported in adults; however, occurrence is much less common, with fewer than 30 reported cases. The diagnostic features of rhabdomyosarcomas in both children and adults are typical morphologic features that may include the presence of cross-striations within the cytoplasm of neoplastic cells. Difficult cases are now usually confirmed by immunohistochemical stains, including myoglobin and desmin.

The other common sarcoma occurring in the urinary bladder is the leiomyosarcoma (Fig. 30.21) (227,351). They are the most commonly reported sarcomas in adults, but overall represent less than 0.5% of all bladder cancers. They can occur in all age groups but tend to be more common in adults. Males are slightly more commonly affected by this tumor, and they are most likely to occur in the dome or lateral walls. Their gross appearance can be varied but often includes a polypoid mass that extends into the lumen of the bladder that may fill the entire lumen. Their cut surface can vary but includes fibrous white or tan myxoid surfaces that may be focally hemorrhagic with areas of necrosis. Microscopically, these tumors are also varied in appearance and resemble leiomyosarcomas elsewhere, being composed of spindle cells with increased cellularity, nuclear pleomorphism, and an increased number of mitoses. A feature seemingly more common in the bladder is prominent myxoid stroma. When features of leiomyosarcoma, which include increased mitoses, pleomorphism, necrosis, and infiltrative borders, are present, these lesions are relatively easy to diagnose. However, in borderline cases, distinct criteria to distinguish them from their benign counterpart, the leiomyoma, have not been established, and this distinction therefore can be difficult. These tumors must be distinguished from sarcomatoid carcinomas, which have been confused with them, particularly on biopsies. Immunohistochemical stains, especially low-molecular-weight keratins, have helped make this distinction. In addition, two pseudotumors that resemble these lesions are the postoperative spindled-cell nodule and the inflammatory pseudotumor. Unfortunately, immunohistochemical stains have not proven helpful in their differential diagnosis, but clinicopathologic correlation has.

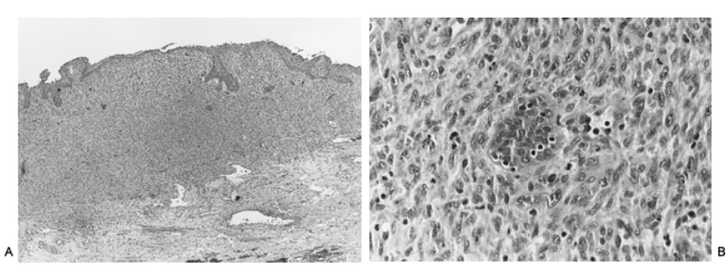

FIGURE 30.21. A: Recurrent low-grade leiomyosarcoma involving the lamina propria. **B:** High-power view of a low-grade leiomyosarcoma surrounding a nest of urothelium.

The benign counterpart of leiomyosarcomas, the leiomyoma, is the most common benign tumor presenting in the bladder. This tumor occurs more frequently in middle-aged women and grossly resembles its counterpart in the uterus.

They can occur throughout the wall of the bladder, including the lamina propria and bladder wall. Their site of origin often determines their gross appearance, with those in the lamina propria often presenting as polypoid masses extending into the bladder lumen. These tumors usually are nonulcerated, which can distinguish them from leiomyosarcomas that often ulcerate. As in other locations, these tumors are often large, and on unusual occasions, weigh several kilograms. Microscopically, they resemble leiomyomas in the uterus, that is, having interlacing smooth muscle bundles separated by a delicate vasculature. Mitoses should be rare to absent; however, a few borderline cases with an increase in mitoses have been reported. These cases fall into a borderline group because distinct criteria distinguishing the benign from malignant smooth muscle tumors have not been established.

CARCINOSARCOMA

Part of "30 - CANCER OF THE BLADDER "

Carcinosarcomas are unusual tumors that occur in many sites, including the bladder. On gross examination, these tumors, when in the bladder, are usually large and generally present with exophytic or polypoid masses. Some pathologists have included this tumor with sarcomatoid carcinomas, which have both spindled and epithelial neoplastic elements. Others treat the carcinosarcoma as a distinct and separate group of tumors. There is little question that, given strict criteria, tumors from the two groups can be separated. In addition, there is little question that there is a group of tumors that has both neoplastic spindled components and epithelial components that are difficult to place in either category. Carcinosarcomas should lack areas of CIS or transitional cell carcinoma elsewhere in the bladder mucosa. Carcinosarcomas are tumors that have intimate association of both a high-grade sarcoma as well as a high-grade carcinoma. The two elements generally stand out one from another, with little merging of the two elements as occurs in sarcomatoid carcinoma. Carcinosarcomas often have distinct malignant mesenchymal components, including chondrosarcoma, osteosarcoma, and rhabdomyosarcoma, a feature that confirms the tumor as a carcinosarcoma. On the other hand, when the sarcomatous portion resembles a leiomyosarcoma or fibrosarcoma, these tumors can be difficult to distinguish from a sarcomatoid carcinoma. In general, these tumors are locally aggressive; however, distant metastases have occurred in a few. These patients have a poor prognosis, with more than 50% of patients dying of their tumor within 1 year. A recent publication by Lopez-Beltran and others (199) demonstrated that, although carcinosarcomas and sarcomatoid carcinomas are usually distinct morphologically, they both have a poor prognosis. Their study demonstrated that the stage best predicted the prognosis in patients with either of these tumors.

Mimics of Carcinoma

A variety of lesions that are broadly classified as inflammatory, metaplastic, or developmental can mimic carcinoma of the bladder, both clinically and pathologically. The importance of these lesions to the pathologist is to avoid their confusion with neoplastic lesions and consequential overtreatment. The urologists' awareness will help in their clinical recognition.

The most common morphologic changes occurring in the bladder that may be considered pseudoneoplastic are von Brunn's nests, cystitis cystica, and cystitis glandularis (10,377). Von Brunn's nests are small, spherical clusters of urothelium that in some cases are connected to the surface mucosa; however, in others, they are just below the mucosa. The incidence of these lesions is high, with an autopsy study revealing that 86% of bladders had these lesions present.

Von Brunn's nests are seen frequently in biopsies and can occasionally mimic carcinoma when they are found in distorted biopsy specimens. These nests of cells can be involved by CIS and, in those cases, especially on biopsy, mimic microinvasive carcinoma.

Often, these urothelial-lined nests develop a central lumen, in which case they are called *cystitis cystica.* Cystitis cystica has been reported in 60% of bladders in an autopsy study (10). In a significant proportion of patients, glandular epithelium is found in these nests, in which case the entity is called *cystitis glandularis.* The cells lining the surface in cystitis glandularis are usually simple columnar cells that are associated with transitional type epithelium (Fig. 30.22). On occasion, the lining cells take on both the morphologic and histochemical characteristics of intestinal epithelium. This form of cystitis glandularis has been recognized for many years and is best designated as *intestinal type of cystitis glandularis* (Fig. 30.23). Cystitis glandularis of the intestinal type is a metaplastic change, and some have suggested that its presence has a higher association with invasive carcinomas. A study of 53 patients who had intestinal metaplasia (Fig. 30.24) associated with exstrophy for greater than 10 years seems to dispel this theory, in that none developed adenocarcinomas and only one developed a transitional carcinoma (63). Cystitis glandularis is also a common lesion found in autopsy series.

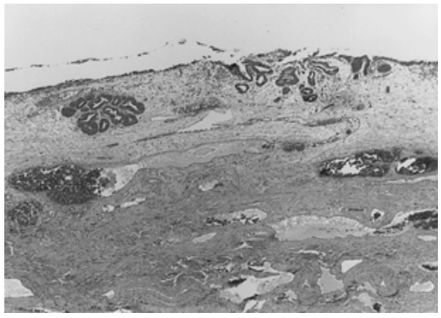

FIGURE 30.22. Chronic cystitis with cystitis glandularis.

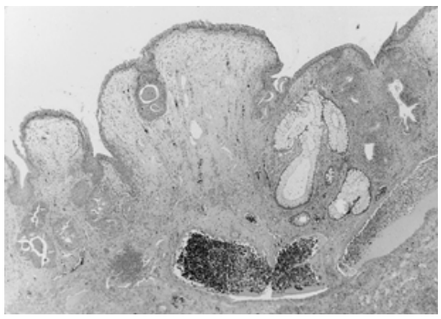

FIGURE 30.23. Chronic cystitis with cystitis glandularis of the typical type and the intestinal type.

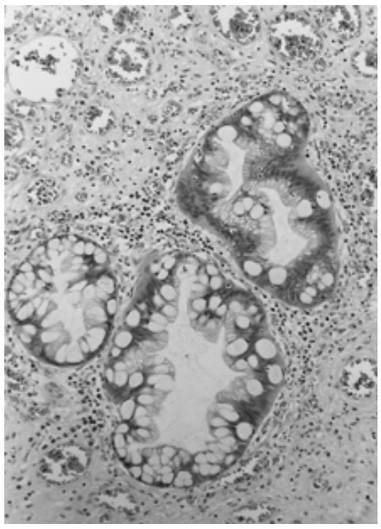

FIGURE 30.24. Intestinal metaplasia that is atypical because of the presence of adenomatous change.

All of these epithelial proliferations are more common around the trigone but occur elsewhere in the bladder. They are often indistinct and not recognized cystoscopically; however, occasionally, they can present with a slightly raised surface and, rarely, even become nodular in appearance.

A more troublesome but less common mimic of carcinoma is *nephrogenic adenoma,* a lesion originally described in a paper by Friedman and Kuhlenbeck (102) (Fig. 30.25). Its name arises from its morphologic appearance, which is most frequently characterized by collections of small tubules lined by cells with clear cytoplasm that resemble the nephron. More recent studies have emphasized additional patterns common to nephrogenic adenoma: cystic, papillary to polypoid, and more rarely, diffuse (252). These lesions are usually associated with an inflammatory reaction, and their irregular contour can give an infiltrative pattern. Fifteen percent of Oliva and Young's cases had glands intermingled with muscle fibers of the muscularis mucosa (252). Most cases of this lesion have been identified in the bladder; however, they do occur elsewhere in the genitourinary

system, including the urethra and ureter. The lesions have been seen in children, and males more commonly have this lesion than females, with a ratio of 2:1. These lesions are associated with previous operations or a chronic irritant, such as bladder calculi. Of interest is that a number of patients with renal transplant have developed these lesions. More recently, similar changes have been found throughout the bladder, and in that context, the lesions have been designated *nephrogenic metaplasia.*

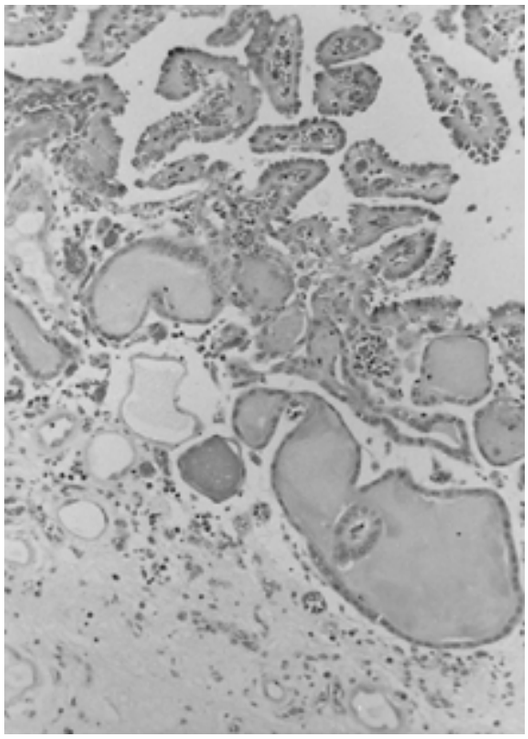

FIGURE 30.25. Nephrogenic adenoma comprising papillae and tubules lined by a single layer of cuboidal epithelium.

One of the most important reasons for recognition of this lesion is distinguishing it from adenocarcinoma, particularly a clear-cell adenocarcinoma (252). Clinically, patients with nephrogenic adenoma are young males with a predisposing factor such as trauma or previous surgery, whereas patients with clear-cell adenocarcinomas are older women without a history of previous bladder problems. Pathologically, nephrogenic adenomas are distinguished from clear-cell carcinoma in that they are small and, although clear cells are present, they are less common than in clear-cell carcinoma. In addition, the cytologic atypia of nephrogenic adenoma and the numbers of mitoses are less than in clear-cell adenocarcinoma. Oliva and Young (252) found that the presence of mitoses in nephrogenic adenoma was rare, with no mitoses found in 76 cases and only a single mitosis in 20 high-power fields found in 4 cases.

A last metaplastic change that is relatively common in the bladder but that can sometimes be confusing histologically with carcinoma is squamous metaplasia (377). It should be remembered that in the area of the trigone, nonkeratinized squamous mucosa is a normal finding in women and should not be referred to as *metaplasia* (Fig. 30.26) (377). Elsewhere in the bladder of women and throughout the bladder of men, both keratinizing and nonkeratinizing squamous mucosa is considered metaplastic change. Squamous metaplasia, especially when it is keratinized, is not difficult to diagnose pathologically but can sometimes be found extensively throughout the bladder, making adequate sampling and identification of carcinomas difficult. In these cases, the identification of a well-differentiated squamous carcinoma can be difficult for the clinician because the malignant area of squamous carcinoma cannot be identified in the extensive areas of squamous metaplasia.

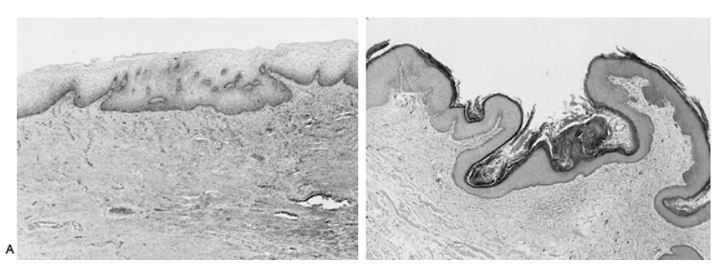

FIGURE 30.26. A: Nonkeratinizing squamous metaplasia—a normal finding when identified in the trigone of women. **B:** Keratinizing squamous metaplasia—an abnormal finding in the bladder.

A variety of papillary or polypoid lesions that are benign and are reactive can occur in the bladder (282). One of the more troublesome polypoid lesions that can occur from a diagnostic pathologist's viewpoint is prostate mucosa.

When present, this prostatic epithelium creates a polypoid lesion, usually in the region of the trigone. In most cases, the prostatic tissue is benign in appearance, and its prostatic origin can now be documented by localizing prostate-specific antigen, or prostatic acid phosphatase, with immunohistochemical techniques (282).

A rare polypoid lesion in the bladder is the fibroepithelial polyp (388). These polyps appear to be composed of proliferating mesenchymal cells within the lamina propria. Often, their stromal cells are atypical, a feature commonly seen when these lesions occur at other sites. On occasion, this atypia can reach a point that it raises the question of sarcoma.

Papillary and polypoid cystitis are clinically more common lesions that present as inflamed short papillae or polyps throughout the bladder (39,387). The lesions appear to arise because of an inflammatory process in which there is edema, chronic inflammation, and vascular proliferation in the lamina propria, creating elevated polypoid structures. When not much edema is in the lamina propria, the lesions are more papillary in appearance. Clinically, these lesions are associated with chronic bladder irritation such as an indwelling catheter or fistula. Pathologically, they must be distinguished from papillary neoplasms. This is most easily done by their lack of complex architecture at low power and bland cytologic appearance.

Occasionally, there can be a proliferation of lymphoid tissue in the lamina propria of the bladder. This is a relatively common finding in the region of a transitional cell carcinoma (296) but is also seen as the sole lesion in rare patients (142,179). Typically, these lesions are small, gray-white nodules, giving the bladder mucosa a cobblestone appearance. On occasion, they are associated with erythema, which can resemble CIS when seen at cystoscopic examination. Microscopically, these lesions are composed of aggregates of lymphocytes, often with germinal centers. Occasionally, they can resemble a lymphomatous infiltrate, but the reactive germinal centers are usually most helpful in distinguishing them from neoplastic infiltrates.

The bladder is the most common site of endometriosis presenting in the urinary tract (314). Patients generally have had a history of endometriosis elsewhere or previous pelvic surgery. When present and seen cystoscopically, the lesions appear as raised cystic structures that are reddish-brown or blue-black, depending on where a patient is in her menstrual cycle. Their gross appearance often leads to the suspected diagnosis of a neoplasm. Because the lesions are often within the wall of the bladder, they can be difficult to biopsy. Microscopically, if a lesion is excised completely, the morphologic appearance is similar to endometriosis elsewhere, in that there are bland-looking, endometrial-type glands surrounded by stroma. There is often congestion hemorrhage and hemosiderin deposition within the lesions. This finding is often associated with a chronic inflammatory infiltrate in and around the stroma. The glands may also be filled with blood and necrotic debris. There are reports of cases composed primarily of endocervical glands rather than endometrial glands, and in some cases, not all glands are associated with stroma. The term *endocervicosis* has been used to diagnose a lesion composed primarily of endocervical glands (54).

Two important pseudosarcomatous lesions involve the bladder, both of which were described in the 1980s. Clinically, these lesions occur as masses that are sometimes pedunculated or ulcerated and, at cystoscopy, appear as neoplasms. Pathologically, they are similar and are confused with leiomyosarcomas because they have many features that overlap with myxoid leiomyosarcoma. The first of these was described by Nochomovitz and Orenstein (245), and then by Ro and associates (284,285). The first authors referred to this lesion as an *inflammatory pseudotumor,* possibly related to nodular fasciitis, and the second group of authors called it *pseudosarcomatous myxoid tumor.* The second of these mimics of sarcoma was reported first by Proppe and colleagues (268) as a postoperative spindle cell nodule of the genitourinary tract. One of their cases presented in the bladder, with three of them presenting in the prostatic urethra. These lesions were as large as 4 cm. All patients in this group had had recent transurethral resections of the prostate or bladder.

In both cases, the lesions are characterized by a proliferation of intersecting fascicles of spindle cells associated with a myxoid background that includes chronic inflammatory cells. In some cases, the lesions have borders that infiltrate surrounding stroma and smooth muscle of the bladder wall. The intersecting fascicles of spindle cells are separated by a thin, delicate, blood vessel network. Collagen is focally deposited in these lesions, and inflammatory cells tend to occur in areas of ulceration or deep within the lesions. The neoplastic cells are generally enlarged without hyperchromatism but often have prominent single nucleoli. In some cases, mitoses have been reported to be increased in number. Immunohistochemical stains have typically shown expression of vimentin and muscle-specific actin, and most have lacked expression of cytokeratin in their critical cells. When cytokeratin is seen, it probably represents cross-reactivity of the cytokeratin antibody with actin filaments.

Both of these lesions are rare, and their distinction from sarcomas can be difficult. Many have been treated by wide excision; however, at least a few have been treated by transurethral resection only. Management of these lesions can be difficult because of the uncertainty of diagnosis and inability to clearly distinguish it from a low-grade leiomyosarcoma.

In summary, a number of pathologic lesions can mimic bladder neoplasms. Both the mucosa and stromal elements of the bladder have diverse proliferative and reactive responses. Recognition of these lesions is important to prevent unnecessary therapy.

STAGING

Part of "30 - CANCER OF THE BLADDER "

The current staging system for bladder cancer evolved from dual origins initially described more than 50 years ago. In 1946, Jewett and Strong (155) first proposed and described a classification of bladder cancer based on the relationship of depth of penetration of the bladder wall to incidence of local extension and metastasis. In 1950, based on Denoix's classification of bladder cancers (71), the Union Internationale Contre le Cancer (UICC) recommended adopting the tumor node metastases (TNM) staging system, which classifies tumors based on the assessment of the extent of the primary tumor (T), the condition of the regional lymph nodes (N), and the presence or absence of metastases (M). Today's TNM classification of bladder cancer by the American Joint Committee on Cancer (AJCC) is based on the evolution of these original staging systems (4).

Jewett and Strong (155) first analyzed 100 autopsy cases of patients with bladder cancer. They discovered that the primary bladder tumor could be segregated into three pathologic stages with increasing incidence of concomitant lymph node involvement, or hematogenous metastases with increasing tumor invasion of the bladder wall. No patient with a stage A bladder tumor (confined to the mucosa) was found to have evidence of metastases, compared with 13% of patients with stage B bladder tumors (involving the muscularis propria), and 74% of those with stage C bladder tumors (involving the perivesical fat). In 1951, Jewett further refined this system based on a clinical study of 80 patients (153). It was suggested that stage B tumors should be divided into superficial (B_1) and deep (B_2) categories (depending on the depth of muscularis invasion). Tumors in the B_1 category behaved much like stage A tumors, whereas those in the B_2 category resembled stage C tumors. In fact, in this report, 14 of 19 patients (74%) with stage A or B_1 tumors survived 5 years compared with only 2 of 61 patients (3%) with tumors involving the deep muscle or perivesical fat. Unfortunately, the separation of stage B into B_1 and B_2 was based on only 18 patients (4 of 5 with B_1 disease survived 5 years compared with only 1 of 13 with B_2 disease).

Nearly 30 years later, in a follow-up editorial entitled, “Comments on the Staging of Invasive Bladder Cancer—Two B's or Not Two B's: That is the Question,” Jewett astutely stated, “It seems probable that our arbitrary dividing line drawn 30 years ago at the halfway level to separate B_1 from B_2 tumors was too superficial. If placed at a deeper level, many of the currently reported B_2 cases would fall into stage B_1, which they often resemble, suggesting that penetration of the muscle rather than the depth of infiltration is the most important determinant of the treatment of patients with bladder cancer” (154).

A modification of the Jewett and Strong staging system was presented in 1952 by Marshall (214), who added stage 0 to include tumors not infiltrating the lamina propria, patients without evidence of tumor in the cystectomy specimen, and those with CIS. Furthermore, stage D was included to define those with evidence of metastatic disease. This was divided into two categories: stage D_1 lesions were confined to the pelvis (including invasion of pelvic walls or rectus muscle below the sacral promontory), and stage D_2 lesions were beyond the limits of the pelvis, including distant metastases of lesions above the sacral promontory. The aortic bifurcation was chosen arbitrarily instead of the sacral promontory to segregate stage D_1 from D_2 lesions when lymph node tumor involvement was present.

In 1968, the UICC published their first edition on the classification and staging of 23 tumor sites (44). Subsequently, in 1977, the AJCC published the first edition of their TNM staging system. It became obvious that a uniform staging system was required. Through a collaborative effort, the recommendations in the publications of the UICC and the third edition of the AJCC's manual became identical in 1987 (362). The TNM staging and classification in the most recent edition (the fifth, published in 1997) of the AJCC system corresponds exactly to the UICC TNM classification (4).

When comparing the Marshall (214) system with that of the current AJCC (4), the Marshall system considers both papillary noninvasive tumors and CIS as stage 0. The AJCC system classifies them as T_a and T_{is}, respectively. Tumors with submucosa (lamina propria) involvement are classified as stage A in the Marshall system and as T_1 in the AJCC system. Marshall subclassifies B_1 as representing superficial muscle penetration, and B_2 as representing deeper muscle involvement. This system currently corresponds to the subclassification of the AJCC system: T_{2a}—tumor invades superficial muscle (inner half), and T_{2b}—tumor invades deep muscle (outer half). This classification is a modification of the 1987 AJCC, in which deep muscle–tumor involvement was designated as T_{3a} (362). Tumors involving the perivesical fat in the Marshall system are classified as stage C, which corresponds to T_3 in the current AJCC system (4). Furthermore, T_3 has been subclassified in the current AJCC system; T_{3a} is microscopic perivesical invasion, and T_{3b} is macroscopic tumor involvement (extravesical mass) (4). This is a modification of the previous AJCC system, which designated extravesical tumor involvement as T_{3b} only. In the recent 1997 AJCC system, T_4 tumors invade contiguous structures (prostate, uterus, vagina, pelvic wall, and abdominal wall). These are subclassified as T_{4a}—involving prostate, uterus or vagina, and T_{4b}—involving pelvic or abdominal wall (4). This corresponds to the D_1 tumors of the Marshall system (214).

Regarding lymph node involvement, the current AJCC system classifies lymph nodes as regional (within the true pelvis) and distant (outside the true pelvis) (4). These are then subclassified as N_1, in a single lymph node (2 cm or less in greatest dimension); N_2, in a single lymph node (more than 2 cm but not more than 5 cm in size) or multiple

lymph nodes (none more than 5 cm in greatest dimension); and as N_3, in a lymph node more than 5 cm in greatest size. The Marshall classification considers patients with regional lymph nodes as D_1, and patients with distant nodes (above the aortic bifurcation) as D_2 (214). Distant metastases are designated as M_1 in the TNM system, and as D_2 in the Marshall system.

It must be emphasized that accurate clinical staging of bladder cancer is critical and necessary, because tumor stage is the most important determinant of therapy. However, despite the best clinical efforts, even with modern imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI), considerable clinical staging errors still occur in patients with bladder cancer; nearly 40% to 50% of patients are being understaged and 10% to 20% of patients are being overstaged. Freeman and associates (94) found that 34% of patients with superficial bladder cancer (T_a, T_1, T_{is}) who underwent cystectomy were pathologically upstaged to muscle-invasive disease or metastatic disease. Of these, only 50% had organ-confined disease, with 8% demonstrating metastatic tumors. Pagano and colleagues (257) reported an overall clinical staging error of 44%, which increased with increasing clinical stage. Similarly, Lerner and associates (195) reported a significant understaging in patients with muscle-invasive, clinically organ-confined disease; 68% of muscle-invasive tumors (T_2, T_{3a}) demonstrated extravesical tumor extension (P_{3b}). The current problem of clinical staging is that the system is only as good as the techniques available to assess the extent of the disease. Furthermore, understaging appears to be increased with higher clinical stages. Despite improvement in various radiographic modalities, the ability to evaluate the extent of the primary bladder tumor as well as the regional lymph nodes remains significantly limited (320). Therefore it must be emphasized that obtaining clear and accurate histopathologic information of the tumor and other sites of the bladder should include the degree of invasion, the grade of the tumor, and the presence or absence of CIS.

The optimal management of bladder cancer requires the early detection, precise clinical staging, and the true assessment of the tumor's biologic potential. Currently, histologic evaluations (including determination of tumor grade and stage) are the primary prognostic variables that dictate treatment strategies for patients with bladder cancer. Although these two conventional histopathologic variables provide a certain degree of stratification of a tumor's biologic potential, a significant degree of tumor heterogeneity remains, even within various prognostic subgroups of bladder cancer. This makes the accurate and reliable prediction of the tumor's aggressiveness difficult. The future of clinical staging, with a more accurate determination of the aggressiveness of a specific bladder tumor, ultimately may involve the application of various molecular or prognostic tumor markers (208,341). The ability to better predict the true biologic potential of an individual tumor would, in turn, facilitate treatment-selection decisions. This would identify those patients who may benefit from adjuvant therapy or more aggressive therapy, and also identify those patients who may require less aggressive treatment strategies. Advances in molecular biology have led to the discovery of certain suspected tumor markers that may influence cancer development and progression. These could clearly influence treatment decisions.

Clinical Staging of Bladder Cancer

Nearly 80% of patients present with some form of hematuria, which may be visible (gross) or discovered on routine urinalysis (microscopic) (88). The hematuria seen in patients with bladder cancer is classically painless and may be intermittent. Furthermore, although the degree of hematuria does not correlate with the extent of the disease, the presence of hematuria requires urologic evaluation. This may be particularly important in patients older than 50 years of age or in those with a known predisposing factor for bladder cancer. Known predisposing risk factors for bladder cancer include a smoking history, known exposure to industrial carcinogens, or having had an indwelling catheter in the bladder for an extended period of time.

Irritative bladder or voiding symptoms are the second most common form of presentation seen in approximately 25% of patients with bladder cancer. Such voiding symptoms may include urinary urgency, frequency, and dysuria and are usually seen in patients with CIS or with an invasive bladder tumor (82,363). Furthermore, patients with irritative voiding symptoms and bladder cancer generally have associated hematuria. Although irritative voiding symptoms are more commonly suggestive of bacterial or interstitial cystitis, the physician must always consider a bladder tumor in any patient with irritative voiding symptoms without an obvious bladder infection.

Although uncommon, patients with bladder cancer may also present with symptoms of bladder outlet obstruction, including urinary retention, pelvic fullness, or suprapubic pain or discomfort with a suprapubic or pelvic mass. Ipsilateral flank pain may occur secondary to ureteral obstruction. Less commonly, when bilateral ureteral obstruction is present, the patient may present with flank pain or renal insufficiency. Evidence of advanced or metastatic disease may present with constitutional symptoms including anorexia, weight loss, and generalized weakness. Patients with bone metastases may present with bone pain or even anemia if there is extensive bone involvement.

The physical examination is usually unremarkable in most patients with bladder cancer. Patients with superficial bladder cancer confined to the mucosa or the submucosa generally have a normal physical examination. A careful physical examination is always necessary to exclude coexistent pathology. All patients should undergo a careful bimanual pelvic examination to determine the presence of a

palpable mass, as well as any induration or fixation of contiguous organs or the pelvic side wall. In the female patient, the vaginal examination allows evaluation of the entire urethra and vagina. Patients with large or advanced bladder tumors may have abdominal tenderness, a bladder mass, or induration on physical examination.

An excretory urogram (intravenous pyelogram [IVP]) is generally performed first to evaluate radiographically the upper urinary tract. This test should be performed before cystoscopy. Radiographic abnormalities of the upper urinary tract may include a cortical defect, hydronephrosis, a poorly functioning or nonfunctioning kidney, and a filling defect identified anywhere along the collecting system (calyces, renal pelvis, or ureter). Any filling defect or abnormality identified on IVP, or if the entire upper urinary tract is not well visualized, can then be further assessed at the time of cystoscopy with retrograde ureteropyelography. Patients allergic to intravenous (IV) contrast material, or with a history of renal insufficiency, may alternatively undergo an ultrasonography of the kidneys, followed by bilateral retrograde ureteropyelography at cystoscopy. This ensures complete radiographic evaluation of the upper urinary tract, and will identify any synchronous upper urinary tract urothelial tumors, which occur in approximately 5% of patients with bladder cancer (251).

Bladder filling defects are identified on IVP in approximately 50% of patients with bladder tumors (140). Large tumors are identified more easily, and are characterized by nonspecific filling defects of the bladder wall. In addition, nonsymmetric bladder wall expansion during the filling phase of the IVP may also suggest a bladder wall tumor (72). Other causes for a bladder filling defect include a blood clot, a bladder fold in a nondistended bladder, or as the result of extrinsic compression from an adjacent organ. To improve the diagnostic evaluation of the bladder, IVP images should be obtained during early bladder filling, along with a distended bladder film, and a postevacuation film.

Bladder tumors associated with ipsilateral hydronephrosis generally suggest an invasive lesion of the bladder (121,123). In fact, Hatch and Barry (123) found ureteral obstruction to be associated with muscle invasion in more than 90% of patients with transitional cell carcinoma and hydronephrosis.

A retrospective analysis of 415 consecutive patients who underwent radical cystectomy for invasive bladder cancer from 1983 through 1993 was recently performed (121). The specific variable of hydronephrosis (unilateral and bilateral) was evaluated as determined by preoperative radiographic imaging studies with regard to pathologic stage and clinical outcome. Of these patients, 299 (72%) demonstrated no preoperative evidence of hydronephrosis, 94 (23%) had unilateral hydronephrosis, and 22 (5%) had bilateral hydronephrosis. All 415 patients were uniformly treated and pathologically staged. A significant correlation between hydronephrosis and advanced cancer stage and decreased patient survival was identified. Of the 116 patients with either unilateral or bilateral hydronephrosis, 85% had muscle-invasive tumors or more advanced disease (in excess of P_2). Of the 94 patients with unilateral hydronephrosis, 83% demonstrated bladder tumors with pathologic evidence of muscle invasion of the bladder (in excess of P_2). This confirms previous reports that patients presenting with unilateral hydronephrosis and bladder cancer generally have muscle-invasive tumors. Furthermore, when evaluating patients with bladder cancer who present with bilateral hydronephrosis, more than 90% of patients demonstrated advanced disease pathologically, with extension outside the bladder (more than P_{3b}, or lymph node–positive disease). Moreover, the 5-year survival for patients with no hydronephrosis was 62%, compared with 45% and 30% for those with unilateral and bilateral hydronephrosis, respectively.

These data obviously suggest that patients with unilateral hydronephrosis have muscle-invasive tumors, whereas those patients presenting with bilateral hydronephrosis have a more ominous prognosis. Obviously, the presence of hydronephrosis (unilateral or bilateral) as determined by preoperative radiographic imaging is an important piece of clinical information that may help dictate therapy and provide prognostic information.

Urinary Cytology

Urinary cytology should be performed in all patients diagnosed with or suspected to have bladder cancer. The evaluation of a voided urine specimen for exfoliated cancer cells may be particularly useful in patients with high-grade bladder tumors, or when CIS is present (19). The limitations of urinary cytology are a result of the normal cystologic appearance of well-differentiated tumor cells, and the fact that well-differentiated tumors cells are more cohesive and less commonly shed into the urine. Cytologic results have been disappointing in patients with low-grade bladder tumors, with an overall sensitivity of approximately 30% (394). In addition, approximately 20% of high-grade tumors or CIS will have a false-negative urinary cytology. A negative voided urinary cytology does not exclude the presence of a bladder tumor. In fact, because most low-grade bladder tumors have a normal urinary cytology, a positive urinary cytology in the context of a low-grade bladder tumor should raise the suspicion of a concomitant high-grade tumor. Even in the presence of a normal radiographic evaluation, a positive urinary cytology should alert the physician to a bladder tumor somewhere along the urinary tract.

Ideally, urinary cytology should *not* be obtained from a first-voided morning specimen, but rather from a well-hydrated patient, to optimize the appearance of the cancer cell. Cellular degeneration occurs in urine that has remained in the bladder for an extended period of time and should be avoided (176). Other factors that may artifactually alter the urinary cytology result include urinary tract infection, indwelling

catheters, bladder instrumentation, radiation therapy, and intravesical immunotherapy or chemotherapy. To improve the accuracy and sensitivity of urinary cytology, saline bladder washings may be used (219). This mechanical action (barbotage) enhances tumor cell shedding and provides better cytologic evaluation. A cytology specimen obtained by barbotage has been reported to be positive in 10% of patients with grade I bladder tumors, in 50% of those with grade II tumors, and in 90% of those with grade III tumors (332).

Recently, a urine antibody test for bladder-tumor antigen (BTA, Bard Diagnostic Sciences, Redmond, WA) has been developed to improve and add to the diagnostic capabilities of routine urinary cytology. The BTA test is an assay for the qualitative detection of BTA in the urine (297). The antigen is composed of basement membrane complexes that have been isolated and characterized from the urine of patients with bladder cancer. In a large, well-designed, prospective, multicenter trial involving 499 patients, the BTA test was found to be more sensitive than urine cytology; the BTA was found to have an overall sensitivity of 40% compared with only 16% for urine cytology in detecting recurrent bladder cancer in patients with low-grade and low-stage tumors (297). Its sensitivity for low-grade tumors is approximately 30%. When stratified by stage, the BTA assay was more sensitive than urinary cytology for T_a tumors (31% versus 4%) and T_1 tumors (48% versus 22%). Furthermore, for grade 2 tumors, the BTA assay was also more sensitive. Clearly, further evaluation of this assay is needed to define its true role in the initial evaluation of patients with bladder cancer. However, because the BTA test is a simple, rapid, and inexpensive adjunct to cystoscopy, and because it is more sensitive than routine urinary cytology for low-grade and low-staged tumors, it may be an attractive method along with urinary cytology for the initial evaluation and surveillance of patients with bladder cancer.

Cystoscopic Evaluation

The diagnosis of bladder cancer is ultimately made on cystoscopic examination of the bladder, and pathologic evaluation of the resected tumor specimen. However, when a bladder tumor is suspected from previous radiographic imaging studies or is identified cystoscopically, or abnormal cells are reported on urinary cytology, a careful bimanual examination is first performed. This should be performed in the lithotomy position with good pelvic relaxation under general anesthesia. This helps determine the presence, extent, and fixation of a palpable bladder mass. If a bladder tumor is palpable before resection, bimanual examination also should be performed following resection of the bladder tumor. The presence of a palpable bladder mass after transurethral resection implies extravesical tumor extension. Conversely, resolution of any induration or a palpable mass following complete transurethral resection suggests a more superficial tumor confined to the bladder. Fixation of the bladder is suggestive of advanced disease. It must be kept in mind that this bimanual examination is very subjective, and is certainly difficult to perform and interpret in obese patients, patients with a previous operation in the lower abdomen, and patients with tumors located posterior to the pubic symphysis. Nonetheless, a bimanual examination should always be performed because it can provide some clinical information.

Cystoscopic evaluation begins with careful inspection of the entire urethra, prostate, and bladder neck. Examination of the bladder should be comprehensive and methodical. Mapping of the entire bladder should be performed before resection or biopsy of any bladder tumors. The number, location, size, and configuration (papillary, flat, sessile, or nodular) of all tumors, and of any associated mucosal abnormalities, should be accurately recorded. The mucosa must be evaluated for areas of irregularity or erythema, which may be consistent with CIS. Retrograde pyelography should first be performed when the upper urinary tract has not been adequately evaluated or is suspicious for a concomitant lesion seen on previous radiographic imaging studies. If an upper urinary tract lesion is identified, ipsilateral ureteral cytology, saline lavage, brushing biopsy, or ureteroscopy may be performed for complete evaluation.

Once the entire urinary tract has been completely evaluated (either radiographically or endoscopically), transurethral resection or deep biopsy of the tumor is next performed. This is important to establish a pathologic diagnosis with determination of tumor grade and depth of tumor invasion. The accurate pathologic determinants of the resected bladder tumor are critical in the clinical staging and treatment decision process of the patient with bladder cancer. Care must be taken during resection or biopsy to ensure an accurate histologic evaluation. The use of cautery should be minimized to preserve the architectural structure of the tissue and to avoid cautery artifact.

Directed bladder biopsies of adjacent and normal-appearing bladder mucosa remote from the primary tumor should also be performed in conjunction with transurethral resection. Mucosal biopsies are best performed with the use of cold cup biopsy forceps. Mucosal biopsies should include (in addition to suspicious lesions) four uniform sites: lateral to both ureteral orifices, the trigone, and the dome of the bladder. Biopsies need not be deep because only the mucosa requires histologic examination. The results of these biopsies are an important adjunct that may influence treatment decisions, particularly in the presence of low-grade superficial tumors. The presence of CIS associated with a low-grade tumor is known to increase the recurrence rate and may warrant early institution of intravesical immunotherapy or chemotherapy (324). In addition, transurethral biopsy of the prostatic urethra and stroma should be performed for complete staging purposes in men; nearly 30% of men with CIS will have prostatic involvement

with tumor, which may also alter treatment recommendations (111).

The ideal method to resect a bladder tumor is to first resect the superficial portion, followed by resection of the deeper portion, along with a portion of the muscularis propria. These specimens should be submitted separately to the pathologist. Care must be taken during the resection of any tumor to prevent a bladder perforation and potential tumor spill. To minimize bladder perforations, resection of the tumor is best performed with the continuous-flow resectoscope while the bladder is only partially distended or filled. In addition, resection must be performed with the patient completely paralyzed under general anesthesia. It should be kept in mind that resecting bladder tumors on the lateral bladder wall may stimulate an obturator nerve reflex with violent contraction of the adductor muscles of the thigh and possible bladder perforation. Once the tumor is completely resected, the site should be fulgurated.

Complete transurethral resection of a small papillary lesion should be performed. Alternatively, electrocautery can be used with papillary lesions after appropriate biopsies have been taken for histopathologic evaluation. Complete resection of an obvious invasive bladder tumor (broad based, sessile), particularly when radical cystectomy is anticipated, should be avoided. Bladder tumors that encroach or involve a ureteral orifice can be completely resected. However, fulguration of the ureteral orifice following resection should be avoided. If resection of a ureteral orifice is necessary, placement of a stent may be prudent to prevent acute ureteral obstruction secondary to edema. Care must also be taken when a bladder tumor is identified in a bladder diverticulum. These tumors should be biopsied rather than resected. This reduces the risk of perforation of the thinned wall diverticula, which by definition lack any muscularis propria. Furthermore, patients with bladder tumors located in a bladder diverticulum are probably best treated with radical cystectomy, and therefore an extensive resection is unnecessary; only a tissue diagnosis is required.

Clinical and Radiographic Modalities in the Staging of Bladder Cancer

Abdominal and transurethral ultrasonography have been used to evaluate the local extent of the primary bladder tumor. Transabdominal ultrasound suffers from poor definition of bladder wall invasion, and has been superseded by other imaging techniques. Transurethral ultrasound may provide a more accurate assessment of the bladder wall and gross depth of tumor invasion, but in reality will provide no additional clinical information over transurethral resection.

Complete clinical and radiographic staging should evaluate the most common metastatic sites for bladder cancer, including the lungs, liver, and bone. A chest radiograph should be performed on all patients. A CT scan of the chest is obtained only when pulmonary metastases are suspected either by history, or because of an abnormal chest x-ray examination. In addition, liver function tests and serum alkaline phosphatase should be obtained routinely on all patients with bladder cancer. All patients with an elevated serum alkaline phosphatase or with complaints of bone pain should undergo a bone scan. A CT scan of the abdomen and pelvis should be performed in patients with suspected metastases, elevated liver function tests, a bladder tumor associated with ipsilateral or bilateral hydronephrosis, or in patients with a T_4 primary bladder tumor. The results of these tests may impact the decision for neoadjuvant therapy. A CT scan of the abdomen and pelvis may also provide some clinical information regarding the pelvic and retroperitoneal lymph nodes, as well as the presence of any liver lesions. The ability of CT to detect lymph node tumor involvement generally depends on the enlargement of the involved nodes. However, as previously mentioned, CT scanning of the pelvis strictly for staging of the primary bladder tumor should not routinely be performed, because it is neither sensitive nor specific enough to evaluate the degree of primary bladder wall–tumor invasion (244). The general agreement is that CT scanning cannot differentiate between superficial and invasive bladder tumors, owing to the similar density values of tumor and normal bladder wall. Furthermore, the evaluation of a bladder tumor extravesical extension with CT scanning is also poor. CT scanning cannot detect microscopic infiltration of the tumor beyond the bladder wall. It should be understood that benign perivesical changes (scar formation following previous operation or transurethral resection) cannot be differentiated from tumor growth on the imaging study (193). This is particularly true following a transurethral resection of a bladder tumor, or following irradiation therapy where edema and artifactual changes in the bladder wall make interpretation difficult. The limitations of CT scanning in the clinical staging of patients with primary bladder tumor must be kept in mind (249).

Commonly, CT scanning is performed to evaluate the regional (pelvic) and the retroperitoneal lymph nodes. However, CT scanning of the abdomen and pelvis may be limited in accuracy, because it may detect only obvious gross extravesical tumor extension, and large (in excess of 2 cm) pelvic or retroperitoneal lymph nodes (249). Furthermore, a reactive or an enlarged pelvic or retroperitoneal lymph node (particularly following resection of a bladder tumor) is not diagnostic of tumor involvement. CT scanning can detect only the presence of enlarged lymph nodes; neither the internal architecture nor the pathologic contents are revealed.

The diagnostic value of CT scanning to stage patients with bladder cancer must be carefully considered. If the clinical investigation suggests an operable bladder tumor, it is not unreasonable to proceed and pathologically stage the patient with a pelvic lymphadenectomy and radical cystectomy. However, despite the limitations of CT scanning,

some will argue that it is not unreasonable to perform an abdominal and pelvic CT scan, which is more sensitive than physical examination in grossly evaluating the regional and metastatic extent of the disease. Furthermore, proponents for neoadjuvant chemotherapy in the treatment of invasive bladder cancer may also argue there is a role for CT scanning of the abdomen and pelvis for staging purposes (301).

MRI studies currently play little role in the evaluation of patients with bladder cancer. The resolution of the pelvic and retroperitoneal lymph nodes and anatomy is not as clear as CT scanning. However, MRI may have a role in the evaluation of suspected bone metastases, because it appears to be more sensitive than both CT and bone scans for this purpose.

Management of Superficial Bladder Cancer

As previously mentioned, most (70% to 80%) newly diagnosed tumors of the bladder are classified as superficial lesions. Superficial bladder cancers comprise a heterogeneous group ranging in both histologic grade (I to III) and depth of invasion (stage). Superficial cancers of the bladder consist of tumors that are either confined to the mucosa (T_a) or invasive into the lamina propria (T_1). CIS of the bladder epithelium is also classified as a superficial lesion. The natural history of superficial bladder cancer is predicted based on a variety of tumor characteristics that estimate the risk for disease recurrence or progression to a more advanced stage. These characteristics include tumor stage at presentation, histologic grade, tumor size, configuration (papillary versus solid), multifocality, associated positive urinary cytology following resection of all visible disease, associated mucosal dysplasia, and failure to respond to intravesical treatment (67,127,163,203,210,359). The heterogeneity of the underlying molecular alterations in superficial bladder cancer further underscores the dramatic differences in their natural history and clinical behaviors (253,335).

Selection of appropriate therapy for a given superficial bladder tumor is largely based on the combination of known risk factors obtained at the time of initial transurethral resection. The information provided by endoscopic resection is necessary to determine the need for, and subsequent therapy following, tumor resection or fulguration. Tumor grade has demonstrated a strong correlation with the risk of progression, the development of metastatic disease, and overall survival (100,163). Although able to maintain the ability to recur throughout a patient's life, low-grade tumors (grade 1) exhibit an exceedingly low risk of progression to muscle invasion (106,270,271). Endoscopic excision or ablation followed by close observation is all that is required for most of these lesions. In contrast, high-grade lesions (grade 3) portend a more ominous outcome, because they are associated with a significantly greater risk of tumor progression, observed in approximately 50% of patients (57,94,127). Moderately differentiated (grade 2) tumors comprise a group of heterogeneous lesions that demonstrate an intermediate risk for both recurrence and disease progression.

Depth of tumor invasion also provides valuable prognostic information and should be used to guide therapeutic recommendations (67,106,151,156,378). Whereas T_a lesions rarely (less than 5%) progress to muscle invasion, nearly half of all T_1 tumors, many of which are also high grade, proceed to invade the muscularis propria if treated with endoscopic resection alone (106,127,151). Superficial tumors that are associated with dysplasia of the surrounding mucosa or CIS demonstrate a more aggressive behavior than lesions of the identical stage without the associated mucosal abnormalities (8). Other tumor characteristics associated with a high risk of tumor progression include large tumor size (89,127), tumor multifocality (67,194,203), lymphovascular invasion (12,94), nondiploid DNA content, high cellular S-phase fractions (20,22,117,118,307), and the absence of tumor cell–surface blood-group antigens (59,60,211,311).

Local Treatment Modalities

Transurethral Resection of Bladder Tumors

Endoscopic resection remains the mainstay of current diagnostic approaches to superficial bladder lesions and plays a central role in management. Complete removal of solitary or multifocal disease can be performed endoscopically to provide valuable material for pathologic grading and staging. Resection into the muscle layer of the bladder allows for definitive identification of invasive disease and proper assignment of therapy. Endoscopic resection or fulguration of initial or recurrent papillary, low-grade lesions can also serve as definitive treatment. Complete endoscopic removal or destruction of all visible tumors should be attempted at the time of cystoscopy and will provide the best chance for success when subsequent intravesical therapy is needed. Although the long-term survival of patients with low-risk superficial bladder cancer treated by endoscopic resection alone is excellent, the limitation of transurethral resection of bladder tumors (TURBT) as definitive therapy for higher-risk lesions is evident from the high incidence (approximately 50%) of recurrent disease and subsequent progression following transurethral resection alone.

Endoscopic evaluation of the bladder is critical in the initial assessment of patients with superficial bladder cancer because it identifies tumor characteristics that will guide initial therapy, provide a risk assessment for disease progression, and determine the need for additional therapy. At the time of all endoscopic evaluations, the location, number, and configuration of all tumor(s), should be documented carefully. The location of the ureteral orifices and the quality of the efflux (clear or bloody) also should be noted. The

entire mucosa of the bladder and prostatic urethra should be examined carefully, with the site and description of all mucosal changes documented. The instrumentation used for biopsy includes the cold-cup forceps and the resectoscope with electrical cutting loop. The cold-cup forceps are used to avulse small samples of mucosa or sections of tumors, usually measuring less than 0.5 cm. Once grasped, the forceps are twisted and pulled to remove the desired specimen. The forceps typically are unable to obtain material from below the lamina propria, and usually do not lead to significant bleeding or perforation. Biopsy forceps equipped with cautery capabilities are available to provide additional hemostasis when required. Alternatively, a Bugbee electrode can be used to control postresection bleeding. The resectoscope is the instrument of choice for removing most bladder lesions. To allow for effective electrical conduction to the resecting loop, an irrigant, such as water, is used with either a continuous or noncontinuous flow set up. The initial pass at the tumor with the resecting loop should be aimed at excising the tumor down to its base. Pure cutting current is preferred to limit coagulation artifact to the biopsy material. Because tumor staging plays an important role in risk assessment and the assignment of therapy, a separate biopsy of the tumor base should be taken. This should include a sample of muscle layer of the bladder wall to provide information regarding the depth of tumor penetration. Once all material for pathologic evaluation has been removed, electrocautery may be applied to obtain complete hemostasis at the biopsy/resection sites. Lesions overlying the ureteral orifices also should undergo complete resection, although resection of the intramural ureter may lead to vesicoureteral reflux. A minimal amount of coagulating current in this region is preferred. This will limit the risk of subsequent obstruction of the resected orifice. During resection of lateral wall tumors, particular care must be taken to eliminate the effects of obturator nerve stimulation. Electrical stimulation of the obturator nerve during resection may lead to a violent adduction of the thigh and result in a bladder wall perforation and potential tumor spill. Complete muscle paralysis may be needed during resection of lateral wall–based tumors to prevent obturator spasm.

Surveillance of other regions of the bladder that are not obviously involved by tumor will aid in identifying field changes (epithelial dysplasia or CIS) associated with an increased risk of disease recurrence (8). Approximately 25% of superficial lesions, and up to 70% of invasive tumors, will have dysplasia or CIS associated with the primary tumor or identified at other sites within the bladder. Although suspicious regions of erythema should always be sampled, random biopsies of more normal-appearing mucosa are less likely to yield positive findings; less obviously involved areas of dysplasia may be identified. Cytologic evaluation of bladder washings obtained at the time of cystoscopy can provide evidence of occult mucosal abnormalities because dysplastic cells are less adherent and more readily dislodged. Some have suggested that cytologies are more useful than random bladder biopsies and may eliminate potential implantation sites provided by denuding regions of mucosa (170). A careful examination of the prostatic urethra, particularly in patients with a positive urinary cytology and no apparent lesion within the bladder, or in patients who are candidates for bladder-sparing protocols, should be included in each evaluation. Loop biopsy of the prostatic urethra using the resectoscope provides information on the status of the prostatic ducts and stroma, as well as the mucosa, and is useful in evaluating high-risk patients. Bimanual examination at the time of resection is mandatory and provides information that may alter therapy or surgical management if a mass is palpable, fixed within the pelvis, or involving surrounding structures such as the rectum.

Complications of TURBT are uncommon, but must be recognized at the time of resection to limit overall morbidity. Bleeding following tumor resection is dealt with appropriately upon completion of the resection with the various forms of available cautery devices. Unrecognized regions of bleeding may become evident postoperatively as the bladder decompresses and relieves the tamponade effect provided when distended. Clot retention that occurs after resection may lead to bladder distention and an increased risk of bladder rupture of the already thinned wall. Perforation of the bladder at the time of tumor resection may occur and can be recognized by visualization of fat within the depths of the resected region. Small extraperitoneal perforations usually can be managed with catheter drainage alone. Following a larger perforation of the bladder, significant amounts of irrigation fluid may extravasate into the pelvis, which can be identified on physical examination as abdominal or suprapubic fullness. Open repair and drain placement may then be necessary. Intraperitoneal perforations, if small, may be managed safely with catheter drainage; however, larger intraperitoneal perforations will require open repair and suprapubic catheter placement. Injuries to intraabdominal structures, such as bowel, requires open exploration and repair. Vesicoureteral reflux may occur after resection of tumors at the ureteral orifices. Less commonly, obstruction of the ureteral orifice occurs, and can be avoided by the use of pure cutting current when resecting orifice-based lesions. Urethral strictures and bladder contractures are uncommon complications following TURBT.

Follow-up after endoscopic resection usually consists of a surveillance cystoscopy and cytologic evaluation every 3 months for the first 2 years. If no recurrence is identified after 2 years, the frequency of cystoscopic evaluations may be decreased to every 6 months, and annually thereafter. Although it is justifiable to decrease the intensity of follow-up over time, the need for long-term follow up, even in patients with low-risk disease, continues throughout a patient's life. Several series have reported at least a 20% recurrence rate in patients who have gone 5 years without evidence of recurrent disease, many of whom

have invasive disease at the time of recurrence (236,357). Flexible endoscopic equipment is well suited for surveillance cystoscopy because it provides visualization of the bladder comparable with that obtained with rigid scopes and provides improved patient comfort, allowing outpatient office evaluation (370).

Upper tract studies, usually consisting of an IVP, are included as part of the initial patient workup. The low risk (5%) of developing upper tract tumors following resection of a superficial bladder lesion suggests that regular IVPs after TURBT are not warranted (79,371,395). The presence of CIS or other high-grade lesions and tumors adjacent to the ureteral orifices increases the risk of upper tract tumors and is an indication for a more stringent follow-up regimen (68,226). Annual upper tract studies are recommended for 2 years, followed by biennial examinations if no evidence of disease is found. The higher rate of upper tract lesions in high-risk patients mandates that long-term surveillance of the upper collecting systems be performed.

Laser Therapy

Laser surgery for superficial bladder cancer is an effective means of destroying superficial bladder tumors (143,326,329). The wavelength emitted by a laser fiber determines the tissue effects, depth of penetration, and degree of tissue ablation. Although a variety of lasers, including the argon (328), holmium (157), and potassium thianyl phosphate (KTP), have been tested to treat superficial bladder tumors, the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has been the most widely used with an end-fire, noncontact fiber (143,291,308,329). In the noncontact mode, the Nd:YAG leads to a coagulative necrosis of tissue with minimal vaporization, limiting the potential for bladder wall perforation. The argon laser also has been used to treat superficial bladder tumors; however, its use is restricted by the low energy output of available surgical fibers, which provides a limited depth of penetration. The KTP laser also demonstrates a lesser degree of penetration than the Nd:YAG. The holmium:YAG laser provides an increased cutting and vaporization ability due to the increased absorption by water. This serves to limit its depth of penetration and may decrease its hemostatic properties. The CO_2 laser, with its longer wavelength, is strongly absorbed by water and currently is not of practical use for endoscopic treatments.

Several advantages in favor of the laser over standard electrocautery resection have been reported and include the coagulation effects of the laser, which lead to minimized bleeding during the procedure and postoperatively. This may therefore limit the need for posttreatment catheter placement. Because no electrical energy is delivered to the bladder, obturator nerve stimulation does not occur with laser use and the stimulation of pain fibers is minimized, potentially decreasing the anesthetic requirements for this procedure. An additional use of the lasers includes the ability to deliver light energy during photodynamic therapy. Another theoretic advantage is the decreased manipulation of the bladder tumor, which may limit the number of cells dislodged and minimize the risk of implantation recurrences. Although theoretically beneficial, implantation of tumor cells at the time of resection is thought to represent only one possible mechanism for disease recurrence. Current information suggests that overall recurrence rates following laser ablation of superficial tumors is not superior to transurethral resection, whereas local recurrence rates are similar to those observed following transurethral resection (25,325).

Disadvantages limiting the use of the laser for the treatment of superficial disease include the risk of perforation of adjacent viscera, particularly the small intestine following absorption of forward scatter of the laser energy. Bowel perforation may occur in the absence of symptoms of a bladder perforation or urinary extravasation. A negative cystogram does not necessarily exclude injury to the bowel. Following laser injury, peritonitis typically develops within 24 hours and requires laparotomy and resection of the injured segment. Additional disadvantages include the loss of valuable staging information because no histologic material is retrieved for pathologic evaluation, and the increased cost associated with equipment and training.

Intravesical Therapies

The well-documented failure of endoscopic resection alone to provide long-term disease control, and the availability of well-recognized, high-risk tumor characteristics, has provided the basis for the development of intravesical treatments. The low absorptive capacity of the bladder, relatively noninvasive access to the bladder lumen, and ability to avoid systemic exposure with intravesical instillation of therapeutic agents has made this a favored approach in the treatment of superficial bladder cancer. Intravesical treatment has the advantage of accessing the entire bladder mucosa, treating multifocal areas of dysplasia or CIS. It provides a means to place the therapeutic agent and the dysplastic or neoplastic cell into direct contact, an absolute requirement for most intravesical agents.

Established roles for intravesical therapy in the management of superficial bladder cancer includes treatment of residual, unresected disease (therapeutic); prevention of subsequent recurrences and tumor progression (prophylaxis); and prevention of tumor implantation perioperatively (adjuvant). The most common indication for intravesical treatment for high-risk patients involves instillations to prevent recurrences following complete endoscopic resection in hopes of eliminating or at least delaying the need for more aggressive therapy. Multiple instillations, delivered at varying dosing schedules, are typically used with or without long-term maintenance therapy, which may continue for

several years. Although so-called field changes consisting of genetic alterations to large areas of the mucosa are largely thought to be responsible for the predisposition to develop subsequent tumors, another proposed mechanism responsible for the high rate of disease recurrence following transurethral resection of superficial tumors is implantation of cells that are dislodged at the time of resection (372). Several studies have demonstrated a beneficial effect of a single perioperative intravesical instillation of chemotherapy to decrease recurrence rates following TURBT (254,396). Although seeding of dislodged cells remains of potential concern, patients undergoing resection of bladder tumors and simultaneous transurethral resection of the prostate (TURP) have not demonstrated an increased risk of seeding in the field of resection within prostatic urethra.

Chemotherapy

Intravesical agents used for the treatment of superficial disease include a variety of chemotherapeutic substances thought to directly mediate tumor cell death. Randomized and nonrandomized studies have demonstrated a role for intravesical chemotherapy in the treatment of superficial bladder cancer. Dosing schedules have varied greatly, and empiric regimens remain in use. The toxicity of intravesical agents manifests as both local and systemic symptoms. Systemic effects are directly related to the extent of absorption of the agent through the bladder. Important factors that determine the absorptive characteristics of a chemotherapeutic agent primarily are related to the molecular weight of the substance. Drug concentration and pH of the intravesical solution, as well as the integrity of the bladder mucosa and drug dwell time, may also effect drug absorption and systemic toxicity. Although animal studies suggest the possibility of secondary malignancies following long-term exposure to intravesical chemotherapeutic agents (6,101,175), no documented direct carcinogenic activity of long-term (maintenance) therapy has been established in humans. Although no direct link is established, some have reported an increased incidence of secondary hematologic malignancies after intravesical treatment with triethylenethiophosphoramide (TEPA, thiotepa) or mitomycin (333). The rationale for long-term chemotherapy has also been questioned, based on the mechanism of action of current chemotherapeutic agents requiring tumor cells to be present for the drug to be effective. This would suggest however, that patients at higher risk of recurrence from multifocal disease or those with a positive cytology after complete endoscopic resection would be appropriate candidates for multiple-dose or maintenance-type protocols.

Studies have examined the efficacy of immediate postresection, single instillation and multiple postresection regimens alone, or in combination with maintenance dosing, that may continue for up to several years following initial resection. A variety of agents have demonstrated the ability to decrease short- and intermediate-term recurrences; however, most large, controlled trials have failed to confirm the ability of intravesical chemotherapy to reduce the long-term recurrence risk following surgery or report a significant decrease in the advantage afforded by such treatment with longer follow-up.

Triethylenethiophosphoramide

The use of thiotepa in the 1960s ushered in the era of intravesical chemotherapy for the treatment of bladder cancer (161). Thiotepa is an alkylating agent, whose cytotoxic effects are based on the ability of the drug to form covalent bonds with DNA, leading to cross-linking of strands and inhibition of protein synthesis. Delivered intravesically at a concentration of 1 mg/mL, the usual dose of thiotepa consists of 30 to 60 mg in sterile water. The drug is left in the bladder for a dwell time of 1 to 2 hours. Typical treatment regimens consist of 4 to 8 weekly instillations, followed by monthly treatments, which are continued for up to 1 year.

As with all chemotherapeutic agents, thiotepa can be used as treatment for residual disease, or as a prophylaxis against disease recurrence, following complete endoscopic excision of all visible disease. Studies evaluating the ability of thiotepa to treat residual, unresected superficial disease (T_a, T_1, and CIS) have reported a complete response in approximately one-third of patients (174,367). Although encouraging, many of the patients defined as complete responders had positive postresection cytologies (174), which has been reported as an ominous prognostic marker following thiotepa therapy (331). Postresection prophylactic instillations of thiotepa can be administered immediately following endoscopic resection as a single dose or as a series of postresection instillations. A single instillation of thiotepa given soon after complete TURBT was reported to demonstrate a 40% reduction in early recurrences compared with endoscopic resection alone. A similar benefit was not observed in patients with CIS (396). The most common indication for intravesical thiotepa has been as a prophylaxis to decrease recurrences and prevent disease progression after complete resection (161,174,367). Multiple instillation regimens of thiotepa used as a prophylaxis have been studied extensively (15,17,41,42,128,246,273,303,396). The National Bladder Cancer Collaborative Group studied 90 patients with superficial bladder cancer, and demonstrated a 35% decrease in early tumor recurrences in patients treated with thiotepa as a prophylaxis (273). Improved outcomes were observed mainly in patients with low-grade tumors (grade 1), whereas patients with high-grade lesions demonstrated no significant benefit. Furthermore, a high rate of disease progression was observed in patients with associated CIS, further suggesting that alternative therapies

should be considered in high-risk patients. Lamm and colleagues (190) reviewed nine controlled studies, which included 1,130 patients treated with thiotepa for prophylaxis, and combined these data to determine the long-term ability of intravesical thiotepa to reduce recurrences. A statistically significant reduction in recurrences was noted, although at 5-year or more follow-up, the overall reduction was approximately 12% in the thiotepa-treated patients compared with those treated by surgery alone. Only five of the nine studies revealed a statistically significant improvement in favor of the thiotepa-treated group, whereas two studies demonstrated a more favorable outcome in the control group. In a randomized study from the European Organization for Research and Treatment of Cancer (EORTC), thiotepa was not shown to be more effective than doxorubicin as a prophylaxis (32). In a comparative evaluation between thiotepa and *Mycobacterium bovis* bacille Calmette-Guérin (BCG), thiotepa was found to be inferior to BCG in the treatment of superficial disease (217). No evidence is available to suggest that thiotepa treatment lowers the progression rates for patients with superficial bladder cancer.

Complications of intravesical thiotepa mainly are related to systemic absorption, a function of thiotepa's small molecular weight (MW = 189 Da), which facilitates transepithelial passage. Myelosuppression is the most prominent systemic manifestation, and presents as leukopenia or thrombocytopenia. Monitoring of hematologic parameters, including platelet and leukocyte counts, is recommended for patients on thiotepa therapy. Other complications include bladder irritation from a chemical cystitis. This typically manifests as urinary frequency and dysuria. The leukemogenic potential of systemic thiotepa is documented and, although no definitive causative relationship has been established, several cases of nonlymphocytic leukemia–myelodysplastic syndrome have been reported in patients following intravesical thiotepa administration (315).

Mitomycin C

Mitomycin C (MMC) is an alkylating agent capable of binding to DNA, inhibiting its synthesis and initiating strand breakage. MMC initially was reported to be effective in the treatment of bladder cancer in 1967 (312). Using a tri-weekly instillation protocol, investigators demonstrated the ablative effects of MMC. Commonly used doses for intravesical MMC are 20 to 40 mg diluted in 20 to 40 mL of sterile water. MMC can be given as a single, postresection instillation or combined with weekly instillations for 6 to 8 weeks. Monthly or quarterly maintenance protocols have also been used for prophylaxis.

MMC instillations have demonstrated efficacy in the treatment of residual, superficial transitional cell carcinoma of the bladder, or as prophylaxis following complete resection of intermediate- or high-risk lesions. Studies using various intravesical MMC protocols have demonstrated its therapeutic efficacy at treating residual T_a or T_1 disease, with most series reporting approximately a 40% complete response rate (229,272,330). A comparative study of thiotepa and MMC for the treatment of residual disease demonstrated the superior efficacy of MMC over thiotepa (39% versus 26% complete response, respectively) (128). MMC also may be used as a second-line agent for the treatment of residual superficial disease after failed thiotepa therapy (128). The National Bladder Cancer Group reported on 117 thiotepa-refractory T_a, T_1, and T_{is} lesions, in which a 27% complete response (negative cystoscopy, cytology, and biopsy) was observed. Others have reported a 20% to 50% complete response for residual disease in patients who have failed thiotepa as first-line treatment (128,150,272,349).

The effectiveness of intravesical MMC as a prophylaxis to decrease recurrences and prevent tumor progression has been studied in a multitude of randomized and nonrandomized studies. The majority of series confirm the short-term benefit of MMC in reducing recurrences following resection by approximately 40% (33,128,146,272,330,358,380). As with other intravesical chemotherapeutic agents, the benefit decreases as the follow-up period lengthens. Tolley and associates (358) reported on a randomized Medical Research Council trial, which included 447 patients with superficial bladder cancer, to evaluate the effects of a single postresection dose or multiple postresection instillations of MMC. After a median follow-up of 7 years, a 20% sustained decrease in recurrence rate was noted in the MMC-treated groups over controls. Interestingly, no statistically significant difference was observed between patients who received a single postresection dose of MMC and those who received multiple doses. A combined analysis of six randomized studies (1,157 patients) with MMC noted an overall 9% benefit in recurrences, with only two studies demonstrating a statistically significant reduction (190). The ability of MMC to prevent tumor progression was suggested initially following a report by Huland and co-workers (146), in a low-risk group of patients receiving long-term MMC instillations following complete resection and negative pretreatment cytologies. Disease progression (stage or grade) was reported in 38% and 6% of controls and MMC-treated patients, respectively. However, multiple other studies (5,171,243,358) have failed to confirm the ability of MMC to prevent either stage or grade progression, to improve overall patient survival, or significantly decrease recurrence rates to the same degree reported by Huland and others.

Systemic complications of intravesical MMC are uncommon and related to its larger molecular weight, which leads to poor absorption. Most complications associated with MMC are local in nature and consist of irritative symptoms related to the development of a chemical cystitis. A unique skin rash consisting of a palmar desquamation also has been

reported and appears secondary to a delayed hypersensitivity reaction. Infrequent complications reported with MMC use include decreased bladder capacity and myelosuppression.

Ethoglucid

Ethoglucid (Epodyl), a derivative of podophyllin, is an alkylating agent that arrests cellular division. Dosing of ethoglucid as a prophylaxis usually consists of four weekly instillations followed by monthly treatments for up to 1 year. Treatment of residual superficial disease with ethoglucid leads to a complete response in approximately 45% of patients (286). Intravesical ethoglucid has been shown to decrease short and intermediate recurrence rates compared with endoscopic resection alone. At 3 years, a 27% improved recurrence rate was observed in the etoglucid-treated group compared with controls (181). In the same study, randomized comparison of intravesical ethoglucid with doxorubicin demonstrated a similar ability of both treatments to decrease recurrences (181).

Systemic side effects, such as myelosuppression, are less common with ethoglucid compared with thiotepa secondary to its slightly larger molecular weight (262 Da). However, local irritation consisting of a chemical cystitis has been reported more frequently with ethoglucid.

Doxorubicin

Doxorubicin hydrochloride (Adriamycin) is an anthracycline antibiotic with antitumor activity. Through its ability to intercalate between bases within the DNA, doxorubicin can inhibit DNA replication and protein synthesis. Doxorubicin has been used as an intravesical agent against superficial bladder cancer in varying doses and schedules. Doses of doxorubicin that have been used range from 30 to 80 mg, usually dissolved in saline, to deliver a final drug concentration of 1 mg/mL. Schedules have ranged from a single postresection dose delivered immediately after resection to multiple weekly doses followed by a maintenance schedule. Doxorubicin has demonstrated efficacy in the treatment of residual superficial disease. Following a weekly regimen for 16 weeks, Lundbeck and co-authors reported a complete response of 52% in 64 patients, the majority of whom had T_a, grade 2 disease (201). However, with increased follow-up, only 39% of doxorubicin-treated patients remained tumor-free at 5 years (200).

Prophylactic use of doxorubicin has been studied in trials using early versus delayed treatment (single or multiple instillations) with or without maintenance. As a single postresection dose, doxorubicin was shown to decrease by 39% short-term recurrences in patients with moderate-risk disease (multifocal, low-grade recurrent papillary tumors) (396). The benefit of early exposure to doxorubicin was further confirmed by a study of the EORTC Group (30832), which suggested that early administration of doxorubicin may be of benefit over delayed therapy in low- or intermediate-risk patients (33). The same group demonstrated that maintenance therapy with doxorubicin provides no additional long-term protection against subsequent recurrence (33). In a pooled analysis of five large, controlled studies evaluating doxorubicin as a prophylaxis, three achieved a significant decrease in recurrence rates with an overall benefit of 15% (190). Comparative studies have not demonstrated a superior effect of doxorubicin when compared with other intravesical chemotherapeutic agents including thiotepa, MMC, and epirubicin. In contrast, BCG has been shown to be a more effective intravesical agent compared with doxorubicin (169,187). Currently no evidence is available to suggest a role for doxorubicin in the prevention of disease progression for superficial disease.

Doxorubicin is a high-molecular-weight molecule (580 Da) with limited systemic absorption. Systemic complications of intravesical doxorubicin are rare, whereas local complaints are more common. Chemical cystitis is the most common adverse side effect (40%), and can lead to withdrawal of therapy and/or bladder contractures.

Epirubicin

Epirubicin (4′-epidoxorubicin), an anthracycline derivative of Adriamycin, was developed in hopes of providing a drug for intravesical use with improved cytotoxic activity and decreased systemic and local side effects. Studies have demonstrated the effectiveness of epirubicin as both a treatment and prophylaxis for superficial bladder tumors. As a treatment for residual disease, 59% of patients demonstrated an initial complete response following eight weekly instillations of epirubicin (183). Longer follow-up revealed that only half of complete responders maintained a disease-free status (182), similar to outcomes reported with Adriamycin (200). The EORTC completed a randomized trial of 399 patients with low-risk disease (solitary T_a, T_1 lesions), comparing a single, immediate postresection, 80-mg dose of epirubicin with controls (saline instillation) following complete endoscopic resection (254). After an average follow-up of approximately 2 years, a 50% reduction in tumor recurrences was observed in patients with both low- and high-risk lesions. Cystoscopy at 5 to 7 weeks after treatment demonstrated a significant early benefit in the prevention of tumor recurrences, providing additional evidence that immediate exposure to epirubicin after resection can effectively treat residual occult disease as well as possibly inhibit tumor cell implantation (254). This study also provided evidence that, in low-risk patients, a single postresection dose was as effective as longer, multiple-dose regimens. Alternative protocols using multiple instillations have confirmed the beneficial prophylactic effect of epirubicin. Comparative studies have evaluated epirubicin versus doxorubicin with contradictory results, demonstrating either an improved outcome with epirubicin (7), or no advantage (254). The overall

superiority of BCG over epirubicin in preventing recurrent disease, particularly in higher-risk patients (T_1, grade 3), has been observed (66,224).

The side effect profile of epirubicin appears improved compared with doxorubicin. Chemical cystitis in up to 10% of patients may occur and lead to cessation of therapy. Allergic skin reactions also have been reported as a rare complication. Similar to doxorubicin, epirubicin is associated with minimal systemic side effects.

Immunotherapy

The importance of the immune system as a surveillance mechanism capable of recognizing and eliminating tumor cells led to the development of strategies that centered on immune system stimulation to both augment cancer cell recognition and promote tumor cell–specific cytotoxicity. Several concepts emerged from experimental immunotherapeutic evaluations: (a) that cancer cells have the ability to evade immune system recognition as an important survival mechanism, (b) that most tumor cells can be made susceptible to immune effector cell–mediated killing following modulation of the immune system, and (c) that modulation of the immune system via supplementation *in vitro* or *in vivo* of appropriate cytokines can mimic immune stimulation leading to tumor-specific cytotoxicity.

Bacille Calmette-Guérin

Mycobacterium bovis BCG is an attenuated strain of mycobacterium developed at the Pasteur Institute by Albert Calmette and Camille Guérin. Its most common use has been as a vaccine for the prevention of tuberculosis (TB). Initial observations that the immunomodulatory effects of BCG may induce antineoplastic activity suggested a possible role in the treatment of cancer. Direct experimentation with BCG as an antineoplastic agent was initially suggested from work on leukemia (218). Although this early excitement led to its investigation as a treatment for a variety of neoplasms, poor efficacy and complications with its administration limited its acceptance.

The use of BCG in the treatment of bladder cancer was strengthened by the work of Coe and Feldman (55), who demonstrated in a pig model that the bladder was able to mount a delayed hypersensitivity-type reaction. In 1976, Morales and associates (234) reported on the results of a successful trial evaluating the prophylactic activity of intravesical BCG to prevent recurrent superficial bladder cancer. Over the next two decades, BCG emerged as the most effective intravesical treatment for superficial transitional cell carcinoma of the bladder, including CIS (50,216,217). Many of the available substrains of BCG (TICE, Frappier, Connaught, Pasteur) have demonstrated activity against superficial tumors. Standardization of treatment regimens using BCG remains controversial. Selection of the optimal strain has been difficult, because different strains have demonstrated variations in mycobacterial viability and/or titer and overall immunostimulatory activity. These variations have contributed to the inability to accurately compare reported trials. Studies on the routes of administration (intravesical, intralesional, with or without intradermal dosing) have established that intravesical exposure alone is adequate to elicit the needed immune response and provides an improved margin of safety compared with intratumoral injections (189).

In contrast to chemotherapeutic agents in which the observed cytotoxic activity typically occurs in a dose-dependent manner, immunotherapeutic substances reach a threshold response beyond which additional exposure may result in the activation of immune regulatory mechanisms that limit the effectiveness of the agent. Immune system stimulation of intravesically administered BCG occurs after binding of the mycobacterium to the bladder via an interaction with the extracellular-matrix protein, fibronectin (50). Fibronectin–BCG interaction (mediated by specific, high-affinity receptors expressed on the mycobacterium cell surface) facilitates uptake of the mycobacterium by the cellular components of the bladder (tumor, epithelial, and immune) and leads to intracellular processing of mycobacterial proteins. These are presented subsequently to immune effector cells, which initiates the production of cytokines capable of nonspecific immune system stimulation via macrophages, natural killer (NK) cells, and lymphocytes (355,397). Experiments characterizing *in vivo* BCG activity demonstrate the absolute requirement for an intact immune system, including sufficient CD4+ and CD8+ T-cell function, so that a delayed-type hypersensitivity reaction can be generated (279). Antigen-specific CD4+ cell stimulation leads to the release of a Th_1 (cell-mediated) cytokine profile, many of which can be detected within the urine of BCG-treated patients, and may serve as a marker of antitumor activity (31). CD8+ cytotoxic T-cell and macrophage activation occurs following cytokine release and serves as the effector cells of tumor antigen–specific and nonspecific cytotoxic activity. Interaction with concomitantly administered agents or drugs that interfere with BCG binding (anticoagulants that effect fibronectin formation) or mycobacterial viability (antibiotics such as isoniazid, trimethoprim-sulfamethoxazole [TMP-SMX]) should be avoided to maximize mycobacterial-bladder interaction, immune system stimulation, and subsequent antitumor effects of intravesical BCG.

Protocols for the use of intravesical BCG have been determined empirically and the optimal regimens have yet to be determined. Differences in biologic activity (mycobacterial titer and viability) among the various available strains of BCG, as well as variations in dosing and duration of the instillation protocol, have made it difficult to establish a standardized regimen. A wait period of at least 1 week, but usually 2 to 4 weeks, after endoscopic resection before the

initiation of an induction phase (consisting of weekly instillations for 6 weeks) is common to all BCG regimens. Unlike chemotherapy, in which a beneficial response may be observed by eliminating tumor cell implantation following TURBT, immediate use of BCG will enhance systemic absorption of the mycobacterium and subsequent complications, including life-threatening sepsis. Maintenance therapy with BCG following induction treatment remains controversial. Studies have been reported that demonstrate no benefit to maintenance BCG therapy (21,145); however, the number of patients evaluated may have underpowered these studies, limiting their ability to detect a reasonable difference in recurrence. Several studies also have reported significantly improved outcomes in patients who had received maintenance instillations of BCG, albeit at the expense of additional side effects. The Southwest Oncology Group (SWOG) randomized 384 patients with CIS, T_1, or multifocal and/or recurrent T_a tumors. Following complete resection, all patients received 81 mg of Connaught BCG intravesically and 0.5 mL percutaneously weekly for 6 weeks. Upon completion, 192 were randomized to receive maintenance therapy, consisting of three weekly instillations and percutaneous treatments at 3 and 6 months and every 6 months for 3 years. A significant improvement in the time to recurrence (36 versus 77 months) was noted in the observation and maintenance groups, respectively. However, no significant benefit in overall survival was observed following maintenance BCG treatment (188).

Several clinical uses for BCG therapy in the management of superficial bladder cancer have been established, and include the eradication of CIS, T_a, or T_1 disease, and as a prophylaxis against disease recurrence and tumor progression following complete endoscopic resection. BCG has demonstrated the ability to eradicate residual superficial papillary disease (T_a/T_1) as well as CIS, but should not be used in place of definitive endoscopic resection (37,61,69,235). A complete response rate of 50% to 60% has been reported using BCG on residual T_a and T_1 lesions. BCG may be used successfully to treat superficial transitional cell carcinoma of the prostatic urethra (35,141,300). Tumor that lies outside of contact with the BCG (tumor involving the prostatic stroma or acini, as well as invasive disease into the muscle layer of the bladder wall) will not be treated effectively with intravesical BCG. Similarly, upper tract tumors also will not be treated effectively with intravesical BCG. Direct instillation of BCG into the upper portions of the collecting system can be used to manage superficial, upper tract transitional cell carcinoma, although this experience is limited (226).

Patients with CIS of the bladder are at high risk for disease progression and require either effective intravesical therapy or cystectomy to eliminate tumor progression. Although many chemotherapeutic agents exhibit activity against CIS, BCG has emerged as the most effective therapy. Overall, approximately 70% to 75% of patients with CIS experience a complete response following an initial exposure to intravesical BCG (61,69,135,137,185,187,188,191). Studies have shown that an initial induction course (six weekly instillations) of BCG will effect a complete response in 31% to 88% of patients. Of those that fail after an initial course of BCG, 39% to 58% can be treated effectively with a second course of BCG immunotherapy (49,120). The timing of the follow-up evaluation after BCG treatment may be of importance in characterizing a lesion as nonresponsive. Herr and colleagues (133) demonstrated that nearly one-third of patients with clinically detectable disease at 3 months after exposure to induction BCG subsequently will demonstrate no evidence of residual disease at 6 months with further observation only. Despite the favorable initial responses to BCG, disease ultimately will recur in many patients, and a significant number will progress in stage and grade. Nadler and associates (240) reported the long-term outcome of 104 patients who had received either one or two courses of BCG for high-risk lesions. With a median follow-up of 65 months, only 25% of patients treated with one course, and 41% of patients treated with two courses, were without disease. Of great importance was the significant number of failures that occurred after a 5-year disease-free interval. Many of the BCG failures demonstrated progressive disease, mandating that long-term follow-up be performed. The rapid recurrence of CIS following BCG treatment portends a more aggressive outcome (34) and may identify a particularly high-risk group of patients who should proceed to additional, aggressive therapy such as early cystectomy.

Extensive experience has been reported comparing the relative efficacy of intravesical chemotherapy and BCG in the treatment of superficial papillary lesions and CIS. A growing body of data now suggests the superiority of BCG as primary therapy for CIS and high-risk papillary lesions over other intravesical agents. Overall, a 20% to 25% improvement in complete responses are observed in patients treated with BCG as a prophylactic compared with patients who received intravesical chemotherapy. Furthermore, long-term evaluation of disease control appears to be maintained following BCG exposure. In contrast, the observed long-term outcomes following intravesical chemotherapy demonstrate that less than 20% of patients with CIS remain disease-free. Although many studies directly comparing MMC, thiotepa, and Adriamycin with BCG suggest a superior response with BCG (70% compared with 30%, 45%, and 40% complete response rates for thiotepa, doxorubicin, and MMC, respectively), conflicting studies have been reported. Witjes and co-workers (379) reported the long-term results of an EROTC randomized trial comparing MMC (30 mg weekly for 4 weeks, then once monthly for 5 months) and BCG (BCG RIVM 5×10^8 bacilli weekly for 6 weeks). Data on 344 patients (median

follow-up of 7.2 years) demonstrated no advantage for BCG in reducing recurrences, disease progression, or overall survival. The results of this study contrast with the SWOG study comparing MMC (only 20 mg in 20 mL) to TICE BCG (50 mg in 50 mL) given in six weekly administrations followed by monthly maintenance for 1 year. Overall, 377 patients at relatively high risk for a disease recurrence were evaluable. Early closure of the study was ordered after an interim analysis revealed a 40% recurrence in the BCG-treated patients compared with a 57% recurrence in the MMC-treated group (185). Lundholm and associates (202) reported an MMC and BCG randomized comparison involving 261 high-risk patients (T_{is} and T_1). At a median follow-up of 39 months, 49% of BCG patients were free of disease compared with 34% of the MMC-treated patients. Studies have also demonstrated improved activity for BCG treatment as a prophylaxis compared with Adriamycin (187,217). Lamm and co-authors (217) reported a 37% improvement in disease-free survival in patients with CIS treated with BCG compared with patients who received Adriamycin. In addition, the superiority of BCG therapy over thiotepa has been documented.

Although most studies have demonstrated the ability of BCG to decrease recurrence rates, the ability of BCG to delay or prevent tumor progression and improve overall survival remains controversial. Most studies evaluating the therapeutic outcome of BCG on superficial bladder tumors have not observed a decrease in disease progression following treatment. This may be due, in part, to a large percentage of relatively low-risk lesions included in most reported studies. Despite high rates of tumor recurrence, the well-documented low risk of progressing to invasion limits the statistic power of most studies to identify a significant difference in disease progression. However, Herr and associates (138) have reported the long-term follow-up of 86 high-risk patients with refractory T_a and T_1 disease (most with associated CIS) who were randomized to receive early intravesical BCG or observation followed by intravesical treatment at the time of failure. At 10 years, progression-free survival was significantly better in the early BCG treatment group (62%) compared with the control group (37%), more than 50% of whom received delayed BCG therapy. In addition, 10-year disease-specific survival was improved in the early BCG–treated group compared with TURBT alone (75% versus 55%, respectively).

The toxicity of BCG therapy remains a major concern when considering treatment options for superficial disease. In general, toxicity of BCG increases with the intensity of the regimen. The route of administration, number of injections, and dose of mycobacterial organisms used affect the type and extent of adverse reactions. Comparisons of toxicity between BCG and chemotherapy suggest a worse profile for BCG. The variability of dose and mycobacterial viability among strains and specific lots has made it difficult to identify and quantitate the toxicity differences between the various strains of BCG. Patients with lowered immune responses are at higher risk for complications from BCG exposure. Patients with active TB, immunologic deficiency syndromes (including human immunodeficiency virus [HIV] positivity), leukemias, or Hodgkin's disease should avoid BCG exposure. Similarly, pregnant patients and transplant recipients on immunosuppressive therapy are not appropriate candidates. Patients with active urinary tract infections should undergo a complete course of antibiotic therapy before BCG exposure to decrease the possibility of systemic absorption of mycobacterium and limit local complaints. Antibiotics administered for cystitis simultaneously with intravesical BCG may decrease viability of the mycobacterium and limit its efficacy.

Toxicities may be categorized as local or systemic, as well as minor and severe. Local symptoms following intravesical BCG are most common (more than 90%) and consist of irritative symptoms. These irritative symptoms are thought to be secondary to a chemical cystitis, but may represent the clinical manifestation of the desired immunostimulatory response. The lack of local symptoms following repeated BCG exposures may signify an inadequate stimulation of an immune response within the bladder. Symptoms consist of dysuria and frequency, and typically begin after the third dose and worsen with subsequent exposures. Pyridium, diphenhydramine, and anticholinergics are recommended for symptomatic relief. Hematuria (43%) may occur in combination with the cystitis and seldom is severe. Gross hematuria, when present, may be problematic and require endoscopic intervention to clear. Subsequent treatments should be postponed until the hematuria clears, to limit the possibility of increased systemic absorption and sepsis. Severe local complications including ureteral obstruction (0.3%) and contraction of the bladder (0.2%) are rare and can be self-limiting after cessation of exposure. Both require postponement of further BCG exposure and long-term anti-TB therapy. Granulomatous prostatitis is a more common local complication following intravesical BCG (0.9%). Prostate examination and prostate-specific antigen (PSA) determinations should be obtained before the initiation of therapy, because both may change following BCG exposure and simulate cancer of the gland. Most cases of granulomatous prostatitis are asymptomatic; however, acute inflammation and urinary tract obstruction may ensue, which requires treatment consisting of isoniazid and rifampin for 3 to 6 months.

BCG is delivered as a live mycobacterial solution and, although its virulence has been attenuated, under the correct circumstances it may disseminate and continue to proliferate as an established mycobacterial infection. It is thought that the dose of BCG used in intravesical protocols should include at least 10 million organisms to be efficacious, a lethal dose if given systemically. Systemic side effects of

BCG include fever, chills, influenza-like symptoms, malaise, pneumonitis, hepatitis, rash, arthralgia, renal abscess, cytopenia, and sepsis. Fevers are encountered frequently (28%) and can be accompanied by chills and malaise. Low-grade fevers (less than 38.5°C) usually are self-limiting and responsive to antipyretics and hydration. Subsequent BCG doses should be postponed until all symptoms resolve, and pretreatment with isoniazid should be given at least 1 day before BCG exposure and continued for 3 days or until symptoms resolve. Higher fevers typically resolve within 48 hours; however, they cannot be distinguished from early, progressive systemic infections. Patients with high fevers that do not resolve within 12 hours should be hospitalized, placed on isoniazid and rifampin with the addition of ethambutol (1,200 mg daily) if patients become critically ill, and closely observed for signs of progressive sepsis. The increased risk of subsequent severe reactions with additional exposures must be weighed carefully against the risks of bladder cancer before recommending continuation of therapy. Granulomatous hepatitis or pneumonitis have been reported in 0.7% of cases, and when they are identified, BCG therapy should be stopped and isoniazid, rifampin, and ethambutol administered for 3 to 6 months. Sepsis following intravesical BCG is the most serious complication encountered. It was reported in 0.4% of patients and can be fatal if not quickly recognized and effectively treated. Intravascular absorption of BCG through the bladder is the common finding in patients experiencing sepsis. Traumatic catheter placement at the time of BCG instillation, active cystitis, and recent endoscopic tumor resection or biopsy may facilitate intravascular absorption. It is recommended that treatment be postponed if a traumatic catheterization is suspected to have occurred before BCG administration. In addition, a minimum of 1 week, and preferably 2 to 4 weeks, should pass after endoscopic biopsy or tumor resection before BCG instillations are initiated.

The diagnosis of BCG sepsis must be made early so that treatment may begin without delay. The association of high fevers, shaking chills, hypotension, mental confusion, coagulopathy, or other signs of sepsis following BCG exposure warrant immediate hospitalization and treatment. Isoniazid, 300 mg, and rifampin, 600 mg daily, along with 1,200 mg of ethambutol daily is recommended. Corticosteroids (prednisone 40 mg per day) may be added in critically ill patients and is recommended over the use of cycloserine. Most recommend 6 months of treatment following a severe systemic complication, although others suggest that a shorter, 6-week course will suffice.

Interferons

Although BCG has proven to be an effective treatment for superficial bladder cancer, its potential for significant adverse effects and intolerance by some patients has led to the search for alternative immunotherapeutic agents. Interferons, a class of naturally occurring glycoproteins, demonstrate a myriad of *in vivo* functions including antiproliferative, immunoregulatory, antiangiogenic, and antiviral activities. The antitumor effects of interferons are thought to occur by both direct and indirect mechanisms. Interferons enhance tumor-antigen expression, which can improve immune cell function and tumor clearance. Interferons have direct antiproliferative effects on tumor cells and have been identified as potent inhibitors of endothelial cell activation, a necessary step in tumor-induced angiogenesis. Both animal studies and clinical trials have demonstrated the antitumor activity of interferons against bladder cancer cells.

The clinical efficacy of interferons for the treatment of residual superficial bladder tumors has been studied in several prospective trials. Although several routes of administration have been used, including intramuscular, intralesional, and intravesical, it appears that intravesical delivery may be most effective. As with other forms of intravesical therapy, comparing published studies of interferon therapy is problematic due to the differing doses and schedules used. Intravesical interferon therapy effects a response in treating residual papillary tumors or CIS in 0% to 67% of patients. In one of the larger multiinstitutional trials evaluating the ability of interferons to treat CIS, Glashan (109) reported a 65% overall response rate (43% complete response, 23% partial response) in patients who had received 100 million units of recombinant interferon-alfa weekly for 12 weeks followed by monthly maintenance for up to 1 year. This study demonstrated that, although interferon therapy was less effective than BCG as front-line therapy for CIS, it was able to eradicate disease in patients who had previously failed BCG therapy. Although no large studies quantitating the effectiveness of interferons on chemotherapy have been published, smaller reports document the ability of interferon therapy to salvage such patients. The results of a larger experience evaluating the ability of interferon to rescue patients with recurrent or persistent disease after BCG treatment are available. Approximately 20% of patients who are either BCG intolerant or with BCG-resistant disease will have a complete response with high-dose interferon treatment.

Several trials designed to study the ability of interferons to serve as a prophylaxis have been completed. Although long-term data are available, short-term recurrence rates of 20% to 60% have been reported. Randomized studies comparing chemotherapy and BCG with interferon treatment also have been reported. A multicenter Italian trial compared MMC with interferon alfa-2b therapy in patients with T_a or T_1 primary tumors. In 287 patients, an 11% advantage in the short-term recurrence rate was found in MMC-treated patients compared with those who received interferon. Randomized studies comparing BCG with interferon consistently have demonstrated responses in favor of

BCG treatment. In addition to second-line treatment, combination therapy that includes interferon along with either BCG or chemotherapy may be effective. Animal studies using murine models of bladder cancer have demonstrated a synergistic response when interferon is combined with an intravesical chemotherapeutic agent or BCG.

These observations are supported by mechanistic data suggesting that interferons work to enhance the immunologic response initiated following BCG exposure.

Bropirimine

Bropirimine is a small-molecular-weight, aryl pyrimidine with immunomodulatory activity. Its antitumor effects are thought to be secondary to its broad-ranging stimulation of the immune system. Bropirimine is capable of stimulating B-cell proliferation, macrophages, NK cells, and lymphokine-mediated T-cell activation, leading to increases in both humoral and cell-mediated responses. As an oral agent, bropirimine has demonstrated efficacy in treating residual superficial transitional cell carcinoma. Most reported trials have used a dosage of 3 g per day for 3 consecutive days each week for up to 1 year. Sarosdy and co-authors (298) reported the results of a phase II trial in which a 61% response rate was observed in 33 evaluable patients with CIS of the bladder. Of the 12 patients who had failed prior BCG therapy, 6 (50%) responded to bropirimine therapy. Upper tract CIS also has been reported to respond to bropirimine. Toxicities include headaches, rashes, arthralgia, and transient hepatic enzyme elevations. Despite initial promising reports, bropirimine has not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of superficial bladder cancer.

Other Immunologic Agents

Keyhole limpet hemocyanin (KLH) is a highly immunogenic protein found in the primitive mollusk, megathura crenulata. KLH serves to enhance immune system function by stimulating a nonspecific and perhaps tumor-specific (by means of cross-reacting antigens) immunologic response. KLH has been shown to decrease bladder tumor growth and prolong animal survival using the murine MBT2 model system. Patients treated with KLH demonstrate an intense inflammatory reaction not unlike the immune response observed following exposure to BCG.

Clinical trials evaluating the efficacy of KLH as a treatment for superficial bladder cancer have demonstrated response rates comparable with those seen for BCG, however with significantly less toxicity. Intravesical KLH was found to provide improved disease recurrence rates when compared with mitomycin or Epodyl. Jurincic and associates (164) reported a 39% versus 14% recurrence in 44 patients treated with MMC 20 mg monthly, or KLH 1 mg subcutaneously, then 10 mg intravesically monthly, respectively. Lamm and co-workers (186) reported a 66% overall response rate in 51 patients treated with KLH for residual disease, noting that patients with CIS responded most favorably. The particular advantage of KLH over BCG is low toxicity associated with intravesical KLH. Indeed, some studies have reported no toxicity associated with intradermal or intravesical KLH, making it a desirable alternative to BCG.

Specific mediators of the immune response also have been used directly to modulate both T- and B-cell antitumor responses. Tumor necrosis factor (TNF) has been evaluated as an intravesical agent in a small group of patients with superficial bladder cancer by the Eastern Cooperative Oncology Group. No long-term responders to TNF therapy have been reported.

Interleukin-2 (IL-2), an immunomodulator used as part of therapy for melanoma and renal cell carcinoma, has been tested as an antitumor agent against superficial bladder tumors. Both intravesical and intralesional IL-2 induced responses; however, further phase 2 trials are needed to establish its clinical efficacy and comparative activity to currently available agents.

Hematoporphyrin Derivatives

Photodynamic therapy consists of the systemic administration of a photosensitizing compound that can be activated following exposure to light of the proper wavelength. The proposed mechanisms by which photodynamic therapy exerts its cytotoxic activity include the production of oxygen singlet and superoxide radicals that produce vascular endothelial and bladder epithelial damage, tissue hypoxia, generation of a nonspecific immune reaction, and intense local inflammatory cell infiltration.

Photodynamic therapy holds promise as a treatment for superficial bladder cancer because, theoretically, it has the ability to treat the entire bladder surface with a single treatment. Prout and colleagues (274) reported that nearly half of 19 patients treated with photodynamic therapy for residual superficial disease had a complete response. Second-line treatment for BCG-refractive or BCG-resistant CIS has been another proposed application of photodynamic therapy. In a recent multicenter study, 36 patients with CIS who had received at least one prior cycle of BCG were treated with a single whole-bladder treatment of porfimer sodium and red laser light (630 nm). At the initial 3-month evaluation, 58% were free of disease; however, at 12 months only 31% remained without evidence of disease (248). The intense inflammatory reaction and subsequent hypoxia secondary to endothelial cell damage leads to a postphotodynamic therapy syndrome consisting of pain, urinary frequency, urgency, and nocturia. A severe adverse consequence of photodynamic therapy is contraction of the bladder, which has been reported in 4% to 20% of patients. Based on the lack of long-term follow-up data on patients

treated with photodynamic therapy, and that 11 of 14 patients in the aforementioned study who failed photodynamic therapy and underwent cystectomy had evidence of extravesical disease, caution must be practiced before recommendation of such therapy in this high-risk group of patients.

Radiation

For those cases of superficial bladder cancer in which transurethral resection and intravesical therapies have failed, definitive treatments such as radiation therapy or radical cystectomy have been used. Experience with radiation therapy as a definitive treatment for superficial disease has not been studied extensively. The available evidence from uncontrolled studies suggests that, overall, radiation therapy is not an effective long-term treatment for T_a disease or CIS. Although some report an initial high response for T_a lesions to radiation, nearly 90% will demonstrate a recurrence within 5 years. Careful evaluation for the presence of associated CIS should be sought in patients under consideration for radiation, because complete responses in patients with CIS are rare. The response of superficially invasive T_1 lesions is related to grade. Higher-grade lesions respond better to radiation as compared with grades 1 and 2 lesions. Some have advocated radical radiation as a treatment for T_1G_3 disease, reporting a 55% to 64% 5-year survival.

Cystectomy

The role of radical surgery in the management of superficial disease is reserved for high-risk patients who are not candidates for intravesical therapy, who have failed attempts at disease control with intravesical therapy, and who have superficial lesions not amenable to endoscopic resection alone. Failure of intravesical therapy manifests as persistent superficial disease, progressive disease with worsening grade or evidence of invasion of the muscle wall, or the development of metastatic disease. For patients with high-risk lesions (T_1, high-grade, CIS), long-term progression rates may be as high as 50% to 80%. The aggressive behavior of high-grade lesions, superficially invasive (T_1) tumors, and CIS must be considered carefully when additional intravesical agents are recommended for patients who have failed initial or second-line intravesical therapy. BCG, recognized as the most effective intravesical agent for high-risk disease, clearly delays the development of progressive disease, but has not demonstrated definitively the ability to prevent the long-term risk of progression. Although studies with shorter-term follow-up documented a decreased progression rate following BCG therapy, long-term follow-up demonstrates no difference in progression in patients treated with or without BCG following resection. Indeed, up to one-third of high-risk patients treated conservatively with BCG will die of bladder cancer if followed for more than 10 years (132).

Radical cystectomy rarely is required for managing superficial bladder cancer; however, when used in properly selected patients, it provides survival rates that are similar to age-matched controls. Freeman and co-workers (94) reported on patients with refractory superficial disease, noting that up to one-third of the high-risk patients who presented for radical cystectomy were understaged. Of the patients with upstaged lesions, 50% demonstrated evidence of extravesical extension or metastasis to the regional lymph nodes. The high rates of extravesical and metastatic disease found at the time of cystectomy in patients with high-grade T_1 tumor and CIS, who failed previous attempts at intravesical treatment, underscore the importance of prompt intervention at the earliest sign of refractory or progressive disease. The advances in continent and orthotopic lower urinary tract reconstructive options has improved patient acceptance of cystectomy and provides an improved quality of life to patients needing early radical intervention.

MANAGEMENT OF INVASIVE BLADDER CANCER

Part of "30 - CANCER OF THE BLADDER "

The successful management of invasive bladder cancer requires a careful understanding of its natural history and recognition of histologic features obtained from the initial biopsy to predict behavior and appropriately direct the use of a variety of therapeutic options available to the urologic oncologist. Histologic grade of the initial bladder cancer remains the single most important predictor of behavior for any individual bladder cancer (163,319).

The natural history of bladder cancer assumes its origin from transitional epithelium. The histologic grade is the most significant predictor of tumor invasion. In general, low-grade tumors (1 and 2) present as superficial disease confined to the mucosa. These tumors have a tendency to recur, but rarely invade, and can be managed conservatively by transurethral resection (TUR). However, high-grade tumors (3 and 4) often present with evidence of deep invasion, are often associated with adjacent or remote CIS, and are associated with an adverse prognosis regardless of presenting stage. Marshall and associates (215) illustrate the 5-year survival for patients with high-grade transitional cell carcinoma (transitional cell carcinoma) managed by segmental resection according to the presenting stage (Table 30.1). At 5 years, there is virtually no difference in survival for patients who present with high-grade tumors, despite being initially diagnosed with superficial disease. Others have reported similar results for patients with high-grade superficial tumors treated by TUR (8,24,90,131,132,151,203). The natural history of high-grade bladder cancer is to invade sequentially the lamina propria and the muscularis propria, to gain access to lymphovascular spaces, and to

invade into the perivesical fat and contiguous structures. As the depth of invasion increases, so does the incidence of metastatic disease to the pelvic lymph nodes and beyond. Important prognostic factors should be obtained at the time of initial biopsy. These include the presence or absence of invasion into the muscularis propria, an assessment of normal-appearing epithelium adjacent to and remote from the primary tumor to detect CIS, or the degree of epithelial dysplasia (8). The degree of involvement of the lamina propria significantly impacts on prognosis for tumors not showing invasion of the muscularis propria (144). Invasion deep into the lamina propria or invasion of the muscularis mucosa implies an ominous prognosis similar to those tumors invading the superficial muscularis propria (130). The presence of lymphovascular invasion also significantly impacts on prognosis. Molecular markers will undoubtedly be used in the future to guide management. Currently, evidence suggests that tumors with a p53 mutation or deletion (based on immunohistochemical staining) show a far greater propensity for progression than similar tumors that have a wild-type or normal p53 gene (81). Other markers such as p21, p16, and RB have been shown to adversely impact on behavior (134,341).

Survival (yr)	Actuarial Expectancy	Untreated (%) (43 Patients)	TURBT (%) (35 Patients)	Segmental Resection (%) (74 Patients)
1	98	42	86	82
2	95	18	71	68
3	93	6	54	58
4	90	6	51	53
5	88	2	51	42

TURBT, transurethral resection of a bladder tumor.
From Marshall VF, Whitemore WF. *Cancer* 1956;9:617.

TABLE 30.1. SURVIVAL FROM FIRST SYMPTOM OF PATIENTS WITH HIGH-GRADE BLADDER CANCER REGARDLESS OF STAGE

Therapeutic options for management of invasive bladder cancer range from conservative measures (endoscopic resection with or without the use of intravesical pharmacotherapy) to more aggressive procedures, ranging from segmental resection to definitive radiation therapy, or the combination of extended TUR with chemotherapy/radiotherapy, and finally, radical cystectomy. Selection of the optimal treatment requires a careful weighing of the consequences of undertreatment, as well as the therapeutic efficacy and side effects related to each form of therapy.

Perhaps the biggest dilemma confronting the urologic oncologist regarding bladder cancer is the limitation of current clinical (T) staging. For example, of the patients thought to have primary transitional cell carcinoma confined to the lamina propria (T_1), 30% will be found to have muscle-invasive disease at the time of cystectomy, and half of those patients already have extension of cancer outside the bladder (96). In general, current clinical staging with IVP, CT, MRI, and the information derived from cystoscopic evaluation and bimanual examination results in at least a 40% understaging (P>T) and a 10% overstaging (P<T) (364). These facts need to be considered carefully when advising the individual patient regarding treatment options. The ultimate goals in management should be to cure the disease and to prevent local progression and development of metastatic disease. Unlike other malignancies (such as prostate cancer), patients who fail the initial treatment of an invasive bladder cancer will likely die of their disease, usually within 3 years of presentation. Furthermore, although efforts have been made to improve treatment of metastatic bladder cancer with chemotherapy, the prognosis is generally poor, underscoring the need for definitive therapy early at the curable stage.

Herr and associates (134) reported the best 5-year survival rates for patients with muscle-invasive transitional cell carcinoma who were managed by systemic neoadjuvant chemotherapy and TUR. In a small group of highly selected patients with documented muscle invasion, 28 achieved T_0 status following TUR and methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) chemotherapy and refused definitive surgery. Of those 28 patients, 17 (61%) remained alive with an intact bladder at 10 years. Most series using TUR as primary management for high-grade, invasive bladder cancer report survival rates ranging from 20% to 45% (24,90,130,144,151,203).

Segmental resection is an attractive option for many patients and physicians, because it implies bladder preservation with surgical removal of the affected part of the bladder. In the properly selected patient, segmental resection appears to provide results that are equal to or better than those achieved by cystectomy (136,247,320). However, great caution must be exercised in recommending segmental resection in the management of high-grade, invasive bladder cancer. In fact, very few candidates are appropriate for segmental resection. In the two largest series

reporting the results of segmental resection, fewer than 5% of more than 5,400 patients who presented with a primary invasive bladder cancer were deemed appropriate candidates for this option, and there have been no substantial series reporting results in the last 20 years (320,364). The problem with segmental resection is the reality that the epithelium remote from the primary cancer is under the same carcinogenic influence that resulted in the primary cancer. The probability of recurrence or understaging the initial cancer places patients who choose segmental resection at great risk for recurrence and ultimate death from metastatic disease. Appropriate candidates for partial cystectomy are those with grade 2 muscle-invasive disease, whose primary cancer is more than 2 cm from the bladder neck with multiple selected biopsies remote from the primary tumor showing no epithelial atypia. Selected patients with small urachal mucinous adenocarcinomas may be appropriate candidates, but in general, these patients are still best managed by cystectomy with orthotopic diversion to the urethra. In highly selected male patients, prostate-sparing cystectomy with orthotopic urinary diversion to the prostatic urethra seems preferable to segmental resection (334). This provides preservation of sexual and urinary function, including ejaculatory function and fertility, while providing a better cancer operation and segmental resection with little added morbidity.

In the 1950s, radical cystectomy emerged as the standard form of therapy for patients with high-grade, invasive bladder cancer. However, the morbidity of the operation, the need for an ileal conduit for urinary diversion, and the fact that early results indicated that only approximately 50% of these patients were cured led many patients to opt for less effective alternatives or to defer cystectomy until the disease was no longer curable. During the 1960s and 1970s, in an effort to improve survival, various protocols of preoperative radiation therapy before cystectomy were attempted but failed to provide any benefit to survival (11,322,327,374,375 and 376).

For the past 30 years, the primary alternative to radical cystectomy has been definitive radiation therapy. Table 30.2 shows the best contemporary published results achieved by radiation therapy, with reported 5-year survival being less than 50% in all series, and few patients ever becoming candidates for salvage by cystectomy (70,110,152,212,310). These results are clearly inferior to those reported in cystectomy series, and places patients at significant risk for recurrence and disease progression.

Series	No. of Patients	Local Bladder Control (%)	5-yr Survival (%)
London Hospital Jenkins, et al. (152)	182	41	40
U.K. Co-op Group Shearer, et al. (310)	157	45	23
Princess Margaret Hospital Gospodarowicz, et al. (110)	121	35	40
Australia Mameghan, et al. (212)	342	45	—
Belgium Netherlands DeNeve, et al. (70)	147	35	31
USC Radical Cystectomy (1971–1999)	1,051		

TABLE 30.2. MUSCLE-INVASIVE BLADDER CANCER: BLADDER SPARING—RADIATION THERAPY ALONE

Recently, a growing interest in bladder-sparing protocols have evolved using a vigorous TUR of the primary tumor, followed by chemoradiation therapy (75,166,306,354). Results achieved by these various protocols appear in Table 30.3 . It is noteworthy that the number of patients treated in the bladder-sparing protocols are few, and despite only short-term follow-up in all series, 5-year survival remains less than 50%, with fewer than one-third of these patients maintaining a functional bladder at 5 years. Importantly, two of the five referenced groups reporting results have subsequently abandoned the bladder-sparing protocol (75,107). None of these groups have addressed the issue of toxicity or true bladder function following the chemotherapy/radiotherapy protocol. In addition, the overall treatment burden of these bladder-sparing protocols is considerable, requiring nearly 6 months of treatment with repeated cystoscopies and biopsies, and with a treatment-related mortality that equals that of radical cystectomy.

Series	No. of Patients	Free of Mets.	5-yr Survival	Native Bladder	Alive with Bladder
Palermo Seretta, et al. (306)	40	47	35	55	33
MGH Kaufman, et al. (166)	53	40	48	58	23
RTOG Tester, et al. (354)	49	33	55	74	—
Florida Given, et al. (107)	40	49	51	53	18
Innsbruck Eberle, et al. (75)	116	41	33	—	17
USC (1998) Radical Cystectomy	1,051				

TURBT, transurethral resection of a bladder tumor.

TABLE 30.3. MUSCLE-INVASIVE BLADDER CANCER: BLADDER SPARING (TURBT + CHEMOTHERAPY + RADIATION)

To reiterate, the primary goals of any treatment of high-grade, invasive bladder cancer should be (a) tumor-free survival, (b) avoidance of pelvic recurrence or metastatic bladder cancer, and (c) quality of life. The development of metastatic bladder cancer following failure of local treatment is nearly uniformly fatal with few durable complete responses from any form of systemic chemotherapy.

Clinicians at the University of Southern California (USC), have developed an aggressive surgical approach for patients with high-grade, invasive transitional cell carcinoma of the bladder, which includes an en bloc cystectomy with bilateral pelvic iliac lymph node dissection and continent urinary diversion (342). Improvement in medical, surgical, and anesthetic therapy have clearly reduced the morbidity and mortality associated with contemporary surgery. This, coupled with the evolution of continent urinary diversion, especially orthotopic lower urinary tract reconstruction to the native urethra, has now provided both male and female patients a more acceptable means to store and eliminate urine, lessening the impact of cystectomy on quality of life.

In 2001, Stein and colleagues (342) reported the results achieved in patients undergoing radical cystectomy for the management of high-grade, invasive bladder cancer. In this group of 1,054 consecutive patients, 69% were without evidence of disease with an overall survival of 62% at 5 years (Fig. 30.27) (342). Nearly all deaths from bladder cancer occurred during the first 3 years following cystectomy. After 3 years, few patients died as the result of bladder cancer. However, in all bladder-sparing protocols, patients continued to be at significant risk and to die of metastatic bladder cancer as long as the bladder remained *in situ.* The 5- and 10-year recurrence-free and overall survival reported in this study is believed to represent the gold standard for which other therapy should be compared and judged.

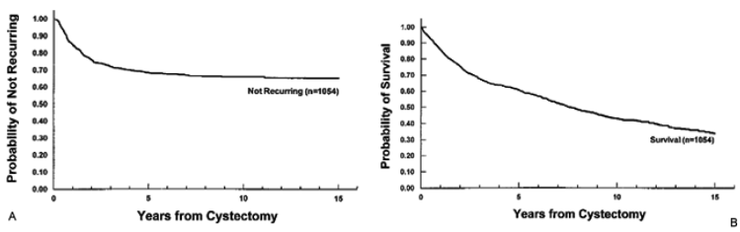

FIGURE 30.27. A: University of Southern California (USC)/Norris Bladder Cancer Experience in 1,054 patients undergoing cystectomy: probability of nonrecurrence. **B:** USC/Norris Bladder Cancer Experience in 1,054 patients undergoing cystectomy: probability of survival.

The importance of pathologic stage as it relates to recurrence-free and overall survival is shown in Fig. 30.28 (342). In addition, certain pathologic subgroups have been identified, which stratify patients into different prognostic categories that help dictate the need for adjuvant therapy following cystectomy (Fig. 30.29). The recurrence-free survival rate of 85% at 5 years is noteworthy, as is the 82% survival rate at 10 years for patients with organ-confined, lymph node–negative disease. No survival difference was observed when comparing superficially noninvasive (P_{IS},P_A), lamina propria–invasive (P_1), and muscle-invasive (P_2–P_{3A}) tumors as long as the tumor was confined to the bladder (342). Similar results for organ-confined transitional cell carcinoma treated by cystectomy have been reported by others (105,267).

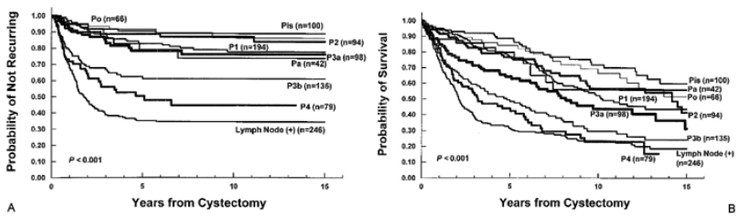

FIGURE 30.28. A: University of Southern California (USC)/Norris Bladder Cancer Experience in 1,054 patients undergoing cystectomy: probability of not recurring by pathologic stage. **B:** USC/Norris Bladder Cancer Experience in 1,054 patients undergoing cystectomy: probability of survival by pathologic stage.

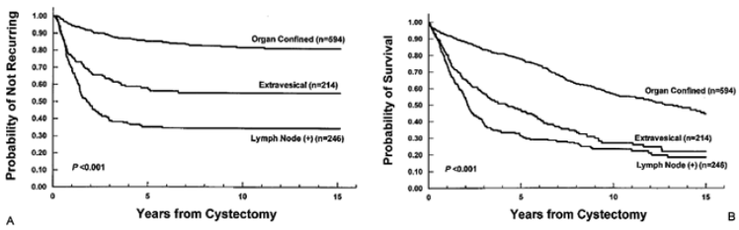

FIGURE 30.29. A: University of Southern California (USC)/Norris Bladder Cancer Experience in 1,054 patients undergoing cystectomy: probability of not recurring. **B:** USC/Norris Bladder Cancer Experience in 1,054 patients undergoing cystectomy: probability of survival according to pathologic groups.

However, once the transitional cell carcinoma escapes the confines of the bladder, prognosis changes. The 5- and 10-year recurrence-free survival for patients with P_{3B},P_4 tumors is only 59% and 56%, respectively, despite being lymph node negative (342). Those patients with extramural tumor demonstrated a significantly higher recurrence rate and worse survival compared with those with organ confined

disease. This suggests that patients with extravesical bladder tumor are at increased risk of recurrence and progression and should be considered for adjuvant forms of therapy following surgery.

Despite an early and aggressive attitude toward high-grade, invasive bladder cancer, approximately 25% of patients undergoing cystectomy for invasive bladder cancer in the USC series were found to have metastatic disease to the pelvic lymph nodes (342). This underscores the virulent and metastatic capabilities of high-grade, invasive bladder cancer. However, it has been shown that an aggressive surgical approach with en bloc pelvic iliac lymph node dissection can cure nearly 35% of these patients. The prognosis in patients with lymph node–positive disease can be further stratified by the number of involved lymph nodes and by the stage of the primary bladder cancer (P stage). It has been reported that patients with fewer than five positive lymph nodes following an appropriate pelvic lymphadenectomy at cystectomy had a 40% recurrence-free survival at 10 years, compared with 23% of patients with five or more involved nodes. The extent of the primary bladder tumor also impacts on recurrence for patients with positive lymph nodes. Patients with lymph node–positive disease, whose primary bladder cancer was organ confined (P_A–P_{3A}), had a significant recurrence-free survival advantage (45%) compared with those whose primary tumor extended outside the bladder (P_{3B}–P_4) (342). Similar observations have been reported by others (105,195,267,368). Although patients with lymph node involvement have the highest recurrence rates, a substantial number of patients who will clearly benefit from a meticulous lymph node dissection remains (267). Nonetheless, patients with lymph node involvement are at high risk for recurrence and should be considered for adjuvant treatment strategies.

Improved medical, surgical, and anesthetic techniques have dramatically decreased the mortality and morbidity of radical cystectomy. In more than 1,054 patients in Stein and associates' series (342), a 2.5% mortality rate has been

reported, which is comparable with other contemporary series of patients undergoing radical cystectomy (93,105). The reported early complication rate at 27% included all complications within the first 4 months of surgery, most of which could be appropriately managed conservatively without further sequelae. This early complication rate is similar to that reported by others (93,105,267). The addition of preoperative therapy (radiation and/or chemotherapy) or the form of diversion performed (continent versus incontinent) did not significantly alter the mortality or morbidity rate in this large group of patients (342). Strict attention to perioperative details, meticulous surgery, and a team-oriented surgical and postoperative approach are critical to minimize morbidity and mortality, and to ensure the best clinical outcomes following radical cystectomy in these patients.

Radical cystectomy provides the best local control for the treatment of high-grade, invasive bladder cancer (342). An overall local pelvic recurrence rate of 7% has been reported. Patients with organ-confined, lymph node–negative tumor demonstrate only a 4% pelvic recurrence, those with node-negative extravesical extension (P_{3B},P_4) demonstrate a 10% pelvic recurrence, and patients with lymph node–positive disease had an 11% pelvic recurrence following cystectomy (342). Currently, no other form of therapy for high-grade, invasive bladder cancer provides comparable local control.

The use of high-dose, short-course preoperative radiation therapy does not reduce the risk of pelvic recurrence regardless of pathologic stage. Local recurrence following radical cystectomy is a highly lethal problem. Few patients can be salvaged by any combination of chemotherapy and/or radiation therapy, with nearly all dying of disseminated disease within 2 years. Patients have been treated who developed local pelvic recurrence as their first site of failure following cystectomy with aggressive combination chemotherapy (MVAC). Some also received radiation therapy and further surgical resection. Only three (10%) became long-term survivors, with a median survival of 9.1 months for the entire group. Patients who failed with distant disease, and who also demonstrated local recurrence did even worse. Patients whose initial failure showed both local pelvic recurrence and distant metastatic disease with aggressive combination chemotherapy (MVAC) also have been treated. There were no long-term survivors, and the median survival was 5.7 months. There were 175 patients treated whose initial failure was outside the pelvis. Only 11 (6%) were cured by aggressive combination chemotherapy (MVAC or cisplatin, methotrexate, and vinblastine [CMV]), with a median survival of 6 months.

These data clearly underscore the lethality of a tumor recurrence following cystectomy. The dismal prognosis of tumor recurrence following cystectomy raises important considerations in the technical performance of radical cystectomy. Traditionally, the operation widely resects the neurovascular bundles leading to loss of erectile function. Some authors advocate nerve-sparing cystectomy in an effort to preserve erectile function (302). However, the best results have reported an efficacy of preserving erectile function of only approximately 35%, and the risk of increasing the incidence of pelvic recurrence remains unclear. Because the lymphatics draining the trigone and posterior bladder wall run along the neurovascular bundles, these patients are best served by radical cystectomy that widely resects the neurovascular bundles and placement of a penile prosthesis that will restore good and effective erectile function without risking increased pelvic recurrence. It also should be noted that clinical staging and preoperative predictor factors currently fail to clearly identify appropriate patients for nerve-sparing techniques.

Development of orthotopic lower urinary tract reconstruction has dramatically reduced the impact of cystectomy and the quality of life issues following removal of the bladder (77,78,343,345). Orthotopic diversion has lessened the need for a cutaneous stoma, eliminated the urostomy appliance, and limited the need for intermittent catheterization. Continence rates following orthotopic diversion are excellent, providing patients a more natural voiding pattern per urethra. Currently, more than 90% of female patients are considered candidates for orthotopic diversion with a low risk of tumor recurrence following reconstruction (343,345). It is believed that the only contraindications to orthotopic urinary diversion are the presence of tumor within the urethra or extension to the urethral margin, compromised renal function (creatinine greater than 3.0 mg/dL), or the presence of inflammatory bowel disease. Even for patients with locally advanced disease, orthotopic urinary diversion can be employed without concern about subsequent tumor-related reservoir complications (124). The option of lower urinary tract reconstruction to the urethra also has been shown to decrease physician reluctance and to increase patient acceptance to undergo early cystectomy for bladder cancer when the disease may be at a more curable stage (124). Whether patients enjoy a better quality of life following cystectomy or bladder-sparing protocols, which require significant prolonged treatment to the bladder with increased potential for tumor recurrence, remains an issue. However, the argument for bladder-sparing protocols has diminished with the availability and successful application of orthotopic urinary diversion following cystectomy.

Age is another important consideration in management options for patients with high-grade, invasive bladder cancer. It is better to provide the best therapeutic options for older patients with high-grade, invasive bladder cancer rather than temporizing or being conservative because of the age of the patient (86). In these patients, a high-grade, invasive bladder cancer is more likely to shorten the life span of elderly patients than other medical age-related problems that can occur as a result of the operation. Four hundred four patients older than 70 years of age (including 52

patients older than 80 years) who underwent radical cystectomy for the management of high-grade, invasive bladder cancer were studied and compared with 762 patients younger than 70 years of age who underwent the same operation (86). The operative mortality rate was 2% in patients younger than the age of 70, 3% in patients ages 70 to 79, and 0% for patients 80 or older. There were no differences in the early complication rate between the three groups. The median hospital stay following cystectomy was 10 days in patients younger than 70 years, compared with 11 days for those patients older than 70 years. In patients older than 70 years, 60% survived more than 3 years without tumor recurrence. Older patients are also appropriate candidates for orthotopic lower urinary tract reconstruction, although continence rates may be less than those achieved in younger patients. Results showed that a total of 85% of patients older than 70 years of age achieved good (52%) or satisfactory (33%) urinary continence. *Good* was defined as requiring no protection, and *satisfactory* was defined as requiring three or fewer pads over 24 hours. In patients younger than 70 years of age, 88% achieved a similar level of continence, but a greater number (73%) judged their continence as good and 15% as satisfactory (78). These findings support the notion that it is better to treat older patients according to their physiologic age rather than chronologic age, and high-grade, invasive bladder cancer remains a lethal disease in patients of all ages.

Perhaps the greatest advantage to radical cystectomy over any other form of therapy is the fact that it pathologically stages the primary bladder cancer and regional lymph nodes. This histologic evaluation provides important prognostic information and, together with the development of molecular markers, helps identify high-risk patients who could benefit from adjuvant therapy (341). Patients with extravesical tumor extension, or with lymph node–positive disease, are at high risk for recurrence and should be considered for adjuvant treatment strategies. In addition, recent information regarding molecular markers such as genes p53, p21, and RB provides additional information that may help identify patients who will truly benefit from certain chemotherapy drugs and indicate those patients who will not benefit from these drugs and can be spared the toxicity (341).

EN BLOC RADICAL CYSTECTOMY AND PELVIC–ILIAC LYMPHADENECTOMY

Part of "30 - CANCER OF THE BLADDER "

Surgical Technique in Male and Female Patients

Preoperative Preparation

Patients undergoing radical cystectomy are admitted the morning before surgery for a mechanical and antibacterial bowel preparation and IV hydration and to be evaluated and counseled by the enterostomal therapy nurse. A clear-liquid diet may be consumed until midnight, at which time the patient takes nothing by mouth. A standard modified Nichols bowel preparation (242) is initiated the morning of admission: 120 mL of Neoloid orally at 9:00 AM; 1 g of neomycin orally at 10:00 AM, 11:00 AM, 12:00 PM, 1:00 PM, 4:00 PM, 8:00 PM, and 12:00 AM; and 1 g of erythromycin base orally at 12:00 PM, 4:00 PM, 8:00 PM, and 12:00 AM. This regimen is well-tolerated, obviates the need for enemas, and maintains nutritional and hydrational support. IV crystalloid-fluid hydration is begun the evening before surgery, and maintained to ensure an adequate circulating volume as the patient enters the operating room.

Patients older than 50 years of age routinely undergo prophylactic digitalization before cystectomy unless there is a specific contraindication. Digoxin is given orally, with dosages of 0.5 mg at 12:00 PM, 0.25 mg at 4:00 PM, and 0.125 mg at 8:00 PM. Evidence suggests that preoperative digitalization may decrease the risk of perioperative arrhythmias and congestive heart failure in the elderly patient undergoing an extensive operative procedure (40,264). In addition, IV broad-spectrum antibiotics are administered en route to the operating room, providing adequate tissue and circulating levels at the time of incision.

Preoperative evaluation and counseling by the enterostomal therapy nurse is a critical component to the successful care of all patients undergoing cystectomy and urinary diversion. Currently, approximately 90% of male and female patients requiring cystectomy for bladder cancer are appropriate candidates for orthotopic diversion (77,339). Patients considered to be appropriate candidates for orthotopic reconstruction are instructed how to catheterize per urethra, should it be necessary postoperatively. All patients are site marked for a cutaneous stoma, instructed in the care of a cutaneous diversion (continent or incontinent form), and instructed in proper catheterization techniques should medical or technical factors preclude orthotopic reconstruction. The ideal cutaneous stoma site is determined only after the patient is examined in the supine, sitting, and standing positions. Proper stoma-site selection is important to patient acceptance and to the technical success of urinary tract reconstruction should a cutaneous form of diversion be necessary. In general, incontinent stoma sites are best located higher on the abdominal wall, whereas stoma sites for continent diversions can be positioned lower on the abdomen (hidden below the belt line), because they do not require an external collecting device. The clinicians at USC also have found the umbilicus to be an excellent site. This cutaneous site allows for easy catheterization and the stoma, if properly placed at the base of the umbilicus, is completely camouflaged and nonvisible.

Patient Positioning

The patient is placed in the hyperextended supine position with the iliac crest located just below the fulcrum of the operating table (Fig. 30.30). The legs are slightly abducted

so that the heels are positioned near the corners of the foot of the table. In the female patient considering orthotopic diversion, the modified frogleg position is used, allowing access to the vagina. Care should be taken to ensure that all pressure points are well padded. Reverse Trendelenburg position levels the abdomen parallel with the floor and helps keep the small bowel contents in the epigastrium. A nasogastric tube is placed, and the patient is prepped from nipples to midthigh. In the female patient, the vagina is fully prepped. After the patient is draped, a 20-Fr Foley catheter is placed in the bladder, and left open to gravity. A right-handed surgeon stands at the patient's left side of the operating table.

FIGURE 30.30. Proper patient positioning for cystectomy. Note that the iliac crest is located at the break of the table. (From Skinner DG, Lieskovsky G. *Diagnosis and management of genitourinary cancer.* Philadelphia: WB Saunders, 1988, with permission.)

Incision

A vertical midline incision is made extending from the pubic symphysis to the cephalad aspect of the epigastrium. The incision should be carried lateral to the umbilicus on the contralateral side of the marked cutaneous stoma site. The anterior rectus fascia is incised, the rectus muscles are retracted laterally, and the posterior rectus sheath and peritoneum are entered in the superior aspect of the incision. As the peritoneum and posterior fascia are incised inferiorly to the level of the umbilicus, the urachal remnant (median umbilical ligament) is identified, circumscribed, and removed en bloc with the cystectomy specimen (Fig. 30.31). This maneuver prevents early entry into a high-riding bladder, and ensures complete removal of all bladder remnant tissue. Care is taken to remain medial and avoid injury to the inferior epigastric vessels (lateral umbilical ligaments) that course posterior to the rectus muscles. If the patient has had a previous cystotomy or segmental cystectomy, the cystotomy tract and cutaneous incision should be circumscribed full-thickness and excised en bloc with the bladder specimen. The medial insertion of the rectus muscles attached to the pubic symphysis are slightly incised, maximizing pelvic exposure throughout the operation.

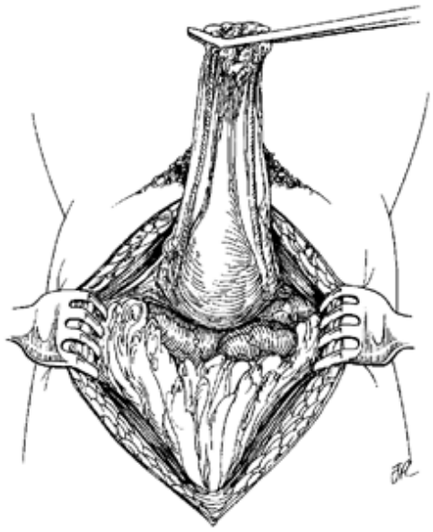

FIGURE 30.31. Wide excision of the urachal remnant en bloc with the cystectomy specimen. (From Walsh, Retik, Stamey, et al., eds. *Campbell's urology,* 6th ed. Philadelphia: WB Saunders, 1992, with permission.)

Abdominal Exploration

A careful systematic intraabdominal exploration is performed to determine the extent of disease and to evaluate for any hepatic metastases or gross retroperitoneal lymphadenopathy. The abdominal viscera are palpated to detect any concomitant unrelated disease. If no contraindication exists at this time, all adhesions should be incised and freed.

Bowel Mobilization

The bowel is mobilized starting with the right colon. A large right-angle Richardson retractor elevates the right abdominal wall. The cecum and ascending colon are reflected medially to allow incision of the lateral peritoneal reflection along the avascular/white line of Toldt. The mesentery to the small bowel is then mobilized off its retroperitoneal attachments cephalad (toward the ligament of Treitz) until the retroperitoneal portion of the duodenum is exposed. Combined sharp and blunt dissection facilitates mobilization of this mesentery along a characteristic avascular fibroareolar plane. Conceptually, the mobilized mesentery forms an inverted right triangle; the base is formed by the third and fourth portions of the duodenum, the right edge is represented by the white line of Toldt along the ascending colon, the left edge is represented by the medial portion of the sigmoid and descending colonic mesentery, and the apex is represented by the ileocecal region (Fig. 30.32). This mobilization is critical in setting up the operative field, and facilitates proper packing of the intraabdominal contents into the epigastrium.

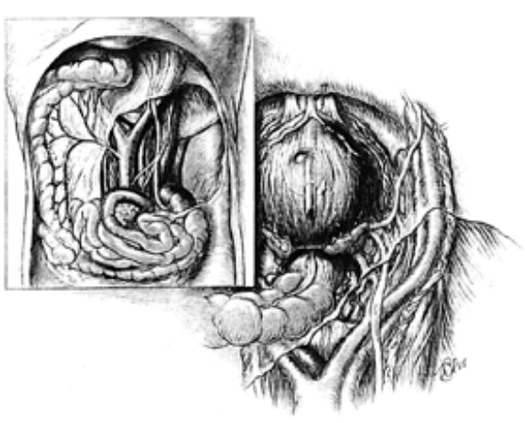

FIGURE 30.32. View of the pelvis from overhead, after the ascending colon and peritoneal attachments of the small bowel mesentery have been mobilized up to the level of the duodenum. This mobilization allows the bowel to be properly packed in the epigastrium and exposes the area of the aortic bifurcation, which is the starting point of the lymph node dissection.

The left colon and sigmoid mesentery are then mobilized to the region of the lower pole of the left kidney by incising the peritoneum lateral to the colon along the avascular/white line of Toldt. The sigmoid mesentery is then elevated off the sacrum, iliac vessels, and distal aorta cephalad to the origin of the inferior mesenteric artery. This maneuver provides a mesenteric window through which the left ureter will pass (without angulation or tension) and for the ureteroenteric

anastomosis to the urinary reservoir at the terminal portions of the operation, and it also facilitates retraction of the sigmoid mesentery while performing the lymph node dissection (Fig. 30.33). Care should be taken to dissect along the base of the mesentery, which prevents injury to the inferior mesenteric artery and blood supply to the sigmoid colon.

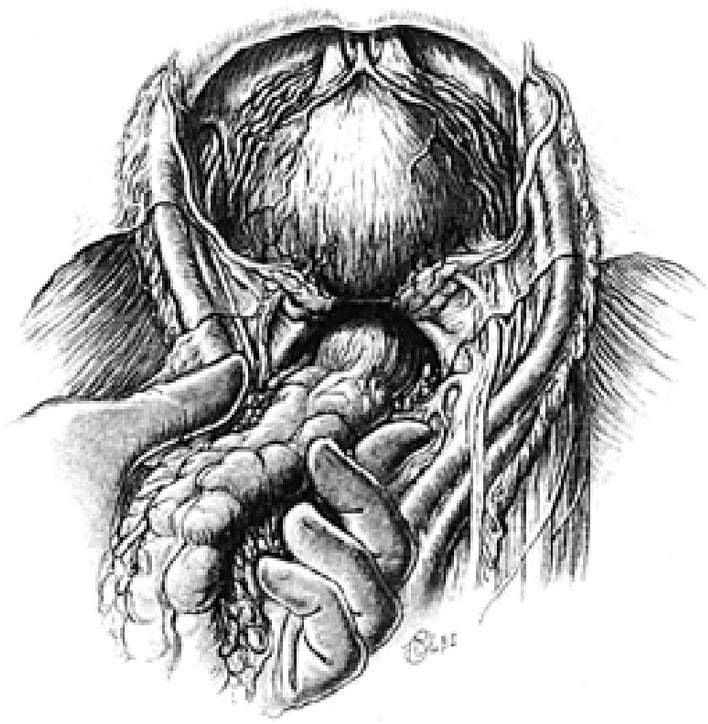

FIGURE 30.33. View of the pelvis from overhead, after the ascending colon and small bowel have been packed in the epigastrium. Note that the sigmoid mesentery is mobilized off the sacral promontory and distal aorta up to the origin of the inferior mesenteric artery.

Following mobilization of the bowel, a self-retaining retractor is placed (these authors prefer a Finochietto retractor). The right colon and small intestine are carefully packed into the epigastrium with three moist lap pads, followed by a moistened towel rolled to the width of the abdomen. The descending and sigmoid colon are not packed, and are left as free as possible, providing the necessary mobility required for the ureteral and pelvic lymph node dissection.

Successful packing of the intestinal contents is an art and prevents their annoying spillage into the operative field. Packing begins by sweeping the right colon and small bowel under the surgeon's left hand along the right sidewall gutter. A moist, open lap pad is then swept with the right hand along the palm of the left hand, under the viscera along the retroperitoneum and sidewall gutter. In similar fashion, the left sidewall gutter is packed, ensuring that the descending or sigmoid colon are not incorporated. The central portion of the small bowel is packed with a third lap pad. A moist, rolled towel is then positioned horizontally below the lap pads, but cephalad to the bifurcation of the aorta. Occasionally, before placement of the first moist lap pad, a mobile, greater omental apron can be used to facilitate packing of the intestinal viscera in a similar fashion to the lap pad. After the bowel has been packed, a wide Deaver retractor is placed with gentle traction on the rolled towel to provide cephalad exposure.

Ureteral Dissection

The ureters are identified most easily in the retroperitoneum just cephalad to the common iliac vessels. They are dissected into the deep pelvis (several centimeters beyond the iliac vessels) and divided between two large hemoclips. A section of the proximal cut ureteral segment (distal to the proximal hemoclip) is then sent for frozen section analysis to ensure the absence of CIS or overt tumor. The ureter is then mobilized cephalad and tucked under the rolled towel to prevent inadvertent injury. Frequently, an arterial branch from the common iliac artery or the aorta needs to be divided to provide adequate ureteral mobilization. In addition, the rich vascular supply emanating from the gonadal vessels should remain intact and undisturbed. These attachments are an important blood supply to the ureter that ensure an adequate vascular supply for the ureteroenteric anastomosis at the time of diversion. This is particularly important in irradiated patients. Leaving the proximal hemoclip on the divided ureter during the exenteration allows for hydrostatic ureteral dilation, and facilitates the ureteroenteric anastomosis.

Pelvic Lymphadenectomy

A meticulous pelvic lymph node dissection is routinely performed en bloc with radical cystectomy. When performing a salvage procedure following definitive radiation treatment (greater then 5,000 rads), a pelvic lymphadenectomy usually is not performed because of the significant risk of iliac vessel and obturator nerve injury.

Generally, the lymph node dissection is initiated 2 cm above the aortic bifurcation (superior limits of dissection), and extends laterally over the inferior vena cava to the

genitofemoral nerve, representing the lateral limits of dissection. The cephalad portion of the lymphatics are ligated with hemoclips to prevent lymphatic leak, whereas the caudal (specimen) side is ligated only when a blood vessel is encountered. Frequently, small anterior tributary veins originate from the vena cava just above the bifurcation, which should be clipped and divided. In men, the spermatic vessels are retracted laterally and spared. However, in women the infundibulopelvic ligament along with the corresponding ovarian vessels are ligated and divided at the pelvic brim.

All fibroareolar and lymphatic tissue are dissected caudally off the aorta, vena cava, and common iliac vessels over the sacral promontory into the deep pelvis. The initial dissection along the common iliac vessels is performed over the arteries, skeletonizing them. As the common iliac veins are dissected medially, care is taken to control small arterial and venous branches coursing along the anterior surface of the sacrum. Electrocautery is helpful at this location, which allows the adherent fibroareolar tissue to be swept off the sacral promontory down into the deep pelvis with the use of a small gauze sponge. Significant bleeding from these presacral vessels can occur if not properly controlled. Hemoclips are discouraged in this location because they can be dislodged easily from the anterior surface of the sacrum, resulting in troublesome bleeding.

Once the proximal portion of the lymph node dissection is completed, a finger is passed from the proximal aspect of dissection under the pelvic peritoneum (anterior to the iliac vessels), distally toward the femoral canal. The opposite hand can be used to strip the peritoneum from the undersurface of the transversalis fascia, and connects with the proximal dissection from above. This maneuver elevates the peritoneum and helps define the lateral limit of peritoneum to be incised and removed with the specimen. In male patients, the peritoneum is divided medial to the spermatic vessels, and lateral to the infundibulopelvic ligament in female patients. The only structure encountered is the vas deferens in the male, or round ligament in the female; these structures are clipped and divided.

A large, right-angled rake retractor (Israel) is used to elevate the lower abdominal wall, including the spermatic cord or remnant of the round ligament, to provide distal exposure in the area of the femoral canal. Tension on the retractor is directed vertically toward the ceiling, with care taken to avoid injury to the inferior epigastric vessels. This provides excellent exposure to the distal external iliac vessels. The distal limits of the dissection are then identified: the circumflex iliac vein crossing anterior to the external iliac artery distally, the genitofemoral nerve laterally, and Cooper's ligament medially. The lymphatics draining the ipsilateral leg, particularly medial to the external iliac vein, are carefully clipped and divided to prevent lymphatic leakage. This includes the lymph node of Cloquet (also known as *Rosenmuller*), which represents the distal limit of the lymphatic dissection at this location. The distal external iliac artery and vein are then circumferentially dissected and skeletonized, with care taken to ligate an accessory obturator vein (present in 40% of patients) originating from the inferomedial aspect of the external iliac vein.

Following completion of the distal limits of dissection, the proximal and distal dissections are joined. The proximal external iliac artery and vein are skeletonized circumferentially to the origin of the hypogastric artery (Fig. 30.34). Care should be taken to clip and divide a commonly encountered vessel arising from the lateral aspect of the proximal external iliac vessels coursing to the psoas muscle. The external iliac vessels are then retracted medially, and the fascia overlying the psoas muscle is incised medial to the genitofemoral nerve. On the left side, branches of the genitofemoral nerve often pursue a more medial course and may be intimately related to the iliac vessels, in which case they are excised.

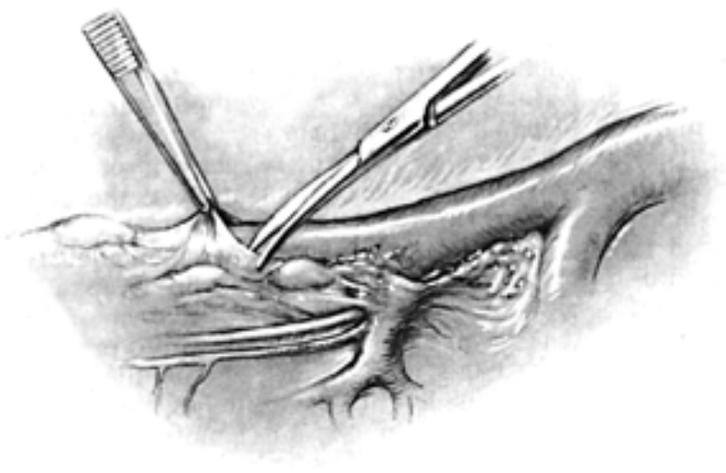

FIGURE 30.34. Technique of skeletonizing the external iliac artery and vein.

At this point, the lymphatic tissues surrounding the iliac vessels are composed of a medial and lateral component attached only at the base within the obturator fossa. The lateral lymphatic compartment (freed medially from the vessels and laterally from the psoas) is bluntly swept into the obturator fossa by retracting the iliac vessels medially, and passing a small gauze sponge lateral to the vessels along the psoas and pelvic sidewall (Fig. 30.35). This sponge should be passed anterior and distal to the hypogastric vein, directed caudally into the obturator fossa. The external iliac vessels are then elevated and retracted laterally while the gauze sponge is carefully withdrawn from the obturator fossa with gentle traction using the left hand (Fig. 30.36). This maneuver effectively sweeps all lymphatic tissue into the obturator fossa and facilitates identification of the obturator nerve deep to the external iliac vein. The obturator nerve is best identified proximally and carefully dissected free from all lymphatics. The obturator nerve is then retracted laterally along with the iliac vessels (Fig. 30.37). At this point, the obturator artery and vein are entrapped between the index finger laterally (medial to the obturator

nerve) and the middle finger medially of the left hand. This isolates the obturator vessels exiting the obturator canal along the pelvic floor. These vessels are then carefully clipped and divided, being sure to stay medial to the obturator nerve. The obturator lymph node packet is then swept medially toward the sidewall of the bladder, ligating small tributary vessels and lymphatics from the pelvic sidewall, and removed en bloc with the cystectomy specimen.

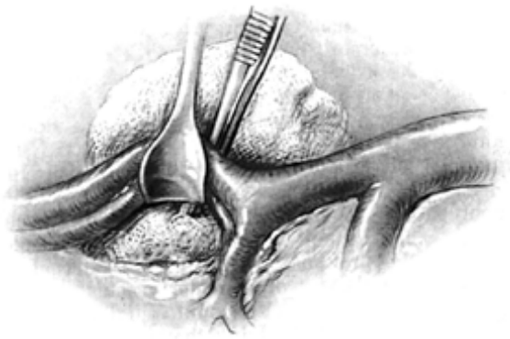

FIGURE 30.35. Technique of passing a small gauze sponge lateral to the external iliac vessels and medial to the psoas muscle.

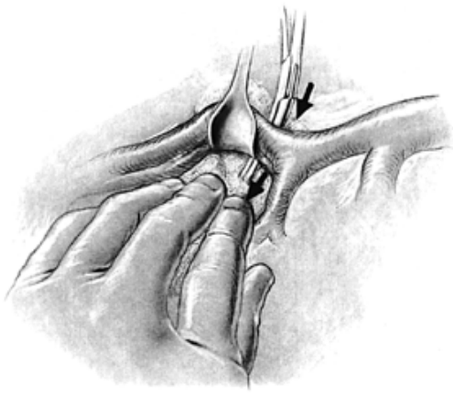

FIGURE 30.36. Technique of withdrawing the gauze sponge with the left hand. This aids in dissecting the obturator fossa, sweeping all fibroareolar and lymphatic tissue toward the bladder.

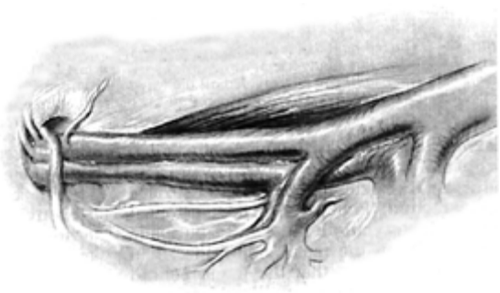

FIGURE 30.37. Obturator fossa cleaned. This allows proper identification of the obturator nerve passing deep to the external iliac vein.

Ligation of the Lateral Vascular Pedicle to the Bladder

Following dissection of the obturator fossa and dividing the obturator vessels, the lateral vascular pedicle to the bladder is isolated and divided. Developing this plane isolates the lateral vascular pedicle to the bladder, a critical maneuver in performing a safe cystectomy with proper vascular control. Isolation of the lateral vascular pedicle is performed with the left hand. The bladder is retracted toward the pelvis, placing traction on the anterior branches of the hypogastric artery. The left index finger is passed medial to the hypogastric artery, and posterior to the anterior visceral branches. The index finger is directed caudally toward the endopelvic fascia, parallel to the sweep of the sacrum. This maneuver defines the two major vascular pedicles to the anterior pelvic organs: (a) the lateral pedicle, anterior to the index finger, which is composed of the visceral branches of the anterior hypogastric vessel, and (b) the posterior pedicle, posterior to the index finger, which is composed of the visceral branches between the bladder and rectum.

With the lateral pedicle entrapped between the left index and middle fingers, firm traction is applied vertically and caudally. This facilitates skeletonization of the anterior branches off the hypogastric artery (Fig. 30.38). The posterior division of the hypogastric artery including the superogluteal, iliolumbar, and laterosacral arteries are preserved to avoid gluteal claudication. Distal to this posterior division, the hypogastric artery may be ligated for vascular control, but should not be divided, because the lateral pedicle is easier to dissect if left in continuity. The lateral pedicle is then divided between large hemoclips down to the endopelvic fascia, or as far as is technically possible. With blunt dissection the index finger of the left hand helps identify this lateral pedicle and protects the rectum as it is pushed medially. Large, right-angle hemoclip-appliers are ideally suited for proper placement of the clips. Each pair of hemoclips is positioned as far apart as possible to ensure that 0.5 to 1 cm of tissue projects beyond each clip when the pedicle is divided. This prevents the hemoclips from being dislodged, resulting in unnecessary bleeding. Occasionally, in patients with an abundance of pelvic fat, the lateral pedicle may be thick and require division into two manageable pedicles. The inferior vesicle vein serves as an excellent landmark, because the endopelvic fascia is just distal to this

structure. The endopelvic fascia just lateral to the prostate may then be incised, which helps identify the distal limit of the lateral pedicle.

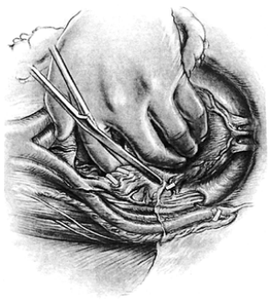

FIGURE 30.38. The left hand is used to define the right lateral pedicle, extending from the bladder to the hypogastric artery. This plane is developed by the index finger (medial) and the middle finger (lateral), exposing the anterior branches of the hypogastric artery. This vascular pedicle is clipped and divided down to the endopelvic fascia. Traction with the left hand defines the pedicle, allows direct visualization, and protects the rectum from injury.

Ligation of the Posterior Pedicle to the Bladder

Following division of the lateral pedicles, the bladder specimen is retracted anteriorly, exposing the cul-de-sac (pouch of Douglas). The surgeon elevates the bladder with a small gauze sponge under the left hand, while the assistant retracts on the peritoneum of the rectosigmoid colon in a cephalad direction. This provides excellent exposure to the recess of the cul-de-sac and places the peritoneal reflection on traction, which facilitates proper division. The peritoneum lateral to the rectum is incised and extended anteriorly across the cul-de-sac to join the incision on the contralateral side (Fig. 30.39). It should be emphasized that the anterior and posterior peritoneal reflections converge in the cul-de-sac to form Denonvilliers' fascia, which extends caudally to the urogenital diaphragm (Fig. 30.40, *large arrow*). This important anatomic boundary in the male separates the prostate and seminal vesicles anterior to the rectum posteriorly. The plane between the prostate and seminal vesicles, and the anterior sheath of Denonvilliers' fascia, will not develop easily. However, the plane between the rectum and the posterior sheath of Denonvilliers' (Denonvilliers' space) should develop easily with blunt dissection. Therefore the peritoneal incision in the cul-de-sac must be made on the rectal side rather than the bladder side (Fig. 30.40, *small arrow*). This allows proper and safe development of Denonvilliers' space between the anterior rectal wall and the posterior sheath of Denonvilliers' fascia (Fig. 30.41). Employing a posterior sweeping motion of the fingers, the rectum can be carefully swept off the seminal vesicles, prostate, and bladder in men, and off the posterior vaginal wall in women. This sweeping motion, when extended laterally, helps thin and develop the posterior pedicle, which appears like a collar emanating from the lateral aspect of the rectum. Care should be taken as this posterior plane is developed more caudally, because the anterior rectal fibers often are adherent to the specimen and can be difficult to bluntly dissect. In the region just cephalad (proximal) to the urogenital diaphragm, sharp dissection may be required to dissect the anterior rectal fibers off the apex of the prostate to prevent rectal injury at this location.

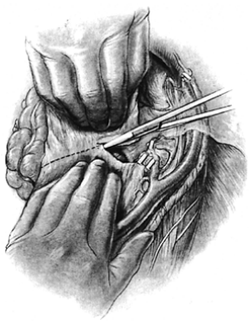

FIGURE 30.39. The peritoneum lateral to the rectum is incised down into the cul-de-sac and carried anteriorly over the rectum to join the opposite side. Note that the incision should be made precisely so the proper plane behind Denonvilliers' fascia can be developed safely.

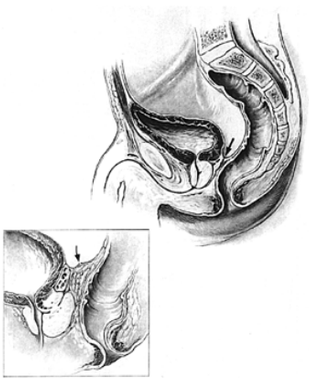

FIGURE 30.40. Illustration of the formation of Denonvilliers' fascia. Note that it is derived from a fusion of the anterior and posterior peritoneal reflections. Denonvilliers' space lies behind the fascia. To successfully enter this space and facilitate mobilization of the anterior rectal wall off Denonvilliers' fascia, the incision in the cul-de-sac is made close to the peritoneal fusion on the anterior rectal wall side, and not on the bladder side.

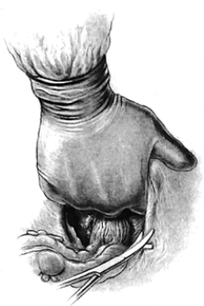

FIGURE 30.41. After the peritoneum of the cul-de-sac has been incised, the anterior rectal wall can be swept off the posterior surface of the Denonvilliers' fascia. This effectively defines the posterior pedicle that extends from the bladder to the lateral aspect of the rectum on either side.

Particular mention should be made concerning several situations that may impede the proper development of this posterior plane. Most commonly, when the incision in the cul-de-sac is made too far anteriorly, proper entry into

Denonvilliers' space is prevented. Improper entry can occur between the two layers of Denonvilliers' fascia, or even anterior to this, making the posterior dissection difficult, increasing the risk of rectal injury. Furthermore, posterior tumor infiltration or previous high-dose pelvic irradiation can obliterate this plane, making the posterior dissection difficult. To prevent injury to the rectum in these situations, dissection of this plane can be facilitated by combining an initial perineal approach from below with sharp dissection from above. If a rectotomy occurs, a two or three layer closure is recommended. A diverting proximal colostomy is not required routinely unless gross contamination occurs, or if the patient has received previous pelvic radiation therapy. If orthotopic diversion or vaginal reconstruction is planned, an omental interposition is recommended to prevent fistulization between suture lines.

Once the posterior pedicles have been defined, they are clipped and divided to the endopelvic fascia in the male patient. The endopelvic fascia is then incised adjacent to the prostate, medial to the levator ani muscles (if not done previously) to facilitate the apical dissection. In the female patient, the posterior pedicles, including the cardinal ligaments, are divided 4 to 5 cm beyond the cervix. With cephalad pressure on a previously placed vaginal sponge stick, the apex of the vagina can be identified and opened posteriorly just distal to the cervix. The vagina is then circumscribed anteriorly with the cervix attached to the cystectomy specimen. If there is concern about an adequate surgical margin at the posterior or base of the bladder, then the anterior vaginal wall should be removed en bloc with the bladder specimen, subsequently requiring vaginal reconstruction postoperatively if sexual function is desired. If orthotopic diversion is planned, some surgeons prefer to spare the anterior vaginal wall. This eliminates the need for vaginal reconstruction and helps maintain the complex musculofascial support system and prevent injury to the pudendal innervation to the rhabdosphincter proximal urethra, both important components to the continence mechanism in women. The anterior vaginal wall is then sharply dissected off the posterior bladder down to the region of the bladder neck (vesicourethral junction), which is identified by palpating the Foley catheter balloon. At this point, the specimen is attached only at the apex in men and at the vesicourethral junction in women.

Anterior Apical Dissection in the Male Patient

This technique of apical dissection in men undergoing orthotopic diversion has been modified recently, based on the excellent functional results observed in female patients undergoing the same form of diversion. These women retain their continence mechanism almost immediately following

removal of the urethral catheter, which has been attributed to the limited dissection performed anterior to the urethra along the pelvic floor. The continence mechanism in men may also be maximized if dissection in the region of the anterior urethra is minimized. This has led to a slight modification in the technique of the apical dissection in the male patient undergoing orthotopic reconstruction.

All fibroareolar connections between the anterior bladder wall, prostate, and undersurface of the pubic symphysis are divided. The superficial dorsal vein is identified, ligated, and divided. With tension placed posteriorly on the prostate, the puboprostatic ligaments are identified and divided just beneath the pubis and lateral to the dorsal venous complex, which courses in between these ligaments. Following transection of the puboprostatic ligaments, the levator muscle fibers are mobilized laterally off the prostate. The apex of the prostate and membranous urethra now becomes palpable. Several methods can be performed to properly control the dorsal venous plexus. An angled clamp may be passed beneath the dorsal vein complex, anterior to the urethra. The venous complex can then be ligated with a 2-0 absorbable suture, and divided close to the apex of the prostate. If any bleeding occurs from the transected venous complex, it should be oversewn with an absorbable (2-0 polyglycolic acid) suture. In a slightly different fashion, the dorsal venous complex may be gathered at the apex of the prostate with a long Allis clamp and a figure-of-eight 2-0 absorbable suture placed under direct vision anterior to the urethra around the venous complex. This maneuver avoids passage of any instruments between the dorsal venous complex and rhabdosphincter, which could potentially injure these structures and compromise the continence mechanism. After the complex has been ligated, it can be sharply divided with excellent exposure to the anterior surface of the urethra, which is now visible. The urethra is then incised just beyond the apex of the prostate, and a series of 2-0 polyglycolic acid sutures are placed in the urethra circumferentially, carefully incorporating the edge of the rhabdosphincter and levator muscle laterally and rectourethralis muscle posteriorly or the caudal extent of Denonvilliers' fascia. The Foley catheter is then clamped with a curved Kocher clamp and transected distal to the specimen removed.

Alternatively, the dorsal venous complex can be sharply transected without dividing the puboprostatic ligaments or without securing vascular control. Cephalad traction on the prostate elongates the proximal and membranous urethra, and allows the urethra to be skeletonized laterally by dividing the so-called lateral pillars, which are extensions of the rhabdosphincter. The anterior two-thirds of the urethra is divided, exposing the urethral catheter. The urethral sutures are then placed under direct vision. Six equally spaced 2-0 polyglycolic acid sutures are placed into the urethral mucosa and lumen anteriorly. The rhabdosphincter, the edge of which acts as a hood overlying the dorsal vein complex, is included in these sutures if the venous complex is sharply incised. This maneuver compresses the dorsal vein complex against the urethra for hemostatic purposes. The urethral catheter is then drawn through the urethrotomy, clamped on the bladder side, and divided. Cephalad traction on the bladder side with the clamped catheter occludes the bladder neck, prevents tumor spill from the bladder, and provides exposure to the posterior urethra. Two additional sutures are placed in the posterior urethra, incorporating the rectourethralis muscle or distal Denonvilliers' fascia. The posterior urethra is then divided and the specimen is removed. The urethral sutures are tagged appropriately to identify their location and are placed under a towel until the urethroenteric anastomosis is performed. Bleeding from the dorsal vein is usually minimal at this point. If additional hemostasis is required, one or two anterior urethral sutures can be tied to stop the bleeding. Frozen section analysis of the distal urethral margin of the cystectomy specimen is then performed to exclude tumor involvement.

If a cutaneous form of urinary diversion is planned, urethral preparation is slightly modified. Once the dorsal venous complex is secured and divided, the anterior urethra is identified. With cephalad traction, the urethra is stretched above the urogenital diaphragm, a curved clamp is placed across the urethra distal to the apex of the prostate, and the urethra is divided distal to the clamp. Care must be taken to avoid rectal injury with this clamp. This is prevented by placing gentle posterior traction with the left hand or index finger on the rectum and ensuring the clamp is passed anterior. The specimen is then removed. The levator musculature can then be reapproximated along the pelvic floor to facilitate hemostasis.

Anterior Dissection in the Female

When considering orthotopic diversion in female patients undergoing cystectomy, several technical issues are critical to the procedure to maintain the continence mechanism in these women.

When developing the posterior pedicles in women, the posterior vagina is incised at the apex just distal to the cervix. This incision is carried anteriorly along the lateral and anterior vaginal wall, forming a circumferential incision. The anterolateral vaginal wall is then grasped with a curved Kocher clamp. This provides counter traction and facilitates dissection between the anterior vaginal wall and the bladder specimen. Careful dissection of the proper plane will prevent entry into the posterior bladder and also reduce the amount of bleeding in this vascular area. Development of this posterior plane and vascular pedicle is best performed sharply with the use of hemoclips, and carried just distal to the vesicourethral junction. Palpation of the Foley catheter balloon assists in identifying this region. This dissection effectively maintains a functional vagina. Furthermore, an intact anterior vaginal wall helps support the proximal urethra through a complex musculofascial support system

that extends from the anterior vagina. The vagina is then closed at the apex and, in the past, was suspended to Cooper's ligament to prevent vaginal prolapse or the development of an enterocele postoperatively. Currently, a colposacralplexy incorporating Marlex mesh, which fixates the vagina without angulation or undue tension, is being performed.

Alternatively, in the case of a deeply invasive posterior bladder tumor with concern of an adequate surgical margin, the anterior vaginal wall should be removed en bloc with the cystectomy specimen. After dividing the posterior vaginal apex, the lateral vaginal wall subsequently serves as the posterior pedicle and is divided distally. This leaves the anterior vaginal wall attached to the posterior bladder specimen. Again, the Foley catheter balloon facilitates identification of the vesicourethral junction. The surgical plane between the vesicourethral junction and the anterior vaginal wall is then developed distally at this location. A 1-cm length of proximal urethra is mobilized, and the remaining distal urethra is left intact with the anterior vaginal wall. Vaginal reconstruction by a clam-shell (horizontal) or side-to-side (vertical) technique is required. Other means of vaginal reconstruction may include a rectus myocutaneous flap, detubularized cylinder of ileum, a peritoneal flap, or an omental flap. Regardless, a well-vascularized omental pedicle graft is placed between the reconstructed vagina and neobladder, and secured to the levator ani muscles to separate the suture lines and prevent fistulization.

It is important that no dissection be performed anterior to the urethra along the pelvic floor in women considering orthotopic diversion. This prevents injury to the rhabdosphincter region and corresponding innervation, which is critical in maintaining the continence mechanism. Anatomic studies have demonstrated that the innervation to this rhabdosphincter region in women arises from branches off the pudendal nerve that course along the pelvic floor posterior to the levator muscles (56). Any dissection performed anteriorly may injure these nerves and compromise the continence status. Some reports suggest that a sympathetic nerve–sparing cystectomy is important in maintaining continence in these women. The autonomic nerves coursing along the lateral aspect of the uterus and vagina have been sacrificed routinely, and the pudendal innervation of the rhabdosphincter region has been relied upon for continence; excellent continence has been observed in women undergoing orthotopic diversion with this technique. Fluorourodynamic studies in women undergoing orthotopic diversion also have identified the rhabdosphincter region as the area that provides the continence mechanism in these women (116). It is possible that preservation of the sympathetic nerves may contribute to the high incidence of hypercontinence and urinary retention requiring continuous intermittent catheterization (124).

When the posterior dissection is completed (ensuring dissection just distal to the vesicourethral junction), a Statinski vascular clamp is placed across the bladder neck. With gentle traction, the proximal urethra is divided anteriorly, distal to the bladder neck and clamp. The anterior urethral sutures are placed as described in the male patient. The distal portion of the catheter is then drawn into the wound through the urethrotomy and divided. The Statinski vascular clamp placed across the catheter at the bladder neck prevents any tumor spill from the bladder. Gentle cephalad tract on the clamped catheter allows placement of the posterior urethral sutures. The posterior urethra is then transected and the specimen is removed. Frozen section analysis is performed on the distal urethral margin of the cystectomy specimen to exclude tumor.

If a cutaneous diversion is planned in the female patient, the posterior pedicles are developed as previously mentioned. Attention is then directed anteriorly and the pubourethral ligaments are divided. A curved clamp is placed across the urethra, and the anterior vaginal wall is opened distally and incised circumferentially around the urethral meatus. The vaginal cuff is closed as previously described and suspended to Cooper's ligament.

Following removal of the cystectomy specimen, the pelvis is irrigated with warm, sterile water. The presacral nodal tissue, previously swept off the common iliac vessels and sacral promontory into the deep pelvis, is collected and sent separately for pathologic evaluation. All nodal tissue in the presciatic notch, anterior to the sciatic nerve, is also sent for histologic analysis. Hemostasis is obtained and the pelvis is packed with a lap pad while attention is directed to the urinary diversion. The pelvis is drained by a 1-inch Penrose drain for 3 weeks and a large suction Hemovac drain for 24 hours. A gastrostomy tube 18-Fr Foley catheter is routinely placed using the Stamm technique. This provides a simple means to drain the stomach and prevents the need for an uncomfortable nasogastric tube while the postoperative ileus resolves.

MANAGEMENT OF THE URETHRA IN PATIENTS WITH BLADDER CANCER

Part of "30 - CANCER OF THE BLADDER "

Indications for Urethrectomy in the Female Patient

In the past, urethrectomy was performed routinely in all women undergoing cystectomy. However, with a better understanding of the continence mechanism in women (56), coupled with sound pathologic criteria in which to safely select appropriate female candidates for orthotopic diversion, urethrectomy is currently performed in those female patients who are not suitable candidates for an orthotopic reservoir, or who would prefer an alternative form of diversion. Currently, 90% of women undergoing cystectomy at the authors' institution undergo orthotopic diversion (339,340). The clinical and functional results in

these women undergoing orthotopic urinary diversion has been excellent.

Urethrectomy is performed at the time of cystectomy in women with a high risk for urethral tumor involvement, in those with known urethral tumor involvement, or in patients who prefer a cutaneous form of diversion. An extensive analysis of female cystectomy specimens removed for transitional cell carcinoma of the bladder demonstrated that tumor involving the bladder neck is an important risk factor for urethral tumor involvement. All cystectomy specimens with carcinoma involving the urethra had concomitant tumor involvement at the bladder neck. However, not all specimens with tumor involving the bladder neck demonstrated urethral tumor involvement. This is an important issue because, although bladder neck involvement with tumor is a risk factor for urethral tumor involvement, approximately 50% of patients with tumor at the bladder neck will have a urethra free of tumor. In this situation, the female patient may be considered an appropriate candidate for orthotopic diversion.

Intraoperative pathologic evaluation of the proximal urethra has been found to be the most critical determinant for orthotopic diversion in women (339). Intraoperative frozen section analysis of the distal cystectomy margin (proximal urethra) has been demonstrated to be an accurate and reliable method to prospectively evaluate the proximal urethra for tumor involvement. Furthermore, because of the potential risk of injuring the continence mechanism with a preoperative biopsy of the bladder neck and urethra in women, coupled with a reliable method to evaluate the proximal urethra intraoperatively, intraoperative frozen section analysis of the proximal urethra is now primarily relied upon for proper patient selection in women considering orthotopic lower urinary tract reconstruction.

Indications for Urethrectomy in the Male Patient

With the increasing familiarity and application of orthotopic diversion, the management of the urethra in the male patient undergoing cystectomy for bladder cancer is of particular importance. Urethral recurrences develop in approximately 10% of male patients following cystectomy for bladder cancer (95). The greatest risk factor for urethral recurrence is tumor involvement of the prostate in the radical cystectomy specimen, with prostatic stromal invasion more ominous than either ductal or mucosal involvement. Patients considering orthotopic diversion traditionally have undergone precystectomy screening of the prostate by means of a deep transurethral biopsy at the 5 and 7 o'clock positions adjacent to the verumontanum, which have been suggested to be the most common sites of involvement of the prostatic urethra, ducts, and stroma with transitional cell carcinoma (295,382).

Recently, the incidence of urethral recurrence in male patients undergoing a cutaneous form of diversion has been evaluated and compared with the urethral recurrence rate in men undergoing an orthotopic diversion (97). Interestingly, the estimated probability of a urethral recurrence at 5 years following cystectomy was significantly increased in male patients with a cutaneous diversion, compared with those undergoing an orthotopic diversion (10% versus 4%, respectively). Even those patients with high-risk pathology (prostate involvement) diverted by means of an orthotopic diversion had a lower probability of urethral recurrence compared with patients with similar pathology undergoing a nonorthotopic form of diversion. The 5-year risk of recurrence in these patients with prostate involvement was only 5% in the orthotopic group compared with 24% for the nonorthotopic group. Although the exact etiology is unknown, it has been suggested that the orthotopic form of diversion may provide some protective effect, perhaps by the mucus or some other secretory product of the intestine, that prevents the development of cancer in the retained urethra (65).

In summary, the current indication for urethrectomy (contraindication to orthotopic diversion) in male patients is believed to include those demonstrating CIS or overt carcinoma of the urethral margin detected on intraoperative frozen section analysis. En bloc urethrectomy is performed at the time of cystectomy in male patients with known tumor involving the urethra. A delayed urethrectomy is performed after patients have undergone a cutaneous form of urinary diversion when prostatic stromal tumor involvement was demonstrated on final pathologic examination of the cystectomy specimen. Patients with prostatic stromal involvement of tumor demonstrated in the cystectomy specimen and who underwent an orthotopic diversion are closely monitored postoperatively with urethral wash cytology for recurrence purposes. Furthermore, a preoperative biopsy of the prostate is no longer performed, because orthotopic diversion is contraindicated only in those patients with overt tumor of the urethra diagnosed on intraoperative frozen section analysis.

CHEMOTHERAPY IN THE MANAGEMENT OF ADVANCED UROTHELIAL CANCER

Part of "30 - CANCER OF THE BLADDER "

In the past 50 years, the progress in the management of advanced bladder cancer has been slow and steady. Objective response rates as high as 65% to 75% have been recorded in the past decade, in contrast to single-agent response rates of less than 10% to 15% in the first recorded series of chemotherapy for bladder cancer. Twenty years ago, sustained response to chemotherapy for metastatic bladder cancer was so uncommon that it allowed reporting only of isolated cases of prolonged survival. Over this period, median survival figures initially increased from 3 to

4 months to 12 months (with the introduction of the MVAC regimen) (197,278) and more recently have been as long as 18 to 20 months, with long-term survival of 20% to 30%, depending on the characteristics of the patients receiving treatment.

Although only 20% of incident cases of bladder cancer are clinically advanced at first presentation, many patients with superficial or invasive disease eventually develop recurrence or metastases, thus the management of advanced, inoperable cancer of the urinary tract is a much more common problem than suggested by the published incidence figures for advanced bladder cancer. Despite improvements in survival, more than 80% of such cases still will result in death from cancer, and more effective strategies of treatment therefore are still required.

Biology of Advanced Bladder Cancer

A biologic continuum exists between superficial and advanced bladder cancer, but little information is available regarding the specifics of the biology of advanced disease. In general, advanced disease is associated with less differentiated histology, aneuploidy, and advanced T stage of the primary tumors. Whereas loss of heterozygosity of chromosome 9 appears to be associated with the initiation of bladder carcinogenesis in superficial disease, advanced cancer appears to require the presence of aberrations of P53 in most instances, with changes mapping to chromosome 17. Similarly, aberrant expression of the epidermal growth-factor receptor (EGFR), transferrin receptor, and the Rb gene are associated with more advanced presentations or with the risk of progression to more advanced disease.

The common sites of metastasis include regional and distant lymph nodes, bone, lung, skin, and liver, and less frequently brain, meninges, vagina, and other intraabdominal sites (18,58,277). The initial presentation depends on the sites of involvement, but also may reflect the nonspecific constitutional features of advanced malignancy, such as asthenia, weight loss, malaise, and fatigue.

When planning treatment, it is important to recognize that the distribution of metastases correlates with prognosis. More prolonged survival is seen in patients with lymph node and soft tissue disease, and a substantially worse prognosis is expected in those with liver, brain, and bone metastases (103,197,299).

This issue is also of importance when attempting to set different series into context. The use of different staging technologies may contribute to different volumes or sites of cancer being included in different series (the phenomenon of stage migration) (85). For example, in the early series of the 1970s and 1980s, clinical examination and relatively crude imaging techniques led to the identification of metastatic disease of a substantially larger volume than is usually found today. Thus entry into treatment programs for metastatic bladder cancer essentially represented “high-volume” disease. By contrast, in more recent series, CT or MRI scans (with a much higher resolving power) may identify tiny metastatic deposits, which may be confirmed as being malignant by biopsy or positron emission tomography (PET). This, in turn, leads to entry into chemotherapy trials of patients with metastatic disease with a much smaller tumor burden and a concomitantly better prognosis. These factors are of real importance when attempting to assess the true benefits of novel treatment programs compared with conventional chemotherapy, and they justify the importance of using randomized trial design to achieve this (276).

There are also clear differences in the results of treatment of transitional cell carcinoma as compared with the nontransitional cell types (adenocarcinoma and squamous carcinoma) of metastatic uroepithelial cancer (197,345). The nontransitional histologies appear to be much less responsive to conventional chemotherapy. For example, in the Intergroup Trial that compared the MVAC combination chemotherapy regimen with single-agent cisplatin (see subsequent discussion), the response rate for nontransitional cell histology was less than one-third that observed for transitional cell carcinoma. Novel compounds (such as paclitaxel) also appear to give lower objective response rates for schistosomiasis-associated nontransitional cell bladder cancer than for transitional cell carcinoma (167).

If a metastatic deposit is biopsied, the most likely histology is transitional cell carcinoma, but there is considerable occult heterogeneity within the individual deposits of transitional cell cancer. This applies with respect to histology, growth kinetics, DNA content, gene expression, and markers of cytotoxic response and resistance; this may affect the outcome of chemotherapy (38,278). Furthermore, the concept that bladder cancer has a stem cell of origin is becoming increasingly respected (38), and may be an important cause of the difficulty of curing this disease. This also may explain the presence of mixed populations of transitional cell cancer and nontransitional histologies within individual metastatic deposits and even within primary tumors.

It also has become increasingly clear that specific determinants of response to chemotherapy can be identified in bladder cancer cells, including p-glycoprotein (38,263,278) and glutathione (262). Recent data have also suggested the possibility that altered expression of P53 may correlate with increased resistance to combination chemotherapy regimens such as MVAC (33). However, it has been shown previously in bladder cancer cell lines that the expression of P53 itself may be upregulated by exposure to chemotherapy. Other determinants of cytotoxic responsiveness, such as expression of thymidylate synthase and the EGFR, also may be relevant to this discussion.

Conventional Chemotherapy

Chemotherapy has been used for metastatic bladder cancer for the past 40 years. However, in the early reported studies, the reproducibly quantifiable response rates were low, and

long-term survival was uncommon (45,384). Most conventional single cytotoxics yield true objective responses in approximately 10% to 20% of cases, including complete responses in less than 5% to 10% (45,384,387).

The most rigorous assessment of response has been documented in randomized clinical trials. Thus a paradoxic decrease was seen in reported objective response rates in some series from the 1960s to the 1980s, largely as a result of the increased precision of reporting and the reduced level of observer bias in randomized studies, although this decrease was also accompanied by the availability of more effective chemotherapy regimens. Response rates also were associated with apparent improvement in overall outcomes, as measured by median and long-term survival, probably due to different case selection and stage migration, although more effective regimens may have been an important factor. Furthermore, the improved outcomes also may have reflected the improvements in supportive care or an increased willingness to treat patients aggressively.

Most randomized trials of single-agent chemotherapy have produced responses of less than 3 to 4 months, with median survival rates of approximately 6 to 8 months. The most active “standard” single agents against transitional cell carcinomas include cisplatin, methotrexate, vinblastine, MMC, and doxorubicin (45,278,384,387).

In the 1980s, combination regimens were developed in an attempt to increase response rates and duration of survival. Initially, the use of combination regimens appeared to improve response rates without a corresponding increase in survival, as reviewed in detail elsewhere (278). Typical combination regimens that increased toxicity without a significant improvement of survival compared with single-agent therapy included cyclophosphamide, doxorubicin, and cisplatin (168,360) and methotrexate and cisplatin (139).

With the development of regimens combining methotrexate, vinblastine, and cisplatin (with or without doxorubicin), higher response rates with more durable remissions were achieved (122,346). At the Memorial Sloan-Kettering Cancer Center in particular, the MVAC regimen was even shown to yield complete pathologic remissions in patients with liver and bone metastases, with long-term survival reported in more than 60% to 70% of complete responders (347).

A multicenter, randomized trial that compared single-agent cisplatin with the MVAC regimen demonstrated for the first time a survival benefit from the combination regimen (197). Cisplatin alone produced a median survival of 8 months, whereas the MVAC regimen gave a median survival of 12 months, similar to the follow-up experience from the Memorial Sloan-Kettering Cancer Center and other nonrandomized trials (Table 30.4) (196). The tail of the survival curve at 2 years confirmed the superiority of the combination regimen, but a long-term follow-up study showed that the majority of patients in both arms died within 5 years (299). However, it should be emphasized that most of the long-term survivors were in the group treated by the MVAC regimen.

Series	No. of Patients	Response CR (%)	Category Total (%)	Median Survival (mo)
Sternberg, et al. (347)	121	26	72	13.4
Tannock (276)	13	43	10.0	
Logothetis (198)	55	35	65	11.0
Bouton-Larouze (276)	67	19	57	13.0
Loehrer, et al. (197)	120	13	38	12.5
McCaffrey, et al. (220,221)	17	12	94	18

MVAC, methotrexate, vinblastine, Adriamycin, and cisplatin.

TABLE 30.4. INTERNATIONAL EXPERIENCE WITH MVAC REGIMEN AND STAGE MIGRATION[29]

Another randomized trial (198) confirmed the superiority of the MVAC regimen, in this instance compared with the combination of cyclophosphamide, Adriamycin (doxorubicin), and Platinol (cisplatin) (CAP). The superiority of MVAC was anticipated, given the lack of difference between CAP and single-agent cisplatin in earlier randomized trials discussed previously.

The MVAC regimen justifiably has been viewed as a standard of care, with several series from the 1980s producing objective response rates in the broad range of 40% to 70%, but with reproducible median survival rates of approximately 1 year (Table 30.4). However, more recent experience suggests that the median survival achieved with the MVAC regimen may have increased by as much as 50% (221), presumably due to the impact of stage migration, case selection, or changes in supportive technologies. This calls into question the definition of what constitutes “standard of care” in 2000.

NEW AGENTS FOR BLADDER CANCER

Part of "30 - CANCER OF THE BLADDER "

In the past decade, several newer cytotoxics have been shown to be active against transitional cell carcinoma, and now are being tested in combination chemotherapy trials. Several of these drugs have objective single-agent response

rates of 25% to 30% in previously untreated patients, or have demonstrable anticancer effect in patients who have previously received chemotherapy for metastatic disease. Some of the more promising innovations include ifosfamide (381), paclitaxel (290), docetaxel (220), and gemcitabine (232,265,336). Of particular interest is the apparent reduction in toxicity compared with more established agents, especially for gemcitabine, ifosfamide, and the taxanes, suggesting the possibility of incorporation into combination regimens without enhancement of toxicity.

However, some previously applied novel drugs have not fulfilled their early promise. For example, trimetrexate, mitoxantrone, and gallium have not found their way into “routine” management of advanced bladder cancer after many years of clinical trial experience, because of either lack of efficacy or unanticipated toxicity. Even the early promise of carboplatin has recently come under a cloud in view of the disappointing single-agent response rates (64) and the disappointing median survival rates of approximately 9 months achieved from the doublet of paclitaxel and carboplatin in several phase II clinical trials (281,366).

It is important to note that the paclitaxel-carboplatin regimen found its way into routine clinical practice without having been validated in any randomized trial, presumably because of reduced toxicity. This occurred despite the fact that the reported median survival (approximately 9 months) appears inferior to that found in current studies with the MVAC and ifosfamide taxol-platinum (ITP) regimens (approximately 15 to 18 months). At present, the ECOG is formally comparing the MVAC regimen against the paclitaxel-carboplatin doublet, but this issue is of great importance in illustrating the danger of future introduction of new regimens into clinical practice without validation in comparisons against established standards of practice.

A proliferation of new combination cytotoxic regimens has been developed, incorporating the taxanes and gemcitabine, in particular, with new and established agents. Phases I and II clinical trials have clearly shown anticancer activity and varying profiles of toxicity from such combinations as gemcitabine-paclitaxel-cisplatin, gemcitabine-paclitaxel-carboplatin, ifosfamide-paclitaxel-cisplatin alternating with doxorubicin-gemcitabine, and many others. To date, no regimen has been proven superior, and it must be remembered that the phenomenon of stage migration may be confounding the interpretation of these new trials.

Thus it is of real importance that novel cytotoxics be validated in well-structured clinical trials, and in particular that randomized comparisons be carried out against standard treatments. For this purpose, the MVAC regimen has been viewed as the gold standard, because it has remained the one regimen proven to yield a survival benefit in randomized trials.

However, as noted previously, what constitutes a “standard” result from the MVAC regimen in the year 2000 must be considered carefully. In past experience, as reviewed in Table 30.1, patients treated with the MVAC regimen were able to expect a median survival of approximately 12 months. However, in more recent experience from the Memorial Sloan-Kettering Cancer Center, it appears that a more realistic median survival is in the range of 16 to 18 months (220). At present, it is not clear whether this apparent increment is a result of stage migration, improved supportive care, case selection, or other factors.

Recently, the combination of ifosfamide, paclitaxel, and cisplatin has produced preliminary results with a response rate of nearly 80% and a median survival of approximately 18 months (220). Although encouraging, these data must be taken in the context of the contemporary Memorial Sloan-Kettering experience with the MVAC regimen. Thus before the ITP regimen can be accepted as a significant step forward, it must be tested against the MVAC regimen or another appropriate standard.

Several groups have demonstrated that gemcitabine can be administered effectively in combination programs with agents such as cisplatin and paclitaxel (206,233,337).

At the Annual Scientific Meeting of the American Society of Clinical Oncology (New Orleans, May 2000), the formal presentation of data from randomized trials comparing the MVAC regimen against the combination of gemcitabine-cisplatin (sponsored by the Eli Lilly Company) was presented. In this study comparing outcomes in approximately 200 cases, a statistically significant reduction in toxicity was observed, with comparable survival figures. Although the study was not designed to demonstrate equivalence, it was clear that no large difference would be observed between the two survival curves, although final confirmation of this observation will require several years of follow-up.

In addition, ECOG is currently comparing the MVAC regimen against the paclitaxel-carboplatin regimen. These phase III trials will clarify what should constitute the standard of care in the first decade of the 21st century.

CHANGING ROLES FOR CHEMOTHERAPY IN LOCALLY ADVANCED, CLINICALLY NONMETASTATIC DISEASE

Part of "30 - CANCER OF THE BLADDER "

In the past two decades, several studies have attempted to incorporate systemic chemotherapy into regimens that include definitive primary treatment, with the aim of reducing the symptoms and size of the primary tumor (thereby facilitating surgery or radiotherapy) and controlling occult systemic metastasis (278). The major approaches for combining systemic and local therapies have included the use of neoadjuvant (first-line) chemotherapy, adjuvant chemotherapy after treatment of the primary tumor, and the use of concurrent chemoradiation therapy or schedules of perioperative chemotherapy. These strategies have been reviewed in detail elsewhere. In brief, phases I and II trials

initially used single agents, such as cisplatin or methotrexate, in combination with definitive radiotherapy or surgery, and showed objective response rates of 40% to 75% in primary tumors assessed endoscopically or at cystectomy. Randomized clinical trials failed to demonstrate a survival benefit from single-agent regimens. Combination regimens, such as MVAC, were also used, confirming high response rates (301); however, nonrandomized long-term follow-up studies did not suggest the occurrence of increased cure rates.

Despite the publication of many promising phases I to II clinical trials, most randomized assessments have failed to demonstrate any survival benefit from strategies of neoadjuvant cytotoxic chemotherapy. Some years ago, a meta-analysis of the early randomized trials confirmed this observation (104). However, it should be noted that most of the trials considered for this analysis used single-agent chemotherapy.

More recently, the first reports of large trials conducted by the EORTC-MRC (Medical Research Council) Intergroup (14a) and by the Radiation Therapy Oncology Group (RTOG) (313) have shown that initial chemotherapy with the combination of cisplatin-methotrexate-vinblastine does not substantially improve long-term survival. In fact, the EORTC-MRC collaboration did demonstrate a small difference in outcome, but it should be noted that the demonstration of this difference required randomization of nearly 1,000 cases. The results of the North American Intergroup Trial, which compared neoadjuvant MVAC followed by cystectomy versus cystectomy alone, have not yet been reported. It seems unlikely that this trial will alter the evolving paradigm in view of the many other trials that have not shown a clinically important difference when neoadjuvant chemotherapy is used for invasive bladder cancer.

Another approach that has been tested extensively is the use of chemoradiation therapy, with the intention of sparing the bladder and thus improving quality of life. Pilot and phase II trials have demonstrated objective (endoscopic) response rates of 50% to 80%, with a high level of bladder sparing in the early years of follow-up, although long-term survival figures have not been truly comparable with those achieved by surgery. However, an important caveat to this statement is that the chemoradiation trials have used clinical staging, compared with surgical staging in the cystectomy series. The most promising approach tested in the phase II setting was developed by Housset and colleagues (144a), and used a complex regimen of a repeated combination of cisplatin, 5-fluorouracil, and radiation. These investigators reported a high rate of bladder preservation and impressive 5-year actuarial survival figures. This approach has also been tested by the RTOG in a nonrandomized fashion, and high initial response rates have also been demonstrated. A randomized trial is required to demonstrate the true safety of this approach. Some clinicians believe that, with the present state-of-the-art options, radical cystectomy (with or without chemotherapy) offers a more reliable means of cure, notwithstanding the aforementioned caveats of stage migration and the limitations of comparing clinically and surgically staged cases.

Apart from a single, randomized trial (conducted by the National Cancer Institute of Canada) demonstrating improved local control from the combination of cisplatin plus radiotherapy versus radiotherapy alone (62), no randomized trials have demonstrated improved overall survival from this approach. In the National Cancer Institute of Cancer trial, the survival trend was in favor of combined modality therapy, but case numbers were insufficient to achieve statistic significance. However, Shipley (313), one of the primary innovators in the field of bladder-preserving chemoradiation for bladder cancer, has argued that chemoradiation should be used to improve local control only, and that it remains for systemic chemotherapy to change overall survival. At present, most studies appear to be concentrating on improving schedules of delivery and combination of chemotherapy and radiation, rather than focusing on the important issue of whether this approach truly confers a survival benefit (275).

Strategies of adjuvant cytotoxic chemotherapy have also been tested. An early randomized trial from the USC was reported as showing a survival benefit from the use of adjuvant cyclophosphamide-doxorubicin-cisplatin (318), although the true utility of this approach has been heavily challenged on the basis of statistic and methodologic flaws. This trial continues to be the subject of interesting debate at USC. More recently, statistically underpowered randomized trials have shown improved disease-free survival from the use of adjuvant CMV or MVAC, but have not shown an overall survival benefit (98,348). The latter trial did suggest a trend in favor of an overall survival benefit, but the study, with less than 100 randomized cases, produced a result that failed to achieve statistic significance.

At present, it is most likely that survival will be improved by the use of adjuvant therapy after resection of the primary tumor. Led by investigators at the USC and Baylor College of Medicine, this hypothesis is being tested in a multicenter, randomized trial in which the molecular prognosticator, P53, determines eligibility for chemotherapy for patients with invasive bladder cancer (stages T_1 and T_2) who have negative lymph nodes after surgery and lymphadenectomy. Patients are randomized to an observation arm or to adjuvant chemotherapy with the MVAC regimen (as the more novel paclitaxel- and gemcitabine-containing regimens have not yet been tested in the context of invasive disease). This study will answer important questions regarding the use of molecular prognostication, as well as defining the true use of adjuvant chemotherapy for patients with invasive, node-negative disease.

With the availability of the various new cytotoxics discussed previously, it is likely that investigators will begin to address the role of these agents in the treatment of locally

invasive, clinically nonmetastatic disease. The reduced profile of toxicity lends itself to multimodality combination approaches, especially because this may facilitate early use after radical surgery. Caution will be required in combining the potent radiosensitizers, paclitaxel and gemcitabine, with radical radiotherapy. These authors believe that it is not appropriate to introduce regimens that have not yet been validated in the context of metastatic disease into front-line, unstructured programs of neoadjuvant or adjuvant chemotherapy. For example, it is possible that paclitaxel-carboplatin, or even gemcitabine-cisplatin, will prove to be less effective than the MVAC regimen for invasive bladder cancer, and thus could constitute ineffective adjuvant treatment for bladder cancer. Thus it will also be important in this setting to complete the appropriate clinical trials (such as the current adjuvant trial of the ECOG) before attempting to modify standards of care in the community.

Current clinical results of patients undergoing radical cystectomy provide the best survival and the lowest local recurrence rates for patients afflicted with high-grade, invasive bladder cancer (342). Orthotopic lower urinary tract reconstruction has improved quality of life for patients following cystectomy and these data provide a standard to which other treatment alternatives must be compared in the future.

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31

URINARY DIVERSIONS AND CONTINENT RESERVOIRS

Kiarash Michel

Jean B. Dekernion

K. Michel: Department of Surgery, Division of Urology, Harbor–UCLA, Torrance, CA 90509; Cedars–Sinai Medical Center, Los Angeles, CA 90048.

J.B. Dekernion: Department of Urology, UCLA School of Medicine, UCLA Medical Center, Los Angeles, CA 90095.

Contents

Radical cystectomy remains the most effective treatment for muscle-invasive or recalcitrant high-grade bladder cancer. Despite advances in chemotherapy and irradiation, no study has demonstrated their equivalence to surgery with respect to survival or locoregional tumor control. Urinary diversions are a necessary component of the modern oncologic or reconstructive urologic surgeon's armamentarium. Over the years, established urinary diversion techniques have been further refined. With improved antibiotics and better perioperative care, the morbidity rates associated with radical cystectomy and urinary diversions have been greatly reduced. Enhanced understanding of urinary, gastrointestinal, and continence physiology has led to the evolution of continent urinary diversions that more closely mimic the native bladder's function. Development of tissue regeneration techniques promises the advent of even better, more physiologic urinary diversions in the future. Today's urologic surgeon can offer myriad options to a patient faced with the need for urinary diversion. This chapter highlights the surgical techniques, caveats, and potential short- and long-term complications associated with the most common urinary diversions performed today.

The surgical techniques have been grouped into three major headings:

1. Incontinent urinary diversions
2. Continent heterotopic urinary diversions
3. Continent orthotopic urinary diversions

PATIENT SELECTION

Part of "31 - URINARY DIVERSIONS AND CONTINENT RESERVOIRS "

The most important factors in selection of the appropriate urinary diversion for a patient include the patient's informed desires, the patient's physiologic function and physical capacity, and the surgeon's familiarity and comfort with different types of urinary diversions. In general, for patients with renal or hepatic dysfunction, or short or diseased bowel, an incontinent procedure using the shortest segment of bowel is used to minimize the metabolic abnormalities associated with prolonged exposure of the bowel segment to urine and to maximize the length of remnant bowel. For patients with functional limitations, incontinent urinary diversions are similarly performed. For all other patients, the various continent and incontinent options are discussed

thoroughly. The potential social and functional implications for each procedure are highlighted. The patient's motivation and personal desires will ultimately dictate the type of urinary diversion performed. Before reconstruction, the upper urinary tract anatomy and function are assessed thoroughly with laboratory examinations and radiologic imaging. In older patients, the colon should also be evaluated before its use in reconstructive surgery.

INCONTINENT URINARY DIVERSIONS

Part of "31 - URINARY DIVERSIONS AND CONTINENT RESERVOIRS "

Cutaneous Ureterostomy

Cutaneous ureterostomy is a particularly useful method of providing urinary diversion in patients with vesical dysfunction and associated ureteral dilation. It has certain applicability as a temporary measure in infancy and childhood before definitive corrective surgery in such conditions as urethral valves, severe bladder outflow obstruction, megacystis, high-grade refluxing ureters, ureteral adynamic segments, and hypoplastic abdominal wall muscles. It can be used with a more permanent intent in situations where bowel anastomoses or reabsorption of urinary constituents by bowel mucosa must be avoided.

The only patients who are truly suitable for a permanent cutaneous ureterostomy are those with at least one grossly dilated thick-walled ureter. The acutely dilated thin-walled ureter may have poor peristaltic power and a potentially compromised vascular supply, compared to a ureter with a thickened muscularis that is generously vascularized by collaterals (94). Cutaneous stomal stenosis, which is a major problem of this technique, is also less likely.

Technique

In general, bilateral cutaneous ureterostomy should be avoided because of the requirement of two separate stoma sites with the attendant requirement of separate urinary appliances. If both ureters are dilated, a double-barreled stoma site can be used. If one ureter is dilated and the other is of normal caliber, a proximal transureteroureterostomy can be performed by spatulation of the normal-caliber ureter to the side of the dilated ureter. The recipient ureter is brought to the skin level as a single-barreled stoma. Externalized stenting should be bilateral.

A considerable length of ureter must be mobilized from the retroperitoneum to traverse the distance to the anterior abdominal wall. Sufficient attention must be directed at avoiding devascularization of the distal ureter by excessive dissection in its periadventitial vascular tissue. Following ureteral mobilization for a doubled-barreled cutaneous ureterostomy, one ureter is brought extraperitoneally to the opposite side. Both ureters are then brought through a small cruciate fascial incision to a predetermined skin site and prepared for stoma creation. The opposing walls of each ureter are spatulated approximately 2 cm, and then the incised edges are anastomosed to each other with interrupted or running absorbable sutures (Fig. 31.1A). To create a projecting ureterostomy nipple, the edges of the common lumen are then everted via a subtle “rosebudding” suture technique (skin edge to 1-cm proximal serosa to mucosal edge) with interrupted absorbable suture (Fig. 31.1B) (24).

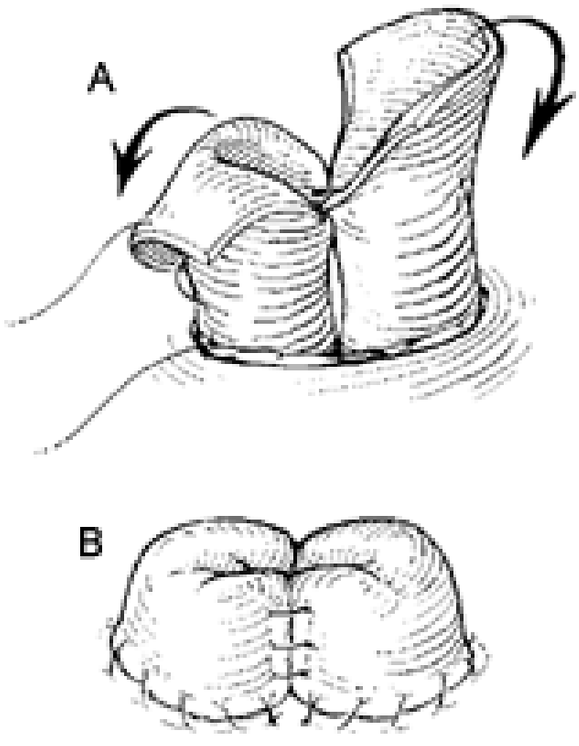

FIGURE 31.1. Double-barreled ureterostomy stoma. **A:** The medial aspects of both ureters are spatulated and joined by interrupted or running 4-0 absorbable sutures. A subtle “rosebudding” suture technique is performed. **B:** Conjoined ureteral terminus everted on itself to create a projecting ureterostomy nipple.

V-flap widening of either the double-barrel or single-lumen ureterostomy stoma may be required in situations where the degree of terminal ureteral circumference is marginal or inadequate for eversion (Fig. 31.2) (115). Similarly, V-flap technique is helpful even in cases of a

dilated single-barreled ureterostomy to ensure a sufficient stomal lumen.

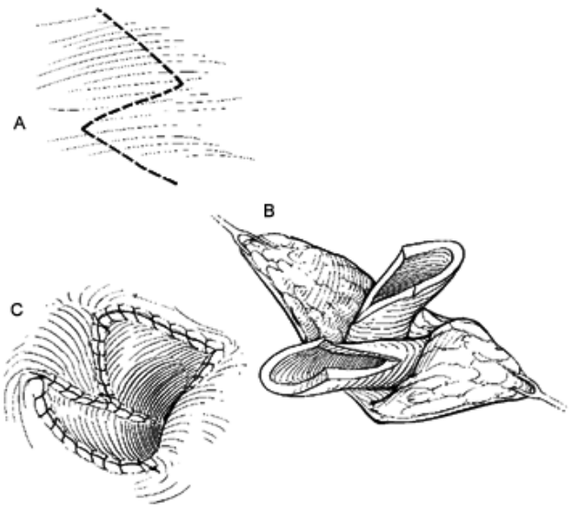

FIGURE 31.2. A-C: Double V-flap ureterostomy stoma.

If possible, the transperitoneal course of the ureters should be covered by anterior and posterior peritoneum sutured together to prevent internal bowel incarceration (115). Suction drainage is advised at the site of a transureteroureterostomy if one has been performed.

Complications and Results

The most serious early complication is necrosis of the ureterostomy stoma. This can result from compromise to the vascular supply because of excessive mobilization or rough handling, too tight an opening in the abdominal wall muscle or skin, or tight eversion of the ureter to form a stoma. There is usually insufficient ureter to resect the necrotic section and to produce an adequate stoma; therefore conversion to an enteric conduit must be performed.

Late complications include stomal stenosis and stomal retraction. Stenosis is usually due to an inadequate terminal lumen circumference, either fashioned or de novo, and may occur in as many as 50% of cases within 7 years (34). Retraction results from inadequate ureteral length initially or shrinkage subsequently. Similar to early necrosis previously described, conversion to an enteric conduit is usually necessary.

Initial results have been reasonable, more so in patients who require only temporary cutaneous ureterostomy. However, because of the high rate of stomal complications (36), the procedure is seldom appropriate for permanent diversion.

Conduits

The first to attempt diversion of the urinary stream into an isolated segment of ileum and ascending colon was probably Verhoogen in 1908 (127). Because of the prohibitive mortality rate, the technique was soon discarded, and ureterosigmoidostomy became the standard method of urinary diversion. With the development of pelvic exenteration as a therapeutic procedure for advanced pelvic malignancies, Bricker (16) was faced with the problem of "what to do with the ureters, since the sigmoid colon and rectum are not available as a receptacle." For these patients he developed a separate ureteroileocutaneous diversion to which an external urinary reservoir was attached. He initially tried to achieve continence of the abdominal stoma by surrounding it either with imbricated fascia of the external oblique muscle or with a fascial sling. Although continence was achieved to some degree over a period of time, none of the patients remained continent. At about the same time, Gilchrist and associates (42) reported on the use of an ileocecal segment as a bladder substitute with an appliance-free continent urinary stoma dependent on the antiperistaltic activity of the terminal ileum and the action of the ileocecal valves. This success was not reproduced by other authors, and the concept was largely abandoned until recently.

Ileal Conduit

Some 50 years after Bricker's first description (in 1950), his ileal urinary diversion remains the most popular form of urinary diversion after cystectomy. Refinements in the operative technique and advances in the field of antibiotics, stomal appliances, and enterostomal therapy over the years have contributed to improved results both in terms of renal function and quality of life (13). Although not without long-term complications, most immediate postoperative complications can be prevented by meticulous surgical technique, a short ileal segment, adequate preoperative bowel preparation, use of perioperative prophylactic antibiotics, construction of a well-vascularized everted stoma, and use of delicate nontraumatic ureteral stents.

Technique

The success of Bricker's operation depends on preserving the vascular supply to the ileal segment and the ureters. Decreased vascularity, the cause of most major short-term complications, is due either to technical errors or to previous radiotherapy. A short segment of ileum, about 12 cm long, should be used. Adequate bowel preparation with antibiotic and mechanical bowel cleansing is essential to prevent infectious complications. In the classic Bricker procedure, the left ureter is brought under the base of the sigmoid mesocolon, without angulation, torsion, or tension, to a point close to the right ureter. The proximal end of the ileal segment either has been closed with a staple line or is sutured with absorbable sutures. Each ureter is spatulated and sutured to a small opening in the lateral aspect of the ileal conduit with absorbable sutures (Fig. 31.3).

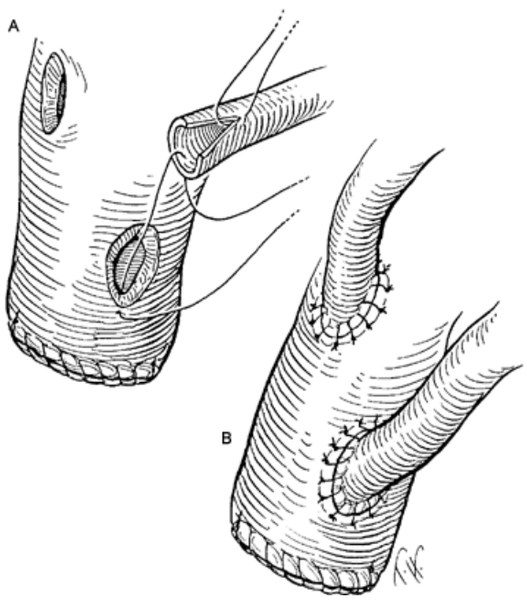

FIGURE 31.3. Bricker procedure for ureteroileal anastomosis. **A:** One-centimeter staggered, elliptoid incisions are made in the ileum. Following spatulation of the ureter, 4-0 absorbable apical sutures are placed at the 6 and 12 o'clock positions. **B:** Additional sutures are placed in an interrupted fashion.

The ureteroileal anastomosis according to Wallace (128) differs from Bricker's technique in that the spatulated ureters are anastomosed to each other before connecting the ureters to the open end of the isolated ileal segment (Fig. 31.4). First, both ureters are trimmed to a convenient point so that the anastomosis is out of the pelvis in the event that radiotherapy becomes necessary at a later date. Shortening of the ureters also will prevent subsequent kinking. Both ureters are then spatulated on the anterior surface for about 1.5 cm, with care taken not to interfere with the blood supply, and joined together with running 4-0 absorbable sutures. The conjoined ureters are sutured to the proximal, open end of the isolated ileum in a similar fashion. The theoretic advantage of the procedure is that the conjoined ureters afford a larger anastomosis to the ileum, thereby decreasing risk of ureteral anastomotic stenosis, and the ability to visualize the ureteral orifices at the end of the isolated segment in case of retrograde instrumentation of the upper urinary tract (40). Its utility is apparent in cases

of dilated ureters requiring larger areas of ileal segment for individual anastomosis. But the surgeon must be aware that the contralateral ureteral anastomosis could be in jeopardy if a kidney and ureter must be removed.

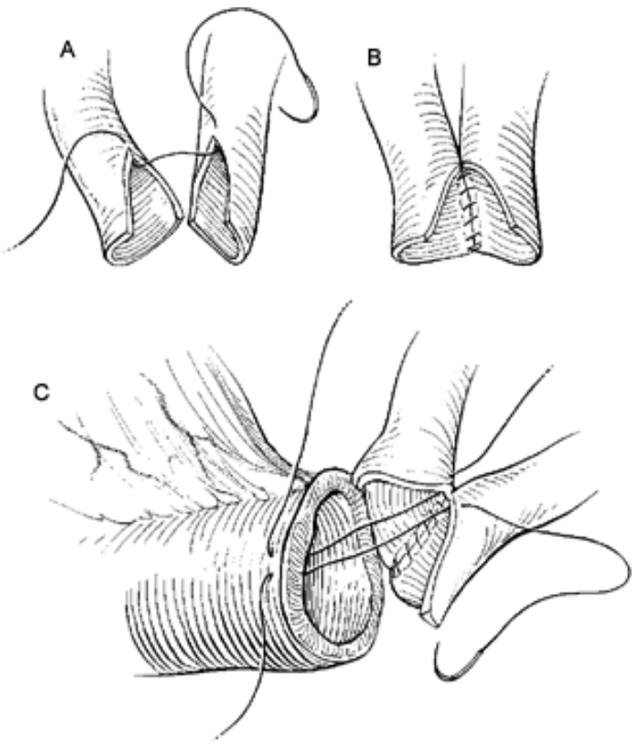

FIGURE 31.4. Wallace procedure for ureteroileal anastomosis. **A, B:** Medial walls of spatulated distal ureters are joined with a continuous, 4-0 absorbable suture. **C:** Conjoined ureters are sutured to the proximal, open end of the isolated ileal segment with similar suturing technique.

Clinical results of a new nonrefluxing ureteroileal anastomosis have been described. The so-called Hammock anastomosis should prevent ureteroileal reflux caused by a retrograde peristalsis of the conduit (59). It replaces the submucosal tunnel used in ureterocolonic anastomoses, which is not feasible in the thin wall of small bowel. The ureters, conjoined in a fashion similar to the Wallace technique, are anastomosed to the side wall at the proximal end of the ileal segment. The conjoined ureteral orifice is then buried into the intestinal wall made elastic and supple by multiple longitudinal and transverse seromuscular incisions. The ureteroileal anastomosis either can be stented with polyethylene stents brought out through the abdominal stoma and removed on the fifth to seventh postoperative day, or left unstented. We invariably use stents.

Proper construction of the stoma should prevent most short- and long-term problems. The site of the stoma should be tailored to the patient's specific anatomy in supine, sitting, and standing positions and should be identified and marked preoperatively by the surgeon or a stomal therapist. A circular opening about 2.5 cm in diameter is made in the skin at the site of the marking and continued bluntly to the fascia. The anterior fascia is opened by a 2-cm cruciate incision (Fig. 31.5). The rectus muscle is separated and the posterior fascia is likewise opened in a cruciate incision sufficient to allow free passage of two fingers. To prevent herniation, the conduit must be passed through the rectus muscle and not lateral to it. The mesenteric margin of the segment should be oriented toward the left shoulder to avoid any tethering, tension, or torsion of the mesentery that may cause vascular compromise to the conduit. Eversion of the stoma for about 1 to 2 cm is accomplished by the

"rosebudding" suture technique. Sutures of 2-0 PGA are passed from the skin edge of the stoma site through the serosa of the conduit 2.5 to 3 cm proximal to the distal end of the ileal segment and then full thickness through the end of the segment (Fig. 31.6A). Two to three interrupted 3-0 absorbable sutures are placed from skin edge to ileal edge between each quadrant suture to complete the ileal rosebud (Fig. 31.6B). No suturing is required at either fascial level. The everted stoma allows a careful and accurate fitting of the stomal appliance and prevents leaks, as well as severe skin changes and stomal stenosis, in most patients. Before closure, the posterior rectus fascia portal should be examined. If the opening is in excess of what is required for the conduit, a few nonabsorbable sutures are used to close any large defect and prevent parastomal bowel herniation. Finally, the proximal end of the ileal conduit should be anchored tension-free to either the sacral promontory or the fascia of the psoas muscle with nonabsorbable suture.

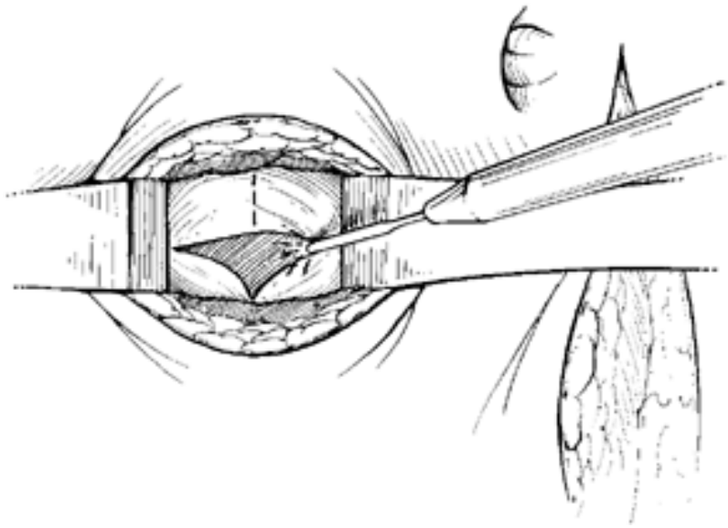

FIGURE 31.5. Construction of the diversion stoma. Following excision of a skin button representative of the conduit, subcutaneous tissues are separated down to the anterior rectus fascia. A cruciated, fascial incision is created in alignment with the skin button.

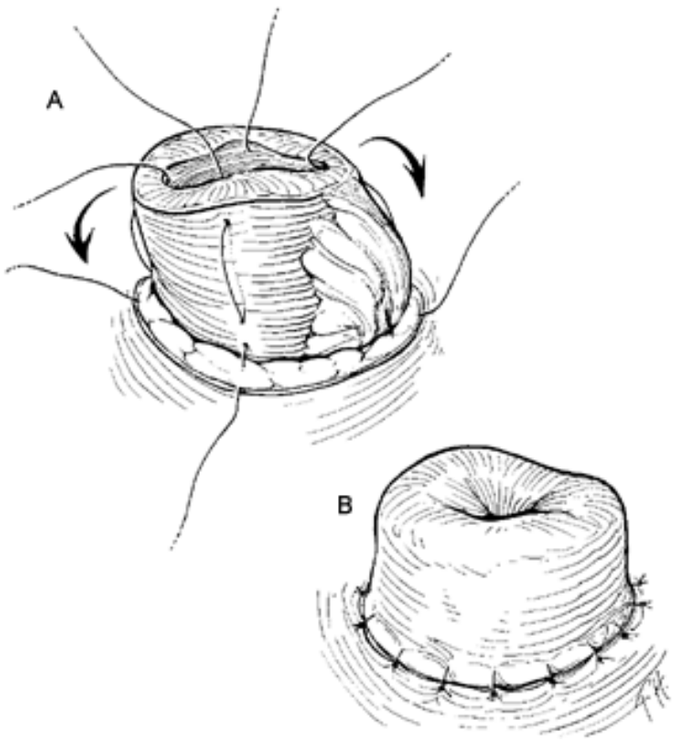

FIGURE 31.6. Rosebud suture technique of stoma. **A:** Four absorbable 2-0 PGA quadrant sutures are passed from the skin edge of the stoma site through the serosa of the conduit 2.5 to 3.0 cm proximal to the distal end of the ileal segment, then passed full thickness through the end of the ileal segment. **B:** Two to three interrupted 4-0 absorbable sutures per quadrant are placed from skin edge to ileal edge.

Complications

Experience and time have documented a significant incidence of both early and late complications following ureteroileocutaneous diversion. Among the early complications, wound infection and wound dehiscence were noted in 13.8% to 25.3% of patients (31,63,64,122) and intestinal obstruction in 6.1% to 23.6% of cases (62,122). Most obstructions respond to conservative treatment, with only 3% requiring surgery. The incidence of urinary leakage from the ureteroileal anastomosis may be as high as 11.3% (70), but most series report an incidence of 2.5% to 4.4% (26,64,122). The incidence of urinary leakage has been reduced by routine use of ureteral stents. Investigators have indicated that these stents reduce the incidence of urinary extravasation to 1% to 3% (8). The rate of early complications is higher in patients who have been irradiated. A high incidence of wound infection, drainage from the anastomosis, and prolonged ileus was reported in patients who received irradiation therapy before surgery (26,70,82,123). The mortality rate subsequent to ureteroileal diversion was about 20% in the early series (17,43), decreasing to 2.0% to 3.3% in more recent series (15,31,70). Among the recognized causes of death are pulmonary embolism, myocardial infarction, and infections.

Late complications are encountered in both children and adults (Table 31.1). Insight into delayed effects of

urinary diversion on the kidneys, which may appear many years after surgery, has been reported mainly from studies on children followed for 10 years or longer (79,86,104,105,110). These studies demonstrate that renal deterioration visible on pyelography occurs in 18% to 56% of patients. The incidence of renal damage is directly related to the status of the upper tract at the time of diversion and to the length of follow-up. The longer the time interval, the higher the incidence of renal damage. Further renal deterioration in abnormal systems is more common than in normal kidneys (83,86,110). Smith (110) showed that subsequent to diverting a normal upper tract, 7% of the renal units at 5 years, 10% at 10 years, and 23% at more than 10 years showed deterioration. In the initially abnormal systems, additional deterioration was documented in 16%, 20%, and 45%, respectively, at the same time intervals. Further renal injury to already damaged kidneys may cause serious or fatal complications (86,92). For these reasons, some authors believe that ureteroileal diversion should not be performed when severe renal insufficiency is present, but rather other modes of urinary diversion without interposed bowel should be used (29,92,93).

Source (ref.)	No. of Patients	Follow-up	Deterioration on IVP (%)	Stomal Stenosis (%)	Ureteral Obstruction (%)	Pyelonephritis (%)	Calculi (%)
Schwarz and Jeffs (104)	96 (children)	2–16 yr	56	32.3	5.2	—	12.5
Middleton and Hendren (79)	90 (children)	1–18 yr	41	42	10	20	9
Shapiro et al. (105)	90 (children)	10–16 yr	18	38	22.3	16.7	8.9
Johnson et al. (63)	181 (adults)	—	29	4.5	7.7	3.9	3.9
Johnson and Lamy (64)	214 (adults)	>6 mo	—	5.1	17.7	13.3	2.5
Sullivan et al. (122)	366 (adults)	5–15 yr	—	5.1	14.7	19.2	4.0

IVP, intravenous pyelography.

TABLE 31.1. COMPLICATIONS AFFECTING THE KIDNEYS IN PATIENTS WITH URETEROILEAL

Obstructions of the stoma, the conduit, or the ureters are major factors leading to renal damage. The incidence of stomal obstruction in adults is about 5% (63,64,122), and in children it ranges between 12% and 52% (93,110). Stomal obstruction may cause back-pressure, affecting the upper urinary tract with impairment of urine flow from the loop. In these cases the loop is elongated, acting not as a conduit but as a reservoir containing varying amounts of residual urine. Early diagnosis and revision of stomal stenosis are mandatory to prevent severe, irreversible renal damage. Obstruction may involve not only the stoma but any part of the loop, and on rare occasions the whole loop may become fibrotic and stenotic, the so-called pipe-stem loop. This late complication was reported in 2.0% to 6.3% of children. Its etiology is not clear, but various factors, including ischemia and infection, have been suggested as possible causes. The loop is noncompliant throughout its length with impaired peristalsis and resultant proximal upper tract deterioration. Attempts to balloon dilate these stenotic loops have been unsuccessful. The only effective management has been replacement of the entire conduit (67). Stoma complications commonly seen include stomal excoriation and urea dermatitis of the surrounding skin. These conditions are usually related to a poorly fitted or improperly placed stomal appliance.

Ureteral obstruction occurring chiefly at the ureteroileal anastomosis was noted among 7.7% to 17.7% of adults and 2.0% to 22.3% of children, typically on the left side, where the left ureter is brought behind the sigmoid mesentery. Intravenous pyelography, antegrade pyelography, and retrograde pyelography in the form of a loopogram study can help localize the site and extent of the obstruction or stenosis. In adult patients who have had diversion for bladder cancer, tumor recurrence at the site of anastomosis or along the ureter is a possible cause of obstruction. Urine cytology and brush histology of the ureter may establish the diagnosis. Initially, endoscopic attempts should be made to manage ureterointestinal anastomotic stenosis not associated with malignant recurrence. Retrograde or antegrade laser incision of the anastomotic stricture is our first approach. The success of this approach is dependent on the length of the ureteral stricture. Strictures of less than 1 cm in length are most amenable to this form of treatment. Open reoperation, although a more invasive intervention, is somewhat more dependable, with a reported lower restricture rate. Any obstruction subsequent to ileal conduit diversion incurs greater risks of stone formation and urinary infection. Stones develop in approximately 4% of adult patients and in approximately 10% of children, and acute episodes of pyelonephritis, in children and adults, occur in 10% to 20% of patients.

In approximately 15% of patients with renal deterioration, no obstruction can be detected. The deterioration in such patients is attributed to infected refluxing urine (79). Experimental studies by Richie and Skinner (90) have shown that infected refluxing urine in dogs with urinary diversion produces pyelonephritic changes in most of the kidneys examined. Because of the increased risk of renal deterioration, all patients with ileal conduits should have periodic urine cultures, serum creatinine assay, and imaging of the upper tract every 6 months for the first 2 years and annually thereafter.

The question of the significance of refluxing contaminated urine from the conduit to the upper urinary tracts has prompted the recommendation for antireflux implantation into the ileum. Although this is technically feasible, the thin-walled ileum does not adequately support the antireflux tunnel, and this procedure has not gained wide acceptance.

Although rarely encountered, parastomal herniation can occur after ileal conduit diversion (50). This complication is best avoided by “defatting” the mesentery that is to be drawn through the fascia window, devascularizing the terminal 1 to 2 cm of the ileal loop, and directing the conduit path through the body of the rectus muscle instead of at its lateral margin. These maneuvers would allow a more limited window to be created in the fascial and peritoneal layers, thereby preventing parastomal hernia formation through a broad fascia defect.

Perspectives

Although the ileal conduit may not be the ideal bladder substitute, it has stood the test of time and is well suited to the bladder cancer patient after cystectomy. With the use of bowel staplers, the ileal segment can be rapidly isolated and ureteral anastomoses accomplished easily and accurately. Most immediate postoperative complications can be prevented by meticulous surgical technique, adequate preoperative bowel preparation, use of perioperative prophylactic antibiotics, construction of a well-vascularized everted

stoma, use of a short ileal segment exiting directly through the rectus abdominis muscle, and meticulous anastomosis of the ureters. We further believe that routine use of ureteral stents for postoperative drainage minimizes the risk of anastomotic urinary leaks. Long-term complications remain a problem but are less difficult in adult patients with bladder cancer than in the pediatric group. It is important to note that severe short-term complications requiring reoperation are rare in the hands of the experienced surgeon (2% to 3% at our institution), and patients can be fitted easily with a reliable appliance that requires changing only every 5 to 7 days. Even though such patients must tolerate wearing an ostomy appliance, they do not need to catheterize a reservoir and usually resume almost all normal activities. For these reasons, the ileal conduit remains the most popular and frequently used method of urinary diversion subsequent to cystectomy for cancer. However, because of the increased success of continent urinary diversions, fewer conduits may be performed in the future.

Jejunal Conduit

In general, construction of a jejunal conduit should be contemplated only for selected cases in which alternative bowel segments are less attractive. Such instances may become apparent in patients with bladder, cervix, uterine, or rectal malignancy who have received significant radiotherapy to the pelvic cavity. Jejunum is typically avoided to prevent the often severe metabolic complications associated with its use for urinary diversions.

If jejunum is selected, the length of the segment should be as short as possible to minimize the potential for metabolic complications by limiting the degree of contact of urine with the jejunal mucosa. This may become a factor when positioning the stoma in that a more cephalad location is usually required, as compared with the stoma site for an ileal conduit. Ureteral stents should be used to divert the urine from contact with the mucosa, thereby lessening the potential for electrolyte disturbance during the initial postoperative period. Otherwise the technical aspects of constructing a jejunal conduit are similar to those of an ileal segment.

Specific considerations concerning postoperative care involve assessment of the patient's electrolyte status. Hyponatremia can be substantial and may lead to the development of secondary hyperaldosteronism. Therefore each patient should be monitored routinely at frequent intervals and evaluated for salt replacement. More than half the patients who undergo this type of diversion ultimately require salt replacement, usually in the form of sodium chloride tablets (44).

Colonic Conduits

Although it was thought that the isolated ileal conduit would eliminate most of the problems previously encountered with ureterosigmoidostomy, the long-term results proved otherwise, and colonic conduits were devised to improve the results of urinary diversion in certain situations. Using colon as a urinary diversion has several advantages. First, the large lumen provides an excellent stoma, which rarely undergoes stomal stenosis. Stomal stenosis and hyperkeratosis are both major problems in childhood urinary diversion. Second, a segment of colon can be chosen that is well outside previous pelvic radiation fields. Third, an antirefluxing ureterocolonic anastomosis can be created by either using the ileocecal valve or implanting the ureters into the tenia of the colon.

Virtually every portion of the colon, based on the colonic arterial arcade, has been used as an isolated urinary conduit. The preferred segment of colon seems to be the proximal sigmoid (3). One must be aware that the colonic wall has no longitudinal branches of collateral vessels, and therefore all the vasa recta must be preserved. In contrast, the microcirculation of an ileal or jejunal submucosal plexus can support a segment of small bowel that has been deprived of its vasa recta. An important aspect of any colonic diversion is the need to demonstrate a normal colon either radiographically or by colonoscopy or both.

Ileocecal Conduit

The ileocecal conduit has certain anatomic advantages over other colonic conduits. The blood supply is abundant and constant; the segment is rarely involved in compromising disease, such as diverticulitis; and its right lower quadrant location facilitates a tension-free right lower abdominal stoma. The ureters are attached to the ileal segment so that the ileocecal valve serves as an antireflux barrier. Libertino and Zinman (68c) described a method of reinforcing the ileocecal valve by wrapping the redundant cecum around the distal 4 to 8 cm of the terminal ileum. Late complications in their series of 150 patients included stomal prolapse requiring operative repair in 4%, ureterointestinal strictures requiring surgery in 3%, parastomal hernias requiring surgical repair in 2%, and small bowel obstruction after 6 months to 2 years in 1.3% of patients.

Transverse Colon Conduit

The transverse colon is well out of the field of any pelvic and lower-abdominal radiation. The main indication for transverse colon conduit is in patients after pelvic radiation with significant radiation changes to the ileum and rectosigmoid. The ends of the transverse colon segment approximate the kidneys on both sides and can be directly anastomosed to the renal pelvis if the ureters cannot be used. The conduit must be constructed so that the distal (left) end emerges as the stoma in an isoperistaltic fashion (Fig. 31.7). The ureters are anastomosed either directly or by an antirefluxing method. In patients with a complete destruction or severe fibrosis of both ureters, the colon can be directly connected

either end-to-end to the right renal pelvis or end-to-side to the left renal pelvis. Stomal position may be either right or left upper or lower quadrants and should be marked preoperatively. Schmidt and Buchsbaum (101) published their long-term results and technical alterations. In their experience in 50 patients over a period of 15 years, they encountered an operative mortality in two (4%) and stable or improved renal function in 48 (95%) of their patients. Significant complications, most of them requiring surgical repair, occurred in almost one-third of the patients. These included parastomal hernia, stomal prolapse, ischemic ureteral stricture or ureteral obstruction attributable to recurrent tumor, nephrolithiasis, conduit stone formation, recurrent ureteral fistula, and incisional hernia.

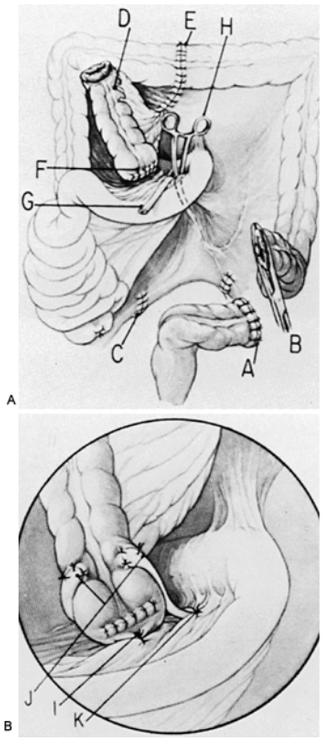

FIGURE 31.7. Transverse colon conduit. *E,* bowel continuity restored. **A:** *A* and *B,* sigmoidal resection and colostomy are optional. *C,* peritoneal closure. *D* and *F,* segment isolated. *G* and *H,* ureters dissected. **B:** *I,* fixation of proximal segment. *J,* ureterocolic anastomosis. *K,* retroperitonealization. (From Schmidt JD, Hawtrey CE, Buchsbaum HJ. *J Urol* 1975;113:308, with permission.)

Ravi and colleagues (87) reviewed their experience in 30 patients, all of whom received pelvic radiation of 65 Gy or more. They encountered no operative mortalities, and 25 (83%) had normal or improved renal function following the diversion. Complications were seen in 11 (37%), half of which required surgical correction. Although at substantial risk for obstruction at the ureterocolonic anastomosis, only three patients (10%) were found to have strictures. They attributed this lower-than-expected rate to resecting the ureter proximally and performing the anastomosis at a level of the midureter.

Sigmoid Colon Conduit

The most common indication for a sigmoid urinary diversion is the young patient who requires a diversion for benign neurogenic disease (65). The redundancy and mobility of the sigmoid and its location in the left lower abdomen offer several advantages for its selection as a conduit. Patients with malignant pelvic tumors are not good candidates for a sigmoid conduit because of the diminished blood supply to the rectosigmoid after cystectomy and the possibility of previous pelvic irradiation. In the patient undergoing total pelvic exenteration, however, a sigmoid conduit can be used because the distal blood supply for healing of a colorectal anastomosis is of no concern. In most centers, sigmoid conduits tend to be limited to patients undergoing total pelvic exenteration because an intraabdominal bowel anastomosis can be avoided.

The construction of the distal colonic conduit is similar to that of other colonic conduits (Fig. 31.8). A tunneled ureterocolonic antireflux mechanism similar to the Leadbetter technique is preferred despite the increased chance of ureteral stenosis and hydronephrosis. The everted, protruding abdominal stoma is usually located in the left lower quadrant, but placement on the right side is also possible if previous operative scars or other deformities preclude the left side.

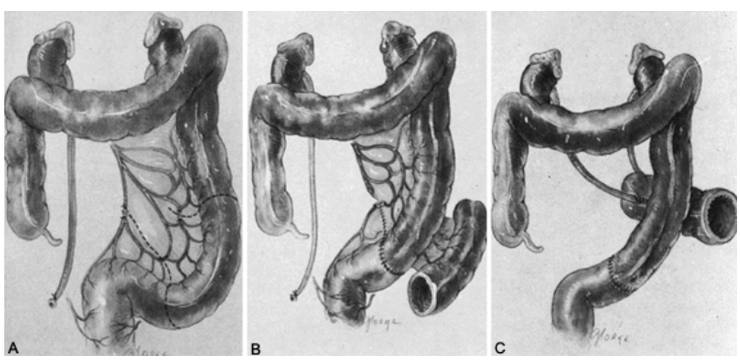

FIGURE 31.8. Sigmoid colon conduit. **A:** Isolation of a suitable sigmoid segment for sigmoid loop urinary diversion. Note that the distal sigmoid mesentery is divided all the way to the sacral promontory, including division of the superior hemorrhoidal artery. This provides maximal mobility of the loop and allows it to function in an isoperistaltic manner. **B:** Division of the proximal mesentery should be quite short, and care should be taken to avoid injury to venous drainage from the segment. The proximal end of the isolated segment is closed, and standard bowel anastomosis is performed medial to the isolated segment. **C:** The right ureter is brought under the sigmoid mesentery. (From Richie JP, Skinner DG. Ureterointestinal division. In: Walsh PC et al, eds. *Campbell's urology.* Philadelphia: Saunders, 1986:2612, with permission.)

The early postoperative complications are similar to those observed with the ileal conduit and other colonic conduits. Late complications are usually due to a failure of the ureterocolonic antireflux mechanism, with hydronephrosis and renal deterioration due to reflux or obstruction (3,35).

Complications

The deleterious effect of ileal conduit diversion on the kidneys has been attributed to the high rate of stomal stenosis and to free reflux of urine from the loop to the

kidneys. The colon segment was introduced to achieve nonrefluxing ureterocolonic anastomosis and to avoid stomal complications. Early reports on colon conduits were encouraging, showing a low incidence of stomal complications (3,81). Stomal stenosis occurred in 0% to 2.8% of patients, pyelonephritis in 7.1% to 17%, and renal deterioration in 8.6% to 22.4% (Table 31.2). However, most patients included in these studies were followed for a short period. Longer follow-up on patients in other series revealed a higher incidence of complications. Elder and associates (35) noted in a group of 41 children followed from 9 to 20 years (average, 13.2 years) a 61.5% incidence of stomal stenosis, a 22% incidence of ureterocolonic stenosis, and a 48.4% incidence of renal deterioration. These data suggest that late stomal and renal complications are not prevented by using a colon conduit.

Source (ref.)	No. of Patients	Follow-up (yr)	Stomal Stenosis (%)	Ureterocolonic Stenosis (%)	Pyelonephritis (%)	Stones (%)	Renal Deterioration (%)
Althausen et al. (3)	70 (children, adults)	2–8	2.8	8.6	7.1	4.3	8.6
Morales and Golimbu (81)	46 (children, adults)	>1–11	—	13	17	4.3	22.4
Elder et al. (35)	41 (children)	9–20	61.5	22	—	16	48.4

TABLE 31.2. COMPLICATIONS OF COLON CONDUIT DIVERSION

Perspectives

The use of the colon conduit as a urinary diversion in children provides a different set of criteria than does its use in adults with bladder cancer, as discussed in this chapter. In the adult, the problem of stomal stenosis is not major, and it can usually be avoided by creating a well-vascularized everted stoma. Therefore prevention of reflux remains the major attribute of the colon conduit. As noted, the value of the antirefluxing ureteral reimplantation is unclear. The paucity of long-term results makes it impossible to discern an actual advantage of antirefluxing procedures versus standard ureteral implantation, even though a theoretic advantage may exist. Ureteral stenosis increases after antireflux reimplantation, although the impact of this problem in adults may not be significant. The undisputed indication for the colonic conduit occurs in the patient who has had

extensive pelvic irradiation with radiation damage to the distal ileum. The transverse colon is the preferred urinary diversion in this situation because it is less likely to be injured by radiation and has been found to have the lowest incidence of associated ureterocolonic anastomotic leakage or stomal complications (7,87,101).

CONTINENT URINARY DIVERSIONS

Part of "31 - URINARY DIVERSIONS AND CONTINENT RESERVOIRS "

Urinary Diversion into the Rectosigmoid

Ureterosigmoidostomy

With the development of continent urinary diversion techniques using the Mitrofanoff principle, ureterosigmoidostomies have been less commonly performed. However, fueled by its simplicity, ureterosigmoidostomies remain popular with many contemporary urologic surgeons. Patient selection is paramount for successful continent diversion by ureterosigmoidostomy. Because of the high risk of potentially severe long-term complications, most would avoid this procedure in younger individuals. Relative contraindications include those patients with neurogenic bladder dysfunction, prior bowel disease or dilated ureters, renal impairment, pelvic irradiation, or hepatic dysfunction. Patients with neurogenic bladder dysfunction may have associated bowel or anal sphincteric dysfunction; thus, if ureterosigmoidostomy is to be considered, it is imperative that an evaluation and assessment of anal sphincter integrity be performed to avoid fecalurial incontinence (114). Patients with prior bowel disease, such as diverticulitis or colon polyps, should be avoided because of the risk of bowel fistula and colonic malignancy postoperatively. Implantation of dilated or tapered ureters into the large bowel is difficult and is associated with a higher risk of subsequent long-term renal deterioration (48).

Patients with established renal impairment are poor candidates for ureterosigmoidostomy or any continent intestinal diversion because of the inherent likelihood of exacerbations of electrolyte and acid–base disturbances with subsequent progressive renal deterioration. Patients with prior extensive pelvic irradiation also are not favorable candidates because of the condition of the irradiated bowel or distal ureters (4,114). Patients with hepatic dysfunction are at certain risk for ammonia intoxication following ureterosigmoidostomy or any continent diversion because of the intestinal reabsorption of ammonium (106).

Technique

The most distal portion of the rectosigmoid is the preferred site for the ureteral anastomosis. After freeing both ureters, they are led through a submucosal tunnel into the bowel lumen. In the Leadbetter technique, the left ureter is brought through the sigmoid mesentery (Fig. 31.9). The anterior tenia is opened at two sites to expose the underlying mucosa, and each ureter is placed into a 3-cm-long trough. Two small openings are made in the mucosa to which each spatulated ureter is carefully anastomosed with fine 4-0 chromic sutures. The muscularis of the tenia is then closed over each ureter with interrupted silk sutures to form the submucosal tunnel.

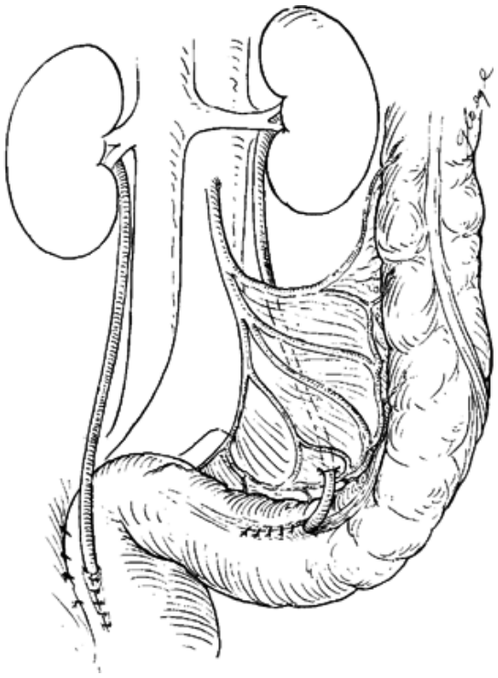

FIGURE 31.9. Leadbetter's combined technique of ureterosigmoidostomy. Note that the left ureter is brought through the sigmoid mesentery and implanted on the anterior tenia. The rectosigmoid is fixed to the lateral pelvic wall of psoas muscle in the region of the right ureterocolonic anastomosis. (From Richie JP, Skinner DG. Ureterointestinal diversion. In: Walsh PC et al, eds. *Campbell's urology.* Philadelphia: Saunders, 1986:2602, with permission.)

Goodwin (45) promoted a transcolonic technique for the ureterocolonic anastomosis (Fig. 31.10). This differs from Leadbetter's method in that the rectosigmoid is opened anteriorly, and the ureters are brought through separate submucosal tunnels in the posterior wall into the bowel lumen. The ureters, either separately or conjoined to form a single lumen, are sutured to the mucosa from inside the bowel lumen.

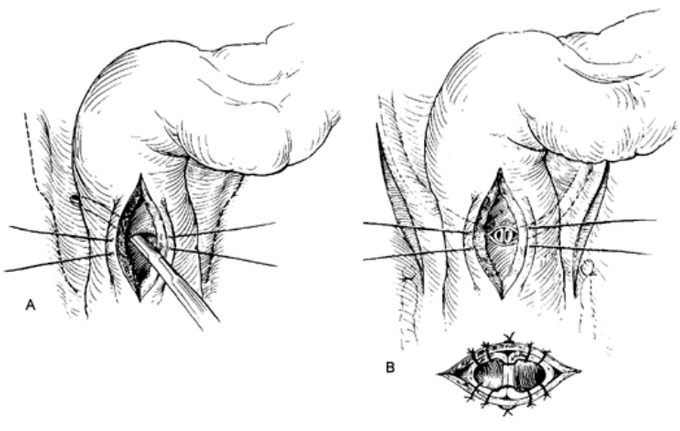

FIGURE 31.10. Goodwin's transcolonic technique of ureterosigmoidostomy. **A:** Note that both ureters are brought through individual submucosal tunnels in the posterior rectal wall. **B:** The ureters are then sewn together medially before they are secured to the colonic mucosa circumferentially. (From Richie JP, Skinner DG. Ureterointestinal diversion. In: Walsh PC et al, eds. *Campbell's urology.* Philadelphia: Saunders, 1986:2603, with permission.)

Results and Complications

Nonrefluxing techniques for ureterocolonic anastomoses have improved the long-term results for ureterosigmoidostomy by decreasing the incidence of ureteral reflux and ureteral obstruction (130,133,134). Comparison between the refluxing and nonrefluxing techniques reported by Wear

and Barquin (130) showed fewer episodes of pyelonephritis and renal damage with the latter technique, although the incidence of acute pyelonephritis and renal deterioration remained high, ranging from 20% to 57% and from 13% to 35%, respectively (33,60,133,134) (Table 31.3). Because all patients undoubtedly have exposure of the reconstructed urinary tract to fecal flora, most investigators recommend long-term antibacterial therapy (33,114).

Source (ref.)	No. of Patients	Pyleonephritis (%)	Acidosis (%)	Deterioration on IVP (%)	Calculi (%)
Williams et al. (133)	57	45	32	35	5
Wear and Barquin (130)	45	57	47	32	
Zincke and Segura (134)	173	26	15	20	4
Duckett and Gazak (33)	19	22	50	13	5

IVP, intravenous pyelography.

TABLE 31.3. COMPLICATIONS OF URETEROSIGMOIDOSTOMY

Early complications after ureterosigmoidostomy are encountered in about two-thirds of patients undergoing this procedure. Wound infection, wound dehiscence, and prolonged ileus are common (134). However, the most serious complication is urinary leakage from ureterocolic anastomosis or from the colotomy incision. The incidence of this complication can be minimized by a watertight ureterocolic anastomosis, the use of ureteral stents, and continuous drainage of the rectal contents. Proper drainage can be achieved by using two rectal tubes that have multiple perforations. Stents and tubes should be irrigated every 4 hours to ensure patency. Although minor leaks usually seal spontaneously without further treatment, major leaks involve a high incidence of complications, such as prolonged ileus, severe acidosis, and electrolyte imbalance. In patients in whom a major leak develops, immediate reoperation with reanastomosis or cutaneous diversion should be performed, and in life-threatening conditions, nephrectomy is indicated.

Electrolyte or acid–base imbalances, encountered in as many as 50% of patients, are caused by reabsorption of urine from the bowel. Reabsorption takes place not only in the sigmoid colon but also throughout the entire colonic mucosa (129). Characteristic laboratory findings in the serum subsequent to ureterosigmoidostomy include high urea levels with normal creatinine, high ammonium and chloride levels, low potassium levels, and metabolic acidosis. To improve acidosis and electrolyte imbalance, it is imperative to avoid prolonged contact between urine and the colonic mucosa. All patients should be instructed to evacuate the rectum every 2 to 3 hours during the day and at least once or twice at night. A lifelong low-chloride diet and

supplemental solution of 10% potassium citrate should be prescribed for most patients.

The association between ureterosigmoidostomy and colonic tumors has been confirmed by numerous studies since the first report by Hammer (49). In reviewing the literature, Leadbetter and associates (68a) found 45 patients with tumors at the site of the ureterocolonic anastomosis, of which 31 were adenocarcinoma, 4 were transitional cell carcinoma, and 4 were benign colonic tumors. It has been estimated that the incidence of colonic carcinoma associated with ureterosigmoidostomy is 500 times higher than in the normal population. The mean lag period for development of carcinoma of the colon for patients following ureterosigmoidostomy after age 40 years was 8.7 years (range, 5 to 14 years), whereas for those who were younger than 40 years, the lag period was 21.4 years (range, 14 to 50 years). The etiology of these tumors is obscure. Mechanical irritation by the fecal stream at the site of the ureterocolic anastomosis (95), the carcinogenic effects of the mixture of urine and feces (30), and the presence of large amounts of carcinogenic nitrosamines in the rectal urine (119) have been suggested as possible etiologic factors.

All patients with ureterosigmoidostomy should be examined for occult blood every 6 months and undergo a yearly intravenous pyelogram and colonoscopy starting 5 years postoperatively (39). Barium enemas are relatively contraindicated because of the potential for reflux of this material to cause associated septic events (133). If a colonic tumor is found, segmental resection of the bowel and cutaneous urinary diversion should be performed.

Ureteroileosigmoidostomy

The principle of interposition of an ileal segment between ureters and functionally intact colon had been suggested by Goodwin (46), who proposed a “ureteroileal undiversion” into the sigmoid. Several methods using a segment of ileum or an ileocecal segment interposed between ureters and sigmoid have been proposed with the intent of reducing the risk of cancer development associated with ureterosigmoidostomies and to improve the ureteral antireflux mechanism. However, currently neither sufficient data nor long-term results exist to suggest that the creation of a low-pressure colonic reservoir with ileum will reduce ureteral reflux with its associated complications. Likewise, it is not established that the interposition of an ileal segment between ureters and sigmoid will prevent the formation of colonic tumors.

CONTINENT CUTANEOUS (HETEROTOPIC) URINARY DIVERSIONS

Part of "31 - URINARY DIVERSIONS AND CONTINENT RESERVOIRS "

Because of the shortcomings of ureterosigmoidostomy and the ileal conduit, continent urinary diversion to the abdominal wall has gained increased popularity among both patients and physicians. In 1950, Gilchrist and associates (42) reported for the first time the use of an ileocecal segment as an appliance-free continent urinary diversion. Continence was based on the antiperistaltic function of the terminal ileum and the action of the ileocecal valve. Since then, various other methods have been proposed, but none of them has proved to be perfect and free of complications when applied clinically.

Most of the techniques have a reported complication rate of more than 10%, the most common being failure of the continence mechanism (73,109). The reservoir usually is continent at low filling, but larger volumes and high intermittent tension of the bowel wall can result in urine leakage (71). All of these methods rely on the coapting ability of bowel under the influence of imbrication, tapering, or intussusception to achieve a suitable closing pressure, but they differ in terms of where this valve is placed—inside or outside of the reservoir. In postmortem studies of isolated ileocecal segments and in vivo barium enema studies, Ashken (5) found that the ileocecal valve was incompetent in more than 50% of the cases. He therefore used a spout of ileum sutured into the open end of the cecum or ascending colon as the valve mechanism of an ileocolic urinary reservoir. Prolapse of the ileal spout with incontinence and difficulty in catheterization required reoperation in 40% of his patients. A variation using an invaginated segment of ileum sewn into the open end of the cecum was described by Benchekroun (10), who named it the “inkwell valve.” As with other cecal reservoirs, the most common complications were prolapse of the inkwell valve and ischemic necrosis with subsequent urinary leakage from the cecal reservoir.

Reinforcement of the ileocecal valve has been attempted in several ways: by imbricating or tapering the terminal ileum, by burying the terminal ileal segment with redundant cecum, or by intussuscepting the ileum either outside the reservoir or through the ileocecal valve and placing the continent nipple into the lumen. Continence of the intraluminal valve was compared with continence of a form of reinforced ileocecal valve, and the intraluminal continence mechanism was more successful (118). The issue of long-term continence remains a central focus in current attempts to popularize continent cutaneous diversions.

Kock Pouch

Kock's (67a) description of a continent ileostomy with its intussuscepted intraluminal valve mechanism eventually led to the development of an intestinal pouch used as a continent urinary reservoir. It is used in many centers worldwide but has been replaced by more simpler methods in most areas of the United States.

Technique

Approximately 80 cm of ileum has to be isolated. Distally, the mesentery and bowel are divided along the avascular

plane between the superior mesenteric artery and the ileocolic artery. The division of the mesentery should extend to the base of the mesentery to ensure sufficient mobility of the efferent limb of the pouch. Before the proximal end of the isolated bowel is closed, several centimeters of the proximal ileum together with a small triangular wedge of mesentery are discarded to enhance the mobility of the reservoir and the small bowel anastomosis. Staples or the conventional technique using two layers of interrupted 4-0 silk sutures can be used to reestablish bowel continuity. The median portion of the detached ileum consisting of two 22-cm-long segments is opened on the antimesenteric border, formed into a U-shaped plate, and sewn together side-to-side with a 3-0 PGA suture (Fig. 31.11A and Fig. 31.11B). The proximal and distal valves are then created by intussuscepting about 12 cm of ileum at each end. For this purpose the mesentery is divided at a length of 7 to 8 cm on each side flush with the serosa of the ileum. The tubular ileum on each end is then intussuscepted with the help of Allis clamps to form two nipples lying in the open pouch. Three to four parallel rows of 4-mm staples, each 5.5 cm long, are used to maintain the intussusception. To prevent late slippage or desussception of the nipple valve mechanism, a folded 2-cm-wide PGA mesh is passed through a small separate window in the mesentery and sewn with seromuscular stitches to the bowel wall to secure the intussuscepted nipple from outside. The mesh of the efferent nipple is also fixed to the abdominal wall to facilitate catheterization of the pouch (Fig. 30.11C and Fig. 30.11E). Both ureters are spatulated, anastomosed end-to-side to the free portion of the afferent nipple, and stented with infant feeding tubes. The pouch is then closed with a single layer of interrupted 3-0 PGA running sutures. Some authors have promoted a two-layer suture to ensure watertightness of the closure. Before the closure is completed, a Medina tube is passed through the efferent nipple into the pouch. The efferent limb of ileum is brought through the abdominal wall, and a flush stoma is created. Posteriorly, the pouch is attached to the sacral promontory with several interrupted PGA sutures.

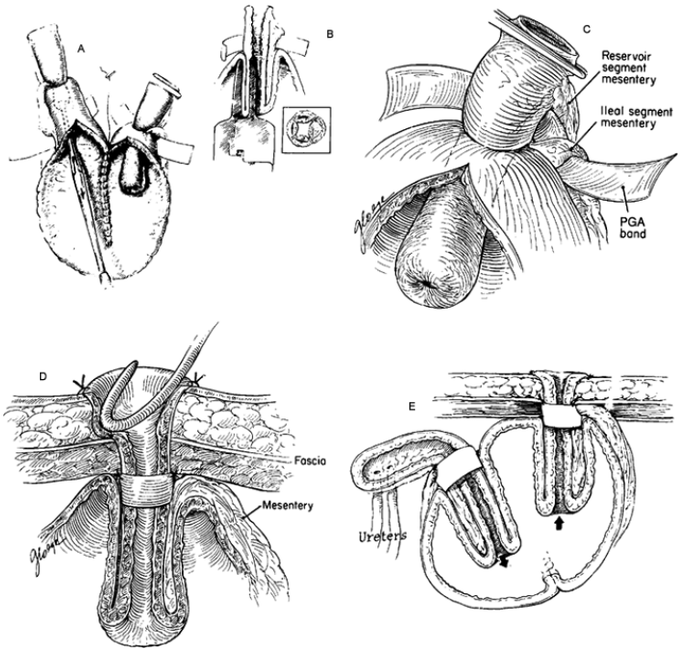

FIGURE 31.11. Kock pouch. **A:** After either defatting the mesentery or dividing it, proximal and distal valves are created by intussusception of the ileal segment. **B:** Fixation is secured with three or four rows of GIA staples. **C:** The PGA strip is passed through a small window in the mesentery of the reservoir and then through a similar window in the mesentery of the adjacent ileal segment. This traps the valve and helps prevent disintussusception. **D:** Improper fixation of the terminal segment makes catheterization difficult, and the catheter does not easily enter the valve. A short segment, fixation of PGA to the external fascia, and fixation of the reservoir to the abdominal wall minimize difficulties with catheterization. **E:** The distal segment is made as short as possible and secured flush with the abdominal wall. Then the PGA mesh must be pulled into the abdominal wall and sutured to the external fascia. The reservoir is then fixed to the abdominal wall with several circumferentially placed sutures. (**A, B:** From Kock NG, Nilson AE, Nilson LO, et al. *J Urol* 1982;128:469, with permission. **C-E:** From deKernion JB, DenBesten L, Kaufman JJ, et al. *Am J Surg* 1985;150:84, with permission.)

Results and Complications

Despite increasing experience and many modifications, the Kock pouch still has a high complication rate. Although the principle of the afferent intussuscepted nipple is highly effective in the prevention of ureteral reflux and has been used in various other diversions (66,120), the intussuscepted efferent nipple remains a source of complications. Skinner and co-workers (109) reviewed their experience in 531 patients undergoing a Kock pouch diversion between 1982 and 1988. Early complications occurred in a total of 86 patients (16.2%), resulting in an operative mortality rate of 1.9% (10 of 531). The late complications encountered in 489 patients were stratified according to the technical changes made over the years. Even in their last series of 239 patients, the overall incidence of late complications was still 22%. Leakage occurred in 15% of the patients, requiring one or several reoperations in the majority of those, and it remained the primary late complication even after modifying the efferent valve fixation. Although this complication rate seems to be lower than that originally reported for the Kock pouch, the number of patients is much smaller.

Mainz Pouch

The Mainz pouch was first described in the English literature by Thuroff and colleagues in 1986 (125). Since then, this principle has been used as a continent cutaneous diversion, as well as bladder augmentation or orthotopic bladder substitution, by an increasing number of urologists worldwide.

Technique

For the continent urinary diversion, 10 to 30 cm of cecum and ascending colon and approximately 50 cm of terminal ileum are isolated (Fig. 31.12A). The colon and about 30 cm of the adjacent ileum are detubularized at the antimesenteric border and sewn together side-to-side with a single layer of running sutures to create an intestinal plate (Fig. 31.12B and Fig. 31.12C). The ureters are brought into the pouch through a 5-cm submucosal tunnel along the posterior tenia of the colon. The ileal mesentery of the tubular portion of the ileum designated for the creation of the continence mechanism is then freed from the ileal wall. The ileum is intussuscepted and stabilized with two rows of staples (Fig. 31.12D and Fig. 31.12F). The intussuscepted segment of ileum is then brought through the natural tunnel of the ileocecal valve and fixed to it with TA-55 staples from inside and outside (Fig. 31.12G and Fig. 31.12H). After stenting of the ureterocolonic anastomosis and insertion of the suprapubic catheter through a separate stab incision in the pouch and abdominal wall, the anterior wall of the reservoir is closed with a single row of through-and-through running sutures (Fig. 31.12I).

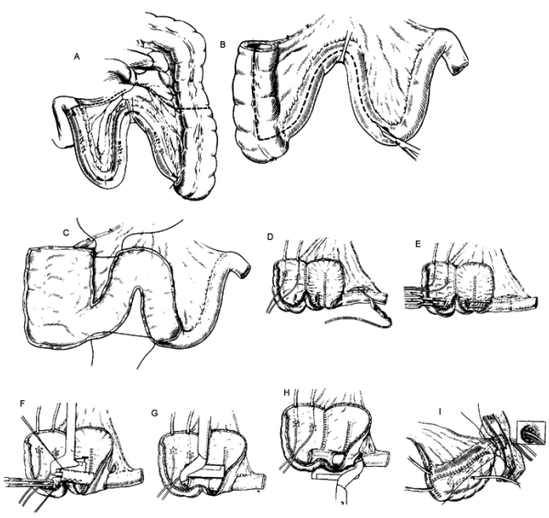

FIGURE 31.12. The Mainz pouch. **A:** The intestinal segment to be isolated for the Mainz pouch continent urinary diversion. **B:** Antimesenteric splitting of the intestinal segment used for the pouch and nipple. **C:** Side-to-side anastomosis of the colon and detubularized ileal loop to create an intestinal sheet. **D:** Ileoileocecal intussusception. The ileocecal valve remains intact. Six to eight cm of proximal ileum are freed from the mesentery. **E:** With Allis clamps, the ileum is pulled through the natural tunnel of the ileocecal valve. **F:** Stabilization of the intussusception by two rows of 4.8-mm staples. **G:** Staple fixation of the intussusception at ileocecal valve (4.8-mm staples). **H:** Staple fixation of the intussusception at the posterior wall of the ileocecal valve (4.8-mm staples). **I:** The efferent loop is anastomosed to the abdominal wall. The preferred site of the Mainz group is the umbilicus (as shown here). (From Thuroff JW, Alker P, Riedmiller H, et al. *J Urol* 1986;136:18,20; and Thuroff JW, Alker P, Riedmiller H, et al. *J Urol* 1988;140:285, with permission.)

Several methods to form a continent cutaneous stoma have been used: abdominal stoma to the left or right lower quadrant, alloplastic prosthesis at the skin level, and an umbilical stoma. All the alloplastic stoma prostheses had to be removed because of infection and were changed to a continent abdominal or umbilical stoma. The best functional and cosmetic results were accomplished with the umbilical stoma, and it is currently the method preferred by the Mainz group.

Results and Complications

A mean capacity of 620 mL, resting pouch pressures between 23 and 31 cm H_2O, and peak pressures up to 43 cm H_2O are reported in the continent diversion patients. Thuroff and co-workers (126) reported their experience

with the Mainz pouch in the first 100 consecutive patients (51 of those underwent a cutaneous continent diversion). No operative mortality and seven major perioperative complications requiring reoperation in three cases were encountered in the total group. Late complications after a mean follow-up of 23 months included valve prolapse or incontinence in 11 patients, all of them in the early series, whereas none of these problems occurred in their series after modifying the technique of fixation and stabilization of the intussuscepted ileocecal valve.

Authors' Modification (UCLA Pouch)

We have experimented with various forms of urinary diversion at our institution. Our initial experience with the Kock

pouch was disappointing because of the high early failure and reoperation rates (32). Subsequently, several forms of detubularized right colonic reservoirs were attempted with varying success. We currently use the detubularized ileocecal reservoir and achieve continence by preserving the ileocecal valve and by tapering and compressing the ileal segment.

Technique

The entire right colon up to the hepatic flexure and approximately 12 cm of the terminal ileum are isolated with their blood supply (Fig. 31.13A). The colonic segment is detubularized along the anterior tenia down to the area of the cecum. At this point, the incision is turned upward to terminate at the junction of the ileum with the cecum (Fig. 31.13B). Creation of the continent valve is a critically important step in the procedure. The segment of terminal ileum is tapered over a 14-Fr Foley catheter with an absorbable gastrointestinal anastomosis (GIA) stapler. Fixation of the ileal limb is probably the most important step in preventing postoperative incontinence. Based on the studies by Raz (88,89), a technique was developed that is different from prior procedures in that the ileal limb is fixed against the wall of the continent pouch in a trough created in its serosal layer with 2-0 absorbable sutures (Fig. 31.13C). Intraluminal pressure is transmitted to the ileal limb, causing compression of the catheterizable portion.

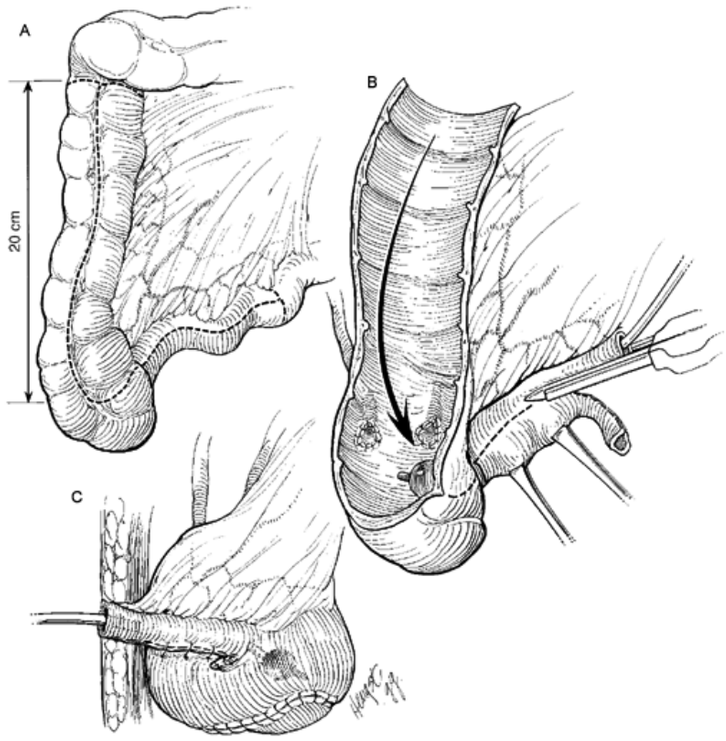

FIGURE 31.13. UCLA pouch. **A:** Right colon to the hepatic flexure and 12 cm of terminal ileum are isolated. **B:** The colonic segment is detubularized along the anterior tenia. The terminal ileum is tapered with an absorbable GIA stapler; the staple line is reinforced with interrupted 2-0 PGA ligatures, and the ureterocolonic anastomoses are performed. **C:** A trough is created in the serosa of the constructed reservoir. The catheterizable limb is fixed to the reservoir in that trough with the interrupted 2-0 PGA sutures. The pouch is closed and the stoma site on the skin surface is prepared accordingly. The pouch is then fixed to the posterior rectus fascia and anterior abdominal wall with a few 2-0 PGA suture ligatures.

Ureterocolonic anastomoses are carried out in a LeDuc fashion (Fig. 31.14). The pouch is created by folding down the ascending colon and suturing it to cecum with running absorbable suture material. Ureteral stents are positioned and a suprapubic tube is brought through the left lower abdominal wall. At a previously determined site, a 1-cm buttonhole is created in the skin, anterior fascia, and posterior fascia. The distal segment of the catheterizable ileal limb is advanced between the rectus muscle. The mesentery of the limb is inspected for tethering or tension. Excess ileal limb is removed, and a flush skin stoma is created that has a somewhat flared configuration to allow easier catheterization (Fig. 31.13C). The skin and limb edges are sutured with interrupted 3-0 PGA suture material. The 14-Fr Foley is left in place. The pouch is then fixed to the posterior rectus fascia and anterior abdominal wall with a few 2-0 PGA suture ligatures.

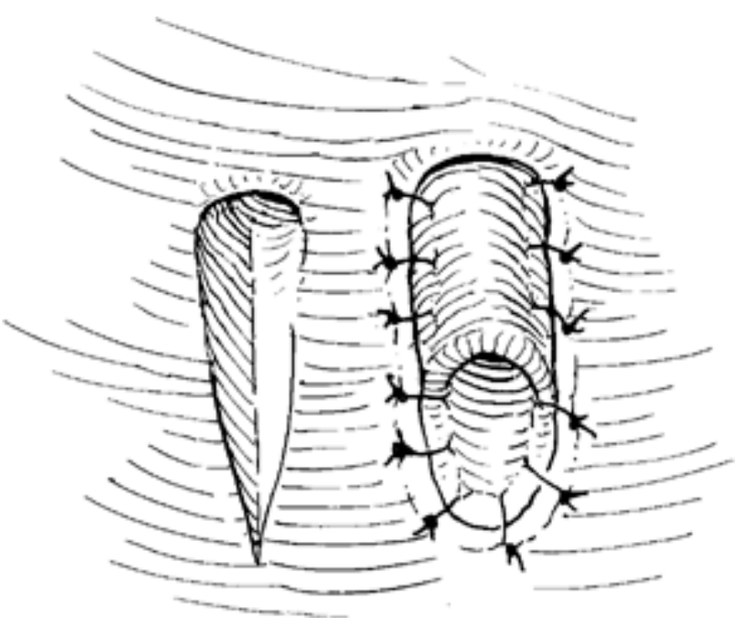

FIGURE 31.14. LeDuc ureterocolonic anastomosis. A 2- to 3-cm mucosal trough is created *(left).* The spatulated terminal ureter is brought through the apex and rested in the trough. Full-thickness 4-0 PGA sutures are placed from the distal posterior ureteral edge to the distal apex of the trough. Mucosal edges of the trough are tacked to the ureteral wall with interrupted sutures *(right).*

The patient returns in approximately 3 to 4 weeks for contrast studies of the reservoir. The ureteral stents and

the 14-Fr Foley are removed and the patient is taught the catheterization technique. If no problems are noted, the reservoir drainage tube is removed.

Results and Complications

Thus far this procedure has been performed in 25 patients. The results at 4 years are gratifying (89). No patient has required reoperation for incontinence, stomal obstruction, or parastomal hernia formation. Two patients had temporary difficulty with catheterization but have not required reoperation. The operative time is only slightly greater than that of the ileal conduit and markedly decreases with experience. The relative ease of the procedure and the excellent early results have prompted us to recommend the operation more widely and with much more enthusiasm than we had for prior methods of cutaneous diversion.

Indiana Pouch

One of the first continent cutaneous pouches to gain wide acceptance in the urologic community was the Indiana pouch developed at Indiana University by Rowland and co-workers (97). The major contribution of this pouch was the creation of a reliable continence mechanism. The pouch has remained popular because of all the continence mechanisms used in continent cutaneous diversions, this mechanism is one of the least technically demanding to construct.

Construction of the mechanism initially relied on the concept of buttressing the ileocecal valve with a double row of imbricating sutures taken to the entire ileal segment (96,97). However, because pressure profiles demonstrated that the continence zone was confined to the region of the buttressed ileocecal valve, it became apparent that the imbricating sutures were necessary only in the region of the ileocecal valve (9).

Technique

In this form of continent diversion (97), approximately 20 to 25 cm of cecum and ascending colon are isolated along with 15 to 18 cm of terminal ileum (Fig. 31.15A). The colon is detubularized about three-fourths of its length starting from the distal end. The ureters are anastomosed through a tunnel along the posterior colonic tenia. The continence mechanism consists of plicated terminal ileum, which reinforces the ileocecal valve (Fig 31.15B). The ileal plication consists of two rows of Lembert sutures 8 to 10 mm apart beginning at the ileocecal valve and extended 3 to 4 cm proximally and reinforced by a second layer of continuous silk sutures (Fig. 31.15C). The remaining ileum can be tapered over a catheter and excess ileum removed by a GIA

stapler. The pouch is created by folding down the opened cecum in a Heineke-Mikulicz configuration and closed with continuous 2-0 PGA suture material (Fig 31.15B). Ureteral stents are positioned, and a suprapubic tube is taken through the lower abdominal wall. A 1-cm buttonhole is made in the skin, anterior fascia, and posterior fascia. The catheterizable ileal limb is advanced between the rectus muscle. Excess ileum is removed. A flush skin stoma is created by sewing the ileal edges to the skin edge with interrupted absorbable suture material. The postoperative care of a patient with an Indiana pouch is similar to that for other right colon continent cutaneous diversions. Cecostomy tube removal and self-catheterization instruction should occur at 3 weeks after surgery.

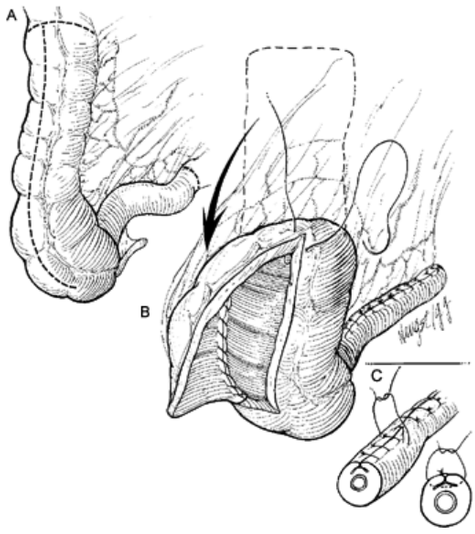

FIGURE 31.15. Indiana pouch. **A:** From 20 to 25 cm of cecum and ascending colon are isolated along with 15 to 18 cm of terminal ileum. The colon is detubularized about three-fourths of its length starting from the distal end. The ureters are anastomosed through a tunnel along the posterior colonic tenia. **B:** The continence mechanism consists of plicated terminal ileum, which reinforces the ileocecal valve. **C:** The ileal plication consists of two rows of Lembert sutures 8 to 10 mm apart beginning at the ileocecal valve and extending 3 to 4 cm proximally, and is reinforced by a second layer of continuous silk sutures. The remaining ileum can be tapered over the catheter and excess ileum removed by a GIA stapler. The pouch is completed by folding down the opened cecum in a Heineke-Mikulicz configuration **(B)** and closed with continuous 2-0 PGA suture material.

Results and Complications

In Rowland and associates' (97) first 29 patients, the average amount of catheterized urine was 291 mL, the average of the greatest volume of urine was 508 mL, and intraluminal pouch pressures did not reach more than 20 cm H_2O. In a report on 91 patients with a minimum follow-up of 6 months, 85 (93%) of the patients had daytime continence, and 69 (76%) of the patients had nighttime continence (99), but most of these patients had to catheterize themselves once at night to remain continent. The reoperation rate, mainly caused by complications with the efferent limb, was 26%. The advantages of the Indiana pouch are its relatively simple construction and an acceptable length of time for the operation. However, endoscopic studies on dogs at our institution have shown that the ileocecal valve, although reinforced by imbrication, undergoes anatomic changes after several months. The ileocecal valve changes to a permanent opening surrounded by a fibrotic ring, and it is unlikely that the actual valve is responsible for the urinary continence (118). Long-term results will show if incontinence will develop in patients after several years.

Florida Pouch

The distinguishing feature of the Florida pouch, described by Lockhart (68e), is the amount of colon used and the manner in which it is reconfigured.

Technique

The entire ascending colon and right third or half of the transverse colon is isolated, along with 10 to 12 cm of ileum. The proximal portion of the large bowel segment is mobilized and rotated laterally to form an inverted U (Fig. 31.16A). The entire large bowel is then detubularized along its antimesenteric border, and the medial limbs of the U are joined with continuous absorbable suture material (Fig. 31.16B and Fig. 31.16C). The ureters are implanted in the posterior plate in standard fashion. Construction of the catheterizable ileal segment continence mechanism is performed in a fashion similar to that for the Indiana pouch. One exception is that Lockhart suggests the application of opposing Lembert sutures, being taken on each side of the terminal ileum, to buttress the ileocecal valve. The standard drainage tubes are positioned and the large bowel plate is then closed side-to-side. The catheterizable limb is then brought through the skin and a stoma is created as previously described for the Indiana pouch.

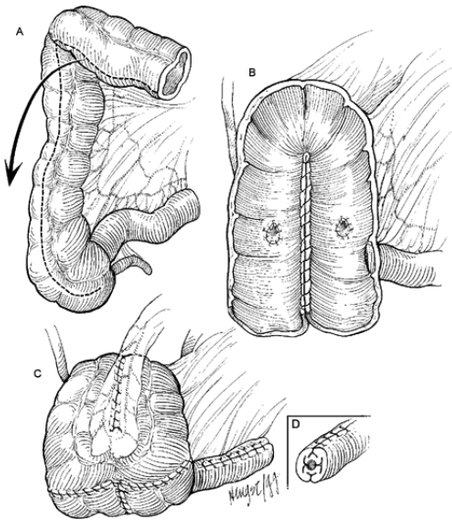

FIGURE 31.16. Florida pouch. **A:** The entire ascending colon and proximal third or half of the transverse colon are isolated, along with 10 to 12 cm of ileum. **B:** The proximal portion of the large bowel segment is mobilized and rotated laterally to form an inverted U. The entire large bowel is then detubularized along its antimesenteric border, and the medial limbs of the U are joined with continuous 2-0 PGA suture material. The ureters are implanted in the posterior plate in standard fashion. **C:** Construction of the catheterizable ileal segment continence mechanism is performed in a fashion similar to that for the Indiana pouch. **D:** Opposing Lembert sutures buttress the ileocecal valve.

Results and Complications

Urodynamics performed on 28 patients revealed pouch capacities of 500 to 1,200 mL, with intraluminal pressures at capacity ranging from 10 to 58 cm H_2O. In more than 100 patients, the overall reoperation rate was reported to be 7%. Seventy patients experienced hyperchloremia, but only four patients, including those with preexisting renal disease, required treatment.

Gastric Pouch

In certain circumstances, the use of stomach to create a urinary reservoir has become an attractive option. A most unique feature of stomach, when compared with the small and large bowel, is its consistent inability for electrolyte reabsorption. This property allows stomach to be considered the preferential reservoir for individuals with preexisting renal insufficiency. In addition, not only does stomach possess an inherent barrier against absorption of chloride and ammonium, but it also has the ability to actively secrete chloride ions (85). Therefore the hyperchloremic acidosis seen with other urinary intestinal diversions is avoided with gastric diversions. Other instances in which gastric diversions are viable alternatives include patients with prior entire lower-bowel irradiation or in whom shortening of the bowel is expected to lead to degrees of malabsorption. In any case, the technical feasibility of its use and its theoretic advantages have promoted clinical trials with gastric pouches, particularly in the pediatric population (2).

Technique

An 8- to 10-cm wedge-shaped segment is isolated from the greater curvature of the stomach. The section is then mobilized on a gastroepiploic vascular stalk by dividing the short gastric vessels proximal to the segment (Fig. 31.17A). The stomach is then closed with continuous 2-0 PGA sutures followed by interrupted simple ligatures at 1-cm intervals. The isolated segment is refashioned into a sphere by folding it back on itself and suturing the edges with a similar suturing technique (Fig. 31.17B). Ureteral implantation is performed in an antireflux fashion bilaterally. A Mitrofanoff cutaneous conduit can be created if the appendix permits. Otherwise, a proximal transureteroureterostomy can be

performed with the ipsilateral distal ureter tunneled into the reservoir and its distal extent brought to a catheterizable site.

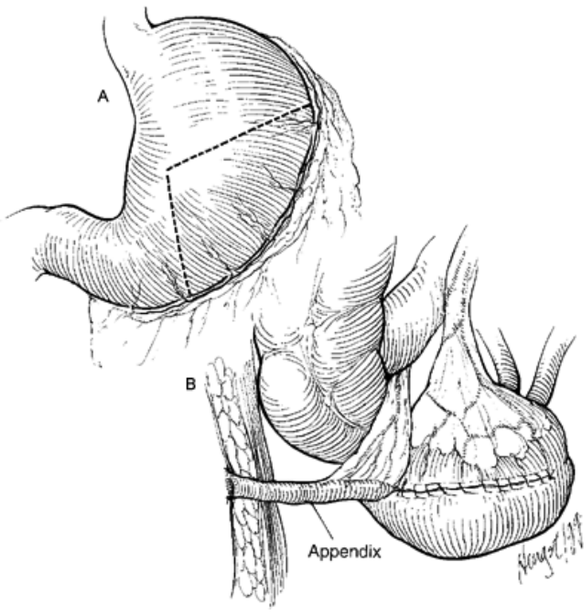

FIGURE 31.17. Gastric pouch. **A:** An 8- to 10-cm wedge-shaped segment from the greater curvature of the stomach is isolated. By dividing the short gastric vessels proximally to the fundus, the vascular pedicle preferably used is the left gastroepiploic artery. **B:** Ureterogastric anastomoses are performed, and the isolated wedge is fashioned into a sphere by folding it on itself and suturing the edges with continuous 2-0 PGA material. Either a patent appendix or native distal ureter is tunneled into the reservoir and then brought to the skin to serve as a catheterization portal.

Results and Complications

Mean pouch capacities of 245 mL and mean end-filling pressures of 35 cm H_2O have been reported (2). The most common side effect of gastric pouches is a dysuria and hematuria syndrome caused by aciduria. This condition is often amenable to acid-reducing therapies such as the use of proton pump inhibitors. Experience with gastric pouches is still limited.

Perspectives

The major short-term complications and the early reoperation rates of continent cutaneous diversions have diminished with further experience and refinements of technique. Improved experience with continent diversions has also resulted in shorter operative times for such procedures. Given the lack of need for external appliances, and continued urinary continence over time, continent diversions have become the diversions of choice for most patients. The associated differences in quality of life associated with continent and incontinent urinary diversion techniques must be addressed and evaluated.

URINARY DIVERSIONS TO THE URETHRA (ORTHOTOPIC)

Part of "31 - URINARY DIVERSIONS AND CONTINENT RESERVOIRS "

The ideal bladder replacement should mimic the function of the native bladder. For example, the neobladder should be able to store an adequate volume of urine at low pressures, have minimal absorption of its stored contents, completely empty volitionally, provide resistance to bacterial translocation, and have a low propensity for mucus production or stone formation. None of the urinary reservoirs in clinical use entirely achieves these goals. With the attempt to develop a satisfactory bladder replacement, many complications were encountered with the outlet of the reservoir. Several variations of intestinal neobladders attached to the urethral remnant in male patients have been introduced. These offer several advantages: no physical or psychologic problems caused by an abdominal wall stoma; continence in most patients, at least during the daytime; the ability to store and empty urine often without the need of a catheter; and an improved body image, resulting in more self-confidence and better sexual performance (13). Initially, a major shortcoming of urinary diversion to the urethra was that high intraluminal pressures existed in the contracting intestinal reservoir. Persistent peristaltic contractions of the intestinal bladder, particularly during sleep, create pressures high enough to overcome the urethral closure pressure and cause incontinence.

To reduce the high-pressure contractions seen in tubular portions of continent urinary diversions, antimesenteric disruption of the circular smooth musculature (detubularization) of the isolated bowel segments has been recommended. Detubularization reduces the frequency and strength of the peristaltic pressure waves and increases neobladder compliance. Detubularized bowel also offers several advantages for reconfiguration necessary to create a neobladder (58,100). Folded detubularized ileum or colon leads to a neobladder with a larger diameter. Volume increases by the square of the radius, and the newly formed neobladder therefore has a much larger capacity than the unopened tubular intestinal segment of the same length. The larger diameter of the reconfigurated neobladder also will also accommodate larger volumes of urine at lower pressures.

Only certain patients are eligible for a urinary diversion to the urethra. Carcinoma *in situ* or an invasive tumor at the bladder neck or anywhere in the urethra is a contraindication. Nevertheless, 8% to 12% of patients with bladder cancer develop a recurrence in a urethra free of dysplasia at the time of cystectomy.

Three basic tenets should be adhered to when considering construction of a continent diversion to the urethra:

1. It is essential that adequate mobilization of the bowel segment and ureters be performed for a sufficient tension-free urethra anastomosis. If tension exists on the urethral anastomosis, the patient is at increased risk of anastomotic leakage and possibly anastomotic disruption. Most important, this tension may be transmitted to the neobladder mesentery, resulting in compromise of its vascular supply, which could ultimately result in ischemia, necrosis, and loss of the entire bladder substitute (1).
2. The second tenet applies to surgeon familiarity with and ability to perform a variety of different diversions. Depending on the integrity of the bowel segment intended to be used, the surgeon may have to resort to an alternative bowel segment or an entirely different type of diversion. Unforeseeable conditions, such as bowel malignancies, anatomic variability, patient instability, or urethral involvement with tumor, may contraindicate neobladder construction. Therefore familiarity with continent cutaneous diversion and incontinent diversion procedures is imperative.
3. Preservation of the intrinsic external urethral sphincter determines the degree of continence. All periurethral tissue must be intact and the entire length of urethra preserved (72).

Ileal Neobladders

Camey Procedure

For years, the Camey or similar procedures were the most popular urinary reservoirs to the urethra. In 1979 Camey and LeDuc (19) reported their positive experience with 90

patients who underwent construction of an ileal bladder after radical cystectomy. In 1984, Lilien and Camey (68d) reported on their long-term results in 25 patients. More than 90% of their patients achieved continence if they adhered to an interval of voiding every 2 to 3 hours. However, the operative mortality rate in 84 patients approached 5% (4 of 84 patients), and in 15% of the patients the procedure was not feasible because of a short or fatty mesentery. Patients were usually incontinent at night unless they emptied their reservoir every 2 to 3 hours. Prolonging daytime intervals of urine evacuation or placement of an artificial urinary sphincter around the urethra resulted in distention of the neobladder and marked hydronephrosis. Others reported daytime incontinence rates as high as 20%. In some of our patients with significant daytime incontinence after a Camey procedure, the measured intraluminal pressure in the reservoir reached 80 cm H_2O. This dampened enthusiasm for the procedure, but the new understanding of the principle of detubularizing and reconfiguring the bowel to lower pressure preserved the role of the ileal neobladder in urology.

The simplest form of reconfiguration is transverse folding of a detubularized bowel segment. In his theoretic deliberations on intestinal neobladders, Hinman (58) demonstrated the gain in volume by reconfiguring detubularized bowel. A 40-cm intact ileal segment, as used for the original Camey urinary reservoir, will hold approximately 160 mL. The same segment folded once and retubularized will hold around 320 mL. If it is folded on itself again, as done for example by Goodwin and associates (47) or Kock and colleagues (67a), its volume will increase to 660 mL.

A modification of the original Camey procedure, the Camey II operation, uses this principle of bowel detubularization to prevent neobladder peristaltic activity and its resultant complications (18). A major component of the Camey II procedure, as in other orthotopic neobladders, is the careful dissection of the urethra from the apex of the prostate. This preservation of an intact urethral stump allows earlier restoration of continence.

Technique

A 60-cm ileal segment is selected that can reach the region of the membranous urethra without tension. Following isolation of the segment and restoration of bowel integrity, the ileal segment is incised along its antimesenteric border throughout its length (Fig. 31.18A). In the region of the ileourethral anastomosis, the incision is spatulated to curve toward the mesenteric border. The entire detubularized segment is folded over itself in the form of a transverse U, with the medial borders of the U sutured together with an absorbable running 2-0 absorbable suture. Both ureters are brought into the lumen through a separate stab incision. For the ureteroileal anastomosis, an antireflux technique described by LeDuc (68b) is used. A 1-cm opening is made in the ileal wall at the site selected for the ileourethral anastomosis. The remaining ileum is closed by folding the segment to complete the neobladder construction. Closure is achieved with running sutures of similar absorbable material (Fig. 31.18B). The ileal sheet is then advanced into the pelvis and the anastomosis to the urethra is performed with six to eight previously placed absorbable sutures. It has been recommended to suture the posterior aspect of the ileal neobladder to the fascia to reduce tension on the anastomosis.

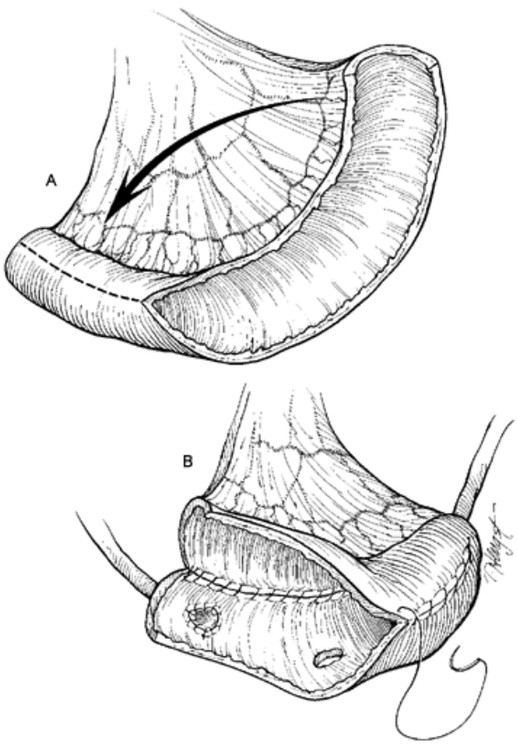

FIGURE 31.18. Camey II neobladder. **A:** Selection of 60-cm ileal segment with appropriate vascular supply and antimesenteric splitting of ileum are shown. **B:** Ileal plate is folded into a transverse U with its medial borders sutured together with continuous 2-0 PGA suture. A site is chosen and a 1-cm opening is made in the ileal wall in preparation for the ileourethral anastomosis. Following the urethral anastomosis, the ureteroileal anastomosis is performed in a LeDuc fashion. The remaining ileum is closed by suturing the anterior wall of the neobladder (following completion of the anastomosis).

Postoperatively, uninterrupted urine drainage must be maintained. Copious mucus formation can obstruct the catheter and subsequently can lead to disruption of the ureteroileal anastomosis. Therefore, as with other types of continent diversions, early irrigation is advised. Otherwise, no substantial differences are noted in the postoperative care of these patients compared with other continent diversions.

Results

The Camey II modification has resulted in improved continence. Intraluminal reservoir pressures have been found to be in the acceptable range of 10 to 40 cm H_2O during filling and at capacity, and nocturnal continence rates of 60% to 75% have been reported.

Studer Neobladder

Studer and co-workers (120) reported on clinical results of an orthotopic ileal bladder replacement using an ileal reconfiguration similar to the cup-patch technique described by Goodwin and associates (47). The antireflux mechanism consisted of simply attaching the ureters to an isoperistaltic proximal limb of 20 cm. This neobladder has particular utility in cases where limited ureteral length is a factor during implantation into the neobladder. The afferent isoperistaltic limb can be extended cephalad to accommodate a shortened right or left ureter.

Technique

A 60-cm ileal segment is isolated approximately 25 cm proximal to the ileocecal valve. The distal 40 to 45 cm of the segment is opened along its antimesenteric border, leaving the proximal 15 to 20 cm intact (Fig. 31.19A). The proximal portion is then rotated 180 degrees counterclockwise on its mesentery, so this portion lies in the right retroperitoneum. The detubularized portion is then folded in half and its medial walls are connected with a running 2-0 PG suture, thereby constructing the posterior plate of the segment. Anastomosis of the urethra to a 1-cm opening in the most dependent portion of the reconstructed ileum is completed over a urethral catheter with five to six previously placed urethral sutures. Standard ureteroileal (Bricker) anastomoses are performed in proximity to the apex of the isoperistaltic proximal limb (Fig. 31.19B). Ureteral stents are brought out through the neobladder and a separate abdominal incision; a suprapubic tube is positioned, and perianastomotic drainage is provided.

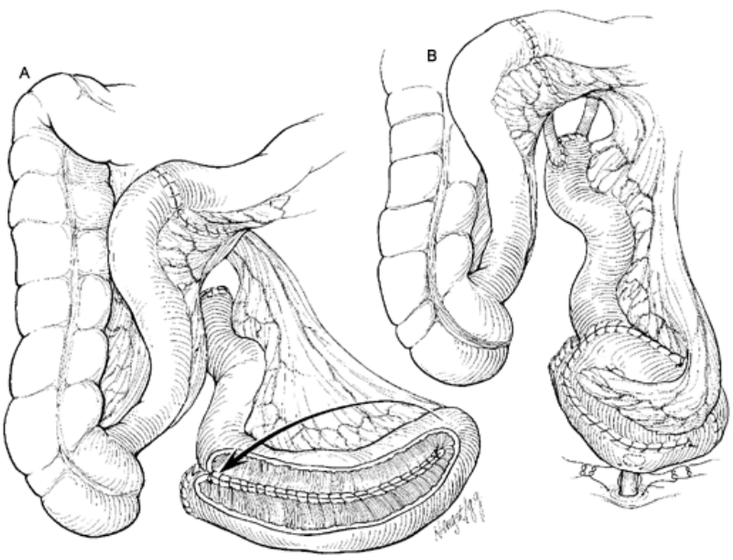

FIGURE 31.19. Studer neobladder. **A:** An ileal segment measuring 60 cm is isolated 20 cm from the ileocecal valve. The distal 40 cm is detubularized along the antimesenteric border and folded in a transverse U configuration. The posterior plate is completed by joining the medial walls with continuous 2-0 PGA suture. **B:** Anastomosis of the posterior plate of the ileum to the urethra is performed with several urethral sutures. Standard ureteroileal (Bricker) anastomoses are performed at the apex of the proximal limb.

Results and Complications

Postoperative bladder capacity initially ranged from 150 to 250 mL. Within 6 months, mean pouch capacity was reported to be 450 mL with intraluminal pressures varying from 20 to 40 cm H_2O (20). In recent patients, daytime incontinence was rare, but nighttime incontinence was seen in almost half the patients (20). The need for surgical revision was rare in both their initial and recent patients. Electrolyte disturbances were seen rarely, although they were more evident when longer segments of ileum were

used. Vitamin B_{12} deficiency has not been seen clinically, probably because of preservation of a reasonable segment of distal ileum. According to radiographic studies, the integrity of the isoperistaltic proximal limb prevents the deleterious effects of any reflux from the resting, filling, emptying, or storage pressures of the neobladder (120).

In a more recent review, Cancrini and colleagues (20) reported on 96 patients who underwent Studer ileal orthotopic neobladders for invasive bladder carcinoma. The mean follow-up was 28 months. Overall, a 6% perioperative death rate and a 6% early postoperative complication rate, all directly related to the procedure, were reported. Of their patients, 24% had late complications requiring hospitalization, and overall, 10% required a second operation. The rate of ureteral strictures was 7%. The cohort's daytime continence rate was 98% at 2 years (97% at 1 year), although 22% exhibited occasional stress urinary incontinence. The nighttime continence rate was 74% at 1 year and 83% after 2 years. The average neobladder capacity was 350 cm^3 at 2 years (330 cm^3 at 1 year), with an associated neobladder pressure at capacity volume of 10 to 20 cm H_2O.

Hautmann Neobladder

To further increase the volume of the ileal neobladder, an M-shaped reconfiguration was introduced by Hautmann and associates (53).

Technique

Approximately 60 to 80 cm of terminal ileum is detubularized and arranged to an M-shaped ileal plate (Fig. 31.20A and Fig. 31.20B). The ureters are implanted directly into the neobladder using LeDuc's antireflux technique (Fig. 31.20C). The urethra is connected to a separate opening in a small, U-shaped ileal flap created by displacing the detubularizing incision from the antimesenteric border to a more anterior position for a length of 5 cm. The neobladder is completed by rolling the ileal sheet around the longitudinal axis and closing it with a single row of through-and-through 4-0 polyglactin 910 running sutures (Fig. 31.20D).

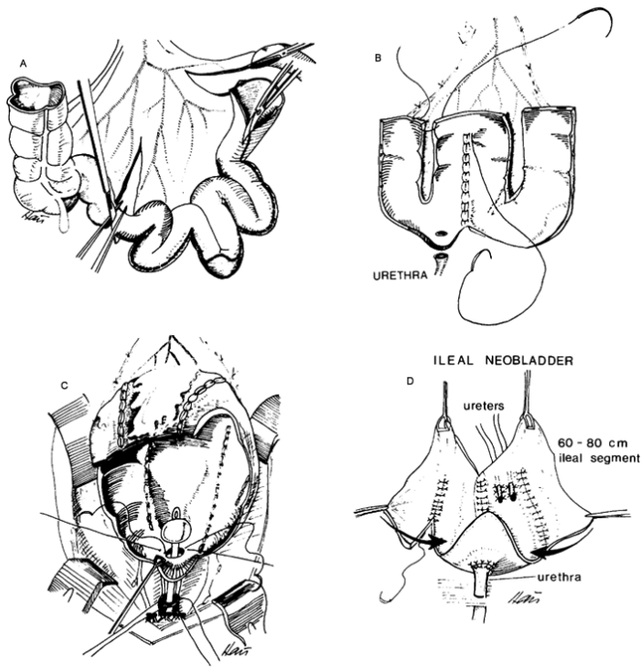

FIGURE 31.20. Hautmann neobladder. **A:** Selection of ileal segment with appropriate vascular supply and antimesenteric splitting of ileum are shown. **B:** A creation of an ileal sheet by side-to-side anastomosis of incised ileum following arrangement in an M (or W) shape. Note position of U-shaped flap for ileourethral anastomosis. **C:** Anastomosis of ileal sheet to urethral remnant with six mattress sutures tied from inside the neobladder (anterior view). **D:** Ureteral implantation into the ileal sheet through separate incisions in the posterior wall similar to the technique described by Le Duc. The urethral remnant has been anastomosed to an opening in the U-shaped bowel flap, and the pouch can be completed as denoted by the arrows. (From Hautmann RE, Egghart G, Frohneberg D. *J Urol* 1988;139:39, with permission.)

Hollowell and colleagues (61) describe using an ileal chimney modification to the Hautmann pouch. For this adaptation, the most proximal 10 cm of the isolated bowel segment is not detubularized. The remnant 50 to 70 cm of ileum is otherwise fashioned as originally described by Hautmann. Instead of implanting the ureters into the pouch, the ureters are anastomosed to the proximal, nondetubularized (chimney) segment.

Results and Complications

A follow-up of the first 100 patients showed promising results. The average maximum capacity was 821 mL, with a mean resting pressure at maximum filling of 26.4 cm H_2O, and maximal pressure amplitudes of 30 cm H_2O (52). In a review of more than 200 patients (56), total day and nighttime continence was seen in 85% at 3-year follow-up. Intermittent catheterization was required in 4% for postvoid residual urine volumes greater than 100 mL. There were five perioperative deaths, an overall complication rate of 7.5%, and a neobladder-related complication rate of 6.5%. Of the patients, 32% required either rehospitalization or reoperation for postoperative problems, such as ileus, abscess, coloreservoir fistula, hydronephrosis, ureteral obstruction, and ureteroileal anastomotic structure.

Hemi-Kock Neobladder

Clinical results with an ileal U neobladder with or without intussusception of the afferent ureter-containing limb have been reported (57). This neobladder has less capacity than, for example, a Kock neobladder, but it is technically simpler to create and requires less time. The hemi-Kock neobladder offers the advantage of an adequate urine storage with acceptable low intraluminal pressure at maximal filling. Basically the same technique as for the cutaneous Kock pouch is used.

Technique

A 45-cm segment of ileum is isolated 30 to 50 cm proximal to the ileocecal valve, detubularized on the antimesenteric border, folded, and sutured together on one side to create a U-shaped intestinal plate, which is then folded transversely to create the reservoir. The same antireflux mechanism as for the cutaneous Kock pouch is used. The urethra is anastomosed to an opening left in the most dependent portion of the suture line uniting the reconfigured ileum.

Results and Complications

In a small series of 16 patients with a relatively short follow-up, Kock and co-workers (67c) demonstrated neobladder capacities of 300 to 500 mL, intraluminal pressures of less than 40 cm H_2O, daytime continence in all, and nighttime continence in 85%. No hydronephrosis has been reported so far, and no reoperation was necessary. Skinner and colleagues (108) reported daytime continence in 94% and nighttime continence in 84%. Early complications were seen in 11%.

Ileocolonic Neobladders

The ileocecal segment in various reconfigurations has been used to form a variety of neobladders. The cecal portion requires mobilization from its fixed position for urinary reconstruction. It has a larger diameter than the ileum and can usually be mobilized without difficulty into any area of the abdomen or pelvis. The orthotopic Mainz (*M*ixed *A*ugmentation *I*leum' *N*' *Z*ecum) neobladder, the ileocolonic neobladder (Le Bag), and the authors' adaptations all offer the advantage of a larger intraluminal volume with a

shorter segment of bowel than is necessary for an ileal orthotopic reservoir.

Mainz Neobladder

The orthotopic Mainz neobladder is a variation of the continent cutaneous catheterizable version of the Mainz. Both share the common principle of using the cecum and a folded ileal segment to create a broad sheet of intestine, which can then be closed in a spherical fashion (124,125).

Technique

Following isolation of a 10- to 15-cm segment of cecum with a 20- to 25-cm segment of ileum, an ileoascending colostomy is performed to restore intestinal continuity, and the mesenteric defect is closed (Fig. 31.21A). The entire segment is detubularized along its antimesenteric border, sacrificing the ileocecal valve. It is sewn together side-to-side in the shape of an incomplete W with a single layer of running absorbable sutures to create an intestinal plate. The ureters are brought into the pouch through a 5-cm submucosal tunnel along the posterior tenia of the colon, anastomosed to the mucosa and stented (Fig. 31.21B). An appendectomy is performed, and a buttonhole incision is created at the base of the cecum, which serves as the site of the urethrointestinal anastomosis. The lateral portions of the intestinal plate are then rotated anteriorly to the right side; urethral and suprapubic catheters are positioned, and the neobladder is closed (Fig. 31.21C).

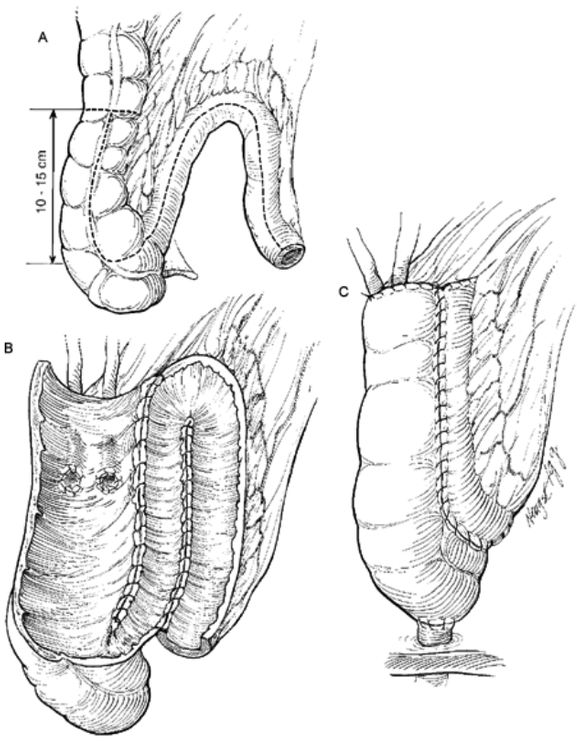

FIGURE 31.21. Mainz neobladder. **A:** From 10 to 15 cm of cecum and ascending colon with 20 to 30 cm of ileum are isolated. **B:** The entire segment is marsupialized along its antimesenteric border, and a broad posterior plate is created by suturing the apposing edges of the limbs to create an incomplete W. Tunneled ureterocolonic anastomoses are performed. **C:** A buttonhole incision is created at the base of the cecal portion for the urethrointestinal anastomosis. The neobladder is closed by folding the lateral limbs anteriorly and suturing in a continuous fashion.

The postoperative care of the Mainz neobladder is similar to that of ileal voiding diversions with an added emphasis on prevention of intraluminal mucus accumulation. Diversions with cecal segments may be found to require more frequent irrigation during the initial postoperative phase because of a propensity for greater mucus production, as compared with diversions that are solely composed of ileum.

Results and Complications

Daytime continence is reported to be greater than 90%, and nighttime continence, with two or three scheduled voids, is noted in 75%. Intraluminal pressures of 31.40 cm H_2O have been noted at mean capacities of 500 mL (126). Late complications primarily consisted of incontinence and urethral anastomotic strictures. Of 34 orthotopic diversions, 4 required either an open or endoscopic reoperation for such complications (126).

Le Bag Neobladder

The Le Bag neobladder is primarily a derivative of the Mainz neobladder that uses a single segment of ileum along with cecum. It consists of two variations of urethral anastomosis.

Technique

Approximately 20 cm of cecum and ascending colon are isolated with a corresponding length of terminal ileum (Fig. 31.22A). The entire segment is detubularized along its antimesenteric border, folded, and the free ileal colonic borders are sewn to one another side-to-side (Fig. 31.22B and Fig. 31.22C). The initial variant of this operation preserved an intact tubularized proximal 3 to 4 cm of ileum, which was then anastomosed to the urethral stump by rotating the neobladder 180 degrees into the pelvis (Fig. 31.22D). This maneuver was subsequently abandoned because it was thought that the intact ileal segment may contribute to postoperative incontinence by its retained peristalsis. The technique was therefore modified to create the urethral anastomosis to a dependent cecal buttonhole. Once the final position of the neobladder has been secured, a small hiatus in the anterior suture line is left open to perform the ureteral implantation (according to the previously described Goodwin technique for ureterosigmoidostomy). Postoperative care is similar to that for other types of orthotopic colonic diversions.

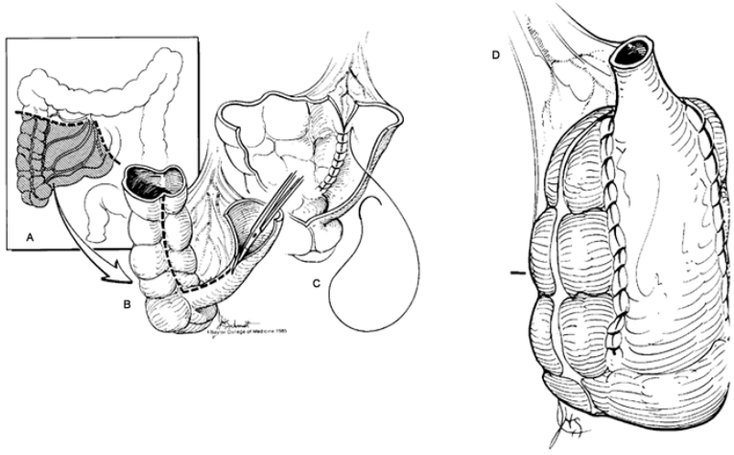

FIGURE 31.22. LeBag ileocolonic neobladder. **A:** Selection of ileocolonic segment with single vascular pedicle. **B:** Commencement of incision along antimesenteric border to create two flat sheets of bowel. **C:** Suturing of ileal and colonic segments. The outer two edges are sutured first. The inner edges are only sutured partially, so that the urethra can be anastomosed through the residual opening (see text). **D:** The completed pouch before 180-degree rotation to enable anastomosis to the urethra. (From Light JK, Engelmann UH. *J Urol* 1986;136:27, with permission.)

Results and Complications

Kolettis and colleagues (68) described their updated experience with the Le Bag orthotopic urinary diversion. Between 1990 and 1995, the Le Bag construction was used in 38 patients with bladder cancer. With a mean follow-up of 14

months, they describe a 21% incidence of perioperative and early complications. The late complication rate was 34%. Of their patients, 29% required reoperations, with 21% requiring open procedures and 8% requiring endoscopic procedures. The rate of ureterointestinal anastomotic strictures was 8%. Overall, the daytime continence rate was 91%. The nocturnal continence rates were not as high, with 46% of their patients being completely continent at night, and an additional 34% exhibiting only mild nocturnal incontinence. Overall, three patients required clean intermittent catheterization for inability to spontaneously empty their urinary pouch. The median pouch capacity was 600 mL, and the mean postvoid residual was 90 mL. Mild hypochloremic acidosis was noted in nearly all of their patients.

UCLA Neobladder I and II

The UCLA, the orthotopic Mainz, and the Le Bag neobladders share the common principle of configuring cecum and ileum together to function as a capacious, low-pressure, continent, spherical, urinary diversion to the native urethra (89,126). In general, the technique of our institution and the recent variant of the Le Bag differ from one another in only a few features, predominantly the technique used for ureteral implantation.

We have recently also applied the concept described by Studer and co-workers (120) of using an intact proximal ileal limb for ureteral anastomoses. When positioned in the right retroperitoneum, this limb can function as an extension or bridge from the diversion to the ureters. This modification has been of significant value in situations where limited ureteral length has placed a ureterocolonic anastomosis in jeopardy of being under tension.

Technique (UCLA I)

A bowel segment consisting of 10 to 15 cm of cecum and ascending colon, as well as 20 cm of terminal ileum, is sufficiently mobilized, assessed for its ability to reach tension-free to the urethra, and then isolated (Fig. 31.23A). An ileoascending colostomy is performed to restore intestinal

continuity, and its mesenteric trap is closed. The right colon-cecal portion is detubularized through its anterior tenia down to the ileocecal valve. The ileocecal valve is sacrificed, and the entire ileal segment is detubularized through its antimesenteric border (Fig. 31.23B). This specific detubularization technique prevents medial redundancy and "bunching" of the distal posterior wall of the neobladder. A broad, posterior plate is created by suturing the opposing medial walls of the cecum and ileum with running 2-0 polyglactin suture (Fig. 31.21C). All suture lines are reinforced with interrupted ligatures at 1.5-cm intervals.

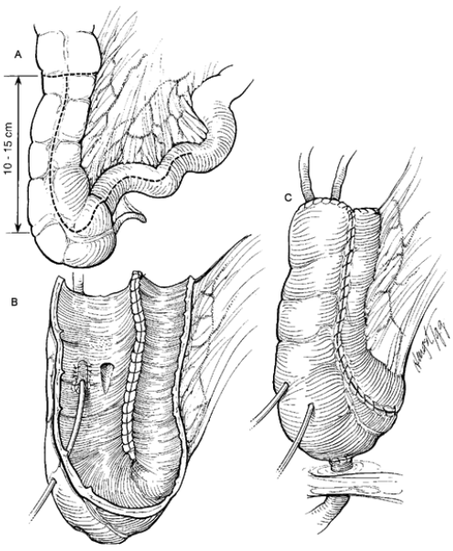

FIGURE 31.23. UCLA I neobladder. **A:** From 10 to 15 cm of cecum and ascending colon with 15 to 20 cm of terminal ileum is isolated. **B:** The right colon-cecal portion is detubularized through its anterior tenia down to the ileocecal valve. The ileocecal valve is sacrificed, and the ileal segment is detubularized through its antimesenteric border. A broad plate is formed by suturing the opposing medial walls with continuous 2-0 PGA sutures. A 1-cm buttonhole incision is created in the most dependent cecal portion of the neobladder. **C:** The urethrocolonic anastomosis and the ureterocolonic anastomoses (Le Duc technique) are performed, and the neobladder closure is completed.

A routine appendectomy is performed, and a 1-cm incision is made in the most dependent area of the cecal portion of the neobladder for a tension-free anastomosis to the urethra. Five to six previously placed 2-0 PGA urethral sutures are then brought full thickness through the incision at the base of the cecum. A urethral catheter is positioned and the sutures are tied.

Ureterocolonic anastomoses are carried out in a Le Duc fashion (Fig. 31.14). The ureters are brought through separate openings in the posterior wall of the midcecum. Instead of creating an antireflux tunnel, the mucosa is simply incised at a length of 2 cm, creating a small trough. The ureters are then spatulated, and three full-thickness 4-0 PGA sutures are placed from the distal posterior ureteral edge to the distal apex of the trough. The mucosal edges of the trough are then tacked to the intact ureteral wall with a few 4-0 PGA sutures. Each ureter is stented with a polyethylene stent, which then can be passed through a small stab wound in the ileum and brought out through the abdominal wall. The neobladder construction is then completed; a suprapubic tube is placed, and perianastomotic drainage is provided.

Technique (UCLA II)

A 10-cm-longer (compared with the UCLA I) ileal segment is isolated with the cecum and ascending colon. The proximal 10 cm of the ileum is left tubularized (Fig. 31.24A and Fig. 31.24B). Otherwise, the neobladder is constructed in a similar fashion until the ureteral anastomosis is performed. The intact proximal ileal limb is rotated to the right retroperitoneum, and Bricker ureteral anastomoses are performed and stented (Fig 31.24C). The remainder of the procedure is the same as that described for the UCLA I. No alterations in postoperative care pertain to either neobladder.

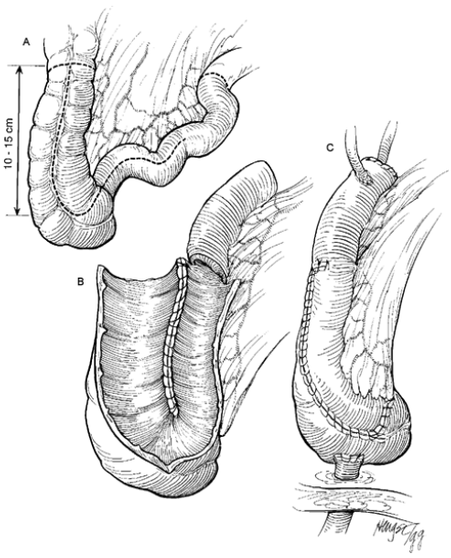

FIGURE 31.24. UCLA II neobladder. **A:** A 10-cm-longer (compared with the UCLA I) ileal segment is used. **B:** The proximal 10 cm is left intact; the medial walls of the detubularized portion are sutured with continuous 2-0 absorbable sutures. **C:** Bricker ureteral anastomoses are performed, and the urethrocolonic anastomosis and neobladder closure are the same as described for the UCLA I neobladder.

Results and Complications

Upon review of our initial experience (10 patients), mean capacities of 450 mL were noted with intraluminal pressure ranges of 20 to 45 cm H_2O. In a review by Raz and associates (89), the clinical, urodynamic, and metabolic results of the UCLA I neobladder were assessed for 19 patients. Follow-up protocol for each patient included an intravenous urogram, serum chemistries, and cystoscopy at 3 months, then every 6 months for 2 years, and then yearly thereafter. Videourodynamics were performed at 6 months after surgery. Mean follow-up was 23 months, with a range of 6 to 42 months. The ability to void to completion was seen in 17 of 19 (89%), with 2 of 19 (11%) requiring intermittent catheterization for postvoid residuals of 400 to 500 mL. Complete daytime continence was noted in 17 of 19 (89%), and stress urinary incontinence requiring protection was seen in the remaining 2 patients. Nocturnal incontinence was noted in 6 of 19 (32%), but 4 of these 6 patients preferred not to wake through the evening to void.

Renal function was stable in all 19 patients. Serum sodium, potassium, chloride, calcium, vitamins B_{12} and D, and folate levels were normal in all patients. Mild metabolic acidosis was seen in 7 of 19 patients (37%). Upper urinary tract radiologic studies demonstrate mild pelvocaliceal dilation in 2 of 19 (11%), both of whom were asymptomatic.

Urodynamic studies revealed normal compliance in all patients and filling pressures less than 20 cm H_2O. Phasic contractions were seen in 9 of 19 (47%). Mean capacity was 575 mL with a range of 350 to 1300 mL. Of the 19 patients, 17 were able to empty their neobladders via pelvic floor relaxation and abdominal straining at acceptable voiding pressures.

No early complications were noted in these 19 patients or 6 others. No subsequent upper tract infections requiring rehospitalization were seen. Late complications were found in 2 of 19 (11%), both of which were ureteral anastomotic strictures that required intraoperative incision. No urethral anastomotic procedures have been required. No chronic diarrhea or osteomalacia has been seen. The authors conclude that this ileocolonic neobladder provides a compliant, capacious reservoir with good functional, urodynamic, and continence results without major complications.

Perspectives

Despite the problems associated with urethrointestinal anastomosis, the neobladder approach theoretically remains the best method of postcystectomy urinary diversion. When combined with sparing of the corporeal nerves to the penis, the best possible result can be achieved, with complete restoration of the patient's body image and retention of sexual function. However, the operation must be used with caution in patients with carcinoma in situ and tumors near the bladder neck or the prostatic urethra. The high incidence of nighttime incontinence with some methods has been unacceptable to many patients and may represent the major deterrent to the wide adoption of the procedure. Long-term follow-up is not available, and the true incidence of stones, retention, and upper tract deterioration is as of yet unknown. Judicious modifications of the procedure, combined with use of an external artificial sphincter in some instances, may improve acceptance of these procedures, representing a major advance in achieving quality of life for

the bladder cancer patient. Our success with the procedure has encouraged us to offer it to most patients with bladder cancer, unless contraindicated. However, some patients still prefer the simpler ileal conduit.

Orthotopic Urinary Diversions in Women

Until the past decade, the concept of orthotopic neobladder construction in women undergoing radical cystectomy had not been extensively entertained. Concerns about risk of urethral tumor involvement, compromising the cancer surgery, and the potential for postoperative urinary incontinence were major reasons orthotopic neobladder construction in female bladder cancer patients had not been evaluated more enthusiastically.

Rationalizations that absence of the "buffering" prostate and prostatic urethra in the female inherently place the female bladder cancer patient at higher risk of primary or secondary urethral transitional cell carcinoma (TCCa) had been raised. However, studies demonstrate results to be different than previously speculated. Ashworth, in a study in which all patients with bladder tumors were cystoscopically evaluated, noted that 4.1% of men had concomitant urethral involvement, as compared with only 1.4% of women with bladder cancer. Retrospective pathologic evaluation of bladder and urethral specimens of women undergoing radical cystourethrectomy for advanced or high-risk TCCa revealed the overall histologic incidence of urethral involvement in patients with TCCa of the bladder to be 2% to 13% (28,112,116). This rather large range of urethral involvement highlights the differences in demographics of each reported group. However, subset analysis of each study reveals a similar finding: No urethral involvement was noted in any case where the bladder neck was not concomitantly involved with tumor. More specifically, Coloby and colleagues (28), Stein (112), and Stenzl (116,117) describe bladder mapping evaluations of women undergoing cystourethrectomy for TCCa. In each study, approximately

21% to 32% of patients had bladder neck involvement. Whereas Stenzl described a 16% incidence of concomitant urethral involvement when bladder neck involvement was noted, Colomby and Stein revealed 33% and 50% incidences of urethral involvement, respectively. Again, in these three large series, in the absence of bladder neck involvement, no urethral involvement was noted at the time of cystourethrectomy. Interestingly, of patients with urethral involvement, 33% to 66% have pT4 disease, suggesting that a significant number of urethral involvements are due to extravesical extension of the tumor and infiltration into the pelvic structures (including the urethra).

Based on the published series, it is suggested that the risk of urethral involvement at the time of cystectomy without any evidence of bladder neck involvement is low. Therefore, based on bladder cancer mapping studies, 68% to 79% of patients would be of relatively low risk for having urethral involvement at the time of radical cystectomy. But what is the long-term recurrence rate of TCCa in the spared urethral segment? This rate, in selected female patients, may be as low as 2% with a 20-year follow-up (117). However, further studies are necessary to validate these results. One reason for this relatively low recurrence, as compared with the urethral recurrence rates noted in male patients undergoing urethra-sparing cystectomy, may be that the female urethra is not only shorter than the male urethra, but the distal one-third to one-half of the female urethra is composed of a squamous histology. This squamous epithelium progresses cephalad with increasing age and decreasing estrogen levels (113,131,132). Therefore, in essence, the risk of urethral involvement at the time of cystectomy or with follow-up for women with bladder cancers not involving the bladder neck is relatively low. Based on these findings, a urethra-sparing procedure can be acceptable from an oncologic standpoint.

The second main concern to address is the risk of postoperative stress urinary incontinence in women undergoing resection of their bladder necks and a portion of their proximal urethra. Anatomic evaluations suggest that preservation of the distal two-thirds of the urethra, the pubourethral ligaments, the pelvic floor musculature, and the urethral rhabdosphincter and its associated innervation (pudendal nerve) is adequate for preservation of urinary continence in women (27,112,117). In fact, most large series reveal that daytime postoperative urinary incontinence in women with orthotopic neobladders is a less common event than expected and may often be caused by inadequate storage pressures or storage volumes rather than inadequate urethral resistance. In smaller series by Cancrini (21), Blute (12), and Hautman and colleagues (55), daytime continence rates ranged from 90% to 100%, and evening continence rates ranged from 70% to 80%. To achieve and maintain these evening continence rates, patients are often required to void or empty their neobladder two to three times per evening to avoid incontinent episodes during the night. In the largest series of orthotopic neobladders in women undergoing radical cystectomy for TCCa, Stein (111) describes an 88% daytime continence rate and an 82% evening continence rate in 34 patients treated at their center.

Interestingly, postoperative urinary retention, or “hypercontinence,” is a more common problem than previously anticipated. Approximately 15% to 20% of women undergoing orthotopic neobladder construction will require clean intermittent catheterization (CIC) for inability to void spontaneously or because of high postvoid residuals (54,135).

Clearly, orthotopic neobladders can be performed in properly selected female bladder cancer patients without compromising the cancer surgery, while achieving acceptable continence levels. But does this procedure provide a better quality of life for women? Anecdotally, surgeons performing orthotopic neobladders state that their neobladder patients are much happier and better off than their other patients who have not undergone orthotopic neobladder constructions. However, the published female neobladder series are still relatively small, and no validated quality-of-life evaluations have been performed to scientifically answer this question.

However, quality-of-life surveys in male bladder cancer patients undergoing incontinent cutaneous diversions versus orthotopic neobladders do not demonstrate any dramatic quality-of-life benefit for the neobladder group. More quality-of-life studies are anticipated and are needed to better answer this question.

Special Considerations for the Female Neobladder Candidate

After the female patient is evaluated from an oncologic, a gastrointestinal, and a renal standpoint, as previously outlined for all patients being considered for a cystectomy and urinary diversion procedure, particular attention should be paid to the following points:

1. Absence of bladder neck involvement
2. Patient's motivation to perform timed voiding to minimize incontinence or neobladder overdistention
3. Patient's understanding and acceptance of up to 20% diurnal and up to 30% nocturnal incontinence rates
4. Patient's acceptance of 15% to 20% risk of hypercontinence with associated need and ability to CIC per urethra
5. Patient's sexual function

The patient's bladder neck should be biopsied preoperatively to preclude bladder neck involvement. Although some advocate only intraoperative frozen histologic evaluations of the bladder neck and proximal urethra (111), we think that preoperative evaluation of the bladder neck will allow both the surgeon and the patient to have a more

concrete surgical plan, rather than deferring the decision to the intraoperative frozen section. The preoperative activity of the patient should be considered, and, when possible, vagina-sparing approaches or surgery for the sexually active patient should be attempted, if the cancer operation will not be compromised.

The most important factor to consider is the motivation of the patient. Is the patient willing to accept the risks of CIC? Is the patient able to learn to perform CIC with the possibility that she may need to CIC several times a day in 15% to 20% of the cases? Is the patient willing to accept the risks of daytime and especially nighttime incontinence? Furthermore, is the patient willing to awaken several times a night to void to minimize her nocturnal incontinence rates? These are not trivial points, and they should be thoroughly discussed with the patient preoperatively to optimize the realistic expectations of the patient and to best select the optimal candidates to achieve the highest level of patient satisfaction postoperatively.

Special Considerations: Preoperatively Incontinent Patients

The surgeon should determine whether the incontinence is due to detrusor hyperactivity, low bladder outlet resistance, or both. Given a low-pressure orthotopic neobladder, urethral pressures of approximately 30 cm H_2O are often adequate for postoperative continence. Routine prophylactic urethral or bladder neck suspension at the time of neobladder construction should be discouraged because this maneuver is associated with a high incidence of postoperative urinary retention.

Surgical Technique

The standard cystectomy in the female patient is modified to account for the following points:

1. Maximizing vaginal preservation without compromising the cancer surgery
2. Optimizing continence preservation by preserving the pubourethral ligaments, the rhabdosphincter, and the pelvic floor diaphragm
3. Creating a high volume–low pressure neobladder
4. Preventing urinary outflow obstruction by preventing “pouchocele” formation (angulation of the neobladder at the neobladder-urethral junction) and by avoiding mucosal folds near the neobladder outlet
5. Preventing enterocele or rectocele formation by reinforcing the endopelvic fascia at the pouch of Douglas
6. Preventing enterovaginal fistulas by interposing omentum between the neobladder and the vagina

Excellent discussions of the surgical technique have been published (12,54,80,113). A brief summary of the procedure follows.

The patient should be positioned in a low lithotomy position with maximal flexion of the operative table at the superior anterior iliac spine. The vagina should be completely prepped and accessible to the surgeon. After the peritoneal reflection is incised along the pouch of Douglas, the bladder can be sharply dissected off of the anterior vaginal wall down to the bladder neck–urethral junction. This maneuver may be facilitated by placing a sponge-stick in the vagina to better delineate the vaginal wall. After the posterior vaginal wall is incised, Allis clamps can be placed on each corner and the vagina can be placed on stretch, thereby increasing the ease of bladder dissection along the anterior vaginal wall. If there is any concern about leaving cancer, the anterior vaginal wall should be resected with the bladder.

The pedicles on each side are taken down to the level of the proximal urethra and bladder neck (the bladder neck is identified by palpation of the Foley balloon with the Foley catheter placed on slight traction). Once the proximal urethra and bladder neck are reached, attention should be turned to the anterior segment of the urethra. The pubourethral ligaments should be spared because they provide major support to the midurethral complex and are integral to female urethral continence. The rhabdosphincter and pelvic floor musculature should be preserved by avoiding dissection beyond the endopelvic fascia. The urethra just distal to the bladder neck should then be clamped and the urethra transected no more than 1 cm beyond the bladder neck.

Regardless of which type of orthotopic neobladder is to be constructed, several key points should be observed:

1. The bowel should be detubularized and an adequate length should be used to ensure an adequate reservoir volume and low storage pressures. Occasionally, postoperative incontinence is secondary to low neobladder storage volumes or high storage pressures.
2. During creation of the neobladder, care must be taken to prevent mucosal folds near the neobladder outlet to prevent outlet obstruction and urinary retention postoperatively.
3. The anatomy of the neobladder should be evaluated to ensure that it is not kinking or folding on itself. Occurrence of such a kink or severe fold can account for postoperative urinary retention. Some authors advocate placing an omental segment between the neobladder and the vagina to support the posterior aspect of the neobladder and to prevent it from folding on itself (117).
4. The pudendal nerve provides the major innervation to the rhabdosphincter and is therefore integral to urinary continence, but the importance of the autonomic innervation to the urethra for continence is debatable. Some authors meticulously preserve the autonomic nerves by preserving the lateral vaginal walls (12,54,55,80); others deliberately transect these nerves as part of their dissection (107,113). No apparent difference in continence

rates is reported by the two schools of innervative philosophy.

5. Placing an omental segment between the neobladder and the vagina will also help decrease the rate of neobladder-vaginal fistulization.
6. With the uterus and bladder removed, the pelvis is at increased risk of developing an enterocele. This occurrence can be minimized by anchoring the vaginal apex to the endopelvic fascia and plicating the cardinal ligaments and endopelvic fascia cephalad to the vaginal apex. This maneuver increases the tensile strength over the urogenital diaphragm and prevents herniation (enterocele formation).
7. Routine “neobladder suspension” to the pubis or Cooper's ligament (maneuvers aimed at preventing or minimizing postoperative urinary incontinence) should be avoided because these maneuvers may dramatically increase the incidence of postoperative urinary retention (54).

Metabolic Complications of Urinary Intestinal Diversion

The pathophysiology of metabolic complications caused by intestinal segments continuously exposed to urine has been studied extensively. Complications include electrolyte abnormalities, recurrent infection, calculus formation, altered hepatic metabolism, abnormal drug metabolism, growth retardation, osteomalacia, and cancer. The causes of these complications can best be described as multifactorial. Many of these sequelae are influenced by the degree to which solute absorption occurs across the intestinal segment. The factors that affect solute absorption include the type of intestinal segment used and its absorptive surface area, duration of bowel contact with urine, concentration of solutes in the urine, pH and osmolality of the urine, renal function, and possibly the time since surgery.

Electrolyte Disturbances

Serum electrolyte complications and the type of electrolyte abnormalities that can occur are primarily dictated by the particular type of bowel used. The electrolyte abnormality that occurs with ileum and colon is a hyperchloremic metabolic acidosis. It can be found in most patients who undergo ileal or colonic interposition to the urinary tract but is generally of a minor degree. The mechanism has been postulated to involve bicarbonate secretion, ammonia absorption, chloride absorption, or impaired distal tubule hydrogen ion secretion. Approximately 70% of patients with ileal conduits have been shown to have some degree of acidosis (23,69), and it can be seen as a severe problem in 10% (102). Similarly, most patients with continent diversions from ileal segments have elevated serum chloride and depressed serum bicarbonate levels (6,76). Up to 80% of patients with a ureterosigmoidostomy will demonstrate and may require therapy for a metabolic acidosis (37). A lower but significant incidence of acid–base disturbances has been reported for other continent diversions, such as the Mainz pouches (65%) and those continent diversions made of ileum (10% to 15%) (14,124).

Symptoms associated with prolonged acidosis include anorexia, weight loss, fatigability, and lethargy. If allowed to persist, the condition could lead to more significant metabolic complications with potentially lethal outcomes (34).

The treatment of hyperchloremic metabolic acidosis involves use of alkalizing agents and chloride transport blockers either in combination or as monotherapy. Alkalinization can be accomplished with oral agents, such as sodium bicarbonate, Bicitra, or Polycitra. These medications may exacerbate preexisting cardiac or renal disease because of the sodium content. In patients in whom excessive sodium loads are undesirable, chlorpromazine or nicotinic acid may be given to limit the degree of acidosis. Of interest is the report of Thuroff and associates (126) on 100 patients with Mainz pouch. Initially, most required alkalization agents to correct a hyperchloremic acidosis, but 6 months after surgery, only half needed these agents, and at 12 months none required therapy.

Electrolyte abnormalities resulting from jejunal interposition for urinary diversion include hyponatremia, hypochloremia, hyperkalemia, azotemia, and acidosis. These result from an excessive secretion of sodium chloride coupled with an increased reabsorption of potassium and hydrogen ions. Dehydration may develop because of subsequent water loss resulting in hypovolemia, renin secretion, and secondary hyperaldosteronism. Symptoms typically seen include lethargy, nausea, vomiting, muscular weakness, and elevated temperature. The treatment for the disorder involves rehydration with sodium chloride and alkalinization with sodium bicarbonate. Long-term supplementation may be needed. If this disorder remains untreated and is allowed to persist, the patient may become obtunded and subsequently succumb.

Patients with urinary intestinal diversion may be found to have hypokalemia and depletion of total body potassium. Frequently seen with ureterosigmoidostomies and rarely with ileal conduits, this depletion is most often caused by renal potassium wasting from renal damage and osmotic diuresis. Moreover, ileal segments, when exposed to high concentrations of potassium in the urine, reabsorb some of the potassium, whereas colon is less likely to do so. Therefore those with ileum interposed probably partially compensate the potassium loss by the kidney, whereas those with colon do not. This explains why total body potassium depletion is seen more commonly in patients with ureterosigmoidostomy and ureterocolonic diversion. One must be cognizant that if hypokalemia is associated with severe acidosis, treatment should involve potassium replacement concurrently with correction of the acidosis. Correction of

the acidosis without appropriate potassium replacement may cause a progressive severe hypokalemia with resultant flaccid paralysis and significant morbidity.

Hypocalcemia and hypomagnesemia are primarily the result of renal wasting and acidosis. Although infrequently manifested clinically, severe deficits of either or both cations can result in neuromuscular dysfunction, altered sensorium, seizures, and death. Treatment should involve supplementation either parenterally or orally depending on the severity.

Bacterial Infections/Sepsis

Patients who have urinary intestinal diversion are known to have an increased incidence of local and systemic infections. The cause is unclear, but there is evidence to suggest that bowel interposed in the urinary tract does not have the ability to prevent local bacterial growth, which then serves as a potential source of local infection and systemic dissemination. Bacteriuria is common in patients with a conduit or continent diversion. It has been shown that up to 80% of patients with conduits have some degree of bacteriuria, with 15% to 20% experiencing at least one septic event (104). Similarly, patients with continent diversion have a 5% to 20% incidence of septic episodes within 1 year of reconstruction (74). The mechanism by which the septic episodes occur is thought to involve ischemic breakdown of the mucosal barrier attributable to overdistention. This mucosal breakdown permits colonized luminal bacteria access to the systemic circulation. Another possibility is that reflux of lumenal bacteria has unimpeded access to the renal parenchyma, resulting in implantation of pathogenic bacteria in the upper urinary tract. Because of the propensity for infection in these patients, proper measures to prevent substantial bacterial colonization or urine stasis should be adhered to. In addition, some favor chronic administration of antibacterials in certain situations.

Calculi

An increased risk of urinary tract calculi exists in patients with intestinal diversions. Patients with an ileal conduit have a 20% incidence, if followed 20 years or more (76). Continent pouch calculi have been noted in up to 30% of patients, depending on the type of continent diversion. Possible etiologic factors contributing to stone development include acidic renal tubule fluid, increased calcium excretion, and persistent urinary tract infection with urease producing bacteria. Inspissated mucus and foreign bodies, such as sutures or staples, may also have a role. Management is dependent on site, stone burden, and underlying cause. Upper tract stones can often be managed similar to patients without urinary intestinal diversion. Pouch or neobladder stones may require an open or percutaneous procedure. In patients with continent cutaneous diversions, stone manipulation through the continent stoma should be avoided because of the potential for damage to the continence mechanism.

Nutritional Disturbances

Nutritional disturbances can be seen when significant portions of the bowel are removed from the enteric tract for urologic reconstruction. Alterations of absorptive processes in particular are seen when small intestine is used, which can result in nutritional deficiencies and their sequelae. Loss of the distal ileum can impair vitamin B_{12} absorption. Chronic vitamin B_{12} deficiency usually results in megaloblastic macrocytic anemia and possibly neurologic deficits. Decreased bile salt absorption, fat malabsorption, and a decrease in absorption of the fat-soluble vitamins can also be seen with distal ileal loss. This may result in severe diarrhea caused by bile acid irritation of the colonic mucosa. In general, the surgeon should be aware of the potential for these deficiencies and should address them by prompt investigation and supplementation, if needed. Loss of portions of the large intestine are usually well tolerated and cause few nutritional problems. However, diarrhea may be severe if extensive portions of the large bowel are removed with the ileocecal valve, potentiating nutritional deficiencies.

Altered Metabolism

Altered sensorium may occur as a consequence of drug intoxication or abnormalities in ammonia metabolism caused by altered hepatic metabolism. Patients with urinary intestinal diversion are more likely to experience this when administered drugs that can be absorbed by the gastrointestinal tract and excreted unchanged by the kidney. Toxic metabolites of drugs capable of intestinal absorption can be problematic, if not rapidly cleared from the blood by the kidney or liver. This has been reported for phenytoin and certain antibiotics that are secreted in the urine unchanged (98). In patients with normal hepatic reserve, acute changes in ammonia loads usually do not result in significant alterations in serum ammonia and ammonia intoxication. However, when hepatic metabolism has been compromised because of sepsis, cirrhosis, and other chronic hepatic diseases, encephalopathy may become apparent. Hyperammonemic encephalopathy has been reported commonly in patients with a ureterosigmoidostomy because of an increased ammonia load coupled with the potential for translocation of bacteria from the intestinal lumen to blood. Treatment of hyperammonemic encephalopathy or ammoniagenic coma involves draining the urinary intestinal diversion, either with a rectal tube, in the case of ureterosigmoidostomy, or a Foley catheter in those with a continent diversion or conduit. These maneuvers prevent urinary ammonia exposure to the intestinal mucosa for extended periods of time. In addition, systemic antibiotics to treat underlying sepsis are recommended. In severe circumstances,

arginine glutamate may be given to complex with ammonia forming an inert substrate. Lactulose can be given orally or rectally.

Bone Demineralization

Bone demineralization and osteomalacia are potential long-term complications of urinary diversion with intestine. Chronic acidosis and renal wasting of calcium and phosphate seem to play a role in this condition. These abnormalities can cause calciuria, decrease calcium-phosphate remineralization, and interfere with vitamin D metabolism, the results of which lead to subtle bone mineral content changes in the majority and severe abnormalities of bone mineral content in a few (75). Correction of acidosis with bicarbonate and administration of vitamin D are useful in such situations. Because bicarbonate and vitamin D are essential for normal bone growth and because these two substances administered in the animal model have been shown to prevent bone demineralization, it would be reasonable to consider administration of an alkali and vitamin D to all patients with urinary diversion and any evidence of bone demineralization. If remineralization does not occur with these measures, calcium supplements and the activated form of vitamin D should be considered.

Quality of Life

Great strides have been made in surgical techniques for performing urinary diversions. As a result, the modern urologic surgeon has several surgical options in his or her armamentarium to perform urinary diversions. However, apart from the surgeon's capability to perform different urinary diversions, the most important factor in deciding which type of urinary diversion to perform should be based on the patient's satisfaction.

An ileal loop diversion has been decreed by many urologic surgeons as inadequate because it promises indefinite need for stomal care and “condemns” patients to “wearing a bag.” Meanwhile, orthotopic neobladders have been embraced by many surgeons for more closely functioning as the native bladder, with better body image and physiologic function. However, the perceptions of the surgeon and the patient are often discrepant. The question is therefore raised: Does the urologic patient enjoy a better quality of life with a neobladder or with an “antiquated” ileal loop diversion? Furthermore, what physical and psychologic impact do urinary diversions have on patients undergoing urinary diversions? Understanding the factors most important to the patient will help physicians better counsel their patients and develop modalities to best address the priorities of patients undergoing these procedures. The importance of quality-of-life issues cannot be overemphasized.

To perform an adequate quality-of-life study, the questionnaire used should be validated. Optimally, all patients evaluated in the given study should have had the diversions performed for similar disease processes. For example, the psychologic point of view of a cancer patient with a urinary diversion may be extremely different than that of a patient with a neurogenic bladder who undergoes a urinary diversion procedure. The baseline and preoperative function and quality of life of patients undergoing these procedures should also be known and available for evaluation. Furthermore, quality-of-life issues at several time points postoperatively should be assessed to better determine the quality-of-life outcomes over time for the patients in question.

In reference to the optimal quality-of-life study, few studies have to date been performed with validated questionnaires, and even fewer studies evaluate homogenous groups (e.g., only bladder cancer patients, only neurogenic bladder patients, only interstitial cystitis patients) in their studies. No study has obtained or described the study population's baseline (preoperative) quality of life, psychologic health, and physical health. Despite these drawbacks, several interesting observations have been made. First, most patients undergoing urinary diversions are satisfied with their quality of life. Up to 95% of patients report an overall good to excellent quality of life regardless of the type of urinary diversion performed (51). Similar results are reported in regard to overall satisfaction with composite body image (51). Overall, 70% of patients describe no limitations on their activities (121), 15% complain of problems with recreational activities, and 24% complain of problems with athletic activities. The areas of greatest dissatisfaction are related to sexual function and sexual satisfaction, with nearly half of all patients complaining of high levels of sexual dissatisfaction (51).

Common problems described by patients include the following:

1. For ileal loop diversions: stomal skin irritation (30%); difficulty caring for stoma and applying device, appliance care or caring for collection device (57%)
2. Continent cutaneous diversions: occasional to frequent problems with stomal catheterization (28%)
3. Orthotopic neobladders: daytime incontinence (23%), nocturnal incontinence or need to awaken to void (56%)

As described, regardless of these areas of dissatisfaction, the general satisfaction of patients with urinary diversions is high.

Quality-of-Life Differences Between Incontinent Cutaneous, Continent Cutaneous, and Orthotopic Continent Urinary Diversions

The results of the few validated studies addressing this question are interesting. Bjerre and colleagues (11) evaluated the quality of life with respect to body image, partner relationships, and global life satisfaction in patients undergoing ileal incontinent cutaneous urinary diversions and

patients undergoing orthotopic Kock pouches. No difference was reported between the two groups. Filipas and colleagues (38) similarly evaluated the quality of life of 56 patients undergoing continent versus incontinent urinary diversions. Again no difference in satisfaction was noted between the two groups in regard to friends, social life, health, income, job, living situation, family life, or quality of life. Gerharz and colleagues (41), likewise, noted no difference between two nonrandomized groups (continent cutaneous reservoir or ileal conduit patients) in overall satisfaction or mental well being. McGuire and colleagues (78) evaluated the quality of life of 92 patients undergoing urinary diversion (ileal loop, Indiana continent cutaneous pouch, or Hautmann ileal neobladders) and compared each group's quality of life to published quality of life of age-based population norms. Interestingly, no physical quality-of-life difference was noted between any of the three urinary diversion groups and age-based population norms. Mental quality-of-life results proved differently. While the quality of life of continent cutaneous and orthotopic neobladder patients was no different than that of age-based population norms, the mental quality of life of ileal loop patients was slightly, although statistically significant, lower than that of the age-based population norms.

Overall, it can be generalized that most patients undergoing urinary diversion procedures will fare well from a quality-of-life standpoint, and that to date, with the relatively few quality-of-life studies performed on urinary diversion patients, no significant difference in quality of life is noted among patients undergoing continent versus incontinent or heterotopic versus orthotopic urinary diversions.

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32
BENIGN PROSTATIC HYPERPLASIA

John T. Grayhack

Kevin T. McVary

James M. Kozlowski

J.T. Grayhack and K.T. McVary: Department of Urology, Northwestern University Medical School, Chicago, IL 60611.

J.M. Kozlowski: Genitourinary Oncology Program, Northwestern University Medical School, Chicago, IL 60611.

Contents

The prostate, the major accessory sex gland of the male, has an exocrine but no established endocrine secretory function. Its secretion provides fluid that constitutes approximately 15% of the ejaculate. Aside from producing a volume-expanding vehicle for sperm, no definitive clinical function in reproduction has been identified for the prostate. The prostate, the prostatic urethra, and the bladder neck play a critical role in normal delivery of sperm in the sexual act. However, the major clinical interest in the growth and function of the prostate has resulted from the frequency with which it is the site of benign and malignant neoplasms and infection. The intimate anatomic relationship of the gland with the bladder neck and urethra increases the importance of these pathologic changes. The current status of our knowledge with regard to benign prostatic hyperplasia (BPH) is summarized in this chapter.

ANATOMY

Part of "32 - BENIGN PROSTATIC HYPERPLASIA "

Embryology

The prostate gland develops from the pelvic portion of the urogenital sinus at a fetal crown-rump length corresponding to a 10- to 12-week gestation (12). The prostate arises after the development of numerous endodermal buds, which initially proliferate throughout the entire length of the primitive urethra. Ultimately, the most extensive areas of proliferation into and about the prostatic anlage occur adjacent to the areas of the ejaculatory ducts and the verumontanum. These areas correspond to the points of termination of the mesonephric duct and its müAdullerian counterpart, respectively (194). The endodermal buds next invade the abundant surrounding urogenital sinus mesenchyme, which is responsible for the development of the connective tissue and muscular constituents of the definitive prostate (Fig. 32.1). Although this process continues throughout the life of the fetus, the gland is well differentiated by the end of the fourth month (12). Normal development of the wolffian and müllerian ducts and urogenital sinus-derived structures is dependent on the testosterone and müllerian-inhibiting secretions of the fetal testis. Conversion of testosterone to dihydrotestosterone, which occurs in both stroma and epithelium, is critical for the development of the prostate. An understanding of the role of growth factors and embryonic control mechanisms in organogenesis in general and in the prostate is currently the subject of intense investigation, as is the phenomenon of so-called imprinting (58,288).

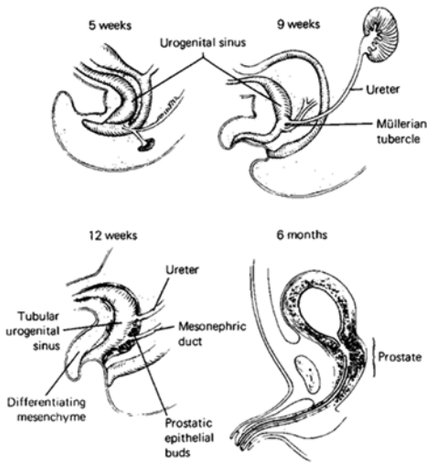

FIGURE 32.1. Embryogenesis of the prostate gland. The prostatic anlage develops from the pelvic part of the urogenital sinus. By the end of the third month, numerous epithelial outgrowths emanate from the prostatic urethra above and below the mesonephric duct. Note the proximity of the surrounding mesenchyme to the invading endodermal buds. (From Tanagho EA. Embryology of the genitourinary system. In Smith DR, ed. *General urology,* ed 8. Los Altos, CA: Lange Medical, 1975, with permission.)

Gross Anatomy

General Considerations

The prostate is a compound tubuloalveolar gland whose base abuts the bladder neck and whose apex merges with the membranous urethra to rest on the urogenital diaphragm (386). The intact adult gland resembles a blunted cone, weighs approximately 18 to 20 g, and measures about 4.4 cm transversely across its base, 3.4 cm in length, and 2.6 cm in its anteroposterior diameter (208). The urethra enters the prostate near the middle of its base and exits the gland on its ventral surface above and in front of its apical portion. The ejaculatory ducts enter the base on its posterior aspect and run in an oblique fashion to emerge and terminate adjacent to the verumontanum. The capsule of the prostate gland is an inseparable condensation of stromal elements that is incomplete at the apex; it does not represent a true capsule (13). Fibrous septa emanate from the capsule, pierce the underlying parenchyma, and divide it into multiple lobules (386). These glandular units drain into branched tubules, which lead into 20 to 30 prostatic ducts. Most of these ducts empty their contents into the prostatic urethra adjacent or distal to the verumontanum (235). These and other relationships are depicted in Fig. 32.2 and Fig. 32.3 .

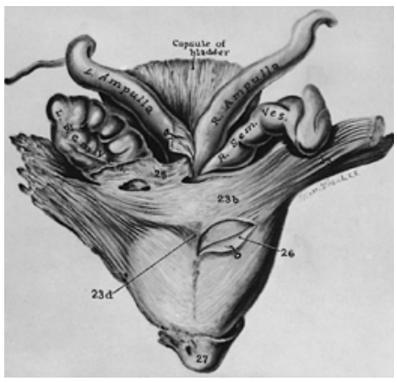

FIGURE 32.2. A dorsal view of the prostate gland, ampulla, seminal vesicles, and bladder. A median sulcus divides the prostate into halves and receives bandlike projections from the retrospermatic branch of the prostatic cord *(23d).* The dorsal capsule of the prostate (26) is synonymous with the anterior layer of Denonvilliers' fascia. Note the caplike investment (27) of the urogenital diaphragm on the apex of the prostate. (From Uhlenhuth E. *Problems in the anatomy of the pelvis: an atlas.* Philadelphia: Lippincott, 1953, with permission.)

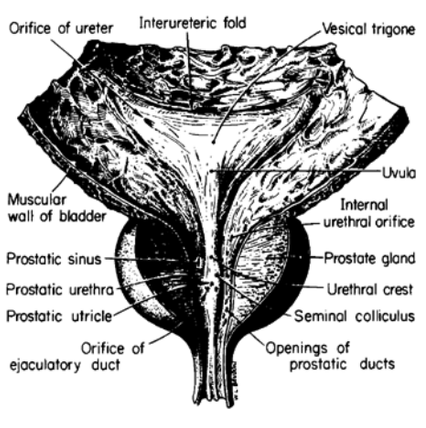

FIGURE 32.3. A frontal view of the bladder and prostate gland. The prostatic utricle sits atop the verumontanum (seminal colliculus) and represents one of two müllerian duct remnants in humans, the other being the appendix testis. Note that the majority of prostatic ducts drain adjacent or distal to the verumontanum. The area extending from the trigone to the termination of the prostatic urethra constitutes the internal urethral sphincter or bladder neck mechanism. (From Woodburne RT. Pelvis. In: Woodburne RT, ed. *Essentials of human anatomy.* New York: Oxford University Press, 1978, with permission.)

Denonvilliers' fascia is a visceral pelvic fascia formed by a condensation of fused peritoneum; it extends from the anterior peritoneal reflection superiorly to the urogenital diaphragm inferiorly. In its caudal extent, Denonvilliers' fascia envelops the posterior surface of the seminal vesicles and remains affixed to the posterior prostatic capsule (386). We suspect that the disputed existence of grossly identifiable anterior and posterior components of this fascial layer (369) as delineated in Fig. 32.4 is the result of their variably fused anatomic status rather than a misinterpreted rectal fascia propria.

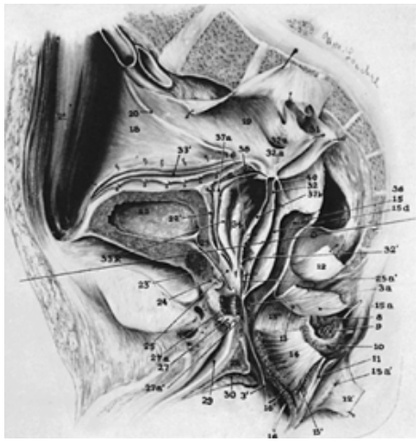

FIGURE 32.4. Detailed anatomic dissection of the retrovesical space. This anatomic approach permits a unique view of the ventral *(37a)* and dorsal *(37b)* leaf of the genital fascia, which envelops the ampulla *(33R)* and seminal vesicle (34). In addition, close inspection reveals the discrete separation of the anterior layer of Denonvilliers' fascia from its posterior (32) component. The last-named item is synonymous with the rectovesical septum. (From Uhlenhuth E. *Problems in the anatomy of the pelvis: an atlas.* Philadelphia: Lippincott, 1953, with permission.)

The endopelvic fascia corresponds to that condensation of extraperitoneal connective tissue that forms a subserous covering for the pelvic viscera and envelops their contiguous neurovascular pedicles. A sheetlike proliferation of the endopelvic fascia contributes to the formation of the puboprostatic ligaments. These avascular facial condensations, varying from a pillarlike to a fan configuration, lie on either side of the prostatic midline. They anchor the anterior and lateral aspect of the prostate to the posterior aspect of the pubis and superior fascia of the pelvic diaphragm (374).

The lateral pelvic fascia, also described as the parietal layer of the endopelvic or prostatic fascia, serves as the fascial envelope to the levator ani muscle and maintains continuity with the capsule of the prostate along its anterior and anterolateral aspects. The tributaries of the dorsal vein complex traverse this fascial layer (Fig. 32.5). Anatomic dissections by Walsh and Donker (372) revealed that the major neurovascular bundles to the prostate are contained posterolaterally within the lateral leaves of this fascia.

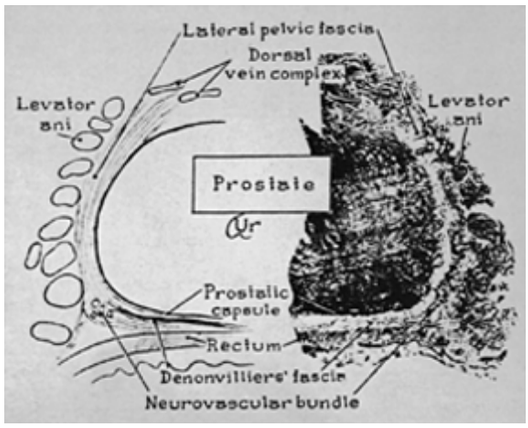

FIGURE 32.5. Cross section through the prostate gland. The levator ani is covered by the lateral pelvic fascia, which contains both the neurovascular bundle and dorsal vein complex. The latter consists of contributions from the dorsal vein of the penis and the plexus of Santorini. (From Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. *Prostate* 1983;4:473, with permission.)

Blood Supply

The prostatovesicular artery, the major arterial supply to the prostate and seminal vesicles, is a branch of the inferior vesical artery that originates from the anterior division of the hypogastric artery and courses medially on the levator muscle to the bladder base. After providing tiny branches to the bladder base, prostate, and tip of the seminal vesicles, its terminal arborizations supply the prostate with its main arterial supply in the form of urethral and capsular branches (208). The urethral branches course along the posterolateral aspect of the vesicoprostatic junction and usually enter the bladder neck and periurethral aspect of the prostate gland at the 5 and 7 o'clock positions (Fig. 32.6). Capsular arteries supply the peripheral portion of the prostatic parenchyma via four to six branches traversing the posterolateral aspect of the gland. Walsh and Donker (372) determined that the nervi erigentes form an extensive plexus enveloping these

capsular branches that serve as a vascular scaffold and a demonstrable anatomic landmark. The anterior division of the hypogastric artery also supplies the inferior aspect of the prostate, as well as the seminal vesicles and vas deferens, with accessory vessels from the middle hemorrhoidal and internal pudendal arteries (208,386).

Wide, thin-walled veins on the lateral and anterior aspect of the prostate gland merge with veins of the vesical plexus and the deep dorsal vein of the penis to form the plexus of Santorini within the puboprostatic space. This confluence of veins empties into the hypogastric vein. Of importance, these prostatic vessels freely communicate with the plexiform venous arborizations (Batson's plexus) that envelop and enter the lumbosacral spine and the wings of the ilia. The lack of competent valves in this nervous system has been postulated by some to provide direct access for embolic spread of prostate carcinoma to the skeletal system (23).

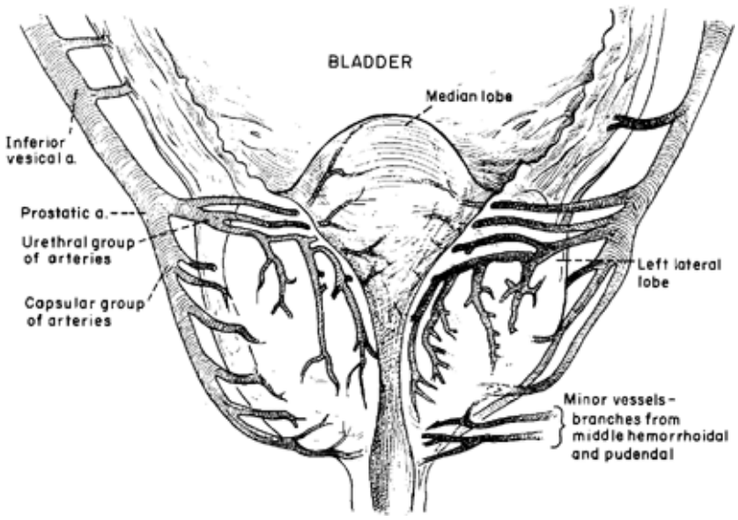

FIGURE 32.6. Arterial supply to the prostate gland. The anterior division of the hypogastric artery supplies the primary (inferior vesical) and secondary (middle rectal and pudendal) branches to the prostate gland. The prostatovesicular artery (prostatic artery) is a terminal tributary of the inferior vesical branch and arborizes into urethral and capsular components. In addition, it supplies the dorsal aspect of the seminal vesicles and bladder base. The urethral branches typically enter the bladder neck at the 5 and 7 o'clock positions, but this relationship is variable and inconstant. Note the presence of four to six branches from the capsular division supplying the outer aspect of the prostatic parenchyma. (From Carson CC III, Malek RS. Transurethral prostatic resection: surgical anatomy of the prostate and prostatic hyperplasia. In: Greene LF, Segura JW, eds. *Transurethral surgery.* Philadelphia: Saunders, 1979, with permission.)

Nerve Supply

In 1982, Walsh and Donker (372) published landmark observations describing the anatomic relationship of the pelvic (autonomic) plexus and the prostate gland. The prostate, other pelvic organs, and corpora cavernosa receive their autonomic innervation from the pelvic plexus, a fenestrated rectangular plate 4 cm long and 2.5 to 3.0 cm high lying retroperitoneally adjacent to the rectum within the sagittal plane (201). Both the parasympathetic and sympathetic divisions of the autonomic nervous system contribute to the plexus. Parasympathetic visceral efferent preganglionic nerve fibers from the second through fourth levels of the sacral cord enter the plexus by way of the pelvic splanchnic nerve (nervi erigentes). This nerve is a composite of five or six branches rather than a discrete entity. The sympathetic component emanates from the thoracolumbar center (T-11 to L-2) and courses via the hypogastric nerve, arborizations of the sacral sympathetic chain (S-4 to S-5), and branches that originate from the autonomic inferior mesenteric plexus and accompany the superior hemorrhoidal artery to join the plexus (201,215).

As stated previously, the prostatovesicular artery provides the macroscopic landmark and extrinsic support for these delicate nerves (Fig. 32.7). They lie outside of the confines of the prostatic capsule and Denonvilliers' fascia but traverse the lateral pelvic fascia (374). The prostate receives its

branches from the pelvic plexus through the lateral leaves of this fascial layer (Fig. 32.5). These observations, initially made by dissections performed in fetal and newborn tissue, have been confirmed by studies in the adult male pelvis (201,215).

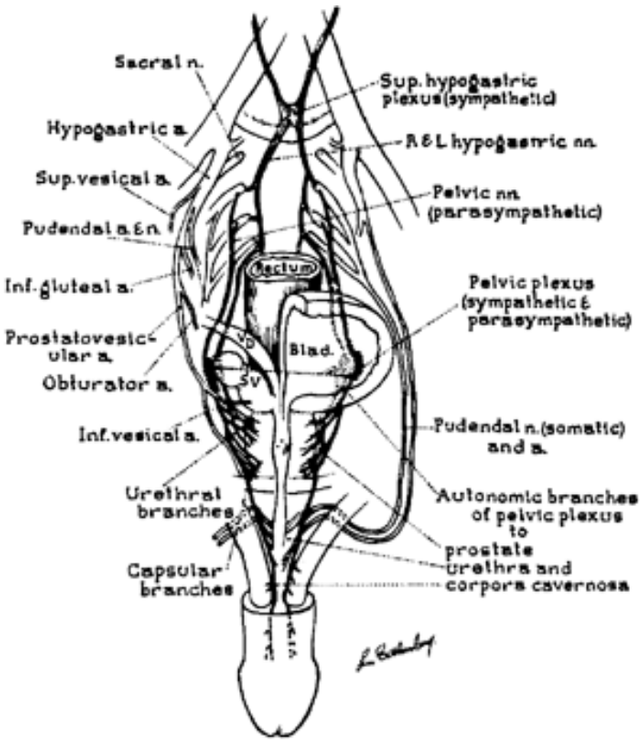

FIGURE 32.7. Innervation of the prostate, urethra, and corpora cavernosa. The branches to the prostate are contained within the lateral pelvic fascia and maintain an intimate relationship with the vascular scaffold created by the prostatovesicular artery. (From Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. *Prostate* 1983;4:473, with permission.)

Lymphatics

Small lymphatic vessels surround each prostatic acinus, ultimately forming larger channels that contribute to the periprostatic plexus on the surface of the gland. This network communicates with branches from the perivesical lymph node group. The first major portal of lymphatic drainage from the prostate is to the iliopelvic lymph nodes (312). This lymphatic network can be conveniently divided into three nodal groups: the external iliac, the internal iliac, and the common iliac. The composition of these groups has been clearly summarized by Lieber (209).

The external iliac lymph node system consists of three separate groups. The lateral chain, consisting of one to three lymph nodes, lies along the lateral aspect of the external iliac artery. The most inferior node in this group is designated the lateral crural lymph node. The intermediate node group traverses the area between the external iliac artery and vein. The medial group of lymphatic vessels, the most significant of the three, lies superior to the obturator nerve and medial and posterior to the external iliac vein. The middle node of this medial chain is called the obturator lymph node; the most inferior node, designated the internal retrocrural node, communicates with the node of Cloquet within the femoral canal and with other deep inguinal nodes.

The internal iliac group (hypogastric chain) most often constitutes four to eight lymph nodes affixed to the areolar investment of the hypogastric vessels. This chain is rarely delineated on lymphography (55).

The common iliac lymph node group represents a continuation of the external iliac chain and also possesses lateral, intermediate, and medial groups. The last, by far the most important, usually consists of three to six lymph nodes. It gives rise to the nodes of the sacral promontory, opposite the second and third sacral foramen. The medial chain of the common iliac lymph nodes provides access to the perigastric nodes. Extensive cross-communication exists between right and left common iliac chains. Figure 33.45 depicts the anatomy of the pelvic lymph nodes and their relationship to the retroperitoneal abdominal lymphatics (see Chapter 33).

Normal Internal Architecture

Regionally organized tissue configurations have gained increasing acceptance in principle, if not in specific detail, in the prostate. Nevertheless, the proposed organization of the fetal, newborn, and adult prostate into discrete lobes has been regarded with skepticism (12,128,212,213,388). With a focus on the development of BPH, Franks (100,101) conceptualized a prostate with an inner (urethral) and outer glandular configuration (Fig. 32.8). McNeal (235) argues,

as did Lowsley, that the urethral (inner) glands be considered separately from the prostate and its intrinsic architecture. However, the major physiologic and biochemical similarities of these glands and those of the prostatic parenchyma weigh against this concept.

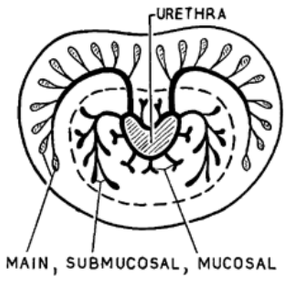

FIGURE 32.8. Cross section of normal prostate gland with the dorsal aspect superiorly placed demonstrating ductular architecture and three relatively concentric glandular arrangements. The mucosal component consists of delicate glands draining into short ducts, which empty circumferentially into the prostatic urethra. The submucosal group contains more extensive arborizations, which empty lateral to the urethral crest. These two groups constitute the periurethral area involved in benign prostatic hyperplasia. The acini constituting the lateral-most group of glands have a distinct cystic configuration. This outer or peripheral aspect constitutes the surgical capsule of hyperplastic glands. (From Grant JCB, Basmajian JV. *Grant's method of anatomy,* ed 7. Baltimore: Williams & Wilkins, 1975, with permission.)

McNeal (235,237) has proposed and promoted acceptance of anatomic subdivisions with probable pathophysiologic significance in the adult prostate. In his studies, McNeal emphasized the use of coronal and oblique coronal sections of prostates obtained between puberty and the third decade of life to study normal anatomy. Tisell and Salander (361), who used meticulous dissection techniques, observed subdivisions of the prostate gland that had several similarities to those reported by McNeal, but they interpreted these as evidence for prostatic lobes.

McNeal observed that the urethra separates the prostate into ventral (fibromuscular) and dorsal (glandular) portions. Approximately midway between the apex and base, the posterior wall of the urethra undergoes an acute 35-degree ventral angulation that serves to segregate the urethra into proximal and distal segments. The verumontanum and ejaculatory duct orifices exist exclusively within the distal segment. McNeal separates the glandular prostate thus delineated into four distinct regions: peripheral zone, central zone, transition zone, and periurethral gland region (Fig. 32.9).

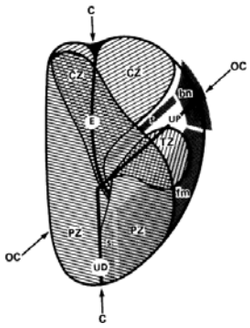

FIGURE 32.9. Sagittal diagram of distal prostatic urethral segment *(UD),* proximal urethral segment *(UP),* and ejaculatory ducts *(E)* showing their relationships to a sagittal section of the anteromedial nonglandular tissues [bladder neck *(bn),* anterior fibromuscular stroma *(fm),* preprostatic sphincter *(s),* distal striated sphincter *(s)*]. These structures are shown in relation to a three-dimensional representation of the glandular prostate [central zone *(CZ),* peripheral zone *(PZ),* transitional zone *(TZ)*]. Oblique coronal plane *(OC)* of Fig. 32.10 and coronal plane *(C)* of Fig. 32.11 are indicated by *arrows.* (From McNeal JE. Normal histology of the prostate. *Am J Surg Pathol* 1988;12:619, with permission.)

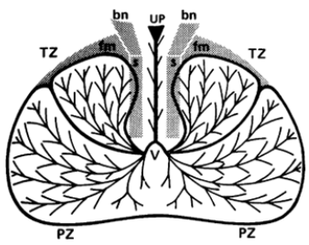

FIGURE 32.10. Oblique coronal section diagram of prostate showing location of peripheral zone *(PZ)* and transition zone *(TZ)* in relation to proximal urethral segment *(UP),* verumontanum *(V),* preprostatic sphincter *(s),* bladder neck *(bn),* and periurethral region with periurethral glands. Branching pattern of prostatic ducts is indicated; medial transition zone ducts penetrate into sphincter. fm, fibromuscular stroma. (From McNeal JE. Normal histology of the prostate. *Am J Surg Pathol* 1988;12:619, with permission.)

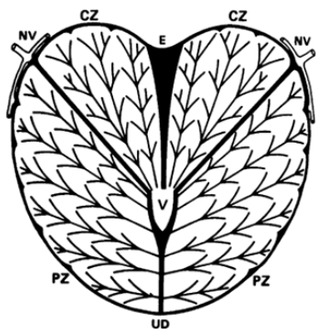

FIGURE 32.11. Coronal section diagram of prostate showing location of central zone *(CZ)* and peripheral zone *(PZ)* in relation to distal urethral segment *(UD),* verumontanum *(V),* and ejaculatory ducts *(E).* Branching pattern of prostatic ducts is indicated; subsidiary ducts provide uniform density of acini along entire main duct course. Neurovascular bundle *(NV)* is located at the junction between the central zone and the peripheral zone. (From McNeal JE. Normal histology of the prostate. *Am J Surg Pathol* 1988;12:619, with permission.)

The peripheral zone constitutes approximately 75% of the glandular prostate. Its ductal system enters the urethra along the posterolateral recesses of the urethra extending from the verumontanum distally to the prostatic apex (Fig. 32.3 and Fig. 32.10).

The wedge-shaped central zone, whose base is positioned superiorly at the bladder neck, occupies approximately 20% of the glandular prostate. Its ductal network closely follows the ejaculatory ducts to the urethra and empties adjacent to orifices of the ejaculatory ducts on the apex of the verumontanum (Fig. 32.11).

The transition zone, accounting for about 4% to 5% of the adult glandular prostate, is not well defined in the prepubertal prostate (234). It consists of two modest lobules of paraurethral tissue anterior to the peripheral zone. Its ducts empty in the posterior lateral recess of the urethra just proximal to peripheral zone ducts. The transition zone is lateral to McNeal's preprostatic sphincter, a smooth muscle cylinder enveloping the proximal urethra from the bladder neck to the base of the verumontanum (Fig. 32.9). The last anatomically discrete area within the glandular prostate is the periurethral gland region, representing less than 1% of the total volume of the glandular prostate. Its ductal network represents a more proximal extension of those of the peripheral and transition zone areas. These various regions have differing acinar, stromal, and cellular configurations. McNeal postulates that the anatomic and histologic similarities of the peripheral and transition zones and periurethral gland region are attributable to a common urogenital sinus embryonic origin. In distinction, he postulates that the close association between the central glandular zone, the ejaculatory ducts, and the seminal vesicles may reflect a common wolffian duct embryonic origin (235).

Last, the anterior or ventral fibromuscular stroma forms an apron that extends distally, covers the entire anterolateral aspect of the glandular prostate, and is responsible for the anterior convexity of the prostate gland. It represents approximately one-third of the tissue within the prostate capsule (237). This unusually distinct area, composed predominantly of smooth muscle fibers, maintains continuity proximally with the detrusor muscle fibers of the bladder neck.

As noted, the so-called capsule of the prostate is a condensation of stromal elements that envelopes the underlying parenchyma in a rather uniform manner (Fig. 32.12) except at the apex. Periodically, distinct septa emanate from the capsular sheath and penetrate the interior of the gland,

segregating it into lobules. The peripheral aspect of the capsule consists predominantly of fibroblasts, collagen, and elastic fibers. The septations differ from the bulk of the capsule in that they contain abundant smooth muscle cells (SMCs). The resulting epithelial folds and papillae are buttressed by the union of capsular septa and filamentous stromal branches. A complex network of lymphatics, blood vessels, and nerves courses through these branches. The capsular septa and stroma represent a dynamic scaffolding system for the underlying parenchyma. As a unit, they constitute 25% to 30% of the total volume of the prostate gland (7,246,252).

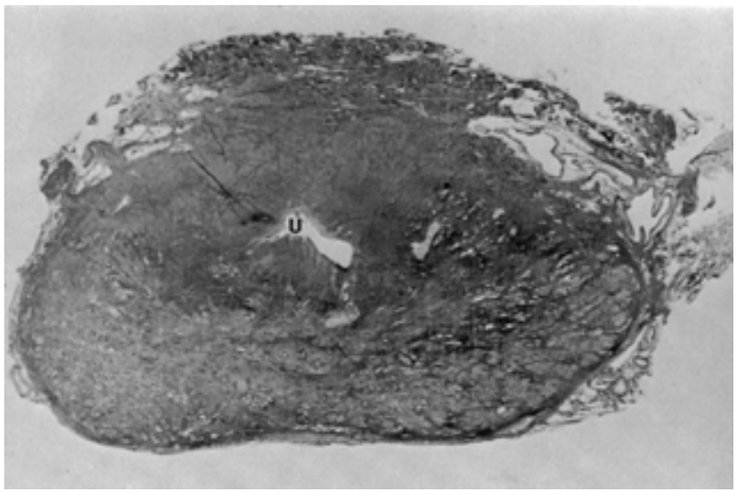

FIGURE 32.12. Transverse section of normal prostate gland. The fibrovascular constitution of the capsule surrounding otherwise normal, peripherally distributed acinar elements is well illustrated. Note the absence of hyperplastic tissue in the periurethral area. (From Kirchheim D. Histochemistry. In: Hinman F Jr, ed. *Benign prostatic hypertrophy.* New York: Springer-Verlag, 1983, with permission.)

Prostatic stroma consists predominantly of SMCs and fibroblasts arranged in close proximity to the distinct basal lamina of the epithelium. However, the fibroblasts tend to be organized parallel to the long axis of these tubulosaccular glands and form a more predictable relationship with the basement membrane (252). The smooth muscle surrounds individual glands and is thought to play a pivotal role in the release of glandular secretions. Furthermore, contraction of the circular smooth muscle of the bladder neck and preprostatic sphincter assists in the elimination of secretions within the prostatic urethra; this smooth muscle probably forms the major working element of the internal urethral sphincter. The anterior and anterolateral aspects of the prostate contain smooth and skeletal muscle, which joins the fibers of the external sphincter, augmenting urinary control in that region (223).

The excretory ducts are lined by simple or pseudostratified columnar epithelium for most of their course, but transitional epithelium is noted distally as they enter the floor and lateral surfaces of the urethra adjacent or distal to the verumontanum. From a teleologic standpoint, these ducts are inefficiently arranged. As noted previously, rather than a single main excretory duct, there are 16 to 32 separate ducts with distinct urethral orifices. Moreover, the ducts have an irregular branching pattern with numerous cystic outgrowths. This serpiginous pattern seems likely to restrict rather than promote the transit of secretions. The ductal network possesses both columnar and basal cells. However, neither has a secretory capability. Analysis of their ultrastructure reveals a few randomly distributed organelles. The generous investment of the ductal compartment by SMCs admixed with nerve axons is noteworthy. These elements appear to be integrally related to emptying the ducts (see Secretory Mechanisms) (84,339).

Blood capillaries that traverse the stromal labyrinth consist of both continuous and fenestrated subtypes. These vessels and their associated nerves probably play an active role in both the elaboration and propagation of the gland's secretions (84).

The acinar epithelium consists of two well-recognized cell types: (a) a tall, columnar glandular secretory cell that is luminal in orientation, and (b) a nonsecretory basal cell that is flattened, cuboidal, and abuts a distinct eosinophilic basement membrane approximately 0.07 to 0.12 mm thick.

Both cell types make direct contact with the latter (Fig. 32.13). The predominating glandular secretory cells possess a variety of distinctive light and electron microscopic features (Fig. 32.14), including the following:

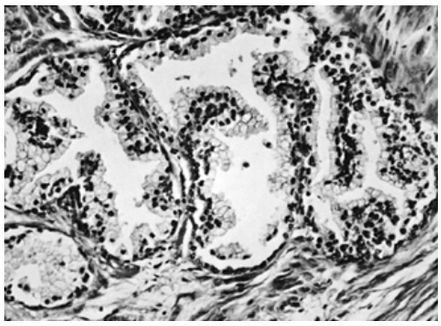

FIGURE 32.13. Photomicrograph of normal prostatic acini demonstrating double cell layers. The latter consists of basal cells and adluminal (secretory) cell components (×200). (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1972, with permission.)

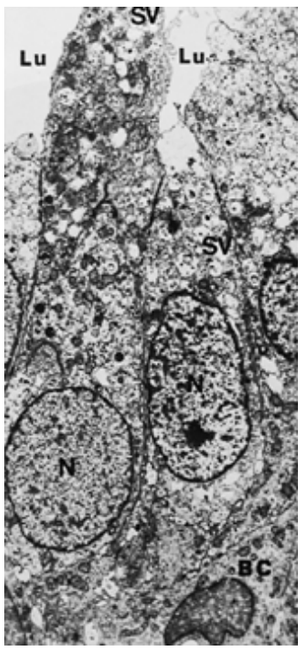

FIGURE 32.14. Electron micrograph of normal prostatic epithelial cells. The adluminal cells contain prominent nuclei *(N)* with mitochondria, lipid droplets, and secretory vesicles *(SV)* easily demonstrated. Apocrine secretion (release of secretory products plus a portion of the cell wall) is reflected by the loss of the villous extension apparent in the center of the field. Merocrine secretion (release of secretory product through the intact cell) is also demonstrated in the prostate. The basal cell *(BC)* abuts a distinctive basement membrane (not shown) and contains a prominently serrated nucleus. Lu, lumen acinus. (From Kirchheim D. Histochemistry. In: Hinman F Jr, ed. *Benign prostatic hypertrophy.* New York: Springer-Verlag, 1983, with permission.)

1. Although typically tall and columnar in profile, the cell may appear compact in areas with high cellular density.
2. Nuclei are located in a dependent position with a long axis paralleling that of the cell.
3. Nucleoli are rarely encountered; they are separated from a double nuclear membrane by punctate areas of delicate heterochromatin.
4. The basal cytoplasm harbors free ribosomes, rough endoplasmic reticulum (RER), and some short mitochondria.
5. The supranuclear area is characterized by the presence of a Golgi apparatus consisting of aggregates of small vesicles and elongated lacunae, RER, some lipid droplets, and secretory granules and vacuoles with a solitary limiting membrane.
6. Active lysosomes and different types of dense bodies, the most prominent of which contains lipofuscin, are present within the apical cytoplasm.
7. The apical cytoplasm contains numerous villiform extensions that project from glandular cells into the acinar lumina that vary in prominence depending on the secretory status of the cell.
8. Glandular cells react with monoclonal antibodies to prostate-specific antigen (PSA), prostate-binding protein, and acid phosphatase. Acid phosphatase is noted predominantly within the secretory vacuoles and lysosomes; in contrast, aminopeptidase and PSA are located in the apical cell border and cytoplasm, respectively.

9. A distinct lateral plasma membrane exists; cell-to-cell contact is accomplished through apical junctional complexes and numerous desmosomes (184,252,339). Cytokeratins (CKs) 8 and 18 appear to be specific for the prostate secretory cell (331).

The basal or nonsecretory cell subpopulation also possesses distinctive histologic and ultrastructural characteristics, including the following (Fig. 32.13 and Fig. 32.14):

1. Basal cells are polygonal in orientation and possess a relatively large nucleus with a serrated border. As with glandular cells, the long axis of the nucleus parallels that of the cell itself.
2. Extension of these cells never appears to reach the lumen of the gland.
3. Their cytoplasm, lacking secretory granules, is more electron dense than that of glandular cells.
4. In addition to lacking secretory granules, basal cells reveal an inconspicuous array of mitochondria, endoplasmic reticulum, and free ribosomes and possess a much abbreviated Golgi apparatus.
5. Despite possessing linear attachments, basal and columnar cells are commonly separated by lacunae containing cytoplasmic projections.
6. Basal cells possess a number of intracytoplasmic filaments, some of which may serve a contractility function (or functions); others are CKs. CKs 5 and 15 appear to be basal-cell specific (331).
7. Pinocytotic vesicles that may facilitate transfer of materials between the glandular and stromal compartments are present.
8. The basal cell compartment appears more prominent in the inner than in peripheral prostatic glands.
9. Basal cells do not react with monoclonal antibodies directed against acid phosphatase, PSA, and prostate-binding protein (PBP).
10. The basal cell compartment is thought to function as reserve or stem cells and to be primarily responsible for tissue repair.

Although cytokeratin characterization distinguishes adult basal and adluminal epithelial cells (22,329,331), Xue and associates (390) identified intermediately located cells with mixed basal and adluminal cell cytokeratins in the developing prostate; they postulate that these may facilitate a transition between basal and adluminal cells. Interestingly, no apparent qualitative differences in CK expression were found between central and peripheral zone tissues (329).

The prostate contains two groups of cells: the neuroendocrine (NE) or endocrine-paracrine (EP) cells, native to the prostate, and inflammatory cells that have the potential to secrete recognized growth factors and other potential growth-modifying agents. With regard to the latter, macrophages and mast cells are encountered in normal prostates; lymphocytic infiltrates are common in BPH (252,342,358). The absence of granulocytes suggests that these infiltrates are not a response to infection; flow cytometric analysis identified T cells (60% to 70%), B cells (15%), and macrophages (15%) in them (103). These cells have been shown to produce potent growth factors. For example, T cells infiltrating human prostate cancers have been shown to produce vascular endothelial growth factor (VEGF), and tumor-derived lymphocytes produce breast tumor and stromal cell–stimulating heparin-binding epidermal growth factor (HB-EGF) and bFGF/FGF_2 (basic fibroblastic growth factor/fibroblast growth factor 2) (281). These cells could provide potent mitogenic stimuli for prostate stromal or epithelial growth (103) and contribute to the pathogenesis of BPH (342).

Neuroendocrine cells rest on the basal cell layer between sensory cells and establish contact with nerves or other NE

cells through open-type dendritic cells. NE cells secrete a range of products varying from serotonin, neuron-specific enolase, bombesin, and somatostatin to human chorionic gonadotropin–like and thyroid-stimulating hormone–like peptides (73). They are present in all areas of the prostate and urethra and in benign and malignant tissue in varying concentrations. NE cells are most numerous in the main periurethral prostatic ducts and are reduced in number in BPH acini (74). Defining the role of NE cells in normal and abnormal prostate growth remains an elusive challenge.

As noted, prostatic stroma is heterogeneous, consisting of fibroblasts (FBs) and SMCs that are arranged in both periacinar and interacinar configurations (70). The fibroblasts tend to be organized parallel to the long axis of tubulosaccular glands and smooth muscle elements surround individual glands and blend with the adjacent stroma. SMCs and FBs comprising the stroma can be readily distinguished *in vivo* and *in vitro* by monoclonal antibodies; for example, smooth muscle α-actin and myosin for SMCs and prolyl-4-hydroxylase and ASO2 (Dianova) for fibroblasts (170,325). Proliferation can be induced in both by growth factors such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor-ß (TGF-ß), insulin-like growth factors I and II (IGF-I, IGF-II), and others (103,343,349). Adult SMCs commonly achieve a highly differentiated contractile phenotype *in vivo.* However, these cells can assume an activated synthetic phenotype with a fibroblast-like appearance, proliferate rapidly, and secrete unique extracellular matrix (ECM) and thrombospondin and tenascin (220) as well as collagen in a developing organism and *in vitro.* Human prostate-derived fibroblasts synthesize bFGF *in vitro* (330,345) but lack an identifiable mechanism to secrete this growth factor. Steroid hormone receptors and expression of 5α-reductase type 2 activity have been documented in prostate stroma (66,70,190,332), as has the secretion of factors such as keratinocyte growth factor, a mitogen for human prostatic epithelial cells *in vitro* (171,177,189).

Overall, accumulating *in vivo* and *in vitro* observations indicate greater qualitative and quantitative diversity in epithelial and stromal components of the prostate than has been appreciated. Traditional phenotypic characterization of cells may fail to identify significant physiologic differences. The dynamic interaction of these cells seems to play a major role in the degree and character of cellular and organ growth. More exact characterization of the cellular components of the internal architecture of the prostate will almost certainly add significantly to our ability to understand and alter pathologic growths of the prostate.

PHYSIOLOGY

Part of "32 - BENIGN PROSTATIC HYPERPLASIA "

General Considerations (171,224,277)

The prostate is a male accessory sex gland that contributes biologically complex, unique secretions to the ejaculate. Its growth and function are normally controlled by external (endocrine) and internal (growth factor, steroid, and protein or peptide) cellular metabolic signals. Functioning testes are necessary for its normal development, growth, and function and probably for development of BPH and carcinoma. Normal adult testes produce and secrete approximately 95% of circulating testosterone (T); this predominant systemic androgen is the major, although very probably not the only, testes hormone controlling prostate growth. Estrogens, prolactin, thyroxin, insulin, and probably other protein hormones and growth factors influence androgen-stimulated growth but have limited or equivocal independent effect on it. Leydig cells secrete testosterone and limited amounts of other androgenic and estrogenic steroids in response to luteinizing hormone (LH) secreted by the pituitary (Fig. 32.15). Normally, dihydrotestosterone (DHT), a reduced product of testosterone resulting from activity of the locally present type 2 isoenzyme of 5α-reductase, is the major proximate prostate growth or function stimulant. Evidence indicates that the androgen receptor (AR) binds DHT preferentially but not exclusively compared with T (171). However, high concentrations of 5α-reductase in the stroma coupled with histochemical observations localizing it to the perinuclear region of the stromal and basal cells without evidence of its presence in glandular cells of the human prostate challenge a simple intracellular T conversion/DHT receptor–activated proliferative concept (332,333) (Fig 32.16). DHT's failure to stimulate human prostate epithelial cell growth *in vitro* provides supporting evidence for this challenge (233). As a result, paracrine and autocrine cellular mechanisms are receiving increasingly prominent consideration in hypotheses regarding epithelial–stromal cell interaction and control of prostatic proliferative and secretory mechanisms (Fig. 32.17). A possible role for circulating DHT produced by extraprostatic type 1 5α-reductase in these phenomena has also been postulated (332). Consequently, concepts concerning the source and role of intracellular DHT in prostatic growth and maintenance need continuing critical reevaluation (229). Current evidence supporting intracellular DHT, whatever its source, and AR binding in the nucleus (58,137) seems substantial. The DHT–AR complex interacts with specific DNA sites with the ultimate production by incompletely characterized mechanisms of regulatory and secretory proteins (Fig. 32.16). Cellular proliferative, apoptotic, and secretory activities are variably affected by this interaction and by a number of other steroid or protein hormones and paracrine or autocrine growth factors. In general, the relative potency or quantity of other androgens secreted by the adrenal (e.g., androstanedione, dehydroepiandrosterone) or testis or resulting from metabolism of testosterone reduces their potential effect on prostatic growth. Biologic availability of circulating androgen is further modified by relatively stable binding to serum proteins such as testosterone-binding globulin. In addition to androgens, estrogen and progestational agents promote prostate

growth under some experimental conditions. Estrone and estradiol result principally from peripheral conversion of testosterone and androstanedione in the male; testicular secretion accounts for a small (25% or less) amount of the circulating estrogen in the male. Prolactin, insulin, and growth or thyroid hormones and a variety of growth factors have demonstrable effect on prostatic proliferative and secretory activity in selected experimental environments. In addition, *in vivo* and *in vitro* evidence for a nonandrogenic prostate-stimulating testicular factor that is presumably a protein and is of particular interest to us is accumulating (129,133). The *in vitro* demonstration that steroid hormone–binding globulin binds to human prostate epithelial cells and is activated to increase cyclic adenosine monophosphate production by estradiol but not DHT adds another possible mechanism regulating prostate growth and function (254).

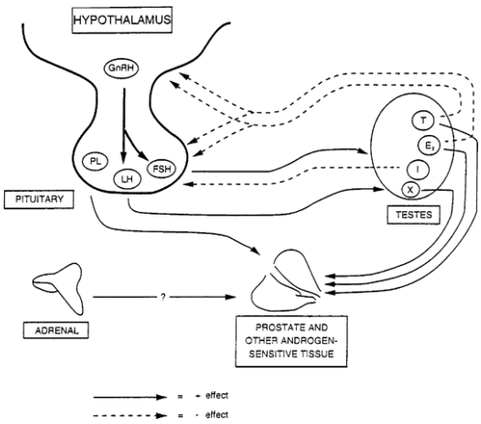

FIGURE 32.15. Endocrine relationship between the hypothalamus, pituitary, prostate, testis, and adrenal (see text for details). E_2, estradiol; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; I, inhibin; LH, luteinizing hormone; PL, prolactin; T, testosterone; X, postulated nonsteroidal testicular accessory sex gland growth factor. In the human, the intraprostatic urethra–ejaculatory duct relationship provides a potential for local, in addition to systemic, exposure to testicular secretions. (Modified from Cheng E, Lee C, Grayhack JT. Endocrinology of the prostate. In: Lepor H, Lawson RK, eds. *Prostate diseases.* Philadelphia: Saunders, 1993, with permission.)

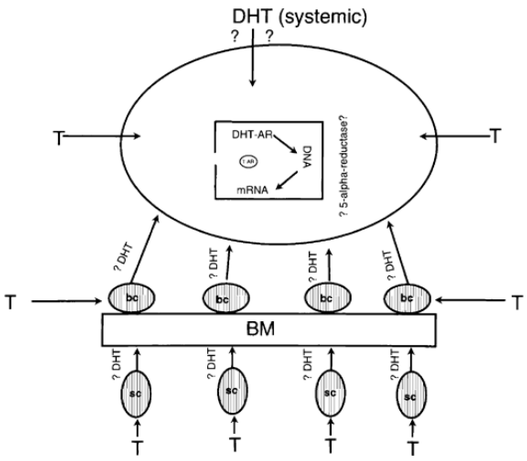

FIGURE 32.16. Abbreviated scheme of T–DHT conversion and mechanism of androgen action in the prostate. Current histochemical evidence in the human (332,333) indicates that 5α-reductase is present in stromal and basal cells but not in epithelial cells. The source(s) of intracellular dihydrotestosterone *(DHT)* is not clearly identified. Presumably, T and DHT can diffuse into the cell. DHT and, to a lesser degree, T are bound to the androgen receptor, forming a steroid–receptor complex. This complex results in transcription of mRNA with the ultimate production of regulatory and structural protein. Many aspects of this diagram are incompletely confirmed and may prove erroneous; however, the challenges posed to traditional concepts warrant consideration. AR, androgen receptor; bc, basal cells; BM, basement membrane; sc, stromal cells; T, testosterone.

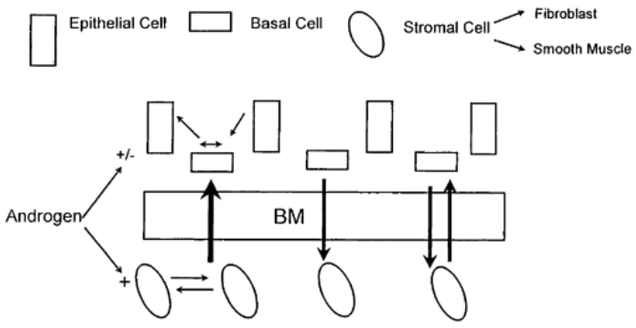

FIGURE 32.17. The interaction between the cellular components of the stroma and epithelium of the prostate is complex and incompletely understood. A variety of stimulatory and inhibitory factors (see text), including epidermal growth factor (EGF), keratinocyte growth factor (KGF), basic fibroblast growth factor (bFGF), insulin-like growth factors (IGFs), transforming growth factor-ß (TGF-ß), and nerve growth factor–like protein (NGF), are secreted in response to androgen and local paracrine-autocrine protein cell signals. The absolute and relative concentrations of the various growth factors lead to changes in the stimulatory/inhibitory environment for particular cells or groups of cells that seem likely to play an essential role in their integrated growth and function. BM, basement membrane.

In addition to the direct effect of testicular and possibly adrenal and pituitary secretions on prostatic cells, the complex interaction of these endocrine organs warrants consideration in this discussion of the control of prostatic growth and function. Normal testicular function is dependent on pituitary secretion of gonadotropin LH and follicle-stimulating hormone (FSH) (Fig. 32.15). Although the interaction of these glycoprotein hormones in the testis is complex (171,224), LH essentially stimulates the Leydig cells to secrete androgen; FSH stimulates spermatogenesis. Secretion of LH and FSH is, in turn, stimulated by the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Testosterone and estradiol exert a negative feedback on the hypothalamus; testosterone also has a direct inhibitory effect on the pituitary. Testosterone essentially modulates LH, whereas estrogen affects both LH and FSH secretion. Inhibin, a Sertoli cell secretory protein, inhibits FSH production. Exogenous hormones are available to suppress, modify, or mimic many of the normal interactions of the testis, pituitary, and hypothalamus (58,171,224).

Prostatic secretions, predominantly a product of the epithelial cells, are involved in the process of insemination

and also probably provide some protection against bacterial infection of the male genitourinary tract (88). The secretory process, described as both apocrine and merocrine, results in prostatic fluid with a biochemical composition reflecting that of the cellular cytoplasm. Evidence from assessment of fractionally collected urine specimens suggests that the secretion of prostatic fluid is an ongoing process in the postpubertal period. Episodic expulsion of prostatic secretions as part of the ejaculatory process is controlled by a complex, integrated neurophysiologic mechanism.

The average volume of normal human ejaculate is 3.5 mL (range of 2 to 6 mL). The prostate secretions (0.5 mL) and the vasal-epididymal-spermatozoa component, about 0.45 mL (276), usually follow the initial secretions of the glands of Littre and Cowper (0.1 to 0.2 mL). They, in turn, are followed by the seminal secretions (2.0 to 2.5 mL) in partitioned or “split ejaculate” collections (224,353).

Secretory Mechanisms (341)

Prostatic secretory activity is under both endocrine and neural control. Observations in animals and, to a limited extent, in humans document that volume and biochemical composition of the prostatic secretions are endocrine dependent (224). Stimulation of the appropriate pelvic nerves results in production or expulsion of prostatic fluid in experimental animal studies. In humans, intraoperative stimulation of postganglionic lumbar sympathetic nerves (L-1 to L-3) produces visible secretion of prostatic fluid in the prostatic urethra (294).

In the dog, nerve-mediated secretion by the prostate is achieved predominantly through acetylcholine released at epithelial effector sites by cholinergic postganglionic sympathetic nerves (84). Sympathetic and parasympathetic agonists increase the volume of externally secreted fluid, although probably by different mechanisms. In the rat (376), α-adrenergic receptor agonists cause expulsion of fluid by smooth muscle contraction. Parasympathetic agents increase secretion of biochemically altered prostatic fluid in the rat (carbachol) and dog (pilocarpine); this physiologic effect persists in the isolated, perfused dog prostate (295). In addition to altering function, accumulating evidence indicates that neural input affects prostate growth (238,341).

Although the exact mechanisms controlling episodic expulsion of prostatic fluid are not clearly established, nerves making up the pelvic plexus and providing autonomic innervation to the prostate play an essential role in this process. In addition to the parasympathetic innervation supplied by the nervi erigentes and sympathetic innervation from the lumbar spinal cord carried in the hypogastric nerves, the pelvic plexus in humans receives sympathetic input directly from the sacral sympathetic chain. Pelvic plexus ganglia are associated with branches of the plexus supplying adjacent organs, and intrinsic preterminal ganglia are associated with intrinsic nerves supplying terminal autonomic branches to the prostate (84). The presence of paracrine signal proteins secreted by neuroendocrine cells adds to the potential complexity of the system that activates and integrates prostate exocrine secretory activity.

Secretory Products

Prostatic secretions, a highly complex, heterogeneous mixture of organic and inorganic compounds, make up about 15% by volume of the seminal fluid. Prostatic fluid is the primary source of seminal fluid zinc, magnesium, calcium, and citrate. Zinc concentration varies from 150 to 1,000 mg/mL (mean of 350 mg/mL). Its bactericidal effect on Gram-negative and Gram-positive organisms may be an important antibacterial factor in the prostate and prostatic urethra (88). Citrate, present in a mean concentration of 376 mg/dL (57), has been used as a biologic indicator of hormonal stimulation (130,224). Although citrate is a major chelating agent for metal ions, its biologic role in the prostate is not clear.

The nitrogenous compound phosphorylcholine and the polyamines spermine and spermidine are secreted in prostatic fluid (52,224). Phosphorylcholine is probably a specific substrate for prostatic acid phosphatase; this enzyme liberates free choline and phosphate ion. Spermine, an aliphatic polyamine, binds to phosphate ions, nucleic acids, and phospholipids (382,383). The association between polyamine production and cellular proliferation suggests a role for the former in malignant transformation and cell growth. Enzymatic degradation of spermine generates reactive aldehydes, giving semen its characteristic odor. These compounds and their polyamine precursors function as antibacterial agents. A large proportion of the cholesterol and phospholipid present in human semen is secreted by the prostate. Analysis of prostatic secretion has revealed a total lipid content approximating 286 mg/dL, with a mean concentration of cholesterol of 80 mg and of phospholipids of 180 mg/dL (322). Sphingomyelin constitutes close to half of the phospholipid component; phosphatidyl serine and ethanolamine plasmalogen contribute the bulk of the remainder (287). Understanding the physiologic role and metabolism of lipids in the prostate has unfortunately generated limited interest.

Two-dimensional electrophoretic gel analysis demonstrates a very large number of distinct proteins in human prostatic fluid (363). Only a limited number of these have been characterized and identified, often by several differing descriptive terms. PSA, and recently its related kallikrein proteases, prostate-secreted acid phosphatase (PAP), ß microseminoprotein, and prostate-binding protein, are among these, with the first three being the predominant secretory proteins (52). The clinical roles for PSA and acid phosphatase have served to focus investigative effort on these enzymes. The evidence indicates a major role for androgen in their secretion.

PSA, a single-chain glycoprotein with a molecular weight of 33,000 to 34,000 kDa, is detected in the prostate only in the epithelial cells. The amino acid sequence of this protein shows a high degree of homology to other serine proteases in the kallikrein family. PSA possesses the substrate specificity of chymotrypsin and trypsin; its enzymatic activity can be inhibited by a wide range of protease inhibitors, zinc, and spermidine (379). PSA is secreted in prostatic fluid and is present in high concentrations in the semen (377). Lysis of the seminal clot through fragmentation of semenogelin, secreted by the seminal vesicles, is probably primarily the result of its activity, although plasminogen activators with molecular weights of 70,000 to 74,000 kDa may play a role (210,289). The promoter PSA gene has a functional androgen-responsive element, supporting the role of androgens in its regulation (52). PSA is present in both benign and malignant cells. Development of assays for PSA and possibly other related kallikrein enzymes has provided an important clinical tool.

PAP, a 102,000-kDa glycoprotein, splits organic phosphatases with optimal activity at a pH range of 4 to 6. A variety of isoenzymes of this secretory product of glandular epithelial have been identified (313). In the dog, the concentration of this enzyme in prostatic secretions reflects biologic androgen stimulation. In humans, the mean concentration of acid phosphatase in digitally expressed prostatic fluid decreases progressively with aging, supporting the presumption of an age-associated decreased androgen stimulation of the prostate (130). No unique or essential role for this enzyme in prostatic growth and function has been documented.

The biochemical composition of variously stimulated and collected male accessory sex gland fluids has been used to evaluate metabolic response to endocrine manipulation in animals. In these studies, secretion of acid phosphatase, fructose, or citric acid has commonly reflected anatomic and metabolic evidence of endocrine stimulation. Biochemical evaluation of prostatic fluid has an established role in assessing degree and nature of accessory sex gland stimulations (105,224). In humans, prostatic massage, a less than ideal procedure, is probably the only technique that allows repetitious collection of relatively uncontaminated prostate fluid specimens that are likely to reflect changes that are occurring diffusely in the gland. Studies of accessory sex gland secretions in humans have yielded interesting and useful data providing evidence for seminal vesicle or prostate stimulation by a systemic nonandrogenic factor in the androgen-depleted aging male (126,130).

Epithelial-stromal Interactions

The prostate, like other organs, is an integrated composite of various types and numbers of epithelial and stromal cells. In the recent past, the challenge to understand its growth and function was pursued by isolating single cell types and characterizing their growth and function. With progress in these efforts, the challenge to identify and understand the mechanisms involved in integrating individual cellular components into a functioning, appropriately responding organ has become increasingly prominent. Factors involved in this integration include anatomic, physiologic, molecular biologic, and other considerations. This brief summary of observations relating to epithelial-stromal interactions focuses on one aspect of this complex phenomenon.

Both external and internal factors are important in controlling the number and specific phenotype of epithelial and stromal cells making up the prostate. Evidence indicating the importance of and mechanisms for stromal-epithelial cellular interaction in modulating normal and neoplastic growth of the prostate is expanding rapidly. Observations of the development of the rat and regrowth of the androgen-stimulated endocrine-deprived prostate of the dog support a primary role of mesenchyme or stroma in determining final organ size. Urogenital mesenchyme can have an instructive, an inductive, or a permissive role with regard to epithelial elements depending on circumstances. Regional variations in prostatic epithelial cell responses to identical androgen exposure *in vivo* (196) and observations of growth characteristics of cell and organ cultures support a major continuing role in growth regulation of the prostate by the stroma (70,355).

Secretions of the various stromal and epithelial cells that make up the prostate have a spectrum of potential roles. These include anatomic cell organization and anchorage, growth factor or steroid storage, directed transmission of cell signals, and permissive passage of secreted cell products. Alterations in these functions can potentially affect normal integrity of the prostate or its component cells. ECM components (e.g., collagen subtypes, fibronectin and other glycoproteins, glycosaminoglycans, sequestered growth factors) are essential for structural maintenance and proper functioning of the tissue-matrix system. The ECM plays a fundamental role in anchorage of epithelial cells and determines their ultimate shape and polarity (122,301). In addition to maintaining structural integrity, the ECM affects multiple cell functions, including (a) the response of epithelial cells to various growth or serum factors (97), (b) the control of gene expression by changing the association of cytoskeleton with the mRNA and the interaction of the chromatin with the nuclear matrix (30), (c) alteration of cellular morphology or function as a result of a “dynamic reciprocity” the ECM shares with the cytoskeleton (30,347), and (d) the avid sequestration of heparin-binding growth factors such as bFGF (15). These observations are supported by *in vitro* and, to a lesser extent, *in vivo* observations. For example, androgen-induced prostate epithelial cell proliferation or ability to secrete PSA is lost in isolated cell cultures (51,98) but maintained in organ culture (70) and in epithelial cells grown on a substrate of basement membrane (98). Furthermore, human prostate epithelial

units (organoids) xenografted into athymic nude mice lack epithelial organization and secretory function despite the presence of androgen until a definite stromal presence is established (152). On the other hand, proliferation of human prostate epithelial cells occurs in cultures with growth factors including epidermal growth factor (EGF) and the acidic fibroblast growth factor (aFGF)-containing bovine pituitary extract in androgen and stroma cell free media (51,67). Thus it appears that androgens are not directly mitogenic to prostate cells *in vitro* and that *in vivo* they probably are proximate signals in a series of signaling events modulated by other growth-promoting substances, including growth factors (362).

Available evidence suggests that the role of epithelial-mesenchymal interactions in androgen-induced regulation of prostate epithelial cell growth and differentiation is a strategic one in the postulated multifaceted signal cascade. The latter may involve cell-to-cell contact phenomena, the release of neurotransmitters, the impact of basement membrane ECM elements, and the production of soluble peptide mediators, so-called growth factors, selectively (Fig. 32.17) (271,282,284,360). Growth factors may stimulate or inhibit cell cycle–mediated events in similar (autocrine) or dissimilar (paracrine) cells; they are mediators of cellular proliferation, differentiation, and cell death (343). Growth factors that share structural and usually functional properties are grouped in superfamilies such as the epidermal and fibroblast growth factor families. Other soluble peptide mediators such as cytokines secreted by cells that are resident in but not an integral part of the prostate tissue (e.g., inflammatory cells) may affect the growth and function of the prostate in an opportunistic way.

Growth factors perceived to have an impact on BPH include EGF, bFGF, keratinocyte growth factor (KGF), IGF, nerve growth factor–like protein (NGF), and TGF-ß. High concentrations of EGF have been identified in prostatic tissues, seminal fluid, and urine (343). Castration markedly reduces and androgen administration restores prostate EGF levels in adult mice, suggesting a role for it in androgen-induced prostate growth (154). Furthermore, the growth of both human and rat prostatic epithelial cells *in vitro* requires the addition of EGF to the culture media (233). In addition to the role of EGF in stimulating growth of epithelium, heparin-binding EGF is a potent smooth muscle mitogen that is potentially secreted by both smooth muscle and epithelial cells (104). However, expression of EGF and its receptor is normal in BPH (343), making its role, like that of androgens, more likely to be permissive than inductive.

The heparin-binding growth factor family includes aFGF, bFGF, int-2, hst-1, FGF-5, hst-2FGF-6, and KGF (351). Of these, bFGF and KGF are most closely linked to the normal and aberrant growth of the human prostate; as noted, aFGF is present in the developing prostate. With respect to bFGF, both prostatic epithelial and stromal cells synthesize this growth factor (2). bFGF is a potent mitogen for prostatic stromal cells but has no direct effect on prostatic epithelial cells, which lack the bFGF receptor (330). Secretion of bFGF does not occur through established secretory pathways because bFGF mRNA lacks a definitive *secretory* signal sequence. Consequently, bFGF release may depend on cell death (298). Released bFGF binds to ECM components (heparin sulfate proteoglycans and glycosaminoglycans), providing a reservoir of biologically active bFGF for target cell interaction (298). Of note, the amount of bFGF mRNA and protein increase markedly in BPH (249). In contrast, KGF, synthesized by androgen-stimulated prostatic stromal cells, is secreted through conventional pathways and unidirectionally induces the proliferation of prostatic epithelial cells, which possess, unlike the stroma, KGF receptors (33,314,391).

The IGF network, including IGF-I and IGF-II, their respective binding proteins (IGFBPs), and the IGF receptors, may play multifaceted roles in cell growth. These include stimulation of proliferation and inhibition of apoptosis, potentially important phenomena in the development and growth of BPH and carcinoma of the prostate. Interest in the insulin growth factor family's role in normal and abnormal prostate growth was intensified by the demonstration that conditioned media from cultured BPH fibroblasts contained a high concentration of IGF-II and had mRNA levels ten times higher than cultured normal prostate stromal cells (63). IGF-I was not detectable in these fibroblasts, nor were IGF-I or IGF-II in prostate epithelial cell cultures (60,62). The following observations deserve consideration: (a) seminal plasma contains IGF-I, IGF-II, IGFBP-II, and IGFBP-IV (309); (b) cultured prostatic epithelial cells are stimulated to proliferate *in vitro* by nanomolar amounts of IGF growth factors and synthesize and secrete both IGFBP-II and IGFBP-IV (61); (c) prostate fibroblasts produce IGFBP-III (61); and (d) Sutkowski and colleagues (349) observed that *in vitro* stimulation of BPH stromal cells by IGF-I could be inhibited by IGFBP-III and that this inhibition could be reversed by PSA. This observation is intriguing and suggests that IGFBP-III is a natural substrate for PSA, and as a consequence, PSA could be involved in regulating IGF activity (60).

Another potentially important observation is the identification of NGF in the stromal compartment of BPH, prostate cancer, and normal prostatic tissue (123). Distinct type 2 NGF receptors have been exclusively identified in prostatic epithelial cells. Clearly, these observations parallel those already described for KGF and its receptor, suggesting that NGF may be yet another undirectional paracrine growth factor of stromal origin that has an impact on the epithelial compartment selectively. The ultimate implications of these findings await further clarification.

TGF-ß is distinct from other prostate growth factors given its dichotomous impact on the epithelial and stromal

compartments. For example, TGF-ß is a potent growth inhibitor for prostatic epithelial cells. *In vitro* exposure to TGF-ß results in growth arrest or death of epithelial cells depending on the presence or absence, respectively, of stimulating factors such as EGF (348). The proliferative phenotype can be induced only in the presence of requisite growth-stimulating factors (i.e., EGF and TGF-α) in the absence of TGF-ß. TGF-ß appears to play a strategic role in the modulation of prostatic epithelial proliferation, growth arrest, and cell death. In contrast, TGF-ß appears to stimulate stromal proliferation, inducing differentiation of fibroblast-like cells into those possessing a smooth muscle phenotype, and modify the composition of ECM (81,102). The latter finding is consistent with the observations demonstrating the association of smooth muscle proliferation and epithelial cell death in proximal regions of the prostatic ductal system (196). The interplay existing between TGF-ß and bFGF may ultimately dictate the relative amounts of stromal or glandular proliferation within the hyperplastic human prostate (343).

NORMAL GROWTH AND DEVELOPMENT OF HUMAN PROSTATE

Part of "32 - BENIGN PROSTATIC HYPERPLASIA "

The human prostate undergoes an increase in size and develops histologic evidence of stimulated growth during three periods of life: (a) before and at birth, (b) during puberty, and (c) with achievement of advancing age (350). The evidence for prostatic stimulation during gestation and at birth is based on histologic studies. During development, the prostatic tubules progress from solid cellular buds at the ends of ducts to bud-acinar combinations to acinar tubular clusters arranged in lobules. The tubules are reported to gradually regress after the first month of life (392). Secretory capacity exists and increases until the last week of gestation. Secretory activity is highest in the lateral and lowest in the posterior peripheral zone. The secretions stain with variable intensity with periodic acid–Schiff stain but only weakly and erratically for PSA (388). Squamous metaplasia was always present in the region of the utricle, often present in various segments of the ducts, and present in the urethra in about one-third of the prostates examined. The foci of squamous metaplasia decreased with maturation of the prostate. The postnatal prepubertal prostate is characterized by an extensive hyperplasia of the duct system. Swyer (350) states that the process of hyperplasia and pseudoacini formation is found chiefly in the central part of the prostate. The end buds of the prostatic duct become more patent with advancing age. The proportion of the gland that is stromal far exceeds the epithelial components. The average weight of the prostate in boys 1 to 10 years of age is 1.4 ± 0.4 g (27). At puberty, the prostate shows marked histologic evidence of stimulation, progressing from enlargement of the end buds of the prostatic ducts to development of somewhat distended alveoli and tall columnar epithelium. Prominent perivascular extrusions that project into slightly distended lumina of these alveoli provide evidence of secretory activity. Although stromal cells (smooth muscle plus connective tissue) are persistently the predominant prostate tissue, the relative smooth muscle contribution decreases in the first and second decade of life but increases to neonatal levels in the third decade (328). The average weight of the prostate for males 11 to 20 years of age is 10.8 ± 3.8 g. During the second and third decade of life, an increase in the number of alveoli contributes to an increased prostate size. During the third decade, there is a gradual, irregular increase in the infolding of the alveolar epithelium. In the fifth decade and later, fewer of these infoldings are seen, and the tendency to cystic dilation becomes evident. After age 20, corpora amylacea are common in prostatic alveoli. Autopsy observations indicate that the average weight of the prostate in the 21- to 30-year age group is 18.1 ± 4 g. In the 31- to 40-year age group, it is 19.1 ± 2.7 g, and in the 41- to 50-year age group, it is 20.2 ± 3.2 g. The histologic characteristics of the prostate in the male with BPH are discussed briefly in the pathology section. Beginning in the sixth decade, the average weight of the prostate increases gradually to 30.9 ± 13 g in the 71- to 81-year age group and 38.8 ± 12.8 g in the 81- to 90-year age group (Fig. 32.19).

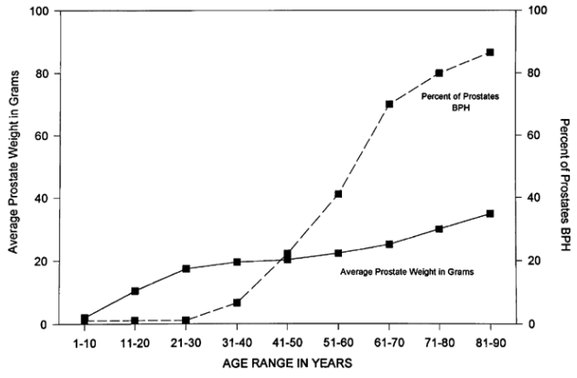

FIGURE 32.19. Age-related changes in histologic benign prostatic hyperplasia *(BPH)* and size of the human prostate. Autopsy prevalence of histologic BPH and changes in average prostate gland weight with advancing age. The increasing prevalence of BPH is much more striking than the increase in average weight. These concomitant observations reflect to some degree the discrepancy between the prevalence of histologic and gross BPH. (Modified from Berry SJ, Coffey DS, Walsh PL, et al. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132:474, with permission.)

BENIGN PROSTATIC HYPERPLASIA

Part of "32 - BENIGN PROSTATIC HYPERPLASIA "

Urinary obstruction as a result of benign prostatic disease has probably been recognized to some degree since the earliest days of medicine. This association was probably first formalized by Riolan in the seventeenth century. In the mideighteenth century, Morgagni (248) provided one of the earliest descriptions of BPH and enumerated many of the potential medical problems attendant to its development. More exact recognition of the pathologic process has been credited to Virchow in the last quarter of the nineteenth century. Since then, information regarding the incidence, gross and histologic characteristics, biochemical composition, associated pathologic and physiologic changes, and pathophysiologic effects of BPH has increased markedly. However, despite increased understanding of normal prostate growth, identification of the cause of BPH remains elusive.

Incidence

Autopsy studies have repeatedly demonstrated an association of BPH and aging based on histologic criteria, calculated or actual prostate weight, or prostate volume. For example, Randall (292) found that histologic evidence of definite or probable BPH exceeded 50% in men over 50 years of age and rose to 75% as men entered the eighth decade. Age-related autopsy prevalence of histologic BPH is

similar in several countries despite differing racial mixes (Fig. 32.18) (167). On the other hand, clinically important mass-producing BPH occurs in only about half (40% to 50%) of men with presumed histologic BPH and is clinically manifested in about half of these (167). Its reported clinical incidence varies appreciably in different parts of the world (83). Based on the combined data from ten autopsy studies, Berry and associates (27) constructed curves for the prevalence of BPH with age (Fig. 32.19). Their analysis implies that BPH is probably initiated before age 30. Their calculated doubling time for BPH weight varies with age, being 4.5 years in the 31- to 50-year age group, 10 years in the 51- to 70-year age group, and more than 100 years in the 70+-year age group. The observed increased mean prostate weight of glands requiring surgical intervention compared to that of glands with hyperplasia recognized at autopsy reinforces the potential role of prostate mass in BPH voiding dysfunction suggested in the Olmsted County–based male voiding pattern studies (117).

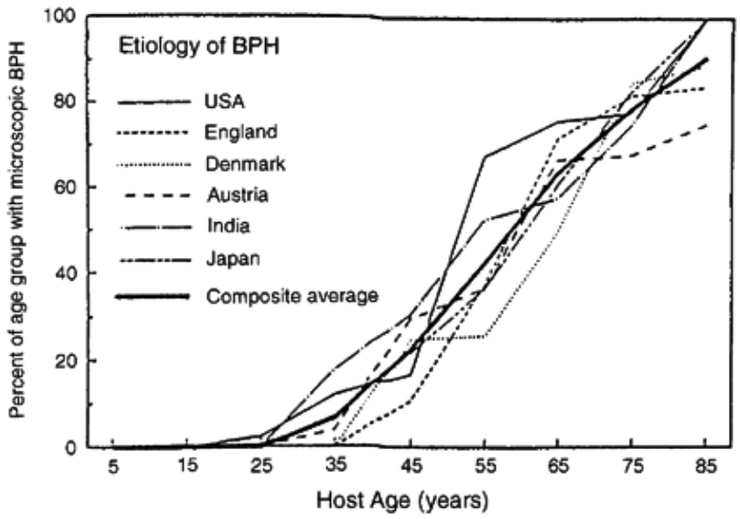

FIGURE 32.18. Age-specific prevalence of histologic benign prostatic hyperplasia *(BPH)* in various geographic male populations. (From Isaacs JT, Coffey DS. Etiology and disease process of benign prostatic hyperplasia. *Prostate* 1989[Suppl 2];33, with permission.)

The clinical literature available on racial and regional incidence of BPH and its impact on individuals is difficult to interpret critically (83,218). The reported data include observations of clinical and pathologic phenomena that use different sampling and evaluation criteria (273), making exact comparisons difficult. Nevertheless, these studies clearly indicate an increasing but quantitatively variable incidence of pathologic or clinical BPH with aging. They suggest that black and white populations in the United States have a similar incidence of BPH, although development of symptoms probably occurs earlier in blacks (71). Blacks in the United States seem to have a higher prevalence of adenomatous hyperplasia than blacks on the African continent. Data from the first half of the twentieth century indicated a much lower prevalence of BPH in native Chinese and Japanese than in white populations (273,311). Data from recent mass screening evaluations in Japan reported a 9.9% and 11.6% prevalence of BPH in men 70 to 79 years of age and 80 years of age and older, respectively (273), reaffirming this impression. Evaluation of the racial background of patients subjected to prostatectomy in Hawaii indicated a relatively diminished requirement for prostatectomy in Chinese and Japanese as compared with white males. However, a series of recent observations suggests that environmental rather than racial or genetic factors play a significant and probably major role in these observed differences in incidence and prevalence of BPH. In a series of 321 unselected autopsies from the Beijing and Shanghai districts of China between 1989 and 1992, more than 30% of the 95 men older than 40 years of age showed evidence of BPH (137a). A study of BPH in rural and urban males revealed a similar prevalence of this benign growth in the urban but not rural Chinese population; dietary differences were thought to play a significant role in this observation (137a). In addition, the increased identification by ultrasound examination of nodular BPH with age (51% in 70- to 79-year-olds) in a community-based study in Shimamaki, Japan (226), as well as the increased prevalence of evidence of BPH in men with Asian ancestry in Hawaii and San Francisco (83,92) compared with native Japanese, seems to relegate race and genetic factors to a limited role in prevalence of clinical BPH. Prospective ultrasound evaluation of monozygotic and dizygotic twins (241), coupled with historical assessments of twins (279) and families with a high incidence of prostatectomy in men younger than 64 years of age (316), supports possible genetic factors in development of BPH. As the result of their twin studies, Meikle and colleagues (241) suggested that hereditary factors substantially contribute to symptomatology but that nongenetic factors have more influence on zonal volumes of the prostate. Overall, the clinical and pathologic observations suggest little racial or genetic influence on the prevalence of histologic BPH but a significant probability that environment,

possibly dietary intake, and possibly genetic factors in a limited patient cohort may influence the rate and degree of development of mass-producing BPH.

Pathology

BPH in humans is a nodular, regional growth with a variegated gross appearance resulting from the inhomogeneous and irregular mixture of glandular and stromal tissue. Although BPH nodules may arise in the peripheral prostate, they are almost always located centrally in the periurethral portion of the enlarged gland (Fig. 32.20). BPH develops in a variety of gross configurations and periurethral sites, resulting in various anatomic designations such as median lobe, median bar, and lateral lobe hyperplasia. Randall (292) observed eight gross anatomic configurations: lateral; posterior commissural or median; lateral and median; subcervical (Albarrán's lobe); lateral and subcervical; anterior commissural; subtrigonal (lobe of Home); and lateral, median, and subcervical lobes (Table 32.1). Bilateral or middle lobe involvement was identified in approximately 59% of Randall's cases. In many instances, the nodular hyperplasia is

separated by a distinct, smooth, cleavage plane from the compressed peripheral prostate that resembles a capsule. The weight of the hyperplastic tissue is highly variable, ranging from a few grams to more than 200 g; no clear relationship between the size of the adenoma and the degree of bladder neck obstruction has been established.

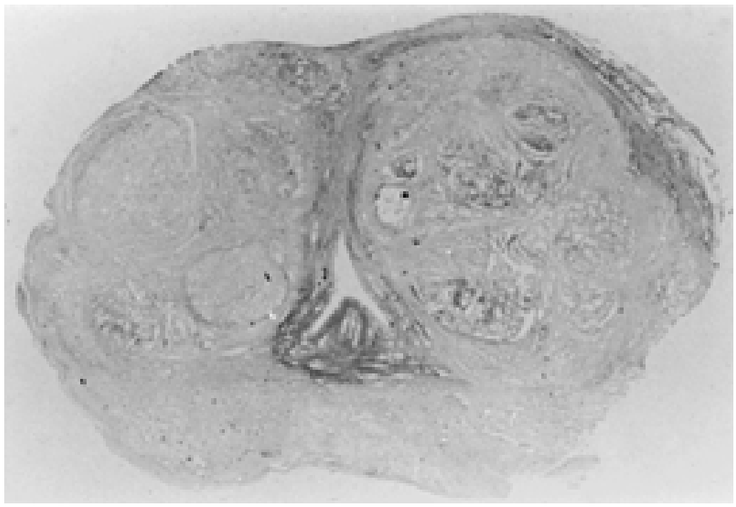

FIGURE 32.20. Transverse section of adult prostate with benign prostatic hyperplasia. The nodular, variegated structure of the periurethral adenomatous tissue is evident. The compressed peripheral prostatic tissue (“surgical capsule”) is evident.

Type	Description	No. of Cases
I	Simple bilateral lobe hypertrophy	32
II	Solitary posterior commissural hypertrophy	31
III	Bilateral and commissural hypertrophy	38
IV	Solitary subcervical lobe hypertrophy	67
V	Bilateral and subcervical lobe hypertrophy	48
VI	Bilater, subcervical, and commissural hypertrophy	3
VII	Anterior (commissural) lobe hypertrophy	1
VIII	Subtrigonal lobe hypertrophy	2

From Randall A. *Surgical pathology of prostatic obstruction.* Baltimore: Williams & Wilkins, 1931, with permission.

TABLE 32.1. INCIDENCE OF TYPES OF LABOR HYPERTROPHY

Observation of the hyperplastic prostate with light microscopy confirms the variable findings suggested by the gross appearance. All the glandular and stromal elements of the normal prostate are involved to a variable degree by hyperplasia. Franks (100) identified five types of nodules based on their histologic characteristics: (a) stromal (fibrous or fibrovascular), (b) fibromuscular, (c) muscular (“leiomyoma”), (d) fibroadenoma, and (e) fibromyoadenoma. He pointed out that true stromal nodules were found only in the subepithelial tissue of the urethra (Fig. 32.21,Fig. 32.22 and Fig. 32.23). Moore (247) emphasized that they arose in the lateral walls of the urethra, well removed from the utricle. He also stated that small stromal nodules were present in every enlarged prostate. Commonly, large nodules are fibromyoadenomas. Glandular elements in the nodule vary a great deal. Acini may be large or small, with some cystic changes. Epithelial cells may be tall-columnar, cuboidal, or flattened low-cuboidal in configuration; they may be arranged peripherally, show papillary infolding, or assume a cribriform pattern (Fig. 32.24). Both ductal and acinar epithelium appear

to be involved in the proliferative process. The acini may have epithelium similar to normal mature glands, except perhaps with more papillary extensions (active), or they may have an inactive prepubertal type of appearance (inactive). Transition zones and buds of proliferating epithelium showing spindle-cell metaplasia are also seen. A number of histologic variants of BPH, including postatrophy, basal cell, cribriform, and atypical adenomatous hyperplasia, as well as sclerosing adenomas and stromal hyperplasia with giant cells, have been recognized. At times, differentiation of these variants from carcinoma can be difficult (32). Franks (101) stated that the ultrastructural appearance of the hyperplastic gland reflects the characteristics noted on light microscopy. Although several observers have reported prominent intercellular lacunae in BPH (Fig. 32.25), critical differences between the cells of the normal and hyperplastic gland have not been identified. Acute and chronic inflammatory changes are common in association with hyperplasia. Interestingly, careful examination reveals that even well-defined nodules almost always merge with the surrounding tissue at some point.

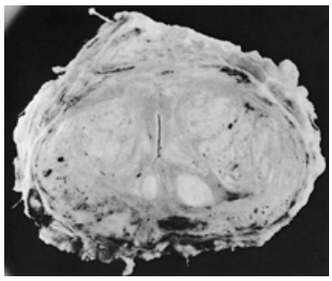

FIGURE 32.21. Transverse section of human prostate gland demonstrating small focal nodules of predominantly stromal hyperplasia. Their modest size and periurethral location are characteristic. Also note concomitant glandular hyperplasia. (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.)

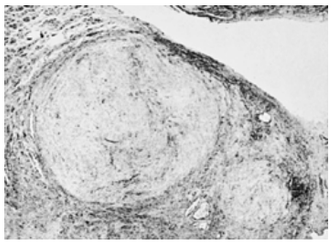

FIGURE 32.22. Stromal hyperplasia. This represents a higher magnification (×10) of the stromal nodules demonstrated in Fig. 32.21. Again, note the close proximity of the urethral lumen. (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.)

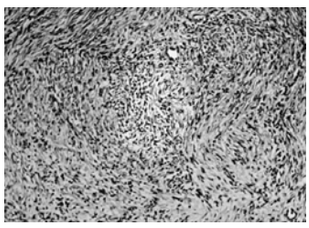

FIGURE 32.23. Stromal hyperplasia (×115). In benign prostatic hyperplasia (BPH), the fibromuscular stroma is often found to loosely envelop adjacent hyperplastic acini or occasionally form discrete compact nodules. In distinction to the hyperplastic process found in breast, the fibromuscular stroma in BPH lacks excessive amounts of elastic tissue. (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.)

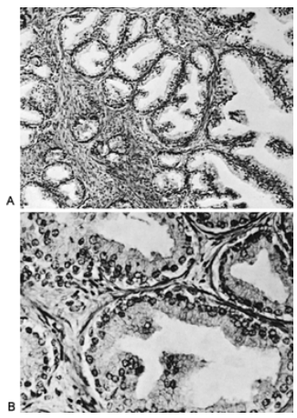

FIGURE 32.24. A: Photomicrograph (×80) of a focus of predominantly glandular hyperplasia. Note occasional papillary infolding, the two-cell layer composition of the acini, and the abundance of surrounding and intervening stromal elements. **B:** Higher-magnification view (×300) better demonstrating the consistent presence of basal and adluminal cell components to the individual acini, as well as the loose intervening stromal component. Adluminal papillary proliferation is well demonstrated. (From Mostofi FK, Price EB. *Tumors of the male genital system,* series 2, fascicle 8, *Atlas of tumor pathology.* Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.)

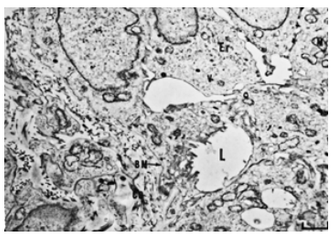

FIGURE 32.25. Electron micrograph of epithelial cells in benign prostatic hyperplasia (×7,000). No distinct ultrastructural differences are noted between normal and hyperplastic prostatic epithelial cells except occasionally prominent intercellular lacunae *(L).* Prominent basement membrane *(BM)* and subadjacent collagen bundles are noted. (From Fisher ER, Jeffrey W. Ultrastructure of human normal and neoplastic prostate with comments relative to prostatic effects of hormonal stimulation in the rabbit. *Am J Clin Pathol* 1965;44:119, with permission.)

Associated Pathology

Infarction of the prostate, thought to occur predominantly in prostates of substantial size exhibiting nodular hyperplasia (1,16,247), is said to be present in approximately 25% of large glands. Acute massive prostatic infarction has been observed in association with septic shock, hemorrhagic shock caused by a ruptured abdominal aortic aneurysm, coronary artery bypass, repair of aortic and iliac artery aneurysms, and pyonephrosis (93). Infarcts vary in size from tiny to 5-cm lesions and are commonly located periurethrally. A speckled, grayish-yellow appearance occasionally associated with hemorrhagic streaks and a sharply delineated, often hemorrhagic periphery are characteristic. Spiro and associates (338) noted prostatic infarction in 85% of the glands in patients with and in 3% of those without acute urinary retention. Others have found no definite or a lesser predominance of identifiable infarction in patients treated for acute retention (8). Prostatic infarcts may be associated with significant elevation of the serum prostate markers (308). Histologically, infarcted areas reveal centrally located coagulation necrosis with hemorrhagic changes in the peripheral margins. Metaplasia of adjacent ductal and acinar epithelium often results in a squamous or transitional epithelial configuration (252). Although acini involved with metaplasia (308) may lack the characteristic basal cell layer, all the cells involved are typically well differentiated and demonstrate no evidence of anaplasia or invasion that would be expected with malignancy.

Prostatic calculi have been recognized with an incidence varying from 7% in prostate pathology specimens to 20% at autopsy, 30% in radiologic studies, and even higher incidence on ultrasound evaluation (128). The calculi have either a lobular or polyfaceted laminar surface (371). Based on their composition, they have been classified as primary, forming inside the acinus, or secondary, forming within the prostatic ducts. Primary calculi characteristically have a nucleus of apatite with concentric layers of apatite and whitlockite. Peripheral layers of whewellite and occasionally weddellite may be present. These calculi may be completely crystalline or have areas with a sizable amount of organic material, or a nucleus suggesting an amylaceous body. Secondary calculi may have a nucleus of whewellite or uric acid (290). Classically, the calculi are deposited within the cleavage line that exists between the nodular hyperplasia and the surgical capsule. On routine radiographs, true prostatic calculi appear as scattered calcifications overlying the pubic symphysis and the superior pubic rami. Multiple clustered calculi may be recognized on rectal examination by characteristic

crepitation. Single calculi have a firmness on rectal examination suggestive of carcinoma.

Two lesions that warrant discussion because of their resemblance to or association with BPH are papillary adenoma of the utricle (aberrant prostatic tissue) and blue nevus of the prostate. Aberrant prostate tissue may involve the utricle, the base and perimeter of the verumontanum, or the entire prostatic urethra. These lesions tend to occur in younger men, manifest clinically most often with gross painless hematuria, and are indistinguishable from adenomatous hyperplasia of the prostate (252). Postmortem specimens suggest that these lesions usually represent a hyperplastic proliferation of normal tissue.

Blue nevus of the prostate may be associated with prostatic hyperplasia and cause confusion with malignant melanoma. Histologically, this lesion is characterized by infiltration of the prostatic stroma by clumps of spindle-shaped cells containing a granular brown, iron-negative, bleachable, Fontana-Masson–stained pigment within their cytoplasm (252).

Biochemical Characteristics

The concentration and content of steroids, enzymes, minerals, and a variety of compounds have been determined in the hyperplastic tissue and compared with normal and carcinomatous tissue. Identification of normal tissue and preservation of its biochemical characteristics for analysis is a problem that requires persistent attention. The variable composition of tissue samples of BPH and carcinoma as demonstrated on histologic study undoubtedly increases the challenge to obtain consistent results in their analysis. Nevertheless, a sizable body of information regarding steroid content, metabolism, and specific binding, as well as other biochemical characteristics of normal and pathologic prostate tissue, has been published in the past 30 years. As analytic techniques have improved, a significant portion of these data have been modified or discarded. The following seems a reasonable summary of the current state of our knowledge.

The observations (90) that dihydrotestosterone and androstenediol are the principal metabolites of radioactive testosterone incubated with human BPH tissue *in vitro* have been adequately confirmed. However, reports that BPH tissue has a higher concentration of DHT than normal or peripheral prostate have not been supported in repeated assessments of appropriately preserved surgical tissue. In these specimens, BPH and peripheral prostate had similar tissue levels of DHT (5.0 and 5.1 ng/g) and testosterone (1.8 and 1.2 ng/g) (373). These findings were eventually confirmed by Bartsch and colleagues (21) and Norman and colleagues (266). A weak correlation was observed between DHT concentration and the content of glandular tissue. Bartsch and colleagues (21) reported low levels of progesterone, estrone, estradiol, and estriol (0.02 to 0.06 ng/g tissue) in surgically removed BPH and normal prostate tissue from kidney donors. In contrast, Krieg and associates (191) found markedly increased estradiol (6.2 versus 2.2 fmol/mg protein) and estrone (7.4 versus 0.9 fmol/ng protein) levels in mechanically separated stroma from suprapubic prostatectomy specimens compared with prostate tissue from six brain-dead 21- to 61-year-old kidney donors. DHT and T concentrations in stroma were similar in surgical and kidney donor specimens but were reduced in prostate epithelium from kidney donors. Normal tissue levels of DHT in BPH tissue seem paradoxic in view of the decreased serum testosterone levels in aging men (125,370); the increased 5α-reductase activity of BPH stroma could partially account for this finding (36) but seems unlikely to do so.

Evidence that 5α-reductase activity is increased two to three times in BPH (35,162,166) and is predominantly localized to the stroma is substantial. Prostatic tissue obtained from 50 men subjected to open prostatectomy and 15 brain-dead organ donors 14 to 38 years of age had 6 to

15 times greater 5α-reductase activity in the crudely separated stroma than did the epithelium regardless of the histology of the prostate (36). These observations suggest that the relatively increased amount of stromal tissue in BPH as compared with normal tissue may contribute significantly to its (BPH) reported increased 5α-reductase activity. Availability of an antibody to 5α-reductase type 2, the isoenzyme present in prostatic tissue, has permitted immunohistochemical evaluation of a variety of tissues for this enzyme. Limited observations demonstrate perinuclear staining of basal and stromal cells in normal and BPH tissue. The predominant staining in BPH as contrasted with "normal" prostate was in the stroma rather than basal cells (332,333). No 5α-reductase antigen was detected in luminar epithelial cells.

Attempts to characterize, localize, and quantify steroid receptors in BPH as compared with those in normal or peripheral prostatic tissue have been persistent. The gene for the androgen receptor has been cloned and sequenced, and its protein product has been characterized (48,58), adding sophisticated tools to study this aspect of androgen effect on cells. With immunohistochemical techniques (225,245) the physiologically important androgen receptor is localized in the nucleus. Evidence suggests that nuclear androgen receptor content is increased in BPH compared with peripheral prostate (59). The presence of estrogen receptors in the prostate has now been confirmed by most investigators. In general, estrogen-binding sites are reported to be more numerous in stroma than in epithelial cells and to be decreased in concentration in BPH as compared with normal tissue (59,77,180,321). Interest in the role of estrogen receptors has been increased by the isolation of a second estrogen receptor in the rat prostate and confirmation of its presence in human prostate (49). Progesterone receptors are also present in appreciable concentrations in the cytosol of prostatic epithelial cells; the concentration in BPH is significantly greater than that in normal tissue (21). However, progesterone receptors have not been identified in the nucleus of prostatic cells. Although the receptor–steroid complexes clearly have significant roles in the growth and function of prostatic cells, the exact mechanisms involved and the significance of receptor data with regard to the development and growth of BPH are still unclear.

Enzymes

Evaluation of the concentration of a series of enzymes involved in steroid metabolism in BPH as compared with normal or peripheral prostate in addition to the previously discussed 5α-reductase has not provided insightful information. Observations of significantly decreased 3α- and 3ß-hydroxysteroid oxidoreductase reductase and 17ß-hydroxysteroid oxidoreductase oxidase activities in surgically removed BPH compared with surgically removed normal prostate (166), changes favoring increased DHT formation in BPH, were not confirmed later by the same group (34). Brendler and colleagues (34) reported a three to six times higher acid phosphatase activity in BPH than in peripheral prostatic tissue. The activity of several other cytoplasmic enzymes, including alkaline phosphatase and lactic dehydrogenase, did not differ in BPH and normal tissue. Histochemical studies have demonstrated marked ß-glucuronidase and *N*-acetyl-ß-glucosaminidase activity in the prostatic epithelium of BPH (265) and of aminopeptidase in normal prostate and BPH (185). However, aminopeptidase activity was diminished or absent in some BPH nodules (185) and was decreased in concentration in tissue homogenates compared with normal tissue (264). Histochemical staining revealed no difference for a group of oxidative enzymes in BPH and normal prostate tissue (264). Interestingly, staining for glucose-6-phosphate dehydrogenase and ß-hydroxybutyrate dehydrogenase activity was almost absent and weak, respectively. Nonspecific esterase and succinic dehydrogenase staining were similar in normal and hyperplastic prostate.

Organic Compounds and Metal Ions

BPH has a high concentration of citric, lactic, and aconitic acids per gram of tissue, but accurate comparisons with the concentrations found in normal tissue are not available. No α-ketoglutaric or succinic acid was detected in BPH (335). Zinc content has variously been reported to be elevated (141) and identical (142) to the high level noted in normal prostatic tissue. Cadmium has been reported to be present in much higher concentration in BPH than in normal tissue (142). Magnesium has been shown to be increased in concentration in the epithelial cells of BPH by histochemical studies and in the tissue by atomic absorption spectrophotometry (141).

Summary of Biochemical Aspects of Benign Prostatic Hyperplasia

As indicated, despite extensive and continuing efforts, no qualitative differences in steroid content or metabolism, enzyme activity, organic compounds, or metal ions have been documented between BPH tissue and either normal prostatic tissue or the peripheral prostate from a gland with BPH. The few quantitative differences in biochemical characteristics reported require confirmation and have not helped identify a unique aspect of the metabolic activity characterizing BPH.

Natural History of Anatomic Benign Prostatic Hyperplasia

The first pathologic evidence of BPH occurs in less than 10% of the men in the 31- to 40-year-old group (Table 32.2). This observation may indicate that the initiating

factor is present in most men of this age, with its effect being recognizable only in a few, or that young men with recognizable BPH have a discrepancy between physiologic and chronologic aging. Evidence of histologic and anatomic BPH increases with age; by the ninth decade the former is identifiable in approximately 90% and the latter in probably over half of men (150). The initial lesion of BPH almost always occurs in the periurethral area proximal to the verumontanum. Although descriptions of the ductal and glandular structure of this area vary, it is generally agreed that BPH arises from an inner set of prostatic ducts and glands that reside within the urethral wall or adjacent to it. McNeal (235) designates the paraurethral portion of this tissue the transition zone; it composes approximately 5% of the normal gland. The histologic characteristics of the earliest BPH lesions are probably variable. Those that develop within the urethral wall are usually composed of a mass of loose embryonic-appearing stroma devoid of glands; however, glandular tissue predominates in early lesions developing in the transition zone (234). McNeal (235) and Franks (101) agree with the latter's statement that stromal and epithelial hyperplasia may occur alone or together. Once the process is initiated, all elements of the normal prostate—stromal and glandular—participate to a variable degree in its progression. The glands in the hyperplastic nodules seem to have the capacity to bud and form new ducts and acini; in contrast to normal tissue, these new glandular elements grow toward each other. Pure stromal nodules rarely reach large size. The variable local response to a postulated inductive agent is evident from the nodular nature of the BPH. Not all the nodules of BPH are in the same phase of development, as is clearly indicated by Moore's observation (247) that small stromal nodules were present in every enlarged prostate. This observation does not preclude the possibility that BPH results from a sequence of initiating and promoting effects that are episodic. Both the average weights of the prostate and the incidence of prostatectomy by decade suggest that once BPH has developed, it is progressive in most men. The rate of growth calculated by Berry and colleagues (27) indicates a prolongation of the doubling time with age. The important question of whether established BPH ever stabilizes or regresses spontaneously cannot be evaluated from the information available. Based solely on clinical criteria, many authors, including ourselves, are of the opinion that both occur (see also Natural History of Benign Prostatic Hyperplasia Voiding Dysfunction).

	Autopsy Studies										Combined Data	
	Pradhan and Chandra (1975)		Swyer (1944)		Harbitz and Haugen (1972)		Franks		Moore		Prevalence of Human BPH	
Age Range (yr)	No. with BPH Total No. (%)		No. with BPH Total No. (%)		No. with BPH Total No. (%)		No. with BPH Total No. (%)		No. with BPH Total No. (%)		No. with BPH Total No. (%)	% Mean ± SEM
1–10	0/11	(0)	0/16	(0)							0/27	0 ± 0
11–20	0/21	(0)	0/13	(0)			0/1	(0)			0/35	0 ± 0
21–30	0/37	(0)	0/21	(0)			0/4	(0)	0/24	(0)	0/86	0 ± 0
31–40	7/38	(18)	0/31	(0)			0/8	(0)	1/28	(4)	8/105	8 ± 8.5
41–50	6/19	(31)	2/28	(7)	4/6	(67)	3/18	(17)	7/23	(30)	22/94	23 ± 30.4
51–60	9/17	(53)	11/33	(33)	21/38	(55)	16/38	(42)	24/65	(37)	81/191	42 ± 9.7
61–70	7/12	(58)	23/33	(69)	49/66	(74)	40/54	(74)	52/77	(67)	171/242	71 ± 7.2
71–80	3/4	(75)	14/17	(82)	64/67	(96)	57/70	(81)	43/63	(68)	181/221	82 ± 11.1
81–>90	2/2	(100)			27/29	(93)	16/19	(84)	18/24	(75)	65/74	88 ± 10.9
Totals	34/161		50/192		165/206		132/212		145/304		528/1,075	

From Berry SJ, Coffey DS, Walsh PC, et al. The development of human benign prostatic hyperplasia with age. *J Urol* 1984;132:474, with permission.

TABLE 32.2. AGE PREVALENCE OF HUMAN BENIGN PROSTATIC HYPERPLASIA (BPH)

Etiology

Identifying the etiology of BPH has been a continuing challenge. The universal regional development of histologic BPH (167) in aging men with testes that produce an androgen-diminished environment (125) is an as yet unexplained paradox that is independent of race and environment. The subsequent development of mass-producing BPH is selective (166) and seems potentially to be related to a variety of factors, at least some of which are associated with environment and lifestyle. In proposing etiologic factors in this common benign growth in humans, the unusual pathologic features of BPH including nodular growth and stromal predominance require consideration in addition to its characteristic periurethral localization. Over time, neoplastic, inflammatory, metabolic and nutritional, vascular, racial, and a variety of other etiologic factors have been considered as causes of BPH (251). Newly identified systemic or local prostatic growth-promoting agents traditionally receive prompt consideration. Evidence has been presented suggesting a genetic factor in a small group of men developing BPH. Currently, four hypotheses regarding the etiology of BPH are prominent: the DHT or altered hormone environment

hypothesis, the embryonic reawakening hypothesis (236), the stem cell hypothesis (167), and the nonandrogenic testis secretory factor hypothesis (129,133). Two of these, the embryonic reawakening and the stem cell hypotheses, focus on intrinsic cellular phenomena. The embryonic reawakening theory proposes that the interaction between glandular tissue of prostatic origin and stroma related to the bladder produces a reawakening of embryonic inductive interactions resulting in tissue with growth characteristics that lead to the development of BPH (236). Subsequent growth of BPH is postulated to be multifactorial (197,277), with altered hormone environment and stromal epithelial interaction having varying degrees of prominence in this phenomenon. The stem cell hypothesis proposes an increase in prostate stem cell number and that of the amplifying and transient cells derived from them as the basic phenomenon leading to the development of BPH. Neither the embryonic reawakening nor the stem cell hypothesis proposes an identifiable inducing mechanism to initiate or sustain the phenomena proposed.

The so-called DHT hypothesis, perhaps more appropriately termed the *altered hormonal environment* hypothesis, and the nonandrogenic testis secretory factor hypothesis center on alterations in testis secretory function or changes in local or systemic hormone metabolism with age that may initiate or sustain phenomena leading to the development of BPH. Several studies demonstrate that with aging the male human develops an androgen-diminished environment. This decrease in systemic androgen is accompanied by stable or possibly slightly altered systemic estrogen and increased steroid hormone binding serum levels (125,137,255). The latter further decreases the biologically available systemic testosterone. Although DHT and androgen receptor (AR) concentrations in BPH tissue are high, they do not differ from peripheral or normal prostate levels. The evidence suggests that androgens are necessary for but not sufficient to induce development of BPH. Estrogens have demonstrated physiologic effects on male accessory sex gland growth, including the prostate in animals (224); this primarily involves the stromal tissue (171). BPH can be induced in the dog by coadministration of androstanediol and estrogen (277,375). The recent discovery of a second estrogen receptor, estrogen receptor-ß (ERß), has stimulated additional speculation about potential mechanisms for and role of estrogen in prostate BPH growth. Of interest, genistein and other phytoestrogens have a much higher affinity for ERß than ERα (49). However, despite the appreciable information from animal experimentation, and human tissue and serum hormone analysis with aging in men, the role of estrogen in the development and progression of BPH remains controversial. Attempts to correlate serum hormone levels with benign prostate pathology in radical prostatectomy specimens (278) and with ultrasound-assessed prostate size and anatomic configuration in twins (241) and longitudinal evaluation of serum hormone levels and manifestations of BPH (108) have also failed to provide insights into its etiology. Excluding the possible significant effects of estrogen imprinting on the neonatal prostate (288), these data suggest that estrogen may share a potential role in BPH mass development with a variety of other variously derived agents. Overall, the multiple studies of changes in known steroid hormone secretory products of the testis have not provided a highly probable explanation for the critical role of the testis in the development and growth of BPH in humans.

The nonandrogenic testis factor (NATF) hypothesis proposes that the testes secrete a nonandrogenic prostate growth-stimulating factor, almost certainly a protein, that plays a critical role in the ubiquitous development of histologic BPH and possibly a contributory role in the subsequent development of mass-producing BPH (129,133,165). Biologic evidence supporting the presence of a nonandrogenic male accessory sex gland growth-stimulating substance in the aging male human was derived from assessment of age-related changes in the concentration of selected prostate and seminal vesicle secretory products and seminal vesicle weight (126,130). The testes were targeted as a source of this hypothesized prostate growth-stimulating agent based on the evidence that neither endogenous nor exogenous testosterone or estradiol could replace a normally functioning testis in producing BPH in dogs (131,176) and evidence for a systemic prostate growth-stimulating substance that was not a steroid in the testis-intact but not the castrated rat. Evaluation of possible secretion of a nonandrogenic prostate stromal cell stimulating protein by the testis (NATF) was carried out using stimulation of the proliferative response of human prostate stromal cells to testicular epididymal plasma derived from human spermatoceles (STEP) *in vitro* as evidence for its existence. Exposure to STEP produced both androgen-independent and androgen-synergistic stromal growth stimulation repeatedly in this system (133). Isolation and identification of the protein (NATF) responsible for this stimulation is progressing. Animal studies indicate that the prostate is exposed to NATF by a systemic delivery route; in addition, the presence of NATF in the testosterone-rich testicular epididymal plasma fosters potential exposure of periurethral prostatic tissue to these independent and synergistic prostate growth-stimulating compounds. We postulate that this exposure induces the almost universal periurethrally localized development of histologic BPH. Subsequent selective stimulation of prostatic mass is postulated to be induced by multiple factors with a significant but less well defined role for exposure to systemic or local NATF.

Pathophysiology

Concepts regarding the etiology of urinary symptoms and sequelae resulting from BPH traditionally focused on the development and progression of mechanical obstruction

from the prostatic mass as the cause. The perception that the mass and configuration of the hyperplasia dictated the degree of outflow blockage undoubtedly resulted from the early experiences in treatment of patients with acute and chronic urinary retention. Renal failure, urinary tract infection, and calculi were common indications for various approaches to relieve bladder neck obstruction. The commonly observed reversal of these serious secondary phenomena and restoration of normal or markedly improved voiding patterns reinforced the mass-obstruction concept. Failures in both of these therapeutic goals were overshadowed by the frequent correction of the various significant problems that existed. Absence of a direct correlation between the size of the prostate and presence or degree of obstruction was recognized as indicated by the designation “prostatism sans prostate” or the admonition “small prostate, big residual.” If functional results of mass removal were less than optimal, the concept of probable persistence of mechanical obstruction was pursued by determining postvoid residual urine to evaluate bladder emptying, carrying out endoscopic reassessment of the lower urinary tract primarily to assess the possibility of persistent mass, and at times performing a simple urodynamic evaluation. Proposals implicating intrinsic prostatic tension from contracting prostate stromal smooth muscle (43,198) or extrinsic tension on the BPH prostate mass by a contracting or contracted prostate capsule (164,272) have been proposed as potentially having important roles in primary or persistent bladder outlet obstruction. The proposed role of stromal smooth muscle–mediated increased intrinsic prostate tension has been reinforced substantially by *in vitro* physiologic and to a lesser degree clinical observations with α-adrenergic agonists and receptor blocker agents, respectively (198). The proposed role of peripheral capsular tension on bladder outlet obstruction is supported by the results of transurethral incision (230,239) and impressively by the report of anterior commissurotomy carried out by Shafik (326). Although α-adrenergic agonist mechanisms may potentially affect voiding in a variety of ways that may complement the effects of BPH (198), these secondary phenomena seem unlikely to play a direct role in the primary BPH-mediated effects on voiding.

BPH-mediated bladder outlet obstruction results in a series of changes in bladder tissue mass, composition, and function; it also affects blood supply and nerve status and function. Although not well documented, it seems probable that the functional status of each of these physiologically important components of the bladder moderates its response to outlet obstruction. Nevertheless, the degree and persistence of the obstruction is thought to play a pivotal role in the resulting anatomic and functional bladder effects. The sequence of obstruction-induced pathophysiologic changes is variable, multifocal, and incompletely characterized (206,229). In humans, outlet obstruction can be the primary cause of physiologic changes varying from hyperfunction and hyperirritability to nonfunction or atony. Evaluation of this spectrum of functional states is difficult and confusing. Consequently, evidence of bladder changes associated with well-characterized bladder outflow obstruction is derived largely from observations in animals; the resulting observations probably are but may not be transferable to humans. In general, partial bladder obstruction results initially in a detrusor muscle hypertrophy and increased bladder weight that are reversible (206,229). Typically, increased muscle mass is associated with increased intravesical pressure on voiding (54). Studies in obstructed pigs demonstrate a decrease in functional bladder capacity, increased residual urine, detrusor instability associated with incontinence, and a prolonged period of hypoperfusion and associated tissue hypoxia (206), a sequence of physiologic changes that seem probable in humans. The human and the pig usually develop a thickened trabeculated bladder in response to outflow obstruction. However, the likelihood that a stable, balanced outlet obstruction or detrusor functional status and response state will be maintained if achieved seems problematic. Chronic retention of urine can lead to a thin-walled, flaccid bladder in the bladder outlet obstructed pig just as it does in some humans. In addition to impaired emptying, persistent obstruction is associated with increased collagen deposition and decreased compliance in humans (229). Rabbits with bladder outlet obstruction (229) develop a change in detrusor muscle myosin phenotype suggesting a trend to a dedifferentiated phenotype.

The varying mixes of anatomic and physiologic alterations described in response to obstruction probably play a major role in the specific bladder and renal changes that occur in individual patients. Currently, loss of bladder compliance is probably the major factor in producing upper urinary tract functional and anatomic damage. The etiology of the involuntary obstruction-related bladder contractions (319) remains problematic, but *in vitro* studies with isolated detrusor muscle from the obstructed pig bladder suggest that they have a myogenic, not neurogenic, basis (206). Fortunately, these involuntary contractions are reversible in clinical practice and animal models with relief of obstruction. Cellules, saccules, and diverticula are recognized and related anatomic bladder changes with potential clinical significance that develop and progress unpredictably. Based on their extensive experience with the pathophysiology of bladder obstruction induced bladder changes, Levin and colleagues (206) suggest that bladder outlet obstruction should be relieved as soon as possible after diagnosis to maximize the chance for bladder recovery.

Clinical Evaluation

Clinical evaluation to assess the presence and degree of voiding dysfunction or the role of BPH in its presence has an increasingly broad spectrum of potential goals. These include providing information for a range of epidemiologic

studies, selecting patients for drug or interventional studies, and providing information and advice to individual patients. The specific goal often plays a significant role in the character and extent of a patient's evaluation. The discussion of clinical evaluation that follows focuses on the management of the individual patient.

The goals of the clinical evaluation of the individual with voiding dysfunction caused by BPH are to identify the patient's voiding or, more appropriately, urinary tract problems, both symptomatic and physiologic; to establish the etiologic role of BPH in these problems; to evaluate the necessity for and probability of success and risks of various therapeutic approaches to these problems; and to present the results of these assessments to the patient so he can make an informed decision about management recommendations and available alternatives. The clinical evaluation centers on an evaluation of symptoms, physical findings, and results of laboratory and selected imaging and endoscopic studies.

Symptoms

Most patients with medical problems caused by BPH have symptoms of dysfunctional voiding. This symptom complex is nonspecific and is identified by many eponyms, including the currently favored nonspecific term *lower urinary tract symptoms* (LUTS) and the traditional term *prostatism,* implying an established etiologic relationship. We prefer the term *BPH voiding dysfunction* once the etiologic relationship with the prostate warrants serious consideration. As emphasized by Blaivis (31), the clinically recognizable bladder response to various stresses or pathologic changes can be the result of overactive (frequency, nocturia, urgency, urge incontinence) or underactive (hesitancy, intermittency, weak stream, urinary retention) detrusor activity. Blaivis (31) states that BPH symptoms are essentially caused by prostatic obstruction-induced impaired detrusor contractility, detrusor instability, or sensory urgency. They have multiple potential causes varying from those primarily associated with the lower urinary tract to systemic diseases (Table 32.3). The symptoms can be associated with primary diseases of the bladder, neurogenic and metabolic disorders, a variety of diseases of the cardiovascular renal system, use of pharmacologic agents (including antihistamines and antidepressants), markedly increased or abnormal fluid intake, and apparently also normal aging. A small group of patients with “silent prostatism” have severe physiologic sequelae of BPH-induced bladder neck obstruction such as bladder atony or renal failure with minimal or no voiding problems.

Other causes of bladder outlet obstruction
Vesical neck obstruction
Prostatic cancer
Adenocarcinoma
Squamous cell carcinoma
Sarcoma
Other rare tumors
Müllerian duct cysts
Urethral obstruction
Stricture
Valves
Impaired detrusor contractility
Neurogenic origin
Myogenic origin
Psychogenic origin
Detrusor instability/hyperreflexia
Inflammatory and infectious conditions
Cystitis
Bacterial cystitis
Abacterial cystitis
Interstitial/tuberculosis/radiation
Carcinoma *in situ* bladder
“Prostatitis syndromes”
Acute bacterial prostatitis
Chronic bacterial prostatitis
Chronic abacterial prostatitis
Fungai prostatitis
Miscellaneous prostatitis

From Blaivis JG. Differential diagnosis. In: Hinman F Jr, ed. *Benign prostatic hypertrophy.* New York: Springer-Verlag, 1983:747, with permission.

TABLE 32.3. DIFFERENTIAL DIAGNOSIS OF BENIGN PROSTATIC HYPERTROPHY

Separation of lower urinary tract symptoms into those related to voiding (delivery) and storage seems reasonable (172). Voiding symptoms include the following: hesitancy, a delay in initiating micturition; intermittency, an involuntary interruption of voiding; weak urinary stream; straining to void; sensation of incomplete emptying; and terminal dribbling. Of these symptoms, the prevalence of a weak urinary stream correlated with increasing age. The storage symptoms include the following: frequency, normal (longer than 3 hours) and abnormal (less than 2 hours); nocturia, awakening to void; urgency, an increasingly strong desire to void; incontinence (urge, stress, overflow, anatomic); and bladder pain (pain in pelvis without voiding) or dysuria (pain and discomfort with voiding). Of these storage symptoms, nocturia, urgency, urgency incontinence, and frequency correlated with increasing age. Jepsen and Bruskewitz's review (172) of prevalence of bother from lower urinary tract symptoms indicated that nocturia was the most bothersome and urgency the second most bothersome urinary symptom, confirming a long-standing urologic dictum. Frequency was judged to have an intermediate bother level. This assessment of symptom bother probably provides a rationale for a difference in symptomatology between patients seeking medical care and those discovered by screening or recruitment. In either circumstance, using knowledge of the patient's perceived or elicited problems to direct thoughtful initial inquiry into the character and circumstances of voiding dysfunction is essential. Selectively supplementing this information with a voiding diary and knowledge of habits regarding food and fluid intake, sleep patterns, medication history, and so on can be invaluable in

directing appropriate diagnostic and therapeutic approaches in patients in whom BPH-induced voiding dysfunction is suspected.

Patients with BPH-induced bladder outlet obstruction may have complications of this problem, including acute urinary retention, manifestations of chronic urinary retention such as overflow incontinence or renal failure, or urinary tract infection. Acute urinary retention is signaled by the sudden onset of a persistent ineffectual urge to void and severe unremitting bladder pain. Retention may be precipitated early in the course of BPH voiding dysfunction by ingestion of decongestants containing an α-adrenergic agonist, antihistamines, or a variety of medications with parasympatholytic properties, including disopyramide (Norpace), tricyclic antidepressants, and numerous tranquilizers (380). Its occurrence postoperatively is well recognized. A retention episode may also be precipitated by a forced and prolonged delay in voiding, by a precipitous increase in urinary output caused by ingestion of ethanol or diuretics, and possibly by chilling.

Persistent or chronic urinary retention may manifest its presence by producing overflow incontinence or renal failure. Patients with a decompensated bladder caused by BPH-induced bladder neck obstruction may have problems of constant dribbling (overflow) incontinence accompanied by evidence of a persistently distended urinary bladder. Similarly, laboratory or clinical manifestations of renal failure may be the initial evidence of a significant upper tract effect of lower urinary tract obstruction. Both constant dribbling incontinence and renal failure have several potential etiologies. However, the possibility of lower urinary tract obstruction as the cause is easily evaluated and warrants consideration even in the absence of preceding or concurrent typical symptoms.

BPH bladder outlet obstruction–induced urinary stasis and accompanying bladder stones or diverticula may predispose to development of urinary tract infection. The predominance of symptoms such as dysuria, stranguria, urgency, and other irritative voiding symptoms often delays consideration of the role of BPH-induced abnormalities in development of the infection. Again, awareness of this possibility and of other diseases that produce similar symptom complexes is essential to minimize clinical diagnostic errors (Table 32.3).

BPH is the most common cause of gross hematuria in men older than 60 years of age. Usually, hematuria from BPH is “initial” or “terminal,” but it can manifest as a significant bleeding problem requiring catheter placement or other acute intervention. Carcinoma of the prostate rarely manifests in this manner.

Symptom Indexes

The construction and use of symptom indexes to evaluate patients with bladder outlet obstruction caused by BPH has escalated. An increasingly scientific approach to target and evaluate appropriate symptoms resulted in the American Urological Association (AUA) symptom index in 1992. Development of this index was preceded by the Boyarsky symptom index, the Madsen-Iversen index, and the Maine Medical Assessment index; an International Prostate Score questionnaire and other assessment tools have been developed essentially concomitantly with the AUA symptom index. The indexes target questions that reflect changes in symptoms; they are not meant to be used as diagnostic screening instruments for BPH or bladder outlet obstruction. Several studies failed to document strong correlations between the AUA symptom index and anatomic and physiologic measurement of BPH effects (18,19,274). Despite the shortcomings indicated, the symptom indexes are recommended and used to compare results of research protocols and are recommended for the initial patient evaluation in an office setting (274) by U.S. and international guidelines. They are also used routinely in drug and interventional protocol studies. Many, including ourselves, have found the AUA symptom indexes to have a limited role in daily practice (173). One of us (KTM) uses them to confirm components of the history and quantify changes in response to treatment.

Physical Examination

The physical examination should be systematic and meticulous; it should be appropriately expanded based on history or observed physical abnormalities. The patient's general appearance and specific externally apparent abnormalities should be noted. The abdomen and genitalia should be examined by inspection, palpation, and appropriate percussion to identify any organomegaly, asymmetry, tenderness, or mass. Ordinarily, the bladder must contain at least 150 mL fluid to allow its detection by percussion; a residual urine in excess of 500 mL will usually produce a visibly distended bladder (44). Eliciting a sense of urgency by suprapubic pressure tends to confirm the nature of the identified mass. Ultrasound provides a noninvasive procedure to clarify the nature of a lower abdominal mass. Visual evidence of marked urethral meatal stenosis or recognition of a urethral or paraurethral mass on palpation may guide further appropriate evaluation.

A properly performed rectal examination provides essential information in evaluating patients with voiding dysfunction. In the male, the genitourinary aspects of the examination are usually enhanced by examining the supported, bent-over patient from behind. After inspecting the anal area, the rectal sphincter tone, noted on inserting the examining finger, provides evidence of the functional status of the somatic, sensory, and motor components of the sacral reflex arc and indirect evidence of parasympathetic input to the lower urinary tract (253). A thorough examination of the rectum, including the sacral hollow, may identify unsuspected

rectal pathology. During examination of the prostate, its size, consistency, and the integrity of its landmarks (median furrow, lateral sulci) should be noted and recorded.

Enlargement of the prostate may be manifested by increases in its normal width (4.4 cm), length (3.4 cm), or thickness. A universally accepted nomenclature describing prostatic size is not available. Perhaps an estimation of dimensions (width, length, vertical prominence) in centimeters constitutes the most reproducible form of assessment. A conventional paradigm for assessing prostatic size involves a grading scale ranging from normal through 4+. A normal gland (approximately 20 g) is about the size of a chestnut and is minimally perceptible on rectal examination. A 1+ enlarged prostate (about 25 g) is about the size of a plum and occupies a bit less than one-fourth of the rectal lumen. A 2+ enlarged gland (about 50 g) is about the size of a lemon and fills somewhat less than half of the rectal lumen. A 3+ enlarged prostate (about 75 g) attains the size of an orange and fills approximately three-fourths of the rectal diameter. A 4+ gland (100 g) may attain the size of a small grapefruit and fill so much of the rectal lumen that adequate examination is difficult. Digital assessment risks failing to recognize the presence or size of an enlarged prostate. On the other hand, a positive recognition of prostate enlargement is almost always confirmed. The consistency and symmetry of the prostate and presence, character, and location of nodules and induration (slight, moderate, stony), particularly with regard to distorting or compromising the median furrow and lateral sulci, should be noted. Crepitation should be recorded, if present. Palpable identification of the normally nonpalpable seminal vesicles or bladder base requires identification of a cause. After anatomic assessment of the prostate, massage should be performed unless acute prostatitis is suspected. Gentle rolling pressure with the examining finger from a lateral to a medial direction, progressing from the prostate base to the apex on each side, followed by stripping of the urethra distally usually produces fluid at the urethral meatus. The fluid should be retrieved on a slide and examined microscopically. Cultures of the expressed fluid directly or in a small volume of voided urine should be considered.

Laboratory Evaluation

Additional tests may aid in formulating the final clinical impression and treatment plan. These include blood and urine analyses, urodynamic evaluation, selected radiologic and ultrasound imaging studies, and cystourethroscopy. Their complexity, risk, and cost affect their selective employment. The urine should be tested for glucose, protein, occult blood, and pH with a multiparameter dipstick, ideally complemented by gross inspection and microscopic analysis of an initial (10 to 30 mL) and midstream sample of a freshly voided urine specimen. Urine culture, localization studies, and urinary cytology warrant selective considerations.

Blood studies may be desirable at the initial evaluation. A complete blood count (CBC), including differential count and gross assessment of platelet number, and a multiparameter chemical profile, including the guideline-recommended serum creatinine, warrant consideration. A careful history and physical examination will usually identify patients at risk for bleeding tendencies. In fact, the best screening test for disorders of hemostasis in surgical patients is a carefully acquired history soliciting examples of bleeding tendencies in the patient and in close relatives (64). In the absence of clinical evidence of a hemostatic disorder, there is only a 0.008% probability that a given patient will have non–drug-induced intraoperative clotting disorders (82,346). Obviously, all surgical candidates should be questioned regarding their use of aspirin, nonsteroidal antiinflammatory drugs, and other agents capable of altering normal hemostasis. The determination of the absolute platelet count, bleeding time, and partial thromboplastin time (PTT) constitutes a reasonable screening procedure to verify clinical suspicions (45). Although controversial (302), the serum PSA level is commonly determined in men in the BPH age group, preferably before the rectal examination.

A urodynamic evaluation tailored to provide critical diagnostic information with the least risk, discomfort, and cost deserves consideration. Residual urine and urine flow rates can be determined noninvasively. An ultrasound assessment of postvoid residual urine in a patient who has been instructed to empty his bladder is the most common urodynamic study performed in our group; the patient is then asked to void again and the void volume also recorded. The postvoid residual has traditionally been used to assess bladder function, to guide diagnostic inquiry, and to evaluate efficacy of treatment efforts. Recently, these roles, particularly with regard to the evaluation of treatment efficacy, have been challenged because of numerically variable residual urine determinations, a feature shared with most urodynamic and other complex physiologic indicators. This failure to determine residual urine volume and use this information with judgment is a questionable practice, especially with the availability of ultrasound to measure volume. The Olmsted County study clearly demonstrates that most men in all age groups empty their bladder with less than 12 mL of residual urine. Approximately 20% of men in each decade from 40 to 80 had residuals of greater than 50 mL. Presence of BPH was disproportionally represented in this group. Men with a postvoid residual greater than 50 mL had a threefold increased risk of developing acute retention (188). These considerations, along with the evidence suggesting that residual urine volume measurements are at least as reproducible as other urodynamic determinations (302), deserve increased emphasis in evaluating the potential clinical roles of residual urine determinations. Maximum flow rate, flow pattern, and volume voided provide important information (see Chapter 26B). Voided volumes less than 150 mL or more than 500 mL provide suspect information.

Review of the available literature indicated that prevalence of urine volumes greater than 200 mL varied with age (4). Data regarding flow rate determination indicate the following (302):

1. A significant variability (most, 1 standard deviation; half, 2 standard deviations) in repetitiously performed individual flow rates
2. A definite tendency toward substantially increased flow rate with sequential determinations
3. An appreciable decrease in maximum flow rate with age with 69% of 75- to 79-year-old men in the Olmsted County study below 15 mL per second and 35% below 10 mL per second

The evidence supporting the use of a peak flow rate of less than 15 mL per second to select patients for therapeutic trials of presumed BPH voiding dysfunction seems challengeable, as does the presumed advantage of flow rate over residual urine measurements. Simultaneous pressure-flow studies appropriately supplemented by video assessments provide the maximum opportunity to differentiate detrusor and outlet effects and have largely replaced the use of the cytometrogram. Data from initial and particularly repetitious urodynamic studies can provide very useful diagnostic and therapeutic insights.

In the past, evaluation of the upper urinary tract by radiologic or ultrasound imaging was commonplace in patients with bladder neck obstruction. Now these assessments are done selectively in patients with a history, physical findings, or laboratory studies that suggest a significant possibility of an important independent or secondary urinary tract abnormality accompanying the bladder outlet obstruction.

Cystourethroscopy to confirm the presence and effect of bladder neck obstruction from BPH is commonly done with local anesthesia in an outpatient setting. The presence, configuration, and site of obstructive tissue can usually be identified, but not its physiologic effect. The latter can be assessed to some degree by determination of residual urine and recognition of the presence and degree of trabeculation (Fig. 32.26) and bladder pathology such as diverticula and stones. Prostate size can be estimated crudely from the increase in length of the prostatic urethra, the degree and length of the adenomatous occlusion, posterolateral and anterior clefting present, and the thickness of the prostate when palpated rectally with the cystoscope in place.

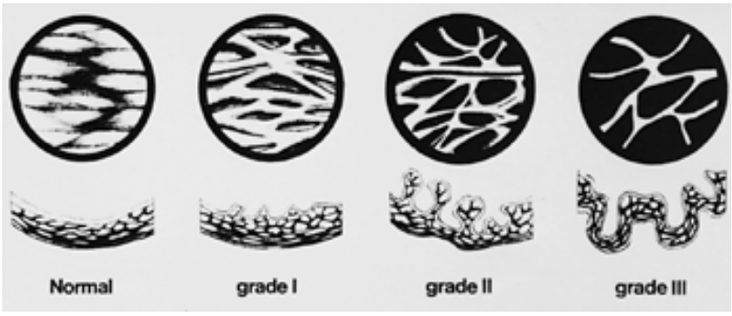

FIGURE 32.26. Grading of bladder wall trabeculation. Tight, compact detrusor muscle bundles ultimately show evidence of hypertrophy and splaying of fibers (grade 1) with the gradual demonstration of multifocal cellules (grade 2) to small diverticula (grade 3). These changes appear to correlate with elevation of opening urethral pressure (degree of obstruction), as well as associated detrusor reflex instability. (From Andersen JT, Nordling J. Relation of prostatic lobes to degree and rate of obstruction. In: Hinman F Jr, ed. *Benign prostatic hypertrophy.* New York: Springer-Verlag, 1983, with permission.)

Rectal or abdominal ultrasound may be used to assess prostatic size and weight with accuracy to within 5%. An assessment of residual urine and possibly the thickness and configuration of the bladder wall may provide some supportive evidence for bladder neck obstruction (5,336). Computed tomography and magnetic resonance imaging studies can provide information with regard to prostatic size, but, again, not its physiologic significance; they are rarely indicated to assess BPH and its associated voiding dysfunction.

Cystography and retrograde and voiding urethrography can at times provide invaluable information with regard to the diagnosis and evaluation of bladder or urethral diverticula. These studies warrant consideration in patients with clinical evidence of bladder neck obstruction who have an unusual course or unexplained findings.

Natural History of Benign Prostatic Hyperplasia Voiding Dysfunction

Data regarding clinically important aspects of the natural history of BPH center on the age-related development and course of anatomic changes in the prostate, BPH-induced dysfunctional voiding symptoms, and pathophysiologic functional changes in the bladder or upper urinary tract. The previously presented information regarding age-associated prevalence of histologic and anatomic BPH has been generated from autopsy observations and rectal or ultrasound evaluation of the prostate in clinical studies. The prevalence of histologic BPH increases progressively from the fourth (8%) through the eighth (82%) decade (27). The prevalence of gross, potentially clinically significant lesions shares this association with increasing age. For example, an autopsy study disclosed a prevalence of histologically confirmed BPH in prostates with gross enlargement of 14%, 37%, and 39%, respectively, in men 50 to 59, 60 to 69,

and older than 70 (300); this prevalence paralleled that of a palpably enlarged prostate found on rectal examination of 6,975 men evaluated for life insurance (217). Limited reported data correlating autopsy prostate weight and histology revealed prostate weights exceeding the 18-g mean normal weight by 50% or more in 61% of 69- to 70-year-olds compared with 18% of 51- to 60-year-olds (127).

The cumulative prevalence of a history and physical examination–based diagnosis of "prostatism" or BPH voiding dysfunction increased progressively from 26% to 79% from the fifth to eighth decade of life in the Baltimore longitudinal study of 1,057 men (Fig. 32.27) (140) and was recorded in 78% of the 2,049 healthy volunteers by age 80 in the Veterans Administration (VA) normative aging study (119). Prevalence as contrasted to cumulative prevalence of symptoms of prostatism was recognized in 26%, 33%, 41%, and 46% of 2,110 men ages 40 to 49, 50 to 59, 60 to 69, and over 70, respectively, in Olmsted County, Minnesota (53). Reports based on a Scottish community study yielded lower prevalence rates than the U.S. studies, and reports on a Japanese cancer screening program yielded higher prevalence rates than the U.S. studies. Interestingly, some symptoms, such as nocturia, weak stream, intermittency, urgency, and incomplete emptying, appear to increase with age, whereas others, such as frequent urination, dribbling, hesitancy, straining, and repeat urination within 10 minutes, did not. An unequivocal role for BPH in the symptom data cited should be viewed with some reservation because although symptom scores and some symptoms showed an increasing prevalence with aging, individual subjects showed a disturbing tendency to have variably present and absent symptoms (10), and several studies have documented a comparable prevalence of similar symptoms in aging women (46,127).

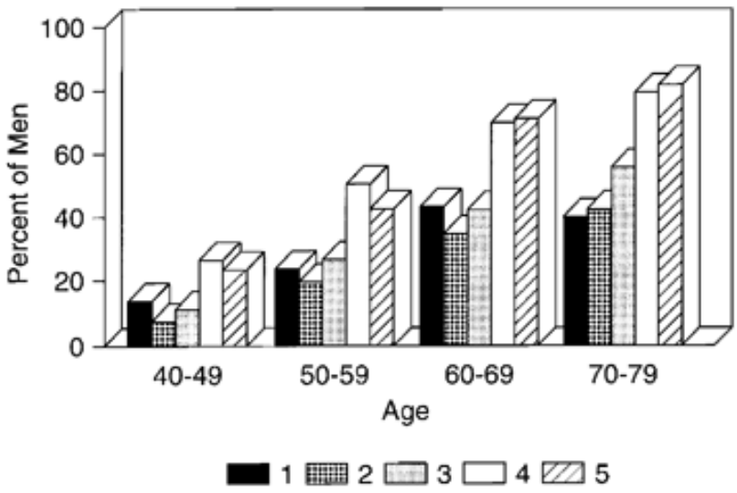

FIGURE 32.27. Age-specified prevalence of benign prostatic hyperplasia. *1,* Community prevalence in Bridge of Allan, Scotland, based on a case definition using symptoms, prostate size, and urinary flow rates (*n* = 699) (108a); *2,* clinical prevalence based on an enlarged prostate on manual rectal examination from a compilation of life insurance examinations (*n* = 6,975) (217); *3, 4,* clinical prevalence in the Baltimore longitudinal study of aging (BLSA) (*n* = 1,057) (140) (*3,* based on presence of an enlarged prostate on manual rectal examination; *4,* based on history and physical examination); *5,* prevalence of pathologically defined BPH from a compilation of five autopsy studies (*n* = 1,075) (27). (From Guess HM. Natural history of benign prostatic hyperplasia. In: Romas NA, Vaughn ED, eds. *Alternate methods in the treatment of benign prostatic hyperplasia.* Berlin: Springer-Verlag, 1993, with permission.)

As indicated, the reported presence of a symptom in a given patient varies appreciably in longitudinal studies without treatment. Of men reporting hesitancy on the initial visit in the Baltimore longitudinal aging study, 27% failed to do so on the second visit and an additional 19% on the third visit (10). Barry (18), Barry and colleagues (19), and Guess (139) summarized consistency of observations from five reports of patients evaluated longitudinally for approximately 3 to 5 years with BPH voiding dysfunction. Symptomatically improved or stable individuals were noted in every study and constituted roughly one-half to two-thirds of the patients who were not operated. The prominence of this improved-stable group is probably inflated by patients with progressive symptoms electing surgery. Nevertheless, the phenomenon of apparently unexplained improved voiding based on symptom and frequently urodynamic assessment is observed repetitiously in the placebo group of short- and longer-term drug studies. Global improvement was reported in 51% and the maximum flow rate increased more than 3 mm per second in 17.7% in the placebo group of the finasteride study (121). The BPH guideline review recorded global symptomatic improvement in 40% of placebo and watchful waiting groups. Multiple factors varying from an inaccurate presumptive diagnosis to behavioral modification may play a role in this phenomenon; they must be identified and evaluated.

Prevalence data on urodynamic assessment of unselected individuals in a community setting is limited but informative. The Olmsted County survey demonstrated a progressive decrease with age of peak median urinary flow from 20 mL per second in 40- to 44-year-olds to 11.5 mL per second in 75- to 79-year-olds and an accompanying decrease of median voided volume from 355 to 222 mL. The prevalence of peak flow rates less than 15 mL per second increased from 24% to 69% in these age groups (118). Although somewhat more supportive of progressive obstruction and possible bladder decompensation, urodynamic data, including peak flow rates, voiding pressure, and residual urine, have variously been observed to become worse, become better, and remain the same (17,29). In addition, despite the age-related association of anatomic BPH and abnormal physiologic voiding parameters, the absence of a correlation in individual men between clinical and urodynamic evaluations (18,19) and limited observations of significant urodynamic evidence of detrusor instability and sensory urgency in older women clouds the interpretation of these findings (47,127).

In considering the natural history of BPH voiding dysfunction, two phenomena—acute urinary retention and development of hydronephrosis or renal failure—deserve

special consideration because of the significant clinical impact they have. Although acute urinary retention is the indication for prostatectomy in approximately 25% to 30% of the operated patients, the risk of having acute retention was highly variable in longitudinal studies. Barry (18) and Barry and colleagues (19) projected 10-year rates from 4% to 73% (17,29). These differences probably reflect the status of the study population. In the community-based Olmsted County study (168), 57 of the 2,115 patients (1,412 were 59 years of age or younger) studied developed acute urinary retention; half of these episodes were related to surgical procedures. Only eight patients required a transurethral resection of the prostate (TURP) within 6 months of retention; one other patient had two subsequent episodes of retention. Severity of symptoms and increasing age increased risk of urinary retention, as did the presence of a low flow rate (less than 12 mL per second) or an enlarged (greater than 30 mL) prostate. The risk of acute retention was increased in young men with intermittency or the necessity to repeat void in 10 minutes. In older men, the presence of symptoms enhanced the risk of retention. The data generated suggested a 23% probability that a 60-year-old would experience acute urinary retention if he lived 20 years. In the 4-year finasteride (Pless) trial of men with BPH-recognized voiding dysfunction, untreated men had a 7% and finasteride-treated men a 3% chance of developing urinary retention. Surgery was carried out in 72% of placebo as compared with 33% of treated patients and 24% with spontaneous versus 10% with precipitated acute retention (231). These observations contrast with the infrequent (2 of 29 men) resumption of normal voiding by individuals randomly presenting in acute urinary retention with a greater than 900-mL retained urine volume observed by Taube and Gajraj (352); in their report, 15 of 34 men with less than 900 mL residual urine were able to void after catheterization without surgical intervention. Overall, approximately two-thirds of the patients presenting in acute retention failed to void. Additional data characterizing the patient population at high risk for developing acute urinary retention and their response to various treatment alternatives must be generated to guide development of reasonable management proposals for this group.

The risk of hydronephrosis with renal failure or of permanent or prolonged detrusor failure in monitored individuals is not documented. Guess (139) cites data indicating that at prostatectomy 7% of men had an elevated plasma creatinine and 5% had upper tract dilation at inpatient evaluation for prostatism. He pointed out that 17% of the cases evaluated for acute renal failure in the Boston VA Medical Center were due to urinary obstruction, with 65% of these thought to be caused by BPH. Sarmina and Resnick (317) documented previously unrecognized renal failure in 34 (3.7%) of 909 men treated for BPH from 1980 to 1986. They estimated that greater than 5% of men with unrelieved BPH bladder outlet obstruction would have chronic renal insufficiency. Patients at particular risk were those with symptoms of prostatism for more than 1 year, a history of enuresis, renal insufficiency, urinary tract infection, or urinary retention or a palpable bladder. Although they agreed with George and colleagues (110) regarding the increased risk of renal failure in men with high-pressure chronic retention, occurrence of this phenomenon has limited documentation and is unpredictable. Unquestionably, hydronephrosis and potentially, but not invariably, reversible renal failure do occur as the result of BPH (174); at one time, an appreciable cohort of the patients subjected to surgery had one or both of these complications. The discriminatory risk factors for their development remains uncertain, as does the rate at which they occur in monitored patients or in those with current sporadic medical care. The results of the prompt versus watchful waiting/delayed TURP VA study suggested compromised detrusor recovery in the watchful waiting group eventually subjected to surgery, but the role of delaying TURP in development of azotemia in two patients could not be evaluated from the information presented (95).

In the longitudinal observations summarized by Barry (18), Barry and colleagues (19), and Guess (139), the cumulative prevalence of BPH surgery varied from 0% to 45% of the patients during limited follow-up. Surgical procedures were predominantly carried out during the first year after diagnosis in the series with high surgical rates. The risk of surgery by age 80 years was considerably greater (29%) for a man 40 years old in the VA normative aging study, carried out prospectively from 1961 to 1982 (119), than in the New Haven Hospital record study (10%), a retrospective analysis of 1953 to 1961 data (218). In both, the incidence rates for BPH surgery increased through the eighth decade. In the Baltimore longitudinal study of aging (10), a change in size and force of the urinary stream and a sensation of incomplete emptying of the bladder in a patient with digitally detected prostatic enlargement were predictive of future prostatectomy. In the Kaiser Permante medical care program analysis cited by Guess (139), the symptoms predictive of prostatectomy were hesitancy, a weak stream, painful urination, loss of bladder control, and nocturia.

Two other observations are of interest. Despite the lack of correlation between prostate size and outflow obstruction, a correlation seems to exist between election of surgical intervention and prostate size (27). Second, there is suggestive evidence from postmortem anatomic assessments supporting clinical impressions that the prostate of some aging men may undergo regression in size (350).

Indications for Treatment

The following are accepted criteria for interventional relief of bladder neck obstruction caused by BPH.

Acute urinary retention is often indicative of end-stage bladder decompensation requiring operative relief. The patient whose retention is triggered by ingestion of drugs such

as α-adrenergic agonists or anticholinergic agents may void satisfactorily once the medication is stopped and the bladder drained for a time. A supervised attempt at decatheterization for minimally symptomatic patients with an incident-related (e.g., postoperative or acute bacterial prostatitis) or spontaneous episode of retention is often reasonable. Use of α-adrenergic antagonists in conjunction with this voiding trial is worthwhile . For repeated episodes of retention, management by intermittent catheterization or continued catheter drainage is possible but is usually an unacceptable alternative to an operative approach. The patient with urinary retention is usually treated satisfactorily by insertion of a urethral catheter. For difficult catheterizations, a percutaneous suprapubic cystotomy tube remains an appropriate alternative that is usually well tolerated and associated with few catheter-related complications. If chronic retention is suspected, the bladder should be emptied gradually to avoid diffuse mucosal cracking and bleeding that may follow rapid decompression. Use of a variety of internalized catheters is currently being evaluated in selected patients at high risk.

Bilateral hydronephrosis with renal functional impairment requires relief of the obstruction to preserve the integrity of the upper tracts. On catheter insertion, a postobstructive diuresis may ensue, requiring meticulous fluid and electrolyte management. The patient's general condition should be optimized before operative intervention is undertaken.

The presence of multiple bladder stones, prominent narrow-necked bladder diverticula, overflow incontinence, and other signs of end-stage bladder decompensation are indications for therapeutic intervention. Recurrent or chronic urinary tract infections caused by an elevated residual urine are also an indication for considering intervention. Acute or chronic bacterial prostatitis should be excluded as a possible source of infection. A careful history, physical examination, and lower tract localization cultures should help clarify this issue.

Gross hematuria is an infrequent but legitimate indication for so-called prostatectomy, particularly when the episodes are multiple and associated with clot retention or significant blood loss. The usual limited initial hematuria associated with BPH is commonly best managed conservatively. Antiandrogen measures such as the use of finasteride almost always have a favorable impact on recurrent prostatic bleeding (96).

Obstructive and irritative symptoms that significantly interfere with the quality of life of the patient are common indications to consider prostatic surgery and other therapeutic approaches. The cause of the symptoms should be established with a very high degree of probability. In the past, most patients have had multiple indications to support the decision to initiate therapy (239). Both the urologic surgeon and the patient must be clearly aware of the results that can be expected and the risks involved in achieving them.

THERAPEUTIC OPTIONS

Part of "32 - BENIGN PROSTATIC HYPERPLASIA "

The options available to patients with BPH have expanded rapidly in the last two decades. In addition to monitored observation, various forms of intervention directed at modifying the physiologic effects of BPH with or without directly altering the prostatic mass or its configuration are being used with varying effectiveness and risk. The following is a brief discussion of indications, techniques, and results of observation, catheterization, and selected medical, tissue-destructive, and excisional approaches currently used to treat patients with BPH voiding dysfunction.

Observation

Patients may see their physician for evaluation of the prostate for a variety of reasons, including voiding symptoms of variable severity and physician-observed prostate-related (or presumed prostate-related) abnormalities. Their evaluation usually includes a history, with particular emphasis on voiding status and degree of bothersomeness; physical examination, including abdominal, genital, and rectal examinations; and indicated laboratory studies, such as urinalysis and serum total or fractionated PSA and creatinine. Determination of postvoid residual urine and urinary flow rate, pressure-flow studies, and urodynamic and endoscopic evaluations are done selectively. The resulting patient cohort may include individuals with recognized significant secondary bladder or renal changes from BPH. In some instances, these changes will be present in patients with minimal symptoms, so-called silent prostatism (incidence less than 5%) (367). Most prostate problem patients have definite but limited complaints or objective findings and only marginal indication for therapy. Guidelines to help triage these patients to immediate treatment or periodic observation are not well established. The number of patients with prostate-related renal functional impairment, secondary stone disease, infection, or markedly decompensated bladder requiring effective, prompt intervention is limited. Physician surveillance at regular intervals varying from 3 to 18 months in our practice is an appropriate recommendation. These episodic assessments include a review of genitourinary symptoms but focus on the patient's major complaints. A symptom score is calculated only as an ancillary aid in assessing the patient's symptom, never as a diagnostic aid or as a substitute for a detailed history. The abdominal, genital, and rectal examinations are supplemented by an office urinalysis, a yearly serum PSA, and other selected laboratory studies. Cystoscopy is used selectively and urodynamic evaluation infrequently to confirm the diagnosis of BPH voiding dysfunction and to guide appropriate management. Indications for urodynamic evaluation typically include concurrent assessment for neurologic or medical diseases that can mimic the voiding complaints associated with BPH. The trigger to consider medical or surgical treatment

must be individualized for patients, taking into account the entire spectrum of the patient's complaints, degree of bother, and results of the objective findings.

The urologic fate of individuals selected for observation is unpredictable. The patient's genitourinary organ and symptom status, general health, and life expectancy play a significant role in his desire and need for various types of intervention. In addition, spontaneous improvement in flow rates and symptoms is common in studies with short run-in control periods. This has led to the one-third improved, one-third stable, one-third worsened paradigm for patients selected for watchful waiting or control populations in studies of limited duration. The improved group probably reflects behavioral modification rather than organic change in the prostate bladder relationship. The data from the Olmsted County observation study (168) and the control groups in the long-term finasteride (231) and VA observation/TURP studies (95) seem to indicate that patients with moderate to severe symptoms (i.e., AUA symptom score greater than 7), low peak urinary flow rates (less than 12 mL per second), increasing size of an enlarged prostate, and older age (older than 70) have increased risk of acute urinary retention and requirements for surgical or pharmacologic treatment. Consequently, monitoring changes in prostate size and objective measures of voiding such as residual urine and flow rate probably provides very useful objective information to guide treatment recommendation. Prolonged observation of a functionally deteriorating lower urinary tract has traditionally been thought to jeopardize functional recovery; the observations in the control group of the TURP VA study tend to support this concept (95).

Although some effects of BPH voiding dysfunction such as renal failure or acute urinary retention clearly require intervention, the decision to treat patients with BPH voiding dysfunction is usually optional. The treatment selected may target the secondary changes resulting from BPH or attempt to reduce or eliminate the BPH mass or its functional effects. The approaches used include catheterization, pharmacologic approaches, and mass reduction or elimination efforts by excision, tissue destruction, or physiologic alterations (Table 32.4).

Mass Reduction	**Physiologic/Physical Manipulation**
Hormonal	Transurethral incision
5α-Reductase inhibition	α-Adrenergic blocker
LH-RH antagonists	**Drainage Maneuvers**
Excision	Catheters
TURP	Transurethral
Open prostatectomy	Suprapubic
Laser prostatectomy	Stents
Tissue destruction—*in situ*	Clean intermittent catheterization
Transurethral microwave thermotherapy	
Interstitial laser coagulation	
Transurethral needle ablation	

LH-RH, luteinizing hormone–releasing hormone; TURP, transurethral resection of the prostate.

TABLE 32.4. CATEGORIES OF BENIGN PROSTATIC HYPERPLASIA TREATMENT

Catheter Drainage

Transurethrally or suprapubically inserted catheters of various materials and configurations have been used acutely, intermittently, or as permanent indwelling conduits to treat the acute and chronic effects of BPH for centuries. Clean intermittent catheterization is discussed in Chapter 26B . Indwelling catheters are subject to displacement and occlusive encrustation; they require periodic planned or incident-provoked replacement. Acute and chronic urinary tract infections complicate their long-term use. In the past two decades, internalized catheters, or urethral stents variously designed from a range of inert materials, have been used in select patients with obstructing BPH and urethral stricture. A prominent middle lobe or median bar is commonly cited as a contraindication to stent placement. Use of titanium (Titan), corrosion-resistant metal alloys (UroLume stent) (138), and more recently, a nickel-titanium thermosensitive alloy, nitinol (Memotherm stent) (113), has improved physical and biologic characteristics of the available stents. Recognition that stents should appropriately extend from just at or distal to the bladder neck to just proximal to the verumontanum or urethral sphincter has facilitated selection of stent length; direct-vision placement under general, spinal, or local anesthesia using the ventral bladder neck as a guide to location has increased achievement of appropriate positioning. Stent design and anchoring mechanisms vary. The nitinol stent expands at body temperature to a maximum diameter of 42 Fr. Metal stents are essentially incorporated in the superficial urethral tissue, permitting catheterization and endoscopic procedures. Proliferative ingrowth of transitional epithelium is a troublesome complication in patients with BPH; it requires treatment such as transurethral resection or fulguration. Stent migration affects voiding and the development of complications.

The reported experiences indicate that almost all patients are able to void promptly or within a few days of stent placement. The latter usually are managed temporarily with a suprapubic catheter. Patients commonly experience frequency, urgency, dysuria, or perineal pain for a few weeks to months after stent placement. Persistent symptoms may respond to anticholinergic medications or infrequently require stent removal. Most patients demonstrate a significant increase in urine flow rate and decrease in residual urine. However, improper stent placement is often responsible for poor functional results and complications. Urinary tract infections complicating stent placement respond to appropriate antibiotic treatment. Removal of stents is challenging. Milroy and Chapple (244) advocate placing a guidewire

through the retrogradely displaced UroLume stent to aid its entrapment in a resectoscope sheet and to facilitate removal. The knitted single-wire construction of the Memotherm stent permits its simple removal by unraveling it by traction on the wire (113). This procedure traumatizes the covering urothelium, however. The majority of reported observations of patients treated with stents are 1 year or less in duration, but there are limited numbers of patients with stents who have been observed for 2 to over 4 years.

Consideration of the use of internalized stents rarely has a high priority in many groups, including ours. The options to achieve mass reduction or physiologic alterations (Table 32.4) that facilitate improved voiding have expanded and can be accomplished with anesthetic and technical risks that are comparable to or less than those related to stent placement, maintenance, and removal.

MEDICAL THERAPY

Part of "32 - BENIGN PROSTATIC HYPERPLASIA "

Use of pharmacologically defined and a variety of so-called alternative medications to attempt to improve BPH voiding dysfunction by reducing BPH mass or producing functional alterations of the voiding mechanism is expanding rapidly. Pharmacologic efforts to reduce prostate mass essentially target known androgen-mediated prostate growth induction or maintenance phenomena. Those aimed to produce physiologic alterations essentially target the α_1-adrenergic agonist modifiable smooth muscle contraction of prostate stroma, bladder, and components of the central nervous system (CNS) affecting voiding symptoms.

Endocrine Approaches

Endocrine-based approaches to management of BPH have focused on disrupting hormone-mediated growth mechanisms characterized in the normal prostate and persisting in BPH. Consequently, most center on attempting to eliminate testis hormone production directly or indirectly (e.g., castration, pituitary hormone inhibition), altering intraprostatic androgen metabolism (e.g., 5α-reductase inhibition), interfering with intracellular transcription of androgen-stimulated events (e.g., receptor blockade), or a combination of these mechanisms. Castration and luteinizing hormone–releasing hormone (LH-RH) agonist administration produce marked regression of the epithelial component of BPH in humans (163,320,381). However, these approaches, as well as administration of estrogens (280) or estrogen-androgen combined therapy (181), have yielded equivocal or limited clinical improvement. LH-RH agonist administration produces a 25% to 30% decrease in prostate volume; a 90% and 75% reduction in prostate tissue DHT and T concentration, respectively; and decreased prostate 5α-reductase activity and androgen receptor levels. With cessation of therapy, prostatic size returns to pretreatment levels (228,285). Flutamide, a nonsteroidal androgen receptor competitor, and cyproterone acetate (323), an inhibitor of gonadotropin release and receptor competitor, have been reported to increase flow rate or to decrease prostate size 23% to 30% (228) in patients with BPH. Other progestational agents, including medrogestone, 17α-hydroxy progesterone, chlormadinone acetate, and gestonorone caproate, have been used in clinical trials without consistent effects on voiding patterns in patients with BPH voiding dysfunction (109,293). LH-RH antagonists induce a substantial and rapid (less than 12 hours) decrease in serum testosterone and DHT. Preliminary evidence suggests increased flow rates and reduction in symptom score comparable to α-adrenergic agonist therapy (200). The applicability of these agents to BPH management has not moved beyond the preliminary stages. LH-RH therapy is frequently associated with hot flashes and sexual dysfunction (87). Gynecomastia and diarrhea are recognized complications of single-drug flutamide therapy (344).

Evaluation of purposely altered androgen effect on BPH and BPH voiding dysfunction currently centers on the results of finasteride administration. Finasteride inhibition of 5α-reductase type 2 activity results in decreased DHT (5.4 to 0.5 ng/g) and increased T (0.3 to 2.2 ng/g) prostate tissue concentrations (266). The following observations of clinical effect seem reasonable based primarily on the results of the 4-year multicenter study of prostate patients with moderate to severe BPH voiding symptoms and a moderately enlarged prostate.

1. Maximum effect on the prostate is delayed at least 6 to 12 months (121,231).
2. Quasi AUA symptom score improvement in finasteride-treated (F) versus placebo (P) patients is definite but slight (all patients F 2.5 versus P 1.0; completed study patients F 3.3 versus P 1.3) (231).
3. Reduction in prostate volume in men completing the study is limited (18%) but contrasts with an increase of 14% in the placebo group; decreased prostate volume in the finasteride group stabilized at 1 year, whereas the placebo group showed progressively increased volume over 4 years (231).
4. Statistically significant but clinically minimal increased flow rate was seen in finasteride-treated men who completed the study (F 1.9 mL per second versus P 0.2 mL per second) (231).
5. Using intention to treat patients, a quasi bother score (range of 0 to 34) and an approximated activity interference evaluation (range of 0 to 28) of finasteride-treated men demonstrated a statistically significant but clinically limited greater improvement at 4 years in both; bother decreased 3.0 versus 1.2 and activity interference 2.5 versus 1.24 in finasteride compared with placebo patients (39).
6. The study was discontinued by 524 (34%) of finasteride-treated and 633 (42%) of placebo-treated men; most perceived lack of improvement or worsening of BPH

voiding dysfunction or desired other medical or surgical treatment. Adverse events accounted for the other (F 11.5%; P 10.9%) withdrawals (231).

7. Acute urinary retention (4% F versus 7% P) and BPH-related surgery (5% F versus 10% P) were reduced in finasteride as compared with placebo patients in the 4-year observation period using an intention-to-treat analysis. In absolute numbers, approximately 100 of 1,384 treated patients avoided these events (231). In this study of symptomatic men with enlarged prostates, patients with larger prostate volume as indicated by PSA measurement seemed to be at greater risk for these events (303).
8. Finasteride has had almost universal success in controlling spontaneous BPH-related urinary bleeding promptly and persistently (96). The prompt control of hematuria contrasts with other therapeutic achievements with this drug. Men with bothersome symptoms and no or little enlargement of the prostate are less likely to show comparable improvement (204). Various aspects of sexual dysfunction and possibly gynecomastia may occur with greater frequency in a limited number of finasteride-treated patients. The effects on libido, erection, and volume of ejaculate are slightly increased with finasteride. Overall, results of these studies should be made available to patients, but definite recommendation for finasteride treatment would seem to depend on the patient's general health, his risk/benefit assessment, and the rapidity at which he expects improvement.

Endocrine therapy for the treatment of BPH voiding dysfunction, regardless of method, is accomplished by reduction of prostate mass. This change in gland volume is limited to components of the prostate that are androgen sensitive. Available data indicate that prostate volume decreases by no more and usually appreciably less than 30% with more meager impact on symptoms. Based on this information, it appears that endocrine therapy has a limited utility in patients with symptoms and signs of bladder neck obstruction (BNO) from BPH. Chronic therapy to prevent disease progression may have a role in some patients but is usually not readily accepted by patients who otherwise feel well.

Adrenergic Antagonists

The most common medical approach to manage effects of BPH voiding dysfunction centers on neuropharmacologic manipulation of the lower urinary tract. Contraction of the autonomically controlled prostate or bladder neck smooth muscle is postulated to be a significant modifiable functional component of BPH-mediated bladder neck obstruction. The predominance of α_1-adrenergic receptors in the bladder neck or prostate (40 times the bladder concentration) helped focus interest on α-adrenergic blocking agents in the treatment of symptomatic BPH. Demonstration that administration of phenoxybenzamine, a nonselective α-adrenergic antagonist, reduced symptoms and improved parameters in patients with BPH voiding dysfunction (43,202) reinforced pursuit of this approach. Efforts to maximize desired physiologic activity and reduce undesirable side effects led to the development and use of selective α_1-adrenergic antagonists. Of these, drugs that can be given once daily, including terazosin (Hytrin), doxazosin (Cardura), and tamsulosin (Flomax), an α-adrenergic blocker with more selectivity for the prostate-dominant α_{1A}- and α_{1D}-adrenergic receptors, are the most commonly used α-adrenergic receptor blocking agents. Despite the subtype selectivity of tamsulosin for the α_{1A}- and α_{1D}- over that of the α_{1B}-adrenergic receptor, there is no evidence that this conveys a clinical advantage for the treatment of symptoms (Table 32.5). The α-adrenergic blocking agents share the characteristic of producing their effects on voiding within hours of administration regardless of prostate size without altering serum PSA or volume. The reported studies of efficacy focus on change in symptom score and peak flow rate. The absolute improvement in maximum flow rate, the clinically important effect, is greater than placebo, yet still relatively small. This increase in maximum flow rate is similar for the various α-adrenergic blockers (Table 32.6). The maximum flow rate achieved is generally between 11 and 13 mL per second; this may represent an achievable

maximum for α-adrenergic blocker pharmacotherapy (50,91,304). In most studies, the decrease in total AUA or comparable symptom score (range of 0 to 35) was approximately 3 ± 1, and the increase in peak flow rate was usually 1 to 2 mL per second. Both are statistically but clinically marginally significant. Assessments of severity, bother, problem, and global scores tended to reinforce this range of activity (115,205,258).

TABLE 32.5. α-ADRENERGIC THERAPY SYMPTOM SCORE CHANGE

Agent	Change in Symptom Score	% Change in Symptom Score
Terazosin	3.3–7.6	33–38
Doxazosin	2.8–5.7	10–40
Tamsulosin	3.3–9.6	35–48

[a]Symptom relief is measured in different ways in the literature, making global assessments difficult to quantitate and compare. The range of improvement in symptom scores in the various α-adrenergic blockers varies from 2 to 5 points on their respective scales. Use of percentage rather than numerical change in score avoids the problem of different scoring systems and is probably a better indicator of the relative effectiveness of these agents. In this fashion, it becomes clear that lower urinary tract symptoms improve anywhere from 30% to 50%. Placebo effect generally ranges 15 to 20 percentage points behind that of the active drug (50,51,304).

TABLE 32.6. α-ADRENERGIC THERAPY FLOW RATE CHANGE

α_1-Adrenergic Agent	Improvement in Flow Rate (mL/sec)	% Flow Rate Change
Terazosin	1.7–3.0	21–34
Doxazosin	1.8–3.2	25
Tamsulosin	1.7	18

Potential cardiovascular and other systemic effects of these drugs may limit their use alone and in particular with other vasoactive agents. Postural hypotension, dizziness, headache, syncope, anesthesia or fatigue, rhinitis, and abnormal ejaculation may complicate α-adrenergic blocker administration. The development of more selectively targeted α-adrenergic blocking agents, coupled with a better understanding of their effects, has been associated with reduced undesirable reactions. Currently available information suggests that tamsulosin may lessen their occurrence selectively and within dose ranges. Patients with complex medical problems often benefit by a coordinated internist-urologist interaction in guiding α-adrenergic blocker therapy.

Indication for use of α-adrenergic blocking agents in patients with BPH voiding dysfunction centers on symptomatic complaints and failure to void satisfactorily. The diagnosis is often not confirmed as objectively as in surgically directed patients. Cystoscopic evaluation of the prostate or the bladder is often omitted despite its use as an exclusionary criterion, and postvoid residual urine is not used regularly to assess therapy. Paradoxically, changes in urinary symptoms and flow rate do not correlate strongly (198,199), leading to questions regarding the role of prostate smooth muscle relaxation in symptom reduction . Effects of α-adrenergic blocking agents on bladder and CNS function could result in the altered voiding patterns observed (198,340). Despite the predominant pharmacologic role of α-adrenergic blocker therapy in treating BPH voiding dysfunction, more than 30% of patients discontinue therapy. This *de facto* dissatisfaction demonstrates the incompleteness of understanding of α-adrenergic blocker effect, as well as an inability to pinpoint the exact cause of BPH voiding dysfunction.

Drug choice depends on primary and secondary (antihypertensive; complications) effects. These drugs are most commonly administered at bedtime to minimize cardiovascular symptoms or hypotension. Terazosin and doxazosin are commonly titrated to establish effective, complication-free dosage levels; most men in the United States receive these drugs at a 5- and 4-mg daily dose, respectively, although limited evidence indicates that double these levels may be optimal. Tamsulosin, commonly given after breakfast, is used at 0.4 mg per day in most men; 0.8 mg daily is slightly more effective but has increased side effects (199). Although many patients have concurrent LUTS and hypertension, treatment for each disease should be optimized individually rather than attempting to treat both simultaneously with a single agent and potentially compromising treatment of both. Most authorities on hypertension suggest that α-adrenergic blockers are a third- or fourth-line drug after (a) angiotensin-converting enzyme inhibitors and (b) calcium channel blockers and diuretics (6,337).

Alternative Therapies

Increasing attention has been paid to plant extracts (or phytotherapy) use by patients to self-treat medical ailments. Use of these products has grown rapidly to an estimated $6 billion yearly expenditure despite the frequent lack of a scrutinized demonstration of efficacy. Saw palmetto, derived from the berry of the American dwarf palm *(Sabal serrulata),* is the most popular of these medications for LUTS. The proposed mechanisms of action for saw palmetto include 5α-reductase inhibition, intraprostatic androgen receptor blockade, and adrenergic receptor antagonism (111). There is little or no evidence that any of these mechanisms play a role in saw palmetto when used clinically. Clinical evidence suggests that this medication does no harm, is associated with few side effects, and has no effect on PSA (211). Placebo-controlled trials and meta-analyses suggest that saw palmetto leads to only minor subjective and objective improvements in men with LUTS (384). Most studies demonstrating any positive effects of saw palmetto suffer from methodologic flaws, small patient numbers, and short treatment intervals. Clearly, large-scale placebo-controlled trials are needed to assess efficacy of these medications. Their U.S. Food and Drug Administration classification as a food additive allows public promotion of these products without regulated manufacture or demonstrated efficacy. Unfortunately, significant questions persist concerning their use.

Summary

Current evidence indicates that medical therapies have variable limited effectiveness in altering the symptomatology and pathophysiologic effects of BPH. Use of drugs with established physiologic effects on the prostate or bladder, alone or combined, warrants consideration in selected patients with acute or chronic voiding problems caused by BPH. The long-term effects of α-adrenergic antagonists and 5α-reductase inhibitors on BPH and its associated voiding dysfunction are not established. The risk that prolonged exposure to therapies with limited effectiveness may permit conversion of a potentially reversible to a permanent voiding dysfunction should not be overlooked. The most cost-inefficient use of health care expenditure is serial treatment with multiple medications followed by surgical or minimally invasive therapies. Prioritizing of these issues for and with patients remains the urologist's challenge and role.

SURGICAL AND RELATED INTERVENTIONAL TREATMENT

Selection of Operative Approach

The term *operative approach* is used here in the broadest sense to include tissue excisional and destructive as well as incisional and other procedures that modify prostate, bladder neck, or urethral relationships without or with alteration in tissue mass. Success in these endeavors depends on identifying BPH as the cause of dysfunctional voiding correctly; recognizing the changes in BPH configuration or mass that have a high probability of correcting or modifying the dysfunctional voiding; identifying alternative approaches to accomplish this goal; and objectively assessing the achievable degree and duration of improvements in voiding and the risk involved to achieve them. In addition, the physical, emotional, and monetary costs are important considerations. Risks of failure to pursue and accomplish an effective treatment require delineation. The discussion of individual approaches in this section represents a combination of reported observations and personal judgments regarding treatment alternatives available.

Physical Intervention

Physical intervention procedures to alter BPH voiding dysfunction have traditionally centered on removal of the hyperplastic, usually adenomatous, growth by open or transurethral surgical excision (Fig. 32.28). Recently, alternative approaches including transurethral incision, laser “prostatectomy,” needle ablation, interstitial laser treatment, and electrovaporization, as well as transurethral thermotherapy, high-intensity focused ultrasound, and balloon dilation, have been used for this purpose. Most of these latter maneuvers, so-called minimally invasive alternative treatments, are usually restricted to glands of limited size without significant median lobe development. Their current status is discussed briefly.

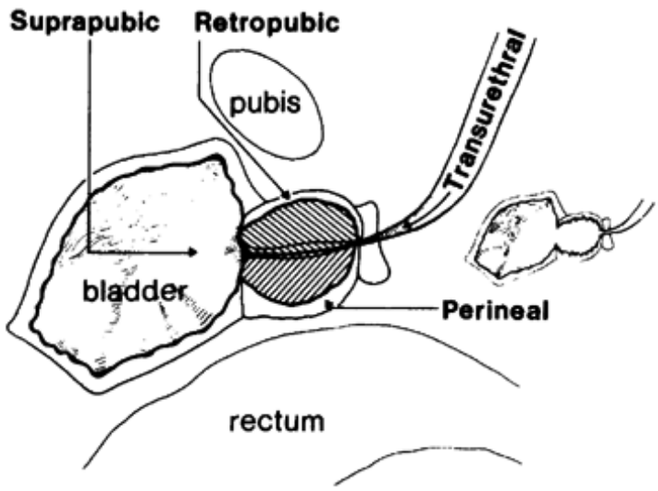

FIGURE 32.28. Traditional surgical approaches for the treatment of benign prostatic hypertrophy. [From Grayhack JT, Sadlowski RW. Results of surgical treatment of benign prostatic hyperplasia. In: Grayhack JT, Wilson JD, Scherbendke MJ, eds. *Benign prostatic hyperplasia, NIMADD workshops proceedings, Feb 20–21, 1975.* US Department of Health, Education and Welfare pub no (NIH) 76-1113, 1976, with permission.]

Surgical Treatment

The goals of surgical treatment of BPH voiding dysfunction are to correct significant pathophysiologic effects of bladder neck obstruction (i.e., renal failure, stone formation, and possibly infection) and to improve the quality of the patient's life by allowing him to void to completion at normal intervals with an excellent urinary stream while retaining good urinary control and unaltered sexual function. The treatment approach that allows these patient-prioritized goals to be reached with the least risk of morbidity and disability should be chosen. The patient's general condition, the size and configuration of obstructing prostatic tissue, the functional status of the bladder, the surgeon's skills, and the patient's preference warrant careful consideration as a so-called prostatectomy is planned.

Preoperative Preparation

Careful assessment of the patient's general and genitourinary status is essential to establish a proper diagnosis and plan appropriate therapy. Prostatectomy is an elective procedure. Even in the patient with the most severe degree of bladder neck obstruction and its anatomic sequelae, the obstruction can be adequately relieved by catheter drainage while the patient's condition is optimized before definitive therapy. Adoption of this concept has played a major role in reducing mortality and morbidity rates of surgical treatment of BPH. Every aspect of the surgical approach to the treatment of BPH has improved, including preoperative assessment, performance of the procedure, and the postoperative management (216). Consequently, the outcomes have been preserved or improved despite the numerically decreased experience of individual urologists (38,153,216,389).

Systemic Considerations

The elderly patient with BPH often has cardiovascular, pulmonary, neurologic, or other abnormalities that affect the choice of and preparation for a therapeutic approach, as well as the anesthetic used. Patients with chronic obstructive pulmonary or valvular or ischemic heart disease may require sophisticated evaluation to provide baseline information, focus preoperative management, and help select the optimal anesthetic approach. Drug allergies and use of drugs that affect coagulation, particularly aspirin or antiinflammatory

agents, should be noted. The status of the veins of the patient's lower extremity warrants attention, as does the integrity of the coagulation mechanism. The risk of postoperative deep vein thrombus (DVT) and pulmonary emboli deserves special mention. Urologic patients contribute significantly to the group of postsurgical patients prone to DVT (20% to 40%) and embolic phenomena (25,65,260). In patients not given prophylactic medication, the incidence of DVT with TURP is 10% (26). Prophylactic measures such as adequate hydration, early ambulation, and use of extrinsic soleal compression of the extremities are advised. High-risk patients such as those with lower extremity venous disease, heart disease such as atrial fibrillation or myocardial infarct, history of malignancy, obesity, or immobility deserve consideration of more aggressive approaches. Intermittent pneumatic compression, our preferred prophylactic measure, appears to reduce risk of lower extremity deep vein thrombophlebitis. Use of heparin at a dose of 5,000 units every 8 hours reduces the incidence of fatal pulmonary embolism without seeming to predispose to major perioperative hemorrhage; however, the incidence of nonfatal wound hematomas increases slightly. Although the efficacy and safety of drug-induced anticoagulation in urologic surgical patients has been questioned (56,368) and is rarely used by us, formal anticoagulation deserves consideration in selected patients at high risk. The use of low-molecular-weight heparin (dalteparin) and dextran have been shown to slightly increase blood loss with TURP (155). The use of other low-molecular-weight heparin agents such as enoxaparin (Lovenox) in this setting has not been reported and is not used routinely in our hands.

Genitourinary Considerations

Renal failure resulting from bladder neck obstruction caused by BPH is often reversible, but unpredictably so. Catheter drainage of the bladder usually relieves the obstruction and results in maximum renal functional improvement. Sarmina and Resnick (317) listed characteristics of patients with obstructive uropathy caused by BPH that are more likely to exhibit irreversible renal dysfunction. This “at-risk” patient profile includes bladder neck obstructive symptoms for more than 1 year; a history of marked enuresis or renal insufficiency; antecedent urinary tract infection; palpable bladder or urinary retention; creatinine clearance of less than 20 mL per minute at hospitalization; and decreased cortical thickness or increased echogenicity on renal ultrasonography. The possibility of postobstructive diuresis resulting in significant hypovolemia following catheterization of these elderly patients exists and must be monitored. This phenomenon is primarily induced by osmotic load but can be associated with some degree of renal tubular dysfunction (114). Fluid administration should be regulated by monitoring urine output, supine and erect blood pressure and pulse rate, serum electrolytes, and creatinine and blood urea nitrogen levels. Excessive fluid replacement can lead to a spiraling fluid intake/urine output phenomenon. Catheter drainage should be maintained until renal functional status has improved sufficiently to restore creatinine and electrolyte blood levels to normal or to stabilize abnormal values. Failure of renal function to improve should signal consideration of suboptimal bladder catheter drainage or supravesical obstruction. Persistent significant azotemia predisposes to platelet dysfunction and bleeding that is often at least partially reversible by presurgical dialysis and by administration of antidiuretic hormone analogue L-desamino-8-D-arginine vasopressin (DDAVP). Renal functional status significantly affects appropriate anesthetic and pharmacologic management in these patients.

Sepsis has been a major contributor to infrequent mortality after transurethral resection (240). Bacteremia occurs postoperatively in 10% to 32% of patients without recognized preoperative bacteriuria (158) and much more frequently in patients with infected urine (68,250). Appropriately timed initiation of antibiotic therapy selected on the basis of *in vitro* culture findings is an accepted and effective presurgical practice in the latter patients. However, prophylactic antibiotic administration to reduce immediate and long-term infection-related risks in patients without preoperatively documented urinary infection has a limited effect on perioperative infections or fever (158), although reduction in the incidence of postoperative bacteremia has been noted (187). Because as many as 20% of prostatectomy tissue specimens harbor demonstrable bacteria (120), antibiotics used for prophylaxis should ideally provide bactericidal tissue as well as urine levels. A recent study using ciprofloxacin 500 mg orally or parenteral cefotaxime demonstrated results that were comparable with but not significantly superior to placebo in achieving satisfactory bacterial prophylaxis (187). Currently, empiric 24-hour intravenous (IV) or intramuscular (IM) antibiotic prophylaxis has become common in prostatectomy patients because of the practice of admission on the day of surgery and rapid postoperative discharge. Patients with increased risk factors for infection such as azotemia, upper tract calculi and other significant abnormalities, significant residual urine, debility and immunocompromised states, and diabetes mellitus are maintained on longer-term oral antibiotic prophylaxis.

Antibiotic prophylaxis is indicated at the time of prostatic surgery or endoscopic urinary tract manipulations such as cystoscopy or urethral dilation in patients who have an increased risk of infection from transient bacteremia because of local organ pathology or prosthesis. The American Heart Association recommends endocarditis prophylaxis for patients with prosthetic cardiac valves (including porcine valves), most congenital cardiac malformations, surgically constructed systemic-pulmonary shunts, rheumatic and other acquired valvular dysfunction, idiopathic hypertrophic cardiomyopathy, a history of bacterial endocarditis, mitral valve prolapse with regurgitation or thickened leaflets,

or recent (6 months) cardiac surgery. Enterococci are the most common cause of endocarditis after gastrointestinal and genitourinary procedures. A standard parenteral regimen of antibiotic prophylaxis for genitourinary surgery and instrumentation consists of 2.0 g of ampicillin (50 mg/kg) IM or IV plus 1.5 mg/kg of gentamicin to a maximum of 120 mg administered within 30 minutes of starting the procedure. Ampicillin 1 g IM or IV or 1 g of amoxicillin orally should be administered 6 hours later for high-risk patients. Moderate-risk patients can be treated with 2 g of amoxicillin orally 1 hour before or 2 g of ampicillin IM or IV within 30 minutes of the planned procedure. In penicillin-allergic patients, vancomycin is substituted for ampicillin (1 g IV infused slowly over 1 hour beginning 1 hour before surgery). High-risk patients include individuals with prosthetic heart valves or a history of endocarditis and those taking continuous oral penicillin for rheumatic fever prophylaxis (357).

Other Considerations

Compared with the 12.5% mean requirement for blood transfusion in patients with TURP and the 35% for patients with open prostatectomy cited in the BPH clinical practice guidelines (230), transfusions are currently rarely required in patients subjected to prostatectomy. Transfusion rates below 1% are now commonly quoted in the literature (186). In a survey of 3,885 patients from 13 institutions, almost all undergoing transurethral prostatectomy between 1980 and 1987, 2.5% required blood during the operation and 3.9% required it in the postoperative period (240). The decreased size of adenomatous tissue removed (256) and the improved preoperative preparation, instrumentation, and anesthetic and surgical techniques all probably contribute to lessen blood loss (112,186). Greene (135) estimated a blood loss of approximately 9.5 mL/g of tissue resected. Blood typing, matching, or consideration of use of autologous blood is used only selectively in our hands. Finasteride use preoperatively has further reduced need for transfusion (143).

Operative Approach

The decision of whether the patient will benefit appreciably from surgical treatment of BPH should be made by a critical evaluation of his symptoms and findings. Once made, selection of appropriate therapy to maximize benefit and minimize risk is necessary. Historically, incompletely removed gross BPH tissue has been associated with failure to correct or early recurrence of BPH-related voiding dysfunction. This failure was frequently corrected by removal of additional tissue. Consequently, the goal to remove BPH tissue completely became an accepted dictum. The results with antiandrogenic and limited interventional therapy, especially when followed by procedures that remove the residual gross BPH, provide further support for this idealized goal. The choices to achieve complete excision of BPH have been open prostatectomy by a variety of anatomic approaches or transurethral resection or its surrogates (Fig. 32.28). Alternative mechanical approaches such as interstitial laser and transurethral microwave thermotherapy are being used selectively with variable immediate and long-term successes. In selecting an appropriate approach for a patient, several factors warrant consideration, including the size and configuration of the adenoma, the presence of other bladder or prostatic pathology such as diverticula or stones, the presence of complicating abnormalities such as fusion or ankylosis of the joints of the lower extremities, a large scrotal hernia, a rigid penile prosthesis, multiple urethral strictures, the skill and experience of the surgeon, and the expectations and prejudices of the patient. Selective use of interventional approaches reduces the risk of procedures and increases the likelihood of achieving a good result. Urologic surgeons should be skilled in a variety of operative techniques to relieve bladder neck obstruction caused by BPH and should use them with objectively identified goals.

Transurethral Resection of the Prostate

Anesthetic Considerations

Restall and Faust (296) cited a variety of reasons regional anesthesia in the form of a spinal or subarachnoid block is highly desirable in patients undergoing transurethral prostatic surgery. Excellent skeletal and smooth muscle relaxation allows easy filling of the bladder and reduces bladder spasms. Bladder perforation, water intoxication, and congestive heart failure are best perceived early by maintaining verbal contact with the awake patient. Airway-related complications (unexpected coughing, gagging, or bucking) are largely avoided with regional anesthesia, and a comfortable, quiescent patient aids in providing hemostasis (232,262). The presence of documented central or peripheral neurologic deficits, potential bleeding tendencies, chronic low back pain, osseous metastases, and lack of patient acceptance weigh against the use of regional anesthesia (37).

Urologists should be aware of the risk of hypotension and postspinal headache associated with subarachnoid block (296). Significant hypotension, usually responsive to additional crystalloid or α-adrenergic agonist administration, can result from the chemical sympathectomy extending to four dermatomes higher than the apparent sensory level. Risk of myocardial infarction is not substantially different in these patients with coronary artery disease with either spinal or general anesthesia. A postspinal headache, which is usually occipital and characteristically relieved by recumbency, is produced by the sustained transdural leakage of cerebrospinal

fluid. If necessary, this can be controlled by use of an epidural patch of autologous blood (72).

Steps Preliminary to Resection

Before the technique of endoscopic resection is discussed, prophylactic vasectomy, management of the urethra, cystoscopy before resection, and the choice and preparation of the resectoscope deserve brief consideration.

The reported 0.2% incidence of epididymitis by Mebust and colleagues (240) in 3,885 patients, only 10% of whom had had a vasectomy, reflects the currently diminished incidence of this complication. Nevertheless, prophylactic vasectomy effectively diminishes the risk of epididymitis (124) and warrants consideration in high-risk individuals with a chronic urinary tract infection, history of prolonged catheter use, previous epididymitis, or increased systemic or local risk factors for infection.

Urethral stricture, reported in 1.5% to 20% of patients after TURP, can be caused by urethral trauma from the resectoscope, catheter, or bacterial infection (148,149,161,393). Emmett and associates (85) found that the external urethral meatus and fossa navicularis of only 62% of men calibrated to 28 Fr or greater; in addition, the anterior urethra calibrated to 24 or 26 Fr in 9%. These sites of natural narrowing of the male urethra affect the selection of an appropriately sized resectoscope sheath. Calibration of the meatus–fossa navicularis and visual inspection of the urethra on insertion of the cystoscope are used to guide this selection. Gentle, progressive, manual dilation will usually allow introduction of the well-lubricated resectoscope sheath. Consideration of prolonged (2 weeks) administration of antibiotics to reduce the rate and severity of postresection stricture is worthwhile (149). A dense, narrow, external meatal or fossa navicularis stricture is best managed by a ventrally or dorsally placed meatotomy (Fig. 32.29). We prefer the latter to prevent a distorted urinary stream postoperatively.

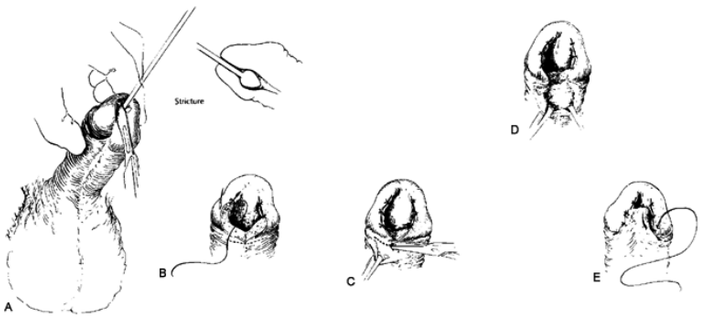

FIGURE 32.29. The technique of urethral meatotomy. Insertion of a bougie into the fossa navicularis facilitates the incision **(A);** placement of continuous approximating hemostatic sutures **(B).** When performed in the ventral aspect of the meatus, significant spraying on urination will often be reported by the patient. This may be obviated by creation of a frenular skin flap **(C–E)** or by performing the initial incision on the dorsal aspect of the meatus. (From Thompson IM. Transurethral surgery. In: Glenn JF, ed. *Urologic surgery,* ed 2. New York: Harper & Row, 1975, with permission.)

Impassable or dense strictures of the distal urethra can often easily be incised at the 12 o'clock position with the direct-vision optical urethrotome by the use of a stenting ureteral catheter as a guide. Their presence may prompt reevaluation of the diagnosis. A perineal urethrostomy may be required if the entire urethra is significantly narrow, in the presence of severe ankylosis of the hip, or in patients with an excessively long (whether naturally or prosthesis produced) penis (Fig. 32.30). Stay sutures incorporating skin and urethral edges serve to provide repetitive access to the urethra. At the conclusion of the endoscopic resection, suture reapproximation of the urethra is generally not required if the urethral catheter is passed in the standard fashion. The skin can be approximated loosely with interrupted absorbable suture material.

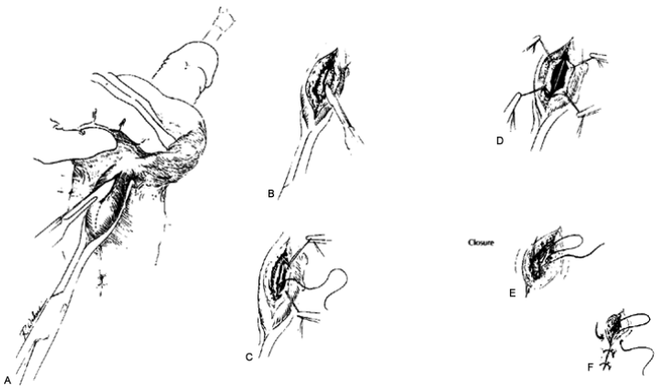

FIGURE 32.30. Technique of perirenal urethrostomy. A Van Buren sound is used to create an accentuated projection of the bulbous urethra in the midperineum **(A).** A 2- to 3-cm vertical incision is then made down to and through the exposed urethral segment **(B).** Stay sutures facilitate exposure of the urethral lumen and ensure reentry capability should that prove necessary **(C, D).** Following completion of the procedure and insertion of the catheter, the urethra may be loosely reapproximated followed by skin closure **(E, F).** (From Thompson IM. Transurethral surgery. In: Glenn JF, ed. *Urologic surgery,* ed 2. New York: Harper & Row, 1975, with permission.)

Cystourethroscopy should precede the resection. Use of a complementary rigid lens system or flexible cystoscope with either direct or video monitoring permits complete evaluation of the urethra and bladder. Passage of the cystoscope under direct vision maximizes the opportunity to recognize urethral pathology and minimizes urethral trauma. Each centimeter increase in the normal 2.5 cm prostate ureteral length from the verumontanum to the vesical neck has been equated with approximately 10 g of

additional prostate weight. The visual anteroposterior distance of the prostatic urethra, the depth and angle of the posterior lateral (5 and 7 o'clock) and anterior (12 o'clock) tissue clefts, the thickness of the prostate on digital examination with the endoscope in place, and the configuration of the prostatic hyperplasia including evidence of subtrigonal extension are useful to estimate the size of the prostatic adenoma and to evaluate the appropriateness of therapeutic alternatives. However, the most accurate method to estimate prostate size is a transrectal ultrasound measuring both total and transitional zone volume. Clefting of the bladder neck is important in differentiating a median lobe and median bar. The relationship of the prostatic hyperplasia to the ureteral orifices, verumontanum, and external urethral sphincter should be noted.

The presence of tumors, unexplained patchy inflammatory changes, calculi, trabeculation, and diverticula should be noted (Fig. 32.26). If identification of the ureteral orifices is difficult, IV administration of methylene blue or indigo carmine may assist in their visualization. Bladder diverticula should be assessed as to number, size, location, and probable emptying ability. An unsuspected pathologic finding may require reevaluation of the planned surgical procedure.

Before the rectoscope is inserted, it should be assembled to make certain all elements are appropriately fitted and working. The resectoscope sheath with deflecting (Timberlake) obturator in place is usually easily passed into the bladder. If a problem is encountered, insertion of the resectoscope may be accomplished under direct vision. If false passages or the prostate configuration make insertion particularly difficult, an endourologic guide-wire system or a small-diameter urethral catheter guide may be helpful in passing the resectoscope sheath into the bladder.

Various working elements, including a rack-and-pinion gear and a spring-activated mechanism, are available to control the movement of the cutting loop. We prefer the spring-mechanism instruments because of their “one-handed” operation. This permits insertion of the index finger of the free hand into the rectum to elevate the prostatic floor and facilitate the resection, particularly of the apical tissue. Many urologists prefer the video camera hookup and the lens eyepiece when performing TURP. In doing so, they watch the video screen for visual monitoring. Advantages of this technique are many, including a more comfortable upright position and keeping one's face away from resectoscope efflux. Potential disadvantages include a brief learning curve, reduced visual field, a reluctance to use rectal manipulation via the O'Conor drape to aid resection of the apex and other elusive sites, and the additional bulk of the resectoscope apparatus. Some urologists prefer instruments that permit continuous flow of irrigating fluid or insertion of a suprapubic drainage device for that purpose (159).

The use of these types of devices is a matter of personal comfort and choice.

Technique of Endoscopic Resection

The anesthetized patient should be secured comfortably in the dorsolithotomy position. A routine abdominal examination of the anesthetized patient may disclose unexpected pathology and serves as a baseline for any subsequent examination. Shaving the genitalia and perineum is unnecessary unless perineal urethrostomy is anticipated. Any one of a variety of standard bactericidal preparations, including hexachlorophene (pHisoHex), povidone-iodine (Betadine), or chlorhexidine applied to the lower abdomen, genitalia, and perineum is adequate. Use of the O'Conor-type rectal shield provides ready, sterile access to the rectum. The grounding pad should be placed so that it will not be dislodged. The irrigating fluid should be maintained at body temperature and positioned at the lowest level relative to the patient that will allow adequate visualization. With these maneuvers completed, the resection may commence.

No one way to perform endoscopic removal of obstructing adenomatous tissue is applicable to all cases. Each urologist will develop an approach and modify it on a case-by-case basis. Despite the multiplicity of potential modifications, some generalizations are proposed.

Before the resection is initiated, the prostatic fossa should be carefully reexamined. The bladder neck, trigone, and ureteral orifices proximally and the verumontanum and external sphincter mechanisms distally should be noted and their relationship to the prostatic adenoma reaffirmed. A nontoxic isotonic or slightly hypotonic solution with satisfactory visual capabilities such as glycine (1.5%) or sorbitol should be used for irrigation.

Prominent obstructive middle lobe or bladder neck tissue that constitutes an impediment to movement of the resectoscope or the flow of chips into the bladder should be dealt with during the earliest phases of the resection. Currents with various characteristics may be desirable during different phases of these procedures. Mixed currents provide greater hemostasis but cut less freely. Undamped currents cut rapidly with little resistance or hemostasis. The urologist should monitor current settings closely during the procedure. Any organized, systematic approach to the resection of the intraurethral adenoma can be used effectively. Some prefer to resect the floor of the prostatic urethra initially. Others use a modification of the Nesbit (259) “encirclement” approach, whereby the anterior and lateral lobe tissue is allowed to “drop” onto the floor of the prostatic fossa for easy resection (135,359). This usually entails initiating the resection at the level of the bladder neck in two sweeping arcs, the 11 to 9 o'clock and 1 to 3 o'clock positions. Bladder neck fibers are exposed but not resected, carrying the longitudinal sweep of the resection just proximal to the base of the verumontanum.

During the initial stages of the resection, the tissue cuts smoothly with minimal effort. The chips thus produced should be boatlike in shape and equivalent in length to the extended loop. A synchronized rocking movement of the resectoscope sheath allows clean cutting of the chips. One should avoid cutting “mini-chips” because this produces an irregular prosthetic bed, which can hide bleeders and reduce operative efficiency . As the resection progresses, more deliberate movements are necessary to engage tissue by exerting a downward pressure on the sheath to facilitate the fulcrum effect. Digital elevation and manipulation of the prostate via the O'Conor shield can be a significant aid at this time. For added protection, the bladder should be partially filled while resection is performed in the area of the bladder neck.

Aggressive resection at the bladder neck, the 12 o'clock position anteriorly, and near the prostatic apex is best postponed until the end stage of the resection. The anterior aspect of the prostatic fossa is thin and easily perforated; it contains the most fragile portion of the external sphincter fibers. Risking overresection in any limited area before the major portion of the adenoma is removed may expose large venous sinuses and compromise the resection. The prostatic apex is best removed at the end of the procedure in a bloodless field with a finger in the rectum.

Hemostasis should be maintained throughout the procedure. Observations of the character and amount of blood in the irrigating fluid as it drains from the bladder will provide valuable feedback of the type and severity of bleeding. Arterial bleeding is identified not only by its bright color but also by its persistence during filling and drainage. Venous bleeding is not only dark but also decreases markedly or disappears with irrigation and increases with drainage. Arterial bleeding should be controlled by precise fulguration. This is facilitated by advancing the resectoscope close to the bleeder to attempt to visualize the vessel “in profile.” The possibility of “ricochet” bleeding with the actual site on the opposite wall or of a cryptic bleeding site that requires further resection to expose it should be kept in mind (136). Identifying bleeding at the bladder neck area can be facilitated by inspection with a nearly empty bladder (Fig. 32.31). Prompt recognition of the presence of transected

venous sinuses is essential and can be facilitated by watching the drainage from the resectoscope. Partially occluding the inflow tubing intermittently may help locate arterial bleeders and identify venous bleeding. Identifying venous sinuses may be difficult; controlling them by fulguration almost always is difficult. The presence of a large open venous channel is an indication to lower the irrigating fluid as low as possible and to complete the operation with dispatch. Persistent inspection in the face of bleeding that is primarily venous can lead to significant fluid absorption and water intoxication. If the patient has signs of significant fluid absorption or the tissue remaining is appreciable, a catheter should be inserted to control venous bleeding quickly by tamponade and the procedure terminated.

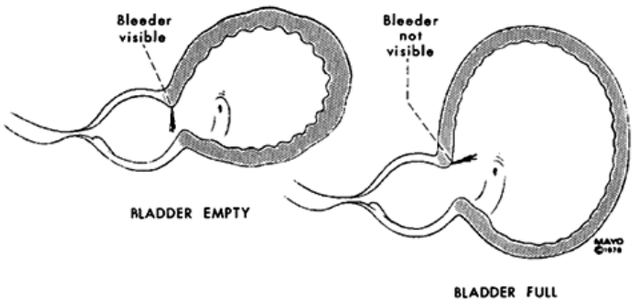

FIGURE 32.31. Arterial bleeding from the bladder neck is best appreciated with a moderately empty bladder, which permits projection of the bleeding site toward the operating surgeon. (From Greene LF. Transurethral prostatic resection: technique. In: Greene LF, Segura JW, eds. *Transurethral surgery.* Philadelphia: Saunders, 1979, with permission.)

The endpoint of the operation should be a cleanly excavated prostatic fossa exposing bladder neck and capsular fibers while leaving intact the trigone and ureteral orifices, the verumontanum, and the external sphincter mechanism. A very limited amount of residual tissue may be left abutting the external sphincter. It is far preferable to repeat the resection than to render the patient incontinent. Residual anterior and anterolateral tissue has been the most common problem we have noted in patients requiring repeat resection within a short time. This technically challenging area should be inspected carefully to make certain it is adequately but not overly resected.

Before the operative procedure is concluded, all tissue must be evacuated from the bladder with a Toomey syringe or similar device. The bladder, particularly diverticula, should be carefully inspected for residual tissue fragments. Reexamination of the prostatic fossa to secure final and adequate hemostasis is then best performed in the normotensive patient. If a venous sinus has been entered, persistent endoscopic searching and fulguration is ineffectual and can aggravate fluid absorption. Placing a Foley catheter with a distended balloon on moderate traction will usually result in prompt cessation of the bleeding. Despite considerable discussion regarding the advisability of using Foley catheter traction, no deleterious effect of this procedure has been documented. Although we share the practice of many in attempting to place and keep the balloon at the bladder neck, the studies carried out by Greene (135) would suggest that a distended balloon at least intrudes significantly into the prostatic fossa. Our practice is to maintain traction at least until the patient is back in his own room and then to release it as indicated by the degree of residual hematuria.

Closed-drainage systems reduce the risk of bacilluria in the postoperative period. The necessity to evacuate clots and maintain free drainage has resulted in the use of a number of different closed irrigating systems. Use of a three-way catheter with continuous inflow and outflow is effective if it is monitored by a skilled nursing group. If obstruction to the outflow tract is not recognized promptly, overdistention of the bladder can increase the problem with bleeding with this system. Intermittent irrigation from a reservoir is also commonly used and is our preference. A Y-tube connector that permits instillation of irrigating fluid into the bladder without breaking the closed system is affixed to the catheter. If it is necessary to break the closed system to irrigate the bladder manually, this should be done with concern for an aseptic technique.

Transurethral Incision of the Prostate

Evidence supporting a dynamic role for the peripheral condensation of stroma that acts as a prostatic capsule in the etiology of BPH-associated dysfunctional voiding has gradually accumulated (164,272). The partial resolution of symptoms noted in the patient with BPH treated with α-adrenergic blocking agents and the results achieved by open excision of the anterior prostatic commissure (326) suggest that capsular contraction or hypertonicity probably is a factor in the pathophysiologic changes resulting in BPH voiding dysfunction in some patients. Clearly, capsular contraction or constriction could augment the degree of luminal obstruction from adenomatous hyperplasia of the prostate.

Transurethral incision of the prostate (TUIP) is an operative approach attempting to disrupt the prostatic capsule to overcome these effects. Most reports of this procedure restrict its use to glands with estimated weights in the range of 30 g or less. A single or bilateral incision is usually made through the bladder neck to verumontanum. A cold or hot knife or resectoscope loop may be used. Incisions located posterolaterally (8 and 4 o'clock) are preferred. Loop excision aids visualization of the prostatic floor (239). Orandi (275) avoids bladder neck and complete capsular incision in young men to reduce risk of retrograde ejaculation. Li and Ng (207) advocate routine exposure of extracapsular fat with a resection from the trigone to the verumontanum. Most often the incision through the bladder neck should cause it to spring open (297). Bleeding and extravasation are associated with capsular division; Li and Ng (207) caution that bleeding should be controlled as soon as it is identified. Biopsies obtained with the resectoscope loop or a biopsy needle are generally desirable (207). Catheter drainage is used routinely in the postoperative period. Although bleeding may be severe and require transfusion, this is uncommon. The BPH panel literature review (230) indicated improved or satisfactory flow rates (7.5 mL per second preoperative to 15.1 mL per second postoperative), reduced residual urine (94%), and satisfactory improvement in subjective symptoms (80%) in patients selected for one of the approaches to TUIP. The reported incidence of retrograde ejaculation varied from 0% to 37%. Stress incontinence was experienced in 1.1% and total incontinence in 0.1% postoperatively. The re-treatment rate was 4% (239). TUIP warrants consideration as an alternative procedure to manage bladder neck obstruction in selected patients, particularly young men with limited prostatic hyperplasia and those wishing to preserve antegrade ejaculation.

Postoperative Management

The postoperative course for most patients undergoing transurethral resection of the prostate is remarkably uneventful (132,239). The estimated fluid absorption of 800 to 1,000 mL in an uncomplicated resection should be kept in mind when ordering postoperative fluids (270). The patient is generally able to tolerate a liquid diet on the day of surgery. The development of bladder spasms should raise a question regarding unobstructed catheter drainage. Bladder spasms occurring without identifiable cause are often difficult to control with the catheter in place despite the use of a variety of anticholinergic agents, including belladonna and opium suppositories, oxybutynin (Ditropan), tolterodine (Detrol), and propantheline (Pro-Banthine). Because straining to eliminate hard, impacted stool may precipitate bleeding, administration of a stool softener is worthwhile. In the absence of documented capsular perforation or significant bleeding, the Foley catheter can generally be removed within 24 to 48 hours. Instillation of sterile saline into the bladder just before catheter removal provides a convenient opportunity to assess the adequacy of the urinary stream and may aid in the passage of small clots and tissue debris. A three-glass voiding cycle should be initiated to assess the volume and color of subsequent micturition. Experiences indicating that day-of-surgery discharge is feasible in patients at average risk with uncomplicated procedures are being reported (389). We usually advise avoiding aspirin and antiinflammatory agents affecting platelet function and blood coagulation until the risk of significant secondary bleeding is minimal (2 to 3 weeks). The patient should be instructed to avoid straining and vigorous physical and sexual activity for several weeks. Epithelization of the excavated prostatic fossa is accomplished by migration and proliferation of transitional cells from resection margins and usually requires 6 to 12 weeks. Consequently, the patient should be informed of the possibility of mild delayed bleeding, often associated with the passage of sloughed tissue or eschar. Increased fluid consumption and realistic restriction of activity are usually successful in abating such symptoms.

Complications

Aside from the potential medical and surgical complications after anesthesia and surgery in general, several problems unique to endoscopic surgery require review. The intraoperative difficulties that must be recognized and discussed include the following: persistent penile erection; obturator spasm; hemorrhage; undermining of the bladder neck and trigone; perforation of the prostatovesical junction, capsule, or bladder; damage to the external sphincter; fragmentation of a prostatic lobe; and burn injury (136).

Persistent penile erection may develop at any point during general or regional anesthesia and may drastically limit endoscopic accessibility of the prostate and bladder. Detumescence often occurs without specific changes in management. Although detumescence may be associated with use of various nonspecific interventions, intracorporal lavage with pharmacologic agents such as phenylephrine (200 μγ per injection) (214) or dilute epinephrine (1:100,000) is currently the procedure of choice. If all of these maneuvers fail, temporary discontinuance of the procedure or use of a perineal urethrostomy should be done (Fig. 32.30).

The obturator reflex is most often triggered during a resection of bladder neoplasms located along the lateral wall but can be initiated during resection of a laterally situated intravesical adenoma. If this reflex is vigorous, exaggerated movement of the ipsilateral leg and pelvis can result in perforation. Use of high-intensity cutting current in a distended bladder predisposes to this event. Although downward adjustment of the current strength and partial evacuation of the bladder may obviate further problems, the risk of recurrent spasm usually requires a more aggressive approach. Use of a muscle relaxant, or alternatively, blocking of the obturator nerve as it traverses Alcock's canal by injection of a local anesthetic agent, usually solves the problem.

The usual techniques for controlling bleeding during transurethral resection are described in the previous section. Persistent significant bleeding as the procedure approaches its termination is usually due to the surgeon's failure to control arterial and venous bleeding during the course of the resection. However, the possibility of a coagulopathy also warrants consideration and selective evaluation, particularly if clotting is absent or poor. As indicated previously, if venous bleeding is suspected, balloon catheter tamponade will usually quickly control the bleeding and demonstrate the validity of this suspicion. If the bleeding is arterial, a systematic inspection of the prostatic fossa with variable, controlled, irrigating fluid inflow should lead to its identification and control. Extra care should be taken to inspect the anterior aspect of the bladder neck with the bladder empty and partially full to identify occult arterial bleeding in that troublesome spot. Balloon tamponade can also be used to control significant arterial bleeding, although direct surgical control is preferable. Every effort should be made to achieve satisfactory hemostasis at the time the patient leaves the operating room. If the bleeding persists despite these efforts and no underlying coagulopathy is identified, an open surgical approach may be necessary to control it either before termination of the resection or in the immediate postoperative period. As indicated, bleeding of sufficient severity to require transfusions occurs infrequently during the resection and in the postoperative period (240). If hypotension and shock develop, hypovolemia usually warrants primary consideration in patients with significant blood loss. However, other potential causes such as sepsis-, cardiac-, and drug-related etiologies should

not be dismissed without consideration, especially in patients with limited blood loss. The neodynium:yttrium-aluminum-garnett (Nd:YAG) laser with the right-angle noncontact fiber has been used successfully to control prostatic bleeding (193).

Frank perforation may occur at the level of the prostatovesical junction, the prostatic capsule, or the bladder itself. In addition to actual electroresection, the trauma from the beak of the instrument or overdistention of a thin prostatic capsule or bladder may be a factor in perforation. Overresection of the bladder neck and trigone may not only lead to perforation but also has been postulated to cause postoperative bladder neck contracture (136). Varying degrees of perforation are more common at the posterior aspect of the bladder neck, but anterior or lateral perforation of the prostatovesical junction is usually associated with substantially greater volume of extravasation. Extravasation associated with prostatic resection is almost always extraperitoneal. Visual evidence of perforation may vary from a cavernous opening with identifiable periprostatic or perivesical tissue to a subtle elongation of the prostatic urethra with eventual elevation and lateral impression of the bladder. The prostatovesical junction may become more distant and distorted. Extraperitoneal perforations in the bladder neck area do not generally produce sufficient abnormality in the irrigation pattern to allow their recognition. If unrecognized, signs of diminished bladder capacity and, in patients under regional anesthesia, peritoneal irritation (including abdominal pain, guarding, and tenderness) and nausea and vomiting may develop. Recognition of a perforation requires an assessment of existing and potential extravasation to guide subsequent management. A cystogram with a drainage film provides useful information. Limited extravasation can usually be handled with catheter drainage and observation. More extensive extravasation in a symptomatic patient usually requires perivesical drainage. The morbidity associated with prevesical space drains placed through a limited low-midline incision is not sufficiently great to warrant extensive measures to avoid it.

Intraperitoneal extravasation usually results from advancing or reinserting the resectoscope sheath vigorously and injuring the bladder dome. This can usually be avoided if the bladder is kept moderately filled. The probability of intraperitoneal extravasation is often signaled by a bizarre irrigation pattern where inflow greatly exceeds outflow and by peritoneal irritative symptoms, including unilateral or bilateral subdiaphragmatic pain. Endoscopic visualization of the bladder defect may be difficult and unnecessary. A cystogram should be performed to document the suspected abnormality. Modest degrees of intraperitoneal perforation can probably be handled with catheter drainage. Massive extravasation in a patient with profound symptoms usually requires lower abdominal transperitoneal exploration with appropriate drainage and possibly closure of the perforation (299).

Under normal circumstances, the internal sphincter constitutes the predominant continence mechanism in men. During the course of an adequate transurethral resection of the prostate, this sphincter mechanism is removed or rendered incompetent (305). The integrity of the external sphincter mechanism must be preserved, or total or stress urinary incontinence will ensue. Injury to the external sphincter mechanism can occur by actual cutting of its muscle fibers, aggressive and injudicious fulguration about the verumontanum and prostatic apex, and mechanical trauma induced by the beak of the resectoscope during the course of the resection of apical tissue. Needless to say, the verumontanum is an invaluable landmark that should be preserved. In general, resections that are terminated proximal or adjacent to the verumontanum are unlikely to be associated with significant injury to the external sphincter. As stated previously, the recognizable sphincter is represented by the area of the urethra that assumes a nearly circular shape and a corrugated appearance as the sheath is advanced into the membranous urethra and approaches the verumontanum area. However, the extent of the complex of smooth and striated muscle that makes up the external sphincter is not clearly demarcated, particularly as the fibers interdigitate and splay out proximally. The anterior muscle in this cone-tube configuration is the least substantial. These considerations should lead to caution in selecting not only the extent of the resection but also the depth distally. This is particularly true anteriorly (see Chapter 26A). When one considers the extent of sphincter resection necessary to affect sphincter function in purposeful external sphincterotomy, the fact that the mechanism of post-transurethral resection sphincter dysfunction is poorly understood becomes clear. Nevertheless, experience has indicated the need for caution in avoiding overresection in the distalmost portion of the prostate.

Resection of a portion of the prostate too large to be evacuated through the resectoscope sheath is an unusual complication that has been described during resection of a prominent intravesical middle lobe. This is avoidable if resection of the pedicle of the adenoma is done last. On completion of the resection, the surgeon can grasp the fragment with the loop or grasping forceps and draw it into the resectoscope beak; the entrapped fragment can then be removed as a single unit. Alternatively, it can be morcellated within the bladder or the prostatic fossa. Delayed retrieval of the fragment poses the danger of catheter occlusion in the immediate perioperative period.

The advent of solid-state electrosurgical units possessing isolated circuitry has made burn injury to patients and surgeons a rare event. Nevertheless, the possibility of inadequate grounding should be considered in the event of a less-than-optimal function of the working element during the resection. As more electronic and metallic devices are implanted in patients, the position of the ground and active electrode may require increased consideration to prevent

interference with the function of these units (11). One other complication can occur as a result of interaction of the electric current with the irrigating fluid, namely, the possibility of an intravesical explosion caused by liberated gases. This potentially volatile interaction of electrical current, hydrogen, and air should be recognized by the urologist.

A variety of perioperative and postoperative complications have been associated with transurethral resection of the prostate. These include hemorrhage, the transurethral resection syndrome, catheter malfunction, development of urethral stricture and bladder neck contracture, urinary tract infection, shock, development of DVT and pulmonary embolus, and disorders of the cardiovascular, gastrointestinal, and central nervous systems.

Significant bleeding in the perioperative period is most often due to faulty intraoperative hemostasis, which has been discussed at length. Some delayed postoperative bleeding, usually caused by sloughing ischemic tissue or, less frequently, clot lysis is a relatively common event. Its incidence decreases as the postoperative period lengthens. In our experience, significant bleeding is far more common in patients who have had intraoperative venous sinus bleeding. It is rare after 21 days. Usually, a significant secondary bleed is controlled by insertion of a catheter, evacuation of clots, and tamponade. Reoperation is occasionally required to achieve complete clot evacuation and to fulgurate the arterial bleeders. Limited bleeding may occur for several weeks after the initial resection, is usually transient in nature, and customarily responds promptly to curtailing physical activity and initiating liberal fluid intake. In patients with prolonged or recurrent bleeding, the possibility of a variety of important contributing hematologic disorders such as disseminated intravascular coagulation, primary fibrinolysis, decreased factor VIII, and von Willebrand's factor warrant consideration.

Many of our current conceptions regarding the etiology of the transurethral resection syndrome stem from the observations of Hagstrom (144) and Harrison and associates (151). The pressure within the prostatic venous system is approximately 10 mm Hg. Uncomplicated resections will ultimately expose multiple small venous sinuses as the resection approaches the capsule. Excessive absorption of irrigating solution can occur if the solution is administered under a pressure that exceeds normal venous pressure, particularly during the course of a lengthy resection (greater than 1 hour). Consequently, most urologic surgeons currently use a nonisotonic irrigating solution such as 1.5% glycine with an osmolality of about 200 mOsm/L compared with the serum osmolality of 290 mOsm/L. Excessive systemic absorption of this solution will result in a dilutional hyponatremia, hypoproteinemia, and ultimately a decreased serum osmotic pressure. Such events promote fluid shifts that are ultimately responsible for cerebral or pulmonary edema. As cerebral edema becomes more pronounced, the intracranial pressure rises and produces the characteristic clinical signs of the so-called transurethral resection syndrome: bradycardia, hypertension, tachypnea, confusion, agitation, muscular twitching, nausea, vomiting, and headache. This chain of events may progress to frank convulsions and coma, particularly if the serum sodium level plummets to less than 120 mEq/L (157). This syndrome was diagnosed in 2% of the 3,885 patients subjected to transurethral resection from 13 institutions reviewed retrospectively by Mebust and associates (240). Transurethral resection syndrome was not listed as a cause of any of the nine deaths in this series. As discussed previously, prompt recognition of increased risk of irrigating fluid absorption is the hallmark of prevention and treatment. The irrigating solution container should be lowered to the minimum level necessary to facilitate visualization. The procedure should be terminated after securing hemostasis and evacuating tissue fragments. Peripheral IV lines should be adjusted to a keep-open rate. Serum electrolyte levels should be obtained promptly to confirm the diagnosis. Our current practice is to obtain a prompt postoperative serum sodium in any patient with a recognized risk factor for increased irrigating fluid absorption, making failure to recognize mild forms of this syndrome unlikely. A serum sodium level less than 120 mEq/L indicates a significant dilutional effect. Intravenous furosemide (Lasix) should be administered. Because the diuretic response of the elderly patient is unpredictable, it seems best to start with a relatively small dose, about 5 to 10 mg IV, and adjust the dosage accordingly. Transient visual disturbances or blindness during the initial stages of this syndrome signify significant CNS toxicity. Although rare, these problems can be distressful to both the urologist and family. Full reversibility is generally reported. In the presence of profound CNS symptoms, the administration of hypertonic saline should be done; the amount required to restore serum sodium levels and osmolality can be calculated. In general, the administration of about 200 mL of 3% sodium chloride solution during a 3- to 6-hour period will produce a dramatic improvement in clinical signs and symptoms. Although concern regarding judicious rapid correction of severe hyponatremia with hypertonic saline to achieve a mild hyponatremic state is probably not warranted from the standpoint of development of a demyelinating lesion of the brain (central pontine myelinolysis), rapid conversion of hyponatremia to normonatremia or hypernatremia, an increase of more than 25 nmol/L with initial therapy, or both, may be a factor in the development of these lesions. This risk is accelerated by the presence of a hypoxic-anoxic episode, alcoholism, or hepatic coma (14). The patient's hourly urine output and fluid intake should be recorded. In the presence of severe cerebral and pulmonary symptoms, invasive cardiopulmonary monitoring in an intensive care setting is advised.

The cause of the transurethral resection syndrome may be potentially more complex than previously suspected (157,315). Immediate or delayed encephalopathic symptoms associated with markedly elevated serum ammonia levels have been reported after TURP with glycine as the

irrigating fluid. With excessive absorption of glycine, several metabolic pathways that involve deamination and liberate free ammonia are activated in addition to the major one involving interconversion of glycine with serine. James and associates (169) have hypothesized that cerebral astrocytes detoxify ammonia by the production of glutamine from glutamic acid. The accumulation of glutamine and its conversion to serotonin, accompanied by a decrease in dopamine and norepinephrine, may be important etiologic factors in the neurologic symptoms of patients with hyperammonemia (157). Patients at high risk include those with documented hepatic disease, marked skeletal muscle atrophy, urinary tract infection and bladder stones, and obstructive uropathy. Treatment is generally supportive, with the realization that the encephalopathy may be somewhat prolonged, lasting up to 36 hours. If seizure activity develops, anticonvulsant medication may be required.

The indwelling Foley catheter can contribute directly to immediate and delayed complications by failing to deflate and indirectly by facilitating urethritis and probably stricture formation. A variety of maneuvers have been used to deflate the inflated retention balloon. These include simple compression of the filling stem, overdistention with additional fluid, injection of mineral oil, and puncturing the balloon with a wire stylet inserted through the access channel or with a fine spinal needle introduced suprapubically. Success has also been reported with procedures using a ureteroscope passed along the catheter or a cystoscope introduced to puncture the balloon after the divided catheter secured by a dangle suture has been pushed into the bladder (24).

The role of the catheter in urethral stricture formation is supported by the decrease in this complication after suprapubic as compared with urethral catheter drainage (149). The potential etiologic role of urethritis is supported by the decreased stricture incidence associated with prolonged antimicrobial therapy after transurethral resection. The urethral meatus should be cleaned of mucus and crusts regularly; the catheter surface should be kept free of foreign substances. The rare development of a severe generalized urethritis with fever warrants an attempt to identify the organism and to institute antibiotic therapy promptly. The catheter should be removed as soon as possible. If an inflammatory reaction such as a meatitis is recognized, gentle, frequent dilation of the inflamed site will usually prevent development of a stricture. In the case of a severe meatitis, our practice is to provide the patient with a dilator and teach self-dilation. If the constricting urethritis is in the more proximal urethra, frequent, atraumatic dilation by the urologist in the postoperative period will also often prevent development of a significant stricture. Concern for the prevention of strictures does not stop with removal of the catheter.

With regard to the related topic of bladder neck contracture, the estimate that as many as 2% of the patients undergoing transurethral electroresection of the prostate have this complication seems high in our experience (136). As indicated in the section on technique, contracture is thought to result from overresection and injudicious fulguration about the bladder neck. Undermining of the bladder neck and trigone may create a free flap that heals as a membrane. Early recognition of the risk of a contracture is facilitated by careful attention to the patient's description and observation of his urinary stream or by routine flow studies. An unusual degree of pain in the postoperative period should also raise suspicion of an inflammatory reaction in the area of the bladder neck. Prompt outpatient endoscopic evaluation is informative and easily accomplished (Fig. 32.32). If a significant constricting inflammatory reaction is identified in this region, gentle calibration and dilation are worthwhile. Contractures usually become manifest with obstructive symptoms from 3 weeks to 10 years after resection, with an average interval of approximately 6 months (136). If gentle dilation does not suffice, reevaluation with endoscopy is advised. If the bladder neck orifice cannot be located endoscopically, IV administration of methylene blue, induction of a diuresis, and use of suprapubic pressure may produce an identifying jet of blue urine. A ureteral catheter passed into the bladder can guide the incision of the constricting ring with an optical urethrotome, Collins knife, or resectoscope loop until it springs open. Once complete division of the constricting tissue band is achieved, more extensive resection of the scarred tissue is probably best avoided. Again, frequent, gentle postoperative calibration and dilation will help prevent recurrence. In recurrent contractures, a Y-V–plasty of the

bladder neck will usually solve the problem and should be considered.

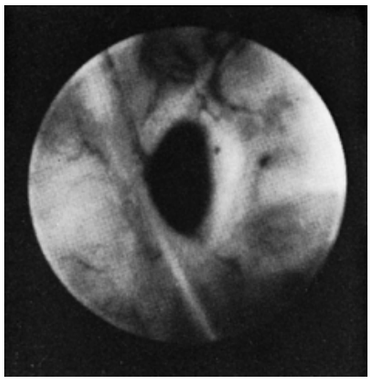

FIGURE 32.32. Typical appearance of bladder neck contracture. The opening to most diaphragmatic contractures can be found in the anterior position near 12 o'clock. (From Greene LF, Holcomb GR. Transurethral resection in special situations. In: Greene LF, Segura JW, eds. *Transurethral surgery.* Philadelphia: Saunders, 1979, with permission.)

Open Prostatectomy

Suprapubic Prostatectomy

As the instrumentation and skills for endoscopic resection of the prostate have improved, the indications for open prostatectomy in the practice of most urologists have diminished. Factors influencing the choice of the suprapubic approach for enucleation of obstructing adenomatous tissue include the presence of a prominent, intravesical component; associated bladder pathology, such as a large, narrow-necked vesical diverticulum or multiple large bladder stones; and the need for an open prostatectomy in an obese patient in whom the retropubic approach is technically more cumbersome (69). Suprapubic prostatectomy is a relatively simple procedure that nevertheless requires meticulous attention to surgical detail (256,267).

After the induction of satisfactory general or regional anesthesia, the operating table should be gently flexed in the modified Trendelenburg position to facilitate exposure of the male pelvis and retraction of the peritoneal reflection. Exposure of the bladder is enhanced if the latter is filled to approximately 150 to 200 mL. Use of a fiberoptic headlight may aid visualization of the prostatic fossa after enucleation.

A transverse (Pfannenstiel) or lower midline incision may be used depending on the procedure planned, the patient's build, and the presence of previous surgical scars. In the preferred Pfannenstiel incision, extending the incision too far laterally should be avoided to decrease the risk of postoperative hernia. Awareness of potential injury to the underlying inferior epigastric vessels is important with either incision. Incision and separation of the thin fascial envelope constituting the umbilicoprevesical fascia and partial separation of the peritoneal reflection from the dome of the bladder facilitate exposure of the partially distended bladder. After stay sutures are placed in the bladder wall, a transverse incision 1.5 to 2.0 cm above the bladder neck provides exposure of the prostatic fossa with minimal risk of disrupting the bladder neck and the prostatic capsule. Incising the detrusor muscle with electrocautery or scalpel exposes the mucosa. After this is incised and the edges of the incision are secured with Alice clamps, it is enlarged by careful lateral digital traction. After evacuating the bladder contents, a single moistened lap pad inserted into the bladder dome provide *s* a buttress for a retractor. Further exposure of the bladder neck can be achieved by placing a Deaver along the lateral vesical wall. Careful examination of the bladder, especially to locate the trigone and the ureteral orifices and identify associated bladder pathology, is important before enucleating the obstructing adenoma. Circumferentially scoring the mucosa bordering the bladder neck with electrocautery prevents excessive tearing during enucleation of the prostate (Fig. 32.33). The enucleation should be initiated by inserting the index finger into the prostatic fossa and cracking the anterior commissure with anterolateral pressure against the larger adenoma. Blunt enucleation should be carried out in the cleavage plane between the surgical capsule and the adenoma with pressure primarily directed against the adenoma (Fig. 32.34).

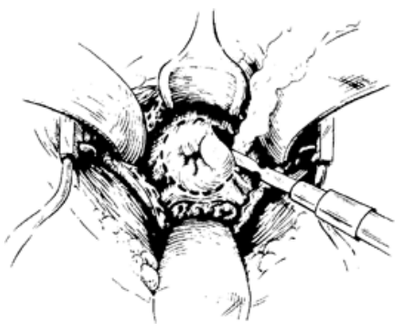

FIGURE 32.33. Circumferential bladder neck incision before transvesical enucleation of prostatic adenoma. The bladder neck is most easily exposed by the placement of small Deaver and malleable retractors laterally and a medium Deaver superiorly. The trigone and ureteral orifices should have been exposed and kept from harm's way. The incision through the mucosa overlying the bladder neck is best established with electrosurgical instruments. (From O'Conor VJ Jr. Suprapubic and retropubic prostatectomy. In: Harrison JH, et al, eds. *Campbell's urology,* vol 3, ed 4. Philadelphia: Saunders, 1979, with permission.)

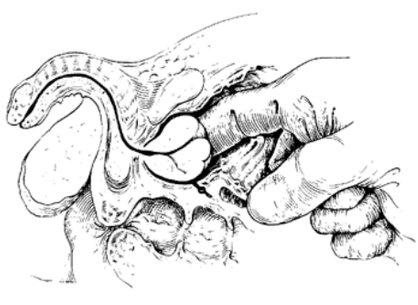

FIGURE 32.34. Finger enucleation of the prostatic adenoma is best accomplished by “cracking” anterior commissural tissue and then establishing the plane between the adenoma and the surgical capsule on both lateral aspects. Although esthetically pleasing, intact removal of very large glands may be ill-advised. In that case, the use of lobe forceps may facilitate the sequential removal of lateral and middle lobe tissue. (From O'Conor VJ Jr. Suprapubic and retropubic prostatectomy. In: Harrison JH, et al, eds. *Campbell's urology,* vol 3, ed 4. Philadelphia: Saunders, 1979, with permission.)

The apex of the adenoma should be separated from the area adjacent to the external sphincter bilaterally; both lateral lobes should be free. The urethra should be divided sharply or bluntly by “pinching” just proximal to the distal apical adenoma. Traction on the distal urethra should be avoided while the capsule is teased from the apex of the adenoma to minimize sphincter injury. Finally, the adenoma should be separated with care from the bladder neck, especially posteriorly in the area of the ureteral orifices. Enucleation may be facilitated by placing the fingers of the free hand or an assistant's hand in the rectum to push the prostate ventrally in a cephalad direction. The sequence of the enucleation should be varied depending on the configuration of the adenoma and the ease of enucleation. At times, the median or subtrigonal lobe should be attacked initially. In a large gland with multiple adenomas, sequential removal is preferable to traumatic removal of the adenomatous growth in toto.

Unusual adherence of the adenoma to the capsule should increase suspicion of carcinoma. Once the adenoma is removed, rapid control of bleeding becomes the major concern. Often, a portion of the blood supply is identifiable as the adenoma is being removed and can be clamped and ligated. Unless bleeding is massive, rapid inspection of the prostatic fossa with supplemental lighting, a narrow Deaver, and partially open ring forceps to aid in the exposure is usually advisable at this time. Irregular tissue tags or fragments can be sharply removed; sizable bleeders can be controlled by suture ligature or by fulguration. Introduction of a gauze pack into the prostatic fossa with blunt-tipped forceps, a standard hemostatic procedure in the past, is now used selectively. It is an excellent maneuver to achieve rapid control of significant bleeding. Placement of side-on (Halsted) hemostatic mattress sutures of absorbable suture incorporating bladder mucosa, bladder neck, and prostatic capsule at 5 and 7 o'clock (Fig. 32.35) is facilitated by use of the so-called genitourinary (five-eighths) curved needle. The needle-bearing end of the tied suture can be used later to anchor the bladder neck to the prostatic fossa. The fossa should be inspected again by retraction as before, and significant bleeding should be controlled with suture ligatures or fulguration. Persistent bleeding from deep in the posterior aspect of the prostatic fossa can be controlled at times by three transverse plication sutures of 0 chromic catgut placed in the prostatic fossa as described by O'Conor (268) (Fig. 32.36). Before trigonalization of the prostatic fossa, a V-shaped wedge can be removed from the 6 o'clock area of the bladder neck if it is extremely tight (Fig. 32.37). Anchoring the bladder neck to the posterior aspect of the prostatic fossa facilitates hemostasis and prevents the formation of an obstructing membrane (Fig. 32.38). This maneuver also aids any subsequent catheter placement. At this point, a 22- or 24-Fr Foley catheter with a 30-mL balloon is directed into the bladder, the balloon is distended appropriately for the size of the bladder neck, and traction is applied.

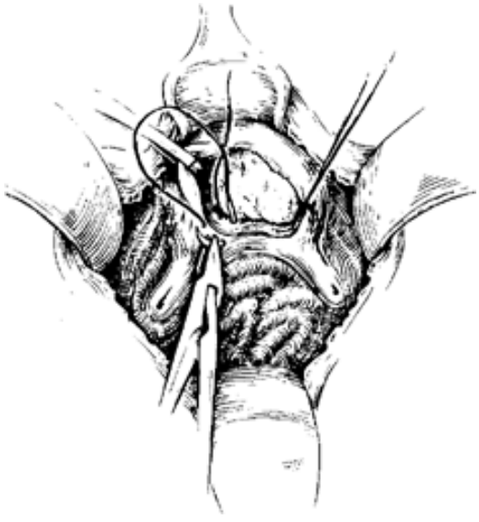

FIGURE 32.35. Placement of hemostatic sutures at the bladder neck. Although the urethral branches of the prostatovesicular artery traditionally enter at the 5 and 7 o'clock positions, this is highly variable. Placement of 0 or 2-0 hemostatic chromic sutures at the bladder neck or within the prostatic fossa is greatly facilitated by the use of $^{5}/_{8}$ curved genitourinary needles and fiberoptic lighting. (From O'Conor VJ Jr. Suprapubic and retropubic prostatectomy. In: Harrison JH, et al, eds. *Campbell's urology,* vol 3, ed 4. Philadelphia: Saunders, 1979, with permission.)

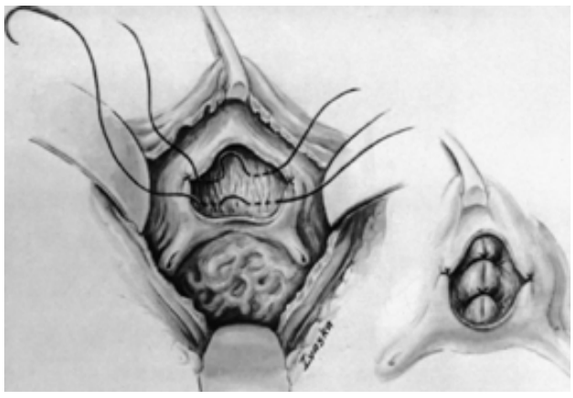

FIGURE 32.36. Placement of hemostatic plication sutures. Uncontrolled bleeding from the depths of the prostatic fossa can often be contained by the placement of several 0 chromic plication sutures into the posterior aspect of the prostatic fossa, creating an accordion-like effect. (From O'Conor VJ Jr. Aid for hemostasis in open prostatectomy: capsular application. *J Urol* 1982;127:448.)

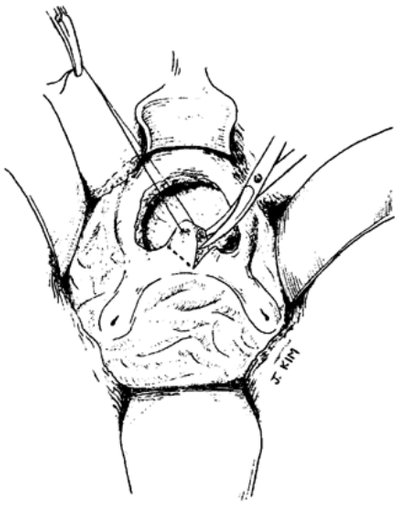

FIGURE 32.37. Wedge resection of bladder neck. Following enucleative prostatectomy, the bladder neck is generally patulous, and routine wedge resection is not necessary. In fact, one can take advantage of the capacious bladder neck by using the previously placed hemostatic sutures to "retrigonalize" the posterior aspect of the prostatic fossa. Should the bladder neck appear unduly snug, a ventrally directed wedge resection can be performed following either suprapubic or retropubic approaches.

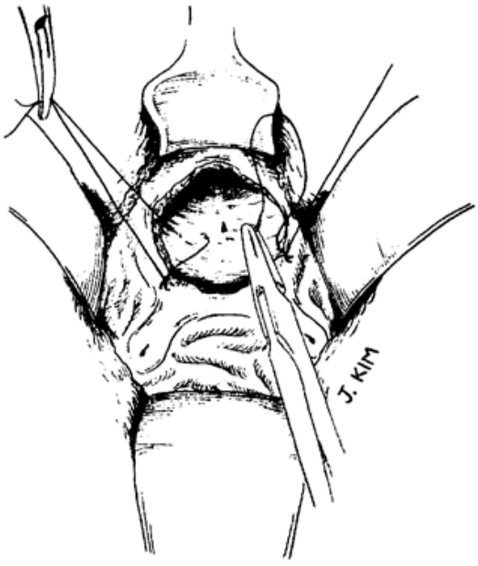

FIGURE 32.38. "Retrigonalization" of prostatic fossa. The previously placed and tied hemostatic mattress sutures at the bladder neck can be anchored to the posterior aspect of the surgical capsule to advance the bladder neck into the prostatic fossa. This maneuver aids hemostasis and facilitates appropriate healing.

Traditionally, problem bleeding has been approached by attempts at direct visualization and suture or cautery control, use of hemostatic agents such as microfibrillar collagen (Avitene) or oxidized cellulose (Surgicel) placed in the prostatic fossa with temporary gauze packing or wrapped around the balloon, or on rare occasions, by an occlusive, preferably removable, pull-out suture of the bladder neck (221). Use of modern endoscopic visualization and hemostatic procedures warrants consideration in these unusual circumstances. A large (28- to 36-Fr) Malecot or de Pezzer catheter placed through a separate stab wound in the bladder dome away from the peritoneal reflexion and the trigone functions as a drainage tube. After removal of all sponges, drains should be placed on each side of the bladder neck and brought through a stab wound just above and away from the symphysis. Bladder closure should be performed in two or three layers. The mucosa can be approximated with a running suture of 3-0 or 4-0 plain catgut, usually incorporating muscle as well. The superficial and deep muscle of the bladder can be reapproximated with interrupted Lembert sutures of 2-0 chromic catgut. The adequacy of closure and hemostasis can be assessed by through-and-through irrigation. The effluent should be pink to clear. The suprapubic tube should exit through a separate, superiorly placed stab wound. The appropriately placed drains and suprapubic tube should be secured at the skin level. Routine wound closure with absorbable sutures should include approximation of the rectus muscle. As the patient awakens from anesthesia, catheter irrigation should be repeated and traction maintained on the Foley catheter with adhesive strapping to the thighs. The urethral and suprapubic catheters are

attached to separate drainage systems and intermittent or continuous closed irrigation used as desired. The patient should be observed as his blood pressure normalizes postanesthesia to ensure that adequate hemostasis has been achieved and patency of the catheter is maintained. Ordinarily, the Foley catheter traction can be released within 12 hours and the catheter removed on the second or third postoperative day. The drains may be removed when clinically apparent drainage ceases or after removal of the suprapubic catheter. The latter has generally been discontinued on the sixth or seventh postoperative day. This schedule is commonly advanced currently. If voiding is not resumed and the suprapubic tube site closed by 48 to 72 hours, reinsertion of the urethral catheter may be necessary. Persistent suprapubic drainage usually requires endoscopic and, at times, cystographic assessment to evaluate the possible presence of persistent obstructing tissue or a foreign body. Other, more remote causes may warrant consideration if the fistula becomes chronic.

Retropubic Prostatectomy

Retropubic prostatectomy using a direct ventral capsulotomy is judged by many to permit a more exact adenomectomy and facilitate direct hemostasis (156). Since its refinement and popularization by Millin (243), this approach has been preferred by many, particularly for BPH associated with prominent intraurethral components.

Antibiotic prophylaxis probably has added importance in the retropubic approach because of the increased risk of osteitis pubis (387). The preoperative preparation and operative approach are identical to those described for suprapubic prostatectomy except for advisability of decompressing the bladder before dissection on or about the prostatic capsule. As the result of experience with radical retropubic prostatectomy, exposure and suture ligation of the dorsal vein on the anterior surface of the prostate to permit incision of the capsule has become a common experience. After placing proximal and distal tagged sutures, a transverse capsulotomy is generally made with electrocautery or a scalpel 1 cm distal to the bladder neck. The capsulotomy should be extended to the lateral borders of the anterior capsule without violating or undermining the inferior edge of the capsule. Establishing the plane between the surgical capsule and the underlying adenoma (Fig. 32.39) is facilitated by using gentle traction on the stay sutures and curved Mayo or Metzenbaum scissors for dissection.

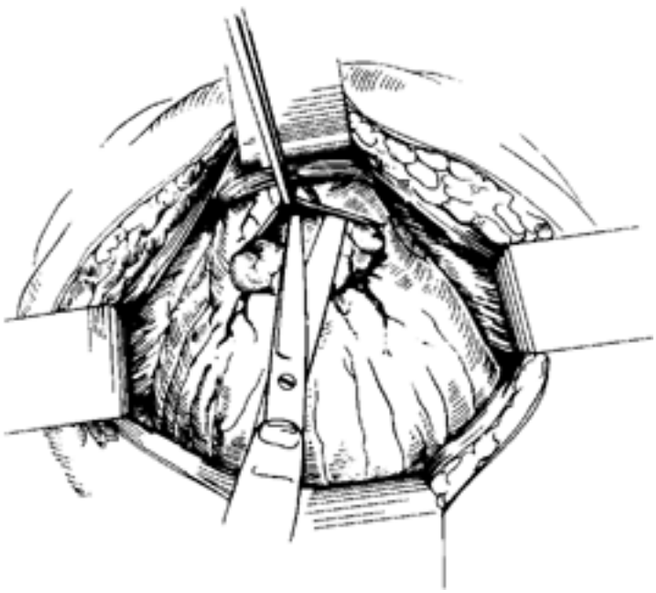

FIGURE 32.39. Retropubic prostatectomy is best performed through a transverse capsulotomy incision. Once the latter is established, the plane between the true capsule and the adenoma is best established with sharp dissection followed by standard digital enucleation. (From Staffon RA. Retropubic prostatectomy. In: Glenn S, ed. *Urologic surgery,* ed 3. Philadelphia: Lippincott, 1983, with permission.)

Once the appropriate surgical plane has been entered, the enucleation of the obstructing adenoma is similar to that described for suprapubic prostatectomy. In general, larger glands are more easily enucleated with blunt-finger or closed scissor-tip dissection. Unexpectedly small glands may be more precisely dissected sharply with curved tissue scissors. The enucleation should usually begin in the apical aspect of the gland. The urethra is easily divided under direct vision at the apex of the adenoma without tension. Bleeding sites are visualized and fulgurated or secured with suture ligatures. The direct access to the prostatic fossa provided by the transcapsular incision facilitates the achievement of hemostasis. After bleeding has been controlled, a wedge resection of the bladder neck may be performed if indicated. Similarly, retrigonalization of the bladder neck to the prostatic fossa should be considered to facilitate hemostasis, accelerate reepithelization, prevent fibrosis, and aid future retrograde catheter manipulations.

A 22- or 24-Fr Foley catheter with a 30-mL balloon should be inserted into the bladder, the balloon inflated appropriately, and gentle traction applied. After the catheter has been inserted, the capsulotomy is closed, usually with interrupted mattress sutures of 2-0 chromic catgut. Closure of the wound proceeds in a fashion identical to that described previously. A suprapubic catheter is customarily avoided but can be inserted if necessary. Again, intermittent or continuous closed irrigation can be used. The urethral catheter is usually left indwelling for 4 to 7 days.

Complications of Open Prostatectomy

Recent reports of short- and long-term experiences with open prostatectomy are conspicuously lacking. Consequently, the improvements in morbidity and mortality rates in surgical procedures in general that have occurred in the last two decades are reflected minimally in the data available regarding these presumably technically mature procedures. The reports of open prostatectomy used for the BPH guideline studies summary (230) were published in 1987 or earlier. The mean perioperative mortality rate was 2.4% (90% CI 1.0% to 4.6%). This compares with the progressively

decreasing mortality rate at our institution: from 8.5% in 1942 to 1950, to 2.1% in 1961 to 1965, to 1.4% in 1965 to 1970, to 0% in 1971 to 1982 (257). The mean and median overall (any complication regardless of severity) complication rate cited in the guidelines is 21% (90% CI 7.0% to 42.7%). The 1.5% mean risk of perioperative intervention for bleeding and 35% risk of transfusion compares with 0.3% and 8%, respectively, by Nicoll and colleagues (261). In the latter series, more than half of the patients undergoing transfusion received 1 unit of blood, an unlikely occurrence today. The guidelines review indicated a mean incidence of epididymitis of 2.6% and of urinary tract infection of 13.4%.

Osteitis pubis is an uncommon postprostatectomy complication that can cause nagging to severe pain in the region of the symphysis, pelvis, or lower abdomen. Although most often associated with the retropubic approach, it can follow suprapubic and transurethral prostatectomy and even simple urethral instrumentation (107). Symptoms usually begin within 6 weeks of the operation. A low-grade fever, limited adduction of the thighs, and significant discomfort on bilateral medially directed pelvic pressure raises suspicion of the presence of osteitis pubis. Radiographic changes in the bone, although not always present, are usually recognizable 2 to 4 weeks after the onset of symptoms (385).

Complications usually but not always recognized with more prolonged follow-up include urethral stricture, with a mean incidence of 2.6%, and bladder neck contracture, with a mean incidence of 1.8% reported in the guideline review of open prostatectomy (230). Both are reported to occur more frequently with a suprapubic than a retropubic approach, but this may be more reflective of the period of data accumulation than the procedures. The mean incidence of new onset of postoperative erectile dysfunction (32% perineal, 16% retropubic, 18% suprapubic) is much lower than the risk of retrograde ejaculation (77%). The median risk of stress incontinence (retropubic, 1.5%; suprapubic, 2.6%) and total incontinence (retropubic, 0.5%; suprapubic, 0.3%) noted in the literature review seems likely to be relatively stable. Postoperative erectile dysfunction and incontinence are phenomena with multiple age-related causes that may be related temporally but not necessarily etiologically to the surgical procedure. The BPH guidelines report (230) cites an estimated re-treatment rate of 2% (CI 1% to 4%) within 1 to 5 years of performance of an open prostatectomy. No data are presented regarding the need for immediate intervention in patients who either are unable to void or have unimproved or worsened voiding dysfunction after surgical intervention. Patients who are unable to void, have persistent drainage from the suprapubic site, have unchanged or troublesome symptoms, or have chronic urinary tract infection require prompt evaluation, usually including consideration of endoscopic, voiding cystourethrographic, or urodynamic studies. Although less common than after TURP, failure to remove obstructive BPH tissue may occur with open procedures. Other factors, especially unsuspected neurogenic dysfunction, may be identified. In a Health Care Financing Administration–sponsored retrospective review of 2,617 Medicare patients undergoing a prostatectomy for BPH in 1985 (168 open, 2,449 TURP), the probability of reoperation in a 2-year time frame was 1.84% for patients undergoing open prostatectomy and 2.72% for those undergoing TURP (354). To our knowledge, no deleterious, long-term, systemic effects of open prostatectomy have been recognized or proposed on the basis of evidence.

Operative Results of Transurethral Resection of the Prostate and Open Prostatectomy

As recently as 25 years ago, a summary of mortality from BPH and its sequelae indicated surprisingly high rates in many countries. Admittedly, these data represent use of different criteria for assignment of cause of death and variable accuracies in reporting and accounting (310). Nevertheless, the development of adequate diagnostic and therapeutic approaches to BPH has been accepted by urologists and the medical community in general as an important advance in improving both survival and quality of life. Surprisingly, despite the fact that approximately 106,000 prostatectomies are performed yearly in the United States and that this procedure ranks high with regard to compensation by Medicare, reliable objective assessments of the effect of this procedure on prolongation of life and its quality are relatively sparse (153,160,389). During the past 50 years, the operative mortality rate associated with all of the commonly performed surgical procedures used to relieve bladder neck obstruction caused by BPH has declined (132) and continues to do so despite a continuing contraction of the pool of individuals who are denied consideration for these procedures because of the severity or multiplicity of comorbidities.

Recent reports in the United States indicate that the risk of mortality from open prostatectomy is much less than 1.0%, and the risk of death to patients undergoing transurethral prostatectomy is less than 0.01% (240,354,378). This low mortality rate seems remarkable, because a selective survey of patients undergoing transurethral resections in the United States in the 1980s showed that a distinct minority (less than 25%) had no significant concurrent medical problems. In this survey, patients older than 66 years of age had a somewhat increased risk of death (0.33% compared with 0.09%); those older than 80 years and those with resected adenomas weighing more than 45 g had an increase in postoperative complications (240). The published results of a multi-institutional retrospective evaluation of 3,885 patients undergoing transurethral resection indicated a postoperative death rate of 0.23% within a 30-day postoperative period or during the postoperative hospital stay, whichever

was longer (240). The common causes of death were sepsis and myocardial infarction. More recent studies report an operative mortality rate of 0% (378). This progressive drop was achieved despite the fact that TURP patients are prone to multiple medical problems. Information from the Medicare claims data suggests that the TURP mortality rate is age dependent, ranging from 0.01% at age 65 to 6.2% at age 85 (20). Roos and Ramsey (306) reported that the mortality rate from prostatectomy is more than double that usually reported if the observations include the 90-day period after operation rather than simply the time from operation until hospital discharge. Roos and colleagues (307) reported that review of data from substantial centralized data banks in the United Kingdom, Denmark, and the province of Manitoba in Canada revealed an increased death rate within a 5-year period in patients subjected to transurethral resection as compared with those subjected to open prostatectomy. The excess risk seemed to be related to death caused by myocardial infarction. The role of patient selection in this outcome, a highly probable explanation in the view of most urologists, could not be confirmed with the data available to the authors. Subsequent efforts attempting to compensate for comorbidity have yielded conflicting results. Malenka and colleagues (222) reported no evidence that comorbidity played a role in the 5-year mortality rate of patients subjected to TURP as compared with those subjected to open prostatectomy in a retrospective chart review of individuals operated at the Manitoba Health Center, Winnipeg, Canada, from 1974 to 1980. Open prostatectomy was the chosen procedure in about one-fourth of these patients. An evaluation based on record reviews of 1,617 Medicare patients operated in 1985 in seven geographically separated states failed to confirm an increased risk of death independent of comorbidity within the 2-year follow-up period in the 93% of patients undergoing TURP (354). In a related study of the incidence of acute myocardial infarction and cause - specific mortality after TURP and transurethral microwave thermotherapy (TUMT), investigators identified a higher number of myocardial infarctions than expected in the general population (145). The incidence of myocardial infarction following TUMT was slightly higher than after TURP. This phenomenon was judged to reflect an association of prostate enlargement and BPH voiding dysfunction with cardiovascular disease rather than being linked to either procedure. We agree with the BPH guidelines assessment (230) as well as others (327) and judge that the data supporting an independent role of TURP in delayed postoperative mortality is unconvincing at this time.

Prostatectomy by any route is a significant surgical undertaking that attempts to achieve a satisfactory functional and symptomatic status in a complex multifunctional system. Mebust and colleagues (240) cited an 18% incidence of complications in the immediate postoperative period after transurethral resection, including bleeding requiring transfusion, clot retention, and infection. Although Roos and Ramsey (306) reported that only 65% of the patients had no surgery-related problems within 2 years after prostatectomy, this figure seems likely to represent an overstatement of true complications because it includes, for example, patients who had a single urethral sounding postoperatively. Our estimate of the nonlethal, postsurgical complication rates after prostatectomy of 15% to 20% (132) compares to the mean incidence of surgical complications regardless of severity of 21% for open prostatectomy, 12% for TUIP, and 15% for TURP reported in the BPH guidelines (230). Not surprisingly, undesirable results occur because of inappropriate patient selection, unrecognized preexisting and imminent pathologic changes, and technical errors. Of the undesirable results, the inability to void and the development of incontinence are thought to be the most disturbing.

In the cooperative evaluation of transurethral resection, 6.5% of patients were unable to void when the catheter was removed, and 2.4% were sent home with an indwelling catheter; more than half of the latter had atonic bladders (240). Seaman and colleagues (324) documented impaired detrusor contractility in 25% of 129 symptomatic men undergoing delayed postprostatectomy urodynamic evaluation. This perplexing voiding dysfunction may result from chronic severe obstruction and may be at least partially reversible with long-term catheter drainage. We frequently use suprapubic catheter drainage in this group, often as a planned approach, to permit achievement of satisfactory symptomatic and objective voiding status.

Center studies report a low incidence of incontinence ranging from 0% to 1.4% for both open and endoscopic procedures (161,269). However, a prospective study of patients subjected to prostatectomy by urologists in the state of Maine reported that 4% had a problem with dripping or wet pants persisting for 1 year after operation (99). This study also reported a 15% incidence of one or more episodes of acute retention caused by blood clots within 3 months of surgery. The BPH guideline studies (230) indicate a median incidence of stress incontinence of 1.9% after open prostatectomy, 1.75% after TUIP, and 2.1% after TURP. The median incidence of total incontinence was 0.5%, 0.1%, and 1.0%, respectively.

With regard to sexual function, retrograde ejaculation is an anticipated phenomenon whose incidence has been reported to vary from 30% to 100% (42,242). A mean probability of retrograde ejaculation of 24.9% for TUIP, 73.4% for TURP, and 77.2% for open prostatectomy reported in the BPH clinical practice guidelines (230) supports the importance of surgical approach and technique in the occurrence of this phenomenon. In general, this postoperative sequela does not constitute a disabling problem for the elderly patient adequately prepared for its eventuality. In contrast to incidence of postoperative retrograde ejaculation, most men who are sexually active and have a willing sexual partner preoperatively maintain satisfactory erectile function after prostatic surgery. Finkle and

Prian (94) reported potency rates of 95%, 87%, and 71% after transurethral, suprapubic, and perineal prostatectomies, respectively. Fowler and associates (99) reported that 5% of the patients in their survey indicated a persistent inability to achieve erections after transurethral resection. TUIP is associated with a 12% and TURP a 14% incidence of postoperative erectile dysfunction.

Current data indicate that previous estimates of re-treatment rates after surgical therapy of BPH have probably represented an underestimate. Taylor and Krakauer (354) cited a 2.7% probability of repeat prostatectomy within 2 years of TURP and a 1.8% probability within 2 years of an open prostatectomy. Many, if not most, of these repeated procedures resulted from technical errors. Others may represent unrecognized diagnostic errors. Roos and Ramsey (306) assessed the reoperative rate to be 17% for transurethral resection, 5% for suprapubic procedures, and 7% for retropubic procedures in an 8-year data accumulation based on Manitoba claims information. Data from Denmark and the United Kingdom (307) indicated a 12% reoperation rate, and data from Wisconsin showed a 16% reoperation rate (263) after transurethral resection in 8- and 7-year operation periods, respectively. The open prostatectomy reoperation rates at 8 years were 5% for Denmark and 2% for the United Kingdom (307). The estimated reoperation rate at 5 years cited in the BPH guidelines is 2% for open prostatectomy, 9% for TUIP, and 10% for TURP. These re-treatment rates include treatment of complications of the surgical procedure and removal of residual or recurrent BPH.

The previously mentioned mortality and morbidity data should not detract from the fact that most, approximately 90%, of all men subjected to prostatectomy for the treatment of BPH demonstrably benefit from the procedure (286,334). A variety of approaches to assess the results achieved by prostatectomy have been advocated and used, including subjective evaluation by the patient and objective assessments based on symptom scores, urodynamic evaluation, or both. Each has its advantages and disadvantages. The varying indications for surgical intervention complicate the evaluation when rigid criteria are used, as does the knowledge that approximately 45% and 40% of patients treated with placebo or watchful waiting report overall symptomatic improvement (230). The percentage of patients who judge their voiding symptoms to be better or much better after surgery varies from 75% to 93%, in part depending on the severity of the patient's initial symptoms and the duration of the follow-up (41,99,203). The BPH guidelines (230) review indicates an overall symptomatic improvement of 98% (90% CI 94% to 99.8%) for open prostatectomy, 88% (90% CI 75% to 96%) for TURP, and 80% (90% CI 78% to 83%) for TUIP. The guidelines data review indicates that the surgical procedures produced about an 80% improvement in symptom scores, appreciably higher than the 30% to 40% range for placebo and nonsurgical therapies. A multicenter randomized trial conducted at VA hospitals compared transurethral surgery with watchful waiting in a group of men classified as having moderate symptoms (378). Transurethral resection was significantly more effective than watchful waiting in improving genitourinary symptoms and avoiding treatment failure. The men who were substantially bothered by urinary problems had a 91% (134 of 148) chance of improvement as compared with 62% (45 of 73) for those with less bother. Complications and re-treatment rates were low. Nielsen and colleagues (263) provided some evidence that the improved symptomatology is maintained in most patients for more than 7 years. In every series, some patients' symptoms are unaffected by the prostatectomy, and some (3% to 12%) are worse. Although many have cautioned that patients with irritative as opposed to obstructive symptoms are at greater risk for poor results (175,203), an evaluation by Jorgensen and colleagues (175) failed to confirm this finding. Clearly, careful evaluation and selection are indicated in patients with predominantly irritative symptoms and may have accounted for the good results (90%) reported in this latter group of patients.

Postprostatectomy urodynamic evaluation usually demonstrates a marked shift in the various urodynamic parameters, including an increase in maximum urine flow rate and voided volume and a decrease in residual urine and voiding pressure that would be anticipated if a mechanical or functional outlet obstruction were diminished or relieved (3,203,263). The mean improvement in maximum flow rates in the BPH guidelines review was 14.4 mL per second after open prostatectomy and 9.8 mL per second after TURP, far greater than any other treatment analyzed except TUIP (approximately 7.3 mL per second). Current assessments tend to interpret the initial and posttreatment postvoid residual determinations with uncertainty and caution. Voiding is usually almost complete in normal individuals, and failure to approximate this normal state with treatment should be documented. Even with the casual way in which the data analyzed were accumulated, the mean posttreatment postvoid residual was less than 25 mL for TURP and open prostatectomy in the BPH guideline literature review (230). Reversal of some of the preoperative urodynamic abnormalities is much less predictable (Table 32.7). Furthermore, normalization or marked improvement of the preoperative urodynamic abnormalities does not necessarily correlate with a satisfactory clinical outcome. The role of urodynamic evaluation in the routine selection and monitoring of patients subjected to prostatectomy is not clearly established (79). However, use of these procedures as a part of preoperative assessment of patients with a symptom complex of equivocal etiology or with a postsurgical result that is less than expected or optimal is gaining increasing acceptance. The selective inclusion of synchronous video pressure-flow cystometry promises to enhance the useful information derived from these studies (324).

Preoperative Cystometric Diagnosis	Postoperative Cystometric Diagnosis (% of Patients)		
	Normal (70%)	Hypersensitive (7%)	Unstable (23%)
Normal (28%)	23	1	4
Hypersensitive (16%)	12	4	0
Unstable (56%)	35	2	19

From Abrams PH. Urodynamic results of surgery. In: Hinman F Jr, ed. *Benign prostatic hypertrophy.* New York: Springer-Verlag, 1983:948, with permission.

TABLE 32.7. COMPARISON OF PREOPERATIVE CYSTOMETROGRAMS IN PATIENTS FOLLOWING PROSTATIC SURGERY

ALTERNATIVE PHYSICAL INTERVENTION APPROACHES

In the past decade, the number of procedures that use new devices and technology, yet are based on old concepts of mechanical disruption or tissue destruction, to modify or eliminate bladder neck obstruction has proliferated. These efforts are not inappropriate. Past experiences indicate that technical improvements and refined understanding have resurrected useful therapeutic alternatives from essentially discarded approaches for a number of medical problems. Enthusiastic reassessment of procedures that may reduce local and overall morbidity and maintain or improve immediate and long-term physiologic results is understandable and laudable. Currently, assessment of these various efforts is hampered by the limited number of patients subjected to evolving selection and technical approaches and the limited period and, at times, the nature of the follow-up information provided. Most of these treatment efforts, including laser and microwave techniques, use heat effects to alter or destroy prostatic tissue.

Heat-induced Tissue Alterations/ Destruction Procedures

Use of local heat to attempt to reduce tissue mass or produce functional change to improve objective and symptomatic effects of obstruction has been attempted repeatedly by numerous approaches since the beginning of the twentieth century. Efforts with hot water administered by irrigation through the rectum or urethra, and a wide range of attempts using electrical current with high-frequency faradic or galvanic stimulation administered via the urethra, rectum, or perineum, have been reported (80). Edwards (80) also cites the rectal thermoprobe heated to 108° to 122°F used by Corbus and O'Conor in the late 1920s and the localized high-frequency current applied directly by transurethral application for short periods of time by Kerwin in the 1930s. Historically, the problems with therapeutic attempts using heat were related to ineffectual, inadequate, or uncontrolled heating of the targeted site and inadvertent heat damage of adjacent tissue.

Three novel basic approaches are currently being used to generate intraprostatic tissue heat and consequent tissue destruction. One uses laser energy, a second, microwave energy, and a third, ultrasound energy. All of these approaches use a source that has the potential to produce quantifiable amounts of transportable energy that can be directed regionally or focused and can be converted with reasonable predictability to regionally confined heat. None yields tissue for analysis. Removal of the heat-damaged tissue usually relies on active participation of biologic phenomena. Transiently increased tissue volume or dysfunctional states frequently require posttreatment catheterization, at times for prolonged intervals.

Microwave Treatment of Prostate Disease

Electromagnetic waves have the potential to penetrate tissue and induce local changes that produce heat. These microwaves are transverse electromagnetic waves with frequency in the range of 30 to 3,000 MHz. The physical properties governing clinical treatment depend on wave propagation that is reflected or scattered in a tissue at interfaces where two substances with different impedence occur. This raises the temperature of the tissues. Those treatments that achieve temperatures of less than 44°C are termed *hyperthermia,* those achieving a temperature of more than 44.5°C are termed *thermotherapy,* and those achieving a temperature above 65°C are termed *thermoablative* (283). To destroy prostate tissue, microwave treatment must deliver a crucial *thermal dose,* defined as a multiplicative product of exposure temperature and duration of exposure. The energy applied by the system is not a predictor of the thermal dose. The critical values are the temperature achieved within the gland and the period for which that temperature is maintained. The amount of energy deposited within a given tissue depends on the size, shape, and electrical properties of the tissue being treated, the frequency and intensity of the microwaves being used, and the size and shape of the microwave antenna. Antenna design can be crucial in the efficient transfer of microwave energy into the prostate as heat. The dipole antenna found on certain microwave devices is designed to exhibit impedence matching with the target tissue. Monopole designs found in other devices (Prostatron) have been found by experimental observation to lack the capability for impedence matching. Differences in impedence matching affect efficacy and translate into higher delivered thermal doses and ultimately greater clinical benefit. Temperature mapping studies have shown that the treatment area within the prostate is not symmetric and that the temperature within the prostate during treatment may be different in different areas of the gland and even at the

same distance from the catheter. Current evidence indicates that substantial intraprostatic temperature elevations are required for thermal ablation and necrosis and optimal clinical outcome. The variation in intraprostatic temperature during treatment results in varying amounts of coagulation because BPH tissues require at least 30 minutes at temperatures greater than 45°C.

Transurethral therapy has been used for both hyperthermia and thermotherapy. However, the need for repeated treatments requiring urethral catheterization has resulted in loss of interest in the use of hyperthermia by this route. The objective of TUMT is thermoablation or thermotherapy to induce necrosis of the obstructive prostatic tissue while maintaining normal temperatures in nontargeted tissues. Significant differences exist between microwave treatment systems. Differences pertaining to the antenna design, the heating pattern generated, and the treatment protocol should be carefully considered when choosing microwave treatment for patients. TUMT was pioneered using the Prostatron (Technomed, France) microwave system, and this system has been extensively investigated. A more recent modification of this system, the so-called high-energy TUMT (HE-TUMT) Prostatron treatment protocol (Prostosoft, version 2.5), has been introduced to enhance treatment efficacy. The more recently developed Targis microwave system (Urologix, Minnesota) has also been the subject of investigations. Less investigated clinical trials include the Microthermer (Laser Electro-optics, London, UK), Prostalund (Lund Instruments, Lund, Sweden), Urowave (Dornier, Germany), Prostcare (Wissenborg, France), and Thermex-II (Direx, Israel).

The Prostatron and Targis devices can generate intraprostatic temperatures of 45° to 70°C. In the current nomenclature, HE-TUMT has become synonymous with the application of these higher thermal doses. In this context, the HE-TUMT has been applied both to the updated Prostatron 2.5 software treatment and to the use of the Targis system by either standard or abbreviated protocols. For optimal results, the thermal dose should be confined to the prostate gland with minimal heating of nontarget tissues such as the rectum, bladder neck, and sphincter. Hitting nontarget tissues increases the risk of complications, limits treatment efficacy by inducing automatic power shutdowns, and reduces the patient's ability to tolerate the treatment. Nontarget heating also necessitates the use of significant anesthesia, reducing the appeal of the outpatient procedure. Both devices use cooling channels on the urethral catheter to preserve the urethral mucosa in an attempt to reduce discomfort and promote a faster recovery.

Patient selection is crucial when considering TUMT. Patient factors such as prostate volume, prostate gland configuration, and willingness to undergo a urethral treatment under local anesthesia must be addressed. Prostates with marked middle lobe configurations may distort the urethral catheter positioning, making for irregular prostate heating. In addition, prostate volume and size at the extremes (less than 25 g or greater than 100 g) may preclude effective heating; thus size constraints should be addressed before beginning treatment. Urethral strictures may confuse evaluation of BPH voiding dysfunction and interfere with proper catheter placement. Such obstructions should be ruled out before treatment. Patients with pacemakers, defibrillators, and pelvic and penile prostheses should not be treated with such devices because of significant mechanical or electronic damage to the devices.

The potential advantages of the microwave technique include the relief of lower urinary tract symptoms with an in-office procedure using minimal anesthesia and a potentially rapid recovery. Because the Prostatron device has a longer period of evaluation, many of the long-term studies of microwave treatment and the associated failures involve this device. Many of the more current devices and software programs have not been available for long enough to be critically evaluated with long-term follow-up. Consequently, this limitation does not necessarily reflect a difference in clinical outcome between devices.

A recent prospective sham-controlled study addressing HE-TUMT in BPH revealed that active treatment resulted in a significant and marked decrease in AUA symptom score from a mean of 20.8 to 10.5 while the sham group also decreased but to a lesser extent (21.3 to 14.3) (195). Peak urinary flow rate in the microwave group increased 51% at 6 months; this postprocedural increase was significantly greater in the microwave than in the sham group. Similarly, quality-of-life score also improved in the active arm. Although follow-up was short (at 6 months), this study demonstrated effective treatment for BPH with an impact on important outcome measures. Of more concern is the durability of improved response in patients undergoing TUMT. Using an HE-TUMT device (Targis), one group of investigators has demonstrated significant improvement in symptom score, quality-of-life score, maximum flow rate, postvoid residual, and decreased mean detrusor opening pressure that was durable at 24 months (356). One provacative study using an older software version (Prostatron 2.0) demonstrated initial significant improvement in patients' level of satisfaction with treatment (146). However, over a 4-year period there was a marked decrease in the number of satisfied patients from 62% at 1 year to 23% at 4 years. The initial decrease in symptoms and increase in flow rates was followed by reversal at the 4-year follow-up. Of concern, two-thirds of patients received supplementary BPH treatment within the 4-year time period. The cumulative risk of subsequent TURP re-treatment of 40.5% at 5 years of follow-up, and a percent cumulative risk of any re-treatment (including α-adrenergic blockers) of 57% (182), added to this concern. In summary, this minimally invasive therapy appears to balance efficacy versus tolerability, and this balance might be tenuous for patients in the long term.

In comparing HE-TUMT versus α-adrenergic blocker treatment in patients with BPH voiding dysfunction, α-adrenergic blockers afford a more rapid improvement in symptoms, voiding function, and quality of life. When compared with HE-TUMT–treated patients, this advantage is present for a relatively brief 6 weeks because HE-TUMT offers a superior clinical outcome after the recovery phase is complete (6 to 12 weeks) (75). Other investigators have identified neoadjuvant and adjuvant α-adrenergic blocker treatment resulting in significantly better early symptom reduction after TUMT, suggesting that post-TUMT complications can be reduced by using α-adrenergic blockers in the immediate post-TUMT period (76).

Currently reliable pretreatment identification of patient characteristics that consistently predict a successful outcome to TUMT is not possible. In one controlled study, the proportion of patients achieving AUA symptom scores less than 9 was similar among patients with initially moderate symptoms versus those with severe symptoms (195). Surprisingly, no significant correlation has emerged between pretreatment prostate volume and TUMT outcomes. However, our experience has been that patients with a prostate volume at the extremes (less than 25 g or greater than 100 g) are less likely to be successfully treated with TUMT therapy.

Complications reported for TUMT cite an overall rate of 38%, including 3% with acute incontinence, 13% with infection, and 11% with urinary retention of a mean duration of 17.5 days (291). One study demonstrated posttreatment convalesce as being relatively rapid, with 55% of patients with less than 3 days at home and a mean of 5 days at home (291). This suggests in some patients relatively early return to full activity. Pain management has been addressed in several prospective studies, with approximately 70% of patients describing discomfort with HE-TUMT and only 30% describing treatment-associated moderate or severe pain. These observations appear to substantiate claims of minimal anesthesia for this technique.

In general, such minimally invasive techniques may strike a precarious balance between patient tolerability and efficacy. The long-term results of this compromise are not yet clear. It should be stressed when considering these types of therapies that the most cost-inefficient treatments of a disease are serial treatments in which patients are run through a gamut of therapies such as α-adrenergic blockers or minimally invasive techniques before more standard prostatic surgery is performed. The old surgical advice of “doing the last operation first” may well apply to many such minimally invasive treatments.

Laser Prostatectomy

The rationale, technical considerations, and results of the use of the laser to reduce prostatic mass are presented in detail in Chapter 6 . Tissue destruction by the laser relies on conversion of light energy to heat. Although laser energy can be delivered through narrow-diameter fibers that can be accommodated in small endoscopes, appropriate direction of the energy and controlling and judging the depth of its penetration have presented continuing challenges.

Because of the potential appeal of an ambulatory prostatectomy procedure and the increased availability of lasers in the operating room, many methods for performing a so-called laser prostatectomy using a variety of laser sources, wavelengths, and beam delivery systems to achieve combinations of coagulation necrosis, tissue vaporization, and cutting have been developed. Although variations in technique and delivery are marked, commonalties of all laser prostatectomies depend on prostate tissue heating by absorption of the laser energy and its conversion into thermal energy. The volume of tissue that heats beyond coagulation temperature (60°C) during these laser prostatectomies is dependent on laser variables (irradiation time and power), delivery fiber variables (diameter, beam angle, divergence, power intensity), tissue variables (carbonization, tissue absorption, and light scatter), and surgical variables such as the distance of the fiber to the tissue and the number of lasings. The Nd:YAG laser has been used for coagulation prostatectomy [visual laser ablation prostatectomy (VLAP)] since the 1990s with a goal of creating zones of coagulation to eventually result in a decrease in prostate outflow obstruction. This technique, although popular with patients and physicians, has been largely supplanted by contact lasers using a variety of techniques but sharing in the attempt to duplicate prostate nucleation akin to a TURP. This newer technique requires tissue vaporization using either the Nd:YAG laser at a high power density or a holmium:yttrium-aluminum-garnet (Ho:YAG) laser. Variable techniques employed use tissue vaporization to enlarge the prostatic urethral cavity and remove prostatic tissue. The pulsed Ho:YAG laser offers an additional thermomechanical vaporization and is used as a cutting tool analogous to the TURP. These laser techniques offer the advantage of reducing blood loss because the wavelength and pulsed energy delivered creates enough heat below the cut prostate surface to provide hemostasis. Another approach to laser prostatectomy includes the placement of interstitial light guides [interstitial laser coagulation (ILC)] directly into the prostatic adenoma during cystoscopy. This allows the creation of larger coagulation lesions than the free beam laser penetration because laser penetration is possible circumferentially around the diffusing fiber tip. With ILC, intraprostatic temperatures rise as high as 85°C, and they are automatically adjusted by intrinsic temperature probes and computerized feedback mechanisms.

Several investigators have reported on the comparison of standard TURP with contact laser vaporization. Using laser vaporization, the symptom score, quality of life, peak urinary flow rates, and postvoid residuals improve similarly although to a variable degree to those found in patients undergoing TURP (78,183,227). Distinct advantages of the

laser approach include reduced blood loss and less concern with patient coagulation status. These patients may also have higher rates of recatheterization and reoperation. Operating time using the laser increases when compared with TURP (116). Urodynamic results were equivalent at 6 months, and effects on continence, potency, and symptoms are similar between both groups (364). Our experiences with this technique are limited; however, we have found it more cumbersome in the operating room and without distinct advantages to physician, patient, or institution. The effectiveness of the interstitial laser therapy is more controversial. This stems from its hybridization of an intra-operating room procedure combined with a minimally to moderately invasive technique. Whether this combination of characteristics supplants a more standard intraoperative intervention is yet to be determined. In the limited number of publications available concerning this technique, it appears that there are significant improvements in AUA symptom scores, flow rates, and postvoid residuals between baseline and relatively short follow-up periods (9 months) (134). One study demonstrated significant increases in peak flow rates from 8.3 to 12.0 in 9 months and marked decreases in AUA symptom scores from 20.2 to 9.8 during the same interval. Although patient groups tend to be small in these limited reports, intraoperative complications are few. A sizable minority of patients subjected to ILC have prolonged urinary retention requiring intermittent catheterization (9). One study reported significant changes in peak flow rates (having increased by 50% from a preoperative average of 7.4 to 11), postvoid residual urine (decreasing by 57%, 102 to 44), and marked changes in symptom scores. Surprisingly, only 8% of patients required re-treatment for persistent obstructive symptoms during a 12-month follow-up period (9). Side effects include retrograde ejaculation and urinary tract infections with a minimal impact on sexual function. A prolonged postoperative mean catheterization of 13 days is less than ideal. At this point, it is not clear what the exact role of interstitial laser coagulation will be; however, it is likely that improvements in efficiency will continue.

Transurethral Electrovaporization of the Prostate

As stated, laser prostatectomy has perceived advantages over conventional TURP, including a nearly bloodless tissue ablation (even in anticoagulated patients) and, possibly, a more abbreviated hospitalization. It has achieved improvements in parity with TURP, as reported in short-term follow-up studies. However, laser-assisted TURP possesses a number of observed and potential disadvantages that have tempered enthusiasm for this approach. Based on previous experiences, failure to achieve removal of most or all BPH tissue constitutes a significant concern as to the durability of the reported results. In addition, laser machines and fibers are expensive, and their use requires an easily acquired, but nevertheless special, expertise. Transurethral electrovaporization of the prostate (TUVP) was developed by making simple modifications to existing TURP equipment in the hope of maintaining the advantages and minimizing the disadvantages of laser prostatectomy at the tissue level.

The strategic component of TUVP is any one of several modifications of a multigrooved electrode that replaces the traditional loop to achieve tissue vaporization for a 3- to 4-mm zone and coagulation of an underlying 1- to 3-mm zone (Fig 32.40). The electric current is concentrated on the outer edges of the resulting ridges, producing a thermal reaction that raises tissue temperatures to greater than 100°C. Because the procedure is performed under glycine irrigation, the desiccated tissue rehydrates, rendering it susceptible to vaporization on a subsequent pass. If bleeding occurs, a coagulation current of about 60 W is used for local control. In theory, the end result eliminates the targeted obstructing prostatic tissues while minimizing both bleeding and water absorption.

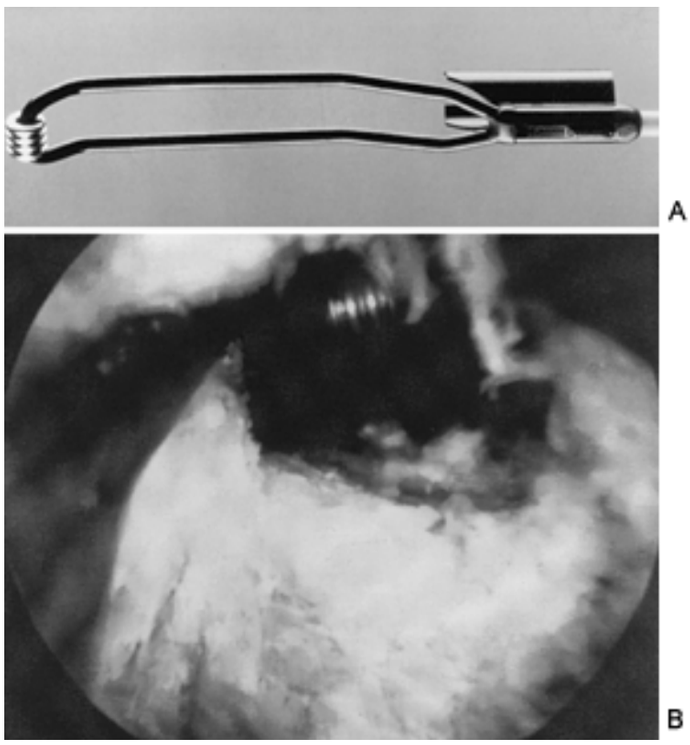

FIGURE 32.40. A: Terminal configuration of Vaportrode electrode. **B:** Tissue effect of TUVP. Too rapid progression of the electrode results in less vaporization and more coagulation. Too slow progression results in vaporization with a greater zone of coagulation, hampering subsequent vaporization. (From Kaplan SA, Te AE. Transurethral electrovaporization of the prostate: a novel method for treating men with benign prostatic hyperplasia. *Urology* 1995;45:566, with permission.)

As described by Kaplan and Te (179), the operative technique is similar to a standard TURP. In general, the middle lobe is vaporized first from the bladder neck to the verumontanum. Overlapping sweeps of the electrode from

1 to 5 o'clock and 11 to 7 o'clock are used to remove the lateral lobes. The surgical goal remains the visualization of the white fibers of the surgical capsule. Desired tissue sampling can be achieved with a standard resectoscope with subsequent resumption of the TUVP. The indwelling catheters are removed within 24 hours. Patients are frequently discharged on the first postoperative day or, increasingly, on the day of the procedure. The reported experiences and personal clinical experiences with TUVP attest to the safety and short-term effectiveness of this technique (106,147,178). As a composite, these studies demonstrate that patients observed for approximately 1 year after undergoing TUVP exhibited a significant improvement in their AUA symptom scores and peak urinary flow rates. None of the patients demonstrated significant changes in hematocrit or serum sodium levels. The procedure has been used successfully in patients on anticoagulation therapy (179). When compared with TURP, TUVP is as effective with regard to changes in symptom scores, postvoid residual urine volumes, and peak urinary flow rates (86). Some investigations report a slight advantage to the standard TURP in the aforementioned outcome parameters, but with significantly longer operative times (178). The incidence of retrograde ejaculation appears to be significantly higher in the TURP group (192). The reported results will require confirmation with additional long-term studies. The reported opportunity to combine visually controlled tissue ablation with increased hemostasis while using familiar, generally available basic equipment to treat BPH voiding dysfunction has significant appeal and apparent promise.

Transurethral Needle Ablation

The transurethral needle ablation (TUNA) procedure uses low-level radiofrequency (RF) energy to coagulate hyperplastic prostate tissue and create zones of heat-induced coagulation necrosis. The RF electrical energy is applied to the tissue by having two electrodes in contact with the patient. The electrode responsible for delivering RF energy and heating the tissue is the “active” electrode with a characteristically small surface area. The second electrode is referred to as the “indifferent,” or return, electrode and is characteristically large in surface area and is applied externally. The indifferent electrode serves to collect the RF current being delivered by the active electrode. Because the indifferent electrode is large in size, RF current is diffuse and therefore no tissue heating occurs. Because the active electrode has a small surface area, RF current is concentrated in the area immediately surrounding the electrode. In the present design, the active role of the electrode is played by two needles, which are deployed at acute angles from the tip of a specifically designed TUNA cystoscope, which is directed strategically into the adenoma. The needle lengths of this active electrode are adjustable to accommodate varying sizes of prostates. During the procedure, the needle temperatures are periodically raised to obtain a temperature of 53°C at the tip of the needle shield, which just barely penetrates the urethral mucosa. Adjacent to the needle tips, temperatures are as high as 100°C. Two centimeters beyond the needle tips, the temperatures approximate normal body temperatures. The high temperatures induce tissue desiccation and coagulative necrosis, which is reabsorbed over several months, causing cavitation that ultimately is filled in by expansion of the surrounding tissue. It is said that patients have a mild sensation of dysuria while the procedure is ongoing, but a significant number supposedly tolerate the procedure under local if not vocal anesthesia. Short-term results of the TUNA procedure to treat symptomatic BPH have been moderately encouraging. In a prospective randomized 1-year clinical trial comparing TUNA versus TURP, both TUNA and TURP resulted in statistically significant improvement in AUA symptom scores, bother, and quality of life (40). Peak flow rates and postvoid residuals were also improved. TUNA had less effect on sexual function, with TURP being associated with a greater incidence of retrograde ejaculation. However, TURP had a statistically significant, greater improvement in AUA symptom scores and peak urinary flow rates than TUNA. This suggests that both procedures are efficacious, but TURP may be more so. Side effects of TUNA include inability to tolerate the procedure, irritative voiding symptoms that can last up to 3 weeks, urinary retention greater than 1 week, hematuria, retrograde ejaculation, and urinary tract infection. Our group has chosen not to use this device as a minimally invasive alternative. Its long-term acceptability will depend on the durability of the results and its comparison with other minimally invasive techniques (318).

High-intensity Focused Ultrasound

Exploration of the use of high-intensity focused ultrasound (HIFU) to achieve selective tissue ablation is in its infancy in clinical medicine. As ultrasound waves propagate through a tissue, they are progressively absorbed and the energy is converted to heat. Therapeutic systems generating clinically significant heat with ultrasound are being developed. With use of these systems, a beam of high-intensity ultrasound is brought to a tight focus at a specific location within the prostate to produce a dense area of thermal energy that can selectively destroy tissue without damage to the surrounding structures. Ultrasonic energy can be focused in a small volume of tissue with the local production of temperatures of 80° to 90°C. The resulting coagulation necrosis achieves a reasonably predictable reduction in tissue volume in targeted tissues (28). Development of a transducer combining the potential for visualization and high-power ablation in the same element was made possible by the use of piezoelectric ceramics. The delivery probe covered with a condom is inserted transrectally. When the ultrasound energy is focused on the prostate, the temperature rises to

exceedingly high levels, inducing protein denaturation, cell death, and cavitation effect. Because high temperatures are reached rapidly within the prostate, each location is treated for a short period of time; multiple sequential targeting is necessary to treat a larger prostate volume. To achieve positional and target accuracy, the prostate must remain completely immobile throughout the treatment. General or regional anesthesia is usually necessary to ensure this and permit extensive thermometry monitoring. Consequently, designation of HIFU as a minimally invasive technique may be questioned. Initial clinical experiences in patients with BPH have been reported. A marked increase (4.8 to 18.2 ng/mL) in serum PSA at 48 hours has been noted. In one study, cystoscopic evaluation at 6 weeks varied from no discernible change to an evident necrotic channel transurethral defect (28). In this group of patients, the AUA symptom score at 3 months decreased by 10 or more in 13 of 15 patients; the average flow rate improved in 13 patients but increased 3 mL per second or more in only 8; and mean residual urine decreased from 154 to 123 mL, with 6 patients showing stable or increased residual urine. In another study consisting of 36 patients, comparable changes were noted (219). At 6 months, the average AUA symptom score of 25 decreased to 13 in these patients. The maximum flow rate increased from 9.0 to 13.4 mL per second, and mean postvoid residual urine decreased from 128 to 57 mL. More recently, Uchida and colleagues (365) reported a preliminary study of patients with BPH; they demonstrated significant changes in AUA symptom scores (20.6 to 11.7), increases in flow rate (8.9 to 15 mL per second), and reduction in total prostate volume (32.2 to 22.8 g). There was a significant urinary retention rate (64%) that required an average of 5 days of catheterization. More disappointing, TURP was performed within 3 years in 31% of these patients, suggesting the early state of development of this technique. Focused ultrasound has a potential advantage of producing very exact and localized tissue-destructive lesions without direct invasion of the lower urinary tract and is an approach that seems to deserve further effort and consideration.

Balloon Dilation

Mechanical dilation of the bladder neck and prostatic urethra has been used in the past to attempt to treat bladder neck obstruction from BPH. It has been undergoing a reassessment with pressured balloon dilation to arbitrarily selected diameters. The recent success of balloon dilation of diseased blood vessels and strictures of the biliary and urinary systems led to a reassessment of the possibility that balloon dilation of the prostatic urethra may result in relief of bladder neck obstruction. Because of the lack of significant clinical effect and high re-treatment rates at relatively short intervals, enthusiasm for this technique has deflated.

At this time, the local anatomic and physiologic goals of balloon dilation are not clearly identified. Disruption of the integrity of the anterior commissure, reduced functional tissue mass, and possible local nerve damage have all been observed or postulated. However, a predominant procedural requirement for successful relief of BPH voiding dysfunction has not been defined. As a consequence of this, procedure-related predictors of successful accomplishment of this goal are lacking. Clearly, some patients void with decreased symptoms and improved objective urodynamic parameters after balloon dilation of the prostate or bladder neck. The mechanism and durability of the improvement have not been clearly identified.

Recently, a procedure combining balloon distention with transurethral water-induced thermotherapy was reported (253a). In this technique, an 18-Fr catheter with a positioning balloon is placed such that the in-series 50-Fr treatment balloon occupies the entire prostatic urethra. Heated water maintained at 60°C is circulated for 45 minutes. Although there was no control group for comparison, the majority of the 125 patients treated had significant changes in their symptom scores and peak urinary flow rates that were durable for 1 year. How this technique compares to other minimally invasive techniques is not known, but it appears to require lengthy periods of catheterization after treatment and a slower symptom improvement time frame. Further investigations using a control group are warranted.

PERSPECTIVES

Part of "32 - BENIGN PROSTATIC HYPERPLASIA "

In this chapter, we attempted to summarize the current status of our understanding of various aspects of growth, development, and pathophysiologic effects of BPH and what can be done about them. We are impressed by the effort reflected in the number of studies of these phenomena, but our enthusiasm for the new information being put on our table is limited. We still do not know why BPH develops universally or why it grows selectively in the androgen-diminished environment of the aging male. Investigative efforts to add insights into these questions are disappointingly limited. Attempts to improve clinical evaluation to identify, understand, and characterize the changes in the urinary tract associated with and resulting from BPH seem at times targeted at the easy to do, measure, or calculate. We continue to think that evaluation of the ability of the bladder to empty and visualization of the configuration of BPH and the changes it may cause in the bladder are important both to help confirm the impression that a patient's voiding dysfunction is probably caused by BPH and to guide treatment efforts. However, we often seem to relegate this information to a secondary role and then fail to document the effect of the various treatment efforts on the diagnostically discriminatory abnormalities we identify. For example, if an enlarged BPH mass that is postulated to be the cause of voiding dysfunction is treated by drugs or physical means such as surgical excision or direct or indirect heat ablation, how often is a decrease in prostatic mass documented? At least with excision, the amount of tissue

removed can be determined and reported. Residual prostatic mass can be assessed after treatment using imaging studies, but this seems to be done, or at least reported, infrequently. Similarly, if a postvoid residual urine is determined to provide evidence of BPH effect on voiding, its posttreatment status should be evaluated and determined. Reports of the effects of various treatment approaches including drugs should contain an appropriate spectrum of physical and physiologic observations, as well as symptomatic status. The concept of an intrinsic functional component to BPH bladder outlet obstruction, whether by internal prostatic or bladder neck constriction or by external prostatic capsular constriction, seems reasonable, but convincing direct evidence of its role is not. The possibility that a behaviorally induced and modifiable functional abnormality can produce significant symptoms and pathophysiologic effects in the lower urinary tract is adequately confirmed in children and, based on data from the control groups participating in drug treatment trials, seems likely to occur in adults. Objective evidence must be presented to correlate symptomatic, physiologic, and anatomic changes after, as well as before, therapeutic efforts.

At this point, we have an escalating number of alternative procedures that attempt to reduce BPH mass in patients with presumed BPH voiding dysfunction. In general, these constitute new approaches to achieve historical aims, namely, appropriate tissue removal and destruction. The procedures have varying advantages and disadvantages that center on the necessity to use anesthesia, risks of adjacent tissue damage or bleeding, use or duration of urethral catheter drainage, rapidity of systemic and local recovery, availability of tissue for histologic study, and durability of effects achieved. To evaluate the effect of these on BPH voiding dysfunction and BPH, we need to accumulate objective evidence of what we have done to the BPH tissue, the effect of this on objective and subjective voiding parameters during and after healing, and longer-term effects on prostatic mass and voiding. This information is necessary if we are going to identify appropriate management alternatives for patients with BPH and voiding dysfunction. Our challenge is to maintain our commitment to identify and do what is best for our patients while being open to new, better ways to do it and especially to new concepts of disease or treatment.

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33
CARCINOMA OF THE PROSTATE

James M. Kozlowski

John T. Grayhack

J.M. Kozlowski: *Associate Professor of Urology and Surgery; Vice Chair, Department of Urology; Chief, Section of Urologic Oncology, Northwestern University Medical School, Chicago, IL 60611.*

J.T. Grayhack: *Professor, Department of Urology, Northwestern University Medical School, Chicago, IL 60611.*

Contents

Adenocarcinoma of the prostate (CaP) is a major factor in the health of the male population in the United States and many other countries in the Western hemisphere. It is the most commonly diagnosed cancer among American males and constitutes the second most common cause of male cancer death (386). Projected estimates for the year 2000 from the American Cancer Society (ACS) suggest that CaP will account for approximately 29% (180,400 cases) of newly diagnosed cancers in males. Similarly, CaP will be responsible for 11% (31,900) of all male cancer deaths (386).

CaP remains the most common malignancy in males. Incidental or latent CaP has been detected in approximately 10% to 20% of prostate tissue specimens analyzed following prostatectomy performed because of benign prostatic hyperplasia (BPH) voiding dysfunction (448,604,1110). Unsuspected CaP has been identified in approximately 30% of autopsy specimens in males older than 50 years of age. Its prevalence increases progressively with age, tripling by the ninth decade.

Prostate-specific antigen (PSA), first characterized in 1979 (1071), has been widely used since the late 1980s to identify individuals with increased risk of CaP. As a consequence, the incidence of CaP in the United States increased significantly in a manner consistent with the pattern anticipated following introduction of a sensitive screening test. Concomitantly, the mean age at diagnosis of CaP was lowered from 70.7 to 68.8 years (650). Furthermore, many cancer registries have reported a distinctive “stage shift” with a trend toward diagnosis at an earlier stage of disease than would be predicted by early cohort studies. Accruing evidence suggests PSA and related testing may be responsible for a reduction in the mortality rate from CaP. Between 1900 and 1995, the CaP death rate in the United States for white men younger than 75 years decreased more than 14% (829). Aside from the pervasive use of PSA testing, no other obvious changes in treatment or diagnosis can logically account for the perceived decline in death rates.

African American men have the highest incidence of and mortality from CaP in the world (21). The differences in the incidence of CaP between white and African Americans are most dramatic in men younger than 65 years; in this age group, whites had a rate of 45.5 per 100,000 compared with 81.5 per 100,000 for African American men (96). Despite the trend toward decreased mortality rates from CaP that have been observed recently, the mortality rate remains greater in African American men than in their White counterparts (668). Specifically, the mortality rate of 55.1 per 100,000 observed in African American men is more than two times that observed in their white counterparts (24.7 per 100,000) (527). This striking difference in incidence and mortality may be due to various factors. For example, African American men have a rate of high-grade prostatic intraepithelial neoplasia (PIN) 50% higher (854), exhibit a greater percentage of high Gleason histotype tumors (769), and present with an advanced pathologic stage more often (646) than white men. However, once adjustments are made for stage and grade at diagnosis, age, number of primary cancers, and initial treatment, there appears to be no difference in the likelihood of CaP mortality between the two races (646). These observations are concordant with those of Eastham and Kattan (491) whose analysis of radical prostatectomy specimens failed to demonstrate significant differences in pathologic stage or grade in white and African American men diagnosed with clinically localized CaP. Furthermore, there was no obvious difference in the rate of biochemical recurrence between the groups, despite the fact that African American men presented with higher pretreatment serum PSA levels (8.0 versus 6.1 ng/mL) and higher PSA densities. The latter two studies suggest that black men presenting with clinically localized CaP in an equal access setting have similar cure

rates following radical prostatectomy. Cultural issues that may contribute to a delay in diagnosis in African American men include inadequate access to health care, a decreased knowledge of the disease, economic issues, concern regarding treatment-related complications, and an inherent distrust of a predominantly white medical establishment (48). The postulated genetic and epigenetic factors that influence the biology of CaP in African American men are discussed in the next section.

Although efforts to identify causal mechanisms in the development and progression of CaP are being pursued vigorously, the etiology of this malignancy remains elusive. The use of molecular methodology to study CaP biologically has resulted in the identification of numerous adverse tumor cell properties that typify biologically aggressive tumors and distinguish them from more indolent neoplasms. To date, none of these exciting observations have become mainstream components of established diagnostic and therapeutic (598) clinical pathways. Techniques to identify the presence of the cancer remain relatively gross and inexact. Although radical prostatectomy offers a patient with locally contained disease an excellent opportunity for cure, the procedure is a major surgical undertaking. Furthermore, many patients with advanced disease may not be amenable to such an approach. No major therapy advances have been forthcoming for the latter group since the observation of Huggins and Hodges regarding the efficacy of androgen ablation (446,447). This assessment must be tempered by the realization that intense clinical effort has added to our diagnostic and surgical skills and that sophisticated scientific approaches are beginning to yield significant insights into the genetic and biochemical nuances of CaP. This chapter presents an overview of this challenging disease.

ETIOLOGY

Part of "33 - CARCINOMA OF THE PROSTATE "

Advancing age is the strongest risk factor for the development of CaP. By the ninth decade, CaP is observed in 67% of male cadavers that undergo autopsy and can be identified in tissue from approximately 37% of patients who undergo transurethral prostatectomy (TURP) (968). These findings are consistent with more generic observations regarding the increased frequency of cancer and cancer-related deaths (827) in the geriatric population. Indeed, the median age for all cancer patients in the United States is approximately 70 years. Potential reasons to explain these associations in CaP patients are numerous. First, malignant tumors that occur after menopause (or andropause) tend to develop over many decades. Second CaP is a chronic disease with increasing survival times. Third, a decline in DNA repair mechanisms and a diminution in constitutive regulators of cellular proliferation occur with aging (279). Finally, older men are most likely to manifest evidence of high-grade PIN. Qian and associates (805) demonstrated the volume of high-grade PIN in 195 radical prostatectomy specimens was positively correlated with Gleason score, pathologic stage, and increasing age.

The postpubertal presence of an intact hypothalamic/pituitary/testicular axis is required for the development and progression of CaP. Men castrated before the onset of puberty have little risk of developing CaP (220). The prostate will not develop without androgens and the normal gland will undergo atrophy if androgen support is withdrawn. Furthermore, the majority of CaPs depend on androgens early in their progression and demonstrate regression following androgen ablation (798). Consequently, implicating excessive androgen stimulation as a primary causal factor in prostatic carcinogenesis seems logical. Despite the logic in this supposition, data correlating the development of CaP in men with increased circulating androgen levels are surprisingly contradictory. Some recent studies support this association (331), while others refute it (134,408). An alternative hypothesis suggests that declining androgen levels may play a causative role in prostatic carcinogenesis. This is based on the observation that as individuals age and the risk of CaP rises, the serum androgen levels fall (533). Prehn (798) has proposed that continued selection pressure in an environment of declining androgen levels may induce hyperplastic foci more resistant to atrophy, less dependent on androgens to support their growth, and more susceptible to oncogenic change.

Epidemiologic observations highlight African American and white males with a strong family history of CaP as constituting two cohorts at increased risk of developing CaP and more prone to disease progression. With respect to African American men, genetic factors have been proposed to account for the observed racial differences in CaP incidence, progression, and mortality, including (a) higher circulating sex steroid levels; (b) shorter androgen receptor CAG (glutamine) repeat length, which enhances androgen-mediated inactivation; (c) genetic variability of the SRD5A1 gene encoding the type 1 enzyme of steroid 5α-reductase; and (d) polymorphic variation in the VDBP gene encoding a vitamin D–binding protein (21,668). Various adverse environmental factors also have been proposed, including (a) higher fetal exposure to circulating androgens; (b) a diet higher in animal fat content; (c) diet deficient in the non–provitamin A carotenoid, lycopene; (d) increased calcium intake, suppressing circulating 1,25 $(OH)_2D$, which in turn increases the risk of developing CaP; (e) reduced consumption of fresh fruits and soy products, which provide high concentrations of protective isoflavones (genistein); and (6) decreased consumption of cruciferous vegetables of genus *Brassica* (broccoli), which contain high concentrations of the isothiocyanate, known as *sulforaphane,* which is an inducer of phase II detoxification enzymes, such as quinone reductase and glutathione S-transferase (74,668).

The first report documenting the presence of a dominantly inherited form of CaP emanated from research conducted at Johns Hopkins Hospital (124,125). The

actual proportion of CaP caused by mutations in autosomally dominant susceptibility genes is approximately 5% to 10% (87,125). Hereditary susceptibility is much more common in men with early-onset CaP and may account for up to one-third of cases diagnosed before the age of 60 years (87) and almost half of those in men younger than 55 years (125). The excess risk varies with the closeness and the number of afflicted relatives. Men with a first-degree relative (brother or father) have a twofold risk, and those with a second-degree relative (grandfather or uncle) have a lesser but still increased risk of developing CaP. The presence of the disease in two or three first-degree relatives or a first- and second-degree relative increases the risk of its development almost fivefold, elevenfold, and ninefold, respectively (125). The increased risk is maximized in relatives of men with the onset of clinically recognizable CaP at an early (less than 53 years) age and is minimized in those with a later (older than 65 years) age of onset. Identification of the hereditary prostate cancer gene 1 (HPC1) on chromosome 1q24-25 was the result of a genomewide search with linkage analysis in which this genetic locus was “linked” to approximately one-third of 79 North American and 12 Swedish families studied (927). Linkage to HPC1 is more prevalent in families of early-onset CaP and is more readily demonstrated in kindred families with many affected members (387). More recently, a CaP susceptibility gene, designated HPCX, has been located to the long arm of the X chromosome (Xq27-28). Expression of this gene appears to account for 15% to 16% of the North American and up to 41% of the Finnish hereditary CaP cases analyzed (1111). Two additional CaP susceptibility genes have been putatively identified and located to chromosome 1q42.2-43 (58) and to chromosome 1p36 (356). Apart from families with multiple cases of breast cancer, germ-line mutations in BRCA1 and BRCA2 appear to have a limited role in familial CaP (88,921).

The genetic basis for sporadic CaP remains elusive. The recent observation of hypermethylation of the regulating sequences of the glutathione S-transferase gene (GSTP1) in human CaP, but not in BPH or normal tissues, may constitute an initial significant step to fill this void (563). More recently, a new prostate-specific gene, designated *DD3,* has been shown to be highly overexpressed in CaP tissue in comparison to adjacent nonmalignant prostatic tissue. The DD3 gene has been mapped to chromosome 9q21-22, and its expression appears to be restricted to the prostate (111). The fact that no extensive open reading frame could be identified suggests that DD3 may be another new member of a growing unique class of noncoding RNAs.

NATURAL HISTORY AND EPIDEMIOLOGY

Part of "33 - CARCINOMA OF THE PROSTATE "

The following characteristics of the natural history of CaP have potential or established clinical importance and warrant emphasis: (a) Histologic carcinoma is identifiable at autopsy in some individuals before the age of 40; its prevalence increases progressively with each subsequent decade. (b) The identical prevalence of histologic CaP at autopsy in various populations is not reflected in the prevalence of clinical CaP. (c) CaP develops predominantly in the peripheral or outer prostate; some evidence suggests that the potential for biologically aggressive behavior may vary between neoplasms originating peripherally, as compared with centrally. (d) Histologic and biochemical evidence suggests the presence of a field change in prostates developing carcinoma. (e) The histologic grade correlates with local development of mass, invasion, and dissemination. (f) Intragland and extragland local spread of carcinoma tends to follow natural anatomic planes and conduits. (g) The pelvic lymph nodes and the bones of the axial skeleton are the identifiable sites of the initial dissemination; the mechanism involved in the predilection for these metastatic sites has not been fully elucidated. (h) Evidence of continued dependence upon androgen for maintenance and/or stimulation of some of the cells in the majority of CaPs is substantial. Observations that support and expand some of these statements are discussed briefly in the following paragraphs.

The development of histologic CaP is an age-related phenomenon. It is infrequently recognized before the age of 50 years. Its prevalence is substantial in autopsy studies in the 50- to 60-year-old age groups (29%) and increases progressively with each succeeding decade, approaching a straight-line relationship on a double logarithmic scale (312,313). Of autopsied males, 40% dying in their seventies and 67% dying in their eighties have histologic evidence of this malignancy. Race and geographic areas have little, if any, documented influence on the autopsy prevalence (139). In contrast to histologic carcinoma, the prevalence of clinical CaP varies significantly in different geographic regions and racial groups in a given region. Black males in Nigeria and the United States have a similar age-adjusted prevalence of incidental CaP, but the former have a lower prevalence of invasive CaP (465). The incidence of clinically apparent carcinoma is sixfold greater in American than Nigerian blacks. Similarly, despite the comparable age-adjusted prevalence of CaP in male inhabitants of Japan and the United States, clinical carcinoma shows as much as a twentyfold greater prevalence in males living in the United States, as compared with those living in Japan. In addition, although the incidence of histologic carcinoma of the prostate in an Oriental male living in Japan and a male of Japanese descent living in Hawaii is essentially comparable, the age-adjusted prevalence of clinical carcinoma for the latter is approximately tenfold greater. However, Japanese Hawaiians have a prevalence rate for CaP of only approximately 50% of that of the local white population (895). Compared with white U.S. males, African American men present at a younger age and with a higher stage and grade of disease (574,828). The probability of an American black man being diagnosed with CaP and of dying from CaP is

85% and 114% greater, respectively, than his white fellow countrymen (675). Furthermore, when white males are compared with American Indians, Hispanics, and Orientals, the latter groups are at relatively low risk of dying from prostate cancer (196,315,643). Unquestionably, variable rates of clinical cancer detection, data accumulation, and reporting may skew these results substantially.

Various epigenetic factors have been linked causally with CaP. These include nutritional and endocrine factors, environmental carcinogens, and exposure to infectious agents (532,533). Dietary differences, in particular the Western-type diet rich in saturated fatty acids, have been thought by some investigators to play a potentially important role in the incidence of carcinoma noted in some of the migration studies and high- or low-risk geographic areas cited (68), but others disagree (675). Vitamin D deficiency (endemic to geographic areas with low ultraviolet radiation) also has been implicated (74). Studies of men of Japanese ancestry in Hawaii have suggested that increased consumption of rice and tofu was associated with a decreased risk of CaP and that consumption of seaweed was associated with an increased risk (905). Recently, Blumenfeld and associates (74) provided a thorough and well-balanced review of the nutritional aspects of prostate cancer. Table 33.1 provides a summary of their observations.

Dietary Factor	Relevant Observations	References
Selenium	Essential trace nutrient found in grains and fish; supplements 200 μg/day associated with a 63% reduction in CaP incidence	Clark, 1998
Vitamin D	Inverse relation with incidence and progression of CaP; $1,25(OH)_2D$ inhibits prostate tumors *in vivo* and *in vitro;* vitamin D analogs possess antiproliferative activity in the presence of functional vitamin D receptors	Schwartz, 1997; Skowronski, 1993; DeVos, 1997
Vitamin E	α-Tocopherol supplementation associated with a 41% reduction in mortality from CaP	Heinonen, 1998
Calcium	High serum levels suppress circulating $1,25(OH)_2D$, which increases CaP risk; selective induction of increased intracellular levels may promote apoptosis	Giovannucci, 1998; Tombal, 1995
Carotenoids	Retinol is the active form of vitamin A; α- and β-carotene are metabolic precursors of vitamin A; reduced levels of retinoic acid in CaP; fenretinide possesses antiproliferative activity	Pasquale, 1996; Pienta, 1993
Lycopenes	A major nonprovitamin A carotenoid; potent antioxidant properties; found in tomatoes and tomato products; the only carotenoid associated with decreased CaP risk	Glovannucci, 1995; Clinton, 1995
Soy isoflavones	Phytochemicals with weak estrogenic properties, potent antioxidants; genistein is the most abundant soy isoflavone; inhibit signal transduction and angiogenesis in CaP; suppress the growth of prostate tumors *in vitro* and *in vivo*	Murphy and Wang, 1994; Akiyama, 1987; Onozawa, 1998
Fatty acids	CaP incidence, progression, and mortality strongly linked to increased consumption of animal fat; total energy intake also may be a positive risk factor; high fat intake associated with increased IGF-1 and decreased IGFBP-3 levels	Ross, 1987; Whittemore, 1995; Kakalmani, 1999
Cruciferous vegetables (genus *Brassica*)	Broccoli, brussels sprouts, and cauliflower contain high concentrations of sulforaphane, an isothiocyanate; induces critical detoxification enzymes such as glutathione S-transferase	Fahey,1997; Zhang,1992
Grape juice and red wine	Contain high concentrations of the phytoalexin, resveratrol; possess antioxidant properties; inhibit COX-1 and COX-2; inhibit the growth of androgen-responsive CaP; decrease the expression and function of the androgen receptor	Mitchell, 1999

Note: Studies cited are from original source.
CaP, adenocarcinoma of the prostate; COX, cyclooxygenase; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein.
Adapted from Blumenfeld AJ, et al. Nutritional aspects of prostate cancer: a review. *Can J Urol* 2000; 7(1):927, with permission.

TABLE 33.1. NUTRITIONAL ASPECTS OF PROSTATE CANCER

Reports of high levels of cadmium and decreased levels of zinc in patients with CaP (507) raise the possibility that exposure to cadmium, other heavy metals, and toxins may affect trace elements found in the prostate and contribute to proliferative abnormalities. Some occupations such as rubber and textile workers, printers, painters, mechanics, loggers, ship fitters, porters, janitors, farmers, and ship receiving clerks have been reported to be associated with a higher risk for CaP (1097,1098).

A very tenuous association exists between the acquisition of sexually transmitted infections and CaP. Sexual hyperactivity or promiscuity as well as antecedent bouts of gonococcal urethritis or other venereally transmitted diseases have been targeted as significant risk factors (886,972). Consistent statistically significant data to support these contentions have not been presented, however. Current evidence would suggest that human papillomaviruses (HPVs), at least HPV types 16 and 18, are not associated with the prostate carcinogenesis (252). Recent data suggest that vasectomy is associated with increased risk of prostate cancer (359). The assessment of the evidence supporting this association led to a statement by the World Health Organization indicating that any causal relationship between vasectomy and the risk of CaP is unlikely. The caveat that further investigation of this possibility is warranted seems appropriate (432).

In summary, current evidence indicates that development of histologic CaP is an age-related phenomenon in males that is not clearly influenced by race; heredity; geographic location; or identifiable environmental, social, physiologic, or disease-related phenomena. However, a number of these factors are associated with an increased incidence of biologically aggressive or clinically important carcinoma. Recognition of the probability that potentially identifiable mechanisms exist for the conversion of histologic to biologic cancer has not yet been accompanied by their identification but almost certainly will be.

The concept that atrophic glandular cells are the typical precursors for development of carcinoma (311,671) has been challenged by evidence suggesting that prostates that develop carcinoma have increased glandular activity compared with BPH (632,633 and 634). The association of high-grade PIN and development of carcinoma has added support for this concept. The probability that both histologically atrophic and metabolically stimulated cells may facilitate development of malignancy would seem to warrant continued serious consideration.

Two anatomic considerations relevant to the development of CaP—its regional distribution and multicentric origin—provide important clinical, and very possibly biologic, information. Most (70% to 75%) of presumably early carcinomas are found in the peripheral portion of the prostate, indicating this as the common site of origin (312,633,671,824). The role that the metabolic characteristics of the cells or simple cell density has in the predilection for this site remains controversial. A comparative analysis of ploidy and volume of malignancies in the peripheral and transition zone of radical prostatectomy specimens (383) tends to support a biologic difference in carcinoma arising in these two areas, as contrasted to the view that the differences in a tendency to invade and perforate were due to anatomic opportunities (631). Greene and co-workers (383) observed nondiploid tumors occurred with a much greater frequency both in tumors less than 1 mL volume (29% versus 0%) and tumors larger than 1 mL volume (94% versus 36%) in peripheral as compared with transition zone tumors. In addition, the median (2.34 mL versus 7.30 mL) and mean (3.6 mL versus 6.0 mL) volume associated with the appearance of nondiploid tumors were much smaller in peripheral as compared with transition zone sites. Recently, Noguchi and associates (715) documented the clinical and histologic characteristics of 148 consecutive transition zone cancers. Their findings are summarized in Table 33.2 .

Histologic Characteristics	Involvement (%)
Organ-confined disease	80
Stage T_{1c} disease	70
Initial positive prostatic biopsy	63
Unilateral TZ cancer	62
Secondary tumor in PZ only	52
Serum PSA ≥10 ng/mL	61
Cancer volume ≥6 mL	36
≥50% Gleason grade 4/5	24
Location within proximal third segment	20
Capsular penetration	15
Anterior positive surgical margin	29
Seminal vesical invasion	2.7
Lymph node metastasis	3.4
Biochemical PSA cure rate	72

PSA, prostate-specific antigen; PZ, peripheral zone; TZ, transition zone (radical prostatectomy specimens).
Adapted from Noguchi M, et al. An analysis of 148 consecutive transition zone cancers: clinical and histologic characteristics. *J Urol* 2000; 163:1751, with permission.

TABLE 33.2. HISTOLOGIC CHARACTERISTICS OF TRANSITION ZONE CANCERS (*N* = 148)

With regard to its multicentric origin, an appreciable incidence of multiple separate tumor sites differing in both size and cellular characteristics (112,659,671) has been noted in both autopsy and radical prostatectomy specimens. These findings suggest a high frequency of multicentric origin and support the possibility of a field change (382). The probability of a diffuse or field change in the prostate that develops malignancy derives further support from two observations: (a) the high incidence of histologically discernible atypical changes (PIN) in the benign glands in the prostate with recognizable adenocarcinoma (740) and (b) evidence of a diffuse biochemical change in the histologically benign tissue and the expressed prostatic fluid of patients with carcinoma (379,380). Whether the changes are premalignant or induced is unclear. Further evaluation of the “field change” concept is derived from the molecular studies conducted by Cheng and associates (164). That study involved an analysis of microsatellite alterations in the DNA from separate tumors in the same prostate specimen. Their study targeted the putative tumor suppressor gene on chromosome 8p and for the BRCA1 gene on chromosome 17q. The pattern of allelic loss documented in that evaluation was compatible with independent tumor origin in 15 of 18 informative cases.

Organized and disorganized groups of cells that share histologic features that lead to the diagnosis of CaP may have other histologic characteristics that make local spread or dissemination probable or improbable. This attempt to characterize biologic activity on the basis of histologic characteristics is commonly translated into a numeric grade. Clinical evidence indicates the development of local tumor mass and invasion, and dissemination correlates with tumor grade (275,376,659,965). For example, Stamey and associates (965) observed that 76% of the carcinomas in 34 radical prostatectomy specimens with a tumor volume of less than 3 mL had 5% or more identifiable Gleason grade 4 or 5 malignancy. On the other hand, 96% of 34 tumors exceeding 3 mL in volume had 5% or more and 46% had 50% or more Gleason grade 4 or 5 malignancy. In another analysis of radical prostatectomy specimens, Miller and Cygan (660) demonstrated a correlation between tumor volume and grade, but small-volume high-grade (Gleason score 7 to 10) and high-volume low-grade tumors clearly were present. Organ-confined disease predominated in glands containing Gleason score 2 (35 of 38; 92%), Gleason score 3 to 4 (81 of 114; 71%) and Gleason score 5 to 6 (49 of 84; 50%); only 6% (3 of 50) of Gleason 7 to 8 and 14% (1 of 7) of Gleason 9 to 10 tumors were organ confined. Even small-volume (less than 1 mL) tumors had identifiable extraorgan disease in all grade groups. Even though Gleason 7 score was packaged with Gleason 5 and 6, a recent analysis of postradical prostatectomy evidence of persistent disease based on clinical and PSA assessments revealed a much higher progression rate in patients with tumors of Gleason score 7 or greater (59%) than in those with tumors of Gleason score 6 or less (13%) (275). Our data (720), based on 251 patients who were subjected to radical prostatectomy for clinically localized CaP, who underwent biopsy before PSA was used as the sole indication for biopsy, and who underwent follow-up for a mean of 6.1 years, are similar. The incidence of extraorgan disease in pathologic assessment increased, and the PSA progression–free survival decreased with each grade grouping (2 to 4, 5 to 6, 7, and 8 to 10) of Gleason score.

Multivariate analysis in both these retrospective studies indicated that Gleason score was the best predictor of progression; in both, the status of the surgical margins enhanced prediction of progression, but less so. Although histologic grade clearly does not approach absolute predictability with regard to intraorgan, periprostatic, or disseminated growth of carcinoma of the prostate, demonstration of high-grade (Gleason 4 or 5) tumor signals a significant risk of biologically aggressive tumor. More recently, Stamey and associates (966) evaluated radical prostatectomy specimens from 379 men with the primary intention of identifying biologic determinants of cancer progression in men treated only by surgical excision. The relative importance of eight morphologic variables was assessed using a Cox proportional hazards model. The variables involved included percentage Gleason grade 4/5, cancer volume, vascular invasion, lymph node involvement, seminal vesicle invasion, capsular penetration, positive surgical margins, prostate weight, and preoperative PSA level. In their analysis, cancer grade expressed as percent Gleason grade 4/5 and cancer volume was highly predictive of disease progression. Positive lymph node findings and intraprostatic vascular invasion were the only other variables that achieved statistical significance. Importantly, biochemical failure increased almost linearly with each 10% increase in Gleason grade 4/5 cancer within the prostate. Of potential significance, the traditional Gleason score, capsular penetration, and positive surgical margins were not independently predictive of failure after radical prostatectomy. These findings must be tempered with the realization that estimating cancer volume can be problematic and associated with significant potential for both intraobserver and interobserver variability. Evidence that other assessments, including ploidy analysis, equal or add to this information has not been convincingly presented at this time.

The routes of growth and spread of carcinoma are important considerations in diagnosis and treatment. Observations of autopsy and radical prostatectomy specimens support the probability that the early growth of CaP is usually intraglandular. The concept that a carcinoma almost always needs a critical mass to progress to an extraorgan or disseminated status probably has general but not absolute validity (660). Prostatic malignancies tend to grow initially along normal tissue planes in the gland. McNeal (631) observed that most cancers less than 3.7 mL in volume tend to follow rather than cross the plane between the transition and peripheral zones. High-grade (Gleason 4 and 5) tumors have a much greater tendency to invade rather than conform to fibromuscular structures. The continuity of intraprostatic and periprostatic tissue planes or conduits such as perineural spaces, ejaculatory duct fibromuscular sheath planes, and spaces between the muscle bundles of Denonvilliers' fascia and the periurethral sphincter afford natural potential organ exit sites for the carcinoma cells (1048). The lack of these planes and the presence of anatomic barriers are proposed explanations for the relative infrequency of periprostatic spread of transition zone tumors (1048).

Perineural space invasion was identified as a unique feature in 50% and the predominant feature in capsular perforation in 85% of a group of radical prostatectomy specimens from patients with stage B (T_2) prostate carcinoma. Anatomically unfacilitated perforation occurred as a unique feature in only 5% and a predominant feature in 15%. The regional localization of extraorgan spread to the area of the superior and inferior neurovascular bundles reflects the importance of these perineural space pathways (Table 33.3) (1048). The concept that CaP cells traverse along the perineural spaces because they constitute a plane of lowest resistance may be an oversimplification. More recently, it has been suggested that the perineural space may

have a microenvironment with growth advantage that may facilitate tumor cell proliferation and dissemination (1134). In this regard, recent studies performed on human pancreatic cancer may have relevance. Perineural invasion extending to the extrapancreatic nerve plexus is the most common route of spread for pancreatic cancer cells and is a histopathologic characteristic of this disease (1134). Molecular analysis of pancreatic cancers has demonstrated an important neurotrophin [nerve growth factor (NGF)] in the cytoplasm of pancreatic cancer cells. The biologic effects of NGF are mediated through tyrosine-kinase receptor proteins, designated Trk (A,B,C), which are coded by the Trk protooncogenes (391). Of great interest, TrkA is avidly expressed in the perineurium of pancreatic nerves but not in pancreatic cancer cells. It therefore has been postulated that enhanced expression of the NGF TrkA system may influence perineural invasion and may contribute to the pain syndrome typical of human pancreatic cancer. NGF is present within the prostate. In addition, the abnormal growth of prostatic epithelium is accompanied by increased TrkA expression and the induction of TrkC expression in epithelial cells (391). It is reasonable to assume that a constitutive affinity exists between CaP cells and the perineural microenvironment. Attraction to the perineural space may be a dynamic process that subsequently results in amplified tumor growth and expression of invasive phenotypes.

	Frequency			
Sites of Extraprostatic Spread	Non-TZ	TZ	Pathways of Extraprostatic Spread	
Lateral pelvic fascia at the posterolateral surface	50%	20%	Along perineural spaces Direct	50%–95% 0%–49%
Denonvilliers' fascia at the rectal surface	19%	0%	Along muscular bundles	100%
Seminal vesicles at the base	23%	0%	Along ejaculatory ducts sheath Direct	91% 9%
Bladder neck at the base	7%	—	Along urethral preprostatic sphincter	100%
Membranous urethra at apex	1%	0%	Along urethral distal striated sphincter	100%

TZ, transition zone cancers.
From Villers A. *Monogr Urol* 1994;15:165, with permission.

TABLE 33.3. SITES, FREQUENCY, AND PATHWAYS OF CANCER PERIPROSTATIC SPREAD IN A SERIES OF 243 RADICAL PROSTATECTOMIES

Involvement of Denonvilliers' fascia is related to extension of adjacent tumor along the planes resulting from fusion of stroma and fascia; it occurs most frequently in the basal area in association with seminal vesicle spread. In one series (1046), seminal vesicle spread was recognized independent of midbase involvement of the prostate in only 13 of 56 incidences; only five of the midbase tumors associated with vesicle spread did not show perforation. The reported predominance of an apical location for positive surgical margins is probably multifactorial but may be related to an anatomically incomplete Denonvilliers' fascia in this region. Although microscopically documented malignant cell bladder neck invasion is relatively uncommon on histologic evaluation of radical prostatectomy specimens (7%) (275,1048), bladder neck and trigonal invasion have been features of advanced carcinoma of the prostate. In these cases, extension into the bladder neck has been observed in approximately 35%, with resulting ureteral obstruction in 8% to 35% (653,853). True rectal invasion is uncommon in most series but was reported in 126 of 1,367 autopsy cases by Saitoh and colleagues (853), a frequency of approximately 9.4%. Invasion of the membranous urethra also is documented infrequently (1%) (1048) in radical prostatectomy specimens and is a finding associated with advanced disease (143).

Sites of commonly recognized extraorgan spread in carcinoma of the prostate are the following: (a) periprostatic and perivesicle, (b) pelvic lymph nodes, and (c) bones of the axial skeleton. In patients subjected to radical prostatectomy, capsular perforation is documented more frequently than perivesicle invasion; as noted, perivesicle capsular perforation accompanies perivesicle invasion 75% of the time (1046) (Table 33.3). Although extraprostatic spread is a clear indication of a biologically active malignancy, the former occurs without concurrent histologic or ultimate clinical evidence of dissemination to pelvic lymph nodes or bone. Seminal vesicle invasion is associated with immediate or delayed dissemination in most patients (1046). Clinical evidence supports the probability that pelvic lymph node and bone dissemination occur independently in some patients, although pelvic node involvement almost always is an identifiable manifestation of systemic disease (275). Patients who have no identifiable extraprostatic disease on histologic evaluation of radical prostatectomy specimens may eventually manifest disseminated disease without a clinically identifiable residual local tumor. This observation and the reverse transcriptase–polymerase chain reaction (RT-PCR) identification of PSA- and prostate-specific membrane antigen

(PSM) producing cells in the peripheral blood of a surprising number of patients with organ-confined tumors on pathologic examination suggest that the risk of vascular dissemination as an early independent event in the natural history of prostatic carcinoma may be much greater than previously appreciated (457,492).

Clinical findings with regard to lymph node spread indicate that the medial group of the external iliac chain situated around the obturator nerves and vessels, the so-called obturator nodes, are the most frequent initial site of identifiable metastatic involvement (630). In order of frequency, the other lymph nodes involved include hypogastric, external iliac, presacral, presciatic, common iliac, inguinal, periaortic, mediastinal, and supraclavicular lymph nodes (143,630,853). The clinical stage, reflecting local tumor mass, and tumor grade correlate with the prevalence of histologically identified lymph node metastasis (687,749). High-grade and increased local tumor mass are associated with increased risk of pelvic lymph node tumor dissemination. The side of lymph node and prostate involvement usually but not always corresponds in a unilateral tumor. Metastatic involvement of the external or common iliac nodes may occur independent of the deep pelvic nodes but does so infrequently. Recognition that periaortic and supraclavicular node involvement occurs in advanced CaP (20,268) is occasionally useful clinical information. Involvement of the axial skeleton is a common event that often correlates with significant lymph node and distant organ involvement (122). In the Veterans Administration Cooperative Urologic Research Group (VACURG) study of patients with stage D carcinoma, the bones most frequently affected by metastasis were the ileum (83%), followed by the ischium (78%), lumbosacral spine (71%), thoracic spine (60%), ribs (53%), femur (48%), and shoulder (39%) (114). The findings in a bone scan evaluation of 176 patients with metastatic CaP in a more recent EORTC study were similar. The location of skeletal metastasis was as follows: pelvis, 73%; dorsal spine, 63%; lumbar spine, 62%, ribs, 61%; cervical spine, 51%; femur, 40%; skull, 28%; sacrum, 25%; and humerus, 24% (935). Metastatic bone sites do not reflect the relative blood flow to the individual structures but may be related to red marrow content. The latter observation probably accounts for the infrequent identification of “hot spots” on radionuclide imaging below the elbows and knees. The radius/ulna and tibia/fibula are relatively deficient in red marrow and would constitute “infertile” sites of metastatic colonization based on the precepts of the “seed and soil” hypothesis of Paget (741). Earlier autopsy studies by Elkin and Mueller (268) revealed bone metastases of the pure osteoblastic variety in more than 50% of cases. A mixture of osteoblastic and osteolytic lesions were observed in approximately one-third of cases and pure osteolytic metastases in less than 10% of patients dying of CaP. Blastic foci often revealed a disorganized array of new bone formation. The mechanism for this stimulated osteoblastic activity has been postulated to be directly or indirectly related to the effect of prostatic tumor cell secretions (467) on hydrolysis of receptor-bound insulin-like growth factors (IGFs) (879). CaP cells produce various well-characterized growth factors of the fibroblast growth factor (FGF) and transforming growth factor-ß (TGF-ß) families (534). Bone morphogenetic protein (BMP)-6, a member of the TGF-ß superfamily of polypeptide signaling molecules, can produce bone formation from mesenchymal cells at extraskeletal ectopic sites. Recently, Maillette and associates (615) used an immunohistochemical technique to demonstrate BMP-6–positive cells in 50% to 65% of radical prostatectomy but not in normal prostate specimens. Although BMP-6 expression did not correlate with Gleason score, over 80% of patients with node-positive disease and all patients who developed skeletal metastases demonstrated BMP-6–positive cells in the primary tumor. These observations suggest a significant correlation between BMP-6 expression and the likelihood of developing bone metastases. Brown and associates (104) used immunohistochemistry, *in situ* hybridization, and RT-PCR to demonstrate CaP cells express many osteoblast-related factors. In their evaluation, osteonectin and osteopontin facilitate tumor cell migration, invasion, and attachment to bone. Osteoprotegerin and its ligand (OPGL) are directly linked to the proliferation of mesenchymal elements within the bone marrow microenvironment and mediate the effects of bone morphogenic proteins and parathyroid hormone–related protein on bone turnover. These investigators suggest that expression of these osteoblast-associated factors by prostate cancer cells, combined with cathepsin K expression by those cells, is ultimately responsible for the initiation and progression of osteoblastic metastases.

The mechanisms of metastatic spread of CaP have been controversial. However, questions concerning lymphatic spread have diminished as evidence supporting the presence of lymphatics in the prostate has been presented (324). Past speculation regarding the mechanism of bone marrow metastasis centered on the role of the perivertebral veins (Batson's plexus). These veins lack valves and presumably provide ready access to the vertebral system. Consequently, this system has been thought to play a major role in the pattern of bone involvement seen in carcinoma of the prostate (42). However, bone scan studies suggest a random distribution of CaP bone metastasis similar to that noted in breast carcinoma. PCR studies cited previously demonstrated an unexpected incidence of presumed malignant cells in the systemic circulation. Consequently, the importance of the venous system with regard to the frequency and site of bone involvement by CaP is open to question (236). Local or regional anatomic relationships seem unlikely to account for this “bone-seeking” affinity of CaP cells. Indeed, skeletal metastases in these patients may reflect a fertile microenvironment more consistent with the “seed and soil” hypothesis

of Paget than serendipitous deposition of tumor cells by a unique venous access system (741).

The sequence and interrelationships of dissemination to lymph nodes and bone are not clearly established. Clinical data from the select group of patients subjected to radical prostatectomy indicate that perforation of the capsule and perivesical tumor invasion occur without recognizable spread to lymph nodes or bone; identifiable lymph node involvement and bone dissemination occur independently of each other. Although recognition of CaP outside the gland in any site is often ultimately associated with evidence of this neoplasm in other sites, this sequence of events is far from inevitable. The common assumption that lymph node involvement always indicates associated bone marrow dissemination, or vice versa, ignores the evidence supporting the site selectivity for metastatic cells.

Metastatic involvement of other visceral organs tends to be a late manifestation of CaP and is usually associated with an overwhelming, multifocal tumor burden. Visceral metastases are often clinically cryptic; their identity and extent become apparent only at the time of postmortem examination. Autopsy studies have cited tumor involvement in a multitude of organs, but those noted most frequently include lungs (49.1%), liver (35.6%), adrenals (17.3%), and kidneys (10.6%) (853). With regard to pulmonary involvement, a correlative autopsy and roentgenologic study (268) revealed over half of the cases of pulmonary metastases were apparent only on microscopic analysis. Their observations coincide with reports of lymphangitic rather than nodular metastases in more than three-fourths of patients with clinically demonstrable lung involvement (567). Recently, Smith and associates (928) reported the development of a putatively solitary, nodular pulmonary metastasis in a patient who had undergone radical prostatectomy for a stage $pT_2N_0M_0$ Gleason 4+5 adenocarcinoma with negative surgical margins 18 months earlier. Following excision of the chest nodule, the patient's PSA reverted to the previously undetectable level with limited follow-up. This rare scenario suggests optimal control of the primary may influence the type and extent of tumor relapse.

The time frame for the development and progression of CaP is highly variable. The regional (racial) differences observed in clinical (versus histologic) malignancies support the presumption of different biologic characteristics and growth rates that correlate with the histologic grade and stage in groups of patients with CaP. Clinically, these correlations are not invariably evident in individuals within the group. Both anatomic and image-documented evidence of tumor growth have been used to provide gross estimates of rates of progression. Less than 10% of patients with a clinically well-differentiated focal CaP (stage T_{1a}, A_1) exhibit progressive disease in follow-up intervals approaching 10 years (117,143,604). Retrospective studies of patients with a palpably organ-confined (T_2), predominantly low-grade, or intermediate cytologic grade carcinoma demonstrated that progression to palpable extraorgan disease occurred in approximately 50% of the observed patients at 5 years. The progression rate was almost linear at 10% per year. These data are surprisingly similar to the 10% to 12% yearly and 60% 5-year progression rate noted in untreated patients with stage C (T_3) carcinoma in the Veterans Administration (VA) studies of carcinoma of the prostate. In the reports separating groups of men with clinically localized CaP by grade, increasing rates of progression were observed with increasing grade. In a pooled analysis of six studies, Chodak and associates (169) found a metastasis-free survival at 10 years of 81% for grade 1, 58% for grade 2, and 26% for grade 3 disease; poorly differentiated CaP also affected mortality from the disease. The median survival of 36 months from detection of metastasis in this report (169) was similar to the 30-month median survival for men with metastatic disease noted in the VA study (65). The effect of age at diagnosis on cancer-specific survival has been controversial. On pooled analysis of untreated patients (169), those who were younger than 61 years at diagnosis had an improved chance of cancer-specific survival at 10 years. Benson (50) concluded that the prognosis for younger and older men was comparable for a given grade and stage of disease. Data regarding individuals with presumed hereditary CaP, characterized in part by early onset of disease, suggest grade and pathologic stage are similar in sporadic and familial prostate cancer groups (125). This observation tends to support the probability they are biologically similar diseases. Increases in serum PSA have been used to calculate tumor doubling times of greater than 4 years in 70% of untreated men with organ-confined cancer and of more than 2 years in 79% of the entire small group of patients studied by the Stanford group. These rates are very similar to the 2.4- and 1.8-year doubling rates for an untreated local/regional and advanced/metastatic prostate cancer, respectively, noted by Carter and associates (124).

Stamey (968) and others expressed the concept that time leads to progressive change in the biologic characteristics of CaP. Epidemiologic evidence of prolonged latency as compared with increased biologic aggressiveness of carcinoma in groups of patients, pathologic evidence of the coexistence of multiple tumors with varying grades and evidence of biologic activity in a radical prostatectomy or autopsy specimen, and the relationship of diagnostic tumor grade to ultimate clinical course seem to argue for identifiable episodic metabolic alterations that may require time to manifest themselves but may occur at any period in the development of individual malignancies.

Associations between CaP and other neoplasms are being recognized in various ways with increasing frequency. Clinically unrecognized and usually, but not always, organ confined, CaP has been identified in 27% to 38% of the specimens from patients undergoing cystoprostatectomy for carcinoma of the bladder (478). In contrast to an expected 5% frequency of second primaries in the general populations,

Liskow and associates (589) noted the development of at least one additional primary cancer in 24 of 146 patients with nonmetastatic carcinoma of the prostate. In patients with multiple primaries, CaP was the initial neoplasm in 75%; approximately 25% had a third primary. Additional primary sites include the gastrointestinal (GI) tract, lymphomas, lung, genitourinary (GU) tract, and skin. The second primary was diagnosed more than 5 years after the first in approximately half the patients. Black men and individuals with high Gleason scores have an increased risk of multiple primaries. Of interest, 5-year actuarial survival rates were virtually identical for the multiple primary and single cancer groups.

PATHOLOGY

Part of "33 - CARCINOMA OF THE PROSTATE "

Malignant prostate tumors can be conveniently segregated into four categories by adapting from the International Histological Classification of prostate tumors as proposed by Mostofi and associates in 1980 (678). These categories include epithelial carcinomas, nonepithelial cancers, miscellaneous (exotic) malignant primary tumors, and tumors metastatic to the prostate (secondary neoplasms).

Cancers originating from the epithelial cells of the prostate constitute well over 95% of all prostatic malignancies (112). They usually originate in the outer portion of the prostate, designated the “posterior subcapsular stratum” by Young (1121), the “outer margin” by Rich (824), the “posterior lobe” by Moore (671), the “outer zone” by Franks (312), and the “peripheral zone” by McNeal (633).

Gross Features

CaP tends to present with a relatively characteristic firm, homogeneous, and often distinctive yellow-orange gross appearance. At times the tumor is gray to white rather than yellow (Fig. 33.1). To be apparent in an enucleated or total prostatectomy specimen, the tumor focus must attain a size approximating 5 mm (677). Early lesions may be uninodular or multinodular, possess an irregular outline, and frequently abut the so-called capsule. They often interface indistinctly with the adjacent normal parenchyma. Involvement of the capsule is common; capsular perforation is reported in more than half of radical prostatectomy specimens obtained from patients with clinically localized prostate cancer (839,1048). Perforation is not confined to large-volume tumors; it has been documented in 71 of 237 tumors (30%) with volumes of less than 3 mL and in 30 (16%) of 185 with volumes of less than 1 mL in one series (660). A scirrhous and granular texture is typical, but soft or “medullary” tumors thought to be associated with an exaggerated epithelial component do occur. Denonvilliers' fascia constitutes a formidable barrier to tumor spread, as noted by Young (1121) and verified by the Stanford group (1048). This accounts for the fact that rectal invasion by CaP has been documented in 1.5% to 9.4% of all reported cases (322,853). Multiple foci of tumors with variable volume and grade are common (see Natural History), a finding that has been interpreted as supporting the concept of a field change in this neoplasm (382). This multifocal distribution also has been interpreted as possibly representing intraprostatic metastasis (633) by intragland extension through a network of intraprostatic ducts, blood vessels, and lymphatics. As stated previously, recent molecular studies strongly validate the “field change” concept (164).

FIGURE 33.1. Advanced, multifocal carcinoma of the prostate. This transverse section of a whole-gland specimen reveals extensive tumor involvement of the left prostatic lobe, with penetration and invasion of the capsule in its posterolateral aspect. Distinct foci of grayish-white–appearing tumor can be seen scattered throughout the remainder of the gland without distinct demarcation from the surrounding normal parenchyma. [From Mostofi FK, Price EB Jr. Tumors of the male genital system. In: Universities Associated for Research and Education in Pathology, National Research Council (U.S.). Committee on Pathology, eds. *Atlas of tumor pathology,* Second series, fascicle 8. Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.]

The loss of intervening or enveloping stroma produces the back-to-back arrangements of the acini, a histologic hallmark of CaP (Fig. 33.2 and Fig. 33.3). Mostofi has noted that evidence of invasion of the surrounding stroma is an important aid in the histopathologic diagnosis of carcinoma (677). Ordinarily, smooth muscle bundles are arranged in a rather organized and concentric fashion around the distinct acinar basement membrane. Focal loss of this basement membrane with islands of neoplastic cells entering the stromal compartment may provide early evidence of tumor invasion. With progression, the normal, whorled, concentric pattern of the smooth muscle bundles is lost, and pockets of isolated smooth muscle fibers separated from one another by malignant glandular elements are seen (Fig. 33.4).

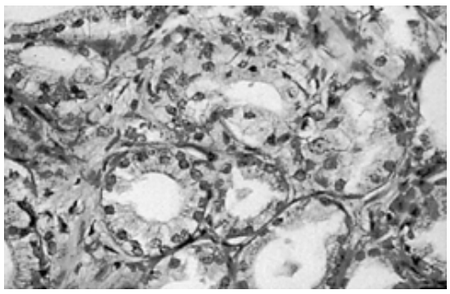

FIGURE 33.2. Well-differentiated carcinoma of the prostate. This tissue section reveals a back-to-back arrangement of glandular elements, a relative deficiency of intervening stroma, and the loss of the double layer of cells characteristic of benign glands. Cellular features include nuclei exhibiting little pleomorphism, the presence of discernible nucleoli, and clear to acidophilic cytoplasm. These characteristics are consistent with a type 1 Gleason's pattern (hematoxylin-eosin, 435× magnification). (Photomicrograph courtesy of R. Oyasu, M.D.)

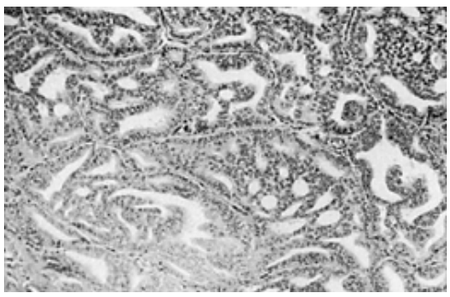

FIGURE 33.3. Cribriform pattern of prostate cancer. This photomicrograph is illustrative of a Gleason's pattern 3 tumor and demonstrates the presence of rounded, expansile masses of medium to large glands that exhibit papillary infoldings (115× magnification). (Photomicrograph courtesy of R. Oyasu, M.D.)

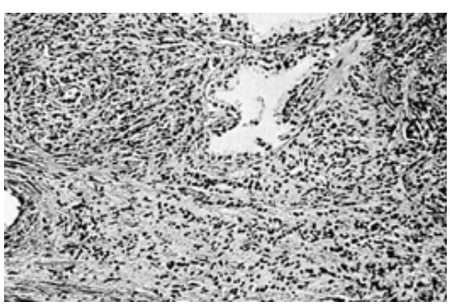

FIGURE 33.4. Poorly differentiated adenocarcinoma of prostate. Photomicrograph demonstrates an “Indian-file” pattern of highly anaplastic prostate cancer cells exhibiting diffuse stromal invasion. Clusters of tumor cells can be seen surrounding normal acini. Note virtual absence of gland formation in this tumor pattern, which would be characteristic of a type 5 Gleason's pattern (hematoxylin-eosin, 189× magnification). (From Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:303, with permission.)

The stroma, a supportive base for the epithelial layer, exhibits a significant degree of cellular heterogeneity, being composed of fibroblastic, smooth muscle, inflammatory, endothelial, and nerve cells (734). Observations suggesting that stromal elements are more than “innocent bystanders”

and that these cells may play a strategic role in BPH and CaP are accumulating (203). Embryonic epithelial-stromal interaction involves an elaborate reciprocal molecular dialog that ensures normal organ development and function (202). Evidence suggests that stromal cells located in the vicinity of malignant lesions receive and transmit altered molecular signals when contrasted to similar stromal elements associated with normal nontransformed epithelial elements (734). Alterations in these stromal cells have been postulated to enhance various tumorigenic phenotypes expressed by transformed epithelial cells (506,831). Indeed, the phenotypic changes associated with these cancer-associated fibroblasts (CAFs) include abnormal migratory behavior *in vitro,* altered expression of growth factors (IGF-I, IGF-II, TGF-1), and facilitating the growth of initiated (SV-40 transfected) or frankly neoplastic prostatic epithelial cells *in vitro* and *in vivo* (317,734). These and many other similar observations suggest that therapeutic alteration of the stromal microenvironment in CaP might effectively abrogate subsequent tumor growth and progression.

Invasion of the intraprostatic perineural spaces has been used as evidence of an invasive process and a histologic criterion for the diagnosis of CaP (Fig. 33.5). Such invasion

has been seen in 85% of incidental and early carcinomas. The microdissection studies of Rodin and associates revealed that these areas are true perineural tissue spaces rather than lymphatic channels. It has been speculated that nerve growth factor–like proteins may be important mitogens for CaP cells (372,391,1134).

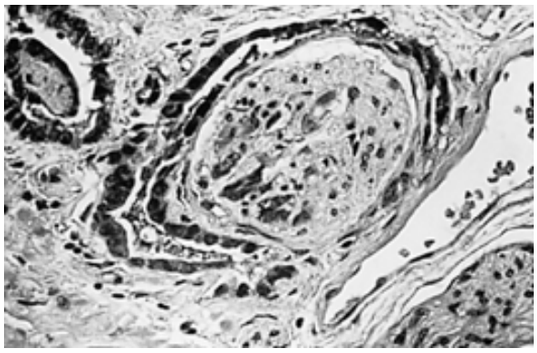

FIGURE 33.5. Invasion of perineural space. Encroachment and invasion of perineural tissues by malignant acinar elements are demonstrated. The perineural spaces are not contiguous with the lymphatic system, but they do provide a pathway of "least resistance" through the prostatic capsule. (hematoxylin-eosin, 459× magnification) (Photomicrograph courtesy of R. Oyasu, M.D.)

Until recently, the anatomic and biologic significance of perineural space invasion was poorly understood. Villers and associates (1047) analyzed 176 radical prostatectomy specimens and noted that in 50% of the cases, capsular penetration occurred exclusively within the perineural spaces. Furthermore, in 85% of the specimens, perineural extension accounted for more than half of the total area of capsular invasion. In most cases, perineural involvement followed the oblique vertical course of the nerve branches superiorly to the region of the prostatic base abutting the superior vascular pedicle. In such cases, transport of tumor cells along extracapsular nerves was measured for distances up to 9 mm, and in 11% of specimens, positive superior pedicle margins were the direct result of perineural space invasion outside the capsular perimeter. For tumors involving the prostatic apex, perineural invasion was associated with positive surgical margins in 89% of cases owing to the short length of the inferior pedicle. Prostate epithelial cell penetration of these perineural spaces has been noted in the absence of malignancy (629).

Skeletal muscle is a normal stromal component within the prostate gland itself (529). Consequently, intermingling of prostate acini with skeletal muscle cells or fibers has no diagnostic significance unless other criteria for carcinoma are established (Fig. 33.6). On the other hand, tumor emboli in unequivocal vascular or lymphatic channels within the prostate does constitute a diagnostic and ominous prognostic sign (677).

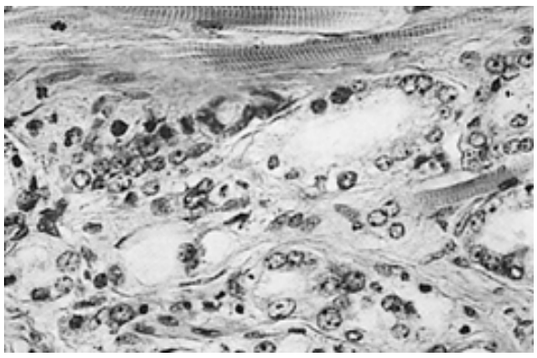

FIGURE 33.6. Prostate cancer adjacent to skeletal muscle fibers. The presence of malignant acinar elements in proximity to skeletal muscle fibers is neither correlated with a poor prognosis nor the presence of capsular penetration. These fibers are normal stromal components. Note prominent cross-striations present in the skeletal fibers as demonstrated in this photomicrograph (459× magnification). (From Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:303, with permission.)

Findings on light microscopy with regard to cellular detail can vary depending on the degree of anaplasia or differentiation of the tumor. Well-differentiated lesions characteristically have a single row of nuclei constituting the acinus; the loss of the double layer of cells present in normal glands is obvious (Fig. 33.2). The nuclei may be diminutive and demonstrate minimal pleomorphism. A thin nuclear membrane with scattered delicate strands of chromatin is commonly appreciated. The cytoplasm is generally clear or acidophilic; the nuclear-cytoplasmic ratio may appear higher than normal. Mitotic figures are encountered infrequently, possibly as a function of a rapid metaphase (677). Antibody staining for specific cytokeratins (CKs) to differentiate basal and luminal glandular cells has become important in assessing the malignant potential of small foci of suspected or equivocal carcinoma (92,1040). Various CK antibodies with differing degrees of specificity for basal and luminal cells are available. As stated in the preceding chapter, the adluminal and basal populations of the prostatic acinus can be distinguished based on their expression of specific CKs. Adluminal cells preferentially express the CKs tandem 8/18 while basal cells are highlighted by monoclonal antibodies targeting CKs 5/15 (909,910). Established CaP cell lines PC-3, DU-145, and LNCaP demonstrate expression of CKs 8/18 but not CKs 5, 7, and 15 (909). The failure of CaP specimens to express CK5 has led several investigators to postulate that these tumors arise from malignant transformation of adluminal epithelial cells (92,696). Verhagen and associates (1040) demonstrated that K14 and K basal reacted with nonmalignant basal cells and that K18 did not. None of the malignant cells tested was positive for K14, all were positive for K18, and some were positive for CK. Consequently, CK antibody information should not be transcribed without documentation.

More anaplastic carcinomas demonstrate considerable variation in cellular and nuclear pleomorphism (Fig. 33.7). The cells may be cuboidal or columnar in shape. Nuclei vary substantially in size, with the nuclear membrane appearing irregularly thickened and the chromatin distribution being quite coarse and random. One or two large nucleoli frequently are encountered, as is a prominent internuclear vacuole. The cytoplasm assumes a granular or vacuolated appearance. The acinar arrangement may be completely lost and replaced with solid cords and clumps of cells (Fig. 33.4).

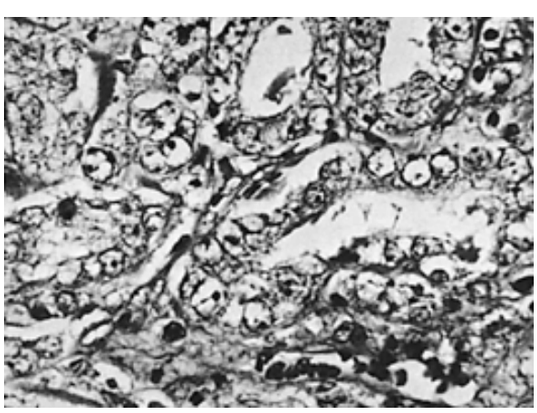

FIGURE 33.7. Anaplastic carcinoma. Photomicrograph represents a grade 3 carcinoma of the prostate. Note the presence of severe nuclear anaplasia with marked vacuolization, pleomorphic nucleoli, an irregularly thickened nuclear membrane, and the presence of a course chromatin pattern (hematoxylin-eosin, 450× magnification). [From Mostofi FK, Price EB Jr. Tumors of the male genital system. In: Universities Associated for Research and Education in Pathology, National Research Council (U.S.). Committee on Pathology, eds. *Atlas of tumor pathology,* Second series, fascicle 8. Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.]

Electron Microscopy

Transmission electron microscopy has revealed ultrastructural abnormalities paralleling the light microscopic features cited. These include enlarged and structurally pleomorphic nuclei and nucleoli, increased numbers of abnormal mitochondria, scanty endoplasmic reticulum with an increase in free ribosomes, prominent intracytoplasmic lipid droplets,

and the occasional demonstration of rod-shaped intranuclear inclusions (Fig. 33.8).

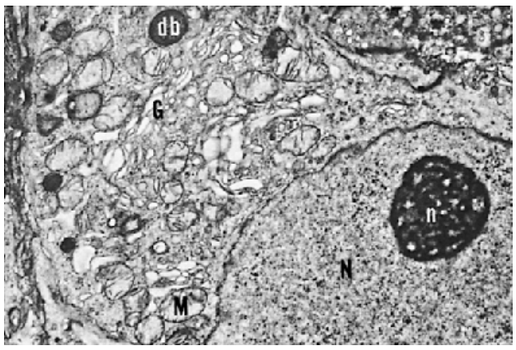

FIGURE 33.8. Ultrastructural features of anaplastic prostate cancer. This electron micrograph reveals a large nucleus *(N),* prominent nucleolus *(n),* abundance of hypertrophied Golgi *(G)* structures, mitochondria *(M)* possessing needlelike cristae, and dense bodies *(db)* (9,300× magnification). (From Fisher ER, Jeffrey W. *Am J Clin Pathol* 1965;44:119, with permission.)

Differential Diagnosis

Various histopathologic entities must be considered in the differential diagnosis of prostate cancer. These include typical hyperplasia (BPH), atypical hyperplasia, basal cell hyperplasia, senile atrophy and associated secondary hyperplasia, metaplasia, granulomatous prostatitis, and involutional changes within the seminal vesicle (677). The features associated with typical BPH, including prominent acini consisting of a basal cell and adluminal cell component surrounded by a prominent collar of avascular connective tissue, usually make the distinction between this lesion and prostate cancer relatively easy. Such is not the case when one or more foci of atypical hyperplasia exist. Because of their potentially premalignant nature, entities previously described as atypical hyperplasia, duct-acinar dysplasia, and intraglandular dysplasia are now designated prostate intraepithelial neoplasia (PIN). Three grades or subsets of PIN were initially described. PIN grade I is characterized by (a) acinar crowding, stratification, or both, with preservation of the basal layer; (b) nuclei of variable size with normal appearing chromatin; and (c) rare nucleoli. In contrast, PIN grade II is associated with (a) increased acinar crowding with some evidence of disruption of the basal layer, (b) nuclei of variable size with increased chromatin, and (c) the occasional presence of large nucleoli. Finally, grade III PIN demonstrates (a) a cribriform-like acinar architecture, (b) disruption of the basal cell layer in 56% of cases, (c) significantly enlarged nuclei displaying an increased chromatin pattern, and (d) the frequent presence of large pleomorphic nucleoli (93). These features are illustrated in Fig. 33.9 . In 1989, an international consensus group proposed that PIN be divided into low-grade (PIN 1) and high-grade (PIN 2 and 3) lesions (80,83,242).

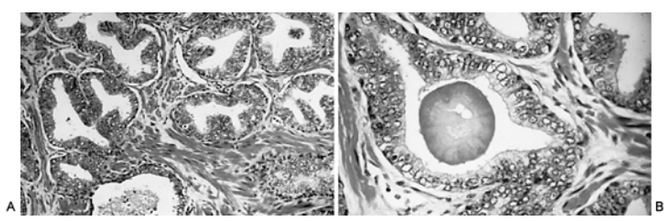

FIGURE 33.9. High-grade prostatic intraepithelial neoplasia (PIN). A pseudocribriform pattern is seen in these photomicrographs **(A, B).** Such acini frequently demonstrate abnormal proliferative activity, large nuclei, pleomorphic nucleoli, and disruption of the basal cell layer. Note the maintenance of intervening stroma (hematoxylin-eosin, **A:** 90× magnification, **B:** 200× magnification). (Photomicrographs courtesy of R. Oyasu, M.D.)

Four architectural patterns of high-grade PIN—tufting, micropapillary, cribriform, and flat—have been recognized (Fig. 33.10). Although most cases exhibit multiple patterns, the tufting pattern predominates and can be identified in 97% of declarative cases (80). No apparent correlation exists between the Gleason grade of the tumor and the associated pattern(s) of high-grade PIN. Thus recognition of the various histotypes of high-grade PIN appears to have only a descriptive or a diagnostic value. High-grade PIN can traverse prostatic ducts by one of three mechanisms. First, the tumor cells can replace normal luminal secretory epithelial, with preservation of the basal cell layer and basement membrane. In the second pattern, tumor cells directly invade through the ductal or acinar wall, disrupting the basal cell layer. The final, and most unusual, pattern of invasion involves invagination of tumor cells between the basal cell and columnar secretory cell layers. The latter phenomenon has been described as “pagetoid spread” (80,83,85). Most foci of high-grade PIN are located exclusively in the peripheral zone (63%) or simultaneously in the transition and peripheral zones (36%). Only 1% of high-grade PIN lesions can be identified exclusively in the transition zone (80,83,85). High-grade PIN exhibits multicentricity in greater than 70% of cases, which further validates the “field change” hypothesis (382).

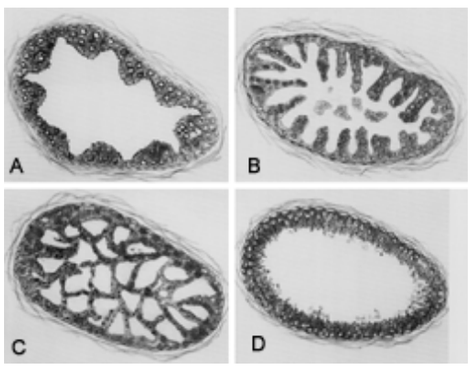

FIGURE 33.10. Illustration of architectural patterns of high-grade prostatic intraepithelial neoplasia (PIN). **A:** Tufting pattern is exemplified by undulating mounds of cells protruding into the lumen. **B:** Fingerlike projections, with or without fibrovascular cores, are seen in the micropapillary pattern. **C:** The cribriform pattern demonstrates a sieve-like pattern. **D:** The flat pattern demonstrates one or two layers of cells. [From Bostwick DG, Amin MB, Dundore P, et al. Architectural patterns of high-grade prostatic intraepithelial neoplasia. *Hum Path* 1993;24(3):298, with permission.]

Most studies suggest that the incidence, extent, and severity of PIN increase with patient age. An interesting study by Sakr and associates (855) demonstrated the presence of PIN in men in their twenties (9%) and thirties (22%). This finding antedated the onset of carcinoma by more than 10 years. The clinical significance of recognizing high-grade PIN is its strong association with CaP. Approximately 82% of step-section autopsy prostates with cancer and 86% of radical prostatectomy specimens with cancer contain high-grade PIN often within 2 mm of invasive cancer (80,85). Moreover, up to 16% of transrectal biopsies performed because of an abnormality of the PSA profile or the digital rectal examination (DRE) contain high-grade PIN (497). Additional studies have shown that patients with high-grade PIN but no cancer in core biopsies have a 50% risk of CaP on subsequent biopsies (812). Several recent studies have demonstrated conclusively that high-grade PIN alone does not contribute significantly to serum total and percentage of free PSA levels (673,812).

From a phenotypic standpoint, high-grade PIN is much more closely related to carcinoma than to benign epithelium. The karyotypic abnormalities of high-grade PIN and invasive CaP are highlighted in Table 33.4 . Tumor cell properties linking high-grade PIN and CaP are summarized in Table 33.5 . The general perception is that high-grade PIN is associated with progressive abnormalities of phenotype and genotype, which lie intermediate between normal prostatic epithelium and invasive CaP (81). Figure 33.11 highlights the strategic role proposed for high-grade PIN in this morphologic continuum.

7q31-q35	8q22.2
8p12-21	8q12.2
8p22	10q
8q22	16q

Adapted from Kozlowski JM, Sensibar JA. Prostate cancer. In: Masters JRW, Palsson B, eds. *Cancer cell lines: human cell culture,* vol. 2. Dordrecht; Boston: Kluwer Academic Publishers, 1999:305; and Bostwick DG, Pacelli A, Lopez-Beltran A. Molecular biology of prostatic intraepithelial neoplasia. *Prostate* 1996;29:117, with permission.

TABLE 33.4. HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA AND INVASIVE ADENOCARCINOMA OF THE PROSTATE: SIMILAR ALLELIC CHROMOSOME LOSSES

Preference for peripheral zone
Multicentricity
Disruption of basal cell layer
↑ Microvessel density
↑ Growth fraction
↑ Mitotic figures
↑ Aneuploidy
↑ c-erbB-2 oncoprotein
↑ EGF
↑ EGF receptor
↑ TGF-α
↑ Proliferating cell nuclear androgen expression
↑ Membrane type 1 matrix metalloproteinase
↑ Collagenase type 4
↑ Lewis^{Y} antigen expression androgen sensitivity
↑ EpCAM levels

EGF, epidermal growth factor; TGF, transforming growth factor.
Adapted from references 34, 83, 784, and 1033.

TABLE 33.5. HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA AND INVASIVE ADENOCARCINOMA OF THE PROSTATE: PHENOTYPIC SIMILARITIES

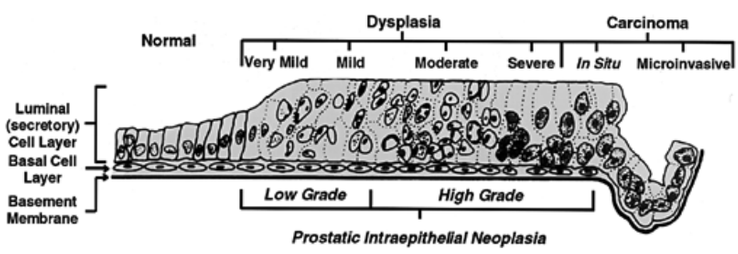

FIGURE 33.11. Proposed model of prostate carcinogenesis. Spectrum of presumed morphologic changes that occur following malignant transformation of normal luminal (secretory) prostate epithelial cells. High-grade prostatic intraepithelial neoplasia (PIN) is thought to be the precursor lesion to invasive acinar prostate cancer. (From Bostwick DG. What is the clinical significance of high-grade PIN? *Contemp Urol* 1998;March:43, with permission.)

Basal cell hyperplasia is a unique, characteristically multicentric variant present in approximately 5% of BPH specimens (677). The closely packed, hypercellular clusters of pure basal cells are difficult to distinguish from CaP (Fig. 33.12). Although generally considered a benign lesion, Mostofi (677) has reported several histopathologic subsets of basal cell hyperplasia, some of which may have ominous significance.

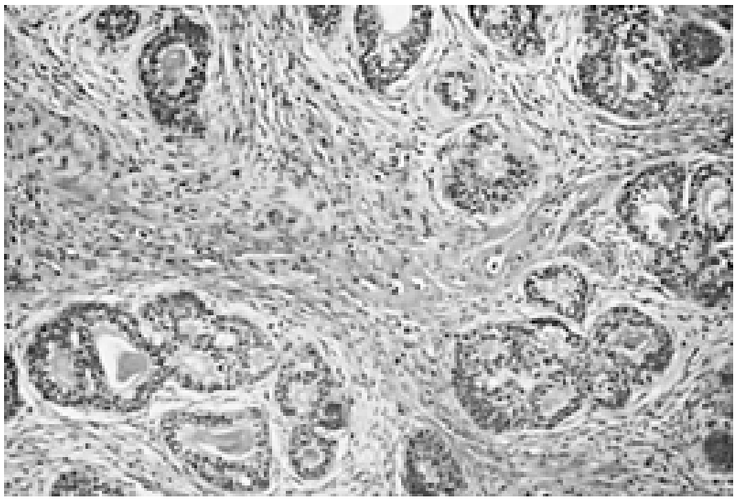

FIGURE 33.12. Basal cell hyperplasia. Basal cells may constitute a reserve population of prostatic cells capable of differentiating into typical secretory columnar elements. In basal cell hyperplasia, multifocal nests of such cells are often seen admixed with glandular and stromal hyperplasia. Carcinoma can coexist as well, especially in the presence of atypical variants. Typical features include rarity of mitotic figures, absence of infiltrative or perineural growth, peripheral palisading of cells within each nest, absence of cytologic atypia, and high affinity of these cells for toluidine blue. Most of these features are demonstrated in this photomicrograph (100× magnification). (Courtesy of R. Oyasu, M.D.)

In senile atrophy, the characteristically small, collapsed acini, which may contain cuboidal epithelium with prominent nuclei, may simulate carcinoma. However, such acini are always surrounded by a distinctive collar of collagenous connective tissue, and the atrophic changes involve the entire lobule diffusely (Fig. 33.13). These involutional or atrophic changes generally commence at approximately the fifth decade and appear primarily in the peripheral or outer zone of the prostate.

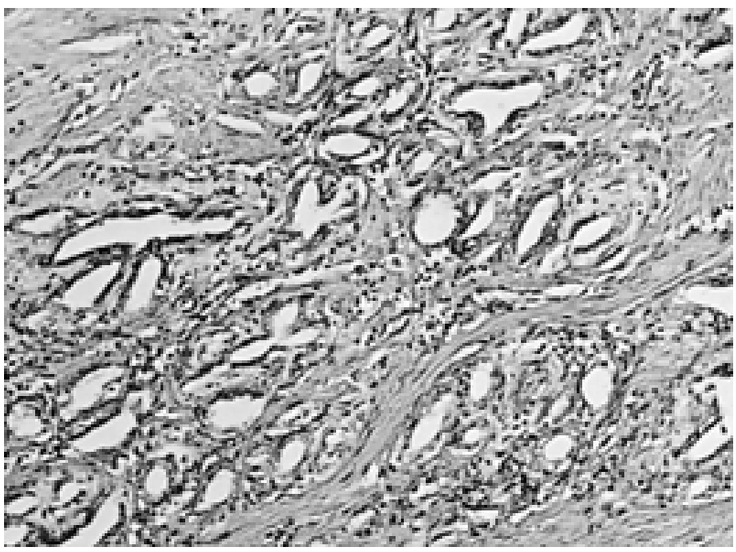

FIGURE 33.13. Senile atrophy of the prostate. The atrophic changes most often involve glandular and stromal elements. The former become collapsed, possess cuboidal cells with prominent hyperchromatic nuclei, and are closely packed. The stroma often undergoes sclerotic atrophy with hyalinization of the collagen component being a noteworthy feature. This photomicrograph (130× magnification) typifies these features. [From Mostofi FK, Price EB Jr. Tumors of the male genital system. In: Universities Associated for Research and Education in Pathology, National Research Council (U.S.). Committee on Pathology, eds. *Atlas of tumor pathology,* Second series, fascicle 8. Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.]

Interpretation of other histologic changes also may be a diagnostic challenge. Granulomatous prostatitis (Fig. 33.14) may present as a sheet of cells with small nuclei and a large clear cytoplasm. At times the cells show marked pleomorphism mixed with inflammatory cells. Multinucleated giant cells also may be present. Histologic changes

associated with a healing infarct may include prominent squamous and transitional metaplasia, but these lack any evidence of anaplasia or invasion. Last, cells with bizarre hyperchromatic nuclei are often encountered in an involuting seminal vesicle. Although these cells may suggest CaP, they possess a normal nuclear cytoplasmic ratio and lack prominent nucleoli and the internuclear halo characteristic of CaP (677).

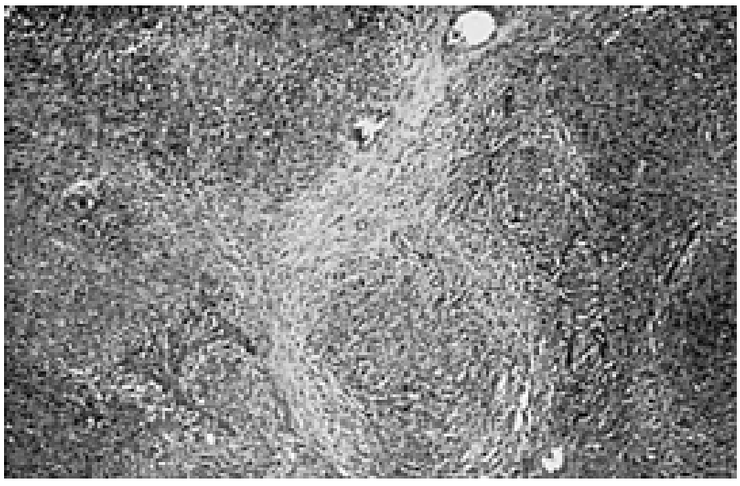

FIGURE 33.14. Granulomatous prostatitis. This process is thought to arise as a consequence of ductal obstruction with subsequent destruction of ductal epithelium and release of irritating protease-rich products into interstitial tissue. Grossly, prominent, firm yellowish nodules may be appreciated. As demonstrated in this photomicrograph (130× magnification), the normal prostatic architecture may be destroyed and replaced with a monotonous array of mononuclear phagocytes, plasma cells, and lymphocytes. Giant cells may be seen and their periductal location is characteristic. (Photomicrograph courtesy of R. Oyasu, M.D.)

Histochemistry

Histochemical techniques utilizing specific antibodies to enzymes and various other proteins are being used with increased frequency to evaluate tissue specimens with recognized or suspected CaP. These procedures are used to identify the tissue of origin of a recognized carcinoma, to accumulate evidence of characteristics that help differentiate benign and malignant tissue, or to provide evidence regarding the biologic potential of CaP. Histochemical confirmation of the presence of PSA and/or prostate acid phosphatase (PAP) provides strong evidence that the prostate is the parent organ of a typical malignancy. Both PSA and PAP usually show a decreasing histochemical content as the degree of differentiation of the malignancy decreases. Recently immunohistochemical techniques to evaluate the presence and possibly crudely quantify human kallikrein 2(hK2), a trypsin-like protease that shares a 78% amino acid homology with PSA, have become available. hK2 converts pro-PSA into enzymatically active PSA capable of complexing with α_1-antichymotrypsin. It is present in benign and malignant prostatic tissue.

The role of CK staining of basal and luminal cells in facilitating recognition of malignancy has been discussed. Established LNCaP, DU-145, and PC3 cell lines demonstrated expression of CK8 and 18 but not 5, 7, and 15 in our experience (909); the latter were observed in BPH. CK5 was selectively expressed in the basal cell population of human prostate (696), a characteristic shared with K14 (1040). Staining techniques using antibodies for proteins expressed by prostate cancer cell lines and clinical tumor specimens are becoming increasingly available, including probes for (a) nuclear androgen receptor (AR) (697), (b) bcl-2 (626), (c) p53 (79), and (d) parathyroid hormone–related peptide (463) and OA-519 (fatty acid synthase) (274). Useful markers of neuroendocrine differentiation include chromogranin A and neuron-specific enolase (455). No cancer-specific antigen has been isolated.

Grading

Grading is an effort to use histologic characteristics of a tumor to predict its biologic activity. Various microscopic observations have been used in this effort. These include the configuration and arrangement of acini; cellular characteristics, including the distinctiveness of cell borders, the degree

of nuclear distortion, and pleomorphism; the number and size of the nucleoli; and significant biologic evidence of behavioral patterns such as invasion of lymphatic or vascular channels or tumor cell volume.

All the systems proposed to grade CaP use the acinar pattern. The Gleason and M.D. Anderson systems use this characteristic exclusively. Others, including the Mostofi, Gaeta, and Mayo Clinic systems, also use the cellular characteristics in this effort. None of the systems described has an established advantage with regard to prediction of biologic behavior of the tumors assessed. The Gleason classification scheme, currently the most popular, uses low-power magnification (40× to 100×) to assess the glandular pattern of the tumor and its relationship to the stromal compartment (Table 33.6 and Fig. 33.15). Five tumor grades progressing from the most (1) to the least (5) differentiated are recognized. Tumor grade(s) 1 through 5 noted in a specimen are recorded; a Gleason score consisting of the sum of the most and next to most prevalent (mass) grade is calculated.

TABLE 33.6. HISTOLOGIC PATTERNS OF ADENOCARCINOMA OF THE PROSTATE

Pattern	Margins of Tumor Areas	Gland Pattern	Gland Size	Gland Distribution	Stromal Invasion
1	Well defined	Single, separate, round	Medium	Closely packed	Minimal, expansile
2	Less definite	Single, separate, rounded, but more variable	Medium	Spaced up to one gland diameter, average	Mild, in larger stromal planes
3	Poorly defined	Single, separate, more irregular	Small, medium, or large	Spaced more than one gland diameter, rarely packed	Moderate, in larger or smaller stromal planes
		or Rounded masses of cribriform or papillary epithelium	Medium or large	Rounded masses with smooth sharp edges	Expansile masses
4	Ragged, infiltrating	Fused glandular masses or "hypernephroid"	Small	Fused in ragged masses	Marked, through smaller planes
5	Ragged, infiltrating	Almost absent; few tiny glands or signet ring cells	Small	Ragged anaplastic masses of epithelium	Severe, between stromal fibers or destructive
		or Few small lumina in rounded masses of solid epithelium; central necrosis?	Small	Rounded masses and cords with smooth, sharp edges	Expansile masses

From Gleason DF, Veterans Administration Cooperative Urological Research Group. Histologic grading in clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:171.

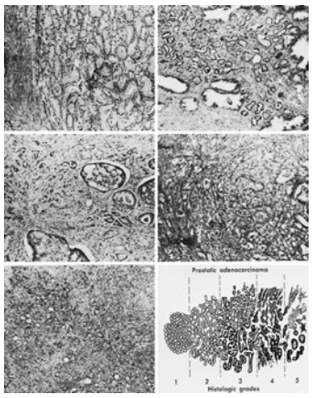

FIGURE 33.15. The Gleason grading system. This assessment is made under low-power magnification (40× magnification; 100× magnification) and involves a determination of glandular differentiation coupled with the growth pattern of the tumor in relation to the surrounding stroma. Representative examples of the five histologic grades are depicted as follows: Pattern 1 **(upper left),** pattern 2 **(upper right),** pattern 3 **(middle left),** pattern 4 **(middle right),** and pattern 5 **(lower left.)** (From Gleason DF, Veterans Administration Cooperative Urological Research Group. Histologic grading in clinical staging of prostatic carcinoma. In: Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:171, with permission.)

Grade (pattern) 1 contains a rather homogeneous array of single, round-to-oval, separate but closely packed glands. Stromal invasion is uncommon and, when present, is expansile in nature. Tumor margins are very well defined (Fig. 33.16). Intraluminal crystalloids (Fig. 33.17), identified in approximately 10% of differentiated prostate cancer specimens and thought to be associated exclusively with malignancy, also have been noted in approximately 3.6% of BPH tissues. Of interest, the biochemical nature of the interacinar crystalloids remains elusive (766).

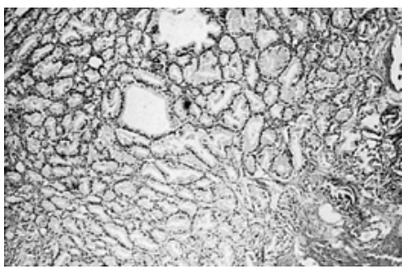

FIGURE 33.16. Gleason pattern 1. Note the rather monotonous array of closely packed acinar elements (hematoxylin-eosin; 130× magnification). Additional features include loss of the basal cell layer and absence of intervening stroma (Fig. 33.2). (Photomicrograph courtesy of R. Oyasu, M.D.)

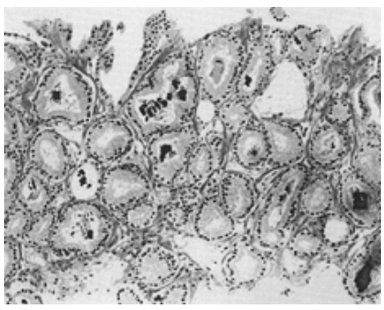

FIGURE 33.17. Prostate adenocarcinoma with intraacinar crystalloids. Dark, well-defined crystals (none uniform in size and shape) are present within the lumens of multiple neoplastic glands. Ordinarily, these crystals are intensively eosinophilic.

Grade (pattern) 2 has an acinar pattern quite similar to that of pattern 1 except that there is less uniformity in glandular shape and often up to one-gland diameter distance between acinar units. A mild amount of stromal invasion is encountered; consequently, the tumor margins are less well circumscribed (Fig. 33.18).

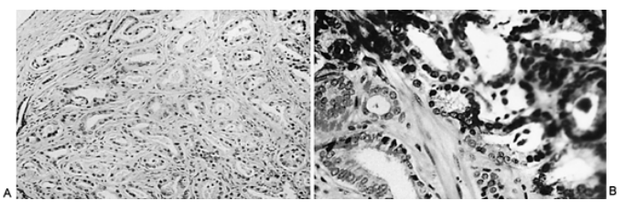

FIGURE 33.18. Gleason pattern 2. These acini demonstrate less uniformity in shape and less cohesiveness than pattern 1 acini (**A:** 130× magnification). Areas of stromal invasion can be appreciated and account for a less well-circumscribed tumor margin (**B:** 400× magnification). (Photomicrographs courtesy of R. Oyasu, M.D.)

Grade (pattern) 3 contains three distinctive subpatterns. The first is characterized by single but very irregular glands separated from one another by more than one gland diameter. Stromal invasion is exhibited to a moderate degree, and the tumor margins are generally poorly defined. The second consists of microglandular nests of cells that form small groups or cords. The last subpattern manifests sharply circumscribed rounded masses of papillary or cribriform epithelium possessing smooth, sharp edges. They present as expansile masses within the stroma, are found in medium to large glands, and also are associated with poorly defined tumor margins (Fig. 33.3).

Grade (pattern) 4 contains two subpatterns. The first consists of coalescence or fusion of ragged glandular masses that exhibit prominent branching. Stromal invasion is marked and the tumor appears quite ill defined. The second subpattern consists of the same morphologic type of tumor except for the presence of large cells with very pale, clear

cytoplasm reminiscent of clear-cell carcinomas of the kidney and designated “hypernephroid” cells.

Grade (pattern) 5 is characterized by irregular infiltrating masses of malignant cells, usually without any gland formation. A second rare variant consists of an irregular cribriform arrangement with central necrosis mimicking comedocarcinoma of the breast. This pattern is typified by extensive stromal invasion, a virtually imperceptible interface between tumor and adjacent normal parenchyma, and its frequent occurrence in small glands (Fig. 33.19).

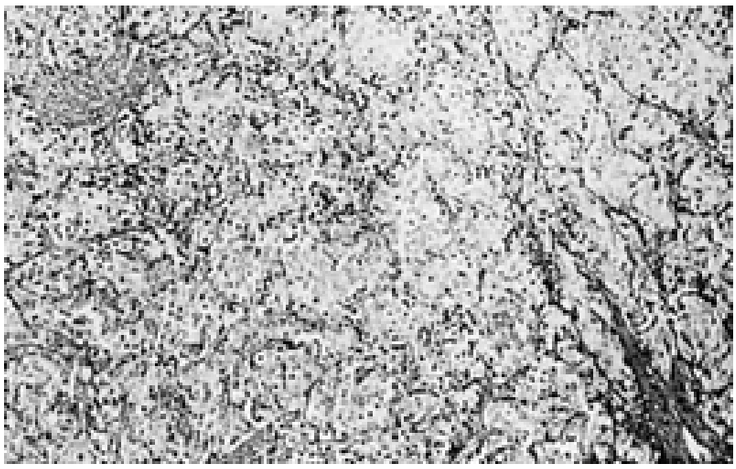

FIGURE 33.19. Gleason pattern 4 to 5. The presence of large cells with pale cytoplasm is characteristic of the “hypernephroid” variant of pattern 4 tumors. The absence of true gland formation and diffuse stromal invasion is more typical of pattern 5 neoplasms (hematoxylin-eosin; 200× magnification). (Courtesy of R. Oyasu, M.D.)

Recognition that approximately 50% of tumors will manifest more than one of Gleason's histologic patterns and that the presence of a histologically heterogeneous tumor had biologic significance led to the use of the sum of the primary and secondary patterns as the Gleason (pattern) score (363). Possible pattern scores range from 2 to 10, with the former being indicative of very well-differentiated tumors and the latter of the highly undifferentiated variety. The Gleason tumor score correlates with various parameters indicative of tumor systems possessing invasive and metastatic capacity. These include the presence of lymphatic and skeletal metastasis, ureteral obstruction, the rate of clinical progression, and cancer death rate (143,363,535). An attempt to augment the biopredictive accuracy of this classification by adding staging to the histologic observations to establish tumor category has largely been abandoned.

The Mostofi, Gaeta, and Mayo Clinic grading systems assume that independent assessment of acinar and cellular detail provides additional prognostic information.

The Mostofi system differentiates tumor-forming glands composed of epithelial cells with slight nuclear anaplasia (grade 1), moderate nuclear anaplasia (grade 2), or marked nuclear anaplasia or completely undifferentiated without gland formation (grade 3). Proponents of this system believe it to be equivalent to the Gleason classification scheme, although this remains to be proved (679).

The Gaeta system used by the National Prostate Cancer Project (328), uses the worst combination of gland morphology and/or cellular anaplasia noted in at least one-third of the tumor specimen to establish grade. Grade 1 tumors consist of well-defined, medium to large glands with uniform normal sized cells with an inconspicuous nucleolus separated by scant intervening stroma. Grade 2 tumors consist of medium to small acini associated with a moderate amount of intervening stroma. Slight pleomorphism and prominent nucleoli characterize the cells. Grade 3 prostate cancers have small glandular elements lacking acinar organization, often with cribriform and scirrhous patterns and

cells with pronounced pleomorphism, containing vesicular nuclei, and acidophilic nucleoli. Finally, grade 4 tumors show round, expansile tumor cell masses without evidence of true gland formation and contain cells that may be quite uniform or very pleomorphic that are not infrequently associated with significant mitotic activity. The proponents of this system cite a definite correlation between the Gaeta histologic grade and the likelihood of lymphatic metastasis, overall tumor stage, and the associated mortality of CaP.

The Mayo Clinic grading system also relies on assessment of glandular structure, cytoplasmic-nuclear-nucleolar morphology, mitotic activity, and tumor invasiveness (532,533). Grade 1 neoplasms consist of glandular elements that are uniform in shape with little intervening stroma, and cuboidal cells with prominent hyperchromatic nuclei and nucleoli and infrequent mitotic activity. Nuclear pleomorphism, diminution in acinar size, and an increase in the surrounding stromal element characterize grades 2 and 3. Grade 4 neoplasms lack distinct acinar structure; the cells have highly pleomorphic, markedly hyperchromatic nuclei, scanty cytoplasm, and frequent mitotic figures. Prominent tonguelike cords of cells are seen invading the surrounding stroma.

Several reports (275,376,720) indicate that histologic tumor grade is the most important predictor of tumor progression. Nevertheless, the recognition that most CaPs are classified as intermediate grade, indicating a variable biologic potential, increases the importance of efforts to identify other indicators of risk of invasion and dissemination. The demonstration that even the lowest grade or most differentiated prostate cancers may possess these characteristics (660) reinforces this need.

Cytology

Currently, the systematic use of transrectal ultrasound (TRUS)-guided prostatic needle biopsies constitutes the most common method of tissue procurement in patients considered at risk for CaP. Nonetheless, patients who exhibit a focal area of induration or nodularity may benefit from the adjunctive use of digitally directed needle core biopsies or transrectal needle aspiration cytology. The latter approach is minimally traumatic and may have appeal in those patients for whom concern regarding the potential for bleeding and infection is heightened. Accurate cytologic assessment of the material obtained by needle aspiration of the prostate is critical to this procedure. This brief discussion should serve to familiarize the reader with the cytologic findings associated with BPH, PIN, the various grades of prostate carcinoma, and various common cellular contaminants. A thorough review of these areas has been provided by Koss and associates (528).

Aspirates of BPH typically contain clusters of flat, cohesive, epithelial cells possessing finely granular cytoplasm, round-to-oval nuclei of uniform size, the distinct absence of mitotic figures, and only the most diminutive nucleoli. The closely approximated polygonal cells that compose these cohesive sheets have well-defined cytoplasmic borders that result in a characteristic honeycomb configuration (Fig. 33.20). Very few detached cells are encountered. Many of the latter are myoepithelial cells containing small, spindly, hyperchromatic nuclei. In the presence of coexisting chronic prostatitis, occasional lymphocytes and plasma cells are noted. Aspirated stromal fibroblasts are generally elongated cells with sharp pointed nuclei, whereas smooth muscle elements possess nuclei with rounded ends.

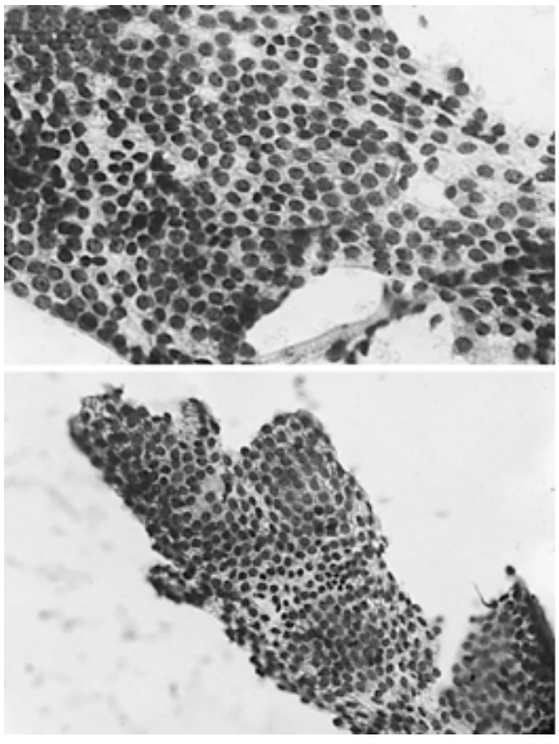

FIGURE 33.20. Benign prostatic hyperplasia (BPH): prostate needle aspirate. Transrectal needle aspiration of benign hyperplastic elements reveals flat sheets of monotonously uniform epithelial cells, which demonstrate a high degree of affinity for one another. The cells constituting such honeycomb clusters have typically normal features and lack the presence of mitoses and prominent nucleoli. Stromal elements (myoepithelial cells) are frequently encountered. The similarity between aspirates of normal prostate (**A:** 200× magnification) and BPH (**B:** 100× magnification) can be appreciated. (Photomicrographs courtesy of D. Hidvegi, M.D.)

PIN is easily confused with invasive CaP when the diagnosis relies solely on cytologic interpretation of fine-needle aspirates. PIN (grade I) may resemble BPH except for the presence of slight nuclear enlargement and hyperchromasia. On the other hand, PIN (grades II and III) may be indistinguishable from CaP and manifest (a) absence

of flat, cohesive clusters, (b) occasional evidence of detached single epithelial cells, (c) enlarged hyperchromatic nuclei, and (d) prominent nucleoli. In most instances, needle biopsy of the prostate is required to establish the diagnosis and exclude the presence of coexistent carcinoma (340,740).

Moderately differentiated CaP (Fig. 33.21) consists of an admixture of rosettelike clusters together with numerous dispersed cells. Honeycombing is never encountered. The detached epithelial cells have characteristic large hyperchromatic nuclei with conspicuously enlarged or duplicated nucleoli. Mitotic figures are seen occasionally. Myoepithelial cell nuclei are not present.

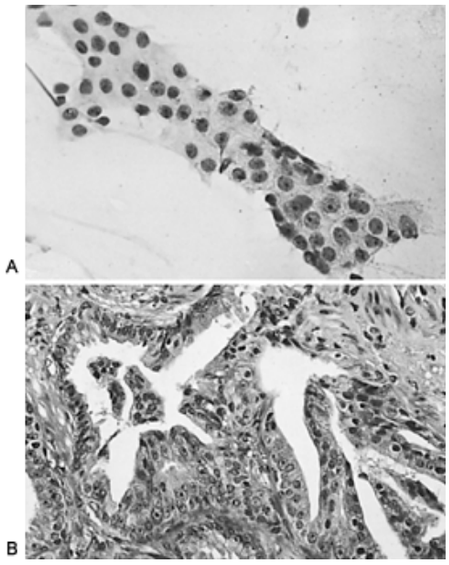

FIGURE 33.21. Prostate needle aspirate of well-differentiated carcinoma. These tumors can be differentiated from benign prostatic hyperplasia by the presence of thick cell clusters, which have lost the typical honeycomb configuration. Detached cells are encountered occasionally, and all cellular elements display hyperchromatic nuclei and prominent nucleoli **(A)** (200× magnification). Note the correspondence of the aspirate to its representative tissue section **(B)** (150× magnification). (Photomicrographs courtesy of D. Hidvegi, M.D.)

Aspirates containing poorly differentiated CaP are very distinctive (Fig. 33.22) and consist primarily of dispersed cells containing significantly enlarged and irregularly shaped nuclei and nucleoli. Abnormal mitotic figures are encountered frequently. The smear pattern is so bizarre that a clear-cut diagnosis of prostate cancer may require histochemical staining to differentiate it from a high-grade urothelial cancer invading the prostate.

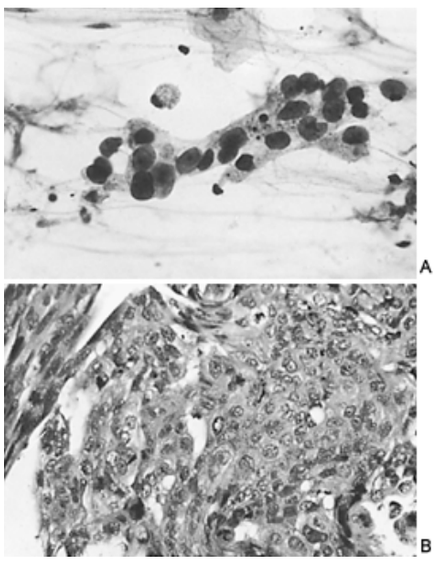

FIGURE 33.22. Needle aspirate of poorly differentiated prostate cancer. Loosely adherent and detached cells predominate and possess pleomorphic nuclei and significantly enlarged nucleoli, and often exhibit mitotic figures. Again, note the similarity between the aspirate **(A)** (200× magnification) and its tissue counterpart **(B)** (150× magnification). (Photomicrographs courtesy of D. Hidvegi, M.D.)

Contamination of the aspirate by cells from the rectum, seminal vesicle, or bladder can result in confusing findings. Transrectal prostatic aspirates may contain some rectal mucosal cells. These cells are generally larger than prostatic cells. They tend to form prominent cohesive sheets, with the typical honeycomb appearance characteristic of BPH. Peripheral palisading of cells with a central rosettelike pattern is fairly typical, as is the presence of small peripherally located nuclei (528). Seminal vesicle cells characteristically containing prominent hyperchromatic nuclei four to eight times larger than normal prostatic nuclei must be distinguished from anaplastic carcinoma. Unlike the latter, however, the cytoplasm is very generous, often vacuolated, and classically contains granular yellow-brown pigment (528). Aspiration of nodules along the midline or close to the bladder neck may result in the inadvertent aspiration of urothelial cells. The latter may consist of prominent, flat, multinucleated umbrella cells or the more diminutive and

elongated subadjacent transitional cells. The presence of either acute or chronic prostatitis may make a definitive diagnosis of CaP difficult (528). In the former, necrotic or degenerating epithelial cells may reveal bizarre aberrations of size and shape. Polymorphonuclear leukocytes are abundant; macrophages are present occasionally. In contrast, chronic prostatitis is often associated with abundant fibroblasts and smooth muscle cells together with a prominent mononuclear cell infiltrate. Foamy macrophages and multinucleated giant cells are also characteristic.

Unusual Prostate Tumors

The preceding discussion appropriately emphasized prostatic adenocarcinomas of acinar origin because they constitute well more than 95% of prostatic neoplasms (112). In this section, we highlight some of the features of infrequently encountered malignant prostatic tumors. For purposes of discussion, these neoplasms can be segregated as follows: (a) atypical adenocarcinomas, (b) sarcomas, (c) exotic primary tumors, and (d) secondary tumors (1075).

Ductal cancers, the largest subset of atypical prostate adenocarcinomas, include carcinomas originating from either the primary or secondary ductal networks, endometrioid (papillary) carcinomas, and transitional or squamous cell cancers. Less frequently encountered neoplasms include mucinous and adenoid cystic carcinomas, along with carcinosarcomas.

The low columnar epithelium lining the primary and secondary ductal system of the prostate contrasts with the transitional cell lining of the periurethral component. Primary and secondary ductal tumors arising from these columnar cells constitute approximately 3% of prostate cancers (142). Primary ductal cancers, thought to originate from the prominent, centrally located, periurethral ductal network, may progress via intraluminal extension or local invasion.

These tumors often present with gross hematuria; cystourethroscopy often reveals the characteristic papillary morphology. The present consensus is that so-called endometrioid carcinomas of the prostate (Fig. 33.23) (639) are variants of primary ductal adenocarcinoma with endometrioid (i.e., papillary) features (277,532,533). Among carcinomas with ductal differentiation, the cribriform pattern is more common than the papillary (or endometrioid pattern). Ductal adenocarcinoma components are generally not assigned a Gleason grade, because doing so has not been shown to be of prognostic significance. At the time of diagnosis, the majority of these tumors are large and of advanced stage. They tend to have a more adverse prognosis than carcinomas without distinctive ductular differentiation (171).

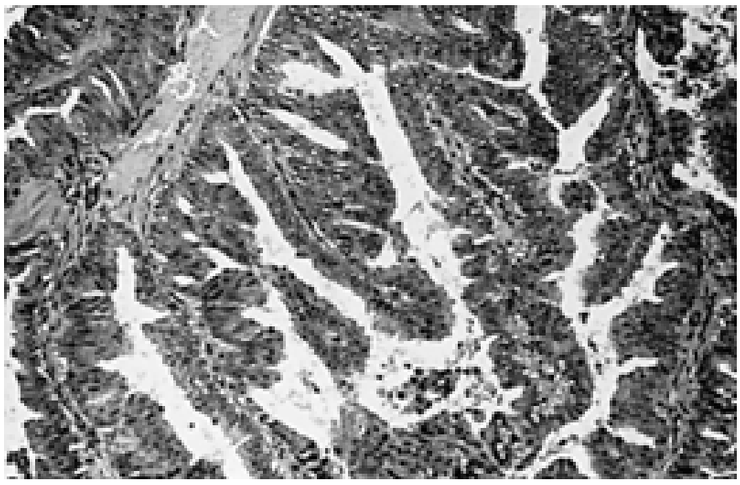

FIGURE 33.23. Endometrioid carcinoma of the prostate. This variant of ductal carcinoma may present as a papillary or infiltrating tumor. The former variety is illustrated here. Note the typical exophytic character. Cells may vary from tall columnar epithelium possessing a vacuolated cytoplasm to aggregates of cuboidal cells in which the cytoplasm is distinctly granular. Such tumors may coexist with foci of atypical hyperplasia and more common variants of primary ductal cancer (76× magnification). (Photomicrograph courtesy of R. Oyasu, M.D.)

Secondary ductal carcinomas, thought to originate in a multicentric fashion from the secondary and tertiary ducts, are associated with desquamation of necrotic debris within the ductal lumen. They often assume a comedo-like appearance. These variants are thought to be more aggressive with a proclivity for early stromal invasion (244,384). Secondary ductal carcinoma may be perceived on rectal examination. Although conflicting information exists regarding androgen dependence of intraductal neoplasms, several studies using special histochemical techniques have documented the presence of PAP and PSA in the majority of them (542,1070). The bony metastases associated with both the primary and secondary ductal cancers tend to be osteoblastic, with associated elevations of blood markers (244,639).

Many patients with metastatic ductal carcinoma respond to androgen deprivation therapy. However, as a group, these patients tend to have a slightly worse prognosis compared with those with tumors arising from acinar elements (142,143). Undoubtedly, some CaP are composed of a mixture of ductal and microacinar elements. With regard to this last subset, recent observations demonstrate that the ductal spread of prostatic (acinar) carcinoma is a frequent event and occurs in approximately half of cases studied (531). Carcinoma cells have been observed to penetrate the wall of benign ducts and gradually replace the normal epithelial component. Such a phenomenon might be easily misconstrued for a primary ductal cancer.

Transitional and squamous cell carcinoma of the prostate are appropriately considered together, because the latter tumor represents a metaplastic variant of the former (680). They typically arise in the central or periurethral ductal transitional epithelium of the prostate gland and constitute 2% to 3% of prostate cancers (Fig. 33.24) (1075). Although they probably share some etiologic factors (see Chapter 30), these tumors must be differentiated from panurothelial

transitional cell carcinomas associated with transitional cell carcinoma of the bladder. At times, differentiation of this malignancy and poorly differentiated prostate carcinoma is challenging. Use of histochemical stains for PSA, PAP, and other selected cellular proteins assists in identifying the cell of origin. Transitional cell carcinoma of the prostate is characterized by local extension in the prostatic stroma and to the bladder neck, regional spread to the pelvic lymph nodes, and distant dissemination to bone and lung. The presence of a palpable rectal lesion usually indicates widespread disease. Bone lesions are commonly osteolytic; lung lesions usually are subpleural nodular deposits rather than the lymphangitic metastasis typically associated with CaP (385).

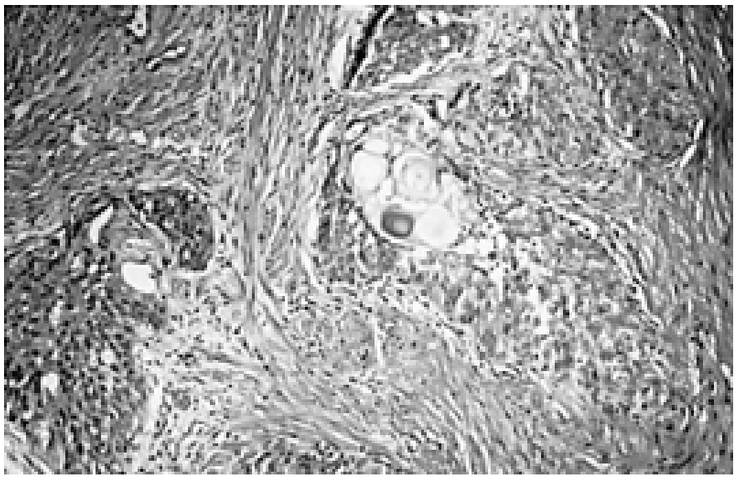

FIGURE 33.24. Transitional cell carcinoma of the prostate. Photomicrograph reveals a large, centrally located prostatic duct totally occluded by transitional cell elements. Approximately one-third of patients with such biopsy findings will have primary transitional cell neoplasms of the prostate without a history of synchronous or metachronous transitional cell tumors of the urethra and bladder (189× magnification). (Photomicrograph courtesy of R. Oyasu, M.D.)

Adenoid cystic and pure mucinous (colloid) carcinomas of the prostate are rare. Adenoid cystic carcinoma (0.01% of prostatic malignancies) has both glandular and cystic elements and often mimics the cribriform pattern of acinar carcinoma (1075). However, the small deeply staining cells resembling basal cells and the hyaline or mucoid material seen in the honeycomb, or Swiss cheese glandular pattern, are distinctive (Fig. 33.25). This tumor pattern also has been reported to originate in Cowper's glands. Mucinous (colloid) carcinoma (694) must be distinguished from both primary acinar adenocarcinoma with mucinous elements and secondary mucin-producing tumors. The latter generally originate from colon, bladder, and Cowper's gland. This designation is reserved for tumors in whom the mucinous component constitutes more than 25% of the tumor. Mucinous carcinoma of the prostate replaces the bulk of the prostate with a diffuse nonpapillary (colloid) pattern of “lakes” containing acidic mucins (Fig. 33.26) that does not disturb the ductal pattern. The lesion usually remains confined to the prostate, indicating a relatively favorable course; local extension and metastasis to the lung, liver, lymph node, and brain have been reported (264). These tumors tend to react positively with PSA and PAP, which distinguishes them from bladder tumors of similar histology. As was true with tumors exhibiting ductal differentiation, a Gleason grading is performed only on the nonmucinous

components of the tumor (690). Pure mucinous prostate carcinomas tend to be hormone insensitive (694).

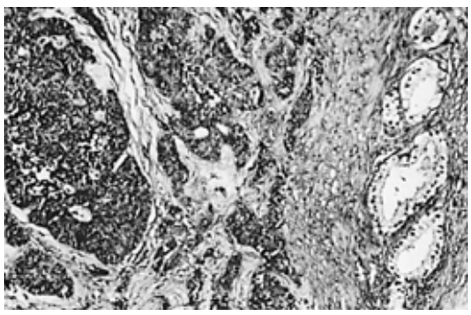

FIGURE 33.25. Adenoid cystic carcinoma. Although several cell types are clearly represented in this photomicrograph, the majority possess deeply staining cytoplasm reminiscent of basal cells (Fig. 33.10). Numerous cystic spaces ("Swiss cheese" pattern) are found in between glandular elements. The latter are surrounded by a prominent mucoid matrix (189× magnification). (From Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:303, with permission.)

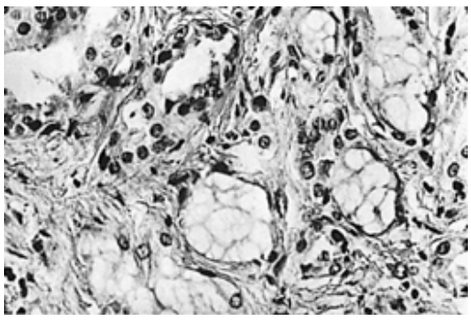

FIGURE 33.26. Colloid carcinoma of the prostate. Mucinous adenocarcinomas as depicted in this photomicrograph often have a soft consistency, as judged by rectal examination. Although nonsulfated acid mucin production can be documented in approximately 75% of prostate cancers, pure colloid carcinomas are rare, with only about 20 cases having been reported. Mucin production can be focally aggregated, as depicted here, or may present as a "mucinous lake," which may replace large amounts of normal parenchyma (459× magnification). (From Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:303, with permission.)

As the name implies, carcinosarcomas contain elements of both adenocarcinoma and sarcoma (Fig. 33.27) (705,1000). Carcinosarcomas usually are manifested by the presence of highly neoplastic cartilage, bone, and smooth or skeletal muscle. A pelvic mass is often appreciated at the time of initial diagnosis, reflecting the aggressive nature of the disease. Metastases to the spine, liver, lung, and lymph nodes occur early in the onset of the disease. Because the sarcomatous element of these lesions is hormone-resistant, androgen deprivation therapy is only temporarily palliative. These tumors are uniformly fatal with a mean survival of 21 months (705).

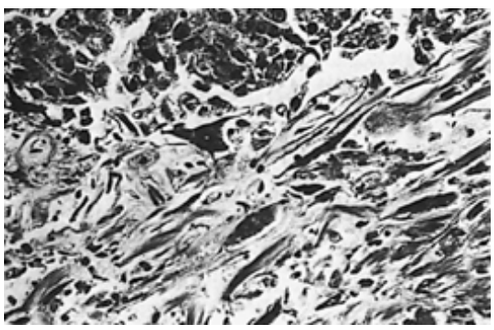

FIGURE 33.27. Carcinosarcoma of prostate. Both carcinomatous *(top left)* and sarcomatous *(bottom right)* elements are depicted in this photomicrograph. In this case, malignant stroma is characterized by the presence of pleomorphic straplike cells not unlike those found in rhabdomyosarcoma (328× magnification). (From Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:303, with permission.)

Pure sarcomas of the prostate are exceedingly rare lesions and constitute less than 0.1% of all malignant prostatic neoplasms (1075). Approximately one-third of these lesions occur within the first decade of life. The most common of these childhood sarcomas is the rhabdomyosarcoma. The latter consists of three histologic subtypes: embryonal (sarcoma botryoides), alveolar, and pleomorphic. This tumor grows posteriorly to involve the rectum and anteriorly to produce a pelvic or abdominal wall mass with impressive rapidity. Lymphatic and hematogenous dissemination occurs early, accounting for frequent involvement of regional lymph nodes, liver, and lungs. When bony metastases occur, they tend to be painful osteolytic lesions. The diagnosis is established by formal biopsy techniques that characteristically reveal large ballooned giant cells often admixed with elongated straplike cells with a typical cross-striation pattern. A discussion regarding the clinical features of these childhood sarcomas is presented elsewhere in this text.

Although 75% of prostatic sarcomas involve males younger than the age of 40 years, these neoplasms do occur in the older age groups. With regard to the latter, the most frequently encountered variants include the leiomyosarcoma, fibrosarcoma, and lymphoma. Less commonly noted lesions include neuroblastoma, neurogenic sarcoma, osteogenic sarcoma, chondrosarcoma, malignant fibrous histiocytoma, fibrosarcoma, and angiosarcomas (1075). The natural history of the more common variants is similar to that of those cited previously. Anterior and posterior extension of the tumor with projection toward the abdominal wall, rectum, and perineum occurs in approximately 75% of these cases. Again, formal tissue biopsy is imperative to establish the diagnosis unequivocally. For example, the very cellular pattern of leiomyosarcoma with characteristic interlacing cell bundles that form a whorled or herringbone pattern (Fig. 33.28) may be difficult to distinguish from stromal hyperplasia (296). Lymphomas and lymphosarcomas may present histologically as a uniform array of large lymphocytes that infiltrate the stroma and acinar elements. These cells often infiltrate between muscle bundles, causing compressive atrophy. A definitive histopathologic diagnosis in these cases may require electron microscopy and an assessment of cytoskeletal features.

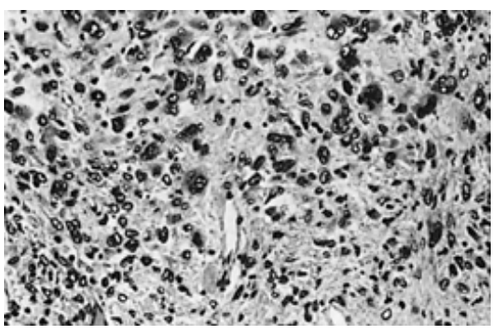

FIGURE 33.28. Leiomyosarcoma of the prostate. These tumors are hypercellular and often present as interlacing bundles of cells suggesting a whorled appearance. Although low-grade leiomyosarcomas may be difficult to differentiate from stromal hyperplasia, the more anaplastic variant depicted in this photomicrograph reveals a highly pleomorphic picture characterized by the presence of occasional multinucleated cells (260× magnification). (From Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:303, with permission.)

The literature contains isolated, anecdotal case reports of various unusual or exotic primary neoplasms involving the prostate. Tumors of the amine precursor uptake and decarboxylation (APUD) system, including extrapulmonary small-cell carcinoma, carcinoid tumors, and paragangliomas, have been noted. Ectopic adrenocorticotropic hormone (ACTH) secretion has been reported with some of

these lesions. Such observations are not surprising, considering that argentaffin and argyrophil cells have been demonstrated within the normal prostate, glands involved with BPH, and prostatic carcinomas. These cells are of neuroepidermal (neuroendocrine) origin and may be demonstrated by specific staining techniques utilizing various potential probes, including chromogranin A, bombesin, CEA, neuron-specific enolase, serotonin, adrenocorticotropic hormone, somatostatin, synaptophysin, parathormone, calcitonin, S100 protein, human heart factor 35, gastrin, and glucagon. Some of these tumors also may arise from differentiation occurring within acinar epithelial cells. Other reported primary neoplasms include malignant melanomas, osteochondrosarcomas, and signet ring adenocarcinomas (1075).

Small-cell carcinoma of the prostate is being recognized with increasing frequency (Fig. 33.29) and possesses the following features in common: prominent size, dissemination at the time of diagnosis, poor prognosis, and a large component of small cells with anaplastic nuclei and scant cytoplasm (690). Its development may be associated with adenocarcinoma, or it may be the sole identifiable tumor component. Limited observations suggest a rapid progression of metastatic androgen-independent disease with involvement of multiple organs. These tumors usually retain evidence of neuroendocrine origin based on immunohistochemical and ultrastructural features. Their development from totipotential high-grade prostate adenocarcinoma also warrants consideration. Prostate cancers exhibit three forms of neuroendocrine (NE) differentiation: (a) small-cell (NE) carcinoma, (b) carcinoid-like tumors, and (c) conventional prostate cancer with focal NE features. The latter is extensive in 10% of cases and constitutes a poor prognostic indicator.

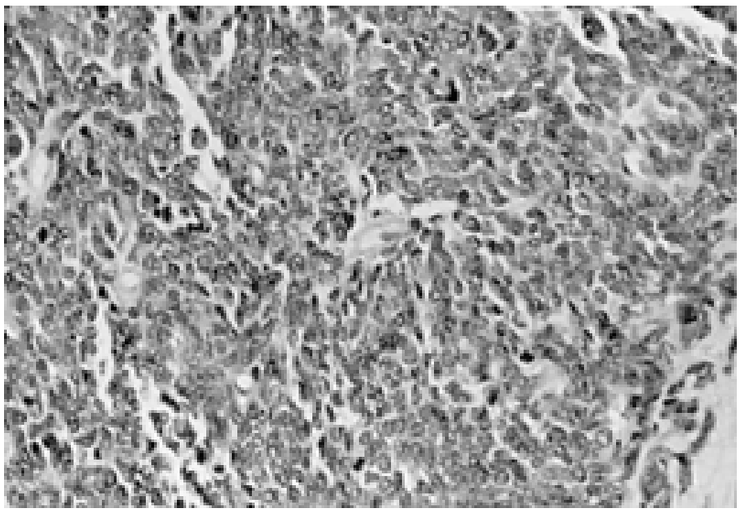

FIGURE 33.29. Small-cell carcinoma of the prostate. These cells exhibit nuclei with condensed chromatin and very scanty cytoplasm (300× magnification). (Photomicrograph courtesy of R. Oyasu, M.D.)

Zein and associates reported one of the most exhaustive studies of secondary tumors of the prostate. On reviewing reports of more than 6,000 autopsies of males with a median age of 66 performed at Roswell Park Memorial Institute during a 25-year period, they noted secondary involvement of the prostate in 328 (5.6%) cases. Prostatic involvement resulted from contiguous or extensive local regional disease in 143. The primary tumors involved the bladder, urethra, colon, rectum, anus, malignant lymphomas, and an assortment of alimentary tract carcinomas and bone or soft-tissue sarcomas. Of 185 (3.1%) true metastatic lesions, leukemia was the most common. In fact, prostatic involvement was demonstrated in 10.3% of all male leukemia autopsies and in 20% of those dying from chronic lymphocytic leukemia. Similarly, 8% of patients dying of non-Hodgkin's lymphoma have prostatic involvement. Of interest, metastasis to the prostate was encountered infrequently in patients dying of Hodgkin's disease. If only nonleukemic, nonlymphoma cases were considered, Zein and co-workers (23) noted prostate involvement in approximately 1% of the autopsied patients. This contrasts to a frequency of 0.5% cited by Johnson and colleagues (471). The most common primary sources encountered in both series were malignant melanoma and lung carcinomas. Other primary sites included pancreas, germ cell tumors, thyroid, stomach, kidney, esophagus, and trachea. Metastases to the prostate gland invariably reflect the presence of a large tumor burden and multiorgan system involvement. In fact, approximately 98% of these patients had extensive disease noted in five or more organs. Although most instances of prostatic metastasis are attributed to the arterial dissemination of tumor emboli, documented cases of venous involvement also exist.

CLINICAL EVALUATION

Part of "33 - CARCINOMA OF THE PROSTATE "

The proper treatment of patients with CaP depends on proper histologic diagnosis, an assessment of those tumor-related properties possessing prognostic significance, and accurate staging. The following sections present an evaluation of our current diagnostic and staging procedures. At present, the diagnosis of CaP depends on at least three steps: (a) recognition of an indication for tissue sampling, (b) selection and utilization of appropriate tissue procurement techniques, and (c) the unequivocal confirmation of the diagnosis. The status of the criteria used to guide each of these steps is discussed briefly in the following sections.

Identification of Risk

Some studies have documented that a substantial proportion of patients diagnosed with clinically localized CaP may anticipate favorable clinical outcomes and normal life expectancies in the absence of early aggressive treatment. In general, this cohort consists of an older population of men with low-grade tumors. Conversely, the risk of death secondary to CaP is substantial in younger patients exhibiting

moderate- or high-grade tumors. Indeed, long-term survival is significantly diminished in patients with CaP spread beyond the capsular perimeter with subsequent involvement of the regional lymph nodes and bone (1014). With respect to this issue, several points are clear. First, the acknowledged disparity between the high prevalence rates for histologic CaP and the relatively low lifetime risk of CaP death (approximately 3%) merely highlights the need to reliably distinguish those tumors destined to adversely affect the quality and/or duration of life from those that will not. Second, avoiding a problem has never solved it.

General Indicators

Increased concern for the presence of CaP is appropriate based on selective hereditary and racial information, symptoms, abnormal findings on the DRE, and the serum PSA profile. The latter two assessments as well as observations made during transrectal ultrasonography (TRUS) are also used to guide appropriate tissue sampling.

Hereditary and Racial Considerations

The importance of hereditary and racial factors with regard to the development of CaP has been covered in detail in the sections on epidemiology and natural history. The American Urological Association (AUA) recently convened a multidisciplinary task force to address the issue of PSA-based screening. It was their consensus recommendation that candidates for early detection testing include (a) men age 40 to 50 with a family history of prostate cancer or African American ethnicity and (b) men age 50 or more with an anticipated life span of 10 years or more (1014).

Symptoms

Until the advent of PSA-based screening in the late 1980s, symptomatic-driven physician encounters were responsible for identifying the vast majority of patients in whom a clinical diagnosis of CaP was made. The traditional teaching that CaP usually does not cause symptoms until it is advanced has most often been confirmed. Problems relating to lower urinary tract voiding dysfunction are most common and those relating to metastatic disease are a distant second in prevalence in these patients. The association with advanced disease reflects the appreciable mass that prostate carcinoma usually must achieve to alter voiding patterns. All of the symptoms characterizing BPH voiding dysfunction occur in these patients. Slow stream, increased urinary frequency, dysuria, and complete retention have historically been identified most commonly in patients with prostatic carcinoma (503), but nocturia, hesitancy, intermittency, sense of incomplete voiding, and urgency also occur. None of these alone or in combination is unique for CaP. In many patients with carcinoma, BPH is the actual cause of the dysfunctional voiding. The physical examination and laboratory evaluation often lead to recognition of increased risk and histologic confirmation of asymptomatic CaP. In addition, unsuspected carcinoma is identified in the excised tissue judged clinically to be BPH. Historically a diagnosis of unsuspected CaP designated stage T_{1a}, T_{1b}, or A_1, A_2 based on the grade and mass of the tumor, has occurred in approximately 10% of men subjected to prostatectomy in the United States. (604). Hematuria occurs in less than 15% of patients with CaP. The suggestion that up to 25% of men with acute urinary retention will have unrecognized CaP as the underlying cause (147) lacks current support. Reports of back, leg, and perineal pain have been present in 20% to 40% of the patients presenting with CaP in the past but constitute a much smaller percentage currently. Constitutional symptoms such as weight loss and general weakness are less common, each occurring in less than 15% of the patients.

Physical Examination

The DRE, preferentially performed with the patient in the supported, bent-over erect or knee-chest position, has traditionally been used to evaluate the size, consistency, and configuration of the prostate to identify changes suggesting a diagnosis of CaP. The presence, configuration, location, intraglandular and extraglandular extent, and the distinctness of the margins of any indurated or irregular area should be noted and recorded. The status of the median furrow and lateral sulci should be assessed and stipulated. The areas at the base of the seminal vesicle and bladder also should be examined for extension of induration. A two-dimensional diagram helps clarify and record the digital findings (Fig. 33.30).

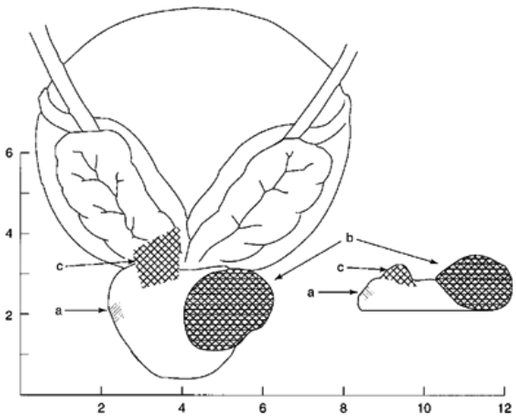

FIGURE 33.30. Diagrammatic representation of findings on digital rectal examination of the prostate gland and seminal vesicles. Nodule configuration is conveyed on the transverse diagram. We conventionally record indurations in a systematic fashion. Minimal degrees of induration are represented by a single series, moderate by a double series, and marked by a triple series of oblique lines. Scale is in centimeters. a-B1 (T_{2a}), tumor involving half of a lobe or less; b-B2 (T_{2b}), tumor involving more than half of a lobe, but not both lobes; c-C (T_{3c}), tumor invades seminal vesicles. (From Kim E, Grayhack JT. Clinical signs and symptoms of prostate cancer. In: Vogelzang NJ, Shipley WU, Sardino PT, eds. *Comprehensive textbook of genitourinary oncology.* Baltimore: Williams & Wilkins, 1996, with permission.)

The classical physical features of CaP include an irregular; stony hard; or notably indurated, flat, or nodular area with indistinct margins. Extension of abnormal findings across normal landmarks increases suspicion of, but is not exclusive for, malignancy. Aside from the median furrow, which is rarely an isolated location for carcinoma, a CaP risk-signaling palpable abnormality may be located anywhere in the gland. Gradually evidence has accumulated indicating that any change in consistency and possibly configuration should lead to consideration of carcinoma as a cause. Alternative causes of a nodule or induration include a calculus, prostatitis, tuberculosis, focal infarction, a postbiopsy tissue reaction, and even a spheroid of benign hyperplasia. X-ray or ultrasound examination usually identifies calculi; microscopic examination of prostatic fluid obtained by massage provides information regarding inflammatory processes. The presence of an alternative cause for the palpable abnormality does not exclude carcinoma. In most circumstances, reexamination after a limited period of observation with or without an active treatment regimen is desirable to confirm the persistence and importance of the palpable abnormality.

Clearly a definite diagnosis of CaP cannot be made on the basis of the physical findings. In a series of 211 patients

subjected to open perineal biopsy because of findings on DRE indicating probable localized carcinoma, only 50% had documented malignancy. A literature review of needle biopsy results in 4,939 patients disclosed that only 39% of patients selected for tissue sampling on the basis of the abnormal DRE were found to have carcinoma (89). Brawer (89) cites evidence from his own experiences, as well as the literature, that indicates that carcinoma is found much more frequently on biopsy of the prostate that is a site of a markedly indurated or nodular area highly suspicious for carcinoma (54%), as contrasted to the simple presence of induration (25%) or asymmetry (12%). The rate of positive biopsies in the latter group was approximately the same as in a group of men with normal glands on palpation who underwent biopsy because of an elevated serum PSA or a planned alternative therapy for BPH (15%).

The limitations of DRE as an indicator of the presence and extent of carcinoma of the prostate are well documented. Hudson and associates (441) found approximately one-fourth of the carcinomas, identified on multiple biopsies of the prostate in a group of men with no or minimal symptoms, were associated with areas of no or minimal induration. In a multicenter study of 6,630 men, the intra-gland location of carcinoma as judged from the findings on a routine four-quadrant sampling in addition to lesion-directed biopsies was found only in quadrant(s) lacking induration in 16 of 42 patients with cancer with serum PSA values of 4 ng/mL or less and in 121 of 183 patients with serum PSA levels of greater than 4 ng/mL. In all 624 patients who had an abnormal DRE as an indication for biopsy, regardless of serum PSA levels, cancer was found in 220 of the quadrants biopsied; 110 of these were from quadrants lacking palpable abnormalities (297). Nevertheless, in this study, which included PSA serum levels and DRE as an indicator for biopsy, 146 (55%) of 264 of the patients with biopsy-identified carcinoma had a suspicious DRE; this was the only indication for biopsy in 48 (18%) patients.

The relative lack of sensitivity and specificity associated with the DRE has prompted some physicians to recommend that it be omitted as a routine part of the physical examination. This nihilistic approach is unwarranted and dangerous for several reasons. First, approximately 20% of prostate cancers with aggressive features are detected in men with PSA levels less than 4 ng/mL (825). Fortunately, many of these tumors will present with an abnormal DRE. In addition, evidence has accumulated from three uncontrolled studies that allow a direct comparison of PSA and DRE as screening tools (100,825). Volunteers in these studies were assessed uniformly with both PSA and DRE. Approximately 18% to 26% had either an abnormal PSA or abnormal DRE. CaP was detected in 3.5% to 4.0% of these populations. Although PSA testing detected more tumors than DRE, PSA and DRE each detected cancers not identified by the other modality. For these and other reasons, the AUA multidisciplinary task force recommended that both tests be used in any early prostate cancer detection program (1014). The DRE should be performed by a knowledgeable, skilled individual who recognizes alternative causes and the possible effects of treatment and/or observation on a palpable abnormality. Coordinating a touch diagram and clinical information is particularly helpful in longitudinal patient assessments.

Physical Imaging

The currently available imaging modalities add little to the combination of PSA and DRE for early detection of prostate cancer. The anatomic information provided by

transrectal ultrasound of the prostate (TRUSP) usually has been superior to that obtained by either computed tomography (CT) scanning or conventional magnetic resonance imaging (MRI). Recently, reported observations suggest endorectal MRI imaging and spectroscopy may be useful to target suspicious areas/sextants and improve the diagnostic yield of subsequently performed TRUSP-biopsies (1083). In this study, tumors were identified based on low-signal intensity on endorectal MRI T_2-weighted images and magnetic resonance spectroscopy identified areas of abnormal metabolism. Knowledge of this combination of findings enhanced the ultimate yield of ultrasound-guided biopsies in patients who were biopsy-naïve and in those individuals who had undergone previous tissue sampling. The proper use of TRUSP in the diagnosis and staging of CaP is contingent upon the urologist's working familiarity with a reliable 7- to 7.5-MHz multiplane instrument and biopsy system (Fig. 33.31); an appreciation of the recognized ultrasonic features of normal prostate, BPH, and prostate cancer; and an understanding of the limitations of this approach.

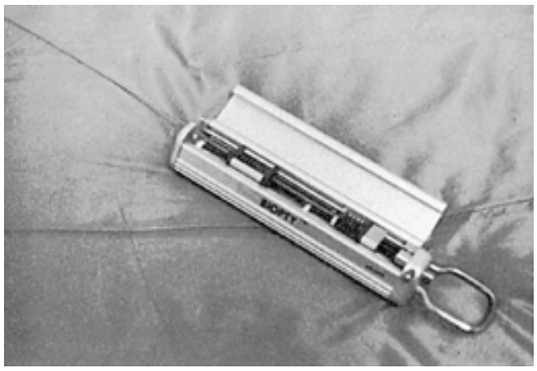

FIGURE 33.31. Example of the Bard automatic biopsy system (i.e., the Biopty gun). (Photomicrograph courtesy of D. Grapey, M.D.)

Ultrasonic imaging of the normal prostate usually identifies distinct peripheral (corresponding to the anatomic peripheral zone) and central (corresponding to the anatomic central and transition zones) regions. The peripheral region constitutes 75% of the normal glandular volume and occupies the posterior, lateral, and apical regions (Fig. 33.32). Its ultrasonographic appearance is typically described as isoechoic. BPH, developing within the anatomic transition zone, expands the central region of the ultrasound image. This often produces a more rounded configuration of the entire gland, with the most noticeable increase seen in the anteroposterior (AP) diameter (Fig. 33.33). The intact capsule is well defined, but areas of thickening may be apparent. The isoechoic pattern may be disrupted by both hypoechoic and hyperechoic foci, which reflect the presence of viscous secretions within prostatic ducts and the presence of calculi and prostatitis.

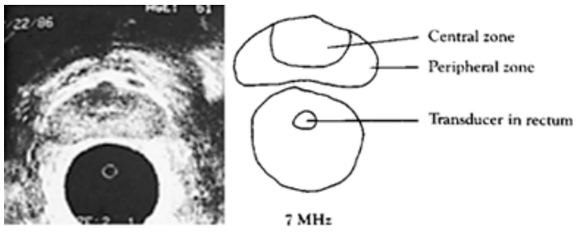

FIGURE 33.32. Transrectal ultrasound of normal prostate. A high-resolution (7-MHz) transducer was used to obtain this transverse scan of the midprostate. Echogenic homogenicity of the parenchyma is apparent along with an echo-rich prostatic capsule. A prominent component of the venous complex is nicely demonstrated in the 1 o'clock position of the capsular parameter. (From Ragde H. *Prostate imaging with transrectal ultrasound.* Seattle, 1986:1, with permission.)

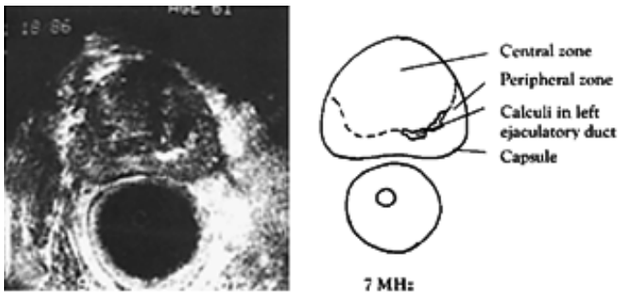

FIGURE 33.33. Transrectal ultrasound of benign prostatic hyperplasia (BPH). Transverse echogram was taken at the level of the verumontanum as demonstrated by the proximity of the *left ejaculatory duct.* The surgical capsule is well defined as an interphase between the prominent adenomatous hyperplasia and the peripheral zone of the prostate. The latter demonstrates homogeneity of its echo pattern and the anatomic capsule is well defined. (From Ragde H. *Prostate imaging with transrectal ultrasound.* Seattle, 1986:1, with permission.)

Attempts to use prostatic ultrasound observations to identify the presence and site of carcinoma of the prostate have been significantly hampered by the failure to identify an echogenic pattern with a high degree of sensitivity and/or specificity for the risk of its presence. The initial experiences with ultrasound resulted in the suggestion that a peripherally located hypoechoic area identified with the available high-resolution equipment indicated a significant risk of CaP (Fig. 33.34). However, an expanding experience demonstrated the limited sensitivity and specificity of this observation. Carcinomas may be associated with hypergenicity, isogenicity, or mixed echogenicity; the hyperechoic patterns with CaP lack the brightness and acoustic shadowing seen with calculi. Hypoechoic foci may result from acute inflammation, infarcts, small nodules of hyperplasia, blood vessels, cystic atrophy, or muscle tissue. In addition, the 20% to

30% of prostate cancers originating in the central or transition zone (631) are difficult to detect on TRUSP. The demonstration of asymmetry, capsular deformity, distorted or obliterated seminal vesicles (Fig. 33.35), and/or a periprostatic mass are observations that raise questions about local extent more often than presence of CaP.

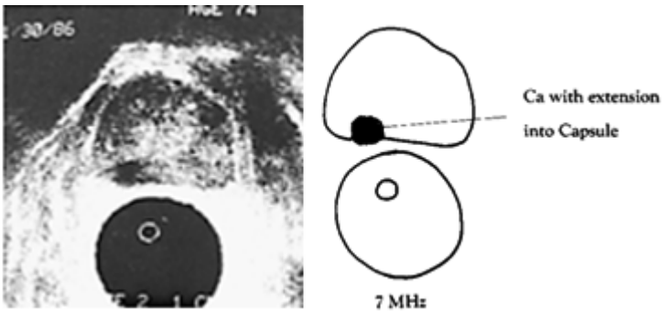

FIGURE 33.34. Transrectal ultrasound of prostate cancer. A conspicuous echo-poor region is seen in the peripheral zone of the prostate on this transverse echogram. The lesion contrasts sharply with the normal aspects of the peripheral zone, which are typically echo rich. (From Ragde H. *Prostate imaging with transrectal ultrasound.* Seattle, 1986:1, with permission.)

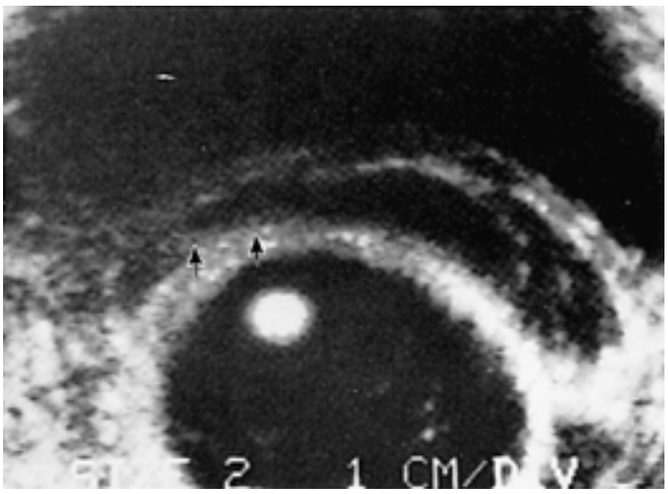

FIGURE 33.35. Obliteration of seminal vesicle *(arrows)* by invasive prostate cancer demonstrated by transrectal ultrasonography (TRUS). Such an observation should prompt a consideration of ultrasound-guided needle biopsy to confirm the presence of stage T_3 disease. (From Waterhouse RL, Resnick MI. The use of transrectal ultrasonography in the evaluation of patients with prostatic carcinoma. *J Urol* 1989;141:233, with permission.)

The limitations of ultrasound evaluation to diagnose risk of CaP have been emphasized by several reported experiences. For example, Devonec and associates (227) reported only 11 (6.7%) of 162 men with demonstrated hypoechoic areas with TRUSP had cancer, and 6 had high-grade PIN on biopsy. Using six ultrasound-guided biopsies, Vallancien (1035) found carcinoma of the prostate in 14 of 100 men without palpable evidence of malignancy; 18 patients had hypoechoic areas on TRUS, but CaP was diagnosed in only 2 of these. In the previously described multicenter diagnostic efforts (145,297), use of characteristic ultrasound abnormality to justify biopsy of patients with a suspicious rectal finding, a serum PSA greater than 4 ng/mL, or both would have resulted in a failure to diagnose 39% of the cancers ultimately detected. In patients with a PSA greater than 4 ng/mL, with or without an abnormality on DRE, exclusive biopsy of TRUS-identified hypoechoic sites would have missed 106 of 203 patients and 243 of 368 prostate quadrants with carcinoma. Even accepting possible equipment or operator deficiencies, the results seem to reflect current practice expectations. The lack of pathognomonic appearance of CaP on TRUS is probably a very significant factor in these disappointing results. The inability to image anatomic transition and central zone tumors well probably has a limited impact. Available evidence suggests that the use of color Doppler ultrasonography (with or without contrast enhancement) does not increase the sensitivity and specificity of this modality to a statistically significant degree (167,702). Currently, the lack of specificity and sensitivity of information currently derived from TRUSP has reduced its role to a selective ancillary one in diagnosis and treatment of this disease.

SERUM PROSTATE-SPECIFIC ANTIGEN

Part of "33 - CARCINOMA OF THE PROSTATE "

PSA was first identified in human prostatic tissue extracts in 1970 (2), purified and characterized by Wang and associates in 1979 (1071), and detected in human serum by Papsidero and associates in 1980. PSA is a single chain, 240–amino acid glycoprotein with a molecular weight of 33 kDa. The human PSA gene is located on chromosome 19 (544). The mRNA of PSA, like other cytoplasmic serine proteases, is translated as an inactive pre-PSA/pro-PSA precursor. Following passage through the intracellular secretory pathway, the signal peptide is cleaved, yielding the proform of the protein. Evidence suggests the conversion of pro-PSA to the mature enzymatically active PSA requires the action of human kallikrein 2 (hK2) (544). Recent evidence suggests that truncated forms of pro-PSA are differentially elevated in the peripheral zone of the prostate, the site where most cancers are localized. Little or no pro-PSA has been identified in the transition zone (656). This observation suggests that pro-PSA is more highly correlated with prostate cancer than with BPH. Cleavage of the propeptide from pro-PSA by hK2 converts PSA to the enzymatically active mature form, which is then capable of complexing with α_1-antichymotrypsin (95). PSA shares sequence homology with the human kallikreins and in fact, a 78% homology with hK2. PSA possesses chymotrypsin-like activity and has a weak interaction with the plasma inhibitor, aprotinin. PSA also has modest overlapping homology with urokinase-like plasminogen activator and is capable of facilitating the degradation of the extracellular matrix.

PSA is primarily produced by adluminal or secretory cells of the prostate and the epithelial lining of the periurethral glands (785). The basal cells of the prostate do not express this protein. It is androgen regulated and one of the most abundant serine proteases in the seminal plasma (1,000,000 ng/mL). Its major physiologic role is to promote the liquefaction of seminal clot. Seminal clotting is due to the presence of semenogelin 1 and semenogelin 2 and fibronectin. PSA targets the semenogelin component, thus liquefying the seminal clot, which in turn facilitates sperm motility. The half-life of PSA is 2.2 to 3.2 days (967).

Molecular Forms of Prostate-specific Antigen

Each PSA molecule contains five immunoreactive, antibody-binding sites or epitopes (1072). The currently available commercial PSA assays detect total PSA, PSA α_1-antichymotrypsin, and free PSA (1072). PSA α_1-antichymotrypsin generally represents between 70% and 85% of the total measured PSA in the serum of men (1041). Free PSA, which typically accounts for less than 30% of total measured PSA, is detected by assays that measure the enzymatically inactive, uncomplexed form (625). α_2-Macroglobulin and other proteins bind a smaller proportion of PSA. α_2-Macroglobulin completely encapsulates the PSA molecule, blocks the epitope sites, and cannot be reliably assayed because of this lack of immunoreactivity (1041). Recently, Ornstein and associates (737) used laser capture microdissection to characterize the intracellular PSA from benign and malignant prostatic epithelium. PSA derived from normal and malignant epithelial cells did not differ in molecular weight or the ability of the respective PSA moieties to bind to α_1-antichymotrypsin. Furthermore, no differences were identified in isoforms of benign- and malignant-derived PSA. These findings indicate that PSA produced by malignant prostate epithelium is not mutated or differentially processed. Last, they documented that the intracellular PSA exists in the "free" form and that binding to α_1-antichymotrypsin occurs exclusively outside of the cell.

Nonprostatic Sources of Prostate-specific Antigen

Low levels of PSA and/or PSA-gene expression have been detected in various tissues, particularly those that have constitutive expression of the steroid receptor superfamily, including the uterine endometrium and amniotic fluid, normal/lactating breast tissue and the milk of lactating women, breast cancer; perianal/periurethral glands, salivary glands, adrenal/renal neoplasms, and various other malignant tumors (785).

Biologic Functions of Prostate-specific Antigen in Health and Disease

As stated previously, the major constitutive role of PSA is to degrade and dissolve the seminal clot by breaking the semenogelin bonds. PSA is a weak matrix-degrading protease. In this capacity, it may facilitate the microinvasion of malignant acinar elements into the extracellular matrix (ECM). PSA is both a direct and indirect mitogen for prostatic epithelial cells. With respect to the latter, PSA is an important regulator of the IGF system. The latter is composed of two ligands (IGF-I, IGF-II), two receptors (IGFR-I, IGFR-II), and six unique binding proteins (IGFBP-1 to IGFBP-6). This IGF system plays a strategic role in the autocrine growth regulation of prostate cancer (15). PSA can function as an IGFBP-3 protease. Through this mechanism of action, PSA cleaves sequestered IGFs from this binding protein, which serves as a negative regulator of cell proliferation. Once released, the two ligands are free to interact with their receptors and stimulate prostatic cell growth. Finally, PSA is a mitogen for osteoblasts and may be one of many factors responsible for the typical osteoblastic reaction following the colonization of red marrow sinusoids by metastatic prostatic cells.

Mechanism of Elevated Prostate-specific Antigen

As stated previously, the prostatic acinous contains the highest concentration of PSA in the body (95). In the normal prostate, the majority of PSA is secreted into the acinar/ductal lumen. Under normal circumstances, only a modest amount of PSA enters the systemic circulation. The latter may be due to the release of PSA from cells undergoing programmed cell death. Formidable barriers are interposed between the prostatic acinous and capillary blood, including the prostate basement membrane, the intervening stroma, the capillary basement membrane, and the capillary endothelial cell (95). Prostate cancer is associated with serum PSA levels at least tenfold higher per gram of tissue than BPH (967). In cancer, there may be loss of polarity and increased fragility of the basement membrane, which would facilitate PSA entry into the systemic circulation (Fig. 33.36).

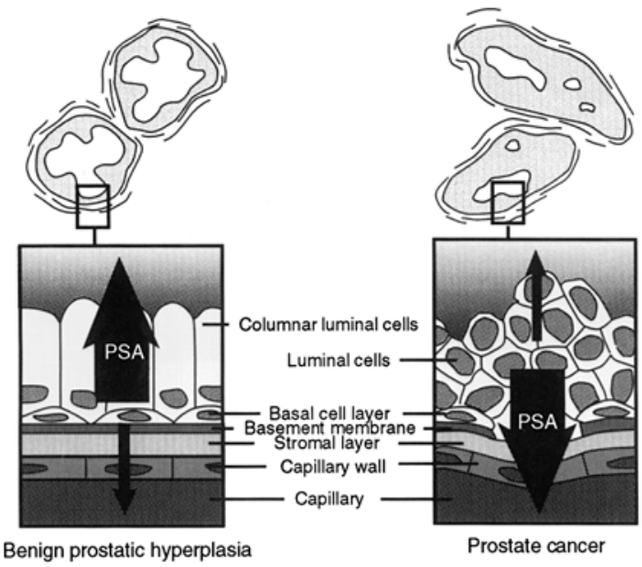

FIGURE 33.36. Normally, significant tissue barriers are between the lumen of the prostate gland and the capillary bed. In prostate cancer these barriers are compromised. PSA, prostate-specific antigen. (From Brawer MK. Prostate-specific antigen: current status. *CA Cancer J Clin* 1999;49:264, with permission.)

Serum PSA levels require critical evaluation to maximize their usefulness with regard to CaP risk. We have always routinely examined prostatic fluid microscopically after rectal examination and used the number of white blood cells (WBCs) present (greater than or equal to 10 WBCs/HPF) (873) to consider the possibility that an elevated PSA serum level might reflect modifiable prostatic inflammation. This practice has recently been supported in principle by the observations of Potts (795). Transient serum PSA elevations have been observed in the following situations: postejaculation, acute prostatitis, subclinical prostatitis, urinary retention; following vigorous prostatic massage, as a consequence of ischemia associated with cardiopulmonary bypass, and following prostate needle biopsy. The literature is equivocal with respect to the impact of cystoscopy and urethral catheterization on serum PSA levels. Most studies do not demonstrate a statistically significant increase in the serum PSA following a routine DRE or TRUS alone. α-Adrenergic antagonists do not affect circulating PSA

levels. On the other hand, finasteride decreases total serum PSA values by approximately 50% after a 6-month course. PSA density is lowered by long-term finasteride therapy, but the percent serum free PSA is unaffected by this treatment. Following the resolution of a significant provocative event, it is prudent to permit 4 to 6 weeks to elapse before using serum PSA levels to serve as the catalyst for clinical decision making (785).

Role of Prostate-specific Antigen in Prostate Cancer Detection

The use of serum PSA levels to identify patients with increased risk of CaP has been the subject of intense evaluation and controversy. The initial stimulus to use serum PSA for this purpose was the unexpected result of several astute clinical observations. Although histochemical observations demonstrated the PSA content of BPH epithelial cells is usually greater than that of CaP cells, Stamey and colleagues (961) presented evidence that the contribution to serum PSA levels by a gram of cancer (3.5 ng/mL) exceeds that associated with a gram of BPH (0.3 ng/mL) by approximately tenfold. More than 50% of patients with organ-confined CaP, as compared with approximately 25% of patients with histologically confirmed BPH, exhibit serum PSA levels greater than 4 ng/mL (727). Similarly, Cooner and associates (184) demonstrated the increased recognition of CaP using a serum PSA level greater than 4 ng/mL to prompt selective ultrasound-guided needle biopsies. Studies by Catalona and associates (149) and Brawer (90) demonstrated that a total serum PSA greater than 4.0 ng/mL in a man 50 years of age or older is associated with an approximately 33% chance of detecting CaP on initial systematic ultrasound-guided needle biopsies. These observations have been confirmed by many other investigators (Table 33.7).

Author	Year	Population	No. of Biopsies	PPV
Babaian and Camps	1991	Mixed	67	31.3
Bazinet, et al.	1994	Referral	565	37
Brawer and Lange	1989	Referral	188	54.2
Brawer, et al.	1992	Screening	105	30.5
Catalona, et al.	1991	Screening	112	33
Catalona, et al.	1994	Screening	1,325	37.1
Cooner, et al.	1988	Referral	96	51.2
Cooner, et al.	1990	Referral	436	35
Ellis, et al.	1994	Referral	541	36.8
Mettlin, et al.	1994	Screening	70	41.4
Rommel, et al.	1994	Referral	2,020	41

Note: Studies cited are from original source.
PPV, positive predictive value.
Adapted from Brawer MK. Prostate-specific antigen: current status. *CA Cancer J Clin* 1999;49:264, with permission.

TABLE 33.7. CORRELATION OF PROSTATE-SPECIFIC ANTIGEN LEVEL GREATER THAN 4.0 NG/ML AND CANCER: CONFIRMATORY STUDIES

As a composite, these and other studies permit several observations: (a) the presence of an abnormal DRE and/or ultrasound observation in a patient with an abnormal serum PSA increases the CaP detection rate, (b) a normal serum PSA does not exclude the presence of identifiable CaP, and (c) an abnormal serum PSA is the single most predictive risk indicator for the presence of CaP. Longitudinal observations in the physician health study using stored sera reinforced these perceptions (332). A serum PSA value greater than 4 ng/mL at the initiation of the study identified 73% of the men who had a diagnosis of CaP in the next 4 years and 87% of those classified as having aggressive cancer. Although maximum validity was obtained with a 3.3 ng/mL serum cutoff value, the gain as compared with 4 ng/mL was considered minimal. Furthermore, the risk of an eventual diagnosis of CaP increases in relation to the initial PSA level observed in these studies of selectively and nonselectively recruited males (148,332). Gann and others (332) noted a fivefold increased risk of CaP and a sevenfold increased risk of aggressive CaP on a longitudinal follow-up for 10 years in men whose single initial serum PSA level was 2.01 to 3.0 ng/mL compared with those with a PSA level of 1.0 ng/mL or less. PSA testing clearly has had a profound impact on CaP screening. Clinical stage T_{1c} prostate cancer (nonpalpable, PSA detected) presently constitutes the most prevalent

clinical CaP stage (797). Less than 20% of these PSA-driven diagnoses reflect the detection of clinically insignificant tumors. Indeed, only 60% of stage T_{1c} prostate cancers are pathologically organ confined (747). Nonetheless, the majority of these tumors are amenable to curative treatment with currently available therapies; they probably account for the recently reported decline in CaP death rate. Current evidence supports the perception that the PSA with DRE improves detection of CaP (145,184) and increases the lead time for diagnosis (332).

Recommended Frequency of Prostate-specific Antigen Measurements for Prostate Cancer Detection

Both the ACS and the AUA recommend annual PSA screening for all men 50 years of age or older. An exception is the recommendation to initiate PSA testing at age 40 for men with a family history of prostate cancer or for men of African American descent (785). Studies conducted by both Carter and associates (129) and Smith and associates (927) suggest annual PSA screening for men with a normal DRE and a stable PSA level of less than 4 and greater than 2.5 ng/mL and biannual PSA screening for men with a normal DRE and a serum PSA of less than 2.5 ng/mL appear safe. Recent data from the Baltimore Longitudinal Study (131) suggesting that using a PSA level of 1.0 mg/mL or less in men aged 65 to discontinue routine evaluation would still result in recognition of 94% of patients developing CaP by age 75 are unlikely to modify these suggestions without additional observations.

Strategies for Enhancing Prostate-specific Antigen Specificity

Attempts to improve the specificity of serum PSA determinations as a risk indicator for prostate cancer have focused on the following approaches: (a) age-specific PSA, (b) PSA density, (c) PSA velocity, (d) PSA transition zone density, (e) free-to-total PSA ratio, and (f) ACT α_1-antichymotrypsin) complex PSA.

Age-specific Prostate-specific Antigen

The mean and median PSA serum levels increase with each decade, and the mean increases at 5-year intervals in men 50 years of age and older (94,208). Clearly, both PSA and CaP increase with age. Oesterling and associates (725) proposed age-related PSA reference ranges to improve prostate cancer detection sensitivity in younger men and specificity in older men. These and other investigators also have recommended further stratification of these age-adjusted reference ranges based on ethnicity (681). These recommendations, summarized in Table 33.8 remain controversial. A lower PSA cutoff in younger men would obviously result in additional unnecessary negative biopsies and generate greater health care costs. In contrast, raising the PSA cutoff level in older men will result in the detection of fewer cancers. The studies by Catalona and associates (145) and Littrup and associates (590) both appear to validate the standard reference range of 0.0 to 4.0 ng/mL as being the most effective and least costly method for screening compared with age-adjusted PSA reference ranges. In addition, Etzioni and associates (283) confirmed previous analyses based on the United States Life Table Actuarial Figures and noted a significant increase in population longevity if 4.0 ng/mL is used as the PSA cutoff for all men compared with the use of age-adjusted cutoffs.

Age Range (yr)	White Patients (ng/mL)	Specificity (%)	Black Patients (ng/mL)	Specificity (%)	Asian Patients (ng/mL)	Specificity (%)
40–49	0.0–2.5	95	0.0–2.0	93	0.0–2.0	95
50–59	0.0–3.5	95	0.0–4.0	88	0.0–3.0	95
60–69	0.0–4.5	95	0.0–4.5	81	0.0–4.0	95
70–79	0.0–6.5	95	0.0–5.5	78	0.0–5.0	95

From Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: A decade of discovery—what we have learned and where we are going. *J Urol* 1999;162:293, with permission.

TABLE 33.8. RECOMMENDED AGE-SPECIFIC PROSTATE-SPECIFIC ANTIGEN REFERENCE RANGES

Prostate-specific Antigen Velocity

PSA velocity assesses the change in PSA over time. It is calculated by the following equation:

[(PSA2 - PSA1/$Time_1$ in years) +

(PSA3 – PSA2/$Time_2$ in years)]

In this equation, PSA1 is the first, PSA2 the second, and PSA3 the third serum PSA measurement. Three PSA measurements should be obtained during a 2-year period or at least 12 to 18 months apart. Using this approach, Carter and associates (124) determined that a PSA velocity of 0.75 ng/mL per year is strongly suggestive of CaP (72% sensitivity, 95% specificity). Unfortunately, the determination of PSA velocity possesses several inherent limitations, including (a) PSA is not cancer specific, (b) PSA velocity is difficult to calculate, (c) biologic variation of PSA on a daily basis is well recognized, and (d) the use of different assays can lead to confounding results (95,785). Other investigators have confirmed that a 0.75-ng or greater annual rate of PSA increase constitutes a risk indicator for men whose initial PSA was 4 ng/mL or less (94,930). However, Smith and Catalona (930) found that 0.4 ng/mL or greater annual

increase was an optimal risk indicator for men whose initial PSA was greater than 4 ng/mL. At present, a PSA velocity of greater than 0.75 ng/mL per year may add useful monitoring information to (a) men with PSA values in a normal range, (b) men being considered for repeat biopsy with an increasing PSA in any range, and (c) possibly any individual with at least two serial PSA measurements in a 2-year period (785).

Prostate-specific Antigen Density

PSA density is the total serum PSA level (ng/mL) divided by TRUS determined prostate volume (mL). Benson and associates (51) introduced this concept in the hope that such an evaluation would help differentiate between prostate cancer and BPH in men with intermediate (4 to 10 mg/mL) PSA levels and a normal DRE. To that end, they recommended a PSA density cutoff of 0.15 (892). Recent large studies conducted by Brawer and associates (89) and Catalona and associates (145) have not confirmed the utility of PSA density. Indeed, Catalona and associates (145) documented that approximately 50% of CaP would have been missed using a cutoff of 0.15. These conflicting results may be related to the difficulty in obtaining accurate/reproducible measurements of prostatic volume by TRUS and the fact that the estimated BPH volume may not correlate with serum PSA levels because of variability of epithelium (PSA-producing) and stroma (PSA-deficient) compartments.

The calculation of transition zone PSA density has emerged in an attempt to improve the specificity of cancer detection by accounting for the proportion of PSA generated by the transition zone. It is calculated by dividing the serum PSA level (ng/mL) by the transition zone volume (mL). Djavan and associates (235) proposed a calculated cutoff for transition zone PSA at 0.35 ng/mL. This cutoff provided a positive predictive value for prostate cancer detection of 74% in 939 men with PSA serum values less than 10 ng/mL. Other studies have failed to confirm the utility of transition zone PSA density (95,586). A major problem is the difficulty in obtaining an accurate and reproducible assessment of transition zone volume.

Free/Total Prostate-specific Antigen

In the ejaculate, PSA exists in the free (noncomplex) form. However, in the serum, PSA is complexed with several protease inhibitors, most notably α_1-antichymotrypsin and α_2-macroglobulin (95). As stated previously, two epitopes remain unmasked in the PSA/α_1-antichymotrypsin complex and are responsible for its detection with immunoassays (total PSA). The complexing of PSA/α_1-antichymotrypsin increases in prostate cancer, but the mechanisms underlying this phenomenon remain elusive. Assays usually using a dual antibody format have been developed to quantitate the PSA complexed to α_1-antichymotrypsin (ACT-1) or contrariwise, uncomplexed to ACT-1 (free PSA). Determination of these PSA fractions are assuming increasing clinical significance (Table 33.9). Catalona and associates (144) conducted the definitive study on the performance of the free-to-total PSA diagnosis of CaP. This prospective, multicenter trial, using the Hybritech assay and a free-PSA no biopsy cutoff of 25% or more for decreased risk of CaP, found this information could reduce biopsies by 20%, while maintaining a 95% cancer detection rate in men with 4 to 10 ng/mL total PSA levels. Assessment of the free-to-total PSA ratio using a 27% cutoff in 914 men 50 years of age and older with serum PSA levels of 2.6 to 4 ng/mL and a normal DRE yielded a 90% cancer detection rate and indicated 18% of unnecessary biopsies could be avoided (144). The detected disease was organ confined in 81% and judged to be clinically significant in 83% of patients undergoing radical prostatectomy. Finally, measurement of the free and total PSA also may permit an assessment of tumor aggressiveness. Carter and associates (129) confirmed a relationship between abnormally low percent free PSA (less than 14%) and aggressive neoplasms characterized by clinical stage T_3, nodal or bone metastases, pathologic positive margins, or a Gleason score of 7 or greater. Indeed, the data suggested tumor aggressiveness might be predicted several years earlier by percent free than total PSA. The currently recommended use for the percent free PSA is to determine whether a patient with a normal DRE and a total serum PSA between 4 and 10 ng/mL would benefit from an initial or repeat biopsy (785). The fact that free PSA is less stable in serum than total PSA needs emphasis. All specimens should be processed within 3 hours of collection and frozen at –70°C if not assayed within 24 hours (1106).

PSA	Probability of Cancer (%)
2 ng/mL	1
2–4 ng/mL	15
4–10 ng/mL	25
>10 ng/mL	>50

% fPSA	Probability of Cancer (%)
0–10	56
10–45	28
15–20	20
20–25	16

DRE, digital rectal examination; PSA, prostate-specific antigen.
Reproduced from Brawer MK. Prostate specific antigen: current status. *CA Cancer J Clin* 1999;49:264, with permission.

TABLE 33.9. PROBABILITY OF CANCER, BASED ON PSA AND PERCENT FREE PSA (FPSA) RESULTS (MEN WITH NONSUSPICIOUS DRE RESULTS, REGARDLESS OF AGE)

The PSA/α_1-antichymotrypsin complex is being investigated as an independent tumor marker to improve CaP. Stenman and associates (981) initially suggested that complexed PSA levels are increased in men with prostate cancer. Using refined assay methodology, Sokoll and associates (944) reported that the specificity of prostate cancer detection was enhanced with the use of complexed versus total PSA in men with total PSA levels between 4 and 10 ng/mL. Meyer and associates (651) reported their analysis of 300 frozen serum samples using assays for complexed, free, and total

PSA. At 95% sensitivity, the specificity was 26.5%, 21.8%, and 15.4%, respectively. The ultimate utility of complexed PSA measurements awaits the outcome of ongoing clinical trials.

Controversial Aspects of Prostate-specific Antigen Screening

Despite the increased detection of organ-confined (and potentially curable) prostate cancer with the use of serial PSA monitoring, many have opposed its use as a screening test for various reasons, including limited sensitivity and specificity; increased monetary, physical and psychologic costs; and the lack of prospective, randomized trials demonstrating unequivocal reductions in prostate cancer mortality with PSA testing (135).

Despite the legitimacy of these counterarguments, PSA monitoring appears to fulfill the prerequisites for a successful cancer screening program, which include (a) an increase in detection lead time, (b) a transient increase in the incidence of the disease since the introduction of a screening test—most previously undetected cases are identified in the cohort at risk, (c) the number of cases exhibiting advanced disease should be reduced at some finite point following introduction of the screening test, and (d) a reduction in mortality should be documented and proportional to the intensity of screening (135). The estimated increase in detection lead time resulting with PSA testing is approximately 5 years, a period intermediate between the 1.7 years noted with mammography and the 10 to 20 years noted with cervical cytology (136,332). The initial rise (and subsequent diminution) in CaP detection rates after the introduction of widespread PSA testing and the subsequent decreased incidence of advanced CaP provide further supporting evidence for its significant effect on the status of clinically recognized carcinoma of the prostate. Although an inverse relationship between disease-specific mortality and the intensity of PSA screening has not yet been demonstrated, CaP mortality in the United States has decreased, particularly among the younger white men most likely to be involved in early detection and treatment efforts (407).

There is little doubt that PSA testing has had a profound impact on the “vital statistics” for CaP (402). Particularly promising are the statistics documenting a decline in the incidence of and mortality from distant stage disease. Nonetheless, it is appropriate to emphasize that population data are complex, with attribution bias (incorrect labeling of death from other causes as death from prostate cancer) being more common than previously acknowledged, and attributing relatively small changes in mortality to any one cause with confidence is inherently difficult (291,402).

Current Status of New Markers for the Detection of Localized Prostate Cancer

As stated previously, human glandular kallikrein-2 shares many similarities with PSA, including a 78% amino-acid sequence identity. Both are androgen-regulated proteases expressed in the prostatic epithelium; they can be detected in serum and seminal fluid, and they form complexes with androgenous protease inhibitors. In addition, hK2 demonstrates a significant positive relationship to prostate volume and PSA level (746). Recently, a research prototype assay for total hK2 (thK2) has been developed. Partin and associates (746) proposed a model for cancer detection using percent fPSA and the thK2-to-fPSA ratio when the PSA is 2 to 4 ng/mL in patients with a normal DRE. Their model identified approximately 40% of the cancers and would require TRUSP biopsies in only 16.5% of men in this particular PSA range. In this evaluation, they used a thK2/fPSA cutoff of 0.25 to identify patients at higher risk for prostate cancer. In a similar analysis, a thK2/fPSA cutoff of 0.18 was a useful discriminator for men with total PSA serum levels between 4 and 10 ng/mL and a normal DRE. Nam and associates (698) evaluated the potential utility of assessing hK2 levels to predict the presence of prostate cancer among patients prescreened by PSA testing. They observed that the mean hK2 levels and hK2/fPSA ratios were significantly higher in patients with prostate cancer than in controls (1.18 versus 0.53 ng/mL, respectively for hK2; 1.17 versus 0.62 for hK2-to-fPSA ratio). In addition, patients with high hK2 measurements have a fivefold to eightfold increase in risk for prostate cancer, adjusting for PSA level and other established risk factors. Two studies by Becker and associates (45,46) also reinforce the utility of hK2 measurements in the discrimination of men with BPH from those with prostate cancer. Obviously, all of these studies are preliminary and the ultimate role of hK2 assays in our diagnostic armamentarium must await the results of additional clinical trials.

IGF-I possesses mitogenic and antiapoptotic effects on both normal and transformed prostate epithelial cells *in vitro* (200,463). Six IGF-binding proteins (IGFBPs) have been identified of which IGFBP-3 is the most prevalent in the serum (493). IGFBP-3 exerts an antiproliferative effect on prostatic epithelium by inducing prostate cell apoptosis and blocking IGF interaction with its receptor (181). Of interest, the studies conducted by Tricoli and associates (1025) demonstrated lower IGFBP-3 plasma levels in African American men than in white men, suggesting that this phenotype could explain in part the increased risk of prostate cancer in that cohort.

Chan and associates (156) observed in a nested case-controlled study within the Physician's Health Study that the risk of CaP was associated with increased IGF-I levels. In addition, IGFBP-3, after adjustment for IGF-I was inversely related to the risk of prostate cancer in that same study. More recently, Djavan and associates (234) evaluated 245 consecutive white men with PSA levels between 2.5 and 15 ng/mL. These patients underwent octant biopsies and a second biopsy was performed 6 weeks later if the first biopsy was negative. In that study, IGF-I serum levels did not enhance the performance of PSA. However, at a sensitivity

of 95%, the specificity of the IGF-I-to-PSA ratio was significantly greater than that of all other parameters. Indeed, a cutoff value of 25 afforded a 95% sensitivity for detecting CaP and would have avoided unnecessary biopsies in approximately 24% of these patients. The study by Kurek and associates (546) also failed to identify an association between IGF-I serum levels and CaP. However, that study did not address the issue of IGF-I-to-PSA ratios.

Prostate-specific membrane antigen (PSMA) is a 100-kDa type II membrane protein, which is expressed in benign prostatic epithelium, high-grade PIN, and prostate cancer (158). The PSMA gene is located on the short arm of chromosome 11 and encodes for a protein with a three-part structure. The latter includes a 19–amino acid internal domain, a 24–amino acid transmembrane domain; and a 707–amino acid external portion (458,718). Two variations of the PSMA protein have been recognized and are designated PSMA and PSM^{1} (spliced variant). PSMA is the predominant form in cancer and possesses a transmembrane domain. PSM^{1} lacks 266 nucleotides near the 5^{1} aminoterminus and does not have this transmembrane domain. PSM^{1} predominates in nontransformed prostatic epithelial cells (375,989).

Anti-PSMA antibodies currently are available to both the intracellular and extracellular PSMA domains (159). Murphy and associates (685,686) suggested that serum PSMA measurements could be used to distinguish late-stage from early-stage CaP or to monitor regressors more effectively than PSA. In a more recent study, Beckett and associates (47) measured PSMA in the sera of 236 normal individuals and cancer patients by Western blot analysis. They observed that PSMA levels increased with age and were significantly elevated in subjects greater than 50 years of age when compared with younger men. Their study did not confirm the previous observations by Murphy and associates (685,686). It is possible that the expanded library of new antibodies may permit the development of a useful sandwich radioimmunoassay to detect PSMA more reliably. Until then, the use of this methodology must be considered investigational. The potential utility of probing for PSMA expression as a staging tool is discussed later in this chapter.

Prostatic Fluid and Urine

Cytochemical and biochemical evaluation of digitally expressed prostatic fluid has been carried out in attempts to identify those individuals at increased risk for the development of CaP. Exfoliated cytology has, at most, a very limited role in diagnosing CaP today. Although some observers have reported a high yield of diagnostic cells in the prostatic fluid and postmassage urine, these results have been difficult to duplicate (532). Attempts to identify individuals with increased risk of carcinoma by biochemical characterization of expressed prostatic fluid have been carried out with the presumption that the metabolic changes associated with cancer are diffuse and involve anatomically normal as well as histologically abnormal cells (field change). The enzyme, protein, polyamine, cholesterol, citric acid, and zinc concentrations, as well as the physical characteristics such as pH and specific gravity, have been determined in the expressed prostatic fluid of patients with normal prostates, BPH, and CaP (380). Compared with normal men and men with BPH, prostatic fluid from men with carcinoma has been found to have decreased concentrations of acid phosphatase and zinc and increased concentrations of the specific complement proteins (C3 and C4) and transferrin. The lactate dehydrogenase (LDH) isoenzyme concentrations are reversed, with LDH5 exceeding LDH1 in patients with carcinoma and BPH. The magnitude of this ratio and the frequency of a ratio exceeding two are greater in patients with cancer than in patients with BPH. The PSA concentration surprisingly has been found to be comparable in men with clinical BPH and cancer, but reduced in individuals with histologically confirmed BPH (503). Basically, these observations tend to confirm a diffuse metabolic change in the prostate with cancer and are compatible with the presumed concept of a field change. Recently, the observations of a prostate-specific membrane antigen with a significant homology with transferrin receptor coupled with the prior identification of transferrin receptor in prostatic cancer cell lines (458,496) has served to reinforce the potential use of prostatic fluid to identify and characterize metabolic alterations associated with and possibly important to the development and growth of CaP. The changes observed in the biochemical composition of prostatic fluid and prostatic cancer have not yet proven clinically useful because of the lack of specificity; however, they have not been explored in conjunction with serum PSA studies.

At this time, the most commonly used and efficient indicators of increased risk of asymptomatic prostatic cancer are the serum PSA levels and the rectal examination. An initial PSA level greater than 4 ng/mL that is persistent with time or following treatment for an inflammatory process usually identified by routine microscopic evaluation of prostatic fluid (greater than 10 WBCs/HPF) is a reasonable level to trigger the consideration of CaP. A significant interval increase in the PSA of approximately 0.75 ng/mL in a patient with an initial PSA of 4 or less or 0.4 ng/mL in an individual with an initial serum PSA greater than 4 increases our concern for the presence of malignancy. Generally, with the first such increase, we elect to confirm the finding and then decrease the interval to 3 to 6 months between PSA determinations and patient evaluations. If the trend (probably more so than an absolute quantitative rate) continues, our suspicion of malignancy increases and a recommendation to biopsy is seriously considered. The DRE is part of our regular interval evaluation. New nodularity or induration that persists on reexamination with or without interval treatment at 2 or 4 months or that is accompanied by an increase in PSA is used to determine the need for biopsy.

Tissue Sampling

TRUSP Biopsies

The goals of tissue sampling are to (a) confirm the presence of CaP if it exists; (b) provide reliable information regarding histologic grade and other indicators of biologic potential; (c) document (if possible) extraorgan spread and intraorgan location and information to assist in estimation of probable tumor mass; and (d) accomplish the sampling procedure with minimal risk, anxiety, inconvenience, and expense. Depending on the patient and clinical circumstances, these goals have variable priorities. Traditionally, tissue-sampling attempts to maximize the probability of identifying a suspected malignancy were almost always site directed. The selection of the site was usually guided by abnormalities recognized on digital examination. In the past several years, ultrasound-detected abnormalities, primarily hypoechoic areas with or without accompanying digital rectal changes, also have been targeted. However, evidence previously cited has led to a consensus that systematic sampling of the entire prostate, in addition to targeted biopsies, increases the yield of diagnostic needle biopsies appreciably. This approach now is used preferentially by many physicians, including us, in patients thought to be at increased risk for CaP (90,145,425).

Hodge and associates (424) introduced the technique of systematic sextant biopsy of the prostate under TRUS guidance. This involved the acquisition of six directed biopsies of the base, middle, and apical portions from each side of the prostate gland in the parasagittal plane. CaP can be identified in approximately 25% of men with a normal DRE and serum PSA values between 4 and 20 ng/mL. Of importance, a positive biopsy rate for a second set of sextant biopsies approaches 20% in those men with initially negative biopsies. Their observations, and those of many subsequent investigators, highlighted concern that the traditional sextant technique may undersample the prostate and that alternative biopsy techniques, particularly those involving the acquisition of more tissue cores, would improve diagnostic yield (511).

Stamey (969) recommended shifting biopsies to a more lateral position to better sample the anterior horn of the peripheral zone. Eskew and associates (280) introduced the five-region prostate biopsy technique, which incorporates the traditional sextant biopsy cores and adds two biopsies from the far right lateral and far left lateral aspects of the prostate gland and three biopsies from the midline. They were able to demonstrate a 35% increase in the prostate cancer detection rate using this approach as compared with the standard sextant technique. These findings have been validated by Presti and associates (799) who confirmed the utility of an 8 to 10 biopsy scheme, which combined the traditional sextant biopsy approach and lateral peripheral zone biopsies (Fig. 33.37). In their study, the indications for biopsy were an abnormal DRE and/or PSA levels greater than 4.0 ng/mL. Using the extended biopsy approach, cancer was detected in 42% of patients. In contrast, traditional sextant biopsies missed 20% of cancers, while a sextant regimen incorporating lateral peripheral zone biopsies of the midgland and base along with the apex missed 11% of the cancers. The increased yield of CaP associated with the acquisition of additional laterally targeted biopsies is consistent with the results generated using biopsy simulation of three-dimensional (3D), reconstructed, whole mount radical prostatectomy specimens (43). Specifically, the 3D models demonstrate that the highest cancer probability areas involve the far lateral crescent-shaped regions of the peripheral zone from the apex to midgland. The acquisition of laterally directed biopsies is particularly important in patients who have a PSA of less than 10 ng/mL (with smaller cancers) and for those patients with a prostate volume greater than 50-mL larger prostates. In both instances, the likelihood of a sampling error is increased and the use of an extended biopsy scheme has both theoretic and practical advantages (799).

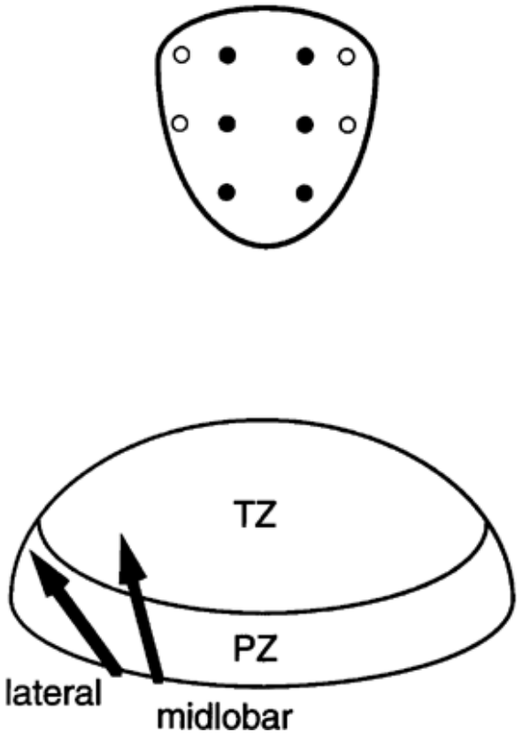

FIGURE 33.37. A ten-biopsy scheme of the peripheral zone *(PZ)* has been proposed by Presti and associates (799). The *dark circles* delineate the sites of standard sextant biopsies. Additional biopsies are obtained from the lateral aspect of the PZ at the base and midgland. An eight-biopsy scheme would eliminate the base biopsy from the standard sextant regimen. TZ, transition zone. (From Presti Jr JC, Chang JJ, Bhargava V, et al. The optimal systematic prostate biopsy scheme should include eight rather than six biopsies: results of a prospective clinical trial. *J Urol* 2000;163:163, with permission.)

Various disposable and reusable instruments are available

to obtain digitally directed needle core biopsies. These include the hand-powered Franklin modification of the Vim Silverman and Tru-Cut needles and the spring-driven Bard biopsy and Microvasive ASAP 18-gauge needle biopsy devices. Currently, the spring-driven devices commonly are used to obtain multiple transrectal biopsies of palpable abnormalities. They can be introduced repeatedly and fired through a larger finger-anchored conduit that serves for multiple reentry. Alternatively, the conduit can be placed through the locally anesthetized perineum with rectal finger guidance into the apex of the prostate. In our hands, this transperineal approach facilitates the sampling of transition zone tumors and the acquisition of tissue from patients with large-volume prostates. It also obviates the need for the repetitious insertion/withdrawal of the entire needle, which has several theoretic disadvantages, including increased risk of bleeding, infection, and needle-track implantation.

The development of multiplane 7- to 7.5-MHz transducers that permit transrectal imaging of the prostate in transverse and longitudinal planes and provide coordinated visual and mechanical guides for biopsy has facilitated targeted site and area biopsies. This approach requires an easily acquired working familiarity with the instrumentation and the ultrasonic features of the normal prostate (Fig. 33.31), BPH (Fig. 33.32), and prostate cancer (Fig. 33.33). Patients are advised to stop aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and other agents capable of inhibiting platelet function for 7 to 10 days before biopsy. Additional preparation includes the use of a Fleet enema and a single tablet of quinolone antibiotic 1 to 3 hours before the biopsy. Systemic antibiotics are administered selectively to patients at high risk such as diabetics and those at risk for bacterial endocarditis.

In general, both the traditional sextant and extended biopsy approaches can be performed without the benefit of anesthesia and with the anticipation of minimal patient discomfort (703). To optimize patient comfort, Nash and associates (701) performed a TRUS–guided prostatic nerve block before systematic needle biopsy and noted significantly enhanced patient satisfaction. Soloway and Öbek (948) modified this approach by using an ultrasound-guided 7-inch 22-gauge spinal needle to inject 5 mL of 1% lidocaine (without epinephrine) bilaterally at the following three prostate locations: (a) at the base near its junction with the seminal vesicle, (b) in lateral aspect of the midportion, and (c) at the apex. These investigators also reported enhanced patient satisfaction. The theoretic disadvantages of this approach include the potential for direct intravascular injection of lidocaine (seizures) and the possibility of injection-induced fibrosis in the vicinity of the neurovascular bundles, which might render a nerve-sparing procedure more problematic (511). More recently, Chun and associates (172) described the benefits of interrectal installation of 10 mL of 2% viscous lidocaine gel approximately 10 minutes before systematic biopsies. They observed a statistically significant increase in patient satisfaction and no apparent complications with this noninvasive anesthetic approach. DRE should be performed before TRUS to ensure the urologist has an accurate perception of the location of suspicious nodules and areas of induration. The multiplane ultrasound probe (with or without balloon) is covered with a sterile condom, properly lubricated, and inserted into the rectal ampulla. It is our preference to initiate scanning at the level of the bladder and proceed in a methodic, stepwise fashion to evaluate (a) bladder base and neck; (b) seminal vesicles; and (c) the base, midzones, and apex of the prostate. Hypoechoic foci, areas of capsular irregularity and distortion of the seminal vesicles usually warrant consideration of biopsy. Routine seminal vesicle biopsies are not indicated but may be of value in patients with: (a) PSA greater than 15 to 20 ng/mL, (b) in the presence of obvious distortion or obliteration, and (c) in the context of asymmetric enlargement (12,1009). Using the ultrasonic needle pathway guide, the biopsy needle tip is located at the proximal aspect of the tissue core to be sampled, and the gun is fired while the lesion is observed and recorded in the sagittal plane. Our current practice is to biopsy ultrasonically or palpably suspicious areas and 8 to 10 additional sites as necessary to accomplish representative regional sampling at the base, middle, and apical areas of each lobe. We concentrate on the peripheral zone and vary the medial and lateral relationship of the biopsy to the midsagittal plane. The larger the gland volume, the more inclined we are to add a random biopsy to an area that has had a targeted biopsy. Objective evidence to identify the optimal biopsy procedure is lacking. The tissue is placed immediately in Bouin's solution. We place all the biopsies from one side in a single container. The additional cost to send each biopsy separately does not seem justified by the information obtained.

After removal of the instrument, the patient is placed in the knee-chest position and gentle digital pressure is applied to the right and left lobes of the prostate to minimize rectal and urinary tract bleeding. The patient is instructed regarding transient hematuria or rectal bleeding. Oral antibiotics are usually continued for 48 hours after biopsy. The patient is advised to notify us promptly in the event of an elevated temperature (100°F), chills, or difficulty voiding.

Hodge and associates (424) demonstrate excellent yields (e.g., cancer in 53% of the patients with a previous negative digitally directed biopsy, biopsy confirmation of cancer in 70% of ultrasonically abnormal seminal vesicles, and 20% of ultrasonically normal seminal vesicles) of TRUS-guided transrectal biopsies with a 2.4% incidence of postbiopsy bleeding, fever, or retention. Histologic evidence of cancer was found in the palpably normal contralateral prostatic lobe in 42% of B1 and 60% of B2 nodules. In an extensive experience, using four-quadrant biopsies routinely in PSA-identified patients, Flannigan and associates (297) found that CaP would have been missed in 137 of 225 patients if only the area identified on rectal examination had been biopsied. Similarly, the CaP would have been missed in 131 of 251 patients if only the hypoechoic lesion

identified on ultrasound had been biopsied. These observations coupled with the recognized false-negative rate of targeted needle biopsy procedures provide a strong argument for routine and extended systematic regional sampling of the prostate of the patient identified as having increased risk of carcinoma. Recent reports suggesting that endorectal MRI and spectroscopy—time-consuming, expensive procedures—facilitate localization of prostate tumor foci and enhance the accuracy of subsequent TRUS-targeted prostate biopsies (761,1083) require confirmation by larger scale clinical trials.

Transrectal Needle Aspiration and Other Techniques

Transrectal aspiration to obtain cell samples for histologic evaluation, widely used in Scandinavia and Europe since its reintroduction by Franzen and associates (314), enjoyed a burst of increased popularity in the United States in the past decade. This experience confirmed the legitimate role of this procedure in establishing the diagnosis of CaP. Transrectal needle aspiration can be carried out as a directed or area tissue sampling procedure in the unanesthetized patient with minimal discomfort.

After a preliminary rectal examination, a Fransen or other needle guide placed on the index finger between the gloves of a double-gloved hand (Fig. 33.38) is introduced into the rectum. The tip of the index finger should be free for palpation. Once the index finger is placed on the suspicious area, a 22-gauge aspiration needle is guided transrectally into the lesion. Special needles with variously configured distal ends to facilitate tissue sampling are available. A syringe connected to the butt of the needle permits the use of negative pressure. The needle is advanced and retracted repetitiously within the prostate to probe the targeted area with variable negative suction before it is withdrawn. An air-filled syringe is used to expel all the aspirated material onto slides. After spreading, the aspirate is air dried or fixed in alcohol, depending on the staining process. The cells remaining can be suspended in a few milliliters of saline solution in the syringe and processed in the Cytospin for cytologic evaluation (Table 33.10). Our usual practice is to carry out a minimum of two aspirations using different needles each time. A preaspiration or postaspiration antibiotic usually is used.

FIGURE 33.38. Instrumentation for transrectal needle aspiration of the prostate. The correct positioning of the Franzen needle guide, 22-gauge aspiration needle, and syringe is illustrated. Before rectal insertion, the double-glove technique should be used. (Courtesy of Dr. George Daniels.)

TABLE 33.10. DIFFERENTIAL DIAGNOSIS OF PROSTATIC ASPIRATES

	Benign Hyperplasia	Well-differentiated Carcinoma	Moderately Differentiated Carcinoma	Poorly Differentiated Carcinoma
Cell clusters	Flat, cohesive	Rarely flat and cohesive, often thick	Usually thick, loose	Rare, thick
Honeycombing	Conspicuous	Rare	Absent	Absent
Myoepithelial cell nuclei	Present	Exceptional	None	None
Detached single epithelial cells	Few with normal nuclei	Few with abnormal nuclei	About equally represented as clusters, abnormal nuclei	Dominant, highly abnormal nuclei
Nuclei	Round, oval, about equal in size, homogeneous	Hyperchromatic, enlarged	Hyperchromatic, large	Hyperchromatic and bizarre
Nucleoli	Absent or tiny	Present	Conspicuous	Conspicuous
Mitoses	Absent	Exceptional	Present	Conspicuous, often abnormal

From Koss LG, Woyke S, Schreiber K, et al. Thin needle aspiration biopsy of the prostate. *Urol Clin North Am* 1984,11:237, with permission.

Until recently, digitally guided transrectal and transperineal approaches for core biopsy were the most commonly used. Transrectal biopsy has the presumed advantages of better digital localization of the needle course and tolerable discomfort without anesthesia. The incidence of postbiopsy infection is increased, and the opportunity to carry out multiple or random contralateral biopsies is restricted. Use of a prebiopsy antibiotic is common. Although the transperineal route can be carried out under local anesthesia, the procedure is conducted optimally with the patient under general or spinal anesthesia. It provides less direct access to the suspicious area and probably less certain sampling of it. Multiple and random biopsies are performed more readily, and the risk of infection is diminished. Ultrasound guidance has been used in an attempt to improve the accuracy of tissue sampling with this biopsy approach (581).

Purposeful diagnosis of CaP by TURP is limited by many, ourselves included, to patients with a large local tumor mass. Others identify the indurated area by rectal examination and then carry out an extended local excision to attempt to sample this area. The effectiveness of this latter diagnostic approach has not been verified. TURP is used very selectively by some, including members of our group, to obtain transition zone tissue from patients with suspected stage T_1 tumors. Open perineal biopsy requires a spinal or general anesthesia, with the patient placed in the exaggerated lithotomy position and limited exposure of the posterior aspect of the prostate with a perineal incision as in the perineal prostatectomy. Passage of an unopened Lowsley curved retractor or a sound into the prostatic urethra to act as a posterior inferior lever for the gland is an important aid in this procedure. After exposing Denonvilliers' fascia in the suspicious area, a wedge biopsy is carried out. If the patient is a suitable candidate, radical prostatectomy can be carried out on the basis of a positive frozen section report. If the frozen sections are negative or equivocal, the biopsy site is fulgurated and irrigated and the wound is closed. The literature contains numerous reports on the specificity and sensitivity of various procedures. However, aside from Hudson's (441,442 and 443) reports from the mid-1950s documenting a significant advantage of open perineal over punch

and transurethral biopsy procedures, prospective studies evaluating the multiple available tissue sampling procedures in the same patient have been avoided. Several studies (297,1035) have demonstrated the advantage of multiple systematic TRUS-guided prostate tissue sampling over targeted procedures in identifying existing carcinoma. Although false-negative observations clearly occur with this approach, their incidence is not clearly established.

Digitally (Table 33.11) and ultrasonically guided targeted biopsies have failed to identify the carcinoma present in an appreciable group of patients. Our review (377) found that false-negative results ranged from 6% to 23% for digitally guided transrectal biopsy and 7% to 27% for digitally guided perineal biopsy. Catalona and associates (148) carried out ultrasonic-guided biopsies on a group of men selected from 10,251 individuals 50 years of age or older on the basis of a serum PSA level greater than 4 ng/mL and a suspicious finding on rectal or ultrasound evaluation. Initial biopsies revealed carcinoma in 296 of 902 patients who underwent biopsy; with serial follow-up, cancer was detected on the second biopsy in 84, on the third in 17, and on the fourth in 4. The yield of positive diagnoses clearly increases with repeated biopsies. The larger the local tumor mass is, the more likely tissue sampling procedures are to be successful. Although conflicting evidence has been presented (823), the report of Liddel and associates (581) indicating an advantage of ultrasound-guided over digitally guided biopsy has been confirmed, especially with the use of the biopsy gun (424,564). A distinct advantage of the ultrasound-monitored procedure is the ability to assess the course of the needle to some degree.

	+DRE, −PSA	+DRE, no PSA	−DRE, +PSA	+DRE, +PSA
1989	5	9	36	62
1990	7	18	28	44
1991	11	23	33	53

+DRE, abnormal digital rectal examination; *−DRE,* normal digital rectal examination; *−PSA,* prostate-specific antigen level <40 ng/ml; *+PSA,* prostate-specific antigen level ≥4.0 ng/mL
[a]Total biopsies reported: 1989 = 196; 1990 = 3,854; 1991 = 1,108.
From Crawford ED, DeAntoni EP: *Urol Clin North Am* 1993;20:637.

TABLE 33.11. POSITIVE BIOPSY RATES (%),[a] BY DIGITAL EXAMINATION AND PSA RESULTS, PROSTATE CANCER AWARENESS WEEK, 1989–1991

Sufficient information (Table 33.12) has accumulated to indicate that needle aspiration, particularly when used transrectally, is a useful tissue sampling procedure to confirm the presence of CaP. Our review of the reported experiences (532) led to the following conclusions: (a) The diagnostic accuracy of fine-needle aspiration (FNA) is equivalent or superior to that of digitally directed core biopsies. (b) Test sensitivity and specificity initially exceeds 90%, but the false-negative rate increases somewhat during the course of long-term follow-up. (c) The degree of cytologic pleomorphism correctly predicts the Gleason sum range in approximately 80% of the cases, being most accurate with respect to poorly differentiated cancers. (d) FNA can detect most stage T_{1b} tumors but is not useful in the identification of patients with stage T_{1a} disease. (e) FNA cannot accurately distinguish PIN from invasive prostate cancer (3,5,168,373,561,699).

			Positive Histologic Diagnosis		Confirmed by Cytology		Positive Cytologic Diagnosis	
Authors	Year	No. of Cases	*n*	%	*n*	%	*n*	%
Esposti	1966	162	58	35.8	52	89.6	55	33.9
Anderson, et al.	1967	64	29	45.3	18	62.1	25	39.1
Ekman, et al.	1967	100	45	45.0	34	75.6	41	41.0
Bachmann	1969	35	9	25.7	7	77.8	9	25.7
Faul, et al.	1971	106	25	23.6	24	96.0	25	26.3
Bandtlow	1972	53	27	50.9	13	48.1	18	34.0
Kaulen, et al.	1973	460	159	34.6	153	96.2	169	36.7
Droese, et al.	1976	288	78	27.1	37	47.4	50	17.4
Ackerman	1976	645	235	36.4	162	68.9	179	27.7

Note: Studies cited are from original source.
Modified from Ackerman R, Muller HA. Retrospective analysis of 645 simultaneous perineal punch biopsies and transrectal aspiration biopsies for diagnosis of prostatic carcinoma. *Eur Urol* 1977;3:29.

TABLE 33.12. INCIDENCE OF PROSTATIC CARCINOMA DIAGNOSED BY PERINEAL PUNCH BIOPSY AND TRANSRECTAL ASPIRATION BIOPSY WITH AGREEMENT IN BOTH TECHNIQUES AS REVIEWED IN THE LITERATURE

Tissue Sampling: Complications

No tissue sampling approach is free of complications (532). The incidence of the more common complications of infection,

bleeding, and urinary retention reported in the past with digitally guided transrectal and perineal needle biopsy procedures has been significantly reduced in recent experiences using ultrasonic guidance and the spring-controlled biopsy devices. A reported infection rate of 16% to 48% after digitally guided transrectal biopsy (143) seems certainly to have been decreased by use of prebiopsy antibiotics. The reported incidence of infection after transperineal biopsy varied from 0% to 3%. Significant bleeding occurred in 1% to 2% of patients after either procedure. Urinary retention was reported in as high as 11% of patients after transrectal biopsy. Less than 1% of patients subjected to transrectal aspiration procedures had a febrile reaction; overall reported complications with this procedure are few. In contrast to these reports Cooner (184) reported an incidence of septicemia of 1% (2 per 206) in patients biopsied with the biopsy gun or Menghini needle transrectally under ultrasound guidance without prophylactic antimicrobials and of 0.5% (3 of 629) in those with prophylaxis. A pelvic hematoma requiring 4 units of packed cells was the only significant bleeding encountered. No patient had acute urinary retention. Hodge (424) reported an overall 2.4% (6 of 251) complication rate after TRUS-guided, spring-driven, transrectal prostate biopsy procedures carried out with preceding enemas and norfloxacin. The complications included rectal bleeding, 1.2%, all in patients on aspirin or NSAIDs; fever, 0.8%; and acute urinary retention, 0.4%. Several factors, particularly prebiopsy rectal preparation and antibiotics, ultrasound control of the direction and extent of the biopsy, and decreased trauma with spring-loaded devices with automated tissue sampling needles probably contribute to the reduced complication rate. Eliminating the need for anesthesia also reduces potential complications and cost.

A confirmed diagnosis with an indication of tumor grade aids us in rational management approaches. Currently, we use TRUS-guided, transrectal, spring-activated needle biopsy in the vast majority of patients. Occasionally, in patients in whom we wish to perform more adequate transition zone sampling, we use a perineally placed access needle through which multiple, variously directed tissue samples are obtained bilaterally with the biopsy or similar device, or, rarely, we carry out TUR tissue sampling. In elderly patients or patients at high risk in whom we desire confirmation of the diagnosis of carcinoma, we often use digitally directed needle aspiration.

Prostate Tissue Sampling Following Proctectomy

The evaluation of men who have undergone previous abdominoperineal resection (APR) for the diagnosis of prostate cancer represents a diagnostic challenge (912). Previously, several relatively ineffective tissue sampling techniques have been proposed, including blind transperineal biopsies, transabdominal ultrasound-targeted biopsies, and TURP. Shinghal and Terris (912) evaluated transperineal ultrasound-guided biopsies in 20 patients with prostate cancer previously diagnosed by TRUS-guided biopsies immediately before radical prostatectomy. Six biopsies were obtained with the patients in lithotomy position. Cancer was detected in only 2 of 20 patients (10%). Simultaneously performed TRUS-guided biopsies were positive in 13 of 20 patients (65%). These observations suggest possibly screening such patients for prostate cancer before the APR. Evaluation of these patients may be enhanced by the use of transurethral ultrasound to guide transperineal biopsies (893). Similarly, recent reports suggest the potential utility for computed tomography-guided and MRI-guided biopsies in this cohort (539,622,744).

Histologic Recognition of Malignancy

The criteria for histologic diagnosis of CaP are detailed in the preceding section on pathology. Histochemical studies for cellular proteins and enzymes are playing an increasingly important role in assessing equivocal light microscopic findings. If the core or wedge biopsy specimen is negative for malignancy, it should be reviewed to make certain that an adequate specimen of prostatic tissue was obtained. The presence of atypia should be noted, recorded, and considered in assessing the need for and timing of rebiopsy.

Staging

Staging is a clinical effort to identify the phase of the natural history of CaP that exists in a patient by documenting the site and the mass of tumor involvement. These observations have importance with regard to selection of the various treatment options currently available. With regard to site, the critical clinical information currently is to separate patients with carcinoma localized to the prostate from those with local or distant spread of the disease. If the disease is recognized to be extraprostatic, knowledge of the sites and organs involved by tumor plays an important role in rational management. Because the mass of the tumor is an important predictor of tumor progression and response to therapy, information derived from attempts to assess the tumor mass usually are used to subdivide tumors at a given site into substages that share a common natural history and treatment response. In some instances a histologic observation, tumor grade, also has been used for this purpose. Although clinical and pathologic stages should not be interchanged in the assessment of results of therapy, the use of selected histologic information has become accepted in most clinical staging studies. Table 33.13 presents representative staging designations in current use.

	Clinical Stage		
Description	AJCC, 1997	Hopkins (Modified Jewett)	Memorial (Modified Whitmore, 1990)
Disease localized to prostate			
Clinically unsuspected, incidental histologic finding	T_1	A	A
Focal, low grade	T_{1a}[a]	A_1[a]	A_1[b]
Intragland lump diffuse or high grade	T_{1b}[c]	A_2	A_2
Tumor identified, needle biopsy (e.g., prostate-specific antigen level elevated)	T_{1c}[c]		
Risk recognized clinically (confined to prostate)	T_2	B	B
Tumor confined to one lobe surrounded by normal tissue;		B_1	
<2 cm (Whitmore)		B_{IN}	B_1
>2 cm			B_2
Tumor involves one lobe	T_{2a}		
Tumor in both lobes	T_{2b}		
		B_2	B_3
Disseminated disease			
Periprostatic, extends through capsule	T_3	C	C
Lateral sulcus			C_1
Extracapsular extension (unilateral or bilateral)	T_{3a}		
Base of seminal vesicle	T_{3b}		C_2
> Base of seminal vesicle and/or other structure	T_{3c}		C_3
Tumor fixed: invades adjacent structure other than seminal vesicle	T_4		
Bladder neck, external sphincter and rectum			
Levator or pelvic wall			
Distant		D	D
Pelvic lymph node	N_{0-1}[d]	D_1	D_1
Bones, lung, etc.	M_{1a-c}[e]	D_2	D_2
Elevated acid phosphatase only		D_0	D_0

AJCC (American Joint Committee on Cancer) 1997. Note that T_0 category is now listed as no evidence of primary tumor (Schroeder, 1992).
[a]Tumor present in 5% or less of tissue.
[b]Tumor present in more than three microscopic foci.
[c]Tumor present in more than 5% of tissue.
[d]N_x, metastasis in regional lymph node(s).
[e]M_{1a}, nonregional nodes; M_{1b}, bone; M_{1c}, other site.

TABLE 33.13. STAGING DESIGNATIONS FOR CARCINOMA OF THE PROSTATE

Staging information designated as clinical routinely uses histologic information to identify stage T_1(A) disease and

for reclassification of patients with clinical stage T_{1a}, T_{2b}, and T_{3c} on the basis of histologic (pathologic) evidence of metastases to the pelvic lymph nodes (N). Because the information provided by lymph node assessment is a factor commonly affecting clinical management, confusing the differentiation between clinical and pathologic staging in this instance is probably appropriate. The current criteria for the various stages used in management considerations are discussed in the following section.

General Staging Classifications

In the TNM staging system, tumors are staged according to three basic components: primary tumor (T), regional nodes (N), and metastasis (M) (Table 33.6). Stage T_1 or A is a designation used for CaP that is clinically unsuspected and is discovered on tissue removed to relieve bladder neck obstruction (stage T_{1a}, T_{1b}; A_1, A_2) or because of an elevated serum PSA (stage T_{1c}). The grade and amount of carcinoma is evaluated histologically in the removed tissue and is utilized to substage the clinically unsuspected tumors into two groups: one with high (T_{1b}; A_2) and one with low (T_{1a}; A_1) probability of biologically aggressive growth. An evaluation of the probability of dissemination using pretreatment serum PSA levels, DRE and TRUSP findings, Gleason score, and other staging procedures (if indicated) is usually carried out. Rarely, an unsuspected intermediate or high-grade CaP involving much of the removed tissue is found associated with secondarily acquired (e.g., histologic evidence of seminal vesicle invasion), evidence of extraorgan spread. These patients are usually classified as having advanced stage disease and, perhaps inappropriately, are removed from the T_1 (A) clinical staging category.

Serial PSAs obtained after transurethral or open prostatectomy often help identify T_1 or (A) patients with low and high risk of progressive or significant residual disease. Observations by Carter (132) and Voges (1053) indicate a serum PSA level of 1 ng/mL or less usually is associated (16 of 17 T_1 patients) with a residual tumor volume less than 0.5 mL in radical prostatectomy specimens whereas higher PSA levels are less discriminatory. Lowe and Listrom (605) have provided several additional insights with respect to this issue, including (a) the identification of increasing age, Gleason score, and percentage of tumor involvement as variables signaling the likelihood of disease progression; (b) the establishment of probability tables for disease progression at 5 and 10 years based on a consideration of these variables; and (c) a recommendation of definitive local therapy in "high-risk" patients. With respect to the last-named, the authors noted a statistically significant advantage of radical prostatectomy over observation alone in producing disease-free survival and a smaller but probable advantage over radiation therapy. The PSA level and/or its rate of change is useful in identifying patients with stage A tumors requiring serious consideration of repeat tissue sampling or therapy.

Patients with histologically confirmed tumor associated with palpable nodularity or induration involving one prostatic lobe are assigned to stage T_{2a}. Clinically apparent involvement of both lobes (without evidence of dissemination) requires assignment to stage T_{2b}. It is important to note that tumors identified in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, are still classified as T_{1c}.

Stage T_3, T_4 (C) tumors that have demonstrated periprostatic extension on clinical examination but have no evidence of distant metastases are classified as stage T_3, T_4 (C). Patients with tumor classified in this stage have an incidence of pelvic node metastases as high as 50% or more (240). Substaging on the basis of the site of extraprostatic tumor extension differs. The 1997 American Joint Committee on Cancer (AJCC) classification separates extracapsular extension (unilateral or bilateral) (stage T_{3a}) from seminal vesicle(s) invasion (stage T_{3b}). The biologic significance of these substages is uncertain. Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T_3, but as T_2. The 1997 AJCC classification modifies the category T_4 for tumors that are fixed or invade adjacent structures (other than seminal vesicles) bladder neck, external sphincter, rectum, levator ani muscles, and/or the pelvic sidewall.

Tumors that have metastasized distantly are classified as stage T_{1-4}, N_{0-1}, M_{0-1}, (D). According to the 1997 AJCC classification, the regional lymph nodes are the nodes of the true pelvis, which are located below the bifurcation of the common iliac arteries and include pelvic, hypogastric, obturator, external/internal iliac, and sacral nodes. N_0 indicates the absence of regional lymph node metastasis. N_1 disease implies metastasis in a regional lymph node or nodes. Laterality does not affect the N classification. The designations N_1 (one regional lymph node 2 cm), N_2 (one regional lymph node greater than 2 cm but less than 5 cm or multiple regional nodes), and N_3 (regional lymph node greater than 5 cm) as proposed in the 1992 AJCC have now been abandoned. Assignment to a M_0 status implies the absence of distant metastasis. The presence of distant metastasis mandates assignment to the M_1 category. The latter has been divided into three subsets by the 1997 AJCC. M_{1a} implies involvement of a nonregional lymph node(s). The latter can include aortic, common iliac, superficial/deep inguinal, supraclavicular, cervical, scalene, or retroperitoneal lymph nodes. Involvement of one or more sites in the skeletal system is designated as M_{1b}. Involvement of other soft tissue sites is designated M_{1c}. Note, when more than one site of metastasis is identified, the most advanced category—pM_{1c}—is used. Individuals with an isolated finding of a persistently elevated serum enzymatic acid phosphatase are designated stage D_0. The current TNM system allows a more accurate quantitation, and to some extent, site identification in the patient with disseminated disease. Table 33.14 and Table 33.15 provide useful versions of the 1997 AJCC staging definitions, stage group assignments, and a tumor-grading nomenclature.

TABLE 33.14. 1997 AJCC STAGING DEFINITIONS

Primary Tumor (T)	
T_x	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_1	Clinically inapparent tumor not palpable or visible by imaging
T_{1a}	Tumor incidental histologic finding in ≤5% of tissue resected
T_{1b}	Tumor incidental histologic finding in >5% of tissue resected
T_{1c}	Tumor identified by needle biopsy (e.g., because of elevated prostate-specific antigen)
T_2	Palpable tumor confined within prostate[a]
T_{2a}	Tumor involves one lobe
T_{2b}	Tumor involves both lobes
T_3	Tumor extends through the prostatic capsule[b]
T_{3a}	Extracapsular extension (unilateral or bilateral)
T_{3b}	Tumor invades seminal vesicle(s)
T_4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall
Primary Tumor, Pathologic (pT)	
pT_x[c]	Organ confined
pT_{2a}	Unilateral
pT_{2b}	Bilateral
pT_3	Extraprostatic extension
pT_{3a}	Extraprostatic extension
pT_{3b}	Seminal vesicle invasion
pT_4	Invasion of bladder, rectum
Regional Lymph Nodes (N)	
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in regional lymph node or nodes
Distant Metastasis (M)[d]	
M_x	Distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis
M_{1a}	Nonregional lymph nodes
M_{1b}	Bone(s)
M_{1c}	Other site(s)

[a]Tumor found in one both lobes by needle biopsy but not palpable or reliably visible by imaging, is classified as T_{1c}.
[b]Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T_3, but as T_2.
[c]There is no pathologic T_1 classification.
[d]When more than one site of metastasis is present, the most advanced category—pM_{1c}—is used.
American Joint Committee on Cancer: *Cancer staging manual*, 5th ed. Philadelphia: Lippincott-Raven, 1997.

TABLE 33.15. 1997 AJCC STAGE GROUP ASSIGNMENTS AND TUMOR GRADING NOMENCLATURE

Stage Grouping				
I	T_{1a}	N_0	M_0	G_1
II	T_{1a}	N_0	M_0	$G_{2,3-4}$
	T_{1b}	N_0	M_0	Any G
	T_{1c}	N_0	M_0	Any G
	T_1	N_0	M_0	Any G
	T_2	N_0	M_0	Any G
III	T_3	N_0	M_0	Any G
IV	T_4	N_0	M_0	Any G
	Any T	N_1	M_0	Any G
	Any T	Any N	M_1	Any G

Histopathologic Grade (G)

G_X	Grade cannot be assessed
G_1	Well differentiated (slight anaplasia)
G_2	Moderately differentiated (moderate anaplasia)
G_{3-4}	Poorly differentiated or undifferentiated (marked anaplasia)

If grouping of Gleason scores is necessary for research purposes, the following grouping is suggested:

Gleason score	2–4	Well differentiated
	5–6	Moderately differentiated
	7	Moderately poorly differentiated
	8–10	Poorly differentiated

Histopathologic Type

This classification applies to adenocarcinoma but not to sarcoma or transitional cell carcinoma of the prostate. Transitional cell carcinoma of the prostate is classified as a urethral tumor. There should be histologic confirmation of the disease.

Evaluation of Local Mass—Periprostatic Extension

Rectal Examination

Efforts to assess tumor mass and the presence and site of extraorgan disease rely on findings on physical examination, primarily the DRE, and various imaging studies including TRUS, MRI, and CT scans. These approaches, especially, the rectal examination, provide useful information, particularly in some patients with extensive disease. However, they all lack sensitivity and specificity for identification of extraorgan disease and quantifying tumor mass.

The prominent role of a carefully performed DRE in staging and substaging CaP has diminished somewhat as the number of malignancies identified without induration or nodularity of the gland has increased. Nevertheless, DRE is the major tool currently available for recognizing locally extensive disease. The extent and configuration of the induration that prompts recognition of probable CaP should be observed and recorded before attempts are made to obtain histologic confirmation of carcinoma by tissue-sampling procedures. Recognition of the violation or obliteration of landmarks such as the median furrow or lateral sulci is particularly important to the staging effort. The incidence of false-positive evaluation such as induration at the base of the seminal vesicle or across the lateral sulci indicating periprostatic spread has not been evaluated systematically. Histologic observations in small groups of patients suspected of having seminal vesicle or capsular perforation on physical examination but nevertheless selected for radical prostatectomy failed to confirm the clinical impression of

dissemination in more than 25% (112,1027). In clinical practice the induration noted on DRE is usually interpreted as confined to the prostate, clearly extraprostatic, or questionable with regard to extent. The presence of previous prostatic disease or surgery, including biopsies, diminishes the critical role of DRE in staging. Histologic examination of specimens removed at radical prostatectomy for presumed local disease indicates a significant incidence of understaging or false-negative assessments by rectal examination (147,968,1048).

The size and location of the induration noted on rectal examination has established validity to provide clinical information for substaging (e.g., $T_{2a,2b}$; B_1B_2). The traditional observation that the extent of induration almost always underestimates the extent of gland replacement by tumor is verified regularly by detailed mapping of radical prostatectomy specimens. Interestingly, these efforts document that the site of induration and histologic carcinoma do not always coincide; this observation has been reaffirmed clinically by the discordant results on DRE and histologic findings following TRUS biopsies (771).

Physical Imaging

Physical imaging procedures, including TRUS, CT, and MRI, have been used to provide information to facilitate local staging of CaP. Personal and reported experiences with TRUS, the most widely used of these procedures, indicate that it is of little assistance in assessing intragland mass or site (126,635,1008). CT and MRI (683,790) also have not been able to differentiate intraorgan benign and malignant tissues reliably. The CT scan has proved as disappointing in identifying periprostate tumor and tumor mass as it has in diagnostic studies (Fig. 33.39) (683,857). In a comparative evaluation of the recognition of organ-confined and extraorgan disease in 62 patients subjected to radical prostatectomy, DRE (62), TRUS (47), CT (41), and MRI (38) correctly predicted the stage in 21%, 65%, 24%, and 56% of the studied patients, respectively. Overstaging occurred in 1.2% (DRE) to 9.5%, and understaging occurred in 77% (DRE) to 33% (TRUS). In several instances the actual and imaging site of capsular perforation did not coincide (250). Although the image obtained using endorectal surface coil MRI appears to provide superior tissue detail to body coil MRI, extraprostatic disease was recognized with approximately the same accuracy by both (68% versus 69%) (161,830). The more recently reported correlation of endorectal MRI and pathologic evidence of extracapsular extension or seminal vesicle invasion in 70% and 90% of cases, respectively by D'Amico (206) conflicts with less than 50% identification of stage T_3 disease with endorectal MRI by Lee (566). Stratifying patients by Gleason grade or number of positive biopsies did not improve the ability to assess pathologic stage. Even more recently, D'Amico (204) suggested a combination of preoperative PSA level, biopsy Gleason score, percentage of positive biopsies, and endorectal MRI T-stage can predict early PSA failure in patients with clinically localized CaP. Finally, the use of magnetic resonance spectroscopy did not appear to provide additional staging information with respect to the presence or absence of extracapsular extension.

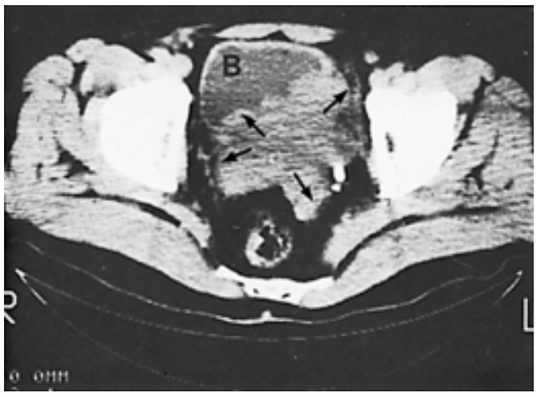

FIGURE 33.39. Pelvic computed tomography scan demonstrating local extension of prostate cancer with involvement of the bladder *(upper arrows)* and seminal vesicles *(lower arrows).* The left ureter (contrast enhanced) appears to be dilated as it approaches the tumor mass. (From Spirnak J, Resnick MI. Clinical staging of prostatic cancer: new modalities. *Urol Clin North Am* 1984;11:221, with permission.)

These and other similar observations (635,683,830) have led us to use TRUS selectively and other standard imaging studies very infrequently to evaluate possible periprostatic spread of prostate carcinoma. If TRUS examination suggests periprostatic spread, we prefer to obtain corroborative ultrasound-guided biopsy evidence before finalizing acceptance of this finding.

In 1997, Partin and associates (747) developed a nomogram that combines PSA, biopsy Gleason sum, and clinical stage to predict final pathologic stage. This approach was based on a logistic regression analysis of the 4,133 untreated patients with clinically localized prostate cancer who underwent radical prostatectomy at one of three institutions: Johns Hopkins University, Baylor College of Medicine, and the University of Michigan. Using the previously stipulated parameters, this nomogram can estimate the 95% confidence intervals for the probability of organ-confined disease, established capsular penetration, seminal vesicle involvement, and lymph node involvement. It is important to emphasize that this nomogram and other similar multivariant algorithms are far from perfect. For example, subsequent validation of the Partin nomogram has demonstrated that it correctly predicts the probability of pathologic stage to within 10% approximately 72% of the time (785). The updated version of this nomogram is depicted in Table 33.16 .

Gleason Score	PSA 0.0–4.0 Clinical Stage							PSA 4.1–10.0 Clinical Stage							PSA 10.1–20.0 Clinical Stage							PSA Greater Than 20.0 Clinical Stage						
	T_{1a}	T_{1b}	T_{1c}	T_{2a}	T_{2b}	T_{2c}	T_{3a}	T_{1a}	T_{1b}	T_{1c}	T_{2a}	T_{2b}	T_{2c}	T_{3a}	T_{1a}	T_{1b}	T_{1c}	T_{2a}	T_{2b}	T_{2c}	T_{3a}	T_{1a}	T_{1b}	T_{1c}	T_{2a}	T_{2b}	T_{2c}	T_{3a}
Organ-confined Disease																												
2–4	90	80	89	81	72	77	—	84	70	83	71	61	66	43	76	58	75	60	48	53	—	—	38	58	41	29	—	—
5	82	66	81	68	57	62	40	72	53	71	55	43	49	27	61	40	60	43	32	36	18	—	23	40	26	17	19	8
6	78	61	78	64	52	57	35	67	47	67	51	38	43	23	—	33	55	38	26	31	14	—	17	35	22	13	15	6
7	—	43	63	47	34	38	19	49	29	49	33	22	25	11	33	17	35	22	13	15	6	—	—	18	10	5	6	2
8–10	—	31	52	36	24	27	—	35	18	37	23	14	15	6	—	9	23	14	7	8	3	—	3	10	5	3	3	1
Established Capsular Penetration																												
2–4	9	19	10	18	25	21	—	14	27	15	26	35	29	44	20	36	22	35	43	37	—	—	47	34	48	52	—	—
5	17	32	18	30	40	34	51	25	42	27	41	50	43	57	33	50	35	50	57	51	59	—	57	48	60	61	55	54
6	19	35	21	34	43	37	53	27	44	30	44	52	46	57	—	49	38	52	57	50	54	—	51	49	60	57	51	46
7	—	44	31	45	51	45	52	36	48	40	52	54	48	48	38	46	45	55	51	45	40	—	—	46	51	43	37	2
8–10	—	43	34	47	48	42	—	34	42	40	49	46	40	34	—	33	40	46	38	33	26	—	24	34	37	28	23	17
Seminal Vesicle Involvement																												
2–4	0	1	1	1	2	2	—	1	2	1	2	4	5	10	2	4	2	4	7	8	—	—	9	7	10	14	—	—
5	1	2	1	2	3	3	7	2	3	2	3	5	6	12	3	5	3	5	8	9	15	—	10	9	11	15	19	26
6	1	2	1	2	3	4	7	2	3	2	3	5	6	11	—	4	4	5	7	9	14	—	8	8	10	13	17	21
7	—	6	4	6	10	12	19	6	9	8	10	15	18	26	8	11	12	14	18	22	28	—	—	22	24	27	32	36
8–10	—	11	9	12	17	21	—	10	15	15	19	24	28	35	—	15	20	22	25	30	34	—	20	31	33	33	38	40
Lymph Node Involvement																												
2–4	0	0	0	0	0	0	—	0	1	0	0	1	1	1	0	2	0	1	1	1	—	—	4	1	1	3	—	—
5	0	1	0	0	1	1	2	1	2	0	1	2	2	3	3	5	1	2	4	4	7	—	10	3	3	7	7	11
6	1	2	0	1	2	2	5	3	5	1	2	4	4	9	—	13	3	4	10	10	18	—	23	7	8	16	17	26
7	—	6	1	2	5	5	9	8	12	3	4	9	9	15	18	24	8	9	17	18	26	—	—	14	14	25	25	32
8–10	—	14	4	5	10	10	—	18	23	8	9	16	17	24	—	40	16	17	29	29	37	—	51	24	24	36	35	42

Predicted probability of each pathologic stage based on preoperative PSA, clinical stage, and Gleason score in the biopsy specimen.
PSA, prostate-specific antigen.
Reproduced from Partin AW, et al. A combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multiinstitutional update. *JAMA* 1997;277:1445–1451, with permission.

TABLE 33.16. THE PARTIN NOMOGRAM

Evaluation of Disseminated Disease

The evaluation of disseminated disease in patients with CaP centers on two related but independent efforts. One is to quantify the probability of disseminated disease and the other is to identify sites involved. An array of approaches is available to aid these efforts. The distinction between the probable and the established is often blurred in clinical practice. Biologic markers, including PSA, acid and alkaline phosphatase, and more recently, PSMA and human glandular kallikrein-2 (hK2), have a range of potential uses. Attempts to identify metastatic sites concentrate on imaging studies with a variable degree of specificity, tissue or cell sampling for histologic and immunohistologic studies, and combinations of those efforts. A brief discussion of the markers, the imaging studies, and to some degree, the combined approaches to evaluate disseminated disease is presented.

Biologic Markers

Although a host of biologic markers have been used to evaluate the probability of disseminated disease in patients with histologically or cytologically documented CaP, only three have contributed sufficient useful information to have been or to be used regularly: serum PSA, acid phosphatase, and alkaline phosphatase. Currently, PSA is used regularly and acid and alkaline phosphatase are used selectively in this effort. Efforts to use PSMA and hK2 markers are being pursued actively with promise.

Prostate-specific Antigen

An impressive amount of data has been accumulated during the past several years regarding the proper role of PSA in the staging and monitoring of patients with CaP (8,278,556,788,962,964,967). Some current perceptions regarding the utility of this marker include the following: (a) In CaP, PSA generally increases with advancing clinical stage and is roughly proportional to the estimated tumor volume. (b) Serum PSA is crudely proportional to the Gleason score of the primary tumor. (c) PSA rises proportionally to the amount of cancer tissue present (3.5 ng/mL per gram in one study) (961,962 and 963). (d) Patients with serum PSA levels of less than 10 ng/mL are most likely to respond to local therapy (1014). (e) Lymph node metastases are unusual in patients with a pretreatment PSA level of less than 10 ng/mL and in patients with a Gleason score of 6 with pretreatment serum PSA levels less than 20 ng/mL (1014). (f) If the PSA is greater than 50 ng/mL, two-thirds of patients have microscopic lymph node metastases, and 90% demonstrate seminal vesicle invasion (963). (g) In the absence of history or clinical examination suggesting skeletal involvement, bone scans are generally not required in patients with pretreatment PSA levels less than 20 ng/mL (1014). (h) It is reasonable to consider a bone scan (even if the pretreatment PSA is less than 10 ng/mL) in patients with a high Gleason histotype tumor (8 to 10) or stage $T_{3,4}$ disease (95). (i) CT and MRI scanning are rarely positive when the PSA is less than 25 ng/mL (10).

PSA is a more sensitive tumor marker than PAP. In the study conducted by Ercole and associates (278), PSA was elevated in 98% of patients with stage D_2 disease compared with an increased PAP noted in 78%. PAP was the only marker elevated in 1% of patients and neither marker was elevated in 2%. Other studies have suggested that PSA is a more sensitive and potentially more useful marker than PAP in this context (8). Despite the recognized advantages of PSA over PAP, we continue to monitor PAP in addition to PSA selectively in multiply treated patients at high risk for relapse.

Acid Phosphatase

PAP, an orthophosphoric monoester phosphohydrolase with an isoelectric point between 4.5 and 5.5, is produced and secreted in large quantities by normal postpubertal and BPH prostatic epithelial cells. Malignant prostatic cells usually continue to produce this enzyme in appreciable, although decreased, quantities. Demonstration of elevated serum levels of acid phosphatase in patients with CaP by Gutman and Gutman (396) and the effect of endocrine manipulation on them by Huggins and Hodges (446) initiated an appreciation of the potential roles of biologic markers in this and other malignancies. Because isoenzymes of acid phosphatase are present in almost all body tissues, acid phosphatase lacks organ and disease specificity. Multiple diverse attempts to improve clinical specificity beyond that provided by selected enzymatic assays have not succeeded (532). Elevations of acid phosphatase serum levels have been noted sporadically in a wide variety of diseases and following surgical and digital manipulation of the prostate (Table 33.17).

TABLE 33.17. DISORDERS ASSOCIATED WITH AN ELEVATION OF SERUM ACID PHOSPHATASE

Organ Site	Condition
Prostate	Carcinoma
	Infarction
	Rectal examination/prostatic massage
	Endoscopic manipulation
	Urinary retention
Reticuloendothelial system	Hairy cell leukemia
	Gaucher's disease
	Niemann-Pick disease
	Eosinophilic granuloma
	Reticulum cell sarcoma
	Hodgkin's disease
Carcinomas with hepatic/skeletal metastases	Breast
	Stomach
	Colon
	Kidney
	Adrenocortical
Liver	Viral hepatitis
	Cirrhosis
	Biliary tract obstruction
	Chlorpromazine hepatitis
Kidney	Chronic glomerulonephritis
	Gouty nephropathy
Skeletal system (primary)	Paget's disease
	Osteogenesis imperfecta
	Osteogenic sarcoma
	Osteopetrosis
	Osteoporosis
Skeletal system (secondary)	Primary hyperparathyroidism
	Multiple myeloma

Modified from Sodeman TM, Batsakis JG. Acid phosphatase. In: Tannenbaum M, ed. *Urologic pathology: the prostate.* Philadelphia: Lea & Febiger, 1977:129.

At present, the following statements seem a reasonable summary of the results of both total and prostatic acid phosphatase determination using the various enzymatic immunologic techniques currently available: (a) Persistent elevation of serum PAP levels as determined by enzymatic procedures in patients with CaP indicates a very high probability of dissemination of the disease outside the prostate to bony or soft tissue, including periprostatic extension. An isolated limited elevation of serum PAP is usually not accepted as an absolute indication of disseminated disease, although, as the DO classification indicates, concern for probable metastatic disease is appreciable. (b) Local and/or distant dissemination of CaP may be present without an elevation of total or prostatic acid phosphatase. (c) Total and prostatic acid phosphatase levels may provide a useful marker to follow the course of patients with CaP after treatment. Although serum PAP may fail to signal tumor progression after therapy, confirmed recurrent posttherapy elevation of serum PAP is an excellent indication of recurrent tumor activity and progression (143,413,789,872).

Alkaline Phosphatase

Alkaline phosphatases, a series of enzymes that hydrolyze phosphate esters at a pH of 7 or greater, are present in various tissues including bone, intestinal mucosa, and liver. Each of these tissues has characteristic isoenzymes that can be assayed in a clinical setting. In addition, a placental form of alkaline phosphatase, designated Regan or tumor isoenzyme, has been recognized.

Serum levels of total alkaline phosphatase are frequently elevated in patients with CaP. These elevations are neither disease nor site specific and are known to occur in a wide variety of clinical disorders (143,413,872). This nonspecificity of total alkaline phosphatase (TAP) diminishes its value for staging CaP. Furthermore, an elevation of bone alkaline phosphatase was detected more frequently than an elevated total alkaline phosphatase (91% versus 87%) in patients with bone metastases evaluated in the National Prostate Cancer Project (1056), suggesting an advantage for it in identifying risk of bone metastases. High pretreatment levels of total or bone alkaline phosphatase may reflect an increased tumor burden and a poor prognosis. Serial determinations of serum alkaline phosphatase have potential value in identifying bone involvement and following the course of the patient's disease (872). For example, the initial rise, or flare, followed by a fall in serum levels frequently seen in patients with bony metastases responding to initiation of hormone therapy provides supporting evidence both for the presence and response of bone lesions (446).

Reverse Transcriptase–Polymerase Chain Reaction Prostate-specific Antigen and Prostate-specific Membrane Antigen

To enhance the recognized usefulness of serum PSA monitoring, several investigators have pursued methods to detect PSA-positive cells within the systemic circulation, lymph nodes, and bone marrow. A major incentive for this effort is the fact that up to 40% of surgically treated patients with CaP subsequently are found to be clinically understaged (492).

One of the earliest studies of the systemic circulation detected PSA-positive tumor cells with analytic flow cytometry in all 25 of the untreated CaP patients with a positive bone scan evaluated (401). Of note, 7 of 15 patients with a negative bone scan also had circulating PSA-positive cells. Indeed, demonstration of more than 2% PSA-positive circulating cells had a greater sensitivity (96%) and specificity (60%) for detection of skeletal metastases than did a serum PSA level of 20 ng/mL (sensitivity 76%, specificity 53.5%). On light microscopy, the PSA-positive cells exhibited characteristic cytologic features, including the presence of multiple nucleoli and slightly clumped chromatin, but were not easily differentiated morphologically from cells of the monocyte/macrophage lineage.

Subsequently, RT-PCR amplification was used to assay for PSA. This technique is capable of recognizing one PSA-expressing cell from a population of 10^5 to 10^7 background cells (492,1105). However, poor differentiation and decreased PSA message of some circulating cancer cells makes their detection in some patients difficult. Attempts to use RT-PCR assay to detect PSA-producing circulating cells in individuals with clinically localized prostate cancer have produced variable results; for example, Katz (492) reported 38.5% (25 of 65) and Seiden (897) only 7.7% positive findings. The results in patients with metastatic disease were similarly discrepant.

RT-PCR also has been used to document unrecognized lymph nodes and bone marrow dissemination. In a retrospective study using paraffin-embedded lymph nodes, Edelstein and associates (251) reported that 88% of 16 patients with a positive RT-PCR assay and no histologic evidence of lymph node metastasis eventually developed metastatic disease; however, recurrent disease also was detected in 30% of 20 patients with pathologic and RT-PCR negative lymph nodes. Recently, Okegawa and associates (731) noted nested RT-PCR was positive in lymph nodes of 2 of 18 patients (11%) with stage pT_{2a} and 5 of 20 (25%) with stage

pT_{2b} disease. Ultimately, these patients all exhibited biochemical recurrence. These investigators acknowledge the potential for false-negative results because half of each lymph node was used for pathologic and the other half for molecular analysis.

With regard to detection of bone marrow micrometastases, Wood and Banerjee (1104) reported that with a mean follow-up of 15.4 months (range of 1 to 43) only 2 of 47 patients (4%) with a negative bone marrow RT-PCR PSA exhibited recurrence compared with 10 of 39 (26%) with positive RT-PCR PSA results. Gao and associates (335) reported a 2-year disease-free survival rate of 96.6% versus 77.5% in radical prostatectomy patients with negative versus positive RT-PCR PSA bone marrow results. Multivariant analysis of their study, as contrasted to Wood and Banerjee (1104), demonstrated bone marrow RT-PCR for PSA was an independent prognostic factor.

At present, RT-PCR analysis of PSA expressing cells in the systemic circulation (and elsewhere) does not have a firm place in our diagnostic armamentarium. Despite the observations by Olsson and associates (733) that demonstrating PSA by RT-PCR in peripheral blood cells was a statistically significant predictor of early biochemical recurrence following radical prostatectomy, neither Ellis and associates (272) nor Gao and associates (335) documented a predictive value for this finding in regard to biochemical recurrence or, in the Gao study, of pathologic stage. In addition to the nonspecificity of the targeted information, these dichotomous results reflect, in part, inherent limitations in RT-PCR technology, which include (a) a lack of standardization of sample collection/processing, storage, and shipping conditions; (b) a lack of uniform methodologic protocols and oligonucleotide primers; (c) varying results among institutions using slightly different methodology; and (d) a predisposition to false-negative and false-positive results (785).

Recently, Israeli and associates (458) reported the molecular cloning of a novel M_r 100,000 prostate-specific membrane glycoprotein, designated PSM. Analysis of its complimentary DNA sequence revealed a 54% homology to the human transferrin receptor mRNA. Unlike PSA and PAP, which are secreted proteins, PSM appears to be an integral membrane protein with a transmembrane domain that helps delineate its intracellular and extracellular portions. Primers derived from both PSA and PSM cDNA sequences used in conjunction with a nested RT-PCR assay facilitate detection of occult hematogenous micrometastatic prostate cells (457). In 77 patients with prostate cancer, PSM and PSA primers detected the presence of circulating prostate cells in 48 of 77 (62.3%) and 7 of 77 (9.1%) patients, respectively. More recently, PSM primers detected presumed micrometastatic disease in 21 of 31 (67.7%) postradical prostatectomy patients with negative serum PSA values. PSA primers detected circulating tumor cells in only 1 of 33 (3%) of these patients. In treated stage D disease patients, PSM primers detected presumed micrometastatic disease in 16 of 24 (66.7%) of the patients as contrasted to only 6 of 24 (25%) using PSA primers. Finally, presumptive evidence of micrometastases was noted in 4 of 40 controls, 2 of whom had evidence of BPH and subsequently developed biopsy-confirmed prostate cancer. A follow-up analysis by Israeli and associates (456) further confirmed enhanced detection of circulating micrometastases using nested RT-PCR in conjunction with PSM primers. Recently, Okegawa and associates (732) reported that nested RT-PCR for PSM in peripheral blood cells was useful for predicting biochemical recurrence with a mean follow-up of 16.7 months and that these results were the most effective parameter evaluated.

As a composite, these studies suggest the development of lymphatic and hematogenous metastasis may be a relatively early event in the natural history of human CaP. Furthermore, molecular approaches seem likely to enhance our ability to detect micrometastatic disease, particularly in patients who are apparently disease free by clinical and biochemical criteria after radical prostatectomy. However, long-term follow-up is necessary to determine the implications of a positive RT-PCR assay for either PSM or PSA in these patients.

Other Biochemical Markers

Several other biochemical compounds have been explored and, in some instances, advocated in patients with carcinoma of the prostate. These include determination of serum levels of creatinine kinase bone band (CK-BB), LDH isoenzymes, isocitric dehydrogenase, phosphohexose isomerase, carcinoembryonic antigen, ribonuclease activity, prostacyclin, and erythrocyte polyamines as well as urinary levels of hydroxyproline, nonesterified and total cholesterol, spermidine, fibronectin, and human glandular kallikrein (789,872).

Several laboratories have confirmed the association of elevated tissue and serum levels of urokinase-type plasminogen activator (u-PA) with CaP possessing the aggressive or metastatic phenotype (343,419,508). A trypsinlike serine protease with a shared structural homology with PSA, u-PA may play an important role in tumor invasion of the extracellular matrix and metastasis. These potential markers are all nonspecific—a factor that undoubtedly has led to limited enthusiasm for their use. Nevertheless, the failure to continue exploration of their possible role (in particular as indicators of tumor response to therapy) may deprive us of useful information.

Bone Metastasis

As noted under Natural History, the bones of the axial skeleton are a common site of metastatic spread of CaP, with identifiable involvement in up to 84% of patients at autopsy (467). Pain, presumably secondary to metastatic spread to the pelvis and lumbar spine, has been and is prominent in the CaP patient with symptoms. The majority of the long-term (21%) and short-term (25%) American College of Surgeons survey patients presenting with stage D

disease had dissemination recognized because of bone involvement. Bone metastases can be present and progress without abnormal findings on serum marker or pelvic lymph node studies. Because the red marrow sinusoids are the first site of bone involvement in metastatic disease, detection of dissemination to bone is often difficult and delayed.

Various efforts to identify metastatic tumor cells in marrow using specific markers were discussed in the previous setting. However, a unique attempt to use a mixture of antisera to PSA, PAP, epithelial membrane antigen, and CK to probe bone marrow aspirates from patients with presumably localized and metastatic prostate cancer deserves mention (616). This antisera cocktail detected large numbers of tumor cells in 11 of 15 patients (73%) with known metastatic disease, and small numbers of tumor cells in 2 of 15 patients (13%) with "localized" disease. In contrast, conventional staining procedures detected tumor cells in only 2 of 15 patients (13%) with established skeletal metastases. Analysis of bone marrow aspirates using innovative immunocytochemical and molecular biology techniques for accurate staging deserves additional consideration. The remainder of the discussion in this section focuses on the imaging studies available to assess bone and/or soft tissue CaP metastasis.

Bone Scan

The radionuclide bone scan is the most sensitive imaging technique to detect skeletal metastases. Bone scans are positive in 10% to 50% of patients with metastatic CaP who have nondiagnostic conventional x-ray studies (874). They have the disadvantage of providing nonspecific information. Several benign and malignant bone lesions, including osteomyelitis, benign and malignant neoplasms, Paget's disease, metabolic bone disease, and degenerative joint disease, as well as trauma, may result in radionuclide "hot spots." Most metastatic lesions from carcinoma of the prostate appear as asymmetric areas of intense uptake of radionuclide (484,957). The distribution and configuration of areas of increased radionuclide uptake aid in assessing the probability they are due to metastatic disease (Fig. 33.40). However, this diagnosis remains doubtful without confirmation on routine or tomographic radiographs, CT or MRI studies, or bone biopsy. On the other hand, presumptive evidence of metastatic carcinoma on bone radiographs, with a bone scan interpreted as negative (false negative) is low, ranging from 0% to 8% (957). The false-negative scans have been associated with lesions producing little or no reactive bone or with the so-called super-scan associated with extensive symmetric metastatic disease that sequesters the majority of the isotope, producing a faint or negligible renal image (Fig. 33.41).

FIGURE 33.40. ^{99m}Tc bone scan demonstrating multifocal areas of increased uptake in the calvarium, maxilla, humerus, ribs, sternum, lumbosacral spine, pelvis, and femur. These findings are certainly consistent with metastatic cancer in a patient with a known prostate primary. (From Spirnak J, Resnick MI. Clinical staging of prostatic cancer: new modalities. *Urol Clin North Am* 1984;11:221, with permission.)

FIGURE 33.41. ^{99m}Tc "superscan" in a patient with metastatic prostate cancer demonstrating faint renal visualization and an intense symmetric uptake of the isotope by the ribs and axial skeleton. (From Spirnak J, Resnick MI. Clinical staging of prostatic cancer: new modalities. *Urol Clin North Am* 1984;11:221, with permission.)

Bone Radiographs

Most CaP patients with bone x-ray films demonstrating metastatic involvement have pure osteoblastic (75%) or mixed osteoblastic-osteolytic lesions (15%). Pure osteolytic lesions (10%) occur much less commonly (1094). The osteoblastic lesions are characteristically multiple and nodular, but many have a mottled appearance or even produce lesions suggesting an ivory vertebra (Fig. 33.42). In attempting to evaluate a particular site identified as abnormal by bone scan, magnification and tomographic techniques may provide useful information. Although other metastatic tumors, including those of breast, stomach, and lung, produce osteoblastic bone responses, these tumors are either uncommon in aging men, or the osteoblastic bone response is an unusual one for them. In an older man, osteoblastic bone lesions suggesting metastatic disease should be considered to be due to CaP until that possibility is excluded. Past roentgenographic and autopsy studies indicated the sacrum, pelvis, and lumbar spine were the bones most involved by recognizable metastatic deposits. Bone scan results suggest the frequency of rib metastasis equals or exceeds that of the pelvis and that metastasis from CaP has a more random distribution than we had appreciated (236). Dodds and co-workers (236) also reported the pelvis, lumbar spine, and sacrum were free of demonstrable disease in 25% of the patients with skeletal metastasis from CaP.

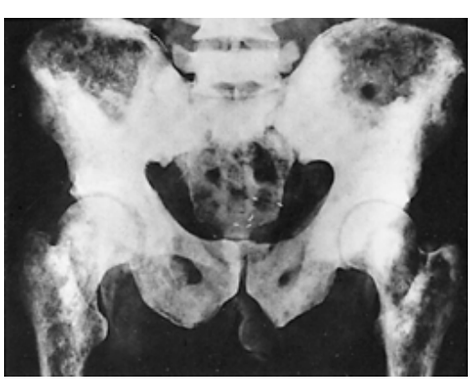

FIGURE 33.42. Osteoblastic skeletal metastases characteristic of prostate cancer. Metastatic bone lesions are discrete dense areas, commonly adjacent to joint surfaces, but do not affect the joint space. [From Mostofi FK, Price EB Jr. Tumors of the male genital system. In: Universities Associated for Research and Education in Pathology, National Research Council (U.S.). Committee on Pathology, eds. *Atlas of tumor pathology,* Second series, fascicle 8. Washington, DC: Armed Forces Institute of Pathology, 1973, with permission.]

Differentiation of metastatic CaP from Paget's disease on the basis of roentgenographic findings can be very difficult (1094). Paget's disease is usually multifocal but not generalized throughout the skeleton; some normal bone remains. The disease is characterized by cortical widening or thickening; accentuation of the bony striae, producing a ropy striated pattern; irregularly associated rarefied or “cystic” and uniformly dense osteosclerotic areas; and an intact periosteum (Fig. 33.43). Males are affected by Paget's disease approximately twice as often as females. The facts that the pelvis is the most frequently affected bone and that Paget's disease and CaP may coexist create a problem in evaluating patients. Roentgenographic observations alone may not allow a satisfactory assessment of the probability of bone metastasis in a patient with Paget's disease. Tumor marker information such as that provided by serum PSA and acid phosphatase is often invaluable in these circumstances. Bone biopsy or marrow aspiration also may be warranted (236).

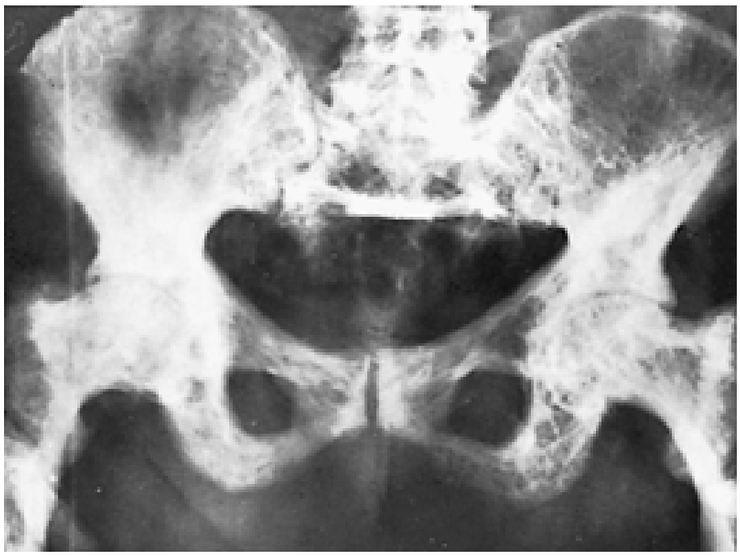

FIGURE 33.43. Paget's disease of the bone. Roentgenographic hallmarks that distinguish such a picture from metastatic prostate cancer include the characteristic cortical thickening, the prominent striated pattern admixed with cystic areas, and an intact periosteum. Unlike blastic lesions, which typically have well-demarcated edges, degenerative sclerosis produces more diffuse changes. Note the distortion of both hip joints. (From Dickson DD, Camp JD, Ghormley RK. *Radiology* 1945;44:449, with permission.)

Computed Tomography and Magnetic Resonance Imaging

At present, CT is not thought to provide significant additional information in the routine diagnosis of metastatic bone disease. Occasionally, however, metastatic lesions in the pelvis, sternum, and vertebral column that are questionable or not evident on routine radiography may be detected by CT studies (816). MRI is a more sensitive and specific study for bone metastases than a bone scan. Metastatic lesions commonly are associated with a decreased marrow signal on T_1-weighted images. Although the T_2-weighted image signal is increased in most bone metastases, it commonly,

but not always, is decreased in association with osteoblastic metastases. Unfortunately, the MRI pattern does not always distinguish metastatic lesions, leukemia, lymphoma, multiple myeloma, and other benign marrow changes; however, thoughtful use of imaging sequences and occasional use of enhancing agents can assist in increasing the discriminatory information provided. We use MRI selectively with patients in whom our suspicion of possible metastatic disease is unconfirmed or requires further supportive evidence.

Albertsen and associates (10) performed a perspective, population-based survey targeting 3,690 men with prostate cancer. Using information captured in primary medical record reviews, they estimated the overall positive yield of bone scans, CT, and MRI in this cohort. They noted that the positive yield of bone scan and CT was less than 5% and 12%, respectively, for men with PSA levels of 4 to 20 ng/mL. These figures dropped to 2% and 9%, respectively, for men who also had a Gleason score of 6 or less. Only men with PSA levels greater than 50 ng/mL and those with Gleason scores of 8 to 10 and PSA levels greater than 20 ng/mL had positive yields greater than 10% and 20% for bone scan and CT, respectively.

Lymph Node and Soft Tissue Metastases

Observations documenting the presence and supporting the importance of an intraprostatic lymphatic system have increased (1088). The iliopelvic lymph nodes, constituting the first echelon of lymph drainage from the prostate gland, can be divided into three main groups: external iliac, internal iliac, and common iliac (845) (Fig. 33.44). The external iliac group consists of lateral, intermediate, and medial chains. Of these, the lateral and medial chains are the most important. The lateral retrocrural lymph node is prominent, relatively constant, and represents the most inferior node of the lateral chain. With respect to the metastatic spread of CaP, the medial chain is the most strategic. The so-called obturator node actually represents the middle node of the medial external iliac lymph node chain. It is located cephalad to the medial retrocrural node, which is the most inferior node in the medial chain and represents a continuation of the deep inguinal lymph nodes.

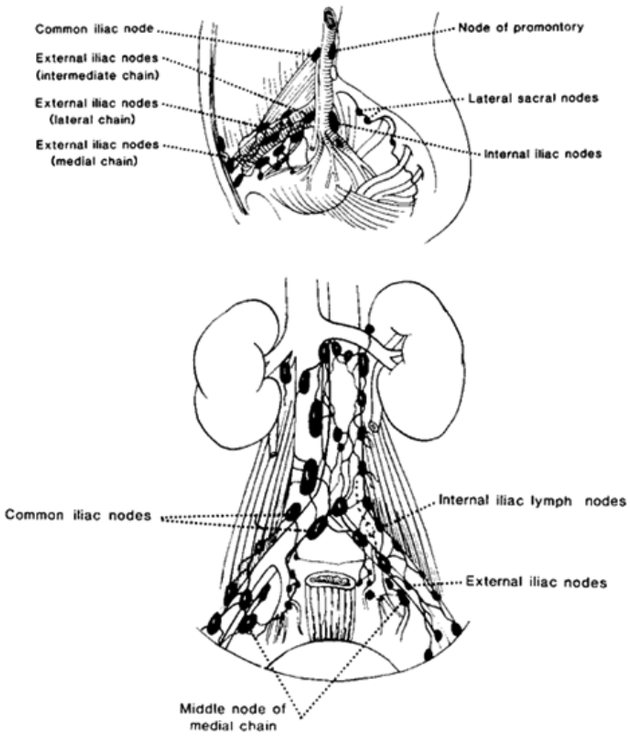

FIGURE 33.44. Sagittal **(A)** and coronal **(B)** views of the iliopelvic lymph nodes. The medial chain of the external iliac lymph nodes ("obturator" nodes) usually constitute the first echelon of lymphatic involvement in prostate cancer. (From Rouviere H. *Anatomy of the human lymphatic system.* Ann Arbor, MI: Edwards Brothers, 1938, with permission.)

Four to eight nodes lie along the internal iliac artery and its tributaries (hypogastric/internal iliac group). These lymphatics are a common site of CaP metastases and are infrequently visualized on standard pedal lymphangiograms.

The common iliac lymph node group, also subdivided into lateral, intermediate, and medial chains, represents an extension of the external iliac lymph nodes. Again, the medial chain is the most important because it constitutes a major pathway by which the pelvic viscera communicate with the periaortic nodes. The nodes of the sacral promontory (i.e., subaortic nodes) are part of this medial chain. It should be emphasized that the right and left common iliac chains are frequently cross-communicative.

Evidence supporting the frequency (18,301) and documenting the importance to clinical stage of pelvic lymph node metastasis from CaP has accumulated rapidly in the last 40 years. As expected from anatomic studies, the obturator, presacral, presciatic, hypogastric, and external iliac nodes are most commonly involved in metastasis (143). The so-called obturator nodes are involved more frequently and usually but not always earlier than other pelvic nodes (367,630). Apparently isolated metastases to other pelvic node sites do occur (307). The incidence of lymph node metastasis is related to the grade, and local mass and anatomic extent of the carcinoma.

With the advent of the use of serum PSA levels as an indication for prostatic biopsy, the prevalence of positive nodes removed at pelvic lymphadenectomy is much lower than it has been in the past (532,533). It approximates 5% or less in stage A_1, A_2, B_1, and T_c patients (355). Danella and associates (210) reported a node positive finding in 1 of 105 (less than or equal to 1%), 6 of 90 (6.7%) and in 5 of 19 (26.3%) stage B_1, B_2, and C patients. Use of stage, grade, and PSA data seems likely to identify a group of patients in whom omission of lymph node assessment before radical prostatectomy or radiation therapy is an alternative that deserves consideration.

The imaging studies such as MRI and CT scanning with and without needle aspiration are currently used very selectively and lymphangiography rarely to evaluate pelvic lymph nodes for the presence of metastatic carcinoma of the prostate. Radioimmunologic and positron emission tomography (PET) scan procedures are being used and evaluated in attempts to achieve more diffuse specific site recognition. The following is a brief discussion of the accuracy, advantages, and disadvantages of these procedures.

Computed Tomography Scan and Magnetic Resonance Imaging

The hope that CT scanning can identify enlarged masses (greater than 1.0 cm short axis) in a large percentage of the patients with pelvic lymph node metastasis has not been realized. The difference in results achieved with lymphoma as compared with metastatic deposits has been attributed to the difficulty in detecting microscopic deposits and in differentiating malignant and nonmalignant nodal enlargement. Experience with CT evaluation in a limited number of patients with various malignancies (565) and stage A_2 to C prostate cancer (49) indicated a false-negative rate of 40% and greater than 80%, respectively. Even nodal enlargement identified on CT scan was not always confirmed (false-positive result in one of two patients). Others have reported both confirmatory and contrary experiences in groups of patients subjected to CT scanning of the pelvis in whom pelvic lymphadenectomy was used selectively (868). An initial reported minimal experience with MRI evaluation of the pelvic structures in patients with clinically localized CaP (683) also indicated a high incidence of false-negative observations with regard to nodal metastases. The accuracy of CT or MRI in identifying enlarged pelvic nodes in patients with clinically advanced periprostatic disease (stage C, $T_{3,4}$) with or without attempted percutaneous aspiration or biopsy has not been evaluated systematically. Despite a strong positive correlation between PSA levels above 25 ng/mL and development of pelvic lymph node metastases, the sensitivity of CT (and probably MRI) scanning for detecting positive lymph nodes in this context approaches a disappointing 30% to 35%.

Lymphangiography

Visualization of the internal architecture of the pelvic lymph nodes by injecting ethiodol or a similar agent into the lymphatics of the dorsum of the foot is an established procedure to attempt to identify primary or metastatic malignancies in these structures. The medial chain of the external iliac nodes, the “obturator nodes,” is usually visualized by foot lymphangiography (647), but the hypogastric chain is demonstrated in only 50% of cases (143). The reported sensitivity and specificity of lymphangiography have varied considerably. Studies reporting an accuracy as high as 85% (138) or a false-positive rate of only 5% (755) conflict (29,105,390) with those reporting a high incidence of false-positive and false-negative observations, with the latter ranging from 40% to 50%. Patient selection is likely to be the major factor influencing the accuracy of the reported studies, although technical aspects of the study, as well as the skill of the radiologist interpreting it (757), may play a role. Currently, we rarely consider using lymphangiography to evaluate the pelvic lymph nodes for metastatic disease in CaP patients.

Radioimmunologic Imaging

Attempts to use tagged antibodies to PAP or PSA to identify and image tumor in metastatic sites are emerging. γ-Scintillation camera imaging 24 to 48 hours after the injection of an IgG ^{131}I-labeled antibody to PAP identified true primary and metastatic tumor sites in seven of the nine patients with metastatic carcinoma of the prostate but failed to identify bone metastasis (366). Babaian and associates (23) reported use of an antiprostatic acid phosphatase monoclonal antibody, PAY 276, labeled with indium-111 (^{111}In) to attempt to image metastatic foci from carcinoma of the prostate. This antibody did identify bone metastases but failed to image lymph nodes containing tumor. Increasing the quantity of unlabeled antibody used decreased PAY 276 concentration in the liver and was associated with increased specificity and sensitivity of the imaging procedure. The ProstaScint scan using the ^{111}In tagged antibody CYT-356, which reacts with cytoplasmic epitope of PSM recently has been shown to enhance visualization of soft-tissue nodal metastases (24) and occult prostate cancer recurrence after radical prostatectomy (480). With respect to lymph node metastases, a negative predictive value of 83% and a positive predictive value of 50% have been observed. At present, the ProstaScint scan appears to have limited value for pretreatment staging (1014). Sodee and associates (938) analyzed a multiinstitutional retrospective study of 2,292 ProstaScint imaging scans of 2,154 CaP patients. Of interest, those patients with newly diagnosed CaP had a significant correlation between PSA and ProstaScint positivity in the prostate bed and pelvic metastases, but not for extrapelvic metastatic disease. ProstaScint imaging has been used primarily to identify metastatic disease in patients who exhibit a rising PSA after radical prostatectomy. The potential utility of this imaging modality in that particular clinical context is summarized in a subsequent section of this chapter.

Positron Emission Tomography

Malignant tumors generally grow at a more accelerated rate than normal tissues, and thus possess increased rates of DNA synthesis, amino acid transport, protein synthesis, and increased rate of glucose metabolism (865). With respect to the latter feature, tumors generally exhibit increased rates of aerobic glycolysis versus most normal tissues. The Fluorine-18 (^{18}F) labeled analog of 2-deoxy-D-glucose (FDG) is transported into cancer cells like glucose by facilitative glucose transporters, and is phosphorylated to FDG-6-phosphate by hexokinase. ^{18}F has a 109-minute

half-life and is generally cyclotron or accelerator produced. Normal FDG *in vivo* distribution in man includes the brain, heart, kidneys, and urinary tract, at 1 hour after tracer injection. FDG-PET has been identified as a useful imaging modality for staging lung, colorectal, and head and neck cancers and melanoma. It appears PET has limited utility with respect to detection and characterization of the primary tumor site in CaP. The latter observation probably reflects the similarity of metabolic activity in most primary prostate tumors and BPH tissue. In addition, anticipated activity in the bladder renders analysis of subtle activity in the prostate difficult. Seltzer and associates (900) compared helical CT imaging and PET and CTY-356 monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate cancer exhibiting relapse after treatment for localized disease. PET and CT were both positive for distant disease in 50% of 22 patients with PSAs greater than 4 ng/mL and in 4% (PET) and 17% (CT), respectively, of 23 patients with PSA levels less than 4 ng/mL. PET and CT had similar detection rates for metastatic disease, which were higher overall than for monoclonal antibody scanning. CT-guided FNA documented metastases (true positive) in only 1 of 6 antibodies as contrasted to 6 of 9 PET-identified patients. These investigators suggest new PET tracers, such as C-11 methionine and C-11 choline, and emergence of informative PET-iterative image reconstruction algorithms may expand the utility of this imaging modality for prostate cancer. In contrast, Sanz and associates (865) observed that PET, using deoxyglucose labeled with ^{18}F, could not reliably identify tumor in the iliac and obturator lymph nodes before surgery. However, in radical prostatectomy patients with biochemical relapse, PET appeared to have better sensitivity than CT in identifying diseases in soft tissues but was inferior to bone scintigraphy in detecting skeletal metastases.

Excision and Histologic Evaluation of Pelvic Nodes

Identification of CaP cells in a pelvic node provides information regarding the biologic activity and the site of the tumor that is important to management decisions. Procedures attempting to identify node metastases that do not allow histologic or cytologic confirmation have limited sensitivity and suspect specificity. Consequently, evaluation of minimally invasive efforts to remove or successfully obtain tissue samples from lymph nodes and other sites potentially or probably involved by metastatic CaP are appropriately ongoing. The probability of recognizable lymph node involvement is related to the histologic grade and mass (clinical stage) of the primary tumor (see Natural History). This information combined with serum PSA levels has been used to attempt to assess the likelihood of node metastases (73,749) and may be useful in guiding decisions regarding the desirability and extent of pelvic node dissection before proceeding with definitive therapy (Table 33.16).

Several groups have documented the ominous prognostic significance of even one microscopically positive node (932,1139). Gervasi and associates (348) presented long-term follow-up information on 511 patients with CaP that had undergone bilateral pelvic lymph dissection and radiation. Although the results of treatment are confused by the high frequency of persistent local tumor, the difference in observed progressive disease at 10 years in N_0 (31%) and all N^+ (87%) regardless of extent of node involvement supports the biologic significance of node involvement. Consequently, an accurate assessment of the status of the nodes with regard to tumor dissemination is highly desirable. The limited sensitivity and suspect specificity of studies that do not provide an opportunity for histologic or cytologic evaluation of the nodes that are common sites of metastasis have been major factors in establishing pelvic lymphadenectomy as a common staging procedure in patients with CaP confined to the prostate and at times in patients with periprostatic disease. The optimal extent of lymphadenectomy, the accuracy of the evaluation for nodal metastasis on frozen and permanent section, and the immediate and delayed risks of the procedure warrant a brief discussion.

A risk-benefit assessment is important to determine the optimal extent of the pelvic lymphadenectomy. The purpose of the procedure is to provide staging information, although a therapeutic effect cannot be excluded. Accurate knowledge of the incidence and interrelationships of metastatic involvement of nodes in the obturator fossa and the external, internal, and common iliac, as well as the periaortic region in patients with prostatic carcinoma judged to be localized to the prostate or periprostatic area is essential to guide this assessment. In patients with nodal metastases staged by lymphangiography and pelvic lymph node dissection (PLND), Pistenma and associates (780) noted involvement of obturator, hypogastric, external iliac, common iliac, and paraaortic groups in 31%, 24%, 22%, 17%, and 18% of cases, respectively. The fact that only 61% (21 of 35) of the 35 solitary node metastases reported by Fowler and Whitmore (307) were located in the hypogastric-obturator area and that 39% (14 of 35) were in the external iliac group of nodes is of particular interest. This group observed a 16% (13 of 82) incidence of contralateral lymph node metastasis only in patients with primary tumors clinically confined to one lobe of the prostate. These observations indicate that a lymph node dissection confined to the obturator-hypogastric region may possibly miss nodal metastases in 15% to 40% of the patients evaluated. Although an extensive systematic study of the relationship of pelvic and abdominal node metastasis is not available, Ray and colleagues (815) noted all 11 patients with extrapelvic node metastasis in their series had concurrent pelvic lymph node involvement.

Recently, Bader and associates (26) performed an extensive PLND in 333 patients with prostate cancer before undertaking radical prostatectomy. Their “extensive” dissection

was performed along the external iliac vein, the obturator nerve, and internal iliac artery. Of this cohort, 77 of 333 (23%) had evidence of lymph node positive disease. Of interest, the median number of nodes removed was 20 (range of 6 of 41) and the median number of positive nodes was 2 (range of 1 of 19). Not surprisingly, the percentage of patients with positive lymph nodes increased with the extent of local disease: organ-confined (10%), capsular infiltration (21%), seminal vesicle infiltration (42%), and gross extraprostatic disease (43%). Of potential importance, internal iliac lymph nodes were positive in 45 of 77 (59%) patients. Of 77 patients, 30 demonstrated additional positive lymph nodes along the external iliac vein and/or obturator nerve. Internal iliac lymph node involvement alone was noted in 15 of 77 (19%). The authors emphasized the potential importance of internal iliac lymph node dissection in that 1 of 5 patients would have been understaged if the dissection template had not included this region. Burkhard and associates (110) analyzed this same cohort to determine which clinical subset of patients actually requires lymph node dissection. They observed that 15 of 75 (20%) patients with lymph node metastases had a PSA less than 10 ng/mL and 36 of 75 (48%) had a preoperative PSA level of less than 20 ng/mL. They observed that 7% of the "low-risk" group harbored micrometastatic disease to the regional lymph nodes. These investigators speculate that the extensive lymph node dissection performed in this study accounts for the higher percentage of patients with positive lymph nodes than would be anticipated based on other recent reports. Whether or not extensive lymph node dissection has a favorable impact on regional tumor control and patient survival must await long-term follow-up.

Intraoperative assessment of the status of the pelvic lymph nodes is particularly important when pelvic lymphadenectomy and radical prostatectomy are carried out as a single operative procedure. Evaluation of node status on the basis of size, configuration, and consistency has not been studied systematically. In one series (151), 88% of tumor-bearing nodes recognized on frozen section were abnormal to inspection. However, the incidence of false-positive gross assessment was not cited. When node metastases are present in patients with clinically localized CaP, the gross assessment of these nodes often does not identify them (false negative). Epstein and co-workers (276) reported that 40 of 310 node dissections for clinical stage A and B carcinoma of the prostate disclosed metastatic disease; the nodes were grossly "unremarkable" in 33 of these cases.

The accuracy and extent of regional lymph node dissection in malignant melanoma and breast cancer has been dramatically influenced by sentinel lymph node mapping. Recent reports emphasized intratumoral or peritumoral injection of a radiolabeled colloid and subsequent identification of sentinel lymph nodes with a handheld γ-probe. In many instances, a similarly injected vital blue dye facilitates visual identification of the pertinent lymph node–bearing areas. Wawroschek and associates (1080) modified this approach before PLND in 80 prostate cancer patients. Ultrasound-guided intraprostatic injection of technetium-99m colloid before pelvic staging lymph node dissection was followed by dynamic lymphoscintigraphy with both early and late uptake imaging. Positive lymph nodes were identified in 23 of 80 patients (29%). Sentinel lymph nodes could be identified intraoperatively with a γ-probe in 20 of 22 patients with micrometastatic disease. Nineteen of twenty-two of these patients exhibited evidence of micrometastatic disease following tissue processing. Of interest, only the sentinel lymph node was involved in 14 of 22 patients. On average, one sentinel lymph node was identified per patient. The authors speculate that further modifications of this approach may enhance the sensitivity of lymph node dissection, shorten operative time, and reduce dissection-associated morbidity.

The accuracy of frozen section analysis for nodal metastases depends on node selection and sectioning procedures as well as on the accuracy of the histologic interpretation. A positive finding on frozen section is almost always confirmed on permanent section (151,276). On the other hand, false-negative evaluations of approximately 3.5% to 16% can be expected (151,276,537,630). Although the surgeon's attitude about the possible therapeutic role of lymphadenectomy may modify his or her determination to pursue intraoperative recognition of nodal metastases, the fact that an appreciable percentage of micrometastases present in grossly normal nodes (67%) (276) can be identified by frozen section studies indicates that these efforts are informative and reasonable.

Lymphadenectomy carried out as a staging or therapeutic procedure in patients with carcinoma of the prostate is associated with definite morbidity but very low risk of death. Early experience (25) reported wound complications were a cause of this morbidity in more than 20% of patients. Risk of wound infection seemed to be decreased by wound irrigation but not by drainage. Postoperative anticoagulation therapy probably reduces the risk of pulmonary embolism (583), but increases the risk of lymphocele formation (141). The incidence of wound (22% versus 30%) and other complications (12% versus 52%) increased when pelvic lymphadenectomy was combined with another procedure, such as radical prostatectomy. Currently, isolated staging pelvic lymphadenectomy is performed infrequently, and often by an endoscopic approach, making comparative assessment difficult.

The extent of the lymph node dissection, the presence of metastatic disease, and the postlymphadenectomy treatment regimen seem to influence the incidence and severity of postoperative complications. The reported incidence of chronic lymphedema of the legs and genital region varies from 0% to 18%. Low rates are apparently associated with a lymph node dissection limited to the hypogastric-obturator

nodes (98) and with avoiding postoperative radiation therapy. An extended node dissection followed by radiation therapy or combined with additional surgical procedures increases the risk of postoperative complications (320,583). Combining a transperitoneal, pelvic, and periaortic node dissection with definitive radiation therapy was followed by development of radiation enteritis in 12 of 13 patients and subsequent small-bowel obstruction in 8 (320).

These observations have been used to guide the surgical procedures used to assess the presence of nodal metastases. The routine evaluation of the abdominal nodes is not advocated at this time. The extent of the pelvic node dissection varies depending on the perceived risk–reward relationship and the surgeon's and patient's priorities. One group, to which we belong, advocates removal of nodes from the level of the common iliac vessels to the circumflex vein using the genitofemoral nerve as the lateral margin, encompassing the nodes surrounding the obturator nerve and vessels, and overlying the hypogastric artery. A few urologists also add a dissection of the presacral nodes. A second group limits the dissection to the medial aspect of the external iliac vein and to the bifurcation of the external iliac artery. With the advent of frequent PSA testing, a distinct “stage shift” has been observed (145), such that fewer patients present with clinically obvious stage D disease. This may well account for the significantly decreased frequency of positive pelvic nodes encountered at node dissection. At this time, most would agree that using tumor grade, clinical and histologic evidence of tumor mass, and serum PSA levels, a group of patients with presumed organ-confined prostate cancer can be identified in whom the limited risk of lymph node metastases makes consideration of omission of histologic assessment reasonable (355).

Surgical Therapy

Surgical procedures play an important role in the staging and treatment of CaP. Pelvic lymphadenectomy generally provides important information with regard to the stage of the tumor and may occasionally have a therapeutic role. Radical prostatectomies (retropubic, perineal, laparoscopic) are performed in an attempt to cure previously untreated localized CaP and select patients with T_3 disease, and along with cystoprostatectomy, they may play a salvage role in a small subset of patients harboring tumor following definitive radiotherapy. Finally, regimens designed to palliate the disease process and improve the quality of life for the patient with CaP often include scrotal orchiectomy as a form of androgen ablation and channel TURP to relieve bladder neck obstruction. The surgeon's role in all phases of CaP management is likely to increase in the future as our surgical armamentarium improves and our attitudes toward aging change. The surgical approaches to CaP with the exception of those used in conjunction with interstitial radiotherapy are discussed briefly in this section.

Preoperative Considerations

The patient with a diagnosis of CaP should be informed about the variable natural history, the advantages and disadvantages of the multiple treatment options, and the differing opinions regarding patient management so that he realizes that an absolute recommendation with regard to treatment is difficult to make. Potential complications to the proposed surgical procedure require discussion. An assessment of cardiac risk seems prudent in patients being considered for radical pelvic surgery, particularly those with a history of coronary artery disease, peripheral vascular disease, diabetes mellitus, and long-standing essential hypertension and in patients with strong family histories of these and other relevant comorbidities. For such patients, the performance of a stress echocardiogram should be considered. Alternatively, dipyramidale-thallium cardiac imaging or a dobutamine echocardiogram is appropriate for exercise-intolerant patients. Often, a consultation with a radiation/medical oncologist will help the patient understand the choices better.

Although the likelihood of rectal laceration during routine radical retropubic prostatectomy is low (approximately 1% to 2%), the potential morbidity following this injury can be reduced by a clear liquid diet and mechanical cleansing of the colon/rectum the day before surgery. With respect to the latter, reasonable options include the use of a Fleet enema, oral Fleet Phospho-Soda, or the use of tap water enemas. In addition, consideration should be given to using a 1% neomycin retention enema (200 to 300 mL, total volume) several hours before surgery. Unless preoperative urine cultures or the need for SBE prophylaxis mandate the use of a specific drug regimen, we generally use cefazolin (Ancef) in our perioperative antimicrobial prophylaxis regimen. If a salvage procedure is anticipated, a formal mechanical and antibiotic bowel preparation before surgery is prudent. We use the Go-Lytely (or Nu-Lytely) mechanical bowel preparation (4 L at 5 PM) with increasing frequency for this purpose. Neomycin (500 mg) and metronidazole (Flagyl, 500 mg) are administered at 1, 2, and 10 PM on the day before surgery (712). When this regimen is followed, the neomycin retention enema is probably unnecessary.

At this point, it is appropriate to revisit the concept of blood use strategy. It is generally recognized that volume replacement is best accomplished by the infusion of crystalloids (and other suitable plasma expanders). The goal of red blood cell (RBC) transfusion is to increase tissue oxygen delivery (13,357). In the absence of an acute critical illness or a history of significant cardiac disease, an appropriate threshold for transfusion should be a hemoglobin level of 7.0 to 8.0 g/dL. On the other hand, transfusion may be considered in patients with these mitigating conditions if

hemoglobin levels fall below 9 to 10 g/dL (13,357). The theoretic advisability of autologous blood transfusion before prostatic surgery was previously alluded to. The impetus for this approach is directly linked to the estimated risks of disease transmission following the transfusion of allogenic blood units (Table 33.18). Autologous blood can theoretically be donated up to 72 hours preoperatively (5 to 7 days is preferred) and may be stored for approximately 35 days. The freezing of autologous units significantly increases their shelf life, but mandates prompt transfusion after thawing. As important technical modifications have been made in the technique of radical prostatectomy, the outcome has become increasingly safe and successful (155,201). One of many important outcome improvements has been a significant diminution in mean interoperative blood loss (1,200 to 1,500 mL). As a consequence, the utility/necessity of autologous blood donation has been questioned. For example, O'Hara and associates (717) estimated that 64% of autologous units were discarded or inappropriately transfused during radical retropubic prostatectomy. Furthermore, studies conducted by Renner and associates (819) documented that up to half of the autologous blood that is collected is subsequently discarded. Current policies do not allow unused autologous blood to be used in patients other than the donor (357). Other potential disadvantages of autologous blood donation are summarized in Table 33.19 . We continue to discuss the relative advantages and disadvantages of autologous blood donation with our patients. Those electing to proceed with such donations are encouraged to bank 1 to 2 units. These patients are maintained on supplemental iron (FeSo4, 325 mg two to three times daily) during the process of donation and for an additional 6 to 8 weeks.

Risk Factor	Estimated Frequency		Deaths per Million Units (*n*)
	Per Million Units	Per Actual Unit	
Infection			
Viral			
Hepatitis A	1	1/1,000,000	0
Hepatitis B	7–32	1/30,000–1/250,000	0–0.14
Hepatitis C	4–36	1/30,000–1/50,000	0.5–17
HIV	0.4–5	1/200,000–1/2,000,000	0.5–5
Bacterial			
Red blood cells	2	1/500,000	0.1–0.25
Platelets	83	1/12,000	21
Acute hemolytic reactions	1–4	1/250,000–1/1,000,000	0.67
Delayed hemolytic reactions	1,000	1/1,000	0.4
Transfusion-related acute lung injury	200	1/5,000	0.2

Adapted from Gilbert WB, Smith JA. Blood use strategies in urologic surgery. *Urology* 2000;55:461, with permission.

TABLE 33.18. RISKS OF BLOOD TRANSFUSION

Advantages	Disadvantages
Prevents transfusion-transmitted disease	Does not eliminate the risk of bacterial contamination or volume overload
Avoids red blood cell alloimmunization	Does not eliminate the risk of administrative error, resulting in ABO incompatibility
Supplements the blood supply	Costs more than the allogenic blood donation
Provides compatible blood for patients with alloantibodies	Results in discarding untransfused blood
Prevents some adverse transfusion reactions	Causes perioperative anemia and increases the likelihood of transfusion

Adapted from Gilbert WB, Smith JA. Blood use strategies in urologic surgery. *Urology* 2000;55:461, with permission.

TABLE 33.19. ADVANTAGES AND DISADVANTAGES OF AUTOLOGOUS BLOOD DONATION

Transfusion-avoidance approaches that may have utility in properly selected patients include (a) intraoperative autotransfusion using cell saver suction and cell-washing devices, (b) acute normovolemic hemodilution, and (c) the use of recombinant human erythropoietin. The relative strengths and weaknesses of these respective approaches are nicely summarized in the review by Gilbert and Smith (357). Of these alternatives, the use of epoetin alfa (recombinant human erythropoietin) is perhaps the most appealing.

The rationale for administering erythropoietin preoperatively is to increase the rate of RBC production in the bone marrow with a resultant increase in red cell volume. Studies conducted by Chen and associates (163) and Rosenblum

and associates (841) validated the safety and efficacy of this approach in men before radical prostatectomy. For individuals with a baseline hematocrit of less than 45%, two doses of 600 IU/kg epoetin alfa, administered 14 days and 7 days preoperatively significantly increased RBC mass and decreased the need for allogeneic blood transfusion. When used in this manner, erythropoietin-induced complications—arterial hypertension, cerebral convulsions, influenza-like syndrome, and an increase in thromboembolic events—documented in patients with chronic renal failure who require long-term administration were not encountered. It appears epoetin has a legitimate role for use in patients with hemoglobin levels less than 13 g/dL, who are about to undergo surgical procedures that entail moderate to significant blood loss, and who are anxious and/or religiously opposed to allogeneic blood use.

The predisposition to deep vein thrombosis (DVT) associated with prostatic surgery was discussed in detail in the preceeding chapter. Indeed, a predisposition for venous thrombosis, migratory thrombophlebitis, arterial emboli, and nonbacterial endocarditis all have been reported in association with CaP (851). Adamson and associates (4) demonstrated that the prevalence of coagulopathy in patients with untreated prostate cancer was correlated with elevations in serum fibrinopeptide A and D-dimer in 40% and 24% of such patients, respectively. Fibrinopeptide A is formed by thrombin-mediated cleavage of fibrinogen. Because its half-life is only a few minutes, fibrinopeptide A is a very sensitive marker of coagulation activity and ongoing fibrin formation. D-dimer is produced as a result of cleavage of cross-linked fibrin by the fibrinolytic enzyme plasmin, and abnormal levels of D-dimer are associated with reactive fibrinolysis. Noncontroversial measures such as adequate hydration, avoidance of techniques or circumstances that increase venous stasis, and use of procedures that increase venous return (i.e., early ambulation and pneumatic compression boots) certainly warrant serious attention. Although mini-dose heparin (5,000 units administered subcutaneously every 12 hours) may also be beneficial when used prophylactically, the incidence of hematomas and wound infections seems to be increased. Catalona and colleagues (141) noted an increased incidence of lymphocele formation following mini-dose heparin therapy. Other investigators have confirmed these observations (942). Of interest, the administration of low-molecular-weight heparin (Lovenox 30 mg administered subcutaneously every 12 hours) into upper extremity sites may diminish the risk of pelvic lymphocele formation. Patients at high risk may require the initiation of an anticoagulation regimen perioperatively, but the urologic surgeon must be aware of the increased risks attendant to such an approach.

Pelvic Lymph Node Dissection

As stated previously, pelvic lymphadenectomy often constitutes the final staging procedure performed before attempting curative therapy for localized CaP. Before radical retropubic prostatectomy, it is most convenient to perform either a standard or modified lymph node dissection using a traditional umbilicus to pubis or a mini-laparotomy incision, popularized by Steiner and Marshall (976). Alternatively, a laparoscopic PLND can be performed as a first-stage procedure with the patient under a separate anesthetic. The latter approach is infrequently used at our institution given its logistic inconvenience and additional expense. A radical perineal prostatectomy may be performed without the benefit of the previous nodal staging or may follow either a laparoscopic or mini-laparotomy approach to the nodes under the same anesthetic. Occasionally, patients with clinical stage C disease based on DRE and/or TRUSP will undergo pelvic lymphadenectomy to determine the status of the regional nodes before finalizing a treatment plan.

The frequency of positive lymph nodes in patients undergoing radical prostatectomy has decreased from 25% to 30% to less than 5% within the past 15 years (9,17,263). Undoubtedly, this development is related to the PSA-induced stage-shift. Epstein and associates (275) documented that men with Gleason scores of less than 7 and PSA values of less than 10 mg/mL have a markedly low frequency of pelvic lymph node metastases; consequently, they may not require pelvic lymphadenectomy. More recently, Alagiri and associates (9) have expanded these limits to include PSA values from 10 to 20 mg/mL and tumors with a Gleason score of 7. PLND is recommended for patients with cT_{2b} tumors, PSA values greater than 10 mg/mL, and primary or secondary Gleason grade 4 pattern on biopsy. Despite these observations, we continue to perform a limited PLND (i.e., removal of the medial group of the extrailiac lymph node chain) in all patients scheduled to undergo radical prostatectomy. The approach generally adds approximately 15 to 30 minutes to the operative time. In our experience, it has been associated with a very low complication rate. Finally, we believe that the results of lymph node dissection provide useful prognostic information that may facilitate the identification of patients most likely to benefit from various forms of postoperative adjuvant therapy.

Surgical Technique

Most patients undergoing pelvic lymphadenectomy alone or in conjunction with radical prostatectomy receive general anesthesia. Peters and Walsh (763) documented that these procedures can be performed using spinal or continuous epidural anesthesia. Patients undergoing the latter techniques required less intraoperative and postoperative blood replacement when compared with patients under general anesthesia. However, the differences between the two groups did not approach statistical significance.

Following the induction of satisfactory anesthesia, it is appropriate to ascertain that TED hose, sequential compression stockings, and heel protectors are properly applied and that the pneumatic compression boots are functioning properly. Exposure within the male pelvis is enhanced by

gently flexing the table 10 to 15 degrees (Fig. 33.45). We do not routinely place the legs in spreader bars, but this has been suggested as a useful maneuver (143). The entire abdomen and genitalia are then prepared and draped in the standard fashion. If a cystoscopic examination had not been done previously, it is our practice to perform flexible cystourethroscopy at this point. This is done with the intention of excluding unsuspected mucosal pathology involving the lower urinary tract and to better ascertain the length of the prostatic urethra and determine the relationship of the prostatic base to the trigonal complex. A 20-Fr Foley catheter (with 30-mL balloon) is inserted and attached to gravity drainage after the sterile operative field has been established.

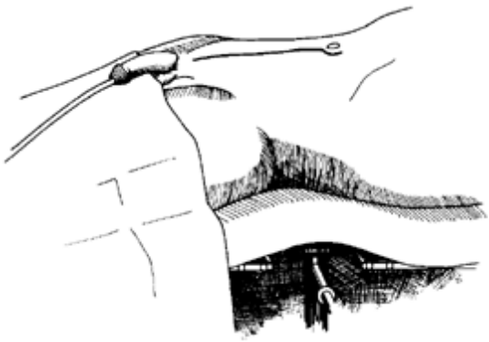

FIGURE 33.45. Surgical positioning suitable for pelvic lymphadenectomy and radical retropubic prostatectomy. Partial elevation of the kidney rest and the lumbar spine area together with 10 to 15 degrees of table flexion optimize exposure to the pelvic depths. The Foley catheter is generally inserted in sterile fashion after draping has been completed. A midline incision from the pubic symphysis arching laterally around the umbilicus is illustrated. (From Crawford ED, Kiker JD. Radical retropubic prostatectomy. *J Urol* 1983;129:1145, with permission.)

Optimal exposure is obtained through a midline incision that extends from the pubic symphysis to the lateral edge of the umbilicus (Fig. 33.45). The posterior sheath should be incised for a distance of 3 to 4 cm above the level of the semilunar line, and the lower aspect of the incision extended over the symphysis to facilitate retraction of the wound and dissection of the peritoneum off the undersurface of the rectus muscles. The latter maneuver exposes the inferior epigastric vessels, which should be preserved. In the obese patient it may be helpful to partially incise the insertion of the rectus muscle bellies. The prevesical fascia is incised and then bluntly separated from the transversalis fascia with a gentle sweeping motion with the fingers. Attention is then directed laterally to the attachment of the peritoneal envelope overlying the femoral canal and the spermatic cord. Blunt and sharp dissection usually permits mobilization of the peritoneum to the level of the bifurcation of the common iliac vessels. Should additional exposure be required, further mobility almost always can be obtained by dividing the transversalis fascia laterally and high on the pelvic wall, with or without concomitant ligation and division of the obliterated umbilical artery and vas deferens. At this point, the structures of the pelvic sidewall should be in clear view. Wound towels are secured to the fascia with 3-0 silk. Moist lap pads buttress the wound edges.

Adequate exposure is essential for this procedure. The spermatic cord is retracted laterally. We prefer the use of a Balfour wound retractor; Deaver or malleable retractor superiorly; a Richardson retractor laterally, and a Harrington, Glass, or malleable retractor medially. During the past few years, we have commonly used the table-mounted, self-retaining retractor unit (Omni retraction).

With the pelvic sidewall thus exposed, the ureter can be identified as it crosses the common iliac artery. When performing a standard pelvic lymphadenectomy, the surgical margins include the genitofemoral nerve laterally, the bifurcation of the common iliac artery superiorly, the circumflex iliac vein distally, and the obturator nerve inferiorly and posteriorly (Fig. 33.46). The fibroareolar investment of the structures contained within these anatomic boundaries can be removed en bloc or segmentally. As stated previously, our current preference is to perform a modified PLND, which entails the removal of the nodal tissue constituting the medial group of the external iliac lymph node chain. The superior border is the bifurcation of the common iliac artery. The medial border is the interface between the external iliac artery and vein. The distal boundary is the circumflex iliac vein/femoral canal. The obturator nerve and associated vessels constitute the posterior limit of the dissection. The template parameters associated with limited, standard, and extended lymph node dissections are highlighted in Fig. 33.46 . We perform a standard lymph node dissection in those patients whose first echelon of lymph nodes demonstrate metastatic involvement and in those patients thought to be at high “up-front” risk for metastatic disease. We are intrigued by recent reports (26) that suggest that even in the modern era, conventional lymph node dissection may underestimate the frequency of metastatic disease, particularly that which involves the internal iliac nodal issues. The optimal extent and role of lymphadenectomy may well require reexamination based on accumulating evidence.

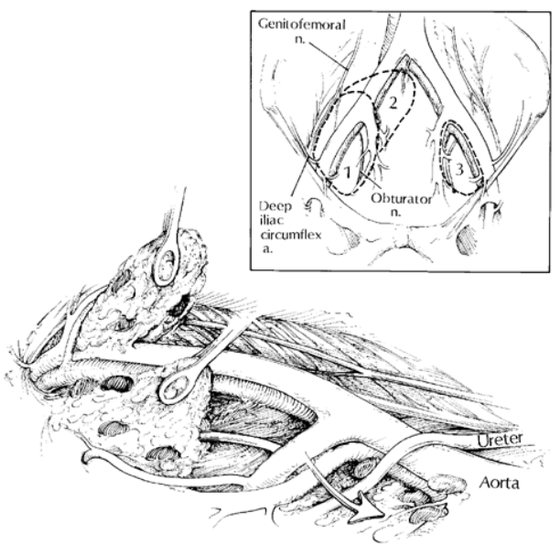

FIGURE 33.46. Pelvic lymph node dissection. The anatomic boundaries of standard *(1),* extended *(2),* and limited *(3)* lymphadenectomy are delineated in the inset panel. In the central illustration, note the removal of the external iliac lymph node packet **(top portion).** The genitofemoral nerve coursing along the surface of the iliopsoas muscle is clearly seen and represents the lateral boundary of the standard pelvic lymph node dissection. Dissection of this lymph node packet terminates at the level of the circumflex iliac vessels, which are seen arching laterally. The hypogastric-obturator lymph node packet **(lower portion)** often can be mobilized off the pelvic sidewall and obturator nerve with careful blunt dissection. Care must be taken to avoid inadvertent injury to the subadjacent accessory obturator vessels.

Mini-lap Lymphadenectomy

The mini-laparotomy staging pelvic lymphadenectomy (mini-lap) was popularized by Steiner and Marshall (976). In this technique, the patient is placed in the supine position and the operating room table is hyperextended to increase the space between the umbilicus and pubic symphysis. A 22-Fr Foley catheter (30-mL balloon) is passed into the bladder and attached to a gravity drainage after inflating the balloon to 50 mL. A 6-cm midline skin incision is made with the distal extent approximately 2 cm from the superior aspect of the pubic symphysis. The anterior rectus fascia between the rectus muscles and the transversalis fascia is incised to permit access to the retropubic space of Retzius.

The peritoneum is mobilized superiorly, and the space of Retzius is entered and developed. A Richardson retractor is used to engage the vas deferens and the peritoneum superior-laterally to enhance exposure. The incision itself can be moved from one side to the other to enhance exposure. Bladder retraction also is facilitated by the use of an Omni retractor. At this point, the node dissection is performed in standard fashion. Of note, the originators of the procedure did not place pelvic drains.

In their report of the first 16 patients on whom the mini-lap procedure was performed, the average intraoperative time was 32 minutes and the blood loss 15 to 20 mL. The mean number of pelvic lymph nodes removed was similar to that described for standard lymphadenectomy. No perioperative complications were reported. In particular, no patient had clinical evidence of a pelvic lymphocele despite the absence of drains. Most patients were discharged on postoperative day 2 or 3. Finally, the authors cite several advantages of the mini-lap over laparoscopic pelvic lymphadenectomy, with an emphasis placed on the shorter operating time of the mini-lap procedure (32 minutes), compared with an average of 2.5 hours for the laparoscopic PLND. They note that the 6-cm incision compares favorably with the four punctures/incisions made for laparoscopic procedures, some of which are as long as 11 mm. Moreover, the mini-lap procedure avoids peritoneotomy and the possible adverse sequela attendant to such a maneuver.

At our institution, the mini-lap is used in concert with radical perineal prostatectomy and as a “stand alone” procedure. Although there are proponents for simultaneous laparoscopic PLND and radical perineal prostatectomy (575), we have been quite pleased with the mini-lap procedure in this context.

Laparoscopic Pelvic Lymphadenectomy

Laparoscopic PLND was originally described by Schuessler and associates (884). Since then, several reports have emerged validating the utility and safety of the procedure (499,555,849). In most instances, the technique used is relatively similar from series to series and is summarized in the following paragraph.

The same preoperative preparation described for patients anticipating radical prostatectomy are initiated for those undergoing laparoscopic PLND. The patient is placed in the supine position. Following the induction of general endotracheal anesthesia, a nasogastric tube is placed and a Foley catheter inserted. The pelvis is gently hyperextended.

Carefully positioned adherent 2-inch-wide straps are placed across the thighs and upper chest to support the patient on the operating table. The arms are adducted to the sides. A pneumoperitoneum is established using CO_2 insufflation following the careful insertion of the Veress needle (Fig. 33.47) or a Hasson cannula through the superior crease of the umbilicus. During this phase of the procedure, the patient is placed in a 15-degree head-down position, which is maintained during the passage of the primary and secondary trocars. With respect to the latter, both a "diamond" and a "fan" configuration can be used. The former involves a creation of four ports: (a) umbilicus—11-mm trocar, (b) the midline of the abdomen midway between the umbilicus and pubic symphysis—11-mm trocar, and (c) two 5-mm trocars, one on either side of the abdomen midway between the umbilicus and the anterior superior iliac spine. The fan array (Fig. 33.48) may be useful in obese patients and consists of five ports: (a) umbilicus-11 mm, (b) one 5-mm port on each side at the level of the anterior superior iliac spine, lateral to the inferior epigastric vessels, and (c) one port on each side midway between the anterior superior iliac spine and the umbilicus. For the latter ports, an 11-mm trocar is used for the left port and a 5-mm (or 11 mm) trocar for the right. As was the case with establishment of the pneumoperitoneum, trocar placement must be done with great caution and under direct vision. The surgeon stands on the side of the table opposite the site of the PLND node dissection.

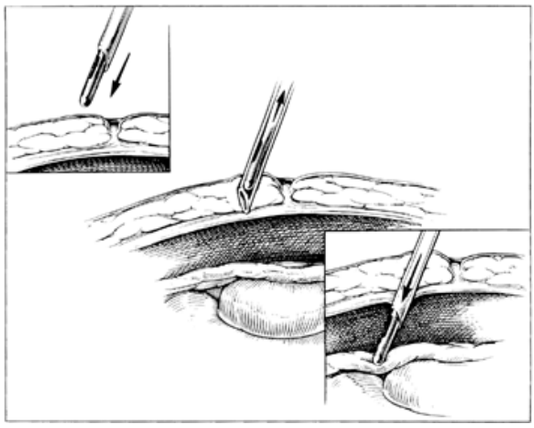

FIGURE 33.47. Insertion of the Veress needle. The needle consists of an inner, blunt, spring-loaded core that retracts on resistance, which exposes the sharp outer sheath. The insertion at the base of the umbilicus is facilitated by tenting the abdominal wall upward. Proper positioning should be ascertained by performing the standard aspiration, saline injection, and saline "drop" tests. (From Loughlin KR, Kavoussi LR. Laparoscopic lymphadenectomy in the staging of prostate cancer. *Contemp Urol* 1992;May:69, with permission.)

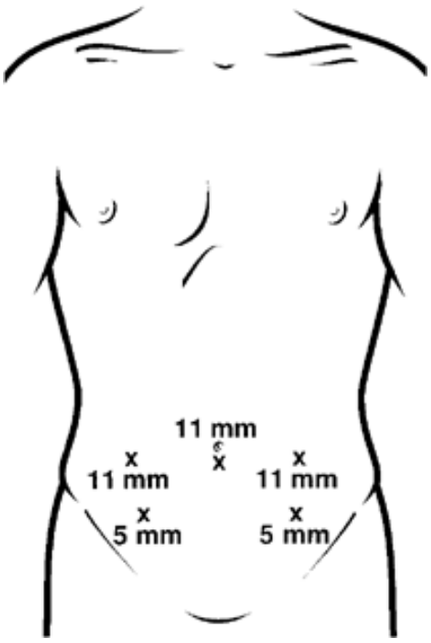

FIGURE 33.48. "Fan" trocar configuration for laparoscopic pelvic lymph node dissection. (From Parra RO, Andrus C, Boullier J, et al. Staging laparoscopic pelvic lymph node dissection: comparison of results with open pelvic lymphadenectomy. *J Urol* 1992;147[3 Pt 2]:875, with permission.)

Winfield and Schuessler (1096) have nicely summarized the steps involved in the limited pelvic lymphadenectomy. In brief, the peritoneum should be incised lateral to the medial umbilical ligament (Fig. 33.49). An inverted V incision may enhance exposure (Fig. 33.50). Next, the vas deferens is identified and incised. The external iliac vein should be identified and dissected from the bifurcation of the common iliac to the pubic bone, developing the lateral border of the nodal packet. The medial border of the packet is developed by dissecting tissue lateral to the medial umbilical ligament until the pubic bone is identified. The caudal border of the nodal packet is developed by joining the medial and lateral inferior corners of dissection by connecting them over the pubic bone. To develop a posterior surface of the nodal packet, the obturator nerve must be identified and dissected from the level of the pubic bone at the point where it disappears beneath the internal iliac vein (Fig. 33.51). The cephalic extent of the nodal packet is defined and freed from the V-shaped area lying between the external and common iliac vein and the obliterated umbilical artery. At this point, the nodal packet can be delivered through the largest cannula and submitted for frozen section analysis. During the course of the node dissection, liberal use is made of carefully activated cautery and Endoclips. After completion of the contralateral side, the trocars are removed in sequence under vision to ensure no significant bleeding occurs at the insertion sites. Following evacuation of the pneumoperitoneum (including the scrotal component), the 11-mm (or larger) trocar sites are closed with

fascial and subcuticular sutures and the 5-mm port sites usually are closed with adhesive skin strips.

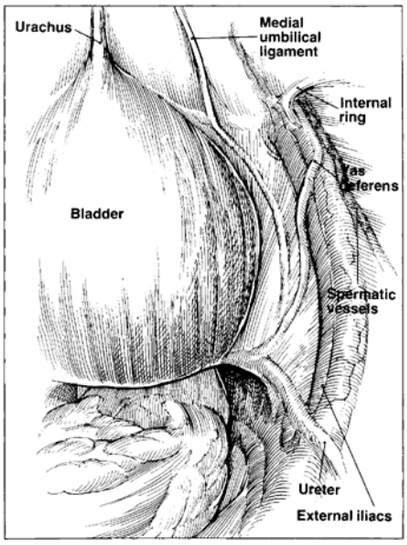

FIGURE 33.49. Standard anatomic landmarks for laparoscopic pelvic node dissection. The peritoneal incision will be placed lateral to the medial umbilical ligament. (Loughlin KR, Kavoussi LR. Laparoscopic lymphadenectomy in the staging of prostate cancer. *Contemp Urol* 1992;May:69, with permission.)

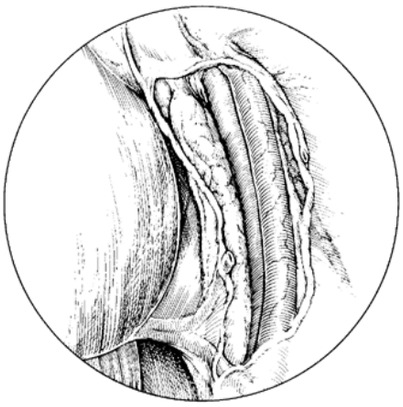

FIGURE 33.50. The laparoscopic dissection has now defined the lymph node packet (medial group of the external iliac lymph node chain), which remains attached distally to the pubic bone. (From Loughlin KR, Kavoussi LR. Laparoscopic lymphadenectomy in the staging of prostate cancer. *Contemp Urol* 1992;May:69, with permission.)

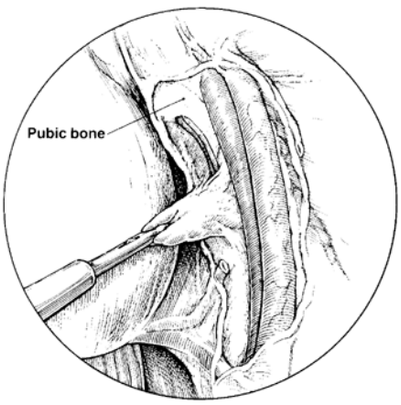

FIGURE 33.51. Following detachment of the lymph node packet from the pubic bone, the obturator nerve and vessels become readily apparent. (From Loughlin KR, Kavoussi LR. Laparoscopic lymphadenectomy in the staging of prostate cancer. *Contemp Urol* 1992;May:69, with permission.)

Das and Tashima (212) described an extraperitoneal laparoscopic staging PLND. In this technique a 2-cm incision is made in the midline approximately 2 cm below the umbilicus. Following incision of the subcutaneous tissue and linea alba, the underlying extraperitoneal space is developed by digital dissection inferiorly/laterally behind the rectus abdominous and the subsequent use of a distention balloon. A 10-mm trocar is then passed through the incision with high-flow CO_2 insufflation. Under laparoscopic vision, another 10-mm trocar is passed 3 cm above the symphysis pubis. Finally two 5-mm working ports are introduced lateral to the rectus abdominous muscle at a level midway between the umbilicus and the pubic symphysis. At this point, the dissection proceeds in a manner quite analogous to that of a standard extraperitoneal, open lymph node dissection. This approach avoids the potential complications associated with transperitoneal access and intraperitoneal dissection. Assessment of the ultimate utility of this modification requires clinical trials comparing it with transperitoneal laparoscopic PLND.

Complications of Pelvic Lymphadenectomy

The complications of pelvic lymphadenectomy are discussed briefly in the section on lymph node metastasis under Staging. If a lymphocele is suspected postoperatively (pain, mass, unilateral leg swelling), a pelvic ultrasound or a CT scan should be performed. A cystogram excludes urinary extravasation; a venous Doppler study can rule out lower extremity DVT. A sizable lymphocele causing symptoms (0.5% to 10% of cases) requires therapeutic intervention. CT or ultrasound-guided percutaneous drainage of the cavity with a pigtail catheter is a reasonable initial approach to this problem. When recognized promptly, prolonged decompression may allow the walls of the lymphocele to collapse and facilitate the sealing of the lymphatic vessels. If drainage persists, instillation of a sclerosing agent (e.g., tetracycline, Betadine) warrants consideration. A recurrent lymphocele is probably best treated with open or laparoscopic marsupialization into the peritoneal cavity (176,437,889). The potential complications of laparoscopy are listed in Table 33.20 and Table 33.21 . Other complications attendant to pelvic lymphadenectomy are uncommon. Transsection of the obturator nerve appears in less than 1% of patients. Complete transection results in an inability to abduct the ipsilateral thigh. Complete transsection should prompt an attempt at intraoperative repair. Generally, two to three 4-0 nylon sutures placed with the aid of 4× loop magnification are sufficient. Fortunately, the lower extremity dysfunction resulting from an unsuccessful repair does not have a significant impact on the quality of life of most patients. Bleeding from the obturator and iliac vessels is most always avoidable and, if encountered, is easily managed with a combination of patience and optimal exposure. Fortunately, ureteral injuries are highly unusual if standard surgical precepts are followed. Ligation, crush injury, and total transsection are probably best managed by ureteral reimplantation. A clean partial transsection may be managed with stenting, primary repair, and adequate drainage.

TABLE 33.20. POTENTIAL COMPLICATIONS OF LAPAROSCOPIC SURGERY

Veress needle and trocar insertion
Extraperitoneal insertion
Vascular injury
Abdominal wall vessels
Major retroperitoneal vessels
Mesenteric vessels
Visceral injury
Stomach
Small bowel
Large bowel
Liver
Spleen
Bladder
Pneumoperitoneum
Emphysema (subcutaneous, preperitoneal, omental)
Tension pneumoperitoneum
Pneumothorax
Pneumomediastinum
Gas embolism
Failure to maintain pneumoperitoneum
Cardiac arrhythmias
Hypercarbia
Hypotension
Surgical injury
Thermal injury
Dissection injury
Inability to complete procedure
Vascular injury
Bowel injury
Bladder/ureteral injury
Nerve injury
Lymphedema/lymphocele
Closure
Unrecognized bleeding
Unrecognized visceral injury
Abdominal wall injuries
Infection
Wound dehiscence
Omental/bowel herniation
Shoulder/diaphragmatic irritation due to retained CO_2

From Capelouto CC, Kavoussi LR. Complications of laparascopic surgery [Review]. *Urology* 1993;42:1.

TABLE 33.21. COMPLICATIONS OF LAPAROSCOPIC PELVIC LYMPH NODE DISSECTION (327 PATIENTS)

Complication	No. Intraoperative	No. Postoperative
Vascular injury		
Epigastric artery	4[a]	—
Medial umbilical ligament	2 (2)	—
Obturator vein	1 (1)	—
External iliac artery	1 (1)	—
Superficial abdominal wall vessel	1	—
Rectus hematoma	—	1
Pelvic vasculature	—	1
Totals	9 (4)	2
Viscus injury		
Ureter	1 (1)	1 (1)
Bowel	1 (1)	2 (2)
Bladder	2 (1)	1 (1)
Totals	4 (3)	4 (4)
Lymphedema/lymphocele	—	5
Infection/wound		
Infected pelvic hematoma	—	2
Superficial wound infection	—	2
Wound dehiscence	—	1 (1)
Totals	—	5 (1)
Gastrointestinal		
Prolonged ileus	—	5
Small bowel obstruction	—	2 (1)
Totals	—	7 (1)
Genitourinary		
Urinary retention	—	7
Prolonged scrotal swelling	—	3
Totals	—	10
Miscellaneous		
Hypercarbia	1	—
Prolonged sedation	—	1
Obturator nerve palsy	—	2
Lower-extremity deep vein thrombosis	—	5
Totals	1	8
Total complications	14 (7)	41 (6)

[a]Injuries requiring open intervention in parentheses.
From Capelouto CC, Kavoussi LR. Complications of laparascopic surgery [Review]. *Urology* 1993;42:1.

Radical Prostatectomy

Selection of patients for radical prostatectomy on the basis of current clinical evaluation presents a problem because of understaging in a significant percentage of patients. For example, early in the Johns Hopkins series, approximately 60% of the patients subjected to radical retropubic prostatectomy had extraprostatic disease on pathologic examination of the specimen removed (254). The survival data on patients with a small localized tumor mass confined to one lobe on clinical examination (stage T_1) (426,1060) support the observation that patients with tumor in this stage are unlikely to have extraprostatic extension. Restriction of the radical prostatectomy to those patients would deprive many others of the possible benefits of radical prostatectomy. As our ability to recognize the presence of extraprostatic extension improves, the possibility for a more selective use of radical prostatectomy without unnecessarily limiting consideration of the procedure probably will be realized. Some groups have used and are using radical prostatectomy in patients with known stage C and D_1 disease. The Mayo Clinic is gaining a considerable experience in these patients and has used orchiectomy as an adjunctive therapeutic measure in this group (1138,1139 and 1140). The therapeutic yield of these attempts to extend radical excision in patients with CaP has been unexpectedly encouraging in the past (1137).

These perceptions notwithstanding, several features define the ideal candidate for radical prostatectomy: (a) clinically localized CaP and select patients with stage cT_{3a} disease; (b) patients whose tumor volumes exceed 0.2 mL; (c) tumor Gleason score greater than or equal to 5; (d) serum PSA less than or equal to 10 ng/mL; (e) a life expectancy of greater than 10 years; (f) and the absence of other, serious comorbid medical conditions (155).

Technique of Radical Retropubic Prostatectomy

In addition to popularizing the retropubic approach to the prostate gland for the treatment of benign disease, Millin was one of the first to describe the technique of radical retropubic prostatectomy (663,664). His approach using division of the urethra as an initial step in the removal of the prostate was adopted by other groups (578,642). Campbell (115) described antegrade removal of the prostate and thought this approach facilitated the vesicourethral anastomosis and minimized blood loss by early ligation of the vascular pedicle. Other investigators (584) adopted and modified this technique.

Reiner and Walsh (818) emphasis of important surgical aspects of the anatomy of Santorini's plexus as it relates to the anterior surface of the prostate facilitated the routine safe ligation of the dorsal vein complex (Fig. 33.52). Despite the innovations noted above, a major source of morbidity of radical prostatectomy was the high incidence of sexual impotence following the procedure. In 1982, Walsh and Donker (1058) presented anatomic observations regarding the location of the branches of the pelvic plexus that innervate the corpora cavernosa and their relationship with the prostatovesicular artery and lateral pelvic fascia. Using these observations, Walsh and associates (1061) modified the technique of radical retropubic prostatectomy to preserve the critical branches of the pelvic plexus and preserve potency in more than 80% of their patients (Fig. 33.53 and Fig. 33.54). Subsequent observations confirmed the efficacy of

the nerve-sparing approach in preserving potency while maintaining adequate margins of resection (140,254). The approach to the nerve-sparing radical retropubic prostatectomy is briefly summarized in the following paragraphs.

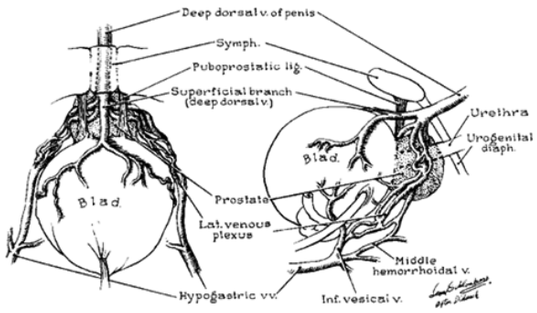

FIGURE 33.52. The anatomy of Santorini's plexus. The structures depicted are devoid of their normal investment of lateral pelvic fascia and fibroareolar tissue. **A:** The anterior view demonstrates the three major branches of the deep dorsal vein of the penis, namely, the superficial branch and the right and left lateral venous plexuses. **B:** The lateral view demonstrates that cutting of the puboprostatic ligaments flush with the undersurface of the pubic symphysis can be performed with impunity because the major venous tributaries are inferior to this avascular plane. (From Reiner WG, Walsh PC. An anatomical approach to the surgical management of the dorsal vein and Santorini's plexus during radical retropubic surgery. *J Urol* 1979;121:198, with permission.)

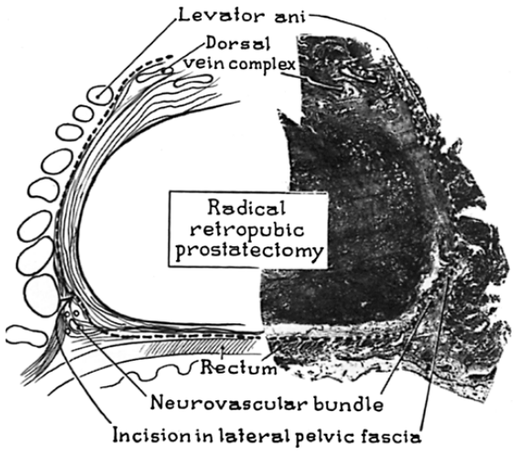

FIGURE 33.53. Cross section of the prostate gland illustrating the surgical approach to the lateral pelvic fascia required to preserve the integrity of the adjacent neurovascular bundle. (From Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. *Prostate* 1983;4:473, with permission.)

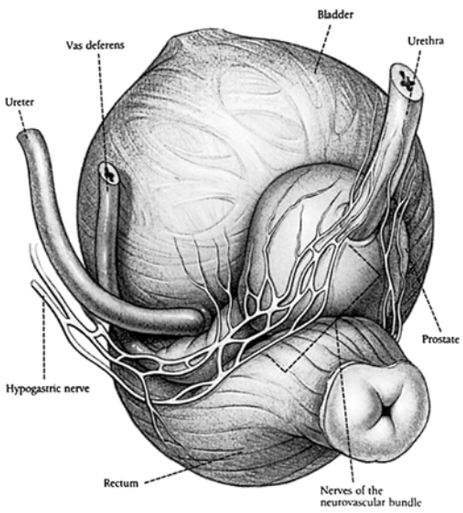

FIGURE 33.54. Oblique perineal view demonstrating the posterolateral distribution of the pelvic splanchnic nerves. (From Resnick MI. Radical perineal prostatectomy. In: *Urologic surgery.* Bristol-Myers, Learning Technology, 1988, with permission.)

The preparatory steps were discussed previously as a preface to the description of pelvic lymphadenectomy. As stated, we flex the table 10 to 15 degrees to enhance pelvic exposure. We have not routinely used straddle bars for the legs or a small sacral sandbag. These techniques are, however, used by other surgeons with good results. It is helpful for the operating surgeon and/or the first assistant to wear a fiberoptic headlight to facilitate visualization of the pelvic depths. We proceed with the nonirreversible steps of prostate mobilization while awaiting the frozen section results. We generally, but not invariably, terminate the operation in the presence of gross lymph node involvement. In the absence of flagrant seminal vesicle extension or capsular penetration, the presence of one or two microscopically involved lymph nodes would not deter us from proceeding with a radical prostatectomy in a younger man.

Before proceeding with radical prostatectomy, it has been recommended that the temporary placement of occlusive vascular clamps on the hypogastric artery laterally significantly decreases intraoperative blood loss (763). We do not use this maneuver, although its selective use may have value. We use a malleable retractor on the inflated Foley balloon (1067), our Omni retractor blade, or the left hand to facilitate bladder retraction and maximize exposure of the anterior surface of the prostate. In each case, care must be taken to avoid tearing superficial veins. In fact, elective ligation of the superficial branch of the deep dorsal vein with 3-0 Vicryl can be advantageous at this point.

Endopelvic Fascia

Once adequate visualization of the prostate has been accomplished, the endopelvic fascia lateral to the prostate should be completely exposed and incised with the point of the scissors (or the no. 15 scalpel) near the point of its reflection along the sidewall of the pelvis. This lateral superficial approach avoids inadvertent injury to the components of the inferior vesical pedicle and adjacent nerves that course under this fascial layer. Once fasciotomy has been established in a focal area, the fibers of the fascia are easily elevated and slit in a lateral curving arc that extends from the bladder neck to the base of the puboprostatic ligaments. Dense adherence of the fascia to the levators is unusual. Remnant levator fibers that loosely adhere to the lateral perimeter of the prostate generally can be swept back into a normal anatomic configuration by gentle sharp and blunt dissection. The latter can be facilitated by the proper use of a sponge stick or Kittner dissector. Once accomplished, this exposes the fused parietal (levator) fascia with prominent periprostatic veins, which reside beneath this layer and the underlying visceral (prostate) fascia (Fig. 33.55) (201).

If bleeding is encountered from communicating pudendal arterial/venous branches (which traverse through the levator musculature), control can be obtained through the application of figure-of-eight suture ligatures of 3-0 Vicryl. Rarely, additional compression is required; this can be facilitated by using small pledgets of Vicryl mesh.

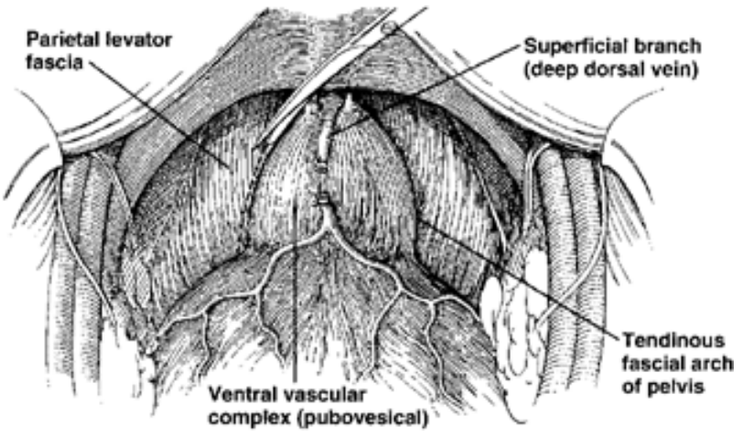

FIGURE 33.55. The superficial branch of the deep dorsal vein has been identified and ligated. The parietal layer of the levator fascia (endopelvic fascia) is incised to expose the lateral prostate. A combination of sharp and blunt dissection permits opening this important anatomic window from the base of puboprostatic ligaments to the bladder neck. Remnant levator fibers can be swept off the lateral perimeter of the prostate with careful blunt dissection. Ultimately, the fused parietal (levator) fascia, the associated periprostatic venous plexus, and the underlying visceral (prostate) fascia will be identified. (From Cummings KB. Refining the anatomic approach to nerve-sparing radical retropubic prostatectomy. *Contemp Urol* 2000;July:46, with permission.)

Puboprostatic Ligaments

On the basis of anatomic dissections performed on hemipelves of normal fresh male cadavers, Steiner (980) determined that the puboprostatic ligaments are not a discrete “band” of fascia that simply affixes the prostate gland to the synchondrosis of the pubic symphysis, but in fact constitute a pyramid-shaped structure that serves as a component of the urethral suspensory mechanism (Fig. 33.56). The latter attaches the membranous urethra to the pubic bone. This urethral suspensory mechanism is composed of three structures: (a) the suspensory ligament of the penis and fascial reflection of the perineal membrane, which are designated the anterior pubourethral ligament; (b) the arcuate and transverse ligaments, which as a group are designated the intermediate pubourethral ligament; and (c) the puboprostatic ligament or the posterior pubourethral ligament. Steiner has described the important structural and functional components of the external striated urethral sphincteric complex, which includes (a) the entire circumferential

musculature of the rhabdosphincter, (b) the anterolateral (pubourethral) ligaments and posterior (median fibrous raphe) fascial investments, (c) innervation of the rhabdosphincter by the intrapelvic branch of the pudendal nerve (somatic), and (d) the innervation of the mucosal and smooth muscle components by way of the urethral branch of the inferior hypogastric plexus (autonomic) (978). Preservation of this sphincteric complex has promoted “no touch” or “avoidance” surgical principles, which subsequently are discussed (430).

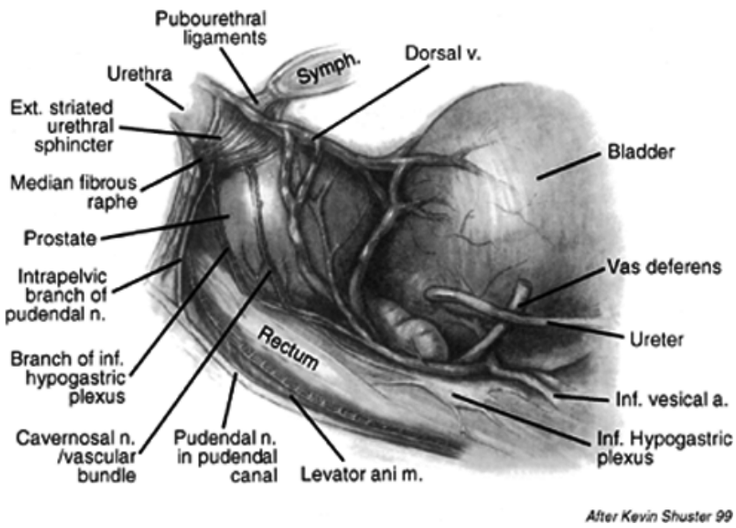

FIGURE 33.56. The paired pubourethral ligaments consist of anterior, intermediate, and posterior divisions. These elements form a median suspensory structure for the proximal pendulous urethra and corpora spongiosum (distally) and the external striated urethral complex proximally under the pubic arch. (From Steiner MS. Anatomic basis for the continence-preserving radical retropubic prostatectomy. *Semin Urol Oncol* 2000;18:9, with permission.)

While maintaining optimal exposure to the anterior prostatic surface, blunt dissection can be used to gently tease the tissue off the periosteum of the pubic arch and to expose the puboprostatic ligaments. Care must be taken to avoid inadvertent blunt injury to the superficial branch of the deep dorsal vein that lies in the midline between the two puboprostatic ligaments and the other components of Santorini's plexus, which diverge laterally and beneath the ligaments. At times, a prominent posterior protuberance of the pubic symphysis can interfere both visually and physically with this and other aspects of the apical dissection. Visualization can be optimized by various techniques, including wedge pubectomy (547); partial resection of the symphysis using an osteotome/bone rongeur (620); and the use of electrocautery if the protuberance is primarily cartilaginous (505). Once they are clearly visualized, the puboprostatic ligaments should be incised flush to their attachment to the pubic symphysis. The curve of the Richter scissors should be pointed ventrally toward the periosteum. The surgeon will notice a very definite “give” when the ligamentous attachments have been finally severed. As long as the tips of the scissors hug the bony arch, very little bleeding is encountered with this maneuver. In keeping with the acknowledged contribution of the puboprostatic ligaments to obtaining normal anterior support of the urethra, it is now our practice to preserve as much of this ligamentous support as possible. Indeed, techniques that permit the routine preservation of this ligament support have been described (469). The total release of this ligamentous support is unnecessary and injudicious as long as adequate exposure of the apical prostate/urethral interface can be obtained.

Dorsal Vein Complex

The previously placed 20-Fr Foley catheter now serves as a guide to the prostatourethral junction. The surgeon should identify the urethra using the catheter as a guide. This is done in anticipation of ligating the dorsal vein complex. The latter is enveloped within a surprisingly thick (2 cm) layer of fibroareolar tissue and lateral pelvic fascia. In our experience it is helpful to maintain cephalad traction on the bladder neck using the left hand with a split-finger approach. The index finger of the right hand is used to identify the depression that localizes the avascular plane that separates the anterior surface of the urethra from the dense wad of tissue through which the dorsal vein complex courses (Fig. 33.57). The tip of a long right-angle clamp (preferably the specifically curved McDougal clamp) is placed at this point and worked through to the opposite side. When the clamp is optimally placed, a subtle “pop” is perceived as it penetrates the first layer of lateral prostatic fascia (518). It should be emphasized that the resistance encountered should be very modest. Exaggerated resistance to the passage

of the clamp will be noted if an improper plane has been traversed and the clamp is in fact passing through prostatic or urethral tissue. Too distal an approach places the rhabdosphincter in jeopardy, given the fact that it measures only 1.5 to 2 cm in total length (518). Then a gentle spreading motion is used to expand the rather narrow and rigid tunnel thus established. Number 1 Vicryl is our preference to ligate the dorsal vein complex and its investing fascia. A simple knot is generally adequate, but a double looping technique or a surgeon's knot may provide some additional security. In general, two ties are placed on the distal aspect. At this point, it is helpful to use a Babcock or Allis clamp to engage the midline tissues overlying the prostate–bladder neck interface. This defines the major area of anticipated back-bleeding, which will occur following transection of the complex. Once grasped, these veins can be controlled with figure-of-eight suture ligatures using 2-0 chromic catgut or Vicryl, either before or after passage of the distal ties. It is important to emphasize that this maneuver can induce the anterior displacement and possible subsequent injury of the neurovascular bundles. To obviate this and other potential technical problems that might endanger the neurovascular bundles, other technical modifications have been proposed. The latter consist of incision of the lateral pelvic fascia, release of the neurovascular bundles, and development of the plane between the prostate/rectum from the lateral aspect of the prostate before proceeding with other aspects of the apical dissection (511) (Fig. 33.58).

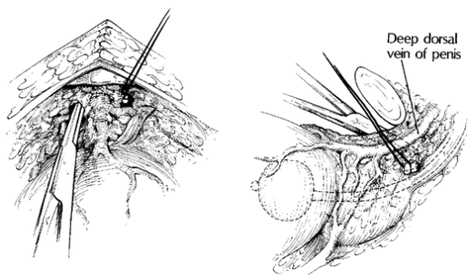

FIGURE 33.57. Control of the dorsal vein complex requires ligation (1 Vicryl) of the vascular component together with a 2- to 2.5-cm mass of investing fibroareolar tissue. The latter is accomplished by establishing the proper avascular plane immediately anterior to the urethral surface. A McDougal or a long right-angle clamp are best suited for this purpose. **Left:** Vertical midline view. **Right:** Lateral view.

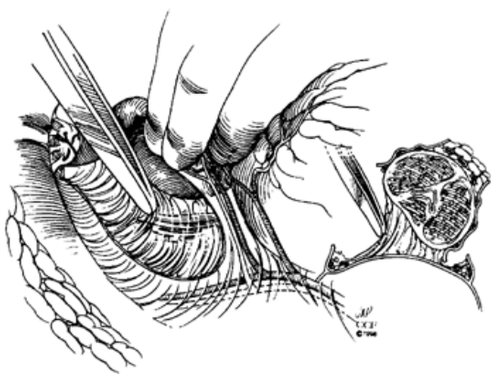

FIGURE 33.58. In this diagram, the lateral pelvic fascia has already been incised (longitudinally) medial to the neurovascular bundles, exposing the groove between the rectum and prostate. Following the release of both bundles with sharp and blunt dissection, the prostate can be rotated gently and the plane between the prostate and rectum further developed. (From Klein EA. Initial release of the lateral pelvic fascia. *Semin Urol Oncol* 2000;18:38, with permission.)

A suture ligature placed proximally anterior to the prostate reduces back-bleeding. Several technical modifications have been described to control the dorsal vein complex. A large needle can be used to undermine this structure and facilitate en masse ligation. In addition, Yu and associates (1122) described their approach, which involves ligation of the puboprostatic ligaments and the dorsal vein complex together as a single unit and then dividing the puboprostatic ligaments and the venous complex cephalad (proximal) to the ligatures. This technical modification was prompted by their concern that adjacent superficial dorsal veins were more likely to rupture as the prostate and bladder dropped posteriorly following transection of the admittedly avascular puboprostatic ligaments. In our experience, this phase of the procedure is infrequently problematic, and for that reason we have not felt the need to adopt such modifications. Admittedly, alternative approaches might be useful in select patients.

Once satisfactory ligation has been achieved, the right-angle clamp is replaced to guide the superior transection of the tissue cephalad to the ligatures (Fig. 33.59 and Fig. 33.60). A no. 15 scalpel or Richter scissors can be used for this purpose. Significant back-bleeding is unusual but can be controlled by temporary tamponade or the use of a few running suture ligatures of 2-0 Vicryl. If the ligatures on the dorsal vein complex are inadequate, significant bleeding may occur. Definite hemostasis usually can be achieved with figure-of-eight sutures. Until the latter can be accomplished, gentle, direct compression with a stick sponge usually suffices. We avoid metal clips in this site. Fiberoptic lighting and a curved GU needle prove useful in this endeavor.

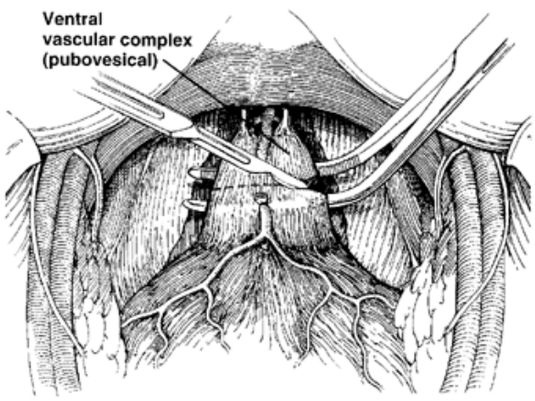

FIGURE 33.59. The dorsal vein (ventral vascular) complex can be undermined carefully with a right-angled clamp and transected using a no. 15 scalpel. With this maneuver, care must be taken to avoid injury to the underlying striated urethral sphincter and its components. (From Cummings KB. Refining the anatomic approach to nerve-sparing radical retropubic prostatectomy. *Contemp Urol* 2000;July:46, with permission.)

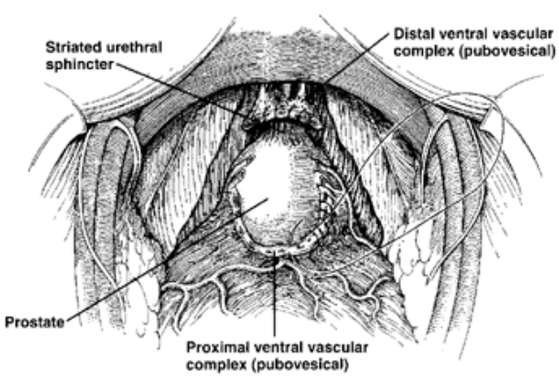

FIGURE 33.60. The ligated stump of distal ventral vascular complex can also be controlled with a running 2-0 Vicryl suture. Alternatively, several carefully placed figure-of-eight sutures of the same material can be used. Back-bleeding vessels from the proximal ventral vascular complex that were not adequately controlled with the initially placed midline suture ligature can be easily controlled with several running 2-0 chromic catgut (or Vicryl) sutures. (From Cummings KB. Refining the anatomic approach to nerve-sparing radical retropubic prostatectomy. *Contemp Urol* 2000;July:46, with permission.)

Urethral Transection

The surgeon should maintain cephalad traction on the apical portion of the prostate using the second and third fingers of the left hand. The membranous urethra is usually

exposed once the dorsal vein complex has been divided. The scissors should then be insinuated alongside the urethra and a gentle spreading motion initiated to separate the urethral wall from the “pillars of the prostate.” The latter represent the ischioprostatic ligaments, which are located lateral to the striated urethral sphincter at the 2 o-clock and 10 o-clock positions. Once accomplished, a right-angle clamp can be placed medial to the tissue along and behind the urethra, freeing it. The clamp can be left in place to facilitate transection or preferably can be substituted with a small Silastic sling. If blunt isolation is difficult, the urethra can simply be carefully divided under direct vision.

The anterior wall of the urethra is incised at its junction with the apex of the prostate. The curve of the scissors (or the no. 15 scalpel) should be directed in an arc toward the prostate, hugging but not resecting the apical tissue (Fig. 33.61). Once the anterior aspect of the urethra has been transected, a sufficient length of the Foley catheter is delivered with a right-angle clamp to permit its use as a holder throughout the remainder of the procedure. After clamping the catheter to maintain the distention of the balloon, the catheter is divided and the distal aspect removed. At this point, we may insert a lubricated 18-Fr red rubber catheter in the distal urethra to help define the urethral lumen and the nontransected (intact) posterior wall with precision. The posterior wall of the urethra is then transected under direct vision. We may place stay sutures in the urethra before or after dividing the urethra, but we do so selectively and with caution depending on the anatomic situation. We regard the internal smooth muscle urethral cylinder as a fragile important component of the urinary control mechanism and consequently attempt to minimize trauma to other distal urethral segments. The latter selectively involves incorporation

of the lateral and anterior components of the striated urethral sphincter with running or interrupted sutures before urethral transection. Lateral tag sutures are then placed to facilitate subsequent transection of the posterior elements of the striated urethral sphincter and to ensure their incorporation with the anastomotic sutures.

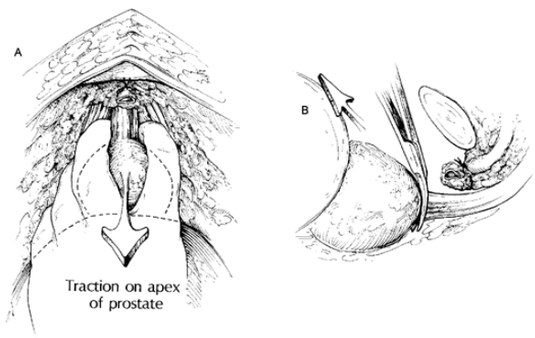

FIGURE 33.61. Exposure of the membranous urethra is facilitated by cephalad traction applied to the prostatic apex **(A).** The endopelvic fascia and puboprostatic ligaments have been incised and the dorsal vein complex with its investment of fibroareolar and fatty tissue has been severed. The neurovascular bundles are represented by the laterally positioned bands of tissue coursing parallel to the exposed urethra. **B:** The proper orientation of the curves of the Richter scissors before urethral transection is shown. Obviously, the junction of the prostatic apex and membranous urethra should first be established by incising the anterior urethral wall. Once this is accomplished, the catheter is mobilized and secured and the posterior urethral segment incised in sequential fashion.

An alternative approach avoiding the placement of a right-angle clamp or tape posterior to the urethra has recently been suggested to replace the risk of stretching or damaging the external striated sphincter as well as its somatic (pudendal) and autonomic (inferior hypogastric) nerve supply and its anterior/posterior attachments. The proposed technical modification involves incision of the anterior rhabdosphincter just distal to the prostatic apex, using scissors or a no. 15 scalpel blade. The anterior 180-degree arc of the urethral wall is then transected, exposing the underlying Foley catheter. Following this, the distal component of the 2 and 10 o-clock anterior anastomotic sutures should be placed using 2-0 Monocryl on UR6 needles. At this point, the right-angle clamp can be used to retract the intraluminal Foley catheter and expose the posterolateral urethra. Once identified, the posterior 180-degree arc of the membranous urethra is incised. The 5 o-clock and 7 o-clock anastomotic sutures are then placed. This approach eliminates manipulation/stretching of the posterior components of the sphincteric complex.

Rectourethralis

The next goal in the dissection is to expose, identify, and incise the rectourethralis without injury to the rectum or the cavernous nerves. A gentle cephalad tug should be maintained on the Foley catheter to facilitate the visualization and severance of this muscle, which is located directly in the midline (Fig. 33.62). Undermining this muscle with a right-angle clamp facilitates its transection and the identification of the intact Denonvilliers' fascia (Fig. 33.63). Once the white Denonvilliers' fascia is exposed, the rectum can usually be freed from the prostate and the seminal vesicles with gentle digital pressure applied to the undersurface of the prostate. If the rectum does not disengage easily, sharp layer-by-layer tissue dissection with the knife or scissors pointed at Denonvilliers' fascia is prudent. Tenting of the rectum is a problem that requires constant concern and attention. If exposure of Denonvilliers' fascia is difficult and uncertain by one approach, we try another. Lateral access to the plane separating the rectum and the fascia is at times much easier from a midlateral or basal lateral approach than a standard apical one. Once Denonvilliers' fascia is clearly identified, the risk of incising or disrupting the rectum or prostate is significantly reduced. The priorities with regard to nerve sparing and periprostatic excision of tissue need to be kept in mind as alternative dissection procedures are explored.

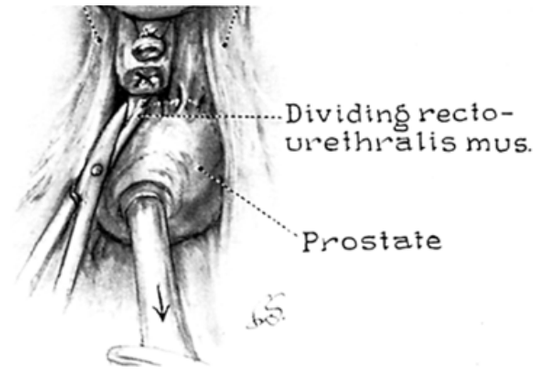

FIGURE 33.62. Division of the rectourethralis muscle. The proper transection of these fibers provides access to the desired midline plane between the anterior and posterior leaves of Denonvilliers' fascia. This can be facilitated by undermining the muscle fibers with a right-angle clamp before incision. (From Walsh PC. Radical retropubic prostatectomy. In: Walsh PC, Gittes RF, Perlmutter AD, et al, eds. *Campbell's urology,* 5th ed. Philadelphia: WB Saunders, 1986:2754, with permission.)

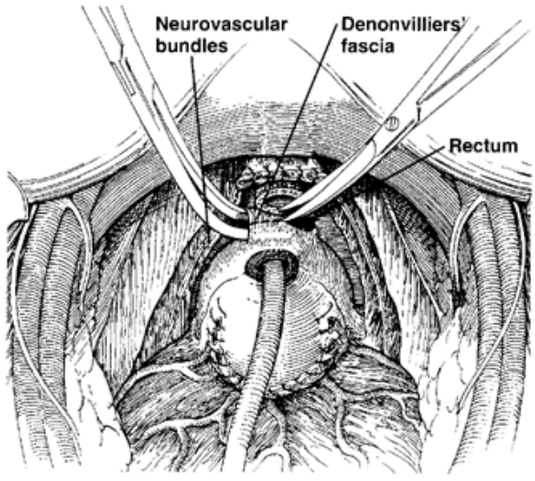

FIGURE 33.63. In this diagram, the lateral pelvic fascia has already been incised and the neurovascular bundles have been freed from the prostate-rectal interphase. The rectourethralis has been undermined with a right-angle clamp and prepared for transection. This generally permits identification of the ideal midline plane between the prostate and anterior rectal surface. If properly performed, Denonvilliers' fascia should be attached to the prostate, which can then be mobilized in cephalad fashion with care taken to avoid tethering the rectal wall. (From Cummings KB. Refining the anatomic approach to nerve-sparing radical retropubic prostatectomy. *Contemp Urol* 2000;July:46, with permission.)

Neurovascular Bundles

The decision to spare the corporal nerves is not inviolate and should be abandoned in favor of a wide excision on one or both sides if the intraoperative findings strongly suggest extension. Contraindications include (a) cT_3 disease, (b) palpable disease at the apex and a flagrant extraprostatic extension elsewhere, (c) tumors exhibiting a significant Gleason grade 5 component, (d) pretreatment PSA levels greater than 20 mg/mL, and (e) preoperative erectile dysfunction. Relative contraindications for nerve sparing include (a) cT_{2b} disease; (b) tumors exhibiting greater than 50% Gleason grade 4 on biopsy; (c) pretreatment PSA levels between 10 and 20 mg/mL; (d) extensive perineural invasion or periprostatic involvement on biopsy; (e) documentation of cancer in three or more needle cores from the same prostatic lobe; and (f) finding of soft tissue reaction involving the neurovascular bundles, which makes interoperative mobilization difficult.

As stated previously, nerve sparing can be initiated before or after urethral transsection. In either case, the exposed edge of the lateral prostatic (pelvic) fascia is used to establish a plane of separation between the prostatic capsule and the overlying prostatic fascia. In general, a right-angle clamp can be insinuated beneath this transparent fascial membrane (Fig. 33.64). Using a no. 15 scalpel blade an “inverted V” incision (Fig. 33.65) can be established from apex to bladder neck (349). During this maneuver, care must be taken to stay well anterior to and parallel with the easily identified neurovascular bundles. The combination of sharp and blunt dissection facilitates the posterior displacement of the neurovascular bundles (Fig. 33.66). Bleeding from small venous and arterial tributaries that may be transected or avulsed during the process of displacing the neurovascular bundles posteriorly often stops spontaneously with gentle compression. Persistent bleeding can be controlled with the careful application of small clips or 4-0 absorbable sutures. The Cavermap is a device that uses intraoperative nerve stimulation with real-time tumescence monitoring to permit identification of the course of the cavernous nerve fibers during radical prostatectomy. Although it has been suggested (516)

that the use of this device may improve the results of nerve-sparing prostatectomy, it is rarely utilized by us.

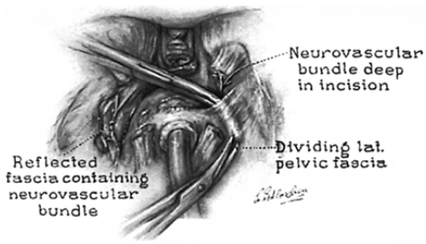

FIGURE 33.64. Division of the lateral pelvic fascia along the anterolateral aspect of the prostate. Dissection within this plane should preserve the integrity of the posterolaterally oriented neurovascular bundle. (From Walsh PC. Radical retropubic prostatectomy. In: Walsh PC, Gittes RF, Perlmutter AD, et al, eds. *Campbell's urology,* 5th ed. Philadelphia: WB Saunders, 1986:2754, with permission.)

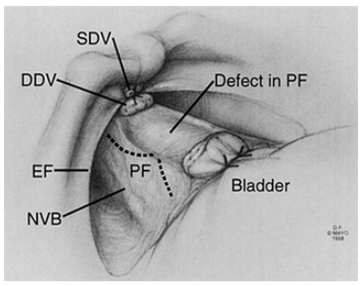

FIGURE 33.65. In this diagram, the dorsal vein complex has been ligated and transected. The *dotted line* demarcates the "inverted V" incision into the lateral pelvic (prostatic fascia). In this incidence, the left neurovascular bundle *(NVB)* is identified deep to the prostatic fascia *(PF)* and the anticipated line of incision. EF, endopelvic fascia; DDV, deep dorsal vein; SDV, superficial dorsal vein. (From Ghavamian R, Zinke H. Technique for nerve dissection. *Semin Urol Oncol* 2000;18:43, with permission.)

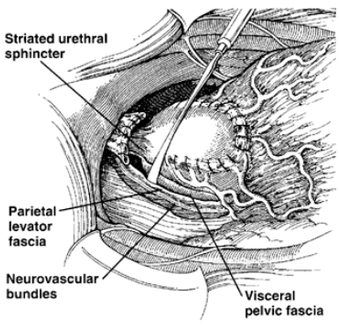

FIGURE 33.66. Additional sharp and blunt dissection permits separation of the neurovascular bundles and the parietal levator fascia from the lateral parameter of the prostate and the visceral pelvic fascia. (From Cummings KB. Refining the anatomic approach to nerve-sparing radical retropubic prostatectomy. *Contemp Urol* 2000;July:46, with permission.)

Cephalad traction on the Foley catheter in concert with judicious blunt dissection (with pressure directed on the prostate/seminal vesicles), facilitates mobilization of these structures and identification of a covering layer of fascia thought to represent, in part, a superior leaf of Denonvilliers' fascia. At this point, the seminal vesicles and their covering fascia are clearly separated from the rectum. The prostate remains attached to its blood supply, the bladder at its outlet, and the vasa, seminal vesicles and the posterior superior extension of Denonvilliers' fascia. The goal to complete the removal of the prostate, and the seminal vesicles, distal vasa/ampulla, and adjacent tissue including Denonvilliers' fascia without or with the nevi erigentes and its adjacent tissue, can be initiated and pursued by an anterior (ventral) or posterior approach. If a posterior approach is chosen, the fascial barrier is usually breeched near the base of the prostate rather than near the vesicle tip and the targeted tissue excision package may become less discrete. On the other hand, identification of the vesicle neck/prostatic urethral junction, the posterior bladder wall, and possibly, the ureters may be facilitated. Identifying, isolating, and clamping, dividing, and ligating the *in situ,* and clipping the specimen, side of the prostate vesicular branches of the inferior vesicle artery (lateral vascular pedicle, Fig. 33.67), as well as preserving or sacrificing the neurovascular bundle, is accomplished with equal ease by either approach.

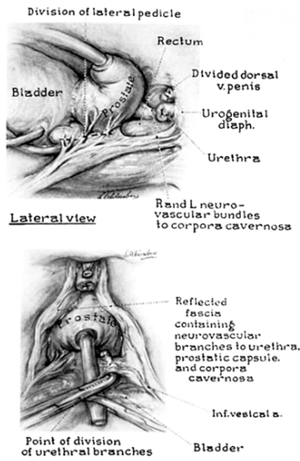

FIGURE 33.67. Transection of the lateral vascular pedicle. To preserve the nervi erigentes, the branches of the prostatovesicular artery should be divided anteriorly, as close to the prostate and seminal vesicles as is consistent with a good cancer operation. (From Walsh PC. Radical retropubic prostatectomy. In: Walsh PC, Gittes RF, Perlmutter AD, et al, eds. *Campbell's urology,* 5th ed. Philadelphia: WB Saunders, 1986:2754, with permission.)

If the posterior approach is chosen, the posterior perivesicle fascial envelope is incised horizontally and the ampulla of the vas deferens is identified, grasped with an Allis clamp, isolated with sharp and blunt dissection, clamped, and divided, and the proximal vas deferens is tied with 2-0 Vicryl sutures. Sharp and blunt dissection is utilized to dissect the seminal vesicles and adjacent tissue. Once completed the vascular pedicle can be divided and secured as described. If the anterior approach is chosen, the surgeon may secure and divide the vascular pedicle without or with the neurovascular bundle. The seminal vesicle fascial barrier remains intact.

Bladder Neck

At this point, the plane between the rectum and prostate/adnexa has been clearly established. The separation of the prostate/adnexa from the bladder neck constitutes the next step in the dissection in the posterior approach utilized by many and is the initial procedure in the traditional anterior approach. The first step in this technique is to identify the interface of the prostate and bladder neck to guide appropriate localization of a ventral transverse cystotomy. If the appropriate site is in doubt, we prefer a cystotomy to a prostatotomy. Following intravenous (IV) administration of Indigo carmine, sharp dissection is used to separate the bladder from the prostate anteriorly and laterally. Most often, a small cuff of bladder neck tissue will accompany the prostate specimen. Placing a small malleable retractor in the bladder after it is entered and a transurethral catheter sling facilitates exposure of the posterior elements. After the trigone and ureteral orifices are identified, the posterior bladder neck is transected using sharp dissection. Care must be taken to remove all middle lobe (subtrigonal) prostatic tissues. The trigonal complex must be kept from harm's way during this maneuver. Following transection of the posterior bladder neck, judicious dissection in the midline aspect identifies the plane that separates the bladder neck and base from the residual elements of the adnexal structure, as well as nonligated components of the lateral pedicle. Usually this plane is easily identified and dissected from the bladder base; if it is not, insertion of catheters to help identify the ureters

warrants consideration. If an initial posterior approach to the vasa/seminal vesicle complex has been utilized, this plane has probably been identified and, at least partially freed from the bladder. With the anterior approach, identification and division of the vasa, a procedure already accomplished with the posterior approach, is usually the next step. Then, with a lap pad or tagged sponges protecting the rectum, the seminal vesicle/vasa, and their adjacent tissues are freed by blunt and sharp dissection. Bleeding is controlled by ligating, clipping, or fulgurating bleeding sites. The tissue cephalad to the tip of the vesicle is secured by clipping or by ligation, divided on the specimen side, and the specimen removed intact. The removed prostate/seminal vesicle: adjacent tissue specimen should be inspected for any capsular or other evidence of incomplete removal. After irrigating the wound gently, the bladder, rectum, and tissue bed are also inspected for bleeding or unrecognized injury. Visualization of effluxing urine in the bladder is a reassuring observation. At this time, the patient's status should be reassessed, reports of results of tissue biopsies obtained, and preparations made as discussed subsequently to proceed with reconstruction of the lower urinary tract.

Inherent advantages of this technique, in addition to its speed and simplicity, are the ability to achieve bladder neck margins unlikely to contain residual prostatic tissues and perhaps the opportunity to resect perivesicle tissue more adequately. Elective bladder biopsy is easily accomplished. Relative disadvantages include the need for a formal reconstruction of the bladder neck using a typical tennis-racket configuration with establishment of an anteriorly located neobladder neck. Another theoretic disadvantage is the loss of additional smooth muscle fibers from the bladder neck, which constitute the remnant of the internal urethral sphincter.

An alternative dissection strategy that is receiving increasing consideration by some involves formal bladder neck preservation. This is easily accomplished once the seminal vesicles and vas deferens have been mobilized using the previously described posterior retrograde approach. Cephalad retraction of these structures facilitates sharp dissection to separate the prostatic base from the bladder neck (Fig. 33.68). During this process, most of the circular fibers of the bladder neck can be preserved circumferentially. An indwelling catheter facilitates identification and separation of the prostatic urethra from the bladder neck proper. The anterior aspect of the urethra is then incised, exposing the indwelling catheter. Following balloon deflation, the catheter is reconfigured as a sling. The posterior urethra is then transected.

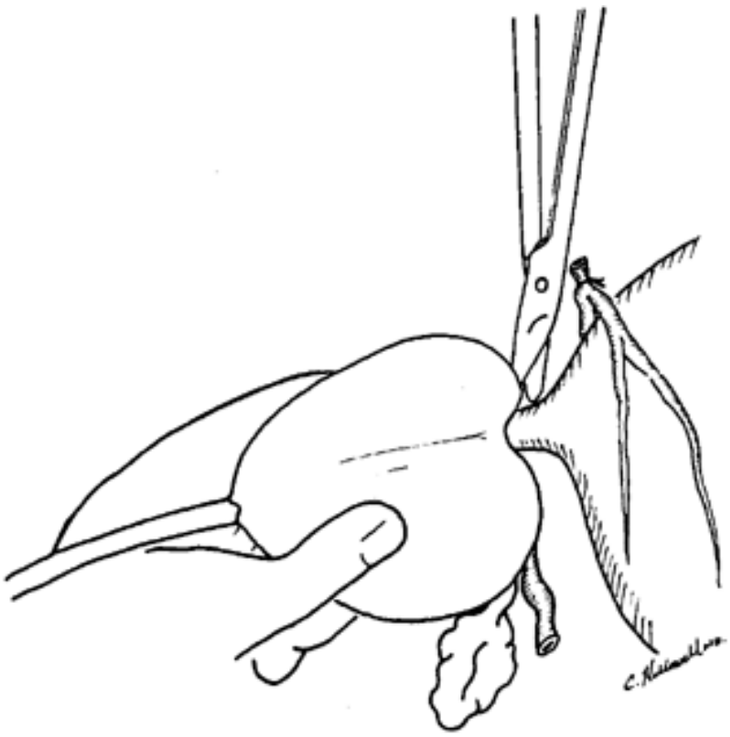

FIGURE 33.68. The mobilized prostate/adnexal structures permit their separation from the bladder neck using sharp and blunt dissection. When done carefully, the majority of the circular fibers of the bladder neck can be preserved. (From Soloway MS, Neulander E. Bladder-neck preservation during radical retropubic prostatectomy. *Semin Urol Oncol* 2000;18:51, with permission.)

One proposed advantage of this approach is the preservation of the circular smooth muscle fibers of the bladder neck (internal sphincter), which may result in a more rapid return of urinary control (510,579,606,951). Although somewhat more time consuming than traditional bladder neck transsection, preservation of the bladder neck minimizes the time necessary for posttranssection reconstruction. It also has been suggested that this approach minimizes the likelihood of anastomotic stricture (330,951). A potential disadvantage is the intuitive likelihood of leaving residual prostatic tissue (cancer) attached to the bladder neck. Studies conducted by Wieder and Soloway (1090), Catalona and Bigg (139), and Lepor and associates (573) suggest that the bladder neck is a rare site of involvement of CaP. Indeed, it is the only positive site in approximately 1% to 2% of patients. Although controversial, it is our practice to carefully obtain representative biopsies, and submit them for frozen section interpretation. It should be emphasized that, despite a trend toward the more rapid achievement of urinary control, there is no statistical difference in ultimate continence, regardless of which bladder neck approach is chosen (606). Finally, we believe it is preferable to perform bladder neck preservation or transsection using sharp dissection, as opposed to electrocautery, to minimize tissue damage.

Before proceeding with the reconstructive aspects of the procedure, several “housekeeping” chores should be performed at this point. The operative site must be carefully inspected to obtain adequate hemostasis. Additional carefully placed suture ligatures of 2-0 or 3-0 absorbable suture may be required in the area of the dorsal vein complex, lateral perimeter tissues, bladder base, and bladder neck. The anterior rectal surface should be carefully reinspected to

exclude inadvertent injury, which can occur during the early phase of the apical section or during the process of mobilizing the seminal vesicles. The dissection zone should be inspected for the presence of suspicious tissue that might represent prostatic remnants. If encountered, these tissues should be removed carefully with sharp dissection and submitted for pathologic evaluation. Obviously, the integrity of the rhabdosphincter should not be compromised merely to remove every vestige of abnormal-appearing apical tissue. In the event that nerve sparing has been performed, it has been recommended that the posterolateral margins of the prostatic specimen be marked with sutures in a line adjacent to the location of the bundles. Those areas can be subjected to frozen section analysis. If tumor is present at the inked margin, it has been recommended that the entire ipsilateral neurovascular bundle be resected en bloc from the urogenital diaphragm to the bladder neck, along with a margin of soft tissue. Once all of these issues have been addressed, the pelvis is then irrigated with several liters of warm sterile water (or a gentamicin-containing solution) as a prelude to reconstruction.

Bladder Neck Reconstruction

Bladder neck closure (if required) should be accomplished with care taken to avoid injury to the ureteral orifices. It has been our preference to use an anterior opening sufficient to admit a “snug” index finger. If this requires partial closure of the bladder neck, we prefer to carry this out posteriorly using full-thickness interrupted sutures of 2-0 chromic catgut. If the orifices are near the edge of the bladder neck incision, posterior closure with carefully placed Lembert sutures will roll them in. To facilitate mucosa-to-mucosa coaptation during the vesicourethral anastomosis, exteriorizing the mucosa of the new bladder neck aperture with interrupted 4-0 biodegradable sutures may be helpful (Fig. 33.69). Tubulization of the anterior bladder neck is rarely necessary and may predispose to anastomotic stricture.

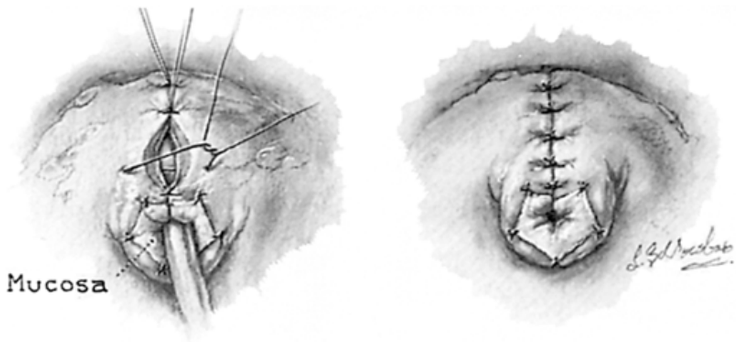

FIGURE 33.69. When bladder neck closure is required, a traditional “tennis-racket” reconstruction is generally sufficient. The “handle” is created using full-thickness 2-0 chromic catgut sutures. If the trigonal complex is in close proximity to the posterior lip of the native bladder neck, inverting Lembert-type sutures can be used to invert the posterior elements and avoid injury/obstruction to the ureteral orifices. The “racket” component of the closure should ultimately admit a “snug” index finger. The mucosal of this new aperture is then inverted with interrupted 4-0 chromic catgut sutures to facilitate a mucosa-to-mucosa reapproximation with the membranous urethra. Although tubulization of the anterior bladder neck is depicted in this diagram, this reconstruction is needed infrequently and can predispose to stricture. Its use can be considered following the removal of large prostates and in situations in which the native anterior tissues are unusually thin. (From Steiner MS, Burnett AL, Brooks JD, et al. Tubularized neourethra following radical retropubic prostatectomy. *J Urol* 1993;150[2 Pt 1]:407, with permission.)

Vesicourethral Anastomosis

Once this anteriorly situated bladder neck aperture has been created, a new pretested 20- or 22-Fr Foley catheter with a 5-mL balloon is inserted and its tip advanced into the open pelvis. Downward displacement of the rectum with a padded hand and/or stick sponge is helpful to present the membranous urethra in its full circumference. To facilitate suture placement, some advocate use of a grooved-urethral sound or perineal compression (if the patient has been positioned with spreader bars).

Various anastomotic techniques, varying from two laterally placed mattress sutures exiting the perineum (Vest sutures) to a multiple suture mucosa-to-mucosa anastomosis, have been advocated. We usually place 2-0 or 3-0 Monocryl urethral sutures with the UR 6 needle at the 5, 7, 3, 9, and 12 o'clock positions. We also use an approximating Halsted mattress suture that incorporates puboprostatic retropubic tissue and proximal and distal urethral tissue at 12 o'clock if necessary. Care must be taken in the placement of the laterally situated sutures to avoid

incorporating the neurovascular bundle, which lies in close proximity. When visibility is poor, a catheter guide helps ensure proper placement of these sutures and incorporation of adequate tissue on the urethral side. We avoid metal suture guides and try to minimize trauma from suture placement or other manipulation.

Lange and Reddy (558) have suggested that construction of the vesicourethral anastomosis can be facilitated by (a) use of the modified dorsal lithotomy position with the legs extended and gently abducted, (b) the application of perineal pressure with a stick sponge to accentuate the presentation of the membranous urethra, and (c) excision of a V-shaped wedge of the pubic symphysis (wedge pubectomy). Although we have not used these techniques, they may be helpful in selected cases. As indicated, we often incorporate a portion of the puboprostatic retropubic and periurethral tissue with these sutures and apply modest traction to them after they are placed to be certain each is well anchored. Before placing the final 12 o'clock suture, the pretested Foley catheter is negotiated between the right- and left-sided sutures; and inserted into the bladder. The balloon is inflated with 10 mL of sterile saline, and protected during placement of the final suture. At this point, it is appropriate to straighten the table if gentle flexion had been used during initial positioning. In addition, the tension should be taken off of the sidewall by gently loosening the retractor unit. Finally, all of the placed sutures should be “snugged” and the bladder brought down toward the urogenital diaphragm. The catheter should be straightened, and the balloon negotiated into a dependent position. It is our practice to tie the sutures in the same sequence they are placed, assisted by gentle downward pressure on the bladder to eliminate tension. Some have advocated construction of a vascularized “sling” of rectus abdominus muscle to support and envelop the anastomotic site. We lack experience with this approach, but believe that, as a routine, sling augmentation of the vesical urethral anastomosis is not required.

Closure

Once the sutures have been tied, the Foley catheter is irrigated to assess the integrity of the anastomosis and to ensure patency. One or two 10-mm flat-type closed-system sump drains are placed through separate, inferiorly directed stab wounds (avoiding the inferior epigastric vessels) and positioned along the pelvic sidewall bilaterally near, but not in direct contact with, the anastomotic site. Securing the Foley catheter with a 3-0 nylon suture through the glans (foreskin) or a heavy nylon suture placed through the eye and brought out the abdominal wound are examples of techniques designed to prevent its inadvertent displacement (Fig. 33.70). Aggressive taping is another alternative. At this point, the wound is irrigated with saline solution and a standard closure is performed. With respect to the latter, we reapproximate the rectus muscle/posterior sheath with loosely tied figure-of-eight sutures of 2-0 or 3-0 PDS. This is done to obliterate the rectus diastasis. The anterior fascia is reapproximated with interrupted (buried) 0-prolene sutures tied in figure-of-eight fashion. The subcutaneous tissues are loosely reapproximated with running 3-0 PDS. The skin is closed with a 4-0 Maxon subcuticular closure, which is reinforced with 0.5-inch Steri-Strips. A medium Tegaderm dressing is placed over the drain site, and the wound is covered with an occlusive gauze dressing.

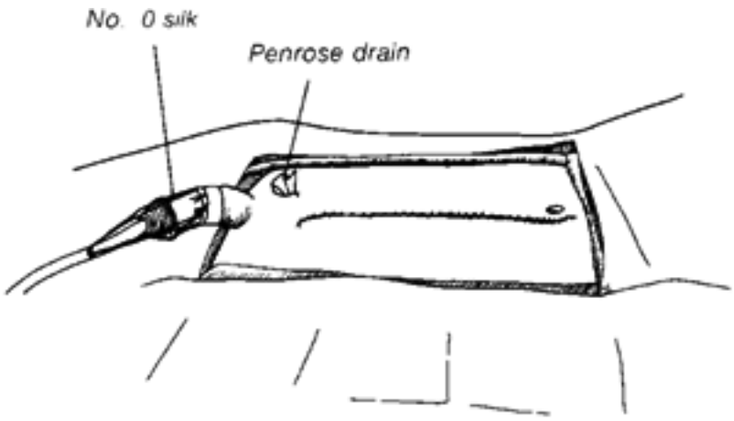

FIGURE 33.70. After completion of the radical retropubic prostatectomy, a Penrose or sump drain should be placed through a separate inferiorly oriented stab wound. It is important to avoid injury to the inferior epigastric vessels. Furthermore, the distal extent of the drain should be carefully positioned so as to avoid direct contact with the anastomotic site. The Foley catheter should be secured as described in the text or as illustrated by using a Velcro strip or adhesive tape to anchor several 0-silk sutures secured to the catheter. (From Crawford ED, Kiker JD. Radical retropubic prostatectomy. *J Urol* 1983;129:1145, with permission.)

Routine Postoperative Course

In general, the postoperative recovery is relatively “routine,” considering the technical complexity of the procedure. Most of our patients are transferred to the floor from the recovery room. IV fluids are maintained until postoperative ileus resolves, generally within 1 to 2 days of the operative procedure. With respect to postoperative pain control, we have been pleased with the results obtained with the use of ketorolac tromethamine (Toradol) after intramuscular injection. This member of the pyrrolo-pyrrole group of NSAIDs should be avoided in patients with a history of peptic ulcer or other conditions predisposing to an increased risk of bleeding. In general, the recommended initial dose is 30 to 60 mg intramuscularly, as a loading dose, followed by 15 to 30 mg administered every 6 hours. Toradol is restricted to short-term therapy (not more than 5 days). Given its demonstrated efficacy and cost-effectiveness, we currently use this approach preferentially for postoperative analgesia.

Early ambulation is a high priority and until the patient is fully mobile, TED hose and an intermittent compression device are used on the lower extremities. These prophylactic measures appear to be particularly warranted in patients with prostate cancer. A recent study conducted by Oefelein

and associates (719) suggests that the patients with prostate cancer do indeed have an intrinsic predisposition to thromboembolism. In their study, more than 5% (12 of 209) of the men diagnosed with prostate cancer had an antecedent thromboembolic event without documentation of any classical risk factors or venous thrombosis. Once the patient is tolerating a general diet, stool softeners [docusate sodium (Colace)] and iron supplements are initiated. It is our current practice to remove the pelvic drains when their respective outputs are quantitated to be less than 10 to 15 mL per 8 hours. In most cases, patients are discharged on the fourth postoperative day, free of drains and with proper instructions provided regarding the management of their indwelling Foley catheter. A urine culture is obtained at the time of discharge.

The patients are advised to take a fluoroquinolone antimicrobial agent every 12 hours starting 3 days before anticipated decatheterization. That event is usually performed 2 weeks postoperatively following the completion of a cystogram demonstrating integrity of the vesicourethral anastomosis. Although we had previously attempted to render our patients catheter free before discharge (209), this prolonged the hospitalization and added to the attendant expense. Moreover, only 62% of those patients were rendered catheter free by day 11. The remainder underwent repetitive cystograms, which may have contributed to the high incidence of anastomotic stricture that was encountered. It should be noted that the latter did respond to single outpatient dilation in most instances, but its incidence seems significantly decreased since we postponed performing an initial cystogram until 2 weeks postoperatively. At that time, almost all anastomotic sites are leak free.

Recent refinements in surgical technique and lingering concerns regarding the discomfort associated with prolonged catheterization have prompted a revisitation of this concept of early catheter removal. DeMarco and associates (222) reported that gravity cystograms were performed on the third or fourth postoperative day in their series of 82 patients. In 70 of 82 patients (85%), the gravity cystogram (with postdrain radiographic views) demonstrated only minimal or no contrast extravasation. In these patients, the catheters were successfully removed before discharge. It appeared that early catheter removal in this group was not associated with the development of symptoms suggesting stricture formation at a minimum follow-up of 6 months. This approach did not adversely affect the return of good urinary control. It is assumed that more precise surgical technique with construction of a near-watertight mucosa-to-mucosa anastomosis accounts for outcome differences when one compares more recent studies such as this with earlier clinical trials.

Many patients experience some hesitancy and a weak stream with accompanying urgency and stress incontinence for several weeks following decatheterization. They should be encouraged and instructed in the management of these symptoms without resorting to a device or aggressive pharmacotherapy. The aggressive use of sphincter exercises and drug regimens for incontinence should be postponed for several weeks following decatheterization. In the great majority, voiding and control improve rapidly.

Complications

Despite the fact that the majority of patients have a relatively uneventful hospital course and a satisfactory surgical result, radical retropubic prostatectomy has been associated with various complications of varying degrees of severity (Table 33.22). A mortality rate of 1% or less would seem to be a reasonable representation of available series addressing this issue (194,450,558,584,654). A recent update of the mortality statistics following radical prostatectomy was compiled by Mark (619), who observed a 0.5% 30-day mortality and a 1.8% 1-year mortality rate. These figures were derived from a 100% sample of Medicare claims in records of patients undergoing radical prostatectomy in 1990. Of note, in the recent American College of Surgeons survey, the operative mortality rate for radical prostatectomy was 0.4% (649). Moreover, it would appear that chronologic age, per se, should not exclude patients from consideration for radical prostatectomy. Middleton (655) compared the mortality and morbidity of the procedure performed on 65 patients 70 years of age or older versus those for 128 men younger than 70 years of age and noted no significant difference in the complications incurred. He concluded that radical prostatectomy is a desirable and safe therapeutic option for all men with clinically localized CaP whose general health suggests a 10-year or greater probable life expectancy. However, it must be emphasized that nonlethal complications occur more frequently in older patients. Catalona and associates (155) documented a 4% complication rate in men in their forties; 9% in those in their fifties; 11% in men in their sixties; and 14% in those men in their seventies.

	Kopecky, et al., 1970	McDuffie and Blunden, 1978	Middleton, 1981	Lieskovsky and Skinner, 1983	Crawford and Kiker, 1983
Number of patients	73	59	50	65	75
Mortality	0	1.7	0	1.5	0
Intraoperative complications					
Rectal injury	1.4	3	2	3	0
Ureteral injury	1.4				
Early complications					
Thrombophlebitis	6.9		12	3	
Pulmonary embolus	2.7		2	4.6	
Wound infection	16			3	5
Lymphocele			2	3	
Urethrovesical dehiscence	4			1.5	
Late complications					
Contracture of bladder neck	12	5	6		2.6
Incontinence	1.4	0	4	3	1.3
Impotence	91	92	100		

From Walsh PC. Radical retropubic prostatectomy. In: Walsh PC, Gittes RF, Perlmutter AD, et al. *Campbell's urology,* 5th ed. Philadelphia, WB Saunders, 1986.

TABLE 33.22. PERCENTAGE OF COMPLICATIONS FOLLOWING RADICAL RETROPUBIC PROSTATECTOMY

Of the potential intraoperative complications, hemorrhage was addressed during the description of operative techniques. Significant bleeding that is difficult to manage usually is associated with inadequate occlusive control of the dorsal vein complex and/or from vessels traversing the levator muscles. With respect to the latter, the use of pledgets of Vicryl mesh provides additional compression and support of mattress sutures targeting bleeders within the lateral muscular element. As stated, use of mattress sutures after temporary tamponade to permit visualization of the bleeding site usually effects satisfactory hemostasis. Should this approach fail, balloon tamponade or exposure of the veins from the penile side of the symphysis warrants consideration; use of a mass ligation with a mattress suture placed from the space of Retzius through the subsymphyseal skin also has been described.

Failure to establish the proper plane when dissecting the posterior aspect of the bladder neck can endanger the ureters. Should a transection injury occur, ureteral reimplantation should be performed. Under these circumstances ureteral stenting is advisable. Ureteral injury was reported to occur in 1.4% of cases in the series by Kopecky and associates (525), but more recent series have not cited this as a complication, and in our experience this is an exceedingly unusual event.

Rectal injury can occur if the proper plane is not established between the Denonvilliers' fascia and the rectum. The risk of this injury is increased by disease process (cancer; prostatitis) or prior procedures (TRUSP biopsies) that obliterate this plane. The incidence of this complication varies from 0% to 3% in the available literature (194,584,654). The injury is usually readily apparent, but the operating surgeon should make a practice of carefully inspecting the anterior rectal surface following the full mobilization of the prostate. If an injury is identified, any ischemic component to the wound edges should be excised. A double-layered interrupted closure with mucosa-inverting sutures of 3-0 or 4-0 silk for the inner row and Lembert-type sutures of 3-0 silk (or 3-0 Vicryl) for the muscular component of the rectal wall is satisfactory. Because the injury occurs below the peritoneal reflection, the rectum will lack serosal covering that would ordinarily provide additional support for the sutures. Additional reinforcements of the closure can be obtained by patching the area of repair with a generous portion of mobilized omentum, endopelvic fascia, and/or preperitoneal fat. In the absence of previous irradiation therapy and in the presence of an adequate bowel preparation, these maneuvers plus manual dilation of the rectal sphincter are probably adequate to protect against leakage from the suture line with subsequent development of an adjacent abscess, rectourethral fistula, or both. When this closure is precarious, a diverting colostomy is certainly indicated. Although it is most convenient to exteriorize a segment of sigmoid colon, a transverse loop colostomy or loop ileostomy is certainly acceptable.

Generic postoperative complications occur in approximately 10% of patients (155) and include (a) thromboembolic phenomena in 2%; (b) vesicourethral anastomotic stricture in 4%; (c) delayed inguinal hernia in 2%; and (d) 1% or less incidence of lymphatic, infectious, neurologic, or other miscellaneous complications. Although the urethrovesical anastomosis usually is watertight within 1 or 2 weeks, persistent extravasation or leakage may occur, particularly if the initial anastomosis is faulty. These leaks will stop as long as the anastomotic site is free of foreign bodies (e.g., a drain), and the Foley catheter is well positioned and functional.

A sizable pelvic hematoma occasionally can develop from persistent oozing at the operative site. This can displace the bladder and lead to a partial disruption of the vesicourethral anastomosis. Modest hematomas usually require no intervention. With natural resolution, the bladder will revert to its normal midline position and any attendant anastomotic leak will subside. A large hematoma that subsequently becomes infected requires evacuation. At times, this can be accomplished by ultrasound- or CT-guided cutaneous puncture with the insertion of a pigtail catheter and irrigation with urokinase (1052). Reexploration of the pelvis for bleeding and infection also warrants consideration. To that end, Hedican and Walsh (409) state that significant

postoperative hemorrhage occurred in 0.5% (7 of 1,350) of radical prostatectomies. They defined the hemorrhage as significant if it required acute transfusion of blood to support blood pressure. Four of these seven patients underwent exploration for bleeding, and three were treated conservatively. Only one of the four patients who underwent exploration experienced prolonged mild incontinence. In the patients treated nonoperatively, the pelvic hematoma drained through the anastomosis, with symptomatic bladder neck contraction developing in all three patients and long-term incontinence in two. It is their recommendation that for patients requiring acute transfusions for hypotension following radical prostatectomy, serious consideration be given to surgical evacuation of the pelvic hematoma.

Despite adequate precautions, the Foley catheter may dislodge. If this happens, a limited and judicious attempt to reinsert a 16- or 18-Fr Foley catheter is reasonable. Should such an effort fail, flexible endoscopy should be performed to identify the anatomic relationships with certainty. This knowledge and the insertion of a guidewire under direct vision usually permit reintroduction of a Foley catheter. If the anastomotic site is well drained and the surgeon is confident of its integrity, a suitable option is to defer the replacement of the catheter and accept temporary urinary extravasation. This is particularly reasonable if the catheter dislodges late in the hospital course.

Even in experienced hands, bladder neck contracture may develop in approximately 4% of cases (155). Potential etiologic factors include (a) the use of electrosurgical instruments to transect the bladder neck with attendant focal devascularization at the anastomotic site, (b) the failure of the surgeon to achieve satisfactory approximation during the placement of the anastomotic sutures, and (c) overzealous attempts to fashion a snug bladder neck aperture (including anterior tubulization). Techniques proposed to reduce the incidence of bladder neck contracture to a reported 1.3% to 5.4% include the following: (a) optimal exposure of the membranous urethra using the modified lithotomy position, exerting perineal pressure with a sponge stick, and wedge pubectomy (558); (b) performing an eight-suture vesicourethral anastomosis (655) or a modified Vest procedure of vesicourethral reconstruction (450); and (c) deliberate eversion of the bladder neck mucosa before anastomosis to obtain a more secure mucosa-to-mucosa realignment (1064).

Development of a bladder neck contracture may be heralded by a spectrum of symptoms ranging from a diminished, thin stream or dribbling, to urinary retention. If an attempt to pass a catheter into the bladder is unsuccessful, urethroscopy should be performed to ascertain the degree of contracture and the location of the aperture. Dilation under direct vision or with filiform and followers or van Buren sounds is usually possible. The former can be accomplished under local anesthesia even with a minute visual opening by steady directed pressure with a 17-Fr cystoscope in a patient with a fully distended bladder. One or two such dilations usually prove sufficient. If not, other options include internal urethrotomy (143) or dilation with the patient under anesthesia followed by the injection of steroids into the area of stricture. Walsh (1067) recommends the injection of triamcinolone acetonide (200 mg) and has noted permanent resolution of the problem with this maneuver. In the event that an obliterative stricture occurs at the urethrovesical anastomosis, continuity may be reestablished using an endourologic technique such as that described by Appel and Lebenson (16). This procedure uses a percutaneously placed suprapubic tube for drainage and to permit antegrade (as well as retrograde) evaluation and manipulation of the strictured area. Potter and Marshall (793) have proposed a more recent variation of this approach. The use of electrocautery is associated with a high incidence of subsequent incontinence and should be avoided.

Mild stress and urgency incontinence are commonly experienced for several weeks following initial decatheterization. In our experience, this is resolved in approximately 80% of patients by 2 months postoperatively. Most patients achieve optimal urinary control within 6 months. Although some patients exhibit additional incremental improvement up to 18 months postoperatively, this constitutes the exception rather than the rule. In most modern series, incontinence is defined as urinary leakage requiring any type of protection (e.g. pads, tissue) to keep clothing dry. Catalona and associates (155) documented some degree of postoperative urinary incontinence in 8% of patients. Approximately 1% to 2% of patients exhibit incontinence severe enough to require surgical treatment. In this same study, 96% of men younger than 70 years of age, and 87% of men 70 years of age, recovered urinary control within 18 months of radical prostatectomy. Of interest, Strasser and associates (987) have documented an age-dependent increase of apoptosis of the striated muscle fibers of the rhabdosphincter. This phenomenon may account for the higher incidence of stress incontinence in elderly patients following radical prostatectomy. Walsh and associates (1062) reported complete urinary control in 92% of patients; stress incontinence in 8%; 6% of patients required one or fewer pads per day; and 0.3% required placement of an artificial sphincter for severe incontinence. In addition to patient age, intrinsic sphincter function is the prime determinant of postprostatectomy control. With respect to the latter, preservation of maximum urethral length and maintaining the structural/functional support of the striated rhabdosphincter appear to be critical for achieving postoperative continence (469). Preservation of the neurovascular bundles does not appear to affect postoperative urinary control (155). In the prostate cancer outcomes study, a population-based longitudinal cohort study with up to 24 months of follow-up, 8.4% of men were incontinent 18 months or more following radical prostatectomy. For such patients, it is our practice to perform video urodynamic testing and flexible endoscopy.

Detrusor instability and bladder outlet obstruction should be managed in a traditional fashion. Lingering incontinence is usually of the stress-type. Patients with a Valsalva leak-point pressure of greater than 60 cm of water may achieve some improvement with collagen injections (368). Patients with leak-point pressure of less than 60 cm of water are most expeditiously treated with an artifical urinary sphincter (368) or consideration of a bulbourethral sling (177,178).

Walsh (1066) and Walsh and associates (1059) have shown that potency can be preserved in 72% of patients when both nerves are left intact. In this group, 58% recovered potency within 6 months, 95% by 1 year, 99% by 18 months, and 100% by 2 years. Potency was recovered in 69% of patients in whom only one neurovascular bundle was preserved. Of note, more than 50% of the patients in this study were less than 60 years old, and only 3% were greater than 70 years of age. It would appear that younger patients with normal or active preoperative sexual function are most likely to recover potency following this procedure. When capsular penetration is suspected by the presence of fibrosis and induration, Walsh (1064) advocates sacrificing one or both nerves as the situation demands. He reports deliberate sacrifice of one neurovascular bundle in 16% of patients with stage B_1N, 35% with stage B_1, and 80% with stage B_2 tumors. In these same groups, both nerves were sacrificed in 5%, 4%, and 12% of cases, respectively. More recently, Walsh (1065), reported the outcomes in 64 men who underwent radical prostatectomy for the treatment of localized prostate cancer. Each of these men were potent preoperatively and had sexual partners. The median age of this cohort was 57 years (range of 36 to 67). All men underwent anatomic radical prostatectomy performed by one surgeon, and the neurovascular bundles were preserved bilaterally in 89% of the patients. Potency, defined as the ability to have unassisted intercourse with or without the use of sildenafil, improved gradually, and by 18 months, 86% of patients were potent (84% of the patients considered sexual bother as none or small). At 18 months, approximately one-third of these patients were using sildenafil intermittently, but only two patients were not able to have intercourse without its use.

Catalona and Bigg (139) reported preservation of sexual potency in 63% (71 of 112) of patients in whom both neurovascular bundles were preserved. In contrast, only 39% (13 of 33) of patients regained potency following a unilateral nerve-sparing procedure. In this series there was a strong correlation between patient age, pathologic stage, and the preservation of potency following a bilateral nerve-sparing technique. Potency was preserved in 81% of patients 40 to 59 years old, 57% of those 60 to 69 years old, and 33% of those 70 to 79 years old. Similarly, preservation of potency was noted in 63%, 75%, 52%, 50%, and 50% of patients with stage A, B, C_1, C_2, and D_1 disease, respectively. The correlation between the quality of preoperative erections and the likelihood of their recovery postoperatively appears to be strong. Approximately 20% of patients with marginal preoperative erections recovered erections as compared with nearly 80% whose preoperative erections were judged to be completely normal. In most patients, postoperative erections were perceived to be less rigid when compared with preoperative erections, but some patients did report erections that returned to their preoperative baseline (155).

In general, the recovery of erections takes longer than the return of urinary control. In most patients, erectile activity resumes within 3 to 6 months following prostatectomy, and further improvement can be anticipated for 18 to 24 months or longer (155). This time frame may be required for surgery-induced neuropraxia to resolve. Montorsi and associates (669) have suggested that the early use of artificial means of inducing erections may hasten the return of natural erections. To that end, suitable patients have been encouraged to initiate therapy with sildenafil (Viagra), intraurethral alprostadil (MUSE), intracavernosal injections of alprostadil, or a vacuum erection device. In most instances, we have encouraged the prompt initiation of such treatment following the removal of the indwelling catheter.

Concern has arisen regarding the possibility that the nerve-sparing modification might compromise already tenuous surgical margins. In the study conducted by Eggleston and Walsh (254), extracapsular tumor extension was infrequently noted exclusively in the vicinity of the neurovascular bundles. Conversely, Stamey and associates (965) have reported the frequent association of positive capsular margins along the course of penetrating nerve fibers. In fact, they advise that the modified nerve-sparing procedure be limited to the contralateral side in stage B disease. Catalona and Bigg (139) noted that the improper application of the nerve-sparing technique may contribute to some instances of positive surgical margins, particularly at the points of urethral transection and establishment of the posterior extracapsular plane. To avoid these problems, they recommend (a) delineation of 1 to 2 cm of membranous urethra distal to the insertion of the paraurethral bands to the prostatic apex to avoid retention of apical tissue in the urethral remnant with the development of a posterior subcapsular plane, (b) isolation of the rectourethralis muscle with a right-angle clamp and its division distal to the posterior lip of the prostatic apex, and (c) conversion to antegrade dissection at the level of the bladder neck to reestablish the proper posterior plane of dissection if the prostatic apex has been undermined. We generally adhere to the absolute and relative contraindications to nerve sparing previously articulated.

Radical Perineal Prostatectomy

The perineal approach to the bladder and prostate has been used since the earliest surgical attempts to treat diseases of these organs. The approach was attractive because it was

direct and avoided risk of injury to most intraabdominal organs; it did not require muscular relaxation; it was a relatively avascular approach to the lower urinary tract; and it provided dependent drainage, a particularly important advantage in the preantiseptic and preantibiotic eras. As these considerations have become less critical, and other concerns, such as more accurate staging and possibly improved preservation of a range of functions have superseded them, the perineal approach for radical and enucleative procedures has become less popular and less frequently used. The exacting knowledge of anatomy and the limited exposure provided by this approach have certainly been factors in its reduced use. Nevertheless the perineal approach to the radical prostatectomy retains many of these inherent advantages.

Recently, interest in radical perineal prostatectomy has been renewed. In part, this is attributable to the advent of laparoscopic PLND and, to a lesser extent, the mini-lap procedure for pelvic lymph node sampling. Another incentive for reconsidering the procedure is the current perception that metastasis to the pelvic lymph nodes are encountered infrequently in most modern series (Table 33.23). For example, Petros and Catalona (768) reported on the frequency of pelvic lymph node metastasis in 521 consecutive patients undergoing radical retropubic prostatectomy between 1983 and 1991. Of 32 patients with clinical stage A_1 disease, none had positive nodes compared with 2 (3.3%) of 61 with stage A_2, 10 (5.3%) of 189 with stage B_1, and 23 (9.7%) of 236 with stage B2 disease. In properly selected patients (low volume, Gleason score of 6 or below, PSA less than 10), it may be reasonable to forego pelvic node staging and proceed directly to a radical perineal prostatectomy.

Reference	No. of Patients	Stage (%)			
		A_1	A_2	B_1	B_2
McLaughlin, et al., 1976	60	—	—	21	30
Paulson, et al., 1990–1988	84	4	25	16	25
Grossman, et al., 1982	82	0	53	17	29
Hackler and Texter, 1980	517	0	24	17	42
Flannigan, et al., 1994	53	—	0	0	42
Oesterling, et al., 1993	275	0	9	4	33
Gervasi, et al., 1989	511	—	22	21	37
Present series	521	0	3.3	5.3	9.7

Note: Studies cited are from original source.
From Petros JA, Catalona WJ: Lower incidence of unsuspected lymph node metastasis in 521 consecutive patients with clinically localized prostate cancer. *J Urol* 1992;147:1574.

TABLE 33.23. PERCENTAGE OF POSITIVE PELVIC LYMPH NODES BY CLINICAL STAGE

The perineal approach has some potential advantages over the retropubic with regard to avoiding rectal injury, controlling blood loss, and accomplishing the urethrovesical anastomosis. Urologists should strive to maintain their knowledge of the anatomy and technique that allows them to carry out this procedure. Patients selected for perineal prostatectomy must be able to tolerate significant flexion of their hips to permit placing them in the extreme lithotomy position. Patients with a wide separation of their ischial tuberosities and low-lying prostates are ideal candidates for this approach.

Proper positioning is critical to the perineal exposure. The desirable flat perineum lying parallel to the floor can be achieved by elevating the buttocks and by marked flexion of the thighs (Fig. 33.71). In achieving this position, pressure on the legs and on the shoulders must be avoided by proper padding and careful placement of supports. The arms should be kept as close to the body as possible; this is often achieved by simply taping the hands to the knees.

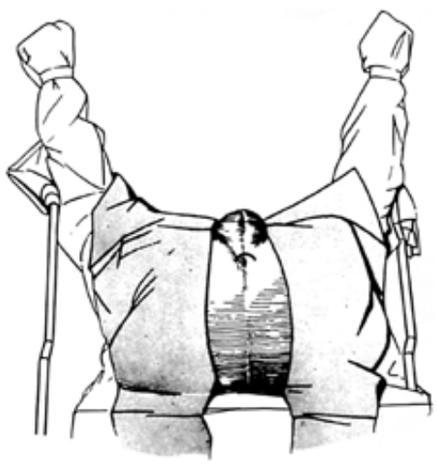

FIGURE 33.71. Exaggerated lithotomy position required for radical perineal prostatectomy. The extremities must be carefully padded and protected to prevent a neurovascular or compartment injury. Also shown is the semicircular skin incision, which should extend between the ischial tuberosities. (From Brendler H. Prostatic hypertrophy and perineal surgery. In: Boyce WH, Glenn JF, eds. *Urologic surgery,* 2nd ed. Hagerstown, MD: Harper & Row, 1975:424, with permission.)

Once the patient is positioned, shaved, prepared, and draped, a curved Lowsley tractor is introduced into the bladder and then withdrawn into the prostatic fossa. A semicircular skin incision extending between the ischial tuberosities is placed appropriately in relation to the mucocutaneous junction for the planned suprasphincteric or infrasphincteric approach to the prostate. The incised skin

and subcutaneous tissue are anchored to an inferiorly placed drape or towel. In the suprasphincteric approach, Colles' fascia is incised sharply on each side of the central tendon. Posteroinferior pressure on the Lowsley tractor is applied to push the prostate toward the perineum. Each ischiorectal fossa is developed superiorly and posteriorly, with the handle of the knife working on the superior aspect of the inferiorly placed index finger until the posterior aspect of the prostate is felt. The index fingers of each hand then are used in a gentle seesaw motion ventral to the rectum and behind the central tendon to isolate this structure. The central tendon is then divided over a clamp (Fig. 33.72). Appropriately designed right-angle (often designated lateral) retractors are placed posterior to the deep transverse perineal muscle on each side, exposing the fibers of the levator ani muscle covering Denonvilliers' fascia. A properly placed pediatric or perineal Omni retractor aids in achieving or maintaining exposure. Often, these fibers fuse in the midline, forming the so-called rectourethralis muscle (Fig. 33.73). At this point Denonvilliers' fascia is hidden by the converging levator ani fibers and the tented-up rectum. With manual retraction, the sponge-covered rectum is reflected posteriorly. The levator fibers can often be separated with the handle of the knife to expose Denonvilliers' fascia (Fig. 33.74). This is usually attempted in the midline at the apex of the prostate just proximal to the urogenital diaphragm. If this is not possible bluntly, careful sharp dissection with the knife as far distal on the prostate as possible, accompanied by blunt lateral and superior freeing of the tissue with the knife handle, will expose this fascia. Use of the lateral retractors to maintain every advantage in exposure that is achieved is critical to this procedure.

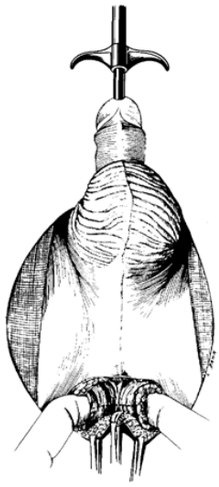

FIGURE 33.72. Delineation of the central tendon following blunt dissection with the intended line of transection marked by the *dashed line.* Note the presence of the Lowsley tractor. (From Brendler H. Prostatic hypertrophy and perineal surgery. In: Boyce WH, Glenn JF, eds. *Urologic surgery,* 2nd ed. Hagerstown, MD: Harper & Row, 1975:424, with permission.)

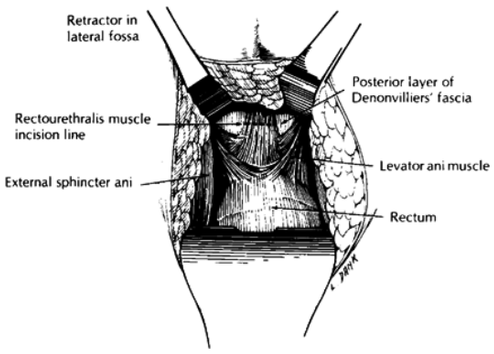

FIGURE 33.73. Midline fusion of fibers of the levator ani muscle (rectourethralis) covering the posterior layer of Denonvilliers' fascia. At this point in the dissection, the rectum would be reflected posteriorly and protected by a surgical sponge. (From Brendler H. Prostatic hypertrophy and perineal surgery. In: Boyce WH, Glenn JF, eds. *Urologic surgery,* 2nd ed. Hagerstown, MD: Harper & Row, 1975:424, with permission.)

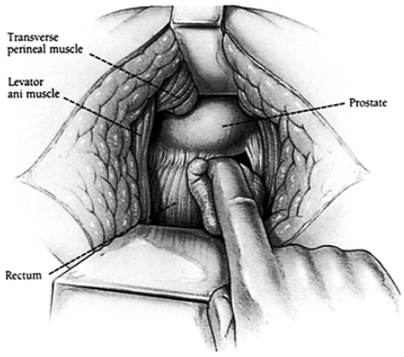

FIGURE 33.74. Establishment of the cleavage plane between anterior and posterior layers of Denonvilliers' fascia. Following transection of the central tendon, separation of the levator ani muscles, and division of the rectourethralis fibers, the desired midline plane between prostate and rectum is delineated with blunt dissection. (From Resnick MI. Radical perineal prostatectomy. In: *Urologic surgery.* Bristol-Myers, Learning Technology, 1988, with permission.)

Following exposure of the shining white posterior layer of Denonvilliers' fascia, the curved tractor is readvanced

into the bladder, the blades opened, and the prostate again levered into the wound. Often, the levator fibers will strip easily from the remainder of the intact Denonvilliers' fascia, making the classic transverse incision to separate the currently disputed posterior and anterior leaves unnecessary. Posterior mobilization should then be carried to the tip of the seminal vesicle. Often, a sponge stick placed on a padded posterior tractor is very useful in dissecting to the level of the pouch of Douglas. The lateral aspect of the prostate is then mobilized by blunt finger dissection between the gland and the lateral prostatic fascia. The dissection to this point should result in very limited blood loss. Persistent bleeding during the exposure of the prostate may indicate that the dissection has entered the wrong plane, for example, the bulbourethral muscle.

After the lateral aspect of the prostate has been mobilized, the membranous urethra can be elongated by gentle posterior traction on the prostate and a right-angle clamp guided around its ventral aspect. The urethra is then divided sharply, hugging but avoiding the apex of the prostate. The posterior lip of the divided prostatic apex is grasped with an Allis clamp and the curved Lowsley tractor removed. A straight Lowsley tractor is used to replace it, and the blades are opened. Gentle traction on this instrument allows better visualization of the prostate in the perineum. The anterior surface of the prostate is then exposed to the level of the bladder neck with blunt dissection. The tractor blades are placed in an AP direction so that the bladder neck can be identified by palpation. The neck is incised sharply anteriorly with the scissors, and the incision is carried around each side posteriorly. At this point, the tractor can be replaced with a red rubber catheter to act as a sling and the bladder inspected to identify the ureteral orifices. If this is difficult, injection of chromogen such as indigo carmine will help. Ureteral catheterization is rarely necessary.

Once the orifices are identified, the bladder neck is incised in its posterior aspect as close to the prostate as the neoplastic involvement will allow. The entire bladder muscle must be divided, exposing the fascia overlying the seminal vesicles and vas deferens. Once this plane has been entered, blunt dissection can be used to separate the bladder from these structures. The vas deferens is identified, isolated, grasped with an Allis clamp, elevated from its bed, clamped, divided, and ligated on each side. Then with the finger of the left hand separating the prostate from the rectum, the vascular pedicle that enters the gland at its superolateral margin is isolated, clipped or clamped, divided, and ligated first on one side and then on the other. Heaney or gooseneck clamps are ideal for this maneuver. Then the tissue along with the blood supply at the tip of the vesicle is clamped, divided, ligated, and the specimen removed. The rectum is inspected to make certain there has been no injury. Minimal oozing from the rectum can be controlled by light fulguration but will usually stop when the patient is taken out of the perineal position. The bladder is inspected to make certain that the orifices are intact. A 22- or 24-Fr Foley catheter with a 5-mL bag is passed through the urethra and brought out the perineum. This serves to identify the distal urethra at the site of the urogenital diaphragm during the subsequent anastomosis.

The bladder neck is then narrowed using a Y-V type of reconstruction similar to that used in the retropubic prostatectomy. A small piece of tissue is then taken from the anterior and posterior bladder neck margins for frozen section evaluation to document the absence of retained prostatic tissue and/or a recognizable tumor. If the ureteral orifices are near the cut edge of the bladder neck, they can be infolded using interrupted Lembert sutures for the tail of a Y-type closure. The bladder neck urethral anastomosis is carried out as described previously. The enhanced apical exposure provided by this approach facilitates the placement of anastomotic sutures. The catheter is positioned just cephalad to the anastomotic site.

Drains are placed in the perineum and brought out through one corner of the perineal wound. The levator fibers are approximated with interrupted chromic catgut sutures, whereas the subcutaneous tissue is approximated with interrupted 3-0 plain catgut and the skin with subcuticular or vertical mattress sutures. The bladder is irrigated. It is our practice to anchor the catheter to the penis with a nylon suture placed through the glans. The patient is removed from the exaggerated lithotomy position with both legs being rotated inferiorly and simultaneously. Because

irrigation is rarely necessary after this procedure, the catheter is simply connected to straight drainage. The perineal wound is covered with a perineal pad held in place by a T-binder.

On the following day, the drain is removed and the wound is then exposed to the air. Perineal care includes the use of a local heat lamp and an antiseptic agent such as povidone-iodine (Betadine) or merbromin (Mercurochrome). In our experience, most of these patients are discharged drain free with an indwelling Foley catheter on the third or fourth postoperative day. The decatheterization scenario is then identical to that previously described for radical retropubic prostatectomy. The use of an approach that stays close to the prostate and out of the lateral prostatic fascia and its adjacent areolar tissue on mobilizing the lateral aspect of the prostate and close to the prostate on clamping the vascular pedicle would seem likely to facilitate preservation of the autonomic nerves important to erection and continued sexual function (approaching 80% in some series). Many perineal surgeons prefer the infrasphincteric approach described by Belt to expose the prostate for radical and simple perineal prostatectomies, because the rectum is certainly in view during this procedure.

As enumerated by Hudson and Hakky (444), radical perineal prostatectomy preserves the following structures: (a) endopelvic fascia; (b) the puboprostatic ligaments; (c) the lateral pelvic fascia; (d) the anterior sheath (postsymphysial muscle and fascia); (e) the lateral lower bladder muscular attachments; (f) the circular bladder neck components, with intact nerve and blood supply; (g) the external striated urethral sphincter, including looping strands that can be “teased” off the apex of the prostate along with intact blood and nerve supply to the rhabdosphincter; and (h) the deep dorsal vein and its branches (444).

Radical perineal prostatectomy can be carried out with a limited blood loss (1% transfusion rate in large series) and complication rate. For example, Paulson and associates (756) performed radical perineal prostatectomy on 76 patients with stage A prostate cancer and reported no instances of perioperative death, rectal injury, or incontinence. Of note, the authors report positive surgical margins in 32% of the cohort, which they attributed, in part, to prior TUR. Walsh (1069) has suggested that the perineal approach provides inordinately thin anterior margins that can be particularly problematic in patients with stage A tumors in whom the disease tends to be preferentially localized to the anterior aspect of the gland.

Frazier and associates (316) compared the outcome of 122 patients who underwent radical perineal prostatectomy with 51 patients who underwent radical retropubic prostatectomy, both for the treatment of organ-confined prostate cancer (stage T_1 or T_2). Although the total operative time was somewhat shorter for the perineal group, the anesthesia time was similar for both groups. There was no difference in the incidence of positive surgical margins, nor was there any difference in the short-term/long-term complication rates between the two groups. Of note, the median estimated blood loss for the perineal group was 565 mL compared with 2,000 mL for the patients undergoing radical retropubic prostatectomy. These favorable results coupled with technical modifications of the radical perineal prostatectomy that permit preservation of the neurovascular bundles and a watertight vesicourethral anastomosis (755) make it an attractive surgical option for these patients.

These perceptions are validated by a more recent comparison regarding the relative merits of radical perineal versus radical retropubic prostatectomy, conducted by Sullivan and associates (993). In general, the results of radical perineal and radical retropubic prostatectomy are comparable. There was no significant difference in operative duration, or the incidence of positive margins or global complications. The advantages of the perineal approach included minimal blood loss, low-intensity postoperative nursing care, low analgesic use, and earlier discharge from the hospital.

Recently, Bishoff and associates (62) conducted a survey that revealed that the incidence of fecal incontinence following radical retropubic and perineal prostatectomy occurs more frequently than previously recognized. The fecal incontinence among radical perineal (18%) and retropubic (5%) prostatectomy patients surpassed the expected incidence of 4% for this age group (60 to 70 years). The incidence was significantly higher for radical perineal prostatectomy patients. The exact mechanism of injury leading to fecal incontinence has not yet been defined. The rectal sphincter consists of subcutaneous, superficial, and deep components. Any or all of these muscles are certainly subject to trauma during the perineal approach to prostatectomy. Prolonged retraction also may lead to neuropraxia. Finally, reconstruction of the levator ani muscles may contribute to damage and possibly prevent proper functioning of the continence mechanism. These authors suggest that a combination of new electromyography techniques with anal rectal manometry may help define preoperatively patients who may be at increased risk for this complication. It would appear that these observations should constitute part of the pretreatment discussion when the risk/benefits of available treatment options are reviewed with patients.

Laparoscopic Radical Prostatectomy

Guillonneau and Vallancien (393) recently reported their experience with laparoscopic radical prostatectomy performed on 120 consecutive patients from February 1998 to May 1999. The procedure is performed with the patient in the dorsal supine position. The lower limbs are abducted to provide access to the perineum. A slightly exaggerated Trendelenburg position also is used. For a right-handed surgeon, five trocars are used. A 10-mm trocar is placed in the umbilicus for the telescope. Three 5-mm trocars are placed in the left iliac fossa, midway between the umbilicus

and pubis, and in the right pararectal fossa. Finally, a 10-mm trocar is positioned in the right iliac fossa at McBurney's point. In their series, the surgeon stands to the left of the patient with an assistant opposite him or her. A voice-controlled robotic arm is used to manipulate the scope to ensure stability of image and to free a hand, which can then be used to manipulate other instrumentation.

The procedure commences with a laparoscopic PLND, which follows the precepts already discussed. To approach the adnexal complex, an incision is made in the lower peritoneal arch, which represents the peritoneal fold along the vesicorectal apposition. This gives access to the vas deferens and seminal vesicles. Through this transperitoneal approach, the vasa deferentia are dissected, coagulated with bipolar current, and transected. A seminal vesicle dissection is the next phase of the procedure. In each case, the tip of the respective seminal vesicle is completely mobilized, and ultimately, only the base of the seminal vesicle remains attached. At this point, the sagittal striations of Denonvilliers' fascia become apparent, and these are incised in a transverse fashion. This approach permits access to the proper plane, which permits identification of prerectal fat that leads to the posterior surface of the prostate. At this point, the bladder is filled to clearly visualize its contours. Dissection is initiated along the lateral aspects of the bladder, medial to the obliterated medial umbilical ligament. This ultimately permits access to the retropubic space and lateral incision of the pelvic fascia. The puboprostatic ligaments are then sectioned and the prostatic apex is released laterally. Santorini's venous plexus is ligated with 2-0 absorbable suture material, but is not transected at this point in order to decrease the risk of bleeding, which would render subsequent phases of the operation difficult. Transsection of this venous complex is delayed until control of the prostatic pedicles has been achieved. An intervesicoprostatic dissection is performed with the intent of bladder neck preservation. Posterior dissection of the bladder neck reveals the previously transected vasa deferentia and the mobilized seminal vesicles. At this point, dissection of the posterosuperior pedicles of the prostate is performed, using coagulation with bipolar forceps. The neurovascular bundles are preserved when prudent to do so. Following this, Santorini's venous plexus is transected and the urethra is identified and incised with a cold knife. Finally, the distal insertion of Denonvilliers' fascia with rectourethralis attachments is sectioned. This releases the operative specimen. A watertight urethral vesicle anastomosis is performed using 6 to 8 polyglactin 3-0 interrupted sutures tied over an 18-Fr Foley catheter. The operative specimen is extracted using a laparoscopy bag after enlarging the trocar site at McBurney's point.

The mean operating time for the first 120 consecutive patients was 239 minutes. Mean interoperative blood loss was estimated to be 402 ± 293 mL. The transfusion rate was 10% overall. Conversion to open surgery was necessary in seven cases, and reoperation was performed in 1.7% of cases. The mean postoperative bladder catheterization time was 6.6 ± 2.4 days. The positive/questionable surgical margin rate was approximately 15%. Serum PSA reverted to undetectable in 94.7% of patients. At 6 months postoperatively, 72% of patients were continent. In patients who underwent bilateral nerve sparing, approximately 45% demonstrated spontaneous postoperative erections.

This same group provided an update on their experience after having performed 20 consecutive cases between January 1998 and December 1999 (393). In that series, the operating time was approximately 3 hours. The estimated blood loss was 250 mL, and the transfusion rate was less than 1%. The open surgical conversion rate was 0%. Postoperative pain was described as minimal, and analgesics were generally not required by postoperative day 2. These patients were discharged home without urethral catheterizations starting on postoperative day 3.

These investigators and others (1) have validated the feasibility of laparoscopic radical prostatectomy. Clearly, in experienced hands, the operation is technically feasible and associated with patient outcomes that appear to be in parity with standard radical retropubic prostatectomy. The potential advantages include a low risk for bleeding and subsequent transfusion, minimal postoperative pain, and rapid urethral decatheterization. The ultimate utility and safety of this approach awaits multiinstitutional confirmation.

Surgical Salvage Following Failure of Definitive Radiation Therapy

Available evidence indicates that a positive prostate biopsy performed more than 18 months after radiation therapy indicates failure of tumor control (870). For patients with stage A and B cancers, recognized local tumor recurrence or persistence 10 years after treatment may approach 36% in patients treated with interstitial and external beam therapy (871), and 26% after iodine-125 (^{125}I) seed implantation (284). It should be emphasized that these studies were not performed with the benefit of either serial PSA measurement or the use of systematic TRUS-guided biopsies. With use of these endpoint parameters, residual disease has been observed in more than 80% of patients having undergone radiation therapy with curative intent (960).

Both radical prostatectomy and cystoprostatectomy have been performed as “salvage” procedures in relatively small numbers of such patients (123,358,614,954).

Neerhut and associates (706) described their experience with salvage radical prostatectomy in 16 patients who failed an attempt at definitive radiation therapy for the treatment of stages A_2, B, and small C prostate cancers. Selection criteria included (a) excellent performance status; (b) a projected life expectancy of at least 10 years; (c) no previous systemic treatment that might mask occult metastases; and (d) the absence of demonstrable nodal, skeletal, or soft-tissue visceral involvement following a thorough staging

evaluation. Although no operative deaths were reported, several major complications were noted, including (a) rectal injury (19%), (b) anastomotic stricture (25%), (c) ureteral transection (6%), (d) stricture at the ureterovesical junction (6%), and (e) total urinary incontinence (25%). In addition, positive surgical margins were observed in 37.5% of patients, with the apical margin most frequently involved. Because the bladder neck margins were rarely problematic, the authors did not believe that radical cystectomy would have improved the overall results. The follow-up period was too short to permit a meaningful analysis of recurrence or survival figures.

Rainwater and Zincke (809) reported similar results in their series of 30 salvage procedures (radical prostatectomy, 27; radical cystectomy, 3). Again, no perioperative deaths were reported, but complications include bladder neck contracture (17%), lymphedema (10%), and total incontinence (10%). Eight patients were upstaged to a D_1 disease. Tumor progression and survival were most dependent on the DNA ploidy status of the tumor.

Rogers and associates (836) provided an update of the Baylor experience with salvage radical prostatectomy for locally recurrent prostate cancer. Forty patients were involved in that series. Most of these tumors were detected by DRE or by increasing serum PSA levels. They reported six (15%) rectal injuries, two of which required temporary colostomy. Of note, urinary incontinence persisted in 18 (58%) of 31 patients. Other serious technical complications occurred more frequently in those patients who had undergone PLND before radiation therapy as compared with the group treated with external radiation alone (31% versus 9%). Of interest, the preoperative PSA levels (but not clinical stage or biopsy grade) correlated most closely with pathologic stage. For those patients in whom the preoperative PSA was less than 10 ng/mL, only 15% had advanced pathologic stage, compared with 86% if the PSA was 10 or more. The best results were obtained in those patients in whom the prostate cancer was confined to the gland or the immediate periprostatic tissue. In that cohort, 82% exhibited no evidence of progression at 5 years.

With respect to operative preparation and technique, several points deserve special emphasis. A thorough mechanical and antibiotic bowel preparation is important to minimize the impact of pelvic contamination in the event of rectal injury. The frequency of rectal injury might be decreased by (a) initial separation of the prostate from the rectum via a perineal approach with completion of the procedure retropubically, (b) the use of a sterile O'Connor shield to permit free and repetitive access to the rectum if the retropubic approach is used exclusively, or (c) adoption of the Campbell (antegrade) approach to facilitate the mobilization of the prostate from the rectum. In the event of rectal injury, devitalized tissue should be excised, a precise two-layer closure performed, and the repaired laceration covered with omentum followed by dilation of the anal sphincter. If the repair is considered tenuous, a diverting sigmoid loop colostomy should be constructed.

More recently, Bochner and associates (76) described the feasibility of performing salvaged radical cystoprostatectomy and constructing an orthotopic urinary diversion in 18 patients in whom definitive radiation therapy for bladder (12) or prostate (6) cancer had failed. The terminal ileum, which demonstrated no evidence of radiation enteritis, was used for neobladder construction in 17 patients and sigmoid colon was used for pouch reconstruction in 1 patient. These investigators did not identify any difference between irradiated and nonirradiated patients with respect to operative characteristics, postoperative outcomes, and postoperative complications. Good day and night continence after surgery was reported by 67% and 56% of irradiated patients, respectively. Patients who exhibited poor postoperative urinary control were successfully treated by the placement of an artificial sphincter.

Pisters and associates (782) describe a technique of salvage prostatectomy with the construction of a continent catheterizable urinary reconstruction. The development of this technique was prompted by the high rate of total urinary incontinence that follows salvage radical prostatectomy (and salvage cryotherapy). In their approach, a wide dissection of the apical tissues is performed, including removal of surrounding skeletal muscle. Similarly, a wide proximal margin is obtained, with liberal transsection of the bladder neck just inferior to the trigonal complex. After completion of the salvage prostatectomy, the bladder neck is closed in two layers with interrupted 2-0 and 3-0 polydioxanone sutures. Reconstruction with an appendicovesicostomy to the native bladder was performed in nine patients. The appendix was mobilized based on its mesentery with the distal cecal tip. The appendix and an angulated component of adjacent cecal wall are transected using the GIA stapler. The appendix is dilated with Hegar dilators, to accommodate a 12- to 14-Fr catheter. Most often, the cecal end is anastomosed to the bladder, and the distal appendiceal tip is brought to the skin for the creation of a stoma; however, the reverse orientation also is feasible. In either event, a V-incision is made in the skin with the apex of the V sutured to a corresponding counterincision on the appendiceal tip. In four patients, an ileovesicostomy was performed in concert with the principles of a modified Monti procedure. In all cases, an omental pedicle flap was placed over the bladder neck closure area.

The authors cite no intraoperative complications. Four patients did experience serious complications requiring reoperation, including colovesicourethral fistula requiring delayed cystectomy; wound dehiscence with disruption of the appendicovesical anastomosis; leakage from the small bowel anastomosis that resulted in a septic death; and stomal stenosis requiring delayed revision. Of the 12 patients, 10 were dry at night and during the day with a catheterization interval of 2 to 6 hours. Two patients (17%) used pads for

incontinence. It would appear that this technique can be used successfully in properly selected patients. Indeed, this approach has several theoretic advantages. Bladder neck preservation permits normal ureterovesical function, prevents reflux, and minimizes upper tract infection/deterioration. In addition, bladder preservation avoids the risk of ureteral anastomotic strictures, which often complicate reconstructive surgery involving radiated ureters. Finally, this approach requires less extensive dissection than a standard cystoprostatectomy with urinary diversion, which may be advantageous in patients with significant medical comorbidities.

The limited number of patients reported does not provide an opportunity to assess the results of these attempts; it does indicate that the radical surgical procedures should not be excluded from the therapeutic options considered in this group of patients. Conversely, given the substantial morbidity attendant to these "salvage" attempts, the majority of these patients may be better served by the prompt initiation of endocrine therapy (152).

Neoadjuvant Hormonal Therapy Before Radical Prostatectomy

Approximately 50% of clinical stage T_2 prostate cancers are noted to be understaged at the time of step-section analysis. This critical and most challenging problem has prompted interest in neoadjuvant hormonal deprivation before radical prostatectomy. In most instances, this constitutes total androgen ablation using a luteinizing hormone–releasing hormone (LHRH) agonist (leuprolide) and an antiandrogen (flutamide) administered 3 months before anticipated radical prostatectomy. The goals of anticipatory treatment are essentially twofold. The first is to achieve downsizing of the prostate gland, which could conceivably facilitate its subsequent removal. Second, it is hoped that this therapy would "sterilize" microscopically compromised surgical margins (Fig. 33.75).

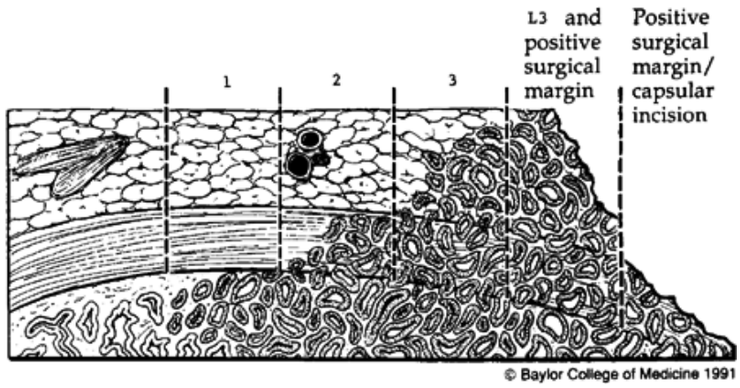

FIGURE 33.75. The various levels of capsular involvement are depicted. Cancer confined within the prostatic glandular tissue is designated level 0. Level 1 represents extension of cancer into the prostatic stroma beyond the level of normal glands. Extension of cancer into but not through the fibrous capsule is defined as level 2 involvement. Finally, extension of tumor into the periprostatic connective tissue, adjacent bladder, or skeletal muscle represents level 3 involvement. (Rosen MA, Goldstone L, Lapin S, et al. Frequency and location of extracapsular extension and positive surgical margins in radical prostatectomy specimens. *J Urol* 1992;148:331, with permission.)

Several investigators reported encouraging results with this approach. Monfette and associates (667) used total androgen ablation before radical prostatectomy in 34 patients and observed (a) a 55% decrease in prostate volume, (b) no pathologically detectable cancer in the surgical specimen in 10 of 34 patients, (c) a 30% to 40% decrease in operative time, and (d) a 50% decrease in operative blood loss. Soloway (947) also reported favorable preliminary results with this approach.

Despite its theoretic appeal, several studies question the ultimate utility of neoadjuvant hormonal deprivation in this setting. In a retrospective analysis, Oesterling and co-workers (725) compared 22 patients with clinical stage T_2 or T_3 CaP who underwent androgen deprivation therapy before radical retropubic prostatectomy to an appropriately matched patient who had not received preoperative endocrine therapy. In this study, the radical prostatectomy specimens from the two groups did not reveal any statistically significant differences with respect to maximal tumor dimension, pathologic stage, or DNA ploidy status. Moreover, it was felt that the serum PSA became an unreliable indicator of disease status after the initiation of preoperative androgen deprivation therapy.

More compelling is the prospective study conducted by MacFarlane and associates (612). In this study eight patients had clinical stage T_2 and 14 had clinical stage T_3 disease. All patients received 3 months of total androgen-ablative therapy. As determined by TRUS, an average 33% downsizing of the prostate gland was achieved. Similarly, the prehormonal therapy PSA values decreased significantly (30 ng/L versus 0.53 ng/L). Of the eight patients with clinical stage T_2 cancer, four had pathologic stage T_2 disease following the protocol. Of the 12 patients with clinical stage T_3 cancer, three had pathologic stage T_2 disease, four had positive pelvic lymph nodes, and the remainder had pathologic T_3 cancer. Only three (15%) of 20 patients in this study demonstrated pathologic downstaging from the clinical stage. Furthermore, preoperative hormone therapy did

not appear to simplify the radical prostatectomy. When compared with a group of 20 consecutive patients with stage T_2 prostate cancer who underwent radical prostatectomy without the preoperative hormonal deprivation, no significant differences were noted with respect to the average operating time or average blood loss.

Recently, Scolieri and associates (890) assessed the outcome of seven randomized prospective clinical trials designed to assess the impact of neoadjuvant hormonal ablative therapy before radical prostatectomy (Table 33.24). They noted a decreased rate of positive surgical margins in 6 of 7 of the randomized prospective studies. Of interest, in none of four randomized prospective series was the rate of seminal vesicle invasion improved. Three of four studies showed no improvement in the incidence of lymph node metastasis following neoadjuvant hormonal therapy compared with controls. Furthermore, no improvement in PSA-free survival was noted. Finally, the complication rates, operative time, operative blood loss, transfusion rates, and hospital stay were comparable in these two groups. This analysis failed to identify any significant improvement in outcome following the use of neoadjuvant androgen ablation, and its routine use before radical prostatectomy cannot be supported based on available data.

References	LHRH	Antiandrogen	Duration of Therapy (mo)
Witjes, et al.	Goserelin	Flutamide	3
Labrie, et al.	Leuprolide	Flutamide	3
Soloway, et al.	Leuprolide	Flutamide	3
Hugosson, et al.	Triptorelin	Cyproterone	3
Dalkin, et al.	Goserelin		3
Goldenberg, et al.		Cryproterone	3
Van Poppel, et al.[a]			1.5

Note: Studies cited are from original source.
[a]Estramustine was given.
LHRH, luteinizing hormone–releasing hormone.
Reproduced from Scolieri MJ, Altman A, Resnick MI. Neoadjuvant hormonal ablative therapy before radical prostatectomy: a review. Is it indicated? *J Urol* 2000;164:1465, with permission.

TABLE 33.24. IMPACT OF NEOADJUVANT HORMONAL ABLATIVE THERAPY BEFORE RADICAL PROSTATECTOMY

Results of Radical Prostatectomy

For properly selected patients (stage T_1, T_2), radical prostatectomy provides excellent results with regard to local disease control and the prospect for long-term, disease-free survival (Table 33.25). The majority of stage T_{1a} prostate tumors are detected in an elderly population for whom these cancers pose little risk of progression from a biologically indolent to aggressive tumor system. The same assurance cannot be provided to the young patient with localized CaP of the prostate incidentally detected. In these patients, the risk of neoplastic progression toward an aggressive and potentially life-threatening tumor (stage $T_{1a\text{-}b}$) is a legitimate concern (968), and radical prostatectomy should not be dismissed as a treatment option. Available evidence suggests that properly staged patients with T_{1b} prostate cancer are excellent candidates for radical prostatectomy. In the absence of regional lymph node involvement and capsular perforation, one can anticipate local recurrence rates of approximately 8% (40) and an overall clinical (non-PSA) cancer progression rate of approximately 10% (143). Elder and associates (266) reported equally favorable results in their analysis of 25 patients with stage T_{1b} prostate cancer. In this series, tumor was entirely confined to the prostate in 88% of the patients, thus suggesting a chance of long-term

cure equivalent to that of patients with pathologic stage T_2 disease. Previous TURP does not seem to have an impact on the morbidity of subsequent radical surgery, regardless of the time frame between one procedure and the other (40). Radical prostatectomy is much more difficult to perform within the context of a patient having undergone an open prostatectomy, unless the two procedures are performed within a week's time (154). In our experience, the procedure in these patients can be facilitated by using combined perineal and retropubic approaches.

Authors	Type of Prostatectomy	No. of Patients	Survival Rates (%)		
			5-yr	10-yr	15-yr
Jewett (*JAMA* 1968;203:115)	Perineal	103	74	50	35
Berlin, et al. (*J Urol* 1968;99:97)	Perineal	116	81	57	38
Kopecky, et al. (*J Urol* 1970;103:641)	Retropubic	73	73	50	
Belt and Schroeder (*J Urol* 1972;107:91)	Perineal	185	78	55	31
Hudson and Howland (*J Urol* 1972;108:944)	Retropubic	26	92	62	
Culp and Meyer (*Cancer* 1973;32:1113)	Perineal	162		72	54
Williams, et al. (*J Urol* 1975;113:380)	Perineal	52	75	35	10
Correa, et al. (*J Urol* 1977;117:328)	Perineal	67	92	79	62
Veenema, et al. (*J Urol* 1977;117:330)	Retropubic	93	90	55	39
Walsh and Jewett (*Cancer* 1980;45:1906)	Perineal	57			51

Adapted from Vadalament RA, Bahn DK, Lee F. Prostate cancer: an overview. In Crawford ED, Das S, eds. *Current genitourinary cancer surgery,* 2nd ed. Baltimore: Williams & Wilkins, 1997, with permission.

TABLE 33.25. SURVIVAL RATES FOLLOWING RADICAL PROSTATECTOMY FOR PROSTATIC CARCINOMA CONFINED WITHIN THE CAPSULE

The superiority of radical prostatectomy as a curative modality receives its greatest support from long-term follow-up studies conducted in patients with stage T_2 tumors who have undergone such treatment. In 1980, Walsh and Jewett (1060) reported on the Johns Hopkins experience assessing the efficacy of radical perineal prostatectomy in patients with clinical stage T_{2a} prostate cancer. Although PLND was not performed in these patients, the 15-year disease-free survival rate reported in this study is 51%. In fact, only 10 (17%) of the 57 patients with T_{2a} tumor subjected to radical prostatectomy by the Johns Hopkins group had documented residual tumor activity in a 15-year follow-up.

In 1979, Hodges and associates (426) reported similar 15-year disease-free survival rates. The efficacy of radical prostatectomy in this subset of patients also is supported by an analysis of the data generated by the Mason Clinic experience. Fourteen of 26 patients were alive 15 years following radical perineal prostatectomy. Of these, 13 were disease free. In the latter series, local recurrence was documented in 5% of 195 patients involved in the study (352,354). Catalona (154) cites an incidence of local recurrence of 7.4% to 9.0% in patients with stage T_1 or T_2 disease subjected to radical prostatectomy. Obviously, such a development is more likely in those patients in whom a portion of apical prostate is inadvertently or deliberately retained. This supposition is based on a study of Byar and Mostofi (112), who documented tumor involvement in the prostatic apex in 75% of cases. Again, properly selected patients with true pathologic stage T_2 tumors fare well after radical prostatectomy. In 1982, Elder and associates (267) reported a 50%, 15-year disease-free survival rate in such patients. These results are contingent on proper patient selection, excluding those with recognized extracapsular disease and regional lymph node involvement.

Walsh and associates (1062) reviewed their experience with 955 men with clinical stages T_1 and T_2 prostate cancer who underwent radical retropubic prostatectomy between April 1982 and March 1991. Using actuarial analysis, the likelihood of maintaining undetectable serum PSA levels at 10 years was 70%. During this same time, biochemical (PSA) relapse was observed in 23%, distant metastases in 7%, and local recurrence in 4% of this cohort. With respect to local recurrence, Pound and associates (796) reviewed the clinical course of 1,916 consecutive men followed during a 14-year period after radical prostatectomy performed at the Johns Hopkins Hospital. Fifty-six men (2.9%) had evidence of local recurrence an average of 6.1 ± 2.7 years following surgery. The mean serum PSA at the time of local recurrence was 5 ng/mL. Of importance, no man had local recurrence with an undetectable serum PSA level. Of interest, 25% of patients exhibiting local disease recurrence maintained undetectable serum PSA levels at 5 years of follow-up, but subsequently exhibited biochemical and clinical relapse. Based on these observations, it was recommended that neither the DRE nor imaging studies be performed in men with undetectable PSA levels following radical prostatectomy provided the patient has had the annual rectal examination recommended for colorectal cancer screening. This caveat is important because, in our experience, most internists appropriately rely on us to examine the rectum. When a subset analysis was performed, the 10-year likelihood of freedom from PSA relapse was 85% for men with organ-confined disease, 82% with focal capsular penetration (perforation), 54% with established capsular penetration (perforation) and a Gleason score of 2 to 6, 42% with established capsular penetration and a Gleason score of 7 to 10, and 43% with seminal vesicle involvement. The generic validity of this relapse risk data was reinforced by the study conducted by Catalona and Smith (150) that involved a series of 925 consecutive men with clinical stage T_1 and T_2 prostate cancer. Of note, the 5-year nonprogression rate was higher in patients whose tumors were not palpable (90% for impalpable tumors detected following TURP, 97% for clinical T_{1c} tumors, and 74% for palpable lesions). They also noted that the nonprogression was closely correlated with pathologic stage.

The role of radical prostatectomy in the treatment of patients with stage T_3 and N^+ disease remains controversial at this time. In the Mayo Clinic experience a combination of radical prostatectomy and androgen ablation (orchiectomy) in patients with stage T_3 and N^+ disease permitted projected 5- and 10-year survival rates in parity with expected survival figures for patients with DNA diploid tumors (894,1143). Such a multimodal approach to locally aggressive or regionally metastatic prostate cancers is indeed intriguing and warrants further consideration. It is currently our impression (and that of others) that achieving optimal control of the primary tumor is an important consideration in those patients with locally advanced and regionally metastatic tumors. This concept, coupled with increasing proficiency in the management of technically challenging cases, has served as the impetus for recommending radical prostatectomy to selected patients with stage T_{3a-b} CaP with or without N^+ disease. In this setting, it is viewed as the first component of a multimodality treatment plan, which may include androgen ablation and adjuvant radiotherapy. Obviously, prospective, randomized clinical trials will be required to rigorously assess the role of radical prostatectomy

in such patients. At present, we use this approach in a highly selective fashion.

The nerve-sparing approach has been criticized in some quarters because of the possibility of compromising surgical margins. Obviously, preservation of the neurovascular bundles should not take precedence over the dictates of pristine cancer surgery. The routine use of intraoperative frozen section taken from the posterolateral aspects of the resected specimen and the bladder neck should mitigate against retention of diseased tissue. As discussed in the section on radiation therapy, microscopically compromised margins and local recurrence can often be managed effectively using external beam radiation therapy, particularly if such intervention is initiated promptly (33,557,813).

The routine availability of serum PSA testing has altered our perceptions regarding disease control. All surgeons are aware that within 4 to 6 weeks of a putatively curative radical prostatectomy, the serum PSA levels should revert to undetectable by conventional assay methods. Several studies have emphasized the serious implications of detectable serum PSA levels following radical prostatectomy. Lightner and associates (585) evaluated 63 patients with abnormal PSA levels 6 to 240 months after radical prostatectomy who by all other criteria were considered to have no evidence of disease. Six patients were ultimately noted to have metastatic disease to bone and/or lymph nodes. Of interest, local CaP also was discovered in five of these patients. The remaining 57 patients were deemed free of obvious disease by all criteria except elevated PSA levels. Ultrasound-guided biopsies of the perianastomotic region were obtained and revealed local disease in 42%. Of note, no local disease was documented in 30 patients who had undergone radical prostatectomy and had normal PSA levels. In an analogous study, 43 patients with persistently elevated PSA levels and negative bone scans underwent both DRE and TRUS. Of 43 patients, 22 (51%) had evidence of persistent disease on ultrasound-guided biopsies. Surprisingly, 21 (95%) of these 22 exhibited an abnormal hypoechoic region adjacent to the bladder, retrotrigone, or perianastomotic site. The DRE was suspicious in only 10 (45%) of 22 patients. Finally, among ultrasound-detected recurrences, 15 (68%) were detected at the first biopsy and 7 (32%) at a subsequent biopsy.

The study conducted by Trapasso and associates (1024) suggests that determination of the postprostatectomy PSA doubling times may provide useful information. For example, the median postprostatectomy PSA doubling times for patients who ultimately progressed to distant metastasis was 4.3 months. This compared with a median value of 11.7 months for those patients who either exhibited clinical local recurrence or who maintained a PSA elevation as a sole indicator of recurrence. With respect to the latter issue, a study conducted by Kassabian and associates (490) is of interest. These investigators collected fresh prostatic secretions from radical prostatectomy specimens immediately after removal. All patients had clinical stage T_1 and T_2 prostate cancers. Eleven (14%) of 76 samples contained malignant cells. Six (55%) of eleven cancers with a Gleason score of 8 to 10 in the prostatectomy specimen had a positive cytology result. In contrast, only 4 of 62 tumors with a Gleason score of 5 to 7 exhibited positive cytologies. It is implied that malignant cells shed during prostatectomy may seed the surgical bed and be responsible for some instances of local tumor recurrence. In the majority of instances, however, it is likely that specimens with grossly or microscopically comprised surgical margins are responsible.

Recently, Pound and associates (796) assessed the time course of disease progression in men with biochemical recurrence following radical prostatectomy. This cohort consisted of 1,997 men who underwent radical prostatectomy, by a single surgeon (Patrick Walsh, M.D.), for clinically localized CaP. None of these men received neoadjuvant therapy and none received adjuvant hormonal therapy before the documentation of distant relapse. The actuarial metastasis-free survival for all 1,997 men was 82% at 15 years following surgery; 315 of 1,997 (15%) developed PSA relapse. Eleven patients were excluded from the study because they underwent early hormonal therapy after documentation of biochemical relapse. Of 304 remaining patients, 103 (34%) developed metastatic disease. The median actuarial time to metastasis was 8 years from the time of PSA elevation. Time to biochemical progression (less than or equal to 2 versus greater than 2 years), Gleason score (greater than or equal to 8 versus less than 8), and PSA doubling time (less than 10 versus greater than or equal to 10 months) were predictive of the probability and time to development of metastatic disease. Following the onset of metastatic disease, the median actuarial time to death was 5 years.

The somewhat analogous study of Jhaveri and associates (470) analyzed the outcome of 1,132 consecutive patients who underwent radical prostatectomy for localized disease: 213 of 1,132 (19%) exhibited biochemical failure. Of this group, 99 patients received androgen ablation and/or radiation therapy at the time of biochemical failure. In this study, the 10-year overall survival rates for patients with biochemical failure (88%) versus no biochemical failure (93%) were statistically similar. These authors concluded that at 10 years, patients with PSA recurrence after radical prostatectomy for localized disease exhibit an excellent overall survival that may be equivalent to those without a detectable postoperative PSA.

D'Amico and associates (204) identified several independent predictors of time to PSA failure following radical prostatectomy, including percentage of positive prostate biopsies at diagnosis of greater than 34%, preoperative PSA level greater than 10 ng/mL, seminal vesicle invasion, prostatectomy Gleason score of 8 to 10, and a positive surgical margin. De la Taille and associates (219) documented that the presence of perineural invasion is statistically correlated with PSA recurrence. In their study, Kaplan-Meier analysis

revealed disease-free survival rates of 24% versus 64% when perineural invasion was and was not present in presurgical biopsy specimens. However, when perineural invasion was compared with postoperative parameters, including disease stage, surgical margins, and seminal vesicle invasion, it was not an independent predictor because of its close correlation with tumor stage. Southwick and associates (953), using a multivariate logistic regression analysis, demonstrated that percent free PSA was the strongest predictor of postoperative pathologic outcome, followed by biopsy Gleason sum and patient age. In this study, organ-confined cancer, Gleason sum less than 7, and small tumors (involving less than or equal to 10% of the prostate volume) were noted in 75% of patients with percent free PSA levels greater than 15%. These favorable parameters were noted in only 34% of patients with percent free values of 15% or less.

Oefelein and associates (722) reported evidence of hematogenous dissemination of prostate cells during radical prostatectomy by using RT-PCR. In a follow-up analysis, Oefelein and associates (721) demonstrated that a positive RT-PCR result from a peripheral venous blood sample 12 months after radical prostatectomy was not associated with prostate cancer progression at a median follow-up of 22 months. Indeed, no significant correlation was observed between a persistently positive RT-PCR result and biochemical failure. They conclude that although a significant proportion of men have biochemical evidence of hematogenous prostate cell dissemination intraoperatively, the longitudinal molecular and clinical follow-up demonstrated reconversion to a negative status as the predominant trend following radical prostatectomy. It seems likely that further insight (and perhaps confusion) will be generated with the advent of assays for urinary PSA levels (226) and RT-PCR methods for the detection of PSA and PSMA mRNA in circulating tumor cells (457,492).

Cryotherapy

Gonder and associates (369a) pioneered the use of transurethral cryosurgery in 1966. Their approach was a blind procedure unsuitable for the treatment of CaP that occupied the peripheral zone of the gland. In 1969, Flocks used a standard perineal exposure of the prostate for the controlled application of cryotherapy under direct vision. This technique possessed intuitive appeal, in that the bulk of the primary tumor and its periprostatic component might be destroyed while preserving the structural and functional integrity of adjacent structures. The temperature at the tip of the cryosurgical probe approaches –180° to –190°C and produces tissue death by various mechanisms, including intracellular dehydration, electrolyte imbalance, crystallization with membrane rupture, protein denaturation, thermal shock, and vascular stasis (596).

Although proponents suggest that this mode of therapy provides a survival advantage equivalent to that of radical prostatectomy at the 5-year level (78), they currently assess its greatest utility to be in the palliative management of large bulky tumors or for local disease control in patients too debilitated to undergo conventional treatment. Loening and Lubaroff (596) reported a total surgical mortality of 1.9% in a series involving 215 patients. However, major complications do arise and consist predominantly of urethrorectal and urethrocutaneous fistulae, which occur in approximately 10.7% of patients. Most of the latter have been successfully treated by prolonged catheter drainage and curettage of the fistula tract.

In addition to the local cytodestructive effects, some investigators have proposed that cryodestruction of the prostate may result in the release of tumor-associated antigens and provide a form of active specific immunotherapy (395). The latter implies an induction of a host immune response as a result of direct exposure to these tumor-associated antigens. The majority of studies, however, have failed to confirm an immunologic response that can be causally linked to cryotherapy (657). Furthermore, most studies have failed to document a systemic antitumor effect attendant to prostatic cryotherapy, despite sporadic reports to the contrary (937).

Open perineal cryosurgery of the prostate has now been supplanted by ultrasound-guided percutaneous cryoablation of that organ. The latter technique relies upon TRUS to facilitate the transperineal placement of 5 to 6 cryoprobes using a stepwise-modified Seldinger technique (563,735). Both liquid nitrogen and gas (argon-based) systems are available to induce freezing, which is dynamically monitored on TRUS and is perceived as an expanding hyperechoic rim that ultimately approaches the rectal mucosa. Damage to the latter is thought to be minimized by proper ultrasound monitoring and facile manipulation of the transducer so as to increase the space between the rectal mucosa and the prostatic capsule. A urethral warming catheter is used in an attempt to diminish injury to that structure. Optimal positioning of the cryoprobes is contingent upon knowledge of tumor location, sites of obvious extracapsular extension, the size of the tumor, and gland geometry (563). Thermosensors also are used to monitor the cryosurgical “iceball” and to determine the number of freeze-thaw cycles required. It has been advocated that large prostates be treated with combined androgen ablation to downsize the gland, which facilitates the cryoablative process.

The data generated to date by these efforts have been limited. Miller and associates (659) performed a retrospective chart review of 62 cryosurgically treated patients with presumed clinical stage C prostate cancer. Of note, only 12 of these patients had histologically confirmed negative lymph nodes. Because of the locally advanced nature of the diseases, cryoprobes were frequently placed outside of the prostate laterally or extended into the seminal vesicles to treat presumed areas of tumor involvement. The authors report an average hospital stay of 2 days and minimal morbidity. With respect to the latter, they

note sloughed urethral tissue (1.3%), urinary incontinence (2.7%), prolonged urinary retention (1.3%), and urethral stricture (1.3%). Posttreatment biopsies revealed no residual detectable prostatic tumor in 94.8% of patients 3 months after one or two such treatments. The median pretreatment serum PSA was 8.90 ng/mL. In comparison, the median postoperative PSA was reported to be 0.10 ng/mL. In addition, 14 of 23 patients with 1 year or more of follow-up who have maintained negative biopsy status also maintained undetectable serum PSA levels (less than 0.4 ng/mL).

Onik and associates (736) used a similar approach in the treatment of 55 patients with presumed localized prostate cancer. The patients were randomized to two groups. In the first group, freezing was performed using two cryoprobes placed multiple times. In the second group, the tumor was frozen using five cryoprobes (3 mm in diameter) placed simultaneously. The study confirmed the superiority of the latter technique. Of the 55 patients, 23 had 3 months of follow-up with posttreatment biopsies. In the group treated with the 5-probe technique (15 patients), only one (6.7%) demonstrated evidence of residual disease on biopsy. Reported complications included rectal freezing, urethrorectal fistula, sloughing of urethral tissue, perineal ecchymosis, penile edema, ileus, and impotence. With respect to the latter, two-thirds of the patients who were potent before the procedure became impotent after treatment.

De la Taille and associates (218) reported on the impact of cryoablation for clinically localized CaP using an argon-based system. In this study, 35 patients underwent cryoablation of the prostate. Nineteen had received and failed radiation therapy. Cryoablation was used as primary treatment for localized CaP in the remaining 16 patients. All patients received 3 months of combined hormonal therapy before cryosurgery. Twenty-two patients (63%) had an undetectable serum PSA nadir after cryotherapy and 30 (84%) patients had a PSA value of less than 1.0 ng/mL. The mean follow up was 8.3 months. The biochemical recurrence-free survival was 70% at 9 months. Achieving an undetectable PSA nadir was important in this regard. Similarly, patients with a preoperative serum PSA level of less than 10 ng/mL had a statistically higher biochemical recurrence-free survival than patients who had PSA levels of greater than 10 ng/mL (86% versus 42% at 9 months). Complications included rectal pain (26%), urinary infection (3%), scrotal edema (12%), hematuria (6%), and incontinence (6%).

Shinohara and associates (913) reported on the outcomes of 134 patients who underwent 147 cryosurgical ablation procedures for the management of prostate cancer. In their analysis, a PSA nadir of less than 0.4 ng/mL should be achieved following cryotherapy. Higher values were associated with a significant risk of continued PSA elevation and a high likelihood of residual disease detected on prostatic biopsy. Local failure was most often noted at the apex and in the region of the seminal vesicles. Neoadjuvant androgen blockade appeared to reduce the risk of biochemical failure in patients with T_1 and T_2 cancers.

Long and associates (599) reported on the preliminary outcomes of 145 consecutive patients undergoing cryosurgical ablation of the prostate. The minimum follow-up was 12 months and the mean follow-up was 36 months in this cohort. Patients with clinical stages T_{1a} $2T_{3c}$ prostate cancer were included. The overall actuarial rates at 42 months for maintaining PSA less than 0.3 and less than 1.0 were 59% and 66%, respectively. The overall actuarial progression-free rate at 60 months was 56%. Not surprisingly, significantly higher morbidities were seen in previously radiated patients undergoing cryosurgical prostate ablation compared with those who had not undergone previous radiation therapy.

The limited follow-up of these and other patients treated with percutaneous freezing makes any meaningful assessment of the ultimate utility of this technique difficult. At this time, cryoablation and its evolving modifications should be viewed cautiously. In addition, the treatment of patients with progressive disease following prostate cryoablation is a significant concern. In our experience the performance of “salvaged” prostatectomy following failed cryoablation is a technically demanding procedure. In most instances, the patient is already impotent. The major postoperative complication in this context is urinary incontinence, which occurs with distressing frequency. The soft tissue changes induced by cryoablation are in parity with those induced by high-dose radiation therapy. This may very well contribute to problems with postoperative urinary control and healing. The use of external beam radiation (with or without neoadjuvant hormonal therapy) has more intuitive appeal as a salvage option but the ultimate efficacy of radiotherapy has not been rigorously addressed.

Electrohydraulic shock waves, high-frequency ultrasound, and hyperthermia also are being explored with respect to their cytodestructive potential (613). Obviously, any claims regarding antitumor efficacy should be subjected to rigorous scientific scrutiny.

Palliative Surgery

Scrotal Orchiectomy

The advantages and disadvantages of the various androgen-ablative techniques are discussed in detail under Endocrine Therapy. In our opinion, scrotal orchiectomy remains the standard against which all androgen-ablative techniques must be compared. None of the alternative approaches to orchiectomy has demonstrated superiority over this procedure. It has the following various advantages: (a) It can be performed quickly and comfortably with the patient under local anesthesia without mortality. (b) The morbidity, which includes superficial wound infection, scrotal hematoma,

wound disruption, and painful cord remnants, is low. (c) Other than its impact on libido, potency, and development of hot flashes and osteoporosis, the systemic effects of the procedure are modest. (d) Upon completion, concerns regarding patient compliance are obviated.

Orchiectomy can be performed by various approaches. We prefer a transscrotal approach through a transverse or midline scrotal incision with the patient under local anesthesia. Routine monitoring of vital signs and IV administration of a mild sedative (e.g., midazolam) can be initiated before the procedure. Following standard surgical preparation and draping, a local anesthetic such as 1% lidocaine or equal volumes of 1% lidocaine and 0.5% bupivacaine (Marcaine) should be injected superficially and into the cord at the base of the scrotum and as a field block at the site of the incision. The skin, dartos, and intervening tunics are incised until the parietal layer of the tunica vaginalis is identified. An extravaginal or intravaginal dissection can be carried out to deliver the testes gently and expose the spermatic cord. The local anesthetic is sprayed or injected appropriately as the cord is freed, isolated into segments by blunt and sharp dissection, clamped securely, and divided. The testis with the adjacent epididymis and distal cord is then removed. It is our practice to doubly tie the cord remnants with a free tie and a suture ligature of chromic catgut. Occasionally, a patient will request insertion of a testicular prosthesis, and this can be done at this time. Additional hemostasis and comfort can be provided by the application of a bulky compressive dressing that can be maintained by the use of elastic-type compression applied in a crossing fashion from the posterior aspect of the buttock to the lower abdomen. Although subepididymal and subcapsular orchiectomy have had their advocates in the past, simple complete orchiectomy as described earlier is our preference.

Channel Transurethral Prostatic Resection

Not infrequently, the elderly patient with locally aggressive or metastatic CaP will be seen with symptoms of significant bladder neck obstruction or acute urinary retention. As discussed in the section on endocrine therapy, the initiation of androgen withdrawal therapy will permit the resolution of obstructive symptoms in most of these patients within 3 to 6 months. If symptoms are severe, patients can be maintained on urethral or suprapubic catheter drainage during this period. Such an approach is reasonable in patients deemed too high a risk for the anesthetic and surgical stress associated with a channel TURP. However, most patients who have significant obstructive sequelae are anxious to achieve a catheter-free status quickly. The majority of patients who are deemed good surgical risks are candidates for channel TURP and scrotal orchiectomy as a combined procedure. The technique of endoscopic resection has been thoroughly discussed in the previous chapter. The urethra may be fixed, rigid, and strictured. When such difficulty is encountered, it may be best to use a smaller (24 Fr) sheath rather than traumatize the friable tissue lining the elongated and irregular prostatic urethra. At times, the resectoscope may best be introduced under direct vision or may need to be introduced over a catheter guide with the bladder full. Once access to the bladder is provided, careful endoscopic inspection of the regional anatomy is imperative. The trigone and ureteral orifices should be identified, if possible, although tumor extension in this area may obliterate normal landmarks. Administration of IV indigo carmine may help identify the ureteral orifices. The verumontanum is usually distinct, but occasionally, the resectionist needs to use rectal palpation to confirm the zone of the external urethral sphincter. The procedure should establish a circumferential channel through the obstructing tissue; in some cases it will be possible to perform a relatively clean endoscopic resection down to the capsule. In other cases, normal landmarks will be obliterated. The goal of the procedure is to achieve satisfactory voiding with control. In previously untreated patients, endocrine control measures usually produce a further reduction in the obstructive symptoms and sequelae.

Radiation Therapy

The first reported application of ionizing radiation for the treatment of CaP was that of Paschkis and Tittinger (750). These investigators used a radium capsule that was attached to a cystoscope, with the latter being positioned in the prostatic urethra for the duration of treatment. Soon thereafter Hugh Young devised radium carriers that were adaptable for intrarectal and intraurethral use. He used interstitial radium needles for the treatment of CaP and reported his technique and results in 1922. Since then, radiation therapy has assumed an important role in the treatment of locally contained and metastatic CaP.

External beam radiation therapy using high-energy photons (x-rays) or heavy-particle beams (neutrons and protons) may provide potentially curative therapy. Routine use of CT scans and computer-based image analysis to construct dosimetry portals has enhanced the safety and efficacy of these approaches. The development of 3D, conformal treatment planning holds additional promise in this regard (580). Similarly, TRUS-guided interstitial radiation therapy (^{125}I and ^{103}Pd) (103,801,1057) has replaced earlier open-implantation approaches (120,1089). These “guided brachytherapy” techniques are associated with more precise seed distribution and an apparent improvement in local disease control. External beam therapy also appears to enhance local disease control as an adjunct to radical prostatectomy when the surgical margins are shown to be compromised on step-section analysis of the postoperative specimen. From a purely palliative standpoint, radiation therapy has demonstrated utility in the management of pain secondary to skeletal metastases, the relief of ureteral

and bladder neck obstruction, and the prevention of painful gynecomastia attendant to the use of estrogen. This section presents a brief analysis of these areas.

General Principles of Radiation Biology

According to conventional nomenclature, 1 gray (Gy) is equivalent to the deposition of 1 joule of energy per kilogram of tissue and equals 100 rad. The latter had constituted the unit of absorbed dose formally used (580). It is now well established that double-strand breaks in the DNA molecule account for most radiation-induced cytotoxicity (269). The M phase and the boundary between G_1 and S phases are the most sensitive to radiation (730,921). Conventional radiation therapy involves the production of high-energy photons that induce these double-strand DNA breaks indirectly through the generation of free radicals, with only a small component of impact attributable to direct DNA damage (398). Thus for optimal effects, the tumor target should be of low volume, well vascularized, and well oxygenated.

Protons are particles of approximately 1,835 times the mass of the electron and carry a single positive charge (991). As was the case with photons and electrons, protons interact primarily by ionization. Indeed, only approximately 2% of their energy is deposited through direct nuclear interactions (924). The point of distinction is that photons and electrons exponentially deposit energy as they travel through tissue, which accounts for significant secondary lateral scatter that mandates use of multifield arrangements. The therapeutic advantage of protons resides in the superior controllability of the beam, which permits deposition of maximum energy within the designated volume from a single port (924).

In distinction, neutrons appear to directly damage DNA and therefore are less dependent on the presence of oxygen to accomplish cell killing. For these reasons neutrons are potentially more advantageous in the treatment of bulky necrotic tumors. In addition, neutron injury to DNA appears to be less reparable than photon-induced injury, and neutron-irradiated cells tend to exhibit less variation in radiation sensitivity across the cell cycle.

In addition to the direct/indirect impact of high-energy photons and heavy particle beams (protons, neutrons) in the breakage of DNA strands, evidence has accumulated that radiation induces programmed cell death (apoptosis) as an additional mechanism, culminating in cellular death (580). The latter is now perceived to be a dynamic process characterized by (a) volume reduction accompanied by an increase in cell density, convolution, and blebbing of the cell surface; (b) chromatin condensation and nucleosomal fragmentation associated with the activation of an endogenous calcium, magnesium-dependent endonuclease; (c) recognition by phagocytic cells; and (d) a dependence upon active protein synthesis (1109).

Figure 33.76 illustrates the classic pathway for apoptosis induction and cell death. It is now evident that tumor-suppressor mutations, oncogene activation, and growth factor signaling all modulate the induction of apoptosis by ionizing radiation (838). It is not fully appreciated how cells actually “sense” the single-and double-stranded DNA breaks associated with exposure to ionizing radiation. In most instances p53 protein activation is a critical early event in this process. DNA damage induced by ionizing radiation results in the binding and activation of several phosphatidylinositol-3–like nucleoproteins. The latter include ataxia-telangiectasia mutated protein (ATM), ATM-related protein (ATR), and DNA-dependent protein

kinase (DNA-PK). These products result in the modification and activation of p53 and its downstream target genes (838). A unique 393-amino acid phosphoprotein, p53 contains distinct domains that mediate transcription activa- tion sequence-specific DNA binding, recognize DNA dam- age, and activate the p53 molecule itself, as well as protein–protein interactions. The intracellular accumulation of p53 is in large part attributable to an increase in its nuclear half-life. Transcription activation mediated by p53 involves the binding of this molecule to a consensus sequence in target genes. The latter encode proteins that are strategic for completion of the cell death pathway and include (a) Bax, the inhibitory binding partner of bcl-2, which pushes cells into apoptosis; (b) IGF-binding protein 3, which binds IGF-I and prevents it from activating an antiapoptotic signaling pathway; (c) $p21^{WAF1/CIP1}$ induces G_1 arrest; (d) Gadd45, which promotes cell cycle arrest and DNA repair; and (e) murine double minute-2 (Mdm-2), which promotes late inactivation of p53 transcriptional activity. These events are summarized in Fig. 33.77 . The apoptosis-activating factors (APAFS1-3) mediate deoxyadenosine triphosphate-cytochrome c-dependent cleavage of procaspases into active enzymes. Ultimately, activation of an enzyme (flipase) induces the translocation of phosphatidylserine from the inner to the outer cell membrane. The latter is then recognized by annexins on the surface of macrophages, which results in the elimination of apoptotic cells by phagocytosis so that they do not provoke an inflammatory response (838).

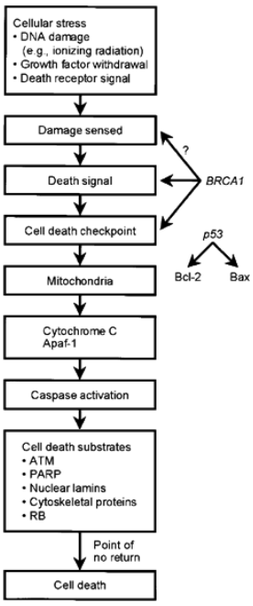

FIGURE 33.76. Classic pathway for apoptosis and cell death. ATM, ataxia-telangiectasia mutated protein; PARP, poly (adenosine diphosphate ribose) polymerase; RB, retinoblastoma tumor-suppressor protein. See discussion in text. (From Rosen EM, Fan S, Goldberg ID, et al. Biological basis of radiation sensitivity. Part 2: cellular and molecular determinants of radiosensitivity. *Oncology* 2000;14:741, with permission.)

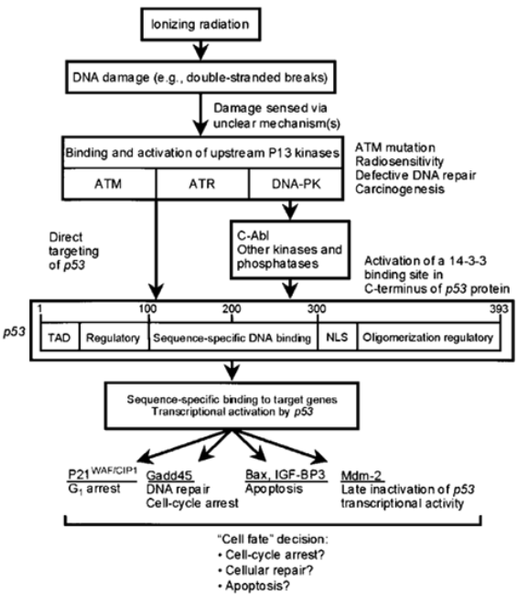

FIGURE 33.77. Small p53-dependent DNA damage response pathways activated by ionizing radiation. DNA damage induced by ionizing radiation causes binding and activation of several phosphatidylinositol-3–like nuclear proteins (ATM, ATR, DNA-PK), resulting in modification and activation of small p53 and its downstream target genes. See text for discussion. (From Rosen EM, Fan S, Goldberg ID, et al. Biological basis of radiation sensitivity. Part 2: cellular and molecular determinants of radiosensitivity. *Oncology* 2000;14:741, with permission.)

Radiation-resistant Phenotype

Irradiated cells arrest for several hours in the G_2 phase of the cell cycle before entering the M phase, which appears to be related to a transient, radiation-induced diminution in the protein cyclin B, which is required for this traverse through the cell cycle (580). It appears that differences in cellular sensitivity to radiation-induced injury may be related to the successful evocation of repair mechanisms during this break in the cell cycle.

Radiation therapy appears to activate signal-transduction pathways mediated by protein kinase CN and tyrosine kinase, which in turn are responsible for the induction of a number of genes (c-fos, c-jun, EGR-1, BRCA1, NF-kB) and proteins (bFGF, TGF-ß, TNF, and TPA) (580). It is assumed that some of these molecular events are strategic to the cell survival following radiation injury.

The p53 gene is linked to the transition from the G_1 to the S phase of the cell cycle (61). It appears that wild-type (i.e., normal) p53 function is required for the sensitivity of many tumor cells to ionizing radiation. Moreover, loss of p53 function, which may occur through mutation, may be associated with resistance to radiation-induced cell killing (628). Most p53 mutations appear to be point mutations in the DNA-binding domain, which results in a mutant protein defective in sequence-specific DNA binding. These mutant p53 proteins fail to activate the Bax promoter. Loss of the ability to transactivate the Bax gene would translate into low levels of Bax protein, which is an important inducer of apoptosis (838). Of note, p53 mutations have been reported in both BPH and CaP specimens (79,166,412,704). With respect to the latter, p53 mutations appear to predominate in high Gleason histotype, androgen-independent, human prostate cancers of advanced stage (79,412,704).

As stated previously, radiation therapy can activate programmed cell death pathways that contribute to cell lethality. The bcl-2 protooncogene is unique in that its expression results in extending the viability of cells, independent of promoting cell division, by abrogating programmed cell death mechanisms (626). Bcl-2 prevents apoptotic death ordinarily induced by the c-myc protooncogene. A noteworthy feature of bcl-2 activity is its ability to block irradiation-induced cell death (902,986). This relationship is particularly intriguing given the fact that high-energy photons and protons produce hydroxyl radicals (the most reactive oxygen free radical species), which in turn induce

oxidative damage to macromolecules such as DNA. Evidence has accumulated that bcl-2 regulates an antioxidant pathway at sites of free radical generation and prevents the latter from inducing apoptosis (422). Bcl-2 is a pore-forming protein of the outer mitochondrial membrane. It is thought to block apoptosis by binding to Apif-1 and/or preventing the release of cytochrome C from mitochondria (838). It has been demonstrated that the bcl-2 protooncogene is constitutively expressed in the basal cells of the prostatic glandular epithelium (423), which, unlike the secretory epithelial cells, are unaffected by androgen withdrawal (549). McDonnell and associates (626) observed that bcl-2 was undetectable in 13 of 19 cases of androgen-dependent CaP. In contrast, androgen-independent cancers displayed diffuse, high levels of bcl-2 staining. The potential association between the latter finding and the emergence of radiation-resistant phenotype is most compelling.

Scherr and associates (881) performed immunohistochemical staining for bcl-2 and p53 on pretreatment needle biopsies in 54 patients who underwent radiotherapy for localized prostate cancer. In this study, a PSA nadir of less than 1 ng/mL after therapy was considered a successful treatment response. Of the bcl-2 and p53 positive cases, treatment failure was noted in 85% and 88% of patients, respectively. Indeed, a combination of both adverse phenotypes was associated with universal treatment failure. If these results are confirmed, it would suggest that probing of biopsy tissues for bcl-2 and p53 expression might facilitate treatment planning and help identify those patients whose tumors are constitutively radiation resistant.

These and other perceptions suggest that relative or absolute radiation-resistance may be a feature of human CaP systems endowed with the following features: (a) high tumor volume/stage (399); (b) high Gleason score (399,952); (c) aneuploid DNA content (952); (d) pretreatment PSA greater than 15 ng/mL (562); (e) androgen-independent tumor clones (1015); (f) mutated p53; (g) increased bcl-2 expression; and (h) increased tumor angiogenesis-microvessel density (399); and (i) specific growth factors such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor/scatter factor (HGF/SF), and IGF-I (838).

Conventional External Beam Radiation Therapy

Various sources have been used to generate high-energy photons ranging from cobalt 60 sources to the present-day linear accelerators. The advantages of the latter include the production of ionizing radiation with higher energy thresholds (4 to 35 MeV), which are capable of being focused onto the tumor target with greater precision and less attendant "scatter" distributed to the normal surrounding tissues.

Benefit-to-risk ratio of external beam radiotherapy is in large part contingent on the proper construction of the fields (portals) of radiation coupled with the timing and amount of ionizing radiation (dosimetry) delivered to the chosen tissues. Before the advent of CT scanning in the late 1980s, radiation oncologists were required to construct the treatment fields by hand. Obviously, the introduction of whole-body CT scanning made accurate, cross-sectional, anatomic imaging readily available (Fig. 33.78). The next major advance in the construction of dosimetry portals occurred in the 1980s with the application of computer-graphics technology to CT scanning, thus permitting the 3D display of regional anatomy, instead of the more traditional two-dimensional imaging (Fig. 33.79) (580). Although 3D conformal radiotherapy using heavy charge particle beams has been available for many years, this method has only recently been extended to external high-energy x-ray therapy (582). Consequently, most of the early data regarding the risks/benefits of external beam therapy have been generated using a four-field box technique popularized by Bagshaw (30,31) (Fig. 33.80). The technique is described briefly in the following paragraph.

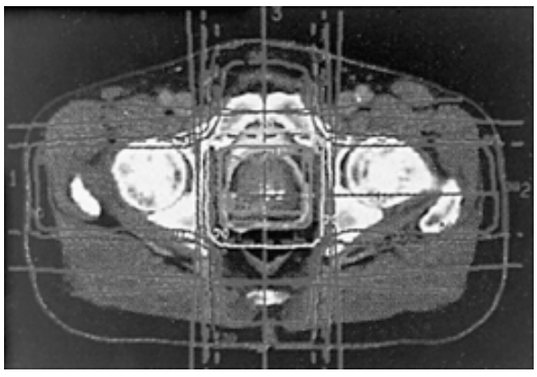

FIGURE 33.78. Example of a computed tomograph–based treatment plan in a patient with prostate cancer. This technique in concert with computer-assisted image analysis greatly enhances the accuracy of external beam radiotherapy. (From Lichter AS, Lawrence TS. Recent advances in radiation oncology [Review]. *N Engl J Med* 1995;332:371, with permission.)

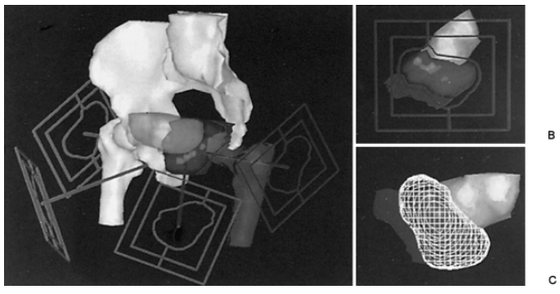

FIGURE 33.79. Three-dimensional treatment planning for radiotherapy of the prostate. **A** demonstrates a three-dimensional view of the pelvis and the orientation of four radiation beams contoured to treat the prostate precisely. **B** is a "beam's-eye-view display," which demonstrates the "view" of the prostate from the perspective of the radiation beam. **C:** Three-dimensional dose display. (Lichter AS, Lawrence TS. Recent advances in radiation oncology [Review]. *N Engl J Med* 1995;332:371, with permission.)

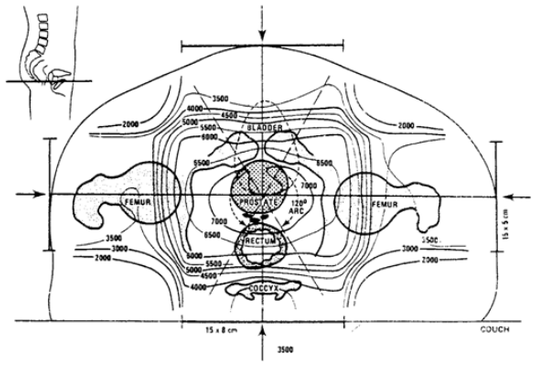

FIGURE 33.80. Anteroposterior and lateral portals of the four-field box technique used by the Stanford Radiation Oncology Group. Also illustrated are the left and right 120-degree lateral arcs for the prostatic boost. (From Bagshaw MA. External radiation therapy of carcinoma of the prostate. *Cancer* 1980;45:1912, with permission.)

Before highlighting the actual radiation portals with indelible ink, the bladder and rectum were identified by the instillation of contrast, a radiopaque marker was placed, and AP and lateral views of the pelvis were obtained. CT imaging was used for further clarification of the pelvic anatomy. Ultimately, the volume of tissue destined for irradiation was quantified. Bagshaw and associates (28) adopted a four-field box technique that was used to treat the pelvis and prostate, with a boost to the prostate delivered via either bilateral 120-degree arches or a four-field technique. The AP portals extended from L-5 to the ischial tuberosities and encompass the entire area of the true pelvis, including the lateral aspect of the iliac nodes bilaterally. The lateral portals

projected in the anterior half of the rectal lumen to the ventral portion of the iliac nodes while maintaining the same superior and inferior limits as described for the AP portals. Whole pelvic radiation was not required for patients who have undergone an antecedent PLND, and appropriate adjustments were made in the dosimetry portals. In general, the radiation therapy was delivered through an isocentric technique that entails a circumferential movement of the radiation source about the patient, who is maintained in a supine position. Pelvic dose has been estimated to range from 48 to 54 Gy and the prostatic dose from 68 to 75 Gy (487).

The Stanford group has reported that for organ-confined CaP (stages A and B), survival rates approach 81% at 5 years, 59% at 10 years, and 36% at 15 years. In the case of extracapsular (stage C) disease, the 5-, 10-, and 15-year projected overall survival falls to 62%, 36%, and 18%, respectively (31).

In 1988, Bagshaw and associates (27) updated their experience with radiation therapy in the treatment of more than 900 patients with prostate cancer. They reported an overall 15-year survival of 45%, 35%, 33%, 20%, and 10% for Stanford stages T_0, T_1, T_2, T_3, and T_4. Disease-specific survival at 15 years for the same patients was 85%, 64%, 45%, 33%, and 15%, respectively. For patients with stage B_1 cancer, the 15-year overall survival was 50%. Of those patients potent before therapy, 86% maintained potency at least 15 months after treatment and 50% for 7 years after therapy.

Hanks (404) has reported a more recent update on the effectiveness of external beam radiation therapy for organ-confined and locally advanced CaP. In this review, he reported on 104 patients with clinical T_{1b}, T_2 prostate cancer with pathologically negative lymph nodes who were treated with external beam radiation. In that study, observed actuarial survival of 87% and 63% were noted at 5 and 10 years, respectively. This contrasts with expected survival figures of 81% and 59% at those same time points. The study also demonstrated a cause-specific mortality of 14% at 10 years. Finally, 87% of patients were reported to be free of clinical recurrence at 10 years.

Hanks (404) also provides an analysis of the impact of external beam radiation on locally advanced T_{2b} CaP in his analysis of the 10-year results from Washington University and the 15-year results from Stanford. He reports a 10-year survival of 61% and 15-year relapse-free survival of 33% in this cohort. As anticipated, the results of external beam radiation therapy in the management of stage T_3/T_4 prostate cancers are less impressive. He demonstrated overall survivals of 35% to 45% at 10 years and 18% to 27% at 15 years. His latter observations were derived from an analysis of stage C CaP reported from multiple single institutions, the Radiation Therapy Oncology Group (RTOG) trials, and the Patterns of Care USA National Averages. It should be emphasized at this point that not all studies enthusiastically endorse the role of radiation therapy in the management of locally advanced CaP. For example, Paulson and associates (753) reported their series of 73 patients with stage C CaP who were randomized to either full-field pelvic irradiation or delayed hormonal therapy. When evidence of treatment failure was first used as an endpoint parameter, no difference could be discerned in disease response between the two treatment groups.

Similar controversy involves the role, if any, of radiation therapy in the treatment of patients with stage D_1 disease. Bagshaw (32) reported an actuarial survival of 58% at 5 years following external beam radiation therapy. On the other hand, Smith and colleagues (931) reported that only 17% of patients with stage D_1 disease who received external beam radiation therapy were free of disease at 5 years. Moreover, when compared with a similarly staged group of patients who did not receive radiation therapy, there was no discernible difference in disease-free survival or control of symptomatic manifestations of local disease. It would seem that nodal irradiation alone offers marginal benefit to these patients.

An element of controversy surrounds the advisability of TURP before definitive radiation therapy in patients with CaP presenting with symptoms of bladder outlet obstruction. Fowler and associates (308) stated that TURP may disrupt intraglandular lymphatic and vascular channels and increase the likelihood of tumor dissemination. McGowan's study (627) was perhaps the most condemning of TURP before the initiation of external beam radiation. In those patients with stage B or C disease, 5-year disease-free survival was reported to be 72% in the radiation-only group as compared with 51% in those patients having undergone prior endoscopic resection. In retrospect, these ominous statistics probably reflect the presence of a relatively greater local tumor mass in those patients with severe obstruction and the common perception that patients with obstructive symptoms from carcinoma have a higher incidence of disseminated disease. Furthermore, despite these theoretic concerns regarding the potentially deleterious impact of TURP before radiation therapy, no detrimental impact was documented in the studies conducted by Hoffmann and associates (428), Kuban and associates (540), Paulson and Cox (752), and Meacham and associates (636).

In patients in whom relief of bladder neck obstruction is deferred, only 10% of patients with stage C cancer required TURP after completion of definite radiation therapy (353). In general, we prefer to perform transurethral incision of the prostate (TUIP) or TURP before radiation therapy in patients whose severe obstructive/irritative voiding symptoms have not responded to androgen ablation and appropriate doses of a long-acting α_1-blocking agent. It is our belief that preemptive treatment is preferable to placement

of an indwelling catheter during the course of radiation therapy or in the immediate posttreatment period.

Conformal External Beam Radiation Therapy

The failure of high-energy photons to eradicate organ-confined CaP can occur for several reasons. First, it has been demonstrated that conventional, two-dimensional treatment planning often underestimates the true volume of the prostatic target, which results in inadequate treatment. Second, it is a common perception that radiation-resistant prostatic tumor clones develop with a relatively high frequency. It has been demonstrated that higher doses are required to improve local tumor control. However, standard treatment planning techniques are associated with significant complication rates if doses exceed 7,000 cGy because of their inability to adequately shield the bladder and rectum (570).

Advances in computer technology have enabled the implementation of 3D conformal radiation therapy (CRT) as an approach to overcome some of the obstacles encountered by conventional radiotherapy. Three-dimensional treatment planning is based on the ability to anatomically define each critical subvolume within the entire 3D space of irradiated tissues and to accurately calculate the dose delivered at each point (569). 3D CRT uses advanced imaging technology for tumor and normal organ segmentation and computer-aided optimization to generate treatment plans that conform the prescribed dose to the anatomic boundaries of the prostate target volume in its entire 3D configuration, while maximally excluding the adjacent normal organs (569). Indeed, the ability to reduce the volume of normal tissues that receive high radiation doses is a critical feature of 3D CRT.

The availability of 3D, computer-aided, “conformal” treatment planning permits precise targeting of the treatment field conformed to the shape of the prostate target (Fig. 33.81). In this approach, radiation beams are contoured to treat the prostate precisely, and the nontarget component of the rectangular radiation beam is blocked by a lead alloy to protect the adjacent normal structures. In addition, short-term observations indicate the dose delivered to target tissue can be increased by at least 10% to 20% without increasing the complication rate (570,580). Improved patient immobilization within individually fabricated thermoplastic casts (Fig. 33.82) and the use of real-time portal imaging devices are integral parts of this new technology (404).

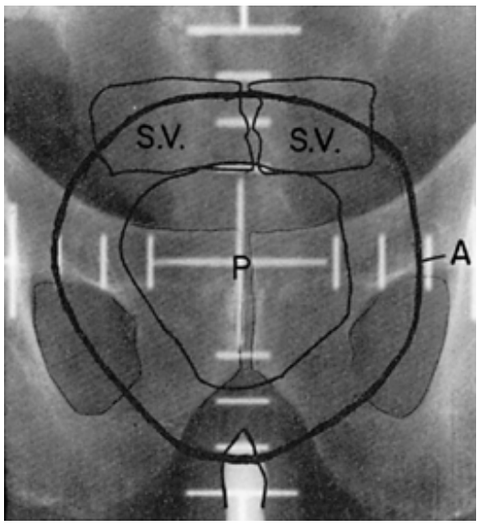

FIGURE 33.81. A-P simulator radiograph highlighting the prostate *(P),* seminal vesicles *(SV),* and portal aperture *(A).* Note that the urethrogram is outlined. (From Hanks GE. Treatment of early stage prostate cancer: radiotherapy. In: DeVita VT, Hellman S, Rosenberg SA, et al, eds. *Important advances in oncology.* Philadelphia: JB Lippincott, 1994, with permission.)

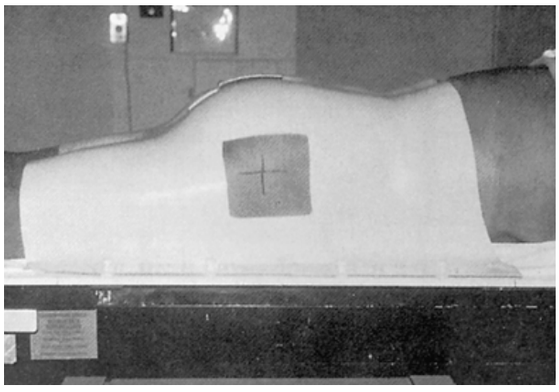

FIGURE 33.82. The development of conformal radiotherapy has been facilitated by the design of thermoplastic immobilization devices, as illustrated in this figure. [From Liebel SA, Heimann R, Kutcher GJ, et al. Three-dimensional conformal radiation therapy in locally advanced carcinoma of the prostate: preliminary results of a phase-I dose-escalation study. *Int J Radiat Oncol Biol Phys* 1994;28(1):55, with permission.]

Leibel and associates (570) reported their preliminary experience in 324 patients with CaP treated with 3D conformal radiation therapy in a phase I dose-escalation study. The treatment planning did not involve pelvic lymph node irradiation because of the absence of a proven benefit for that treatment extension (570). This study included patients with clinical stage T_1 to T_3 disease. Minimum tumor dose was 64.8 to 66.5 Gy in 87 patients, 70.2 Gy in 138, 75.6 Gy in 69, and 81.0 Gy in 30. Fifteen percent of patients required medication for relief of rectal symptoms and 34% for urinary symptoms. Only two (0.6%) patients experienced grade 3 to 4 late complications. The 3-year actuarial probability of survival with a normal serum PSA level was 97% for patients with stages T_{1c} and T_{2a}, 86% with stage T_{2b}, 60% with stage T_{2c}, and 43% with stage T_3 disease. A multivariate analysis demonstrated that biochemical relapse was likely in patients with an initial PSA greater than 20 ng/mL, stage T_3 or greater, and a Gleason histotype of 7 or more.

Three-dimensional Conformal Radiation Therapy and Intensity-modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) combines two advanced concepts to deliver 3D conformal radiation therapy: (a) inverse treatment planning with optimization by computer and (b) computer-controlled intensity modulation of the irradiation beam during treatment (1005,1128). Multiple IMRT beams with different profiles are used to achieve a composite with a homogenous dose distribution within the planning target volume. The addition

of IMRT to 3D CRT requires both hardware and software modifications that permit a coplanar, five-field technique designed to treat patients to prescription-dose levels of greater than or equal to 81 Gy, while at the same time minimizing the risk of significant rectal and bladder toxicity. Figure 33.83 depicts the impact of dose on local control as assessed by prostate biopsies performed at 2.5 years or longer following 3D CRT/IMRT. Studies by Zelefsky and associates (1128) demonstrate that use of IMRT is associated with an impressive reduction in both acute/late urinary and rectal toxicity in patients with prostate cancer treated to 81 Gy. Leibel and associates (569) also have confirmed the favorable impact of intensity modulation on the conduct of high-dose 3D CRT. Table 33.26 depicts the incidence of late complications by RTOG morbidity grade in 1,100 staged T_{1c} to T_3 prostate cancer patients treated with a combination of 3D CRT/IMRT to dose levels of 64.8 to 86.4 Gy.

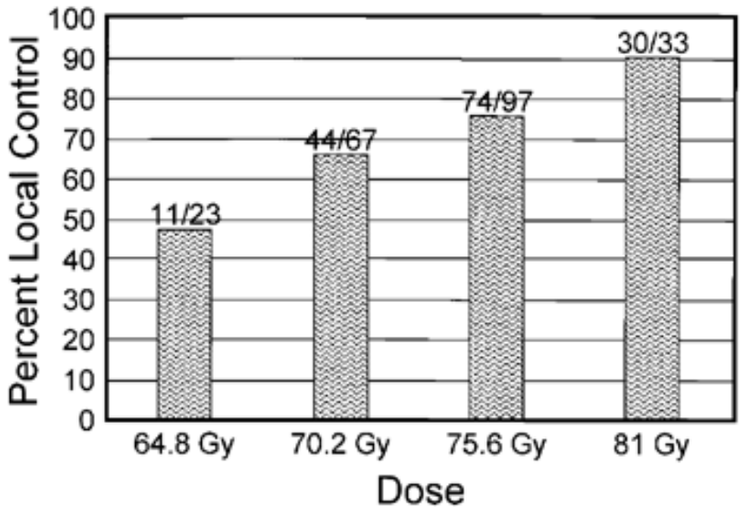

FIGURE 33.83. Impact of dose on local control, as determined by prostate biopsies performed greater than or equal to 2.5 years following 3D-CRT/IMRT. The number of patients with negative biopsy specimens per total number biopsied is depicted above each bar. [From Leibel SA, Fuks Z, Selefsky MJ, et al. *PPO Updates* 2000;14(10):1, with permission.]

	Complication No. of Patients/Total (%)	
Grade[a]	Rectal	Urinary
None	817/1,100 (75)	829/1,100 (75.5)
Grade 1	167/1,100 (15)	153/1,100 (14)
Grade 2	104/1,100 (9)	101/1,100 (9)
Grade 3	11/1,100 (1)	17/1,100 (1.5)
Grade 4	1/1,100	0

[a]RTOG morbidity grading system.
CRT, conformal radiation therapy; IMRT, intensity-modulated radiation therapy.
Adapted from Lawton CA et al. *Int J Radiat Oncol Biol Phys* 1991;21:935.

TABLE 33.26. INCIDENCE OF LATE COMPLICATIONS BY GRADE IN 1,100 STAGE T_{1C} to T_3 PROSTATE CANCER PATIENTS TREATED WITH 3D CRT/IMRT TO DOSE LEVELS OF 64.8-86.4 GY

Heavy Particle Therapy

Russell and associates (850) compared the efficacy of fast neutron radiotherapy used in a mixed-beam (neutron/photon) treatment schedule with conventional photon irradiation alone in 91 patients with stage C or D_1 CaP. Actuarial survival at 8 years was 63% for the mixed beam group and 13% for patients receiving only conventional treatment. Furthermore, “apparent” freedom from locally recurrent CaP was 77% and 31% for the mixed beam and photon-only groups, respectively. In this particular study posttreatment biopsies were performed randomly, and no conclusions can be drawn regarding the impact of fast neutron radiotherapy in respect to the complete histologic eradication

of CaP in this cohort. Laramore and associates (559) published a final report of that same RTOG-sponsored phase III clinical trial. The 10-year results for clinically assessed local control were 70% for the mixed-beam group compared with 58% for the photon group. Overall survival was 48% for those patients receiving fast neutron radiotherapy versus 29% for the photon-only group.

As of 1992, 14 centers worldwide were performing proton beam treatments, including three in the United States. Virtually all proton beam therapy has been based on machines designed and installed for basic high-energy particle physics research. In the update provided by Suit and associates (991), a phase III trial of proton beam therapy as the "boost" dose in the treatment of stage T_3 CaP had generated interesting results. In this study all patients received 50.4 Gy × four-field "box" technique using 10 to 25 MV x-ray beams. These patients were then randomly assigned to receive the "boost" dose by either conventional x-rays or protons. The final dose levels of the prostate were 68.4 Gy or 75.6 CGE (60 CoGy equivalent) for the x-ray and proton treatments, respectively. The local control results in the two arms were 81% and 89%, respectively, at 5 years. Whether the theoretic advantages of proton beam therapy will translate into durable clinical results awaits confirmation.

Complications of External Beam Radiotherapy

Catalona (154) has nicely summarized the complications attendant to external beam radiation therapy. GI tract symptoms are quite common and occur in 30% to 40% of patients while undergoing such treatment. These symptoms most often manifest themselves approximately the fourth week of therapy and commonly include diarrhea, rectal pain, and tenesmus. Although common, these symptoms are rarely disabling, and 95% of patients can continue the treatment protocol uninterrupted. Approximately 12% of patients will have longer-lasting GI symptoms, which include chronic diarrhea and anorectal disease (ulcers, fistulae, strictures). The incidence of severe chronic radiation proctitis induced by pelvic irradiation is reported to be 2% to 5% (509). These symptoms include diarrhea, tenesmus, abdominal pain, and rectal bleeding. Less common but more ominous complications include perforation, stenosis, and ulceration. Conservative management includes the use of a low-residue diet, steroidal enemas, and laser therapy or electrocoagulation to halt bleeding. Hyperbaric oxygen therapy improves the microvascular environment and may have a beneficial impact on treatment-refractory radiation proctitis (509). Despite these symptoms, diverting colostomies are rare (less than 1%). GU symptoms are noted with an equivalent degree of frequency, with the most common being urinary frequency and dysuria. Hematuria is uncommon as an acute complication (5%). The incidence of urethral stricture has been cited as between 4% and 8% and seems more likely if bladder neck surgery has immediately preceded radiation therapy (353,814,914). It seems advisable to defer the initiation of external beam therapy 6 to 8 weeks following such procedures.

In the absence of previous pelvic surgery, it is unusual to develop disabling lymphedema of the genitalia and lower extremities. The incidence of this complication rises, however, to approximately 40% in patients having undergone previous lymphadenectomy using standard surgical margins. This complication has been minimized by the use of a limited lymphadenectomy or by using a radiation portal restrictive to the prostate. Severe cutaneous erythema is unusual with the use of modern-day linear accelerators, but occasionally a patient will have a localized problem in the intergluteal fold. Finally, the number of patients experiencing erectile dysfunction following radiation treatments seems highly variable even in reports from the same institution. Recent reports by Zelefsky and associates (1128) suggest the frequency of impotence following external beam radiation ranges from 25% to 60% and from 15% to 25% after permanent radioactive seed implantation (1128). These same investigators documented that sildenafil improved erectile function in greater than two-thirds of patients with postradiotherapy impotence. Patients with less severe dysfunction were most likely to benefit from this pharmacologic intervention. Potosky and associates (792) assessed health outcomes after radical prostatectomy (n = 1,156) versus external beam radiotherapy (n = 435). Almost 2 years after treatment, men who had undergone radical prostatectomy were more likely than men receiving radiotherapy to be incontinent (9.6% versus 3.5%; p <.001) and to have higher rates of impotence (79.6% versus 61.5%; p <.001). Large and statistically significant declines in sexual function were observed in both treatment groups. In contrast, men undergoing radiotherapy reported greater declines in bowel function then did men receiving radical prostatectomy. Many of the chronic complications listed earlier may be due to small-vessel occlusive disease secondary

to radiation-induced endarteritis obliterans. A compilation of the complications associated with radiation therapy is depicted in Table 33.27 .

	Massachusetts General Hospital	M.D. Anderson Hospital	RTOG	Totals
Number of patients	74	153	104	331
Treatment period (yr)	1980–1983	1984–1988	1978–1982	
Median followup (yr)	7.3	3.3	9.4	6.1
Number of treatment mortality	0	0	0	0
Number of severe complications	0	0	0	0
% Incontinence	1.4	0	—	0.4
% Loss of full potency	55	—	67	63
% Diarrhea:				
Incidence	1.4	2.0	7.7	3.6
Persisting	0	0	0	0
% Genitourinary strictures:				
Incidence	4.1	2.6	11.0	5.4
Persisting	0	2.6	1.0	1.2
% Hematuria:				
Incidence	10.8	2.6	5.8	5.1
Persisting	2.7	1.3	1.0	0.9
% Rectal bleeding:				
Incidence	14.9	2.6	3.8	5.4
Persisting	2.7	0	0	0.6

From Shipley WU, Zietman AL, Hanks GE, et al. Treatment-related sequelae following external beam radiation for prostate cancer: a review with an update in patients with stage T_1 and T_2 tumors. *J Urol* 1994;152:1799.

TABLE 33.27. COMPLICATIONS (GRADES 2 AND 3) FOLLOWING EXTERNAL BEAM RADIATION FOR STAGES T_1 OR T_2 PROSTATE CANCER

Interstitial Radiation Therapy

Interstitial radiotherapy has intuitive appeal because of the theoretic ability to deliver supralethal doses of ionizing radiation directly to the area of the primary tumor while sparing the surrounding uninvolved tissues. The appeal of such an approach also lies in the fact that it is technically less demanding than radical prostatectomy and can provide the patient with some reasonable assurance that urinary control and sexual potency will be preserved.

Historic Perspective

Although Barringer reported the transperineal implantation of radium needles in 1917, only isolated reports of this therapy appeared until Whitmore and associates (1089) popularized ^{125}I implantation. Some attractive properties of the ^{125}I isotope include (a) the emission of pure irradiation that simplifies dosimetry calculation; (b) a half-life of approximately 60 days, ensuring potentially cytotoxic levels of irradiation to the involved tissues for approximately 1 year; (c) a half-value of tissue penetration of approximately 1.7 cm, providing relative protection of the surrounding tissues and to persons in contact with the patients; (d) the theoretic ability to deliver 25,000 cGy to the center of the prostate and 18,000 cGy to its periphery during the year of therapeutic efficacy (103,154). Conversely, disadvantages of ^{125}I therapy include (a) its long half-life somewhat complicates the administration of adjunctive external beam radiation therapy, (b) the construction of the radioactive seeds with welded ends interferes with a homogeneous circumferential radiation field, and (c) the short depth of penetration requires extremely accurate placement of the seeds to obtain a homogeneous distribution of radiation (417). This latter feature was particularly problematic when the retropubic implantation technique was used.

The implantation technique popularized at Memorial Sloan-Kettering Cancer Center was preceded by a limited extraperitoneal PLND performed through a lower midline incision. After completion of the lymphadenectomy, the endopelvic fascia was incised bilaterally, permitting partial mobilization of the gland. When adequate retropubic exposure of the patients had been obtained, a specifically designed instrument (Mick or Henschke) was used to deposit between 40 and 70 radioactive seeds at approximate intervals (5 mm). Manual examination of the rectum was required to ensure proper positioning of the needles (17 gauge and 15 cm long) through which two to four seeds are deposited. Needles were removed after insertion of the radioactive seeds. Periprostatic veins were commonly lacerated during the insertion of the needles, requiring sustained tamponade after their removal to obtain adequate hemostasis. Because accurate seed placement was impossible in the presence of a very thin peripheral rim of tissue, patients who had undergone a previous TURP or open prostatectomy generally were excluded from this procedure. Similarly, patients with clinical stage B_2 or C disease were poor candidates for retropubic ^{125}I implantation because the

large tumor burden generally exceeded the penetration capability of the isotope. Finally, antecedent or subsequent external beam radiation therapy was fraught with significant risks due to unpredictable tissue damage.

In 1982, Grossmann and associates (389) provided a reanalysis of the initial 100 patients treated with this technique and originally reported by Whitmore in 1980 (1088). The overall 5-year survival rate was 95% for stage B_1, 64% for B_2, and 59% for stage C lesions. Tumor-free survival, however, was noted to be 66% for B_1, 30% for B_2, and 21% for stage C neoplasms (154). In 1983, Whitmore (1089a) presented 5-year disease-free survival data for T_1, T_2, T_3, and T_4 tumors, citing results of 79%, 53%, 45%, and 19%, respectively. In that study, he noted a local recurrence rate of approximately 7% without any apparent relationship to tumor grade. However, distant treatment failure was directly correlated with tumor grade, being noted in 14% of low-grade tumors and 67% of poorly differentiated prostate cancers. Patients with one positive lymph node and any T category were found to have an actuarial survival of 71.5% compared with 52.4% if two nodes were involved.

Herr (417) summarized the complications attendant to retropubic ^{125}I implantation, which included (a) an operative mortality of 0.5% for 800 patients treated; (b) thromboembolic disease in 7% of patients, (c) complications of pelvic surgery in approximately 10% of patients, including lymphocele formation, abscess, hematoma, and pelvic cellulitis; (d) self-limited irritative voiding symptoms; (e) lower extremity and genital edema in 2% of cases; (f) proctitis, which usually resolved within 1 year; (g) impotence in 10% of patients; and (h) rectourethral fistulae. The development of the latter was most likely in those patients with large glands treated with high doses of radiation, those individuals requiring TURP following ^{125}I implantation, and patients exposed to external beam therapy either before or after seed implantation.

In 1972, Carlton and associates (120) popularized^{198} Au implantation combined with external beam therapy. The unique features of ^{198}Au include (a) the emission of both ß and γ radiation, (b) a half-life of 2.7 days rendering the seeds virtually depleted of radiation 3 weeks after implantation, (c) a half-value layer (penetration) in tissue of 4.5 cm so that exquisitely accurate seed placement was not necessary, and (d) an intrinsic energy higher than ^{125}I (420 keV versus 28 keV).

These inherent properties of ^{198}Au simplified patient selection. Because of its higher energy threshold and greater depth of tissue penetration, precise seed placement was not a critical factor. Therefore patients who had undergone TURP or open prostatectomy were not excluded from treatment. Similarly the procedure potentially was available to patients with large primary tumors (up to 6 cm) with or without involvement of the prostatic urethra, bladder neck, or seminal vesicles. Furthermore, in the presence of severe obstructive voiding symptoms, a TURP could be performed with a 6-week hiatus before the implantation of gold seeds (870). Patients with stage A_2, B, and C_1 lesions were considered reasonable candidates for this treatment. Patients were excluded if they had a history of pelvic irradiation, significant anorectal disease, or a primary tumor in excess of 6 cm in diameter.

The technique involved a limited PLND performed through a lower abdominal transverse incision. The endopelvic fascia was divided lateral to the prostate, which permitted partial mobilization of the gland. Following adequate retropubic exposure of the prostate, a special needle implanter was used to deposit six to eight high-activity grains throughout the prostate, concentrating in the area of palpable abnormality. This technique provided a dosage of approximately 3,500 cGy to the tumor. In the presence of seminal vesicle involvement seeds were implanted in that area as well. Two to 3 weeks following implantation, adjunctive external beam radiation therapy was initiated using a linear accelerator. For patients with node-negative disease, 4,500 cGy was delivered to the prostate during a 12-week period. More than 1,000 patients were treated with this protocol. For patients with clinical stage A_2 disease, the disease-free survival rate at 5 years was 38%. Moreover, none of these patients remained disease free at 10 years. For stages B_1, B_2, and C_1, disease-free survival at 5 years was reported as 71%, 59%, and 46%, respectively. For the same stages, 10-year survival figures approached 54%, 26%, and 40%, respectively (870).

A more recent analysis conducted by Gervasi and associates (348) compared the incidence of local recurrence based on clinical recognition of progressive disease in patients with node-positive and node-negative status. This study revealed a local recurrence incidence of approximately 85% in node-positive patients and, in contrast, of 34% in node-negative patients at 10% and 41% at 15 years, respectively.

The reported complications of ^{198}Au implantation combined with external beam radiation include (a) lymphocele formation in 2% of patients; (b) wound infection in 4%; (c) a 10% incidence of thrombophlebitis; (d) mild lower extremity or genital edema in 10%; (e) mild symptoms secondary to irritation of the bladder, rectum, and urethra; and (f) erectile dysfunction ranging from 2% to 40%. No incontinence was reported. Several episodes of rectal injury occurred early in the Baylor series (870).

TRUSP-guided Prostate Brachytherapy

The advent of the anatomic radical prostatectomy and conformal radiation therapy diminished enthusiasm for open prostatic implantation substantially. However, the development of TRUSP (and CT-guided) implantation via a transperineal approach has been responsible for a renaissance of interest in brachytherapy for the management of early stage CaP (1057). Blasko and associates (71) pioneered

ultrasound-guided, transperineal, prostate brachytherapy. A conceptually similar approach using CT scans (instead of ultrasonography) was developed at Memorial-Sloan-Kettering Cancer Center at approximately the same time (1057). The ultrasound-guided approach popularized by the Seattle group has been easily explanted to other institutions and constitutes the current mainstream approach of prostate brachytherapy.

The prototypic ideal candidate for prostate brachytherapy should meet several relatively well-defined criteria, including a high probability of localized disease (stage T_1T_{2a}), a pretreatment serum PSA level of less than 20 ng/mL, low to intermediate Gleason score, a projected life expectancy of at least 10 years, and a reasonable surgical risk for a formal anesthetic of 1 to 2 hours duration. The prostatic volume should be less than 60 cm^3 and pubic arch interference must be excluded by pretreatment CT imaging. In the latter circumstance, needle placement in the anterolateral portion of the prostate gland is problematic. In most incidences, 3 to 6 months of androgen ablation can effectively downsize the prostate and eliminate pubic arch interference. The efficacy of this treatment must be validated by repeat CT imaging. In general, previous transurethral or open prostatectomy constitutes contraindications to the procedure because stable seed implantation within the periurethral tissues is quite difficult. In addition, such patients have been prone to urethral necrosis/sloughing and subsequent incontinence. Some have proposed that this represents a relative and not absolute contraindication and that the presence of at least 10 mm of normal prostatic tissue around the prostatectomy defect can ensure accurate and safe completion of the procedure (742). In our practice, this contingency remains an absolute contraindication. Rarely, the presence of abundant corpora amylacea (with acoustic shadowing) mitigates against accurate seed placement. Finally, patients with moderate to severe obstructive/irritative voiding symptoms that fail to respond to optimal pharmacologic management may be poor candidates for seed implantation given the high probability that the procedure and its aftermath may exacerbate these symptoms.

Following candidate selection, an accurate ultrasound volume study of the prostate must be performed. Transverse “cuts” through the prostate are obtained and captured in increments of 5 mL from base to apex. These images are evaluated to specify the target volume that will receive the prescribed radiation dose. Computer planning programs use this volume data to determine the number of seeds required to achieve this dose and the optimal placement of seeds. We prefer a loading pattern that adheres to the principles of uniform rather than peripheral distribution (995). This conceptual paradigm and its inherent advantages are highlighted in Fig. 33.84 .

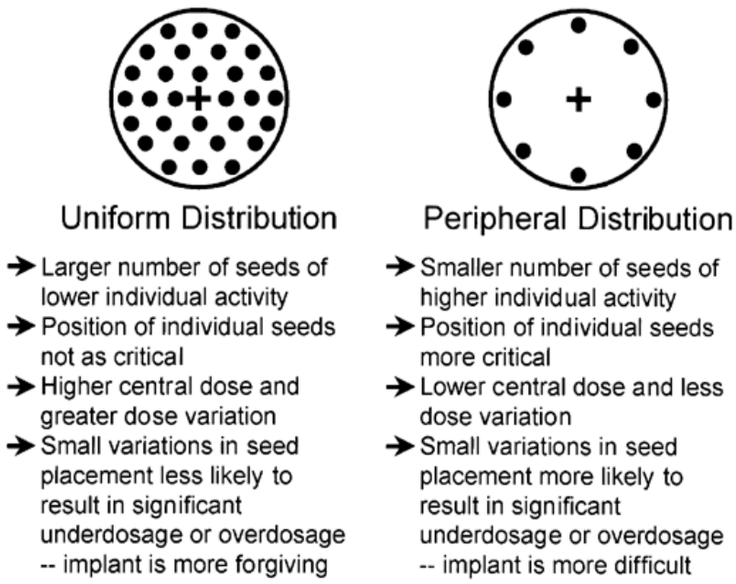

FIGURE 33.84. The relative advantages of uniform versus peripheral seed distribution. (From Sylvester J, Blasko JC, Grimm P, et al. Interstitial implantation techniques in prostate cancer [Review]. *J Surg Oncol* 1997;66:65, with permission.)

In some incidences, patients with more advanced disease (stage T_{2b}, Gleason score 7 or greater, PSA greater than 15) may be considered suitable candidates for brachytherapy approach. In this circumstance, we tend to use a multimodality approach. Most patients are pretreated with total androgen ablation for 3 to 6 months. This treatment is followed by conformal external beam radiation (4,500 cGy) to the prostate and pelvis. An interstitial brachytherapy boost completes this treatment plan (995).

Preparation for the actual procedure is relatively simple. In our practice, most patients are placed on an α-blocker several weeks before the date of surgery. A clear liquid diet is instituted 1 day before implantation. Patients undergo a modified bowel prep and receive appropriate perioperative antimicrobial coverage.

The procedure itself is performed under general or regional anesthesia. The patient is placed in the lithotomy position with both knees at the same height and the buttocks flat on the table surface. An attempt is made to duplicate as much as possible the position established for the ultrasound volume study. The scrotum is anchored to the abdominal wall with sterile adhesive drapes. In our practice, we have not found it necessary to contrast enhance the bladder before the procedure. We previously used an abbreviated urethral catheter through which water-soluble jelly could be instilled to enhance the real-time identification of the urethra so as to avoid injudiciously close seed implantation. We no longer find this approach necessary and instead use liberal transverse/longitudinal imaging, combined with C-arm fluoroscopy. The transrectal probe is inserted and attached to a stabilization unit, which is locked into position on the operating table. The perineal template is secured in position. Real time ultrasound imaging of the prostate is meticulously performed from base to apex at 5-mm intervals. These images are then compared with the hard copy generated during the ultrasound volume study. An electronic grid is superimposed on the image of the prostate and corresponds to the needle-guiding template attached to the stabilization unit (Fig. 33.85).

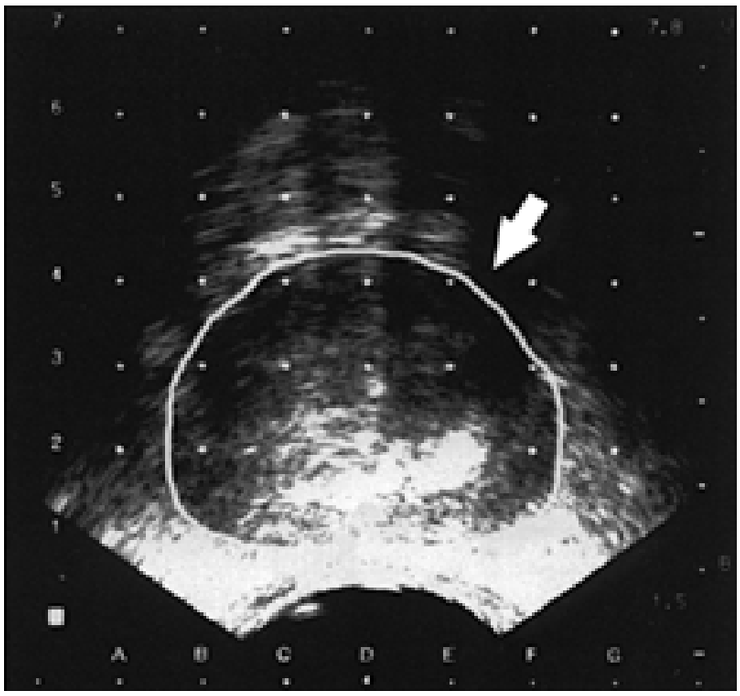

FIGURE 33.85. Transfers ultrasound image of prostate (*arrow* points to outline) in which the electronic grid is superimposed. This image corresponds to that of the needle-guiding template. (From Pais VM, Focht T, Canaday DJ, et al. Brachytherapy for prostate cancer. *Infect Urol* 2000;May/June:59, with permission.)

In the past, we have used two stabilization needles to prevent movement of the gland during the procedure. We and others have noted that this step may in fact produce tissue distortion. Placement of such stabilizing needles is not required in the majority of cases. The urologist and radiation oncologist must both agree that the real-time image accurately duplicates the volume study, particularly with respect to symmetry and the positioning of row one. Ideally, the latter should be a few millimeters within the posterior projection of the prostate. Care must be taken to avoid implantation too close to the rectal wall. The urologist and radiation oncologist work in concert with respect to the placement of the preplanned needles/seeds. Given our desire for homogeneous seed distribution, placement begins from the top row down and from lateral to medial. Once the needle is optimally situated, the radiation oncologist, who holds the stylet in stable position, dislodges the spacer. The urologist (with a gentle and consistent motion) withdraws the 17-gauge needle, and real-time imaging permits identification of the seeds as they are homogenously distributed. Snap fluoroscopic films also validate these observations. Additional seeds beyond the number dictated by the treatment plan are generally ordered to treat any unplanned areas of underdosing. Once completed, cystoscopy is performed and any displaced seeds are removed using grasping forceps. A 20-Fr Foley catheter is then inserted and the patient is taken from the operating room after a thorough radiation safety check has been performed. Although this procedure can be performed in the outpatient setting, it is our practice to admit the patients overnight with the intent of removing the Foley catheter the following morning. To minimize postimplantation edema, patients are given a single dose of IV Decadron (4 mg) and promptly started on a daily dose of a cyclooxygenase-2 (COX-2) inhibitor (Vioxx 25 mg). Prevacid is usually administered for GI protection.

Postimplant analysis is an important process that should be performed in all patients undergoing prostate brachytherapy. CT-based studies appear to be the best approach for postimplant dosimetry. Because the reported half-life of postimplantation edema is approximately 10 to 14 days, the best time to obtain this study may be 30 days after implantation (794). The D90 dose, the minimum dose to 90% of the prostate volume, appears to be a critical variable for assessing the accuracy of prostate brachytherapy. Patients with a D90 dose greater than 140 Gy have been shown to have a 4-year PSA relapse-free survival rate of 92%, whereas those with a

D90 dose less than 140 Gy have a 4-year PSA relapse-free survival rate of only 68% (794).

Iodine-125 is the most common permanent radioactive isotope used for prostate brachytherapy. As stated previously, ^{125}I emits a low energy (27 keV photon) and possesses a half-life of 60 days, which results in a relatively low initial dose rate of 7 to 10 cGy per hour at the prescription isodose contour (72). Palladium-103 (^{103}Pd) was introduced in 1987. The characteristics of ^{103}Pd are similar to ^{125}I in that it emits a low-energy photon with an average energy of 21 keV. It differs in that its half-life is 17 days with a resultant initial dose rate of 20 to 24 cGy per hour for a typical prescription dose (72). Consequently, it was thought ^{103}Pd might be more suitable for prostate cancers with a Gleason score of greater than or equal to 7 because these tumors were thought to have faster intrinsic doubling time than low to moderate grade tumors. However, clinical data have been reported for both ^{125}I and ^{103}Pd and do not indicate any difference in biochemical control regardless of tumor grade (794). In our practice, ^{125}I is the predominant isotope used for seed implantation.

In general, prostate brachytherapy is a well-tolerated procedure. Nonetheless, various complications have been identified. Acute complications, which occur during or soon after the procedure, generally involve perineal pain/ecchymosis/swelling or temporary urinary retention. These complications have been identified in up to 5% of patients. Subacute complications occur within 2 to 4 months following implantation and generally involve obstructive/irritative voiding symptoms. Late complications, which develop as a result of chronic normal tissue damage from radiation, have been identified and include proctitis, hemorrhagic cystitis, impotence, and urinary incontinence (especially in patients who have had the antecedent transurethral or open prostate surgery). The most common complications and their relative frequencies are summarized in Table 33.28 .

Series	Therapy	Incontinence	Impotency	Radiation Proctitis	Urinary Retention	Urethritis
Priestly and Beyer	125-I	1%	—	1%	—	4%
Blasko, et al.	125-I	TURP 17% Non-TURP 0%	Age >70, 50% Age <70, 15%	2%	7%	7%
Wallner, et al.	125-I	0%	19%	12%	0%	—
Blasko, et al.	XRT + 125-I	TURP 13% Non-TURP 0%	Age >70, 50% Age <70, 15%	6%	4%	4%
Kaye, et al.	125-I ± XRT	TURP 11% Non-TURP 1%	25%	9%	5%	1%
Dattoli, et al.	XRT + 103-PD	1%	23%	—	7%	—
Mate and Grossman	XRT + 192-Ir HDR	0%	—	—	2%	—

Note: Studies cited are from original source.
HDR, high-dose rate brachytherapy; TURP, transurethral resection of the prostrate; XRT, external beam radiation.
Adapted from Pais VM, Focht T, Canaday DJ, et al. Brachytherapy for prostate cancer. *Infect Urol* 2000; May/June:59, with permission.

TABLE 33.28. COMPLICATIONS OF CLOSED TRANSPERINEAL BRACHYTHERAPY IN EARLY-STAGE PROSTATE CANCER

Before leaving the subject of complications, the concept of seed migration should be briefly addressed. The radioactive seeds used in brachytherapy are cylindrical, 4.5 mm long, and have a diameter of 800 micron (213). The rate of seed embolization (into the pulmonary vasculature) is approximately 10% to 22% of all cases, whereas the number of seeds that may embolize are between 2 and 8 per 1,000 of those implanted (645). Embolization to the right ventricle has been reported (213). To date, no detrimental effects from seed migration have been reported. The use of linked seeds embedded in an absorbable suture material (Vicryl) has been associated with a reduction in the embolization rate to less than 1% (1002). These constructs are expensive and certainly less “forgiving” with respect to the implantation procedure.

Most of the published data on the results of transperineal permanent isotope prostate brachytherapy are evaluations of patients chosen for low risk of extracapsular disease. Table 33.29 depicts the results of recent series. According to these studies, 4- to 10-year biochemical control rates range from 63% to 92%. Blasko and associates (72) reported 9-year outcomes in 230 patients treated with ^{103}Pd monotherapy. These investigators used a modification of the ASTRO definition of PSA relapse free using survival (two instead of three consecutive increases). Favorable-risk patients had a 94% 5-year PSA relapse-free survival rate (84% at 9 years). Intermediate- and unfavorable-risk patients had PSA relapse-free survival rates of 82% and 65%, respectively. Prestidge and associates (800) have reported that biochemical control rates correlate with postbrachytherapy biopsy rates. Their data indicate a close correlation between

PSA control and biopsy results, with 80% of biopsy patients having a negative result.

Study	No. of Patients	Median Follow-up (mo)	Actuarial Results	Definition of Success or Failure
Blasko, et al. (1) 2000	230	42	84% 9-yr PSA-RFS	Modified ASTRO definition (2 PSA rises)
Potters, et al. (22) 1999	717	41	82% 5-yr PSA-RFS	ASTRO definition[a]
Stock, et al. (23) 1998	134	32	92% 4-yr PSA-RFS	PSA >1.0 ng/mL or 2 PSA rises (for radiation dose >140 Gy)
Grado, et al. (19) 1998	490	27	79% 5-yr DFS	2 PSA rises
Ragde, et al. (2) 1998	206	119	65% 10-yr DFS	Failure defined as PSA >0.5 ng/mL
Zelefsky, et al. (26) 1999	145	24	82% 5-yr PSA-RFS	ASTRO definition[a]
Storey, et al. (25) 1999	193	35	63% 5-yr PSA-RFS	ASTRO definition[a]
Critz, et al. (21) 1996	1,020	36	79% 5-yr DFS	Failure defined as PSA >0.5 ng/mL
Beyer and Priestle (18) 1997	489	35	83% 5-yr DFS	Defined as PSA <4.0 ng/mL
Dattoli, et al. (20) 1996	124	42	76% 4-yr DFS	Defined as PSA <1.0 ng/mL

Note: Studies cited are from original source.
[a]Three consecutive PSA value rises.
ASTRO, American Society of Therapeutic Radiation and Oncology; DFS, disease-free survival; PSA-RFS, prostate-specific antigen relapse-free survival.
From Potter SL. Permanent prostate brachytherapy: Lessons learned, lessons to learn. *Oncology* 2000;14:981, with permission.

TABLE 33.29. RESULTS OF RECENT SERIES REPORTING ON PERMANENT PROSTATE BRACHYTHERAPY

The combination of external beam radiation (with or without neoadjuvant androgen ablation) followed by an interstitial brachytherapy boost can be considered in selected patients with a significant risk of microscopic extracapsular disease. In these patients, monotherapy would be expected to have a high local recurrence rate given that seed implantation delivers tumoricidal doses of radiation energy only 5 mm from the capsular parameter. Ragde and associates (806) reported on 54 patients treated with conventional external beam radiotherapy to 45 Gy followed by permanent ^{125}I implant delivering 120 Gy. With a median follow-up of 119 months, the 10-year likelihood of maintaining a PSA level less than 0.4 ng/mL was 75%. Only 24% of these patients had Gleason scores of greater than 7 and only 41% exhibited PSA levels greater than 10 ng/mL. Table 33.30 summarizes some of these results.

Series	No. of Patients	Initial Median PSA[a]	Stage	Therapy	No. of Months Follow-up (Median)	Crude Local Control	Actuarial PSA[a] Follow-up Results
Blasko, et al.	57	13.5	T_1–T_3	XRT + 103-Pd	35	97%	64% <1.0 at 5 yr
Kaye, et al.	31	12.6	T_1–T_2	XRT + 125-I	29	—	90% <4.0 at 2 yr
Mate and Grossman	99	13.9[b]	T_1–T_3	XRT + 192-Ir HDR	28	—	84% <4.0 at 3 yr
Stromberg, et al.	33	15.4	T_{2B}–T_3	XRT + 192-Ir HDR	13	—	92% <4.0 at 1 yr

[a]Prostate-specific antigen in ng/mL
[b]Mean.
HDR, high dose rate brachytherapy; PSA, prostate-specific antigen; XRT, external beam radiation
From reference 806.

TABLE 33.30. CLINICAL RESULTS OF MODERATE-DOSE EXTERNAL BEAM IRRADIATION PLUS TRANSPERINEAL INTERSTITIAL BRACHYTHERAPY BOOST IN EARLY-STAGE PROSTATE CANCER

Despite the accumulation of a vast amount of data over the past 10 years, several uncertainties remain regarding prostate brachytherapy. First, the disease-free survival rate at 15 years and beyond has not been established. Second, the potential utility of routine neoadjuvant androgen ablation needs to be defined. Finally, the role of permanent brachytherapy as a salvage treatment for failed external beam radiation remains controversial. Beyer (59) described a retrospective review of 17 consecutive men seen and treated with permanent brachytherapy for recurrent CaP following an attempt at definitive external beam radiation. The 5-year actuarial freedom from second relapse was 53% in this cohort. Patients with a PSA of 10 ng/mL or less and

low-grade tumors were most likely to respond to therapy. Acute and transient toxicity was easily managed. However, there was a 24% risk of incontinence at 5 years in these patients. A final area of controversy involves the routine use of high-dose combination radiotherapy for the treatment of localized (197,1125) and locally advanced (500) prostate cancers. Encouraging short-term results and acceptable toxicity profiles reported in these series await multiinstitutional validation.

Neoadjuvant Hormonal Therapy

Early attempts to use androgen ablation as a therapeutic adjunct to radiotherapy were disappointing. In the Stanford experience, the 10-year survival rate for patients with stage A and B disease that were so treated was 30% compared with 60% of patients receiving radiotherapy alone (814). Even for patients with stage C disease, the 10-year survival rate was better in the group treated exclusively with radiotherapy (30% versus 20%). Catalona (154) suggested that the initiation of androgen ablation might significantly diminish the proliferative index of the androgen-dependent subpopulations, rendering them less susceptible to the lethal impact of ionizing radiation.

The preceding studies were conducted before the advent of current pharmacologic approaches. For that reason, interest has been renewed in the potential value of neoadjuvant hormonal therapy used before and during the conduct of 3D conformal radiation therapy. Despite the perceived advantages of 3D treatment planning, it is recognized that this approach may not fully encompass the target volume in certain geometrically unfavorable lesions without including a substantial volume of normal tissue within the high-dose dosimetry region. Conceivably, diminution in prostatic volume, which accompanies hormonal therapy, might improve the geometry of the target volume and optimize the efficacy of treatment (1127). In a recent phase I/II clinical trial, neoadjuvant leuprolide acetate (Lupron) and flutamide (Eulexin) were administered 3 months before and concomitant with 3D conformal radiotherapy. The target population included those patients with bulky, geometrically unfavorable prostate cancers. The study demonstrated that the median percentage of target volume reduction after neoadjuvant hormonal therapy was approximately 25%. This treatment also translated into a significant diminution in the amount of radiation exposure to the rectum, bladder, and small bowel.

A similar approach was used in a phase III trial of androgen suppression before and during radiation therapy for patients with palpable T_{2c}, T_3, and T_4 prostate cancers and unknown nodal status. This was conducted under the auspices of the RTOG 8610. In this study, patients were randomized to receive either 2 months of goserelin (Zoladex) and flutamide (Eulexin) before and concomitant with radiation therapy or radiation therapy alone. The latter consisted of irradiation of the pelvic lymphatics to 45 ± 1 Gy and a boost to the prostate of 20 to 25 Gy to a minimum total tumor dose of 65 Gy. After 3 years of follow-up, the actuarial local control rate was 84% with neoadjuvant therapy and 71% with radiation alone, and disease-free survival was 46% versus 26%, respectively. With respect to the latter, the criteria consisted of (a) no evidence of clinical progression, (b) no positive rebiopsy, and (c) a PSA less than 4 ng/mL and not rising. Although the overall survival benefit remains unclear, the results were deemed so encouraging that in future RTOG trials, combined therapy of goserelin plus flutamide with radiation is to become the standard treatment arm with which other modalities will be compared (Table 33.31).

	% 3-Yr Endpoint		
Analysis	Total Androgen Deprivation with Goserelin Acetate and Flutamide Plus Radiation Therapy	Radiation Therapy Alone	*p* Value
No evidence of disease survival[a]	61	43	<.001
Local failure[a]	16	29	<.001
Prostate-specific antigen less than 4.0 ng/mL[b]	46	26	<.001

[a]Clinical.
[b]This level is used as a response indicator not representing cure.
From Hanks GE et al. *J Urol* 1994;152:1775.

TABLE 33.31. RTOG STUDY (86-10) OF ANDROGEN DEPRIVATION AND RADIATION

Following the initiation of a total androgen ablation, serial PSA levels should be monitored to determine the point at which the PSA nadir is achieved. In general, this requires a minimum of 2 to 3 months. Once this point is identified, 3D conformal radiation therapy is initiated with the intent of maintaining androgen ablation until the radiation arm of treatment is completed. This approach, which has been commonplace in the United States, has been questioned by European investigators who recently conducted and completed a multiinstitutional clinical trial that suggests the potential utility of prolonged androgen ablation following the completion of external beam

radiation. Indeed, this suppression was maintained for an average of 3 years and a survival advantage was documented in this cohort. Additional studies will be required to determine whether androgen ablation should be maintained following completion of radiation therapy. Other logical questions that arise involve the potential utility of either androgen ablation or the use of intermittent hormonal therapy in this clinical context.

The study by Granfors and associates (374) is intriguing. These investigators assessed combined orchiectomy and external beam radiation therapy versus radiation therapy alone for patients with nonmetastatic CaP (with/without pelvic lymph involvement). After a median follow-up of 9.3 years, clinical progression was seen in 61% of the radiotherapy-alone patients and in 31% of the combined treatment patients. Mortality was 61% and 38%, respectively, and the cause-specific mortality was 44% and 27%, respectively in groups 1 and 2. The outcome differences favoring combined treatment were mainly linked to lymph node–positive tumors. Patients with node-negative tumors had no significant difference in survival. Combined modality therapy was associated with better progression-free, disease-specific, and overall survival rates. This study also suggests that early androgen deprivation is superior to deferred treatment in such patients.

Of interest is the recent observation that estramustine phosphate may act as a radiosensitizing agent. This drug binds to microtubule assembly proteins (MAPs), producing an arrest of cancer cells at metaphase. *In vitro* studies using the human prostatic carcinoma cell line DU-145 demonstrated that the presence of estramustine phosphate is associated with a 23% increased sensitization to radiation therapy (262). It is conceivable that estramustine phosphate used alone or in concert with neoadjuvant androgen ablation may enhance the impact of 3D conformal radiotherapy.

Adjuvant Radiotherapy

Several studies validate the contention that external beam radiation administered in the adjuvant setting enhances local disease control in those cases following radical prostatectomy in which the surgical margins are compromised and capsular/seminal vesicle involvement is appreciated on step-section analysis of the surgical specimen. Ray and associates (813) noted a 5- and 10-year disease-free survival of 57% in those patients treated promptly following prostatectomy in whom incomplete excision was documented. This compares with 5- and 10-year survival rates of 40% and 20%, respectively, for those individuals treated after the onset of a palpable local recurrence. These authors suggest the initiation of such treatment within 4 months of prostatectomy when incomplete excision has been documented.

In 1986, Gibbons and associates (351) reported their series of 45 patients following radical prostatectomy who were noted to have microscopic extension of the disease beyond the gland. Of those patients treated with external beam therapy, local recurrences were noted in only 5% as compared with 30% of the untreated cohort. In their experience, delayed radiotherapy of a local recurrence was usually ineffective with regard to retarding disease progression. Other investigators have reported similar results (33,126,557,911).

Kaplan and Bagshaw (486) reported their experience with external beam radiotherapy administered to 39 patients following radical prostatectomy. In this study, the only evidence of persistent disease in 37 of 39 patients was detectable levels of serum PSA. Two patients had palpable recurrences. Pathologic analysis of surgical specimens revealed positive margins (24 of 34), positive seminal vesicles (17 of 32), positive lymph nodes (8 of 37), and a Gleason score of 7 or greater (29 of 38). With a mean follow-up of 26.8 months, local control has been achieved in all but one patient. Of note, the PSA was rendered undetectable 12 months following radiotherapy in 17 (44%) patients who were designated in the low-risk group. Conversely, the serum PSA remained detectable or continued to rise in 18 (46%) patients, who were then designated the high-risk group. Of the latter, 9 of 18 had bone metastases while under observation.

Freeman and associates (318) described 114 patients with pathologic stage C CaP who had undergone bilateral PLND and radical retropubic prostatectomy. Postoperative adjuvant radiation (median of 45 Gy) therapy (without hormonal treatment) was given to 95 of these patients with a median follow-up of 4.4 years. They noted 5- and 10-year actuarial survival rates of 94% and 70%, respectively, for the adjuvant radiotherapy group and the controls, and of clinical plus PSA recurrence at 34% and 46%, respectively. Similarly, disease-specific 5- and 10-year actuarial survival rates were 99% and 78%, respectively. At 5 and 10 years, the chance of clinical recurrence was estimated at 6% and 13%, respectively. Patients with high Gleason scores (8 or greater) and seminal vesicle involvement (stage C3) had the worst outcomes. In their analysis, disease-specific survival and survival without clinical recurrence of patients treated with adjuvant radiotherapy as compared with radical prostatectomy alone were improved over historical controls. Our experience (720) using a retrospective pairwise comparison of patients subjected to adjuvant radiation as compared to nonradical patients indicated a therapeutic advantage for the former.

Most of the these studies involved regimens using a 50- to 60-Gy total dose delivered to the prostatic bed. Proctitis-diarrhea, local skin reactions, lower extremity edema, and urethral stricture were commonly reported complications that were treatable or self-limited in the majority of cases. Most advocates for this approach recommend a 3-month hiatus following radical prostatectomy to ensure adequate healing of the vesicourethral anastomosis and other aspects

of the wound. In those incidences when the potential need for adjuvant radiotherapy is deemed likely, performance of a modified PLND with preservation of lymphatic tissue lateral to the external iliac vessels is advisable to minimize the likelihood of lower extremity edema. In addition, radiation therapy should be delivered to the prostatic bed (rather than the whole pelvis) to further minimize the risks of disabling lymph edema and other related toxicities.

The utility of adjuvant radiotherapy following radical prostatectomy is not universally acclaimed. Paulson and associates (754) failed to demonstrate any advantage for patients with pathologic stage C disease treated with adjuvant radiation therapy following radical perineal prostatectomy when compared with those patients receiving only surgical treatment. In a more recent analysis of this problem, Ellis and Lange (271) emphasized that most of the adjuvant radiotherapy series had short follow-up and did not include serum PSA or ultrasound-guided biopsies of the prostatic bed as endpoint parameters. In their series of 14 patients with elevated PSA levels and unremarkable DREs who received adjuvant radiotherapy, positive needle biopsies were documented in four (28%) patients, which was not deemed to be statistically different from the frequency of positive needle biopsies in similar groups of patients not subjected to adjuvant radiotherapy. They also emphasized that serum PSA levels decreased to undetectable in 8 (53%) of 15 patients subjected to adjuvant radiation therapy. However, this admittedly beneficial impact was not durable in the majority of patients.

Despite attempts at optimal patient selection before radical prostatectomy, between 14% and 41% of patients currently exhibit tumor extension to the surgical margin on final step-section analysis. In this latter group, biochemical (PSA) relapse is identified in 33% to 62% of these patients (716). A slow PSA velocity after radical prostatectomy and a long interval between radical prostatectomy and PSA relapse probably indicates the presence of localized disease. Conversely, a rapidly detectable (PSA) with a high PSA velocity following surgery most often indicates metastatic disease. The standard clinical evaluation of these patients is generally unrewarding. The DRE is usually normal. Targeted biopsies of the vesicourethral anastomosis are positive in only 40% to 50% of cases. CT and bone scan imaging are generally nondeclarative in patients with PSA values less than 20 ng/mL. Indium-111 capromab pendetide (ProstaScint) is a radiolabeled monoclonal antibody to PSMA, which may have clinical utility in the evaluation of PSA recurrence following radical prostatectomy. A multicenter study evaluating ProstaScint imaging in this context, found a sensitivity of 75%, a specificity of 86%, and an accuracy of 81% for this imaging modality (420), which compared favorably to an accuracy of only 48% for CT/MRI. Similarly, Elgamil and associates reported a sensitivity of 89%, specificity of 67%, and an accuracy of 89%, in a series of 100 similar patients. ProstaScint imaging is most useful for detecting recurrence in the prostatic bed and within lymph nodes. Petronis and associates (767) correlated the percent of positive ProstaScint scans with PSA values at the time of recurrence. Even for PSA values between 0.1 and 1.0 ng/mL, ProstaScint imaging was positive in 60% of cases. Between PSA levels of 1.1 and 10 ng/mL, scan positivity ranged from 60% to 83.3%, but for PSA values at recurrence above 10.1 ng/mL, all patients had a positive scan; however, in the latter only approximately 22% exhibited positive scans in the prostatic bed only. These results suggest that even at very low PSA levels, a substantial tumor burden exists. Kahn and associates (479) noted that 70% of men with a normal ProstaScint scan outside the prostatic fossa achieved a complete response after salvage radiotherapy versus only 22% who had a positive scan outside the prostatic fossa and pelvis.

Several recent series have validated the utility of adjuvant radiation therapy in the treatment of patients exhibiting an isolated PSA elevation following radical prostatectomy (572,716,779,1004,1043). Although PSA cutoff values of 1.0, 1.6, 2.0, and 2.5 have been advocated (306), no clear-cut consensus regarding this issue exists. It appears that when radiation therapy is given for postoperative biochemical relapse, it should be instituted at the earliest possible time (contingent with adequate healing) rather than assuming that a similar outcome will result in patients with a PSA below a certain level (779).

In our practice, patients are selected for adjuvant radiotherapy on the basis of tumor cells histologically present in the periprostatic tissue. The identification of cells on the capsular margin is a relative but less definite indication. The grade of the tumor is an important consideration, as are the age of the patient and his priorities. We usually wait a minimum of 3 months after surgery and prefer to have the patient's urinary control optimized and his urinary symptoms minimized before embarking upon treatment. We generally treat the prostatic bed and immediately adjacent site with 5,800 to 6,500 cGy.

Evaluation of Treatment Results

Until recently, the evaluation of treatment results following external beam radiation therapy for CaP was rendered difficult for various reasons, including (a) the variability of treatment regimens used; (b) the often unrecorded use of adjunctive endocrine therapy; (c) lack of accurate pathologic staging in the absence of PLND; (d) the use of different staging systems and the frequent lack of stage breakdown into clinically recognized subset categories; (e) lack of uniformity with regard to the criteria used to assess the continued presence of disease, particularly the frequent lack of histologic confirmation of treatment efficacy as discerned by TRUSP-guided biopsies and serum PSA levels; and (f) the inconstant rates of local tumor regression following the completion of radiation therapy, rendering an assessment of local disease control more difficult. With respect to the

latter, it had been thought that approximately 75% of all overt treatment failures occurred within 24 months of completing the respective course of therapy, but this remains a highly variable phenomenon (814) and does not reflect the sensitivity of serum PSA measurements to detect evidence of biochemical relapse.

Despite these acknowledged deficiencies, several interesting and historically relevant statements can be made regarding the conceived efficacy of external beam radiation therapy in the treatment of prostate cancer. As summarized by Catalona (143), when stages A_2 to C were aggregated, clinically demonstrable treatment failure was apparent in one-fourth to one-third of cases. Of the latter, 50% to 65% reflected the presence of metastatic disease, 25% to 30% manifested both local and distant failures, and approximately 10% reflected local failure by predominantly DRE criteria. Not unexpectedly, local failure was deemed most likely in the presence of high-grade tumors (607) and in the presence of advanced-stage disease (707). Again, the validity of the statistics reflecting local disease containment must be tempered with the realization that these perceptions were made without TRUSP biopsies and sequential serum PSA monitoring. Both of these "outcome variables" are discussed briefly in the following paragraphs.

Egawa and associates (253) made some interesting observations regarding the role of sonographic monitoring of prostate cancer after definitive radiation therapy. In their study, 30 patients underwent TRUSP before and after definitive radiotherapy. Before treatment, one or more discrete hypoechoic areas characteristic of cancer were noted in 29 (97%) of the patients. Six months after completion of radiation therapy, a hypoechoic lesion was still observable in the original pretreatment area in 19 (79%) patients. Sonography demonstrated persistent lesions in 65% of 17 patients at 12 months, 79% of 14 patients at 24 months, and 75% of 8 patients at 36 months. Of interest, the maximum diameter of the hypoechoic lesion decreased by a mean of 41% when evaluated 12 months after radiotherapy. This study suggests that hypoechoic lesions noted pretreatment can be monitored by TRUSP after definitive radiation therapy.

Before the advent of TRUSP, postradiotherapy prostatic needle biopsies were performed with digital guidance. Despite the perceived inaccuracies of such an approach, the information generated from such studies is of great importance. For example, in the Baylor series of 510 patients with stage A_2, B, or C_1 prostate cancer treated with radioactive gold seed implantation and external beam radiotherapy, one or more needle biopsies were obtained in 140 patients who had no evidence of local or distant recurrent disease 6 to 36 months after completing treatment. A local recurrence developed in 60% of the 45 patients with a positive biopsy and in 19% of those with a negative biopsy. The probability of local recurrence for patients with a positive biopsy was 52% at 5 years and 72% at 10 years; it was 12% and 30%, respectively, for those with a negative biopsy (871). The relatively poor prognosis with a positive biopsy was present in every stage or grade subset. The prognostic significance of positive and negative biopsy findings seems to extend to the likelihood of disease-free survival (Table 33.32). These observations are all the more compelling when one considers the results of recent studies using systematic TRUSP-guided needle biopsies in patients having received definitive radiotherapy. Kabalin and associates (477) reported positive ultrasound-guided biopsies in 20 of 22 patients with normal postradiotherapy DREs. These findings call into question the reliance on DRE to indicate absence of tumor following radiotherapy. Indeed, a study by Crook and associates (199) demonstrates that TRUSP alone is not better than DRE in predicting a positive postradiotherapy biopsy. Their study and a multitude of others strongly support serum PSA measurements as the best indicator of biologically active tumor following radiotherapy. This latter issue is addressed in greater detail later in this section.

		% Local Failure	
Study	Biopsy Status	5 Year	10 Year
Scardino, 1988	Positive	52% (40%)[a]	72%
	Negative	12% (7%)	30%
Kuban, et al., 1985	Positive	44%	75%
	Negative	8%	24%
		% Disease-Free Survival	
Study	Biopsy Status	5 Year	10 Year
Scardino, 1983	Positive	30%	12%
	Negative	82%	82%
Kuban, et al., 1985	Positive	32%	19%
	Negative	82%	62%

[a]Parenthetical values represent
( ) = local failure with a negative prostate examination.
From Kuban DA, Schellhammer PF. *Oncology* 1993;7(p. 2):29.

TABLE 33.32. LONG-TERM FOLLOW-UP OF PATIENTS WITH PROSTATE CANCER TREATED WITH RADIATION THERAPY

The majority of studies tend to support the concept that a positive biopsy occurring more than 18 to 24 months after the completion of radiation therapy is an ominous prognostic indicator and suggests the presence of residual, viable tumor fully capable of expressing its intrinsic phenotypic characteristics, including those of invasion and metastasis. For example, the studies of Kiesling and associates (502) revealed no significant decrement in positive biopsies when analysis was performed at 12, 18, and 36 months. In that study, positive biopsies were noted in 64%, 57%, and 67% of cases, respectively. More important, of those patients with negative biopsies, 14% had metastatic disease as compared with 28% in the positive biopsy group. These findings

contrast the recent observations of Crook and associates (199) correlating the results of routine TRUSP biopsies with DRE, TRUSP, and serum PSA measurements in 100 patients with prostate cancer (stages T_{1b}-T_4) treated with radical radiotherapy. They noted negative biopsies in only 52% of patients at 12 months. Of 31 patients with a positive first biopsy who had a second or third examination, 21 converted to negative at 16 to 29 months. Of note, all of these patients maintained normal or decreasing PSA levels. A compilation of postradiotherapy biopsy results summarized in 1991 is presented in Table 33.33 .

TABLE 33.33. THE RESULTS OF NEEDLE BIOPSY OF THE PROSTATE AFTER RADIATION THERAPY

Reference	Treatment	No. Pos. Biopsy/Total (%)
Freiha and Bagshaw, 1984	External beam radiation	39/64
Kabalin, et al., 1989	External beam radiation	25/27
Kiesling, et al., 1980	External beam radiation	39/68
Scardino and Wheeler, 1985	^{198}Au with external beam radiation	56/146
Schellhammer, et al., 1980	^{125}I alone	15/57
Ross, et al., 1982	^{125}I with external beam radiation	9/30
Bosch, et al., 1986	^{192}I with external beam radiation	15/29
Klein, et al., 1988	^{192}I with external beam radiation	4/15
Present study (Marinelli, et al., 1992)	^{192}I with external beam radiation	18/81

From Marinelli D et al. Follow up prostate biopsy in patients with carcinoma of the prostate treated by ^{192}Iridium template irradiation plus supplemental external beam radiation. *J Urol* 1992;147:922.

A brief analysis of several recent series serves to highlight the importance of the pretreatment and posttreatment serum PSA levels as prognostic indicators of treatment outcome following radiotherapy for CaP. Studies by Zietman and associates (1136) and Lee and associates (562) concluded that a pretreatment serum PSA level of more than 15 ng/mL constitutes the most powerful predictor of probable failure with conventional radiation therapy. In the former study, if the initial PSA levels for stages T_1 and T_2 tumors were greater than 15 ng/mL, the projected 4-year rate of freedom from biochemical failure was only 7%. Similarly, the study of Lee and associates demonstrated that the freedom from biochemical failure for patients with stage D_1 tumors and a pretreatment level of greater 15 ng/mL was only 38% at 3 years.

The biologic implications of an abnormal posttreatment PSA level are equally compelling. Ritter and associates (832) concluded that the failure of PSA to reach levels equivalent to those reported in disease-free males was a multivariate predictor of subsequent failure. They also observed that delayed versus early PSA increase was associated with clinically localized versus metastatic first recurrence. In 1993, Stamey and associates provided an update on 124 unselected consecutive patients who underwent serial PSA determinations after radiotherapy to the prostate, with a mean overall follow-up of 6 years. During year 1 of irradiation the PSA level was decreasing in 82% of patients, stable in 5%, and increasing in 14%. Of those patients observed longer than 1 year (*n* = 80), 51% had increasing values, whereas 41% were stable. Of note, the latter group had a mean PSA level of 2.9 ng/mL with a variation less than 1 ng/mL on serial determinations. In their extended follow-up of 113 of these patients, 78% exhibited precipitously increasing PSA levels at a mean follow-up of 5 years postradiotherapy. By their criteria, a total of 23 patients (20%) appeared cured with a PSA level of less than 1.7 ng/mL at a mean follow-up of 9 years. The remaining 80% of the patients in whom radiotherapy failed were thought to exhibit accelerated growth of tumor clones, which were repopulated during and following radiotherapy. The studies of Willett and associates (1092) and Zelefsky and associates (1126) suggest that an even more stringent endpoint should be chosen for the serum PSA following radiotherapy. Each of those studies concluded that patients whose PSA values did not reach less than 1 ng/mL after radiation therapy for prostate cancer were unlikely to be long-term clinical disease-free survivors. Indeed, several studies have identified a close correlation between the posttreatment serum PSA and the likelihood of positive TRUS-guided prostatic needle biopsies (Fig. 33.86).

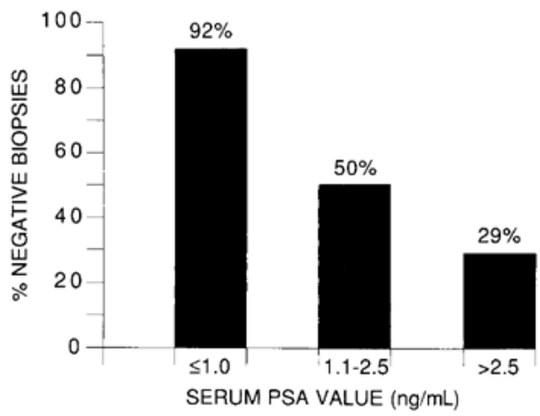

FIGURE 33.86. Rate of negative postradiation prostate biopsies is closely correlated with concomitant PSA values. (From Dugan TC, Shipley WU, Young RH, et al. Biopsy after external beam radiation therapy for adenocarcinoma of the prostate: correlation with original histological grade and current prostate specific antigen levels. *J Urol* 1991;146:1313, with permission.)

In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) held a consensus panel to identify guidelines for PSA recurrence after radiation therapy. The panel agreed on four guidelines. First, biochemical failure is not justification, per se, to initiate additional treatment. It is not thought to be equivalent to clinical failure. However, it is an early appropriate endpoint for clinical trials. Second, three consecutive increases in PSA values reasonably define biochemical failure after radiation therapy. The use of three, rather than two, consecutive values reduces the risks of falsely declaring biochemical failure due to “bouncing” PSA. Critz and associates (197) described the latter phenomenon in patients who had undergone radioactive seed implantation followed by external beam radiation. The PSA bounce was observed in 35% of men. The median time to PSA bounce was 18 months from the time of implant, and 92% of bounces were observed within 36 months. Third, no definition of PSA failure has,

as yet, been shown to be a surrogate for clinical progression or survival. Fourth, nadir PSA is a strong prognostic factor, but no absolute level is a valid cut point for separating successful and unsuccessful treatments. The nadir PSA is viewed to be similar in prognostic value to pretreatment prognostic variables.

Hanlon and Hanks (406) observed that patients who survived 48 to 60 months without a rise in serum PSA levels have a high probability of cure. Within this context, they observed no treatment failures after 6 years.

Several recent studies validate the importance of high radiation doses delivered by external beam radiation (608,1034) as well as high-intensity radiation delivered through the use of combined brachytherapy/external beam radiation (198). With respect to external beam radiation, it would appear that total delivered radiation doses in excess of 72 Gy are required to have a favorable impact on high Gleason histotype tumors. The study by Critz and associates (198) revealed that posttreatment PSA levels less than or equal to 0.2 ng/mL defined freedom from disease after radiotherapy.

The ultimate importance of the Gleason score on the outcome following radiotherapy is emphasized in the study of Roach and associates (833). These investigators evaluated patients entered on four prospective phase III randomized trials conducted by the RTOG between 1975 and 1992. For purposes of this study, death was disease-related if death was certified as due to prostate cancer, complications of treatment, or unknown causes with clinically active malignancy. The 10-year disease-specific survival for patients with Gleason scores of 2 to 5, 6 to 7, and 8 to 10 was 87%, 75%, and 44%, respectively, following radiotherapy. Of all the parameters evaluated, the Gleason score was the single most important predictor of death in the first 10 years. More recently, Kattan and associates (491) constructed a pretreatment nomogram for predicting the outcome of 3D conformal radiotherapy in prostate cancer patients (Fig. 33.87). This study was a retrospective, nonrandomized analysis of patients treated at Memorial Sloan-Kettering Cancer Center between 1988 and 1998. Clinical parameters of the 1,042 patients included stage, biopsy, Gleason score, pretreatment serum PSA level, whether neoadjuvant androgen deprivation therapy was administered, and the radiation dose delivered. Biochemical PSA treatment failure was scored when three consecutive rises of serum PSA occurred. A validated nomogram was established that predicts the probability of remaining free from biochemical recurrence for 5 years. This approach, if validated by other institutions, might be useful for treatment selection by both physicians and patients.

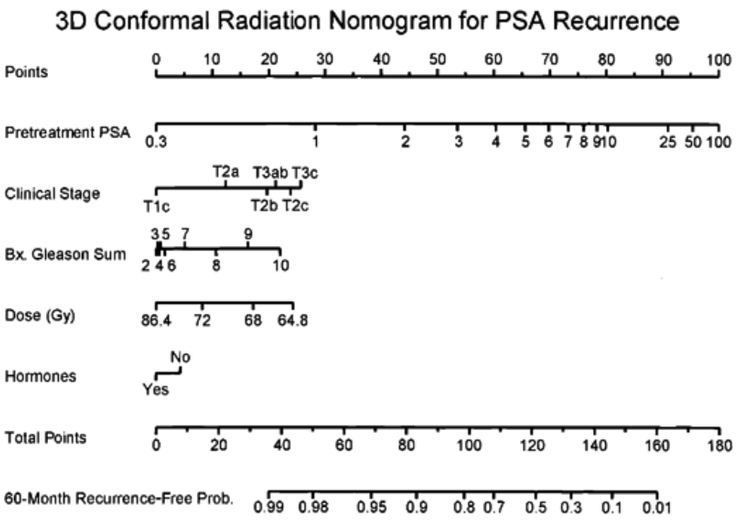

FIGURE 33.87. For each of the evaluation parameters [pretreatment prostate-specific antigen *(PSA),* clinical stage, biopsy Gleason sum, dose, and hormones], draw a straight line upward to the Points axis to determine how many points toward recurrence the patient receives for the given observation. The sum of the points achieved for each predictor should be determined and located on the Total Points axis. A straight line should be drawn down to find the patients probability of remaining recurrence free for 60 months. This nomogram is thought not to be applicable to a man who is not otherwise a candidate for radiation therapy. (From Kattan MW, Zelefsky MJ, Kupelian PA, et al. Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. *J Clin Oncol* 2000;18:3352, with permission.)

Palliative Radiotherapy

External beam radiation therapy has a definite role in the management of pain attendant to skeletal metastases from CaP. Androgen-ablative techniques, particularly orchiectomy, can produce a rapid and profound improvement in such painful sites. Consideration of radiation therapy is warranted in those patients who fail to show an adequate response to androgen withdrawal, particularly those with precarious lesions in the spine or weight-bearing areas. In the study by Benson and associates (54), 42% of patients had complete relief of pain following the completion of 3,000 to 3,500 cGy delivered to the painful site. Another 35% exhibited partial relief of symptoms. Higher doses of irradiation (5,000 to 6,000 cGy) may be required for the relief of ureteral obstruction refractory to androgen withdrawal therapy. Although some authors have reported good results (120), others have been less enthusiastic about its efficacy (653). Many weeks may be required for satisfactory resolution of the obstruction, suggesting the wisdom of using indwelling double-J stents, if feasible. A role for radiation therapy in treating bladder neck obstruction due to locally aggressive CaP is not established. As noted in the section on endocrine therapy, androgen ablation with or without a temporary percutaneous suprapubic cystotomy tube can successfully relieve bladder neck obstruction in the majority of patients within 3 to 6 months and may obviate the need for a channel TURP in high-risk patients. Recently, hyperthermia has proven to be a useful adjunct to 3D conformal radiation therapy and androgen ablation in the management of locally advanced prostate cancers associated with urethral obstruction/hematuria; rectal obstruction/bleeding; genital edema; and ureteral obstruction/hydronephrosis (483). In some incidences, this approach was effective even within the context of antecedent radiation failure.

Finally, patients with painful multifocal skeletal metastases may be benefited by the technique of half-body or whole-body irradiation (494,847). This technique involves the administration of a 600-cGy dose to the upper body followed by a 4- to 6-week hiatus, after which time approximately 800 cGy is delivered to the lower body half. The side effects of treatment are not inconsequential and include severe nausea and vomiting and the expected consequences of bone marrow suppression. As noted by Keen (494), pain relief can be rapid and complete in 28% of patients, with another 70% demonstrating some improvement. As with the application of external beam therapy for focally painful lesions, the lumbosacral spine seems to be a difficult area in which to provide effective palliation (143).

Robinson and associates (835) administered the calcium analog strontium-89 (^{89}Sr) to patients with prostate cancer with painful multifocal skeletal metastases. Response rates in excess of 80% were noted following the IV infusion of 50 to 60 Ci/kg. Strontium-89 is a ß-emitting isotope, possesses a half-life of 50.5 days, and follows the biologic pathways of calcium, which in theory provides access to all sites of osteoblastic metastases. Strontium-89 is available as a sterile isotonic solution for IV administration as a single outpatient injection. Each vial contains a single dose of ^{89}Sr chloride (4.0 mCi) in 4 mL solution. More recent studies have demonstrated pain relief in more than 70% of patients (195,791). In general, pain relief is not immediate but begins between 10 and 20 days postinjection, with relief maintained for a mean of 6 months (range of 4 to 15 months). The treatment may be repeated at 3-month intervals contingent on the patient's peripheral blood count. The therapy is well tolerated except for the development of hematologic toxicity (especially thrombocytopenia), which may become manifest at higher doses and following repeat dosing. At present, its primary utilization is for the treatment of symptomatic, multifocal skeletal metastases in patients with hormone-refractory prostate cancer who would otherwise be considered for hemibody radiation. These observations have been validated by more recent studies (321). The section involving treatment of metastatic hormone-refractory prostate cancer addresses the potential utility of other radioisotopes (samarium-153; rhenium-186).

Endocrine Therapy

In 1941, Huggins and Hodges (446) published their landmark observations establishing the efficacy of androgen-ablative/suppressive

therapy in the treatment of patients with disseminated CaP. Because normal prostatic epithelial cells were known to undergo atrophy following androgen ablation, and cancer cells shared biochemical and histologic characteristics with normal cells, an equivalent response to androgen withdrawal was predicted and found to occur in the neoplastic subset. Unfortunately, the presence of relatively or absolutely androgen-independent cells became apparent early in the endocrine treatment of CaP and has been the main focus of additional treatment efforts since the introduction of this therapy. With regard to the latter, experimental observations in the Dunning R3327-H rat prostate carcinoma model tend to support the presumption that CaP consists of androgen-dependent, androgen-sensitive, and androgen-independent cellular subpopulations (Fig. 33.88) (452). The necessity for a critical level of systemic androgen for the proliferative activity of most prostate cancer cells is supported by experimental observations in this rat tumor model and by the clinical observation that approximately 70% of patients with advanced CaP exhibit beneficial responses to androgen-ablative/suppressive therapy (821,1022).

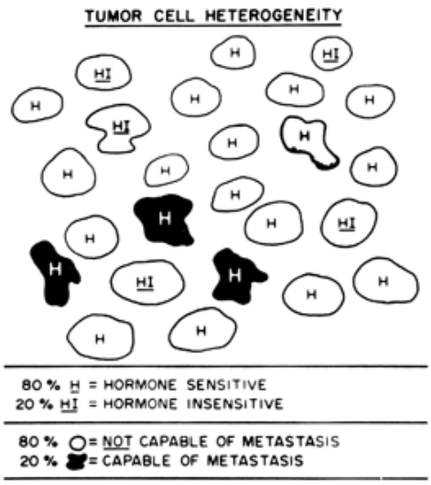

FIGURE 33.88. Human prostate cancers probably consist of hormone-sensitive and hormone-insensitive subpopulations. Each subset is composed of cells possessing varying potential for invasiveness and metastatic capacity. Adding to the complexity, primary tumors may differ substantially from their synchronous and metachronous metastases. In turn, these metastatic foci may differ from one another in a wide variety of phenotypic characteristics. (From Coffey DS, Isaacs JT. Control of prostate growth. *Urology* 1981;17[Suppl]:40, with permission.)

Available Therapeutic Modalities

The interstitial cells of Leydig are responsible for the production of 95% of all circulating androgen in the form of testosterone (1063). Cells constituting the zonae fasciculata and reticularis of the adrenal gland are responsible for the remaining 5% of circulating androgen through the production of dehydroepiandrosterone (DHEA) and androstenedione. Our present perception suggests that the gonadal source of androgen is the predominant and most biologically effective circulating moiety. The ultimate importance of adrenal androgen in stimulating normal or malignant prostatic epithelium has not been clearly established. Various therapeutic approaches are available to eliminate or suppress circulating androgen; these include regimens involving (a) primary gonadal mechanisms, (b) indirect gonadal suppression, (c) the administration of end-organ antagonists, and (d) methods involving panandrogen suppression (Table 33.34 and Fig. 33.89).

TABLE 33.34. FORMS OF ENDOCRINE THERAPY IN METASTATIC PROSTATIC CANCER[a]

Ablation of Androgen Sources	Inhibition of Luteinizing Hormone–Releasing Hormone or Pituitary Luteinizing Hormone	Inhibition of Androgen Synthesis	Antiandrogens
Orchiectomy	Diethylstilbestrol	Medroxyprogesterone	Medroxyprogesterone
Adrenalectomy	Chlorotrianisene (TACE)	Aminoglutethimide	Cyproterone acetate
Hypophysectomy	Conjugated estrogens (Premarin)	Spironolactone	Flutamide
	Medroxyprogesterone (Provera)	Medrogestone	Medrogestone
	Diethylstilbestrol diphosphate (Stilphostrol)	Cyproterone acetate	Bicalutamide
	Polyestradiol (Estradurin)		Nilutamide
	Cyproterone acetate		
	Leuprolide		

*Some drugs have multiple sites of action.
Adapted from Elder JS, Catalona WJ. *Urol Clin North Am* 1984;11:283, with permission.

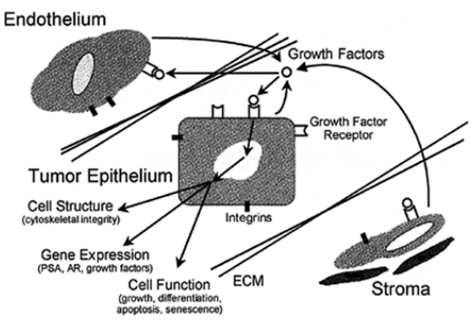

FIGURE 33.89. A dynamic reciprocity appears to exist between the tumor cell and the nontransformed constituents of the host microenvironment. The latter includes stromal elements, surrounding extracellular matrix *(ECM),* organ-specific microcapillary endothelium, and a wide array of growth factors and their receptors. AR, androgen receptor. (From Sokoloff MH, Gerber GS. Emerging therapies for the treatment of advanced prostate cancer. *New Develop Prostate Cancer Treat* 1999;4:36, with permission.)

Ablation of Primary Gonadal Function

Of the potential approaches to eliminate gonadal secretion, *scrotal orchiectomy* remains the standard of therapy for various reasons. (a) It results in a prompt, 95% reduction of serum testosterone, often achieving castrate levels within 3 hours following surgery (609). (b) It is exceedingly

unlikely that castrate levels of serum testosterone will be exceeded at any point in the postoperative course (517). (c) The procedure can be performed in the outpatient setting with the patient under local anesthesia without demonstrable mortality and with minimal morbidity. (d) Most men accept the procedure without long-term psychologic sequelae. (e) Although scrotal orchiectomy obviates some of the long-term side effects associated with pharmacologic androgen ablation (breast enlargement/tenderness, chemical hepatitis, diarrhea), it is associated with that constellation of problems designated the "androgen deprivation syndrome." The latter includes diminished or absent libido in most patients and impotence, which develops in one-half to three-fourths of patients (270); loss of muscle mass; a propensity toward weight gain; changes in cholesterol and fat metabolism; diminished stamina; emotional distress (416); demineralization of bone (osteoporosis); and the induction of hot flashes (249,416,672,770). A brief discussion of the latter two issues is warranted at this point.

Osteoporosis is a significant health problem in the white population in the United States. It has been estimated that more than 16% of white women and 5% of white men will suffer at least one vertebral bone fracture because of osteoporosis in their lifetime (641). Thus preexisting osteopenia and osteoporosis appear to be common in men with prostate cancer before the initiation of androgen deprivation therapy (1085).

In a study of men with non–stage A CaP, 13% of castrated men but only 1% of noncastrated men experienced fractures. The overall incidence of osteoporotic fractures in men with nonstage A cancer has been estimated to be approximately 4.3%, and nearly one-fourth of these fractures have been attributed to androgen deprivation therapy (1084). In a more recent study by Wei and associates (1085), it was determined that 88% of men undergoing androgen deprivation therapy for more than 1 year fulfilled the bone mineral density (BMD) criteria for osteopenia or osteoporosis at one or more sites. Indeed, men who received androgen ablation for more than 1 year had significantly lower BMD in the lumbar spine than men who had not started treatment. Using regression analysis, an estimated 48 months of androgen deprivation therapy was thought to be necessary to develop BMD criteria for osteopenia in the lumbar spine for a man without such evidence before the initiation of therapy.

In the study conducted by Daniell and associates (210a), the average BMD decreased 2.4% and 7.6%, respectively, during years 1 and 2 following castration. Similar losses were documented in men undergoing chemical castration. Average BMD decreased 1.4% to 2.6% per year 3 to 8 years after uninterrupted androgen deprivation. Postcastration bone loss was greater in men who were obese, younger than 75 years, and who failed to exercise regularly.

For men likely to require long-term androgen ablation, consideration should be given to obtaining a pretreatment

BMD evaluation and to repeat this assessment every 1 to 2 years thereafter. In addition, daily supplements of calcium (500 mg) and vitamin D (700 units) have been shown to significantly reduce vertebral fractures in men and women over the age of 65 years (770). Alendronate (Fosamax) is a potent biphosphonate that inhibits osteoclast-mediated bone resorption. In postmenopausal women with osteoporosis and in patients with steroid-induced osteoporosis, Alendronate significantly increases BMD and reduces the incidence of major osteoporotic fractures in postmenopausal women (489). A recent study confirmed the utility of Alendronate (10 mg per day) for the prevention of osteoporosis in men (738). Its use within the context of patients undergoing androgen deprivation therapy remains to be defined. Nonetheless, the use of this agent, in concert with calcium and vitamin D supplements, should be considered in men undergoing androgen ablation who develop significant osteopenia/osteoporosis. All of these therapeutic approaches should be administered with caution and monitored appropriately. Finally, a modification of this regimen may prove beneficial to patients with CaP bone metastases. Van Veldhuizen and associates (1037) demonstrated that the oral daily administration of 2,000 units of vitamin D improved pain control, muscle strength, and quality of life in this patient population. It should be emphasized that elderly men are prone to vitamin D deficiency because of decreased exposure to ultraviolet light and decreased ability of aging skin to synthesize vitamin D (888).

Karling and associates, (488) evaluated the frequency and duration of hot flashes in 77 men with CaP treated with either orchiectomy- or gonadotropin-releasing hormonal analogies. Of the 63 evaluable patients, 43 (68%) reported hot flashes during treatment of CaP for a prolonged period. Furthermore, the commonly held notion that there is a gradual diminution in frequency and duration of hot flashes posttreatment may be incorrect. Indeed, approximately three-fourths of men report distressing hot flashes that begin 1 to 12 months after the initiation of therapy and continue a mean of 30 months or more until death (160).

Fortunately, effective treatment exists for this problem. Loprinzi and co-workers (600) evaluated the effect of megestrol acetate (Megace) for the treatment of vasomotor hot flashes in women during menopause and in men who had undergone androgen-deprivation therapy for CaP. This double-blind, placebo-controlled study demonstrated that 74% of the megestrol acetate group (20 mg twice daily) exhibited a decrease of 50% or more in the frequency of hot flashes during the first 4 weeks of therapy. Moreover, the degree of efficacy was noted to be identical in both men and women. The efficacy of low-dose megestrol acetate (20 mg twice daily) also was confirmed in a study conducted by Smith (930). He noted that 70% of treated patients exhibited a complete response, while another 20% had a greater than 50% decrease in the severity of vasomotor hot flashes. This study also confirmed the equivalent efficacy of diethylstilbestrol (DES) (0.5 mg daily) in this regard. Because DES was associated with a higher incidence of side effects, Megace was the preferred agent in the management of this problem. Clonidine has been evaluated in this context but it does not appear to decrease hot flash frequency or intensity significantly (600). Venlafaxine hydrochloride, a structurally novel antidepressant that inhibits neuronal serotonin and norepinephrine uptake recently was shown to be associated with a significant reduction in the frequency and intensity of hot flashes with low-dose (12.5 mg orally twice daily) therapy in men undergoing androgen ablation therapy. Patients suffering from mastodynia (painful breasts) may benefit from the use of tamoxifen (10 mg orally three times daily).

Three currently available pharmacologic agents—aminoglutethimide, spironolactone, and ketoconazole—possess the ability to suppress androgen production in both the testes and the adrenal glands. *Aminoglutethimide* inhibits the enzymatic (desmolase) conversion of cholesterol to pregnenolone and has a negative impact on the function of the cytochrome P-450 microsomal enzyme system. These metabolic events effectively inhibit adrenal steroidogenesis with a less profound impact on the gonads (69,137,864). Its side effects include anorexia, nausea, skin rash, lethargy, vertigo, nystagmus, and hypothyroidism. Because it interferes with an early step in adrenal steroidogenesis, the administration of aminoglutethimide (750 to 2,000 mg per day) requires concomitant supplementation with cortisone (20 to 25 mg per day) and fludrocortisone (Florinef, 0.1 mg per day).

Spironolactone and ketoconazole inhibit both adrenal and gonadal steroidogenesis. *Spironolactone* (100 to 400 mg per day) blocks the action of the 17α-hydroxylase enzyme and interferes with the secretion of testosterone, dehydroepiandrosterone, and androstenedione (1063). Its side effects include gynecomastia, erectile dysfunction, diarrhea, lethargy, mental confusion, urticaria, drug fever, and sporadic cases of agranulocytosis.

Ketoconazole (400 mg every 8 hours) interferes with cytochrome P-450–dependent 14-demethylation and blocks the conversion of lanosterol to cholesterol. It also partially inhibits another P-450–dependent enzyme, 17,20-desmolase, thus affecting the conversion of C21 to C19 steroids (1020). Ketoconazole has been reported to decrease serum testosterone to castrate levels within 4 hours of administration (1020). Although glucocorticoid supplementation is rarely necessary, administration of ketoconazole is associated with weakness, lethargy, hepatic dysfunction, impotence, GI tract upset, and gynecomastia (445,1020).

In patients with previously untreated stage D_2 CaP, ketoconazole may be equivalent to orchiectomy in its ability to rapidly reduce pain; it is safer than DES for patients with vascular disease and, unlike gonadotropin-releasing hormone analogs, is not associated with a “flare” response (787). Unfortunately, dosages approaching 1,800 mg per day

may be necessary to maintain serum testosterone levels less than 100 ng/dL. Despite such doses, testosterone levels begin to rise after 1 month, and low normal levels are reached after 5 months (1038). Therefore ketoconazole is not effective as long-term, unimodal therapy. The strict 8-hour dosing intervals required to maintain testosterone suppression, coupled with severe toxicity mandating cessation of therapy in 30% to 40% of patients, further detract from the drug's utility. Long-term objective responses are rare when the drug is administered to patients who have failed previous androgen-ablative therapy.

Indirect Gonadal Suppression

Indirect inhibition of testicular androgen synthesis by affecting the pituitary secretion of gonadotropins can be accomplished by the administration of estrogens, progestational agents, and LHRH agonists. Among the estrogen moieties, *DES* (1 to 3 mg per day), *conjugated estrogens* (Premarin, 1 to 10 mg), and ethinyl estradiol (0.5 to 1.0 mg) have documented efficacy and appear in parity with one another in terms of effectiveness (67). Parenteral preparations of DES diphosphate (1 g intravenously for 7 days) and polyestradiol phosphate are effective and have been shown to rapidly diminish serum testosterone levels (35,302,609,837).

Oral estrogens induce the formation of specific liver-synthesized protein—the result of “the first pass effect.” Of these proteins, coagulation factor VII is one of the most strategic because it has been linked to the progression of atherosclerotic disease, and an increase in factor VII has been correlated with the deterioration of coronary status after the initiation of oral estrogen therapy in patients with prostate cancer (207,414). The parenteral administration of estrogen avoids this “first pass effect” and previous studies have demonstrated that polyestradiol phosphate (PEP) at doses of 240 mg per month IM can suppress testosterone production to castrate levels without any adverse impact on the liver. Recently, Hedlund and associates (410) randomized 915 patients to receive intramuscular injections of 240 mg PEP every second week for the first 8 weeks, followed by a maintenance dose of 240 mg every month, bilateral orchiectomy, or administration of LHRH agonist triptorelin plus flutamide. At a median follow-up of 18.5 months, no evidence of a difference in overall survival or in cardiovascular mortality was identified. PEP was associated with the lowest drug cost and the lowest accumulative direct costs and was thought to be the most cost-effective of the regimens tested. It was proposed that this intramuscular administration of PEP should be included as a serious therapeutic option in the endocrine management of CaP. Obviously, confirmatory clinical studies are required before accepting this proposal.

In addition to these agents, two other estrogen-containing compounds have documented clinical efficacy in the treatment of advanced prostate cancer. *Chlorotrianisene* (TACE) is a synthetic estrogen whose administration (12 to 25 mg) has been associated with positive clinical response despite the incomplete suppression of luteinizing hormone (LH) or testosterone levels.

Estramustine phosphate (EMP) (600 mg/m^2 per day) is a conjugate of estradiol and nitrogen mustard whose mechanism of action was thought to depend on the estrogen moiety for tumor target affinity and the nitrogen mustard component for cytotoxicity. Recent studies revealed that the mechanism of action of estramustine phosphate (EMP) is not related to either its estradiol or alkalylating activity. Indeed, the ultimate *in vitro* and *in vivo* cytotoxic effects of this agent are attributable to inhibition of microtubule assembly by the intact steroid-nitrogen mustard molecule, which is the direct consequence of the binding by estramustine phosphate to critical proteins MAPs (880). In one study, uncastrated patients treated with EMP had a significantly longer duration without progression when compared with a similarly matched cohort treated with DES (53). EMP monotherapy may produce transient, objective response rates of 26% to 63% in patients with CaP who have failed previous hormone therapy (55,665,950).

Although these agents have several possible mechanisms of action, including inhibition of the 3 α-hydroxysteroid dehydrogenase enzyme (1115), and a possible direct toxic impact on the prostatic epithelial cell, their effectiveness in controlling CaP of the prostate is thought to be due to inhibition of pituitary LH release with subsequent diminution of serum testosterone to castrate levels (44,834). Gynecomastia and fluid retention are common potential side effects of estrogens. The incidence of cardiovascular complications such as myocardial infarction, stroke, and venous thrombosis is clearly increased in patients given 5 mg per day of DES and would seem likely to be a risk factor with administration of any estrogen (67,113,114,228). Although high dosages of estrogen often elicit GI tract upset, this symptom is particularly troublesome with the administration of EMP (52). Impotence occurs in 30% to 80% of patients (56).

Megestrol acetate (120 mg per day), medroxyprogesterone acetate (20 to 200 mg per day), and *progesterone* are progestational agents that have been used in the treatment of stage D CaP. These agents suppress pituitary LH release, inhibit steroidogenesis, block 5α-reductase, and bind to ARs in the prostate gland (344,346,347). Compared with DES, progestational agents are associated with a reduced risk of cardiovascular morbidity and gynecomastia. However, they are associated with a loss of libido and with erectile dysfunction. What is more important, prolonged administration (within 2 to 6 months) of these agents has been associated with a secondary rise in testosterone levels, significantly blunting their clinical utility (345). The latter “escape

phenomenon" can be prevented by the concomitant administration of 0.5 to 1.5 mg estradiol (346,347).

Some of the side effects of estrogen therapy can be controlled. For example, the gynecomastia associated with DES administration can be prevented by full-breast irradiation before the initiation of treatment. This may be delivered as a cumulative dose per breast of 1,200 cGy in three fractions or as a single dose of 800 cGy per breast (329,760). Such treatment must be completed before estrogen administration because once initiated, the glandular hyperplasia is not reversible. However, the discomfort associated with gynecomastia can be relieved with delayed radiation therapy. Furthermore, the thrombogenic side effects of estrogen can be diminished by using low-dose therapy. Good clinical response has been noted with doses of DES as low as 1 mg per day. When such therapy is initiated, serum testosterone levels should be monitored periodically because castrate levels may not be maintained (113,303). In addition, prophylactic administration of drugs such as aspirin or dipyridamole (Persantine) may prove efficacious in minimizing thromboembolic events associated with estrogen administration (257).

More recently, the *LHRH agonists* have been used to produce indirect gonadal suppression (287,288,1018,1076,1077). Their major mechanism of action stems from a super-stimulation of the pituitary that ultimately results in down regulation of the LHRH receptors leading to a refractory condition of anterior pituitary cells to LHRH secretion (863). This process occurs during a 1- to 3-week period, during which time there may be supersecretion of both LH and testosterone with a twofold to threefold increase above normal levels of the latter. The transition to castrate levels of serum testosterone occurs gradually during a 2- to 4-week period (931,1095). In addition, animal studies have suggested that LHRH agonists also may cause a quantitative decrease in the number of LH receptors expressed on the Leydig cells (863). Administration of these agents to patients with metastatic CaP has been associated with an apparent transient tumor stimulation manifested by increases in acid phosphatase levels and skeletal pain in some patients. This phenomenon, also designated the "flare response," is of particular concern in patients with impending cord compression and may be avoided by administering low doses of DES or flutamide 3 to 4 weeks before and 1 month during the administration of therapy. Impotence and hot flashes are reported in the vast majority of patients (530).

Goserelin and *buserelin* are available as depot preparations. These constructs may blunt the transient increase in serum LH levels, which may occur with daily subcutaneous (50 ng per day) or intranasal (two to three times per day to achieve a dose 100 to 500 ng) therapy and also may result in lower serum testosterone levels (1081). Several studies have demonstrated that LHRH agonists induce an endocrinologic effect equivalent to that of orchiectomy, produce clinical effects in parity with those seen following orchiectomy and DES, and are associated with side effects that are significantly less severe than those following DES administration and are equivalent to castration (170,192,759,933). Once relapse is noted (androgen-resistant phase), hormonal suppression should be maintained by continuing the LHRH agonist or by performing an orchiectomy because certain tumor subpopulations may be relatively androgen-responsive. Finally, these agents are expensive, and long-term administration may constitute a financial burden to some patients.

Oefelein (724) recently reported that the median duration of castrate level testosterone was 6 months after a single 3-month (LHRH) agonist injection. In a follow-up study, 32 men *on androgen-ablative therapy for prostate cancer* were treated with 3-month (22.5-mg) leuprolide acetate injection (721). Serum testosterone and PSA levels were obtained every 28 days beginning on the ninetieth day after the last 22.5-mg leuprolide injection. The median duration of castrate level testosterone was 6.0 months. *The median serum PSA at enrollment and when the castrate testosterone threshold of 0.2 ng/mL was exceeded remained stable with no significant change observed during this interval.* A significant association was observed between an increasing duration of physiologic castration after LHRH agonist injection and advancing patient age and increasing duration of hormonal therapy. The latter observations may reflect diminished testosterone recovery after gonadotropin suppression in the aged population. These studies suggest that strict adherence to the advised every 3- or 4-month redosing schedule (depending on the depot preparation used) may be unnecessary. By monitoring serum testosterone levels, redosing could be held in abeyance until serum testosterone concentration rises above castrate levels. Obviously, implementation of this approach might permit a doubling of the dosing interval and the corresponding 50% reduction in medication costs.

Recently, a 1-year leuprolide delivery system (Viadur) was developed. The latter consists of a 4 × 45-mm cylindrical, titanium implant which uses osmotic pressure to deliver the drug continuously at a controlled rate for 1 year. To insert the implant, subcutaneous tissue 5 to 10 cm above the antecubital crease of the inner arm is anesthetized and a 5-mm incision is established. The implant is positioned with a disposable implanter in the fossa between the biceps and triceps muscles. Fowler and associates (309) reported the outcomes of 80 patients who underwent implantation with the Viadur system. They concluded that this leuprolide implant effectively suppressed testosterone concentrations to less than the castrate threshold and maintained that suppression throughout the study. Side effects associated were essentially the same as those reported with standard LHRH agonists depot preparations.

The development of

GnRH receptor antagonists would be expected to be devoid of the initial androgen-stimulation characteristics GnRH agonists (183). Abarelix is the first GnRH receptor antagonist in a sustained-duration formulation to progress through clinical trials. This agent blocks GnRH and inhibits LH production, which in turn suppresses the production of testosterone and DHT. Abarelix does not cause an initial stimulation of LH production, testosterone, or DHT (341). Garnick and associates (341) demonstrated that prostate gland volume significantly decreased (median of 35%) in the course of treatment with Abarelix (1 mg). Serum testosterone concentrations decreased to chemically castrate levels (less than 50 ng/dL) by day 15 for most patients. During this same interval, the PSA decreased to less than 4.0 ng/mL in the majority of patients. Garnick and associates (342) and Campion and associates (116) have reported the results of a recent phase II study. In this study, the abarelix depot formulation was compared with depot formulations of leuprorelin and goserelin, with or without concomitant antiandrogen use. Two hundred and nine patients were treated with abarelix depot, 100 mg on days 1 and 15 and then 50 to 100 mg every 4 weeks. A concurrent control group of 33 patients was treated with the alternative regimens. Abarelix induced rapid chemical castration (day 8) in 76% of patients compared with 0% in the other groups. Testosterone surge occurred in all of the other groups but in none of the abarelix-treated patients.

End-organ Antagonists

Cyproterone acetate and megestrol acetate are the two primary steroidal antiandrogens. Cyproterone acetate (250 to 300 mg per day) is a derivative of 17-hydroxyprogesterone and may suppress testosterone production by inhibiting pituitary LH release through a poor gestational effect (843) coupled with its ability to block the C21-19 desmolase enzyme (143). Both steroidal antiandrogens block the interaction between androgens and the receptors in the target tissues. In addition, they possess some progestational activity and consequently lower LH production. Megestrol acetate is used less often than cyproterone acetate as a primary treatment for metastatic CaP. When used as monotherapy, neither agent can effectively suppress androgen production; consequently, plasma testosterone levels ultimately rise toward normal range. Cyproterone acetate appears to be devoid of most side effects except impotence and gynecomastia (933).

Three generations of nonsteroidal antiandrogens have been developed. Flutamide (Eulexin) is a first-generation nonsteroidal antiandrogen. Flutamide has an affinity for ARs in the hypothalamic pituitary system and they paradoxically increase testicular testosterone production by supranormal stimulation of LH release (803). Flutamide possesses a relatively short half-life of approximately 5.2 hours. Its active metabolite is hydroxyflutamide. The standard dosage is 250 mg three times daily. The efficacy of high-dose (1.5 g per day) and low-dose (750 mg per day) monotherapy has been assessed in several studies (803,943). In general, the two dosage levels of flutamide have equivalent antitumor impact; however, few patients can tolerate the side effects of prolonged high-dose therapy. In previously untreated patients with stage D_2 CaP, the clinical impact of low-dose flutamide monotherapy was equivalent to that of DES (1 to 3 mg per day) and estramustine phosphate. For patients with CaP refractory to conventional hormonal therapy, infrequent and transient responses have been reported to flutamide (750 mg per day), and most studies have shown little evidence to support a major role for flutamide monotherapy in this setting (611,940). The side effects associated with flutamide administration include gynecomastia, rash, depression, nausea, vomiting, and liver function abnormalities. With respect to the latter, Gomez and others (369) evaluated 1,091 patients with stage C or D CaP treated with flutamide in concert with LHRH agonist. They noted fourfold or more increases in serum aspartate aminotransferase and alanine aminotransferase in only 4 (0.36%) of 1,091 patients. All clinical and biologic manifestations of liver toxicity disappeared following the discontinuation of flutamide. It was recommended that serial serum aminotransferase measurements be obtained 2 and 4 weeks after the initiation of flutamide therapy to detect early signs of hepatic injury. Potency seems to be preserved in most patients treated with flutamide (611,941).

Nilutamide (Nilandron) is a second-generation antiandrogen. It possesses a long half-life of approximately 45 hours and is thus amenable to once-daily dosing (300 mg per day). This feature may ensure a more permanent saturation of AR binding sites. As with flutamide, nilutamide is effective in preventing LHRH agonist–induced tumor flares (468). Common side effects include nausea, alcohol intolerance, and decreased adaptation to darkness. These side effects abate following discontinuation of the drug. Approximately 50% of patients maintain libido and potency.

Bicalutamide (Casodex) is a third-generation antiandrogen with a prolonged half-life of 5 to 6 days. Dosages ranging from 50 to 150 mg per day can be conveniently administered. Like the other nonsteroidal antiandrogens, Casodex effectively blocks the tumor flare associated with LHRH agonists. In patients with existing metastatic disease, pretreatment with Casodex (or flutamide, nilutamide) should be initiated 2 to 4 weeks before the administration of the LHRH agonists. The standard maintenance dose of bicalutamide is 50 mg per day when used in concert with an LHRH agonist for the purpose of total androgen ablation. Boccardo and associates (75) recently evaluated the impact of high-dose (150 mg per day) bicalutamide monotherapy. In their study, patients were randomly allocated to receive either high-dose bicalutamide monotherapy or maximum androgen blockade (flutamide plus goserelin). Bicalutamide monotherapy yielded comparable results relative to standard treatment with total androgen blockade. However, it was associated with fewer side effects and produced a better quality of life. More recently, Iversen and associates (461)

compared bicalutamide monotherapy (150 mg per day) with castration in patients with nonmetastatic locally advanced CaP. In that study, there were statistically significant benefits in the bicalutamide monotherapy group in the two quality-of-life parameters of sexual interest and physical capacity. The highest incidences of adverse events were the pharmacologic side effects of hot flashes in the castration group, and breast pain and gynecomastia in the bicalutamide group. The frequency of other types of adverse events was low. Bicalutamide was well tolerated, with few drug-related withdrawals from study. However, a common problem with bicalutamide monotherapy is cost, which proves to be prohibitive for many elderly patients.

Attempts at Complete Androgen Suppression

The concept of successfully suppressing both testicular and adrenal androgen production in patients with metastatic CaP has a certain theoretic appeal. Various such approaches have been attempted and include (a) combined orchiectomy and adrenalectomy, (b) hypophysectomy (919), (c) orchiectomy and the subsequent administration of an antiandrogen (258,362,468,762), and (d) the use of LHRH agonists together with antiandrogens to effect complete androgen suppression (193,223,460,550). Adrenalectomy and hypophysectomy have been used for the treatment of advanced prostate cancer refractory to castration or estrogen administration, although a few reports are available regarding the use of such approaches in untreated patients (60). Neither approach has been associated with profound or long-standing subjective or objective improvement in such patients (381). Obviously, the use of either adrenalectomy or hypophysectomy commits the patient to a lifetime of glucocorticoid replacement therapy.

A new wave of enthusiasm has been engendered by the availability of pharmacologic approaches to panandrogen suppression. Labrie and associates (550,551) treated more than 200 patients with stage C and D CaP with leuprolide (to suppress the production of testosterone) and flutamide (to block the impact of adrenal androgens). They report positive responses in over 97% of patients and an 89.2% probability of survival at 2 years compared with a 40% to 60% probability with leuprolide, estrogen, or orchiectomy monotherapy. This drug regimen is predicated on the hypothesis that CaP is unusually sensitive to androgens and that androgens of adrenal origin play a significant role in accelerating disease progression in patients previously exposed to conventional monotherapy. It also is assumed that androgen-insensitive clones arise only when androgen blockade has been incomplete (255). The latter view contrasts with the alternative hypothesis, which assumes that androgen-sensitive and androgen-insensitive clones emerge soon after malignant transformation occurs. Progression of the disease after hormonal therapy is thought to result from the uncontrolled proliferation of the androgen-insensitive subpopulation that is due to aberrations in autocrine or paracrine growth control, possibly involving the exaggerated production of growth factors and their receptors.

Crawford and associates (192) conducted a randomized, double-blind trial involving 603 men with previously untreated stage D_2 CaP. Three hundred patients were randomized to receive leuprolide plus placebo, while the remaining 303 men received leuprolide plus flutamide. The latter group exhibited a longer progression-free survival (16.5 versus 13.9 months; $p = .039$) and an increase in the median length of survival (35.6 versus 28.3 months; $p = .035$). Improvement was most noteworthy in patients with minimal disease and a good performance status and was particularly apparent during the first 12 weeks of treatment. Finally, the flare reaction associated with 8% to 32% of cases involving leuprolide monotherapy was significantly abolished by the addition of flutamide. In the analysis of progression-free survival, the authors chose to discount changes in the bone scan noted at the first 3-month assessment. An analogous study conducted by Denis and associates (223) compared the impact of goserelin acetate and flutamide with bilateral orchiectomy in 327 patients with metastatic CaP. They observed that the time to first subjective disease progression was statistically longer in favor of the combination therapy (87 weeks versus 52 weeks for the orchiectomy arm). Janknegt and others (468) evaluated the impact of orchiectomy and nilutamide (versus placebo) in a similar cohort. They noted that progression-free survival was significantly longer in the nilutamide group (20.8 months versus 14.9 months). Median time to death from CaP was 30 months in the placebo group and 37 months in the nilutamide group. Finally, objective evidence of disease regression was noted more frequently in the nilutamide group (41%) than the placebo arm (24%). It should be emphasized that neither the rate of progression-free survival nor the increase in the rate of overall survival reported in these studies approaches the claims of Labrie and associates (550,551).

Recently, Eisenberger and associates (258) reported on their randomized clinical trial which involved 1,387 patients with metastatic CaP. All underwent bilateral orchiectomy and were randomized either to receive placebo (687) or flutamide (250 mg every 8 hours). The overall incidence of toxic effects was minimal, but diarrhea and anemia were more prominent in the flutamide-treated patients. The difference in overall survival between the two groups was not significant. Flutamide was not associated with enhanced benefit in patients with minimal metastatic tumor burden. These findings conflicted with those of an earlier trial conducted by the same authors, which suggested a small but statistically significant advantage to patients undergoing total androgen ablation (192). Recent enthusiasm for the use of finasteride in combination with antiandrogens and LHRH agonists as a form of “triple” hormonal therapy

should be tempered, pending the results of adequately controlled clinical trials. To date, such data are not available.

Other studies have not demonstrated superiority for total androgen blockage. Schulze and associates (885) did not observe a survival advantage for patients with stage C or D CaP treated with bilateral orchiectomy and cyproterone acetate versus orchiectomy alone. Similarly, Schroeder and associates (883) assessed the impact of buserelin versus buserelin plus cyproterone acetate in patients with stage D_1 or D_2 CaP. Again, the superiority of total androgen withdrawal over testicular androgen suppression alone could not be demonstrated. Keuppens and co-workers (501) reported the results of a clinical trial in which 327 patients with metastatic prostate cancer were randomized to either bilateral orchiectomy or treatment with Zoladex and flutamide. Although a statistically significant increase in time to subjective and objective progression was recorded in favor of the combination group, there were no statistically significant differences in time to death by cancer or overall death. Iversen (462) reported the results of an analogous study. Again, a small but statistically significant difference in time to objective progression or death from CaP was found in favor of the combination group. However, there was no difference between the treatment groups in overall survival. Of importance, treatment-related adverse events are more common in pharmacologically treated patients (460). At this time, the conflicting data would suggest that attempts to achieve total androgen ablation likely will have a minor impact on the results of treatment of patients with CaP.

Antiandrogen Withdrawal Syndrome

Scher and Kelly (877) evaluated the impact of the discontinuation of flutamide in patients treated with combined androgen blockade who exhibited evidence of disease progression during the conduct of this therapy. In their study, of the 35 patients with increasing PSA values, 10 (29%) demonstrated a significant diminution in serum PSA following cessation of flutamide. The PSA decline was greater than 80% in 7 patients and greater than 50% in 3. The median duration of this decline was approximately 5 months (range of 2 to 10+). This biochemical response also was associated with improvement in clinical symptoms. Dupont and associates (246) made the same observation. They evaluated a similar cohort of 40 patients with stage D CaP who were exhibiting evidence of disease progression despite flutamide/LHRH or flutamide/surgical castration treatment. Following the cessation of flutamide, the serum PSA decreased by 90% or more in 19 (63%) of the 30 responding patients and normalized in 17 (57%). The average duration of response following cessation of flutamide was 440 days. Sartor (867) also validated the existence of the flutamide withdrawal syndrome in 48% (14 of 29) of their patients with evidence of disease progression despite multipharmacologic therapy. More recently, evidence of a similar withdrawal phenomenon has been associated with the antiandrogen Casodex (713).

The etiology of this withdrawal phenomenon has not been definitively ascertained. Preclinical studies involving the LNCaP cell line have demonstrated that a specific point mutation in the steroid-binding domain of the nuclear AR results in paradoxic growth stimulation following exposure of the cells to estrogen, progesterone, androgens, and various antiandrogens, including hydroxyflutamide, nilutamide, medroxyprogesterone acetate, and cyproterone acetate (887,1120). Gaddipati and associates (327) evaluated advanced-stage CaP specimens and determined that the frequency of mutations involving the identical region in the nuclear AR was present in approximately 30% of evaluated specimens. The obvious implication is that flutamide and all other antiandrogens may promote growth stimulation in CaP systems that have undergone mutational events involving the nuclear AR gene. Several alternative hypotheses have been proposed. For example, flutamide may induce distinct conformational changes after binding to a normal AR, and the resulting conformational changes result in the activation of mutant androgen response elements (867). It also has been proposed that clones of prostate tumor cells that are hypersensitive to very low levels of androgens evolve with time (552).

Regardless of the etiologies, the observation of the flutamide withdrawal syndrome is important. Many patients will exhibit an excellent biochemical and clinical response to androgen-ablative therapy for periods ranging from several months to several years. Once the serum PSA consistently rises from the posttreatment nadir value, concern must exist regarding the emergence of the androgen-independent phenotype. If such patients are being maintained on total androgen ablation, serious consideration must be given to the cessation of the antiandrogen for fear that continuation of this drug will have adverse consequences.

Use of 5α-reductase Inhibitors

Testosterone is converted to dihydrotestosterone by 5α-reductase isoenzymes, type 1 and type 2, with the latter predominating in human urogenital tissues (1011). Expression of the 5α-reductase type 2 isoenzyme has been detected in the basal epithelial and stromal cells of the normal prostate but not in the secretory (adluminal) cells (918). In addition, the type 2 isoenzyme is detectable in prostate cancer stromal cells but is absent in the tumor epithelium (918). The latter observation further validates the concept that the basal cells or cells with a unique basal cell phenotype are lost in prostate cancer.

At present, there is enthusiasm to assess the potential role of 5α-reductase inhibitors in the prevention and treatment of CaP. With respect to the former, the National Cancer Institute initiated the multiinstitutional finasteride CaP prevention trial. Obviously, it will take many years before

the outcome of that effort is mature. However, the observations by Silver and associates (918) would suggest that the tumor-associated stroma is the likely target for any putative chemoprotective influence exerted by finasteride.

Fleshner and Trachtenberg (300) conducted a pilot study in which 10 patients with treatment-naive, clinical stage C and D_1 CaP were treated with a combination of finasteride (5 mg twice daily) and flutamide (125 to 250 mg three times per day). All patients were potent before the initiation of therapy, and eight remained potent during the conduct of the study. The mean serum PSA level in these patients was 34.3 ng/mL. At 3 months, the mean PSA level of all patients was 3.8 ng/mL. As anticipated, the serum testosterone level increased in all patients and gynecomastia was noted in three. This study does not permit an assessment of the durability of a response to this unique form of "sequential androgen blockade." It does, however, suggest that this treatment regimen may offer a benefit similar to total androgen blockade with fewer side effects. Obviously, multiinstitutional clinical trials are required to further address this issue and to ultimately determine the role of finasteride in our oncologic armamentarium.

Use of Prolactin Inhibitors

In addition to attempts to block androgen production and end-organ effects directly, therapeutic regimens have been devised based on evidence from studies of normal prostate indicating a synergism between androgen and other protein hormones. Concern regarding the potential role of prolactin has been based on its ability to augment testosterone effect on prostatic growth, to stimulate release of dehydroepiandrosterone and androstenedione (466), demonstration of its presence along with follicle-stimulating hormone (FSH) in immunohistochemical studies of the prostate, and on the observation that elevated serum levels of this hormone negatively affected prognosis in patients with advanced CaP (637). Levodopa (0.5 to 5.0 g per day) and bromocriptine (7.5 mg per day) have been used clinically in attempts to eliminate prolactin-related androgen synergism (189). The use of either agent can be associated with GI tract symptoms (anorexia, nausea, vomiting). In addition, levodopa has been noted to produce hypotension; cardiac arrhythmias; and central nervous system aberrations, including confusion, agitation, hyperactivity, blood dyscrasias, and hepatic dysfunction. Aside from transient improvement in pain (286,783,852), no clear clinical effects of these efforts have been evident.

The potential side effects of the various androgen-ablative approaches are summarized in Table 33.35 and their impact on serum testosterone levels is delineated in Table 33.36 .

	Orchiectomy	Estrogens	LHRH Agonists	Antiandrogens
Cardiovascular	–	+[a]	–	–
Tumor flare	–	–	++	–
Gastrointestinal tract distress	–	+	–	+
Impotence	++	++	+++	–
Gynecomastia	–	++++	–	++
Hot flashes	+	±	++	–
Minor wound	+	–	+	–
Mortality	±	+	–	–

[a]Dose-dependent.
+–++++, frequency of occurrence; –, not recognized; LHRH, luteinizing hormone–releasing hormone.
From Grayhack JT et al. Carcinoma of the prostate—hormonal therapy. *Cancer* 1987;60(3):589.

TABLE 33.35. MORBIDITY AND MORTALITY OF ANDROGEN DEPRIVATION THERAPY[a]

	First Week	Long Term	Duration	Need for Monitoring
Orchiectomy	Castration	Castration	Indefinite	No
Estrogens	Decreased	Castration	Reversible	Yes
Luteinizing Hormone-releasing Hormone agonists	Elevated	Castration	Reversible	Yes
Progestational agents	Decreased	May rebound	Reversible	Yes
Pure antiandrogen	Elevated	Elevated	Reversible	?
Steroidogenesis inhibitors	Castration	Unknown	Reversible	Yes

From Grayhack JT, Keeler TC, Kozlowski JM. Carcinoma of the prostate—hormonal therapy. *Cancer* 1987;60:589, with permission.

TABLE 33.36. EFFECT OF ANDROGEN-DEPRIVATION THERAPY ON SERUM TESTOSTERONE LEVELS

Response to Treatment: Prognostic Indicators

Approximately 20% of patients with advanced CaP fail to demonstrate an objective response to androgen-ablative therapy. From both a practical and theoretic standpoint, it would be useful to segregate those patients likely to respond to androgen suppression from those who will be refractory to such approaches. Several potential prognostic indicators, including assessment of histologic, flow-cytometric, biochemical, and molecular parameters, have been discussed in this chapter. Obtaining representative tissue for these studies represents a problem in all these efforts. Our experience with using grade as a criterion suggests that needle biopsy of the prostate provides tissue representative of the tumor as a whole approximately 75% of the time (339). Multiple biopsies may not eliminate this problem (70). The potential of tissue alteration as a result of the sampling procedure further complicates the evaluation of parameters of biologic potential by these approaches.

Recently, four interesting sets of observations have provided further insights into the various biologic characteristics of CaP and other correlations with biologic behavior. First, Prins and associates (802) used immunocytochemistry and stains of the AR to study paraffin-embedded tumor sections of AR-positive tissue. The receptorgram resulting from image analysis of the AR revealed a unimodal or

multimodal peak within a narrow concentration range in 17 of 18 hormone therapy responders. In contrast, the receptorgram of those failing endocrine therapy was highly skewed or clearly bimodal. The authors suggest these observations may have a useful clinical role.

Second, Stege and associates (973) reported on the cytosolic PSA tissue content of prostate (T-PSA) cancer needle biopsies as related to DNA in a series of patients without bone metastasis at diagnosis who were followed at least 71 months or until death after orchiectomy or medical castration. None of the patients with high T-PSA showed progression, irrespective of cytologic grade ploidy, or stage of the neoplasm.

Third, Wise and associates observed a high level of antiinflammatory cytokines [interleukin (IL)-4, IL-6, IL-10] in the serum of patients with hormone refractory CaP. In contrast, these patients—men with hormone sensitive CaP and BPH—as well as controls had comparable levels of serum proinflammatory cytokines (IL-1, IL-2, INF-γ, and THF-α). These three studies provide insights into differing characteristics of hormone refractory CaP that may provide opportunities to expand our clinical understanding of and approaches to the problem.

Finally, a study of the CWR22 human prostate cancer xenograft, by Agus and associates (6), identified a sequence of biologic phenomena associated with androgen withdrawal in this model. Early events following androgen ablation included a decrease in AR expression, a short-term increase in expression of p53 and p21/WAF1 proteins, and a marked decrease in the Ki67 proliferative index. Mid-to-late events included progressive and sustained increases in p27 and p16 protein expression, a decrease in retinoblastoma protein expression, and an increase in the transcription factor E2F1. Changes in apoptosis were not observed in this model system, suggesting that androgen withdrawal results in a cell stress response with increased p53 protein producing a cell cycle arrest without activation of p53-mediated apoptosis. The proliferative index is decreased through the action of the cyclin-dependent kinase inhibitors p27 and p16. Emergence of androgen-independent sublines was associated with murine double minute (mdm) to protein overexpression and increased expression of cyclin D1. Both the latter phenotypes prompt the release of these cells from cell cycle arrest.

Several clinical observations also have been evaluated in an effort to predict the long-term effect of endocrine manipulation in patients with disseminated CaP (Table 33.37). Carpenter and colleagues (121) found a correlation between the postorchiectomy decrease in size of the prostate as assessed on ultrasound and subsequent disease stabilization. Several nonendocrine parameters are available that may provide predictive information regarding the adequacy of hormonal response. Of these, the serum PSA and PAP appear to be the most useful. Gutman and Gutman (396) demonstrated that patients who had elevated levels of serum acid phosphatase at the time of initial diagnosis fared poorly when compared with those patients with similar-stage disease but normal serum acid phosphatase levels. Following the initiation of androgen ablation, a failure of PAP to normalize or to approach 50% of the pretreatment values

correlates with a poor prognosis (610). Moreover, Vihko and associates (1045) noted a distinct relationship between the rapidity with which PAP falls and the length of response to endocrine therapy. They noted that patients whose PAP levels returned to normal within 7 days of treatment showed no evidence of disease progression during the first year of follow-up. Similar observations relating to the degree and rapidity of postandrogen withdrawal fall in serum PSA levels have been made, and they appear to be very useful predictors of the length of response to these procedures. For example, Zagars and co-workers (1123) evaluated the outcome for patients with pathologic stage D_1 CaP who underwent immediate androgen-ablative therapy following PLND. In this group, posttreatment PSA levels were a very sensitive index of treatment response and ultimate outcome. For example, those patients who achieved undetectable serum PSA levels experienced only a 5% incidence of disease progression at 8 years. In contrast, all patients who failed to achieve undetectable serum PSA levels exhibited relapse within that time frame. Of interest, the pretreatment PSA levels were not predictive of outcome.

D_0	Disease confined to prostate gland with elevated acid phosphatase
D_1	Positive pelvic lymph node involvement
$D_{1.5}$	Rising PSA after failed local therapy (radiation or resection)
D_2	Bony and/or soft-tissue metastases
$D_{2.5}$	Androgen-independent prostate cancer (may be called *HRPC*)
	Rising PSA after androgen ablation/castrate serum androgen levels
D_3	Hormone-insensitive prostate cancer (true HRPC)

HRPC, hormone-refractory prostate cancer; PSA, prostate-specific antigen.
Adapted from Crawford ED, Blumenstein BA. Proposed substages for metastatic prostate cancer. *Urology* 1997;50:1027.

TABLE 33.37. STAGES OF ADVANCED PROSTATE CANCER (STAGE D)

Serum alkaline phosphatase determinations are of less specific utility when compared with measurements of PSA or PAP because the former enzyme is frequently elevated in the presence of skeletal or hepatic metastasis from any variety of neoplasm. With regard to CaP, a transient elevation of serum alkaline phosphatase is frequently noted following the initiation of hormone therapy. Although the etiology of this flare phenomenon is poorly appreciated, it seems to be associated with a favorable response to therapy (872).

These relatively crude clinical observations have the advantage of reflecting an effect on either the entire local or systemic tumor burden so that they minimize the problem related to sampling. None of the available indicators of disease progression and androgen responsiveness is sufficiently reliable to permit exclusion of any patient group from the potential benefits of androgen-ablative therapy (378).

Timing of Hormonal Therapy

Advanced-stage CaP has a high rate of natural progression. For example, the VACURG has shown that the median survival time of men with roentgenographic evidence of bony metastasis is somewhat less than 12 months (114). Involvement of pelvic lymph nodes by metastatic CaP is associated with clinically identifiable metastatic disease in 50% of patients at 36 months and 80% of patients at 52 months following diagnosis (39). These patients with no D-positive disease have a reported 5-year survival of approximately 50% (1054). These findings are not restricted to patients with definable metastatic tumor burdens, because the VACURG has shown regular progression of patients with stage C carcinoma to recognizable stage D in 30% of patients in 24 months and in half of patients at 52 months following diagnosis (113). There is little doubt that androgen-ablative therapy remains the accepted first-line treatment modality for patients with metastatic CaP. There is considerable controversy, however, with regard to the appropriate timing of such therapy. This apparent dilemma exists because of the lack of definitive evidence that hormonal manipulation prolongs survival and from the conclusions of the VACURG study that suggested that delayed hormone therapy has no adverse effects on survival (65).

It is relatively easy to construct a list of absolute or relative indications for the initiation of hormonal therapy. The onset of frank paraplegia due to spinal cord compression or clinical evidence of impending neurologic involvement mandates the urgent initiation of such treatment, preferably orchiectomy. Obviously, the patient should be observed with vigilance to ascertain the need for emergency decompressive laminectomy and other adjunctive therapeutic measures (steroid and radiation therapy). Similarly, few urologic surgeons would contest the validity of initiating androgen-ablative therapy in patients presenting with intravesical or extravesical ureteral obstruction secondary to progressive CaP. Retrograde or antegrade passage of double-J ureteral stents may be a necessary adjunctive treatment. Approximately three-fourths of the patients with hydronephrosis demonstrate significant improvement following the initiation of castration or multimodal endocrine therapy (653). Extension through the posterior layer of Denonvilliers' fascia with subsequent rectal obstruction is decidedly rare but certainly constitutes an indication for prompt hormonal therapy and diverting colostomy (322). The obvious presence of bone pain due to metastasis, anemia, weight loss, and other systemic symptoms of disseminated disease constitutes legitimate, although perhaps not urgent, indications for treatment. Bladder neck obstruction due to locally aggressive disease can be significantly improved in approximately 65% of men within 6 months of androgen deprivation, with most patients responding within 2 to 3 months (299). This last clinical situation lacks universal acceptance as an indication for the initiation of hormone therapy.

The proponents of delayed initiation of hormone therapy cite several presumably supportive arguments in favor of that approach. Approximately 50% of untreated patients with clinical stage C or pathologic stage D_1 disease will manifest 5-year survival patterns without apparent disease progression (753,882). Another source of reluctance on the part of urologists to initiate hormone therapy is the undesirable side effects of treatment (previously discussed) on the patient without symptoms. Finally, the advocates of delayed hormonal therapy can cite theoretic objections rooted in the biology of tumor systems. Theoretically, a reduction in the mass of androgen-dependent cells in the absence of effective inhibition of the growth of androgen-independent subpopulations could release the latter from a

state of decreased proliferation and ultimately augment their growth and dissemination (14,866). More recently, it has been proposed that androgen-independent cells that survive androgen-deprivation therapy may originate because of the ability of a small number of initially androgen-dependent stem cells to adapt to the altered hormonal environment through the induction of androgen-repressed protective mechanisms (820).

Various arguments also can be offered to support the contention of those urologists favoring the prompt initiation of hormonal therapy (532,538,1036,1123,1141). Although the causal mechanism is uncertain, the survival advantage of patients with advanced prostate cancer in the postendocrine as compared with the preendocrine era is prolonged (711,1042). In the VACURG study, treatment of patients with stage C disease with either 1 or 5 mg of DES daily reduced the recognized progression in 52 months following diagnosis from 50% to 10% (113). Furthermore, limited data suggest that the combination of radical prostatectomy coupled with immediate endocrine therapy may possess an advantage over sequential therapy in patients with diploid tumors with regard to disease progression and perhaps survival (1137,1139). Certainly, the early initiation of hormone therapy permits the recognition of nonresponders to such treatment at a point in their disease process before profound weight loss, anemia, and generalized inanition develop.

Theoretically, these hormonal nonresponders would be better candidates for additional multimodal therapy because of the presence of smaller tumor burdens and their enhanced physical status. In his analysis of the Dunning R-3327H rat prostatic adenocarcinoma model, Isaacs (454) determined that prompt initiation of endocrine therapy prolonged survival and that the concomitant use of chemotherapy (cyclophosphamide) was most efficacious when both therapies were begun promptly and simultaneously.

A reanalysis of the VACURG data (66) tended to support the efficacy of early rather than delayed hormonal therapy. Finally, Byar and Corle (112a) presented the most recent reanalysis of the VACURG data and concluded that younger patients with high-grade tumors (Gleason score 7 to 10) and advanced stage disease derive a survival benefit from the initiation of hormone therapy (DES 1 mg) begun at diagnosis. Patients with low-stage disease and low-grade tumors (Gleason score 2 to 6) probably do not need hormone therapy.

More recently, Messing and associates (648) reported on 98 men who underwent radical prostatectomy and pelvic lymphadenectomy and who were found to have nodal metastases. These men were randomly assigned to receive immediate antiandrogen therapy (either goserelin or bilateral orchiectomy) or were followed until disease progression. After a median of 7.1 years of follow-up, 7 of 47 men who received immediate hormonal therapy died, as compared with 18 of 51 men in the observation group. The cause of death was CaP in 3 men in the immediate treatment group and in 16 men in the observation group. They concluded that immediate antiandrogen therapy after radical prostatectomy and pelvic lymphadenectomy improved survival and reduces the risk of recurrence in patients with node-positive CaP. Several explanations were offered to explain the conclusions generated in this study as compared with that of the original VACURG. First it was proposed that patients with less residual cancer are more likely to benefit from prompt and effective androgen ablation as compared with those confronted by substantial tumor burden. This theory underscores the potential importance of controlling the primary tumor and initiating treatment when the metastatic tumor burden is minimal. These results confirm those of investigators at the Mayo Clinic (691,894). In the latter series, only patients with tumors that consisted of DNA diploid cells had a survival advantage with immediate therapy and that advantage was evident only after 10 years of therapy. The study by Messing and associates (648) was a prospective and randomized clinical trial unlike the retrospective study conducted by the Mayo group. Further validation of the potential value of early hormonal therapy emanated from the study conducted by Bolla and associates (77). In that study patients with clinical stage T_2 or T_3 prostate cancer who received goserelin during external beam radiotherapy and for 3 years thereafter had significantly higher survival rates than similar patients who received radiotherapy alone.

Observations such as these raise legitimate questions about concepts that have guided common practices in treating patients with CaP. We can no longer dismiss the possibilities that early rather than delayed hormone therapy, surgical tumor mass reduction, and radiation/hormone therapy synergism, for example, as well as other novel approaches may have a place in treating patients with this disease. A healthy degree of management uncertainty will probably persist for some time as we appropriately scurry to obtain new data and understanding. In the meantime, we judge it appropriate to use the various tools we have to characterize the patient and his disease to select appropriate choices from alternatives such as early versus delayed initiation of hormone therapy for consideration in management of CaP patients.

Intermittent Endocrine Therapy

It appears that both genetic (453) and epigenetic (106) influences contribute to the emergence of the androgen-independent phenotype. With respect to the latter concept, various compelling preclinical studies have been conducted using the androgen-dependent Shionogi mouse mammary carcinoma. These studies suggest (a) that the parenteral tumor consists of stem cells that are initially androgen-dependent; (b) that following androgen-withdrawal, tumor cell killing is limited to two to three logarithms before

compensatory adaptive mechanisms emerge, including disappearance of ARs from the nucleus and expression of androgen-repressed genes such as c-fos and c-myc; (c) that part of this adaptive response also involves the induction of genes that may protect the tumor cells from programmed cell death, such as TRPM-2 (clusterin); and (d) that the alterations in the hormonal environment attendant to androgen withdrawal play a significant role in the induction of the androgen-independent state (106,820). LNCaP tumor cells can adapt to reduced androgen availability by increasing the AR mRNA levels (2.5-fold) and the AR protein levels (15-fold), thus increasing their sensitivity to androgen, which suggests that prostate tumor cells may adapt to the altered hormonal environment induced by antiandrogen and/or androgen ablation therapy by increasing the transcriptional activity or steroid affinity of the AR as a potential survival mechanism. LNCaP cells that have adapted to an androgen-free environment are hypersensitive to very low concentrations of androgen and their growth is, in fact, repressed by moderate androgen concentrations.

These and other *in vitro* observations prompted animal studies using the Shionogi mouse tumor to determine whether the ultimate emergence of the androgen-independent phenotype could be delayed by intermittent androgen suppression. In this study, the tumor was transplanted into a series of male mice, each of which was castrated when the estimated tumor weight became approximately 3 g. Once the tumor regressed to 30% of its original weight, it was again transplanted to the next noncastrated male animal. This "cycle" of transplantation and castration-induced regression was repeated through four generations before the androgen-independent phenotype emerged. The implication of this study is that a similar "cycling" of androgen-ablative therapy might prolong the time to emergence of the androgen-independent phenotype threefold to fourfold.

A modest amount of clinical information exists that tends to support this concept. Klotz and co-workers (515) reported on their experience with 20 patients with advanced CaP. The median duration of endocrine therapy before the withdrawal of treatment was approximately 10 months. Disease progression occurred at a median of 8 months following interruption of therapy. All of these patients who relapsed had a rapid clinical response following the resumption of androgen-ablative treatment. It has been suggested that the most attractive patients for this approach are those individuals who achieve undetectable serum PSA levels following the initiation of total androgen blockade.

Several recent clinical studies attest to the potential utility of intermittent androgen deprivation (IAD). Grossfeld and associates (388) conducted a study involving 47 patients with clinically localized CaP. No patient was found to have systemic disease before the initiation of therapy. In this study, androgen deprivation was continued 1 to 2 months after serum PSA became undetectable or a nadir level was reached. Therapy then was reinstituted after serum PSA reached a predetermined level. The serum PSA level at which therapy was reinstituted was individualized for each patient and was determined by one of the following parameters: (a) serum PSA level greater than 50% of the pretreatment level, (b) serum PSA level greater than 10 ng/mL, or (c) patient request. In this study, only 1 patient failed to respond to reinstitution of treatment and that patient was found to have metastatic disease during his second cycle of treatment. These investigators believe that IAD is a viable treatment option in selected patients with clinically localized prostate cancer.

Strum and associates (988) reported on 52 patients with CaP treated with IAD. Prior treatment in this group included (a) none in 29 of 52, (b) radical prostatectomy with PSA relapse in 13 of 52, (c) failed external beam radiation therapy in 4 of 52, and (d) treatment failure following radical prostatectomy and external beam radiation in 6 of 52. Most exhibited localized disease (46%) or PSA relapse following an attempt at definitive therapy (37%). Four percent and ten percent of patients were assigned clinical stage D_0, D_1, or D_2, respectively. Therapy was stopped upon achieving an undetectable serum PSA level (median of 1 year). Patients were followed off therapy and advised to restart androgen ablation if the PSA level reached greater than or equal to 5.0 ng/mL. In 28 patients who maintained an undetectable serum PSA level for greater than or equal to 1 year, their median off-phase duration was 29 months with 9 (32%) still off IAD after median follow-up of 62 months. Multivariant analysis revealed several significant independent factors associated with prolonged off-phase duration, including undetectable PSA on androgen deprivation therapy greater than or equal to 1 year, PSA-only recurrence after local therapy, and reaching a testosterone level greater than or equal to 150 ng/dL in greater than or equal to 4 months off androgen ablation.

According to Gleave (365), the definition of PSA nadir should be the lowest serum PSA level attained following institution of androgen ablation and, by definition, plateaus out and falls no further. Studies conducted by Goldenberg and associates (366) and Gleave and associates (364) suggest that patients initially should be treated for a minimum of 9 months because PSA nadir and maximal soft tissue regression (when definable) are not reached until 8 or 9 months in many cases. Ideally, androgen ablation should be continued until maximal tumor regression has been induced, but stopped before constitutive development of the androgen-independent phenotype (365). The length of the "off cycle" remains somewhat empirical but should be long enough to permit normalization of libido and reversal of the other symptoms associated with the androgen deprivation syndrome. In addition, the off cycle should be of sufficient duration to permit testosterone-induced tumor cell differentiation (365). Factors that can influence the decision to reinitiate therapy include pretreatment PSA levels, stage,

PSA velocity, presence of symptoms, and tolerance of androgen ablation therapy (365). A reasonable PSA "trigger point" for the resumption of androgen ablation in patients being treated for postradiotherapy or postprostatectomy recurrences is a value greater than or equal to 4 mg/mL (365). Similarly, the PSA "trigger point" for the resumption of androgen ablation in patients with metastatic disease would be values ranging from 10 to 20 mg/mL. It would appear that biochemical failures following radiotherapy or surgery are the groups most likely to benefit from intermittent hormonal therapy (77).

A recent concept related to IAD is the potential value of initiating finasteride when patients are taken off cycle. With this strategy, a shift would be induced toward elevated tissue testosterone levels while maintaining suppression of DHT production. Preclinical studies have suggested that testosterone induces more differentiated tumor phenotype. The latter is at least theoretically more likely to maintain a low proliferative potential while the patient is off cycle.

It must be emphasized that the concept of intermittent androgen suppression remains a novel hypothesis, the validity of which must be ascertained through multiinstitutional clinical trials that are currently ongoing. Finally, it is important to state that this concept is not incompatible with the early initiation of androgen-ablative treatment. It merely suggests that once initiated, carefully orchestrated "cycling" may also be beneficial with respect to maintaining a small tumor volume expressing a predominantly androgen-dependent phenotype.

PC-SPES

PC-SPES is an herbal combination used by patients with prostate cancer that consists of the following eight herbs: chrysanthemum, isatis, licorice, *Ganoderma lucidum,* Panax, pseudoginseng, *Rabdosia rubescens,* saw palmetto, and scutellaria (skull cap) (285,397,433). Mass spectrometry has shown that PC-SPES contains estrogenic organic compounds that are distinct from DES, estrone, and estradiol (232). In the latter study, the clinical activity of PC-SPES was evaluated in eight patients with hormone-sensitive prostate cancer, and it decreased serum PSA concentrations in all eight. It also decreased the serum testosterone concentration in the six men tested. All patients had breast tenderness and loss of libido, and one had venous thrombosis. Thus this unregulated herbal dietary supplement had a clinical impact and side effects similar to those of pharmacologic doses of estrogen.

De la Taille and associates (218) performed a preclinical and clinical study assessing the impact of PC-SPES. The *in vitro* evaluation was designed to assess the impact of PC-SPES on the induction of apoptosis using prostate cancer cell lines LNCaP, PC3, and DU145 as the tumor targets. All the cell lines exhibited a significant dose-dependent induction of apoptosis following exposure to PC-SPES. Furthermore, immune-deficient mice xenografted with the PC-3 cell line exhibited reduced tumor volume compared with sham-treated controls when they were treated with the PC-SPES extract from the time of tumor implantation but not when the treatment was begun 1 week after tumor implantation. Of interest, the testis, prostate, bladder, and seminal vesicles of the treated mice were significantly reduced in weight when compared with the sham-treated animals. In the clinical arm of their study, 69 patients with prostate cancer were treated with three capsules of 320 mg PC-SPES daily. Eighty-two percent had decreased serum PSA levels at 2 months, 78% at 6 months, and 88% at 12 months after treatment with PC-SPES. Side effects included nipple tenderness in 42% and phlebitis requiring heparinization in 2%.

Small and associates (926a) evaluated the impact of PC-SPES on 35 patients with androgen-independent prostate cancer and noted that 19 of 35 (54%) had a PSA decline of greater than 50%, including 8 (50%) of 16 patients who had received prior ketoconazole therapy. Median time to PSA progression was 16 weeks. Of 25 patients with positive bone scans, 2 had improvement, 7 had stable disease, 11 had progressive disease, and 5 did not have a repeat bone scan because of PSA progression. As a composite, these and other studies suggest that PC-SPES may have some activity in the treatment of both androgen-dependent and androgen-independent prostate cancer. This activity may be related to an induction of program cell death and/or a decrease in the expression of AR (397,433,434).

Objective Assessment of Therapeutic Efficacy

The patterns of metastasis exhibited by CaP make the objective assessment of treatment response following the initiation of androgen-ablative therapy somewhat difficult. Until the advent of TRUSP, accurate assessment of changes within the prostate gland with regard to consistency, tumor extension, and overall tumor volume have been dependent on the evaluation afforded by digital examination. Changes in the status of the two common sites of metastases, the pelvic lymph nodes and osteoblastic bone lesions, are likewise difficult to identify or quantify. Even the validity of sequential analysis of serum PSA and PAP has been questioned with the recognition that these levels may fluctuate in patients without treatment or result from faulty handling of the specimen or methods (714,872). These difficulties have required the segregation of large numbers of patients into nonevaluable or stable categories. Clinical and scientific intuition suggests that this subset of patients is undergoing dynamic changes that merely elude our current evaluation procedures.

Even with currently available methods, legitimate assessments can be made with regard to treatment efficacy in a substantial number of patients. Huggins and Hodges (446) were able to convincingly document a significant diminution in serum acid phosphatase following castration in

patients. Since then, various studies have reinforced these observations, documenting a greater than 50% decrease in levels of serum PAP in the vast majority of patients treated with the spectrum of available endocrine therapy. Serum PSA now plays a preeminent role in monitoring untreated patients or those subjected to radical prostatectomy or radiation therapy and in patients with endocrine-treated metastatic disease.

Bone scans provide an estimate of cellular activity but give little information regarding bone density (786). Despite this limitation, several studies have documented discernible improvement in bone scans of patients treated with various androgen-ablative therapies. The observed incidence of improvement varied from 48% in a study comparing the efficacy of EMP with DES (63) to 27% by Shearer and associates (907), and 16% as documented by Fitzpatrick and associates (295). The results were even more disparate in the LHRH studies in which Labrie and associates (550) reported 100% of patients with improved bone scan as compared with 1 (8%) of 12 reported by Faure and associates (288). Carefully using our current evaluation procedures, such as TRUSP and serum and urine markers, and developing new techniques to assess the effect of therapeutic procedures on tumor growth are critical to permit identification of effective treatment regimens in patients with CaP without relying on cumbersome, incomplete, and inaccurate survival information.

Hormone-refractory State: The Role of Additional Hormonal Therapy

Patients with stage D_3 (androgen-refractory) disease have a dismal prognosis, with a mean survival of less than 1 year (147). That the vast majority of patients with stage D disease ultimately demonstrate disease progression despite hormonal therapy is an ominous clinical reality whether AID cells preexist or develop in the primary tumor and its metastasis. Despite numerous attempts, no significant palliative or survival advantage has ever been conferred with regularity by further efforts to eliminate androgens or their effects in these patients. Only a selective sampling of such attempts is discussed in the next few paragraphs.

Several studies have assessed secondary DES administration in patients who failed to benefit from orchiectomy. Most of these studies revealed transient objective improvement in 20% to 30% of patients, but no demonstrable survival benefit was discernible (711). Clinical improvement was noted in 20% of patients treated with high-dose DES (Stilphostrol) after failing previous endocrine therapy; three of these patients had a decrease in acid phosphatase levels (174). Conversely, several studies evaluated the effect of orchiectomy following the failure of estrogen therapy. For example, Stone and associates (984) noted one partial objective response and four stable responses in 21 patients after secondary orchiectomy and Klijn and associates (514) reported enhanced survival compared with those treated with estrogens following orchiectomy.

Antiandrogens and inhibitors of steroid synthesis have shown modest efficacy when used as secondary modes of endocrine therapy. Flutamide (and other nonsteroidal antiandrogens) has been associated with favorable objective responses in between 20% and 30% of patients who have failed prior endocrine therapy. However, these responses were of very short duration and produced no apparent survival benefit (700,940,983). Data concerning cyproterone acetate produced discrepant results; several studies report favorable responses ranging between 50% and 70% in patients with advanced-stage prostate cancer (936,1087). Conversely, Tvetor and associates (1028) observed little demonstrable evidence of tumor regression in a similar group of patients.

TREATMENT OF METASTATIC HORMONE-REFRACTORY PROSTATE CANCER

Part of "33 - CARCINOMA OF THE PROSTATE "

The objective and subjective response of 75% of the patients with metastatic CaP to androgen-ablative therapy has a major positive impact on their management. Unfortunately, after a quiescent period of a few months to several years, most patients develop the uncontrolled growth of so-called hormone-refractory prostate cancer (HRPC). PSA monitoring has permitted earlier recognition of increasing tumor load, magnified the apparent response rates to initial hormone therapy, and extended the recognizable period of survival after development of hormone refractory tumor growth. The ominous probability that half of the patients with HRPC cancer would die within the first year following relapse and the majority of the remainder in the next (143,923) has been modified by the lead time lengthening associated with PSA monitoring of CaP patients. Nevertheless, although problems from progressive disease seem delayed, they are expected. These observations provide an incentive to better understand the biology of HRPC and to develop novel durably effective and well-tolerated therapies.

Mechanisms Underlying the Emergence of Androgen-independent Tumor Clones

Although the actual mechanisms underlying the emergence of HRPC remain unclear, both genetic (453) and epigenetic (106) events appear to play a role in this phenomenon, which is typified by cellular de-differentiation. At present, there is no uniform consensus regarding when HRPC first emerges.

The studies conducted by Isaacs and Coffey (453) using the Dunning rat model of prostate cancer support the concept that *the development of HRPC is a relatively early event at the clonal level*. This perception is supported by more recent studies involving PIN, which have identified

phenotypes within PIN foci that are frequently noted in high-grade HRPC. Examples of the latter include frequent identification of aneuploidy (83,57); gains of chromosome 7 (85,804); and the frequent occurrence of allelic loss at chromosomes 7q31-q35, 8pl2-21, 8p22, 8q22, 8q22.2, and 8ql2.2 in both PIN and invasive prostate cancer (83,85,273,1051) (Table 33.4). Also intriguing is the identification of telomerase activity (which prevents apoptosis), present in 92% of CaP (1130), and in PIN (73%), BPH (50%), atrophy (16%), and normal-appearing tissue (36%) located adjacent to prostate cancer foci. This shared enzymatic characteristic could be due to the presence of occult cancer cells or shared molecular alterations that are histologically not apparent. In distinction, the studies conducted by Koeneman and associates (519) could identify telomerase activity in only 4 of 25 samples (16%) of high-grade PIN. Furthermore, all telomerase-positive PIN foci exhibited a diploid DNA content. As stated previously, telomerase is the ribonucleoprotein that adds telomeric repeats to the ends of chromosomes. Excessive telomere shortening can lead to genomic instability. The subsequent gains/loss of genomic DNA is a characteristic feature exhibited by metastatic CaP. In the study conducted by Donaldson and associates (237) there appeared to be a direct correlation between reduced telomere DNA content in CaP specimens and subsequent disease recurrence and death.

We previously addressed the role of bcl-2 oncoprotein with respect to inhibition of program cell death or apoptosis in CaP systems. Indeed, it has been suggested that bcl-2 may play an important role in the emergence of hormone resistance, and several studies have demonstrated enhanced expression of bcl-2 in HRPC (182,626). In the study conducted by Baltaci and associates (34), bcl-2 staining was detected consistently in the basal cell layer of the ducts and acini in BPH samples. No staining was ever apparent in luminal cells. Bcl-2 immunoreactivity was present in 10 of 15 high-grade PIN lesions. Bostwick (85) provides a detailed summary of the phenotypes that link high-grade PIN with invasive (and hormone refractory) CaP.

Recently, Craft and associates (190) performed studies using a novel human prostate cancer xenograft (LAPC-9), which was propagated by serial passage in male severe combined immunodeficiency disease (SCID) mice. This xenograph expresses PSA and wild-type AR. Following castration, LAPC-9 cells undergo growth arrest and persist in a dormant androgen-responsive state for approximately 6 months. Ultimately, spontaneous androgen-independent outgrowths develop. In this model, progression to androgen independence occurs through two distinct states, initially escaping dependence on androgen for survival and, ultimately, for growth. They demonstrated that the latter stage of androgen independence results from clonal expansion of androgen-independent cells present at a frequency of approximately 1 per 10^5 to 10^6 androgen-dependent cells. They postulated that prostate cancers contain heterogeneous mixtures of cells that vary in their dependence on androgen for growth and survival. Treatment with antiandrogen therapy provides selective pressure and alters the relative frequency of these cells, leading to androgen-independent cancers.

The studies conducted by Bruchovsky and associates (106) using the androgen-dependent Shionogi mammary carcinoma model support the hypothesis that immediately following tumor transformation, most, if not all, of the cells constituting the primary tumor are predominantly androgen dependent. HRPC clones emerge during the course of tumor progression. This event may be influenced by both genetic instability, which is inherent in proliferating tumor systems, and environmental (epigenetic) factors (i.e., sustained androgen ablation).

The molecular mechanisms underlying the emergence of HRPC are almost certainly multifactorial. One popular concept is that methylation of CpG islands results in gene inactivation and that methylated sequences are heritably silenced. CpG islands, cytosine-rich areas located in the 5′ regulatory region of a given gene, are unmethylated in most normal adult tissues (739). The methylation of this critical region of the genome can block transcription of downstream sequences that may be critical to normal cellular homeostasis. Examples of aberrant CpG island methylation possibly relevant to the emergence of HRPC include the inactivation of the CDKN2/pl6/MTSI gene (a cell cycle regulator) (415) and loss of E-cadherin expression (which decreases cell-cell cohesiveness) (371).

Alterations in the structure and/or expression of the AR gene also may play a role in emergence and progression of HRPC. The AR gene, located on the long arm of the large X chromosome, codes for a transcription factor within the super family of steroid receptors. Exon 1 encodes the transactivation domain that mediates target gene transcriptional activation. Exon 1 also encodes two polymorphic polyamino acid tracts—poly-Q $(CAG)_n$ and poly-G $(GGC)_n$ (842). Taplin and associates (1003) demonstrated that 5 of 10 HRPC metastases contained mutations in the ligand-binding domain of the AR gene. More recently, single-strand conformational polymorphism analysis and DNA sequencing of the entire AR gene coding region revealed base changes leading to amino acid substitutions in the AR in 44% of 25 advanced primary prostate cancers before endocrine treatment (1016). Marcelli and associates (617) performed a more recent evaluation. These investigators analyzed the frequency and relevance of mutations in the coding region of the AR in genomic DNA extracted from 137 specimens of CaP. The overall number of mutations detected was 11 (8%). Of interest, no mutations were detected in any of the 99 patients with organ-confined disease. Eleven mutations were detected in exons 2 to 8 in 8 of the 38 patients with stage D_1 disease. In contrast to previous reports, these data suggest that AR mutations may be rare and may not play a strategic role in

the initial phase of prostatic carcinogenesis. The presence of a significant number of AR mutations in metastatic disease does suggest that these mutations may play an important role in the most advanced stages of this disease process. Finally, Koivisto and associates (521) reported an interesting series of observations. These investigators studied six prostate cancers diagnosed during finasteride treatment for BPH. Comparative genomic hybridization detected genetic alteration in four tumors. Xq and 6q were the most common alterations. The recurrent Xq gains prompted these investigators to study the involvement of the AR gene. One tumor Xq gain had a threefold amplification of the AR gene. This suggested that tumor development in finasteride-treated patients may require increased AR copy number and expression as has previously been shown for prostate cancers recurring during hormonal therapy. In another tumor, an Arg 726Leu mutation of the AR gene was identified. This mutation previously has been reported to affect the transactivational properties of the AR gene.

Description of the Cellular and Molecular Characteristics Associated with the Androgen-independent Phenotype

Numerous adverse tumor cell features have been associated with poorly differentiated HRPC, including the following:

1. Gleason grade 4 or 5 (532)
2. Tumor volume greater than l mL (968)
3. Tetraploid/aneuploid DNA content (906)
4. Abnormal cell shape, motility, and negative surface charge (127,666)
5. Decreased nuclear AR expression (102), despite intact/amplified AR genes
6. AR gene mutations (327) and certain polymorphisms (shorter CAG repeat length) in the AR (361)
7. Gains of chromosomes 7 and 8 (998)
8. Deletion of a putative metastasis suppressor gene (KAI 1) on chromosome 11 P11.2 (449)
9. Increased tumor neovascularity (91,289)
10. Enhanced expression of urokinase-type plasminogen activator, which promotes matrix degradation and its receptors (343,495)
11. Aberrant expression of growth factors, their receptors, and binding proteins (304,427,977)
12. HER-2/neu overexpression (EGFR activity) (230,692,917)
13. p53 gene mutations (controls G1-S breakpoint) (79,412,626,704)
14. Upregulation of the bcl-2 gene with inhibition of programmed cell death (626)
15. Decreased tumor cell cohesiveness and increased invasiveness associated with reduced expression of E-cadherin gene and/or deletion of the α-catenin gene (674,826,1031,1032)
16. Upregulation of thymosin B-15, which enhances tumor cell motility
17. Increased endothelin-1 and endothelin receptor expression (708,709)
18. Elevated serum levels of TGF-ß1 (459)
19. Loss of expression of TGF-ß1 type I and/or type II receptors (394,504)
20. Increased IL-6 expression (activates AR) (421,728,1029)
21. Decreased expression of neutral endopeptidase 24.11 (inactivates neuropeptides) (743)
22. Loss of cyclin-dependent kinase inhibitor p27 Kipl (394,1119)
23. Differential expression of the nuclear matrix protein, designated YL-I (553)
24. Increased expression of the RET protooncogene tyrosine kinase growth factor receptor on chromosome 10qll.2 (214)
25. Preferential adhesion to human bone marrow endothelial cells (568)
26. Overexpression of caveolin-1 (inhibits apoptosis, mediates molecular transport, augments signal transduction activities) (1118)
27. Overexpression of COX-2 (decreases E-cadherin expression, overexpression of matrix-degrading enzymes, increased production of angiogenic factors) (593)
28. Overexpression of matrix metalloproteinases (476)
29. Inactivation PTEN (tumors suppressor) gene located at 10q 23.3 (1050)
30. Overexpression of parathyroid hormone-related protein (autocrine/paracrine growth factor; binds to receptors on osteoblasts and stimulates bone formation/resorption) (241)
31. Enhanced expression of the GBX2 homeobox gene (upregulates transcription of the IL-6 gene) (334)
32. Increased expression of osteonectin/SPARC (antiadhesive protein involved in cell–matrix interactions, migration, and androgenesis) (1013)
33. Defective generation of ceramides (a key sphingolipid mediator of apoptosis) (1073)
34. Overexpression of neuropeptides (calcitonin, serotonin, somatostatin, bombesin/gastrin—a releasing peptide, thyroid-stimulating hormone, neurotensin) with subsequent induction of type 4 collagenase (896)
35. Increased expression of the proliferation marker KI-67, a nuclear antigen and molecular marker associated with disease progression (682)
36. Increased intracellular levels of SGP-2 (clusterin), apoptosis inhibitor (975)

Several recent and important observations have enhanced our understanding of the genomic changes associated with CaP. These studies involve sophisticated molecular approaches that expand the data generated using basic cytogenetic analysis and include fluorescence in situ hybridization

(FISH); comparative genomic hybridization (CGH); and tissue microdissection, DNA extraction, and polymerase chain reaction (PCR) amplification to determine microsatellite alterations.

Step-section analysis performed on whole-gland specimens containing CaP most often reveals the presence of multiple tumor foci (533). It has been debated whether these observations reflect a “field change” phenomenon (382) or merely represent intraglandular spread following unifocal tumor development. Studies conducted by Cheng and associates (164) involved a molecular analysis of microsatellite alterations in the DNA from separate tumors in the same prostate. Their study focused on factors for the putative tumor suppressor gene on chromosome 8p and for the BRCAI gene on chromosome 17q. The pattern of allelic loss documented in that study was compatible with independent tumor origin in 15 of 18 informative cases. This finding tends to validate the “field change” hypothesis.

Using FISH analysis, Takahashi and associates (998) evaluated needle biopsy cores from randomly selected radical prostatectomy specimens and documented gains of chromosome 7 and 8 in 76% and 59% of aneuploid tumors (998). A higher Gleason score correlated with gains of chromosome 7 and 8 and advanced tumor stage with gains of chromosome 7. A similar analysis of paraffin-embedded radical prostatectomy specimens (997) noted that gains of chromosome 8, aneusomy of chromosome 8, and aneusomy of chromosome Y correlated highly with systemic cancer progression. Multivariate analysis subsequently demonstrated that gains of chromosome 8 and aneusomy of chromosome Y were significant independent predictors of systemic cancer progression.

CaP allelotyping studies revealed frequent loss of heterozygosity (LOH) on chromosomes 8p (50%), l0p (55%), l0q (30%), 16q (31% to 60%), and 18q (17% to 43%) (132,545). Visakorpi and associates (1049) expanded these observations by performing CGH to screen for DNA sequence copy number changes along all chromosomes in 31 primary and 9 recurrent uncultured prostate carcinomas; 74% of primary prostate cancers showed DNA sequence copy number changes. Losses were five times more common than gains and most often involved 8p (32%), 13q (32%), 6q (22%), 16q (19%), 18q (19%), and 9p (16%). Of note, frequent gains of 7, 8q, and X were associated with prostate cancer progression and the development of hormone-independent growth.

Cher and associates (165) also used CGH to study CaP metastases in patients who had received no prior treatment and compared these observations with those generated from an analysis of primary or recurrent tumors in patients who had received long-term androgen-deprivation therapy. In treatment-naive metastatic foci, several altered chromosomal regions were documented, including 8q gain (85%), 8p loss (80%), 13q loss (75%), 16q loss (55%), 17p loss (50%), and 10q loss (50%). Of interest, the observations generated in the “treated” group were very similar to those of the “treatment-naive” group. The study also demonstrated several previously undetected regions of frequent loss including 2q (42%), 5q (39%), 6q (39%), and 15q (39%). Gains of chromosomes lp (52%), lq (52%), 3q (52%), and 2p (45%) also were documented. Of interest, African American patients demonstrated a significantly higher frequency of gain of the 4q 25 to q 28 region.

It is suspected that the regions of loss contained known or candidate tumor suppressor genes. Chromosome 5q31 contains the α-catenin gene, which is an obligatory component of the E-cadherin-mediated cell adhesion complex (325). PC-3, DU-145, and TSU-PRI HRPC cell lines have reduced or absent levels of α-catenin or E-cadherin (676). LOH at 7q31.1 (c-met oncogene locus) is correlated significantly with a higher Gleason score and lymph node metastasis (781,996). Chromosome 10q22. L-qter harbors the candidate tumor suppressor gene Mxil (248). The Mxil protein is thought to repress c-myc activity, and loss of this suppression may lead to c-myc activation (1129). LOH at 10q23.3, a region commonly deleted in CaP, may involve the loss of the candidate tumor suppressor gene designated PTEN/MMACI (994). Inactivation of this gene may contribute to the acquisition of metastatic potential in CaP. Another putative metastasis suppressor gene has been mapped to human chromosome llpll.2 and has been designated KA I1 (238). KAI1 expression is significantly reduced in human CaP cell lines derived from metastatic foci (PC-3, LNCaP, TSU-PRI, and DU-145). The retinoblastoma susceptibility gene (RBI) is located on 13ql4. Approximately one-third of CaP exhibit LOH at this locus (165,185). Chromosome 16q contains the E-cadherin locus. E-cadherin is required for normal calcium-mediated cell-to-cell adhesion. Its expression is frequently lost in high-grade, androgen-independent CaP involved with invasive/metastatic potential (1031,1032). Recent studies suggest that there is a separate region of 40% loss at 16q24 that may contain another important tumor suppressor gene (165). More than 50% of prostate cancers analyzed demonstrate allelic loss of at least one locus on chromosome 17q, which contains the BRCAI gene (336). Finally, the p53 tumor suppressor gene is located on 17p and is known to be mutated in 20% to 25% of metastatic prostate cancers (165).

Regions of gain contain dominant oncogenes whose expression is amplified with increased copy number. The epidermal growth factor receptor (erbB-I) is located on chromosome 7p (165). Chromosome 7 trisomy is associated with higher grade and advanced-stage CaP (11,36). The c-met oncogene maps to chromosome 7q31 and is amplified in 40% of metastatic HRPC (781). Chromosome 8q24 harbors the cMyc oncogene. Of note, CGH analysis suggests the presence of a potentially important oncogene at 8q21.3 (165). The H-Ras oncogene is located at llpIS.5, but this region is not identified as a common region of gain in prostate cancer. CGH analysis indicates a gain in the region

of chromosome 17q that includes BRCAI (165). In distinction, the PCR-based analysis conducted by Gao and associates (336) noted a frequent loss of LOH at that locus. The erbB-2 oncogene is located at 17ql2 (543). Chromosome Xql2 contains the AR gene, which demonstrates a significant degree of amplification in patients with tumor recurrence following protracted androgen-ablative therapy (165). As stated previously, increased frequency of gains in the region 4q25-q28 is a prominent feature of prostate cancer developing in African Americans (165). It is theorized that a gene at that locus may be increased in activity and responsible for a more rapid rate of disease progression demonstrated in this cohort (97,773).

Konig and associates (524) performed a cytogenetic characterization of several androgen-responsive and unresponsive sublines of LNCaP. The hormone-responsive sublines did not show any aberrations in chromosome 8. In contrast, the unresponsive sublines showed rearrangement of the short arm of chromosome 8, resulting in deletion of the 8p23˜pTer region. Thus partial deletion of the 8p region may be linked with the development of androgen-independence.

The Ten Steps of the Metastatic Cascade

The metastasis of androgen-dependent and androgen-independent CaP constitutes a multistep process, which involves many well-defined tumor cell–host cell and cell–matrix interactions. Indeed, a dynamic reciprocity appears to exist between the tumor cell and other nontransformed cellular elements that constitute the host microenvironment. It would appear that both unidirectional and bidirectional signals are elaborated that can facilitate or inhibit subsequent tumor growth and progression. Figure 33.89 illustrates some of these concepts. To be successful, those tumor cells endowed with invasive and metastatic capacity must successfully complete every step of this process. With respect to the latter, the following ten progression events have been identified: (a) the transforming event, (b) tumor vascularization, (c) local tissue invasion, (d) penetration of lymphatics and venules, (e) detachment of invading tumor cells, (f) embolization of tumor cell aggregates, (g) arrest in capillary beds, (h) extravasation through capillary beds, (i) growth in distant organ microenvironments, and (j) the development of “second order” metastasis. It is important to have a conceptual familiarity with these defined components of a metastatic cascade. Each progression event constitutes a unique “target” for future therapeutic intervention. Figure 33.90 schematically summarizes these ten critical steps responsible for the pathogenesis of a metastatic lesion.

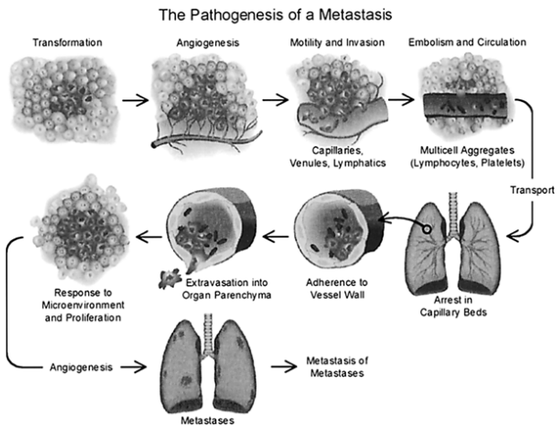

FIGURE 33.90. Successful completion of the metastatic process involves more than simply anatomic or “mechanistic” issues. It is now believed that an affinity exists between the tumor cell and the host microenvironment that is ultimately colonized. This phenomenon has been described as the “seed and soil” hypothesis. It should be emphasized that the process of metastasis consists of multiple sequential steps. All of these must be successfully completed to produce a clinically relevant metastasis. Angiogenesis must be induced to support the growth of both the primary neoplasm and its metastasis. See also Color Figure 33.90. (From Fidler IJ, Kumar R, Bielenberg DR, et al. Molecular determinants of angiogenesis in cancer metastasis [Review]. *Cancer J Sci Am* 1998;4[Suppl 1]:S58, with permission.)

Hormone-refractory State: The Role of Additional Hormonal Therapy

Patients with metastatic HRPC have a dismal prognosis, with a mean survival of less than 1 year (147). The majority of patients with stage D_3 disease (Table 33.37) ultimately demonstrate disease progression despite antecedent and ongoing hormonal therapy. The latter may be attributable to the existence of hormone-dependent, hormone-sensitive, and hormone-insensitive cellular subsets existing within the primary tumor and its metastases. An alternative theory suggests relative androgen dependence in all of the cells constituting the primary tumor with changes in androgen requirement developing after treatment and time. Despite numerous attempts, no durable benefit has been conferred by further efforts to eliminate androgens or their effects.

Even more informative from the standpoint of biologic phenomena is the conversion of the end-organ AR blockade compounds such as flutamide (Eulexin) and bicalutamide (Casodex) from an apparent physiologic antagonist to a physiologic agonist of HRPC. Whether the mechanism of this role reversal (see Antiandrogen Withdrawal Syndrome) is due to cellular alterations or to cellular selection phenomena, it has a sufficient measurable impact on the growth of HRPC to be identifiable in approximately one-third to more than one-half of the patients with a duration of over a year in some (246,877). Several possible basic mechanisms may account for this phenomena (see below). However, regardless of the cause, the observation of the “antiandrogen withdrawal syndrome” is important.

Many patients exhibit an excellent biochemical and clinical response to androgen-ablative therapy for periods ranging from a few months to several years (or longer). Once the serum PSA consistently rises from its posttreatment nadir, concern must exist regarding the emergence of HRPC. If such patients are being maintained on total androgen ablation, serious consideration must be given to the cessation of the antiandrogen component for fear that continuation of these agents will have an adverse impact. Conversely, if the patient has been treated with monotherapy (scrotal orchiectomy or LHRH agonist), consideration should be given to the addition of an antiandrogen with the anticipation that 30% to 40% of such patients may exhibit a diminution in the serum of PSA levels (and perhaps other objective evidence of improvement) for a finite period of time (generally less than 4 to 6 months). Figure 33.91 illustrates some commonly encountered clinical scenarios and provides reasonable management options.

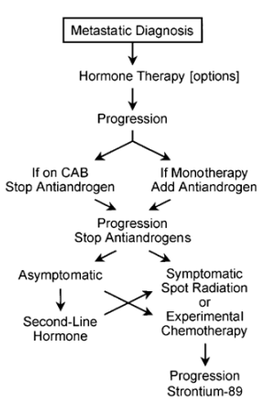

FIGURE 33.91. Treatment decision tree for patients with metastatic disease. (From Pienta KJ. *Advances in the treatment of metastatic prostate cancer.* Ann Arbor, MI: Biomedical Communications, University of Michigan, 1997:1, with permission .)

Following antiandrogen withdrawal (in an otherwise asymptomatic patient), a trial of observation should be entertained before any consideration is given to subsequent therapeutic intervention. *High-dose bicalutamide* (150 mg per day) exhibits modest efficacy in the management of HRPC, particularly in those patients who have received long-term flutamide therapy (475). Joyce and associates (475) reported 7 of 31 patients demonstrated PSA declines of greater than 50% for 2 months for an overall response rate of 22.5%. A surprising response rate of 43% was observed in those patients previously treated with flutamide. A favorable response was associated with an increased performance level and decreased analgesic requirements. Failure

to achieve a flutamide withdrawal response did not preclude a subsequent response to high-dose bicalutamide. This regimen was well tolerated. Mild exacerbation of hot flashes was the most common side effect. Possible explanations for this response in flutamide-treated patients may reflect the selection of tumor cells with one of the following characteristics: (a) overexpression of AR, (b) alternations in AR associated coactivator proteins, or (c) presence of mutated AR.

Several studies have assessed *secondary DES administration* in patients who failed to benefit from orchiectomy. Most of these studies revealed transient objective improvement in 20% to 30% of patients, but no demonstrable objective benefit was discernible (711).

Citrin and associates (174) reported clinical improvement in 20% of patients treated with *high-dose Stilphostrol* after having failed previous endocrine therapy. Three of these patients also were noted to have a decrease in acid phosphatase levels. Conversely, several studies evaluated the effect of orchiectomy following the failure of estrogen therapy. Of particular interest was the study of Klijn and associates (514), who reported that patients treated with secondary orchiectomy following estrogen failure had enhanced survival as compared with those treated with estrogen following orchiectomy. The potential toxicity of DES is well known and is characterized by nausea, vomiting, fluid retention, gynecomastia, congestive heart failure, coronary artery disease, DVT, stroke, and pulmonary embolism. At 1 mg per day, DES does not produce consistent suppression of testosterone levels, but the observed therapeutic benefit appears to be equivalent to that of 5 mg per day. DES at 3 mg per day remains the basis for comparing the efficacy of new treatments for stage D CaP (157).

Antiandrogens and inhibitors of steroid synthesis have shown modest efficacy when used as secondary modes of endocrine therapy. *Flutamide* has been associated with favorable objective responses in between 20% and 30% of patients who have failed prior endocrine therapy. However, the duration of response was very short and no survival benefit was apparent (700,940,983). The data concerning *cyproterone acetate* are somewhat more perplexing in that several studies report favorable responses ranging between 50% and 70% in patients with advanced-stage prostate cancer (936,1087). These contrast sharply with the study

of Tvetor and others (1028), who observed little demonstrable evidence of tumor regression in a similar group of patients.

Several studies have involved the assessment of *aminoglutethimide* as a second-line treatment modality with subjective improvement being noted in 9 of 12 patients in a study by Rostom and co-workers (844). In that study, however, no objective responses were noted. This is in contrast to the study of Worgul and associates (1107) who observed a surprising 48% objective response rate in 23 relapsing patients treated with aminoglutethimide. The concomitant administration of glucocorticoids in all of the aforementioned studies makes the assessment of subjective response all the more tenuous because these adrenal steroids are notorious for their ability to produce a sense of well-being approaching euphoria at times (662). Indeed, low-dose prednisone alone (10 mg per day) has been associated with a response rate of approximately 12% in patients with symptomatic HRPC (1001).

The results of ketoconazole studies are somewhat easier to interpret because concomitant corticosteroids were not used in the early studies. Objective responses were noted in 45% of patients treated with this agent following conventional endocrine therapy relapse (1093). A currently popular regimen includes *ketoconazole (400 mg every 8 hours) and supplemental hydrocortisone (20 mg per day).* Ketoconazole is an antifungal agent that blocks the 17,20-lyase enzyme in the adrenal gland and testis. Because the response to ACTH stimulation is blunted in the presence of high-dose ketoconazole, steroid supplementation is advisable. Caveats regarding the use of ketoconazole include the following: (a) Ketoconazole requires an acid environment for dissolution and absorption, and bioavailability in patients taking H_2 blockers is poor. (b) It is eliminated by hepatic metabolism and should be used with caution in patients with liver dysfunction. (c) Ketoconazole may induce GI/hepatic toxicity. Obviously, the physician must be attentive to the development of steroid-induced complications, including fluid retention, glucose intolerance, immunosuppression, poor wound healing, Cushing's syndrome, osteoporosis, and mental status changes. This combination regimen results in a transient PSA reduction in 60% of patients (926). Surgical adrenalectomy and hypophysectomy have been attempted in the past with little objective benefit and only transient subjective improvement (821). Finally, the potential utility of combining an antiandrogen (i.e. bicalutamide) and a 5α-reductase inhibitor (i.e., finasteride) awaits clarification.

In conclusion, it appears that further hormonal maneuvers remain a viable option in some patients with progressive prostate cancer following suppression of gonadal and adrenal androgen. Clearly, antiandrogen withdrawal is a mandatory maneuver before proceeding to other regimens. Certain patients will continue to respond to hormonal manipulation even after antiandrogen withdrawal. At present, it is not possible to dissect that cohort most likely to respond to additional manipulation from nonresponders. Such insight must await clarification provided by a detailed molecular analysis of their respective tumors (926). Bubendorf and associates (108) conducted an interesting, preclinical study. Using a cDNA microarray, they evaluated gene expression in the hormone-refractory prostate cancer xenograft designated CWR22R and its hormone-dependent counterpart (CWR22). Among 5,184 genes surveyed, expression of 37 (0.7%) was increased more than twofold in CWR22R. Conversely, the expression of 135 (2.6%) genes was reduced by more than 50% in that particular animal model. The genes encoding IGF-binding protein 2 and 27-kd heat-shock protein (HSP 27) were among the most consistently overexpressed genes in the hormone-refractory variant. Despite limited critical insights, the therapeutic approaches discussed may be reasonable in asymptomatic patients with low-volume metastatic disease who exhibit biochemical evidence of the hormone-refractory state (776).

Chemotherapy: A Historic Perspective

In the early 1970s, many clinical trials were initiated with the hope of identifying cytotoxic agents possessing demonstrable efficacy in the treatment of disseminated HRPC.

The chemotherapeutic agents found to be modestly effective when used as single agents in the treatment of metastatic CaP were cisplatin, doxorubicin (Adriamycin), cyclophosphamide, fluorouracil, lomustine (CCNU), dacarbazine (DTIC), methotrexate, streptozotocin, and estramustine (154,1019,1113). The last two agents seemed best suited for use in patients with compromised bone marrow reserves as a result of antecedent radiation therapy (760,949,950). Unfortunately, only 10% of these patients demonstrated partial tumor regression when such agents were used, and the response was generally short-lived, averaging approximately 6 months (154,261). Although various drug combinations were used, none produced results that were statistically superior to single-agent therapy. Regrettably, available studies have failed to demonstrate a significant survival advantage in patients with metastatic CaP undergoing conventional cytotoxic therapy. Table 33.38 and Table 33.39 summarize the early experience with single-agent and combination drug therapies that have been used in patients with disseminated prostate cancer.

Antitumor Agent	No. of Patients Treated	Responses (%)
Doxorubicin	76	14 (18)
Analine mustard	37	5 (14)
Cisplatin	137	40 (29)
Cyclophosphamide	119	43 (36)
Dacarbazine	55	15 (27)
Estramustine	163	45 (28)
Fluorouracil	81	17 (21)
Hydroxyurea[a]	58	19 (33)
Lomustine (CCNU)	10	4 (40)
Melphalan	15	1 (7)
Methotrexate	58	24 (41)
Semustine (methyl-CCNU)	27	8 (30)
Nitrogen mustard	23	10 (43)
Prednimustine	85	11 (13)
Procarbazine	39	5 (13)
Streptozocin	38	12 (32)
Vincristine	34	5 (15)

[a]Chlorotrianisene also administered with hydroxyurea.
From Slack NH, Murphy GP: *Urology* 1983;22:1, with permission.

TABLE 33.38. SINGLE ANTITUMOR (NONHORMONAL) AGENTS TESTED IN PROSTATE CANCER

Combination Antitumor Agents	No. of Patients Treated	Responses (%)
Cyclophosphamide		
+ Fluorouracil (5-FU)	72	14 (19)
+ Doxorubicin	145	57 (39)
+ Methotrexate (MTX)	4	3 (75)
Estramustine		
+ 5-FU	25	8 (32)
+ Prednimustine	75	12 (16)
+ Vincristine	99	26 (26)
+ Methyl-CCNU	21	1 (5)
+ Cisplatin	42	14 (33)
+ Stereocyst	75	21 (28)
Doxorubicin + cisplatin	17	9 (53)
Estramustine + cisplatin + MTX	9	4 (44)
Cyclophosphamide + MTX + 5-FU	2	1 (50)
Cyclophosphamide		
+ 5-FU + doxorubicin	21	12 (57)
+ 5-FU + MTX	20	7 (35)
+ Doxorubicin + MTX	12	9 (75)
+ Doxorubicin + (BCNU)	22	7 (32)
Vincristine + 5-FU + MTX + prednisone + melphalan	25	18 (72)
Estramustine + cyclophosphamide + 5-FU + cisplatin	15	7 (47)

From Slack NH, Murphy GP. *Urology* 1983;22:1, with permission.

TABLE 33.39. COMBINATIONS OF ANTITUMOR AGENTS TESTED IN PATIENTS WITH ADVANCED PROSTATE CANCER

In addition to the conventional systemic administration of such chemotherapeutic drugs to patients with stage D CaP, several alternative modes of administration have been attempted, including (a) the use of such agents in an adjuvant setting, (b) the initiation of chemohormonal therapy, (c) intraarterial infusion chemotherapy, and (d) cytotoxic therapy following androgen priming. Unfortunately, none of these initiatives proved to be of durable benefit.

Several studies have been conducted to assess the potential efficacy of the combined use of cytotoxic therapy in conjunction with androgen ablation. In a study by Murphy and associates (687), patients with stage D CaP who had not undergone previous therapy were randomized to the administration of DES or orchiectomy versus DES combined with cyclophosphamide versus cyclophosphamide and estramustine. Analysis of the data revealed no statistically significant difference in any of the treatment groups when assessed for duration of therapeutic response or overall survival. In an analogous fashion, there seems to be little benefit associated with the administration of systemic chemotherapy to untreated patients with disseminated prostate cancer before androgen ablation (451).

Sella and co-workers (899) reported their results of a phase II study that involved the use of *oral ketoconazole (1,200 mg per day) and doxorubicin (20 mg/m^2 in a 24- hour infusion administered once weekly).* These investigators observed a 55% PSA response rate. Moreover, partial responses were seen in 7 of 12 patients with measurable soft tissue disease. Serious cardiac toxicity was encountered and 45% of these patients required hospitalization for treatment-related complications. The development of clinical adrenal insufficiency in 63% of patients prompted a recommendation that subsequent studies include administration of corticosteroids.

One of the most controversial approaches involving the use of systemic chemotherapy was the initiation of androgen priming before the administration of chemotherapeutic agents. This approach hypothesized an enhanced sensitivity to chemotherapy as the result of the expected stimulation of tumor proliferation by administration of exogenous androgen. However, a study using a 10-mg daily dose of fluoxymesterone (Halotestin) as the priming agent for 4 days followed by IV cyclophosphamide and methotrexate (MTX) did not demonstrate any substantive benefits. Furthermore, exacerbation of bone pain occurred in many patients and cord compression was noted in one (990). These discouraging results tempered enthusiasm for similar studies. However, Dawson and associates (216) reported 3 complete and 8 partial responses in their study of 15 patients with hormone-refractory prostate cancer treated with fluoxymesterone (5 mg orally twice daily for 3 days) followed by carboplatin (800 mg/m^2) administered every 28 days and followed for 3 days by the same fluoxymesterone regimen. Of note, 9 of 15 patients were alive 42 months or longer. It remains a matter of conjecture whether these favorable responses can be attributed to the regimen of androgen priming used in this study as opposed to the impact of carboplatin alone (880).

Cytotoxic Chemotherapy: Current and Future Approaches

The development of more effective treatment strategies will require (a) the further assessment of drug analogs possessing reduced toxicity and/or enhanced antitumor activity, (b) the use of conventional agents via new schedules and routes of drug delivery, and (c) the development of compounds possessing novel mechanisms of action (217,880).

For example, doxorubicin is moderately effective in the treatment of metastatic CaP due to its ability to bind to DNA and inhibit DNA replication and DNA-dependent RNA synthesis. Unfortunately, it possesses well-defined cardiotoxicity, especially as the cumulative dose approaches 550 mg/m^2. However, even low cumulative-dose regimens may be dangerous in patients with a history of ischemic heart disease, congestive heart failure, cardiac arrhythmia, and a low ejection fraction. For these reasons, the development of *mitoxantrone*, an analog of doxorubicin with reduced cardiac toxicity, is an important development that might expand the utility of this family of cytotoxic agents for the elderly population at risk.

Moore and associates (670) administered mitoxantrone (12 mg/m^2 IV every 3 weeks) and prednisone (10 mg orally daily) to 27 patients with HRPC. Methods of assessment included quality-of-life analyses, pain indices, analgesic scores, and the National Prostatic Cancer Project (NPCP) criteria. Of 25 assessable patients, 9 (36%) demonstrated improvement in social and emotional functioning, as well as in pain and anorexia. One of seven patients with measurable disease achieved a partial response and 12 exhibited stable disease. None of the patients experienced serious nonhematologic toxicity and there was no evidence of febrile neutropenia.

Tannock and associates (1001) randomized 161 hormone-refractory patients with pain to receive mitoxantrone (12 mg/m^2 body-surface area by IV infusion every 3 weeks) plus prednisone (10 mg per day) or prednisone alone. The primary endpoint was a palliative response defined as a 2-point decrease in pain as assessed by a 6-point pain scale completed by patients without an increase in analgesic medication and maintained for two consecutive evaluations at least 3 weeks apart. Secondary endpoint parameters included a decrease of 50% or more in the use of analgesic medication without an increase in pain, duration of response, and survival. In that study, a palliative response was observed in 23 of 80 patients (29%) who received mitoxantrone plus prednisone. In contrast, 10 of 81 patients (12%) who received prednisone alone exhibited a palliative response. The duration of response was longer in patients who received chemotherapy (median of 43 versus 18 weeks); 11 of 50 patients randomized to prednisone treatment responded after the addition of mitoxantrone. There was no difference in overall survival between the two groups. Most responding patients exhibited an improvement of quality-of-life parameters and a decrease in the serum PSA level. A parallel study was performed by Kantoff and associates (485) under the auspices of the Cancer and Leukemia Group B Study 9182. In that study, patients with HRPC were randomized to receive hydrocortisone alone or in combination withmitoxantrone. Table 33.40 provides the comparative outcomes of these two similar clinical trials.

Study	Therapy	No. of Patients	>50% PSA Decline (%)	Symptom Relief (%)	Overall Survival (mo)
Tannock, et al.	Mitoxantrone + prednisone	80/161	33	29	12
	Prednisone	81/161	22	12	11.5
Kantoff, et al.	Mitoxantrone + hydrocortisone	119/242	33	14	11.1
	Hydrocortisone	123/242	18	8	12

PSA, prostate-specific antigen.
See text references 485 and 1001.

TABLE 33.40. STEROIDS WITH AND WITHOUT MITOXANTRONE

More recently, the favorable Canadian experience prompted a randomized phase III comparison of mitoxantrone plus prednisone versus prednisone alone (1001). In that study, palliative response was the primary endpoint. Of the 80 patients randomized to mitoxantrone and prednisone, 29% met the criteria for a palliative response in comparison with 12% of 81 patients who received prednisone alone. The duration of palliative responses was longer in the mitoxantrone plus prednisone arm period. However, there was no significant difference between median survival between the two groups. Table 33.41 provides a comparison of outcome in the mitoxantrone phase III Canadian trial and the Cancer and Leukemia Group B Study 9182. The latter study was designed with survival as its primary endpoint and quality of life as a secondary endpoint. In that study, no overall survival benefit was demonstrated. However, there was an improvement in pain control in the chemotherapy arm. Overall, studies of mitoxantrone plus glucocorticoids have demonstrated that as many as 40% of patents will have improvements in pain and quality of life as a result of this treatment, although impact on overall survival does not appear to be significant (929).

	Canadian Trial (1001)			CALGB Study 9182 (485)		
	Mitoxantrone + Prednisone (n = 80)	vs.	Prednisone (n = 81)	Mitoxantrone + Hydrocortisone	vs.	Hydrocortisone alone
Primary Endpoint	Palliation 29% vs. 12% Duration of palliation (median weeks) 43 vs. 18			No survival advantage		
Secondary Endpoints	Improved time to progression 24 weeks vs. 10 weeks p = .0001 No difference in survival 48 wk vs. 46 wk			Improved time to progression 31 weeks vs. 17 weeks p = .065 Mitoxantrone associated with improved pain control Improved objective response rate 8.9% vs. 1.6% p = .01		

CALGB, Cancer and Leukemia Group B.

TABLE 33.41. MITOXANTRONE PHASE III CANADIAN TRIAL AND CALGB STUDY 9182

These studies highlight the fact that mitoxantrone plus prednisone is a well-tolerated regimen in this cancer cohort. This drug is a semisynthetic anthracenedione, which shares some structural similarities to doxorubicin. Mitoxantrone has a more favorable toxicity profile than doxorubicin and is associated with very little nausea, vomiting, or alopecia. The dose-limiting toxicity is myelosuppression, with neutropenia limiting the starting dosage to 12 to 14 mg/m^2 every 3 weeks (670). The study by Tannock and associates (1001) also indicates that measures of health-related quality of life are both objective and relevant endpoints to assess prognosis and outcome after the initiation of palliative therapy.

Recent studies have demonstrated that *estramustine phosphate* induces the disruption of microtubules and inhibits microtubule assembly by binding to MAPs (880). In addition, estramustine binds to P-glycoprotein and has been observed to favorably modulate the multidrug-resistant phenotype, which can abrogate the effectiveness of such agents as vinblastine and paclitaxel (Taxol) (956,1117). Because the antimitotic effects of vinblastine are mediated through its binding to tubulin, its use in concert with estramustine, which exerts its antimitotic activity through a different mechanism, is appealing.

Seidman and associates (898) treated 25 patients with progressive HRPC using estramastine/vinblastine. Of the 24 patients with an elevated serum PSA before therapy, 54% exhibited a greater than 50% decrease in PSA levels on at least three consecutive biweekly determinations. They also noted that the median decrease in PSA in responding patients was 64% and the median duration of response was 7 months. Two partial responses were noted in five patients who had biodimensionally measurable disease. In a similar study, Hudes and associates (438) treated 36 accessible patients with *oral estramustine phosphate (600 mg/m^2 on days 1 to 42) and vinblastine (4 mg/m^2 intravenously once a week for 6 weeks).* These treatments cycles were repeated every 8 weeks. They observed that PSA decreased from baseline by at least 50% in 61% of the patients. In eight patients, the PSA diminution was greater than 75% of the pretreatment baseline. In seven patients with measurable nonosseous disease, they observed one partial response and one minor response. However, 12 of 28 patients with assessable pain noted significant responses to this therapy. This drug regimen

was easily administered and generally well tolerated. Leukopenia was mild, with only three episodes of grade 3 or 4 toxicity being recorded and no febrile neutropenic events or episodes of thrombocytopenia. Nausea related to oral estramustine was the chief nonhematologic toxicity. Other side effects attributable to estramustine included lower extremity edema and breast tenderness. There were four episodes of significant cardiovascular toxicity, which were probably related to the estrogenic effects of estramustine. The neurologic toxicity associated with vinblastine (paresthesia, constipation, and muscle cramps) was generally manageable. The combination of *estramustine plus vinorelbine* (another vinca alkaloid) also appears to have activity in the management of HRPC (119).

Paclitaxel (Taxol) also binds tubulin, inhibits microtubule disassembly, and suspends cells in mitosis. Despite the rather disappointing performance of Taxol monotherapy in the treatment of CaP, preclinical studies demonstrated its ability to abrogate the invasion and metastasis of human prostate cancer systems. In addition, Speicher and associates (955) demonstrated the synergistic cytotoxic effect of paclitaxel (Taxol) plus estramustine, *in vitro,* in both estramustine-resistant and wild-type DU145 human prostatic carcinoma cell lines. They also noted that the concentration of Taxol found to enhance the toxic effects of estramustine was 100-fold less than levels found in the serum of patients treated with that agent clinically. For these reasons, Hudes and associates (440) initiated a clinical study involving 17 patients with HRPC. They were treated with *Taxol (120 to 140 mg/m^2 by 96-hour infusion on days 1 to 4 every 3 weeks)* and *oral estramustine (600 mg/m^2 daily)*. Of 17 patients, 10 demonstrated a decrease in their baseline PSA of more than 50%. Moreover, of the six patients with measurable disease, three achieved a partial response. The most common reported toxicities were nausea, peripheral edema, fatigue, diarrhea, and transient rises in transaminase levels. Hematologic toxicity was mild.

Preclinical studies have suggested that *estramustine phosphate and etoposide (VP-16)* may constitute yet another drug combination capable of inhibiting the proliferation of HRPC (772). Etoposide exerts its antitumor effect by stabilizing the topoisomerase II–DNA cleavable complex, which ultimately leads to ligation inhibition (597). In addition to its ability to bind to microtubule-associated proteins and P-glycoprotein, estramustine phosphate is preferentially taken up by prostate epithelial cells and binds to the nuclear matrix (186). These observations prompted a phase II clinical trial evaluating this drug combination in patients with HRPC (775). This study involved 42 patients who received oral estramustine (15 mg/kg per day) and oral etoposide (50 mg/m^2 per day) in divided doses for 21 days. After a rest period of 7 days, the cycle was repeated until evidence of disease progression was noted. Of 18 patients with measurable soft tissue disease, complete responses were noted in 3 patients and partial responses in 6 patients. Furthermore, pretreatment PSA levels decreased by at least 50% in half of the patients and by at least 75% in 28% of the cohort tested. Finally, 25% of patients demonstrated improvement and 38% demonstrated stability in their bone scans. Table 33.42 summarizes the results of phase II of two-drug and three-drug regimens involving estramustine-based chemotherapy for the treatment of HRPC.

		Response	
	No. of Patients	Reduction in Measurable Disease	Decline in PSA Level
Two-drug Regimens			
Estramustine plus vinblastine	92	6/25 (24%)	48/88 (55%)
Estramustine plus vinorelbine	25	0/5 (0%)	9/24 (38%)
Estramustine plus etoposide	160	32/68 (47%)	76/155 (49%)
Estramustine plus paclitaxel	34	4/9 (44%)	17/32 (53%)
Estramustine plus docetaxel	34	5/18 (28%)	20/32 (63%)
Three-drug Regimens			
Estramustine plus etoposide plus vinorelbine	25	2/3 (67%)	14/25 (56%)
Estramustine plus etoposide plus paclitaxel	40	10/22 (45%)	26/40 (65%)

Note: Studies cited are from original source.
[a]In some cases, data from more than 1 clinical trial were included, and dosing schedules have slight variations.
HRPC, hormone-refractory prostate cancer; PSA, prostate-specific antigen.
Adapted from Smith DC. *Chemotherapy for advanced prostate cancer.* American Society of Clinical Oncology, 2000:585.

TABLE 33.42. RESULTS OF PHASE II CLINICAL TRIALS OF ESTRAMUSTINE-BASED CHEMOTHERAPY REGIMENS FOR HRPC[a]

Cyclophosphamide (Cytoxan) is an alkylating agent that has demonstrated activity against a wide variety of solid tumors. Unfortunately, early studies failed to demonstrate a profound impact of this agent when administered intravenously in standard doses. For example, Saxman and associates (869) performed a phase III clinical study assessing the impact of Cytoxan alone or in combination with doxorubicin plus methotrexate in the management of HRPC. The overall response rate in all patients with measurable disease

was approximately 13% (in both arms). Furthermore, there was no apparent added benefit to the three-drug regimen when compared with cyclophosphamide alone (186).

More recently, Small and associates (925) administered *doxorubicin along with dose-escalated cyclophosphamide and granulocyte colony-stimulating factor (G-CSF)* in 35 patients with hormone-resistant prostate cancer. These patients were treated every 21 days with fixed-dose doxorubicin (40 mg/m^2) and Cytoxan (800 to 2,000 mg/m^2) along with G-CSF. Of 15 patients, 5 (33%) patients with measurable disease obtained an objective response. Of 35 patients, 16 had a greater than 50% decrease in PSA levels. Although nonhematologic toxicity was minimal, approximately one-third of the cycles were associated with grade 4 neutropenia.

Raghavan (808) administered *oral cyclophosphamide* to 30 patients with HRPC at a dose of 100 mg/m^2 each day for 14 days. The patients received a 14-day rest period before the next cycle. This study contained six objective responses (20%); most patients demonstrated symptomatic improvement. Similarly, encouraging results were demonstrated in a study conducted by Maulard-Durdux and colleagues (624). In that study, *oral cyclophosphamide was administered with oral etoposide* to patients with HRPC apparent. Approximately 35% of patients exhibited a reduction in PSA level, and almost 75% of these treated patients acknowledged relief of bone pain.

Various new cytotoxic agents are under investigation. *Camptothecin and its analogs (irinotecan and 9-aminocamptothecin)* are inhibitors of the nuclear enzyme topoisomerase I. Like topoisomerase II, this enzyme plays an important role in DNA replication. In a study conducted by Hudes and associates (439), topotecan was administered to 34 patients with HRPC in a phase II trial. The drugs were administered using a standard schedule 1.5 mg/m^2 daily times five. Although only 1 of 13 patients with measurable disease had an objective response, 6 of 34 had a response by PSA criteria. Myelosuppression was a common side effect documented in this study. Other new agents being pursued in the management of HRPC are an oral platinum compound (JM-216) and an anthrapyrazole derivative (CI-958) (929).

Denmeade and associates (225) reported a very interesting preclinical study. In an attempt to target a set of toxic therapies, specifically to metastatic prostate cancer sites, these investigators *synthesized an inactive prodrug by coupling the primary amine of doxorubicin to the COOH-terminal carboxyl of a 7-amino acid peptide carrier (Mu-His-Ser-Ser-Lys-Leu-Gln-Leu)*. They previously documented that the 7-amino acid peptide could be hydrolyzed specifically by the serine protease PSA, which would then liberate the active cytotoxin (L-leucyl-doxirubin). They observed a significant cytotoxic response to the prodrug when targeting the PSA cell line LNCaP. This therapeutic vehicle, of course, had no cytotoxic effect on PSA-nonproducing TSU prostate cancer cells *in vitro*.

HRPC manifests a "pan-resistant" chemotherapy phenotype for several reasons. Prostate cancers exhibit rather long *in vivo* doubling times, estimated to range from 4 months to 2 years. It is assumed that a large proportion of the tumor population resides in the resting or dormant phase of the cell cycle (G_0). Tumor targets are generally most susceptible to cytotoxic agents when they are actively cycling. In addition, Sullivan and associates (992) evaluated paraffin-embedded formalin-fixed resected prostates that were chosen based on Gleason grade and surgical stage. Immunohistochemistry was used to detect the expression of multidrug resistance protein (MRP), topoisomerase II-α, and p53, glutathione S-transferase, bcl-2, and P-glycoprotein. They demonstrated that all of the proteins were expressed in resected prostate except for P-glycoprotein. The expression of the other proteins increased with the Gleason grade. In addition, the expression of MRP, topoisomerase II-α, and p53 increased with the surgical stage. These results suggested that drug resistance gene products are expressed in prostate cancer at the time of surgical resection. They postulated that the chemotherapy refractory nature of CaP appears to reflect a constitutive phenotype that is present in early prostate cancer.

Anti-Growth Factor Strategies: Rationale and Results

The actual cellular mechanisms underlying the mitogenic activity of androgens and the emergence of HRPC are unknown. Recent evidence suggests that androgens may modulate the response of benign and malignant prostatic cells through the "upregulation" of other hormone and growth factor receptors, including the epidermal growth factor (EGF) receptor (887,1023). Thus dihydrotestosterone (DHT) may be a strategic component in an elaborate autocrine "loop" involving a cascade of signaling events intimately associated with the expression of various growth factors and their receptors. In keeping with this hypothesis, the transformed phenotype may be associated with the uncontrolled production of mitogenic growth factors or receptors or the failure of malignant cells to synthesize or respond to specific inhibitory growth factors (i.e., TGF-ß). For example, Wilding and associates (1091) showed that the secretion of transforming growth factor-α (TGF-α) by the hormone-responsive prostate cancer cell line LNCaP is increased by DHT. They hypothesized that androgens may increase EGF receptors by inducing the production of TGF-α, EGF, or both. The androgen-resistant phenotype may emerge when clonal populations of tumor cells attain the ability to constitutively produce the requisite mitogenic growth factors and bypass the need for androgen "priming." For example, Hofer and associates (427) demonstrated that the HRPC cell line PC-3 is capable of synthesizing and secreting factors that are mitogenic for other prostate cancer cells (e.g., DU-145).

Subsequent studies confirmed that the mitogen in question is TGF-α (908).

The IGF system is comprised of two ligands (IGF-I, IGF-II), two receptors (IGFR-I, IGFR-II), and six unique binding proteins (IGFBP-1 to IGFBP-6). The IGF system appears to play a strategic role in the autocrine growth regulation of prostate cancer cell lines (777). IGF-I levels are elevated in the serum of patients with CaP (156). IGF-II expression is elevated in CaP compared with benign tissues. A higher concentration of IGFBP-2 is present in the serum of CaP patients compared with controls. Recently, Figueroa and associates (293) demonstrated differential expression of IGFBPs in high versus low Gleason score prostate cancers. Specifically, expression of IGFBP-2 and IGFBP-5 was higher, while that of IGFBP-3 was lower in high versus low Gleason score specimens. IGFBP-2 binds to IGF-II with a tenfold to twentyfold greater affinity than IGF-1. IGFBP-2 possesses an RGD sequence that may facilitate binding to cell surface receptors, thus potentiating IGF delivery to its mitogenic receptor. IGFBP-5 is preferentially expressed in stroma of both benign and malignant prostate tissue and has a high affinity for extracellular matrix components. Such binding is associated with decreased IGFBP-5 affinity for IGF-I, resulting in higher local IGF-I bioavailability and ensuring aggressive prostate cancers a readily available supply of mitogenic IGFs to support continued growth.

In contrast, IGFBP-3 is thought to function as a negative regulator of cell proliferation (810) by sequestering free IGFs and thus preventing interaction with their receptors. In addition, IGFBP-3 gene expression is induced by other growth-inhibitory (and apoptosis-inducing) agents. Finally, IGFBP-3 appears to induce apoptosis through a novel pathway independent of either p53 or the IGF/IGFR-mediated cell survival pathway. Expression of IGFBP-3 is increased in PIN but decreased in invasive cancer specimens (1006).

Based on these perceptions, a high IGFBP-2-to-IGFBP-3 expression ratio should result in enhanced tumor proliferation and aggressive behavior (293). In fact, tumors with a high Gleason score demonstrate 95% and 117% higher expression ratios compared with tumors of low Gleason score and benign tissue, respectively.

Novel strategies to block components of this growth factor "cascade" have been investigated. *Suramin*, a polysulfonated napthylurea developed 75 years ago to treat trypanosomiasis inhibits the binding of various tumor growth factors including PDGF, TGF-α or TGF-B, EGF, and IGF-I to their cell surface receptors when administered intravenously. It can abolish tumor cell stimulation by the mitogens (259). Furthermore, suramin inhibits nucleic acid–related, lysosomal, and extracellular enzymes, as well as, angiogenesis and tumor cell motility. In addition, several studies document its ability to inhibit PC-3 cells *in vitro* (591,1144).

Several clinical studies using different continuous or intermittent IV administration regimens of suramin to HRCP patients have reported varying evidence of a desirable effect including serum PSA and soft tissue mass reduction (260,337,691). Table 33.43 provides an overview of the results of recently completed suramin trials. However, this drug is currently used with reservation for two reasons: (a) It has numerous and appreciable toxicities, including adrenal and renal failure; sensory and motor polyneuropathy; an allergic rash; hematologic abnormalities, including coagulopathy and thrombocytopenia; a reversible vortex keratopathy, and others (259,338,588). (b) In addition, other clinical observations indicating tumor response are suspect because of reports suggesting these, especially PSA reduction, are primarily the result of administration of hydrocortisone to control adrenal failure (840).

Study	Schedule	Evaluable Patients	≥50% PSA Response	Measurable Disease Response
Myers, et al.	Continuous infusion	38	21/38 (55%)	6/17 (35%)
Eisenberger, et al.	Intermittent infusion	31	24/31 (77%)	6/12 (50%)
Mendoza, et al.	Intermittent infusion	21	9/21 (43%)	2/11 (18%)
Petrylak, et al.	Intermittent infusion	28	13/28 (46%)	2/11 (18%)
Reyno, et al.	Intermittent infusion	38	20/38 (52%)	0/4 (0%)

PSA, prostate-specific antigen.
From Pienta KJ. *Advances in the treatment of metastatic prostate cancer.* Ann Arbor, MI: Biomedical communications. University of Michigan, 1997:1, with permission.

TABLE 33.43. RESULTS OF RECENTLY COMPLETED SURAMIN TRIALS

Recently, Tu and associates (1026) reported on their experience with *suramin and doxorubicin* in a phase I clinical trial. Doxorubicin was administered weekly (20 mg/m^2) and suramin was administered over 2 hours twice weekly at increasing doses. Of interest, the response rates in terms of measurable disease and serum PSA level were 50% and 60%, respectively. Not surprisingly, suramin therapy was associated with the development of neuropathy in 13% of the treated patients. Finally, Dawson and associates (215) recently completed an interesting study in which a poor-prognosis group of patients with previously untreated metastatic prostate cancer were treated with *suramin, leuprolide, and flutamide*. Forty-five patients had bone metastases and 25 had measurable soft tissue disease. Forty-one (82%) had

severe disease. The overall response rate in 49 assessable patients was 3 complete responses and 30 partial responses for an overall response rate of 67%. These encouraging results have prompted a recommendation that a phase III trial be initiated to assess the impact of this drug combination with hormonal therapy alone.

Somatostatin, a cyclic tetradecapeptide found in high concentrations in the stomach, intestines, pancreas, and hypothalamus and other areas of the brain (876), inhibits the secretion of several important pituitary (prolactin, growth hormone) and GI (insulin, glucagon, gastrin, secretin, cholecystokinin, and vasoactive intestinal polypeptide) hormones (876,904). In addition to its endocrine effects, somatostatin inhibits various strategic growth factors, including IGF, EGF, PDGF, FGF, and TGF-α. The ability of somatostatin to inhibit prolactin and endogenous growth factors suggests a potential therapeutic role in the management of prostate cancer. However, despite evidence of enhanced inhibition of tumor cell lines such as Dunning R-3327H by administration of somatostatin or its analogs primarily along with LHRH agonists (875,916) and recent evidence that octreotide acetate, a somatostatin analog, inhibits experimental angiogenesis (211), these observations have not translated into significant clinical therapies.

C225 IgG_1 is a chimerized mAb that competes with both EGF and TGF-α for binding to the EGF receptor. Mendelsohn (644) and others have demonstrated that the antitumor properties of this chimerized antibody may be multifactorial and include inhibition of cell cycle progression, induction of apoptosis, inhibition of angiogenesis, inhibition of tumor invasion/metastasis, and inhibition of repair or recovery following exposure to chemotherapy or radiation. The ultimate role of this human:chimeric mAb C225 in the management of advanced-stage prostate cancer (either alone or in combination with other therapies) remains to be defined. The same holds true for the ultimate impact of the Herceptin mAb against HER-2.

Differentiation-inducing Therapy

The development of agents capable of inducing differentiation and favorably modulating adverse tumor phenotypes could be of great therapeutic benefit. Despite the theoretic appeal of this novel therapeutic approach, the clinical application of differentiation-inducing agents such as retinoic acid and its derivatives, sodium butyrate, somatostatin analogs, vitamin D_3 and its derivatives, sodium phenylacetate/phenylbutyrate, and 5-azacitidine has been hindered by insufficient bioavailability, patient toxicity, and/or lack of durable therapeutic benefit (392,934,1010).

Retinoids are differentiation-inducing agents thought to act on nuclear-binding proteins, which act as transcription factors (602). There are two types of retinoid receptors: retinoic acid receptors (RARs) and retinoid X receptors (RXRs). These receptors belong to the superfamily of steroid hormone receptors. The α-, ß-, and γ-subtypes of the RARs and RXRs have unique and conserved amino and carboxy terminal domains (602).

Kelly and associates (498) conducted an interesting study involving patients with HRPC. Fourteen patients were treated with daily oral dosing of all-trans-retinoic acid (ATRA), 50 mg/m^2 every 8 hours. In addition, their study involved the treatment of 16 androgen-independent and 4 androgen-dependent patients with a combination of 13-cis-retinoic acid (10 mg/kg per day) and interferon-α_2 (3, 6, or 9 million units daily). Both therapies were well tolerated, with fatigue and cheilitis being the most common adverse events. Clinical activity as assessed by radiographs and serum PSA was minimal, and the majority of patients progressed within 3 months. Of note, one patient with androgen-dependent disease had prolonged stabilization for more than 1 year. Although the majority of cases (95%) showed no gross histologic changes, an increased PSMA immunoreactivity was seen in 7 of 9 (78%) cases. Despite these very modest antitumor effects, this study suggests a role for retinoids in modulating the expression of PSMA on prostate cancer cells. The minimal antitumor activity demonstrated may in part reflect observations by Lotan and associates (602) who demonstrated that RAR-ß and RXR-ß mRNAs are selectively lost in both prostate cancer and adjacent morphologically normal prostatic tissue.

Finally, DiPaola and associates (233) reported on the results of the phase I clinical trial that involved the use of *13-cis-retinoid acid, interferon-α , and paclitaxel* in patients with advanced stage prostate cancer. They demonstrated that this regimen is surprisingly well tolerated. Furthermore, the combination of retinoic acid and interferon caused a 33% decrease in paclitaxel clearance probably secondary to an inhibitory effect on its metabolism. Finally, the combination of cis-retinoic acid and interferon favorably modulated the expression of bcl-2 *in vitro*. It is conceivable that a combination of differentiation-inducing agents, immune modulators, and cytotoxic agents can be used effectively in the management of advanced prostate cancer. Obviously, additional studies are needed to determine the validity of this perception.

Epidemiologic data suggest that *vitamin D_3,* obtained from dietary sources and sunlight exposure, protects against mortality from prostate cancer (187). The most active vitamin D metabolite, 25-dihydroxyvitamin D_3, regulates the growth and differentiation of several human CaP cell lines *in vitro* (661). The antiproliferative effects of $1,25(OH)_2D_3$ appear to require the expression of the nuclear vitamin D receptor (VDR) (661). *Vitamin D analogs,* which are less likely to promote hypercalcemia, may prove to be of some value alone or in combination with other agents in the management of advanced stage prostate cancer. Numerous analogs are currently under investigation. With respect to the latter, *in vitro* studies conducted by Chen and associates (162) suggest that both 25-hydroxy

vitamin D_3 and 19-nor-1α, 25-dihydroxy vitamin D_2 may be useful in this regard.

Angiogenesis Inhibitors

As stated previously, the elaboration of angiogenic peptides is critical for the growth of the primary tumor and its subsequent metastatic foci. Prostate cancers have been shown to overexpress hypoxia-inducible factor 1-α. The latter activates transcription of genes, encoding glycose transporters, glycolytic enzymes, and vascular endothelial growth factor (1132,1133). This overexpression therefore fulfills the two universal characteristics of solid tumors—their need for neovascularization and increased glycolysis. VEGF signal transduction is believed to occur primarily by way of the high-affinity membrane receptor tyrosine kinases FLT-1 and FLK-1 (1007). Ferrer and associates (290) have documented the presence of both receptor subtypes in prostate cancer. In addition, Duque and associates (247) have confirmed the presence of increased plasma levels of VEGF in patients with metastatic prostate cancer. Clearly, therapeutic strategies designed to abrogate the angiogenic cascade in HRPC could have strategic value.

TNP-470 is a semisynthetic analog of fumagillin, which possesses very potent antiangiogenic and antitumor activities. TNP-470 inhibits the *in vivo* growth of the HRPC cell line PC-3 and has a significant additive antitumor effect when administered with cis-platinum (1114).

Linomide, a quinoline-3-carboxamide, inhibits the growth and metastasis of rat prostate cancer *in vivo* (but not *in vitro*) by interfering with tumor angiogenesis and macrophage infiltration (1055). In an *N*-methylnitrosourea initiation-androgen promotion model, administration of oral linomide at a daily dose as high as 25 mg/kg per day for at least 1 year was without major toxicity and inhibited the development of seminal vesicle and prostate cancers in male rats by more than 50% (474). Tumor-associated macrophages can either promote angiogenesis in tumors by secreting tumor necrosis factor-α or inhibiting angiogenesis by producing granulocyte-macrophage colony-stimulating factor (GM-CSF), which in turn stimulates production of the antiangiogenic protein plasminogen activator inhibitor type 2 (473). Linomide is unique among the antiangiogenic agents tested, in that it inhibits the stimulatory effects of tumor-associated macrophages on tumor angiogenesis. The coordinated loss of androgen regulation of VEGF is associated with the progression of CaP to the HRPC phenotype (472). It appears VEGF is constitutively expressed and upregulated in HRPC by cellular hypoxia, not by androgens. In hormone-dependent CaP, VEGF levels are directly regulated by androgen. Indeed, a major reason underlying tumor regression following androgen ablation may be the marked diminution in tumor-associated VEGF levels.

COX-2 is an inducible enzyme that catalyzes the formation of prostaglandins from arachidonic acid. It is expressed in prostate cancer specimens and cell lines (593). COX-2 inhibitors possess antiangiogenic and antitumor activities (621). Preclinical studies conducted by Liu and associates (593) confirm that inhibition of COX-2 suppresses angiogenesis and the growth of prostate cancer *in vivo*.

Table 33.44 provides examples of novel classes of antiangiogenic drugs in clinical development. Figure 33.92 depicts the various components of the angiogenic cascade that are fertile targets for antiangiogenic drug therapy.

Class of Drug	Examples	Mode of Action	Stage of Clinical Development
Matrix metalloprotease (MMF) inhibitors	Marimastat, AG-3340 Bay 12-9566	Inhibit MMPs, especially MMP-2 and MMP-9	Randomized phase II studies completed
Vascular endothelial growth factor (VEGF) Receptor inhibitors	SU-5416	Inhibits	Phase I trials completed, phase II open
Anti-VEGF antibody	Humanized anti-VEGF Antibody	Blocks VEGF activating Receptor	Phase II studies
Antiintegrin antibodies	Humanized αvβ3 integrin Antibody	Cause endothelial apoptosis By blocking αvβ3 integrin	Phase I studies completed
Endogenous protein Inhibitors	Angiostatin, endostatin	Unknown, generated by MMP and other proteases	Awaiting formulation before phase I studies
Vascular targeting agents	CM101	Fixes complement, causing vasculitis in new vessels	Phase I studies completed

Adapted from Jones PH, Harris AL. The current status of clinical trials in anti-angiogenesis. *PPO Updates* 2000;14(1):1, with permission.

TABLE 33.44. EXAMPLES OF NOVEL CLASSES OF ANTIANGIOGENIC DRUGS IN CLINICAL DEVELOPMENT

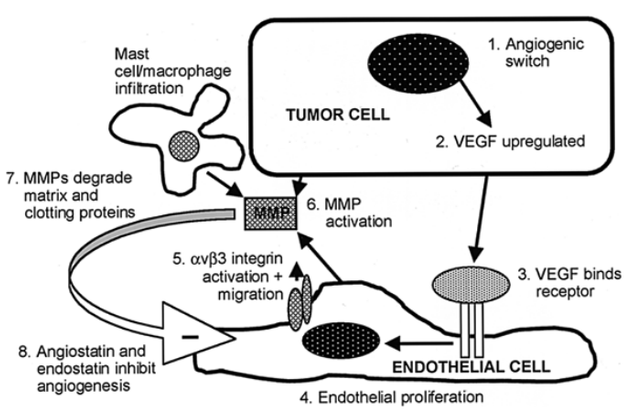

FIGURE 33.92. The various components of the angiogenic cascade that are fertile targets for antiangiogenic drug therapy. MMP, matrix metalloproteinases; VEGF, vascular endothelial cell growth factor. [From Jones PH, Harris AL. The current status of clinical trials in anti-angiogenesis. *PPO Updates* 2000;14(1):1, with permission.]

Inhibitors of Tumor Cell Adhesion

The oral administration of *modified citrus pectin* was capable of inhibiting spontaneous metastasis of the Dunning rat prostate cancer MAT-LyLu (773). This agent interferes

with cell–cell interactions mediated by cell surface carbohydrate-binding galactin-3 molecules and inhibits adhesion of these prostate cancer cells to rat endothelial cells. More importantly, administration of the drug significantly reduced the incidence of pulmonary metastases in the experimental group compared with controls. Clinical trials are currently in progress. Hsieh and Wu (435) observed that modified citrus pectin can directly inhibit proliferation of HRPC cells *in vitro*, an effect associated with downregulation of cyclin B and p34cdc2.

Induction of Apoptosis

Programmed cell death (apoptosis) involves an epigenetic reprogramming of the cell that results in an energy-dependent cascade of biochemical and morphologic changes that occur within the cell, resulting in its death and subsequent elimination (224). Dysregulation of apoptosis is a hallmark of most cancers (817). As stated previously, prostate cancers evade the apoptotic pathway through many mechanisms, including increased bcl-2 expression, mutated p53, and upregulation of the antiapoptotic gene SGP-2 (clusterin) (652,975).

Agents capable of inducing programmed cell death (i.e., apoptosis) in prostate cancer systems have shown promise in preclinical studies. *Thapsigargin* is a sesquiterpene γ-lactone, which selectively inhibits the sarcoplasmic and endoplasmic reticulum calcium-dependent ATPase pumps. Studies conducted by Furuya and associates (326) demonstrate that the initiation of programmed cell death in HRPC cells exposed to this agent is a consequence of elevated intracytoplasmic calcium. It appears the endoplasmic reticulum calcium-ATPase pump constitutes a new therapeutic target for activating apoptosis.

ß *-Lapachone* is a simple plant product that exhibits antitrypanosomal effects, inhibits reverse transcriptase and gene expression, impairs DNA repair, and inhibits the catalytic activity of DNA topoisomerase I through a mechanism different than camptothecin (577). ß-Lapachone induces apoptosis in human prostate cancer cells by a mechanism independent of p53 expression. Furthermore, ectopic overexpression of bcl-2 does not confer significant resistance to ß-lapachone–induced apoptosis.

Eiseman and associates (256) evaluated a *novel spermine analog (1,12-Diaziridinyl-4,9-Diazadodecane)* on the growth of hormone refractory prostate cancer cell lines *in vitro* and *in vivo*. They observed that this compound has potent antitumor effects against these tumors via induction of apoptosis. Furthermore, this compound increases the radiosensitivity of human prostate cancer cells by decreasing the apoptotic threshold to radiation.

Liu and associates (592) evaluated the impact of a *selective COX-2 inhibitor (NS 398)* on the growth of LNCaP cells. They observed that this compound induces apoptosis in this cell line and downregulates bcl-2 expression, concomitantly.

Finally, studies conducted by Miayake and associates (652) and Gleave and associates (364) confirm the potential utility

of *antisense bcl-2 oligodeoxynucleotides* with respect to delaying the progression to androgen independence, inducing apoptosis, and promoting chemosensitization within Shionogi and LNCaP tumor systems.

Dietary Factors and Kinase Inhibitor Therapy

There appears to be a direct correlation between average dietary fat consumption and the death rate from CaP (19). Long-term, high-fat diets may predispose to increased androgen levels that are subsequently stimulatory to prostate growth (522). Indeed, the reduction of dietary fat has been shown to slow the growth of tumors established from CaP cells in murine xenograft models (1074).

Tomatoes are the primary dietary source of lycopene, a non–provitamin A carotenoid with potent antioxidant activity. Clinton and associates (179) identified the presence of lycopene in the prostate at concentrations that are biologically active in laboratory studies, supporting the hypothesis that lycopenes may have direct effects within the prostate and contribute to the reduced prostate cancer risk associated with the consumption of tomato-based foods. Other potentially beneficial dietary factors include increased fruit consumption and vitamin E/selenium supplementation (360,411).

The isoflavones contained in soy (particularly genistein) inhibit tyrosine kinase activities, and by this mechanism, probably exert their constraining influence on cellular growth (522). Receptor tyrosine kinases are glycoproteins consisting of an extracellular portion that binds ligands, a transmembrane helix, and a cytoplasmic portion. Receptor tyrosine kinase family members include the receptors for epidermal growth factor, FGF, platelet-derived growth factor, stem-cell factor, vascular endothelial growth factor, and nerve growth factor (640). Obviously, abrogation of this component of catalytic pathway could have strategic therapeutic importance.

Flavonoids such as quercetin and genistein have been shown to inhibit tumor cell growth *in vitro* and a significant degree of this inhibition is related to their ability to inhibit tyrosine kinase activities. The new flavone designated *flavopiridol (L86-8275) possesses selective antitumor activity in vitro* and *in vivo* for prostate carcinoma cells (243). Flavopiridol is a potent inhibitor of cyclin-dependent kinase type 1, the mediator of cell cycle progression from G_2M phase and cyclin-dependent kinase type 2, whose activity appears at the G_1-S boundary. Senderowicz and associates (901) reported the results of a recently completed phase I clinical trial using continuing infusion flavopiridol in patients with refractory neoplasms. Antitumor effect was observed in certain patients with renal, prostate, colon cancer, and non-Hodgkin's lymphoma.

TRK is a high-affinity tyrosine kinase–linked receptor for nerve growth factor and it has been implicated in prostate cancer growth (231). *The TRK tyrosine kinase inhibitor designated CEP-751 (KT6587)* has been shown to inhibit prostate cancer growth in nine different animal models independent of the tumor growth rate, androgen sensitivity, metastatic ability, and state of tumor differentiation (231).

Proline-directed protein kinase F_A is overexpressed many fold in various human cancers relative to normal controls (1116). *Antisense suppression of proline-directed protein kinase* F_A has been shown to enhance the chemosensitivity in human prostate cancer cells and suggests that this protein kinase may play an important role in controlling multidrug resistance in HRPC (1116).

Immunotherapy

Efforts to identify potential cellular targets for immunologic therapy and approaches to enhance, depress, or modify their roles in development and growth of CaP in man had been pursued with various degrees of vigor and very limited success for many years. These earlier efforts included attempts to use nonspecific immune potentiating agents, various cytokines, monoclonal antibodies acting directly or as carriers of cytotoxic cellular agents, and other approaches (533). For the most part, these efforts with the exception of those attempting to identify new antigenic targets and develop antibodies to them are the targets of limited current effort. On the other hand, efforts to develop and characterize tumor-specific monoclonal antibodies to form immunoconjugates capable of targeting disseminated prostate cancer seem to be escalating.

Ideally, this concept requires monoclonal antibodies reacting uniformly with benign/malignant prostate cells and lacking diverse cross-reactivity with nonprostatic tissues. Pastan and associates (751) isolated an IgM-κ subtype monoclonal antibody, PRI, that reacted uniformly with the surface of 25 of 26 prostatic adenocarcinomas. It also reacted with the surface antigen on normal prostate epithelial cells and cells isolated from BPH specimens. Brinkmann and associates (101) demonstrated that the cloned variable regions of the light and heavy chains of the PRI antibody could be used to construct a recombinant immunotoxin that was very cytotoxic to antigen-positive LNCaP cells. It is proposed that recombinant Fab forms of PRI can be constructed to facilitate the delivery of isotopes or drugs to prostate cancer cells.

Promising preliminary studies also have been conducted using the In^{111} indium CY-356 radioimmunoconjugate designated *In^{111} capromab pendetide* for detection of occult prostate cancer recurrence (480). ProstaScint (capromab pendetide) is a murine monoclonal antibody 7EI 1-C5.3 directed against the cytoplasmic epitope of PSMA. The utility of this approach to detect sites of occult prostate cancer in postprostatectomy patients with an abnormal serum PSA has been discussed previously. A phase I dose-escalation study using Y-CYT-356 monoclonal antibody

conducted in 12 patients with hormone-refractory prostate carcinoma demonstrated 58% of patients had at least one site of disease imaged (221). Myelosuppression was the dose-limiting toxicity. One patient developed a human antimouse antibody 4 weeks after treatment, indicating limited immunogenicity. No patient had a complete or partial response based on PSA antigen and/or radiologic criteria. Recently, Bander and associates have completed a phase I clinical trial assessing the efficacy of the antibody designated J591. The latter is a mouse monoclonal antibody to PSMA. J591 binds to the extracellular part of PSMA. Following binding, the complex is internalized into the cell. This targeted access to the prostate cancer cell suggests that the J591 antibody could be linked with toxins and that this complex might induce selective killing of prostate cancer cells.

Cytotoxic T lymphocytes recognize protein antigens as small peptides (9 to 10 amino acids) associated with class I molecules of the major histocompatibility complex (MHC) (1100). The identification of tumor-associated antigens (and individual epitopes) recognized by human T lymphocytes could prove to be highly beneficial. Correale and associates (188) identified *novel PSA peptides*, designated *PSA-1* (amino acids 141 to 150) and *PSA-3* (amino acids 154 to 163), capable of eliciting specific cytotoxic T-cell responses to prostate carcinoma cells. Each candidate peptide contains consensus amino acid motifs for binding to HAL-A2, the most common type of class I molecule; both these peptides lack strong homology with PSA-related kallikrein proteins; and both peptides are capable of stabilizing HAL-A2 class I molecules on the surface of human T-2 cells, which are defective in antigen presentation. The investigators generated four different cytotoxic T-cell lines to these peptides and demonstrated that these T-cell lines could lyse PSA-positive, HAL-A2–positive LNCaP. These studies provided the rational basis for the use of PSA peptides (or recombinant vectors) in the development of highly specific anticancer vaccine immunotherapy protocols.

Genetic Immunotherapy

Lack of an effective immune response in patients with HRPC may be due to weak tumor antigenicity or a tumor-immunosuppressive environment. The goal to improve this adverse tumor-host relationship and facilitate immune recognition and destruction of malignant CaP cells is worthwhile (659). Although still in its infancy, cytokine-mediated gene therapy for CaP may hold promise in this regard.

For example, efficient recognition of tumor cells by helper T lymphocytes requires the expression of unique tumor associated antigens in concert with class II MHC expression (Fig. 33.93). Immunotherapy based on GM-CSF or IL-2 gene transfer is capable of reconstituting this expression (860). Similarly, efficient interaction of cytotoxic T cells with their tumor target depends on the expression of

these same tumor-associated antigens and tumor cell class I MHC. Immunotherapy using gene transfer of interferon-γ or TNF-α augments this facet of immune interaction (860,861).

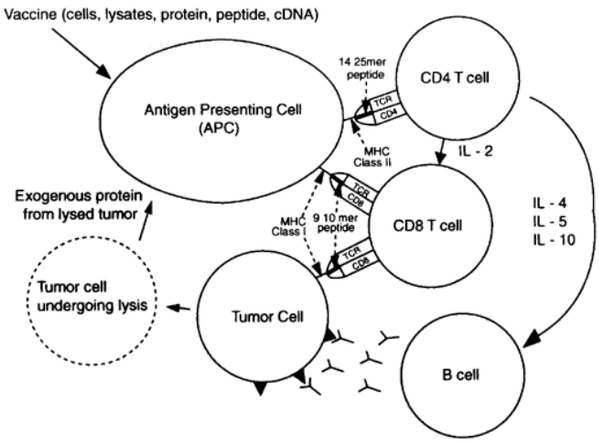

FIGURE 33.93. Activation of the immune system. (From Foon KA. *Vaccine therapies for epithelial cancers.* American Society of Clinical Oncology, 2000:730, with permission.)

Early phase I clinical trials involving gene therapy of urologic cancers used a relatively simple approach. In brief, portions of the primary tumor are removed and established in a tissue culture to expand this pool of malignant cells. A retroviral vector is used to incorporate a given immunostimulatory gene into the DNA structure of the tumor cell. The transfected tumor cells are then radiated to inhibit tumorigenicity. A series of inoculations of the resulting vaccine preparation was carried out in the tumor-bearing host (861). Simons and associates (920) reported on the results of a phase I human gene therapy trial involving eight immunocompetent prostate cancer patients who were treated with autologous, GM-CSF–secreting, irradiated tumor vaccines prepared from *ex vivo* retroviral transduction of surgically harvested cells. Their study demonstrated that both T- and B-cell immune responses to human prostate cancer could be generated by this approach.

Preclinical studies using the Dunning rat R3327-MatLyLu prostatic tumor model that is in some ways analogous to hormone refractory metastatic human prostate cancer were reported by Vieweg and associates (1044). The IL-2–secreting, irradiated tumor cell preparations were capable of curing animals with subcutaneously established tumors. Moreover, this treatment induced immunologic memory that protected these animals from subsequent tumor challenge.

Table 33.45 describes the characteristics of those vectors commonly used for therapeutic gene delivery. Table 33.46 summarizes the characteristics of currently active gene therapy strategies. Finally, Gotoh and associates (370) reported the feasibility of a *PSA promoter–based gene therapy* for androgen-independent human prostate cancer.

Vector	Duration of Therapeutic Gene Expression	Efficiency of Gene Transfer	Comment
Retrovirus	Stable long term	Variable	Labile *in vivo*
Adenovirus	Transient	Highly efficient	Immunogenic
Poxvirus (vaccine)	Transient	Highly efficient	Immunogenic
Nonviral plasmid (liposomes or gene gun)	Transient	Inefficient	Fewer safety concerns than with other vectors

Adapted from Sanda MG. Biological principles and clinical development of prostate cancer gene therapy. *Semin Urol Oncol* 1997;15:43, with permission.

TABLE 33.45. CHARACTERISTICS OF VECTORS FOR THERAPEUTIC GENE DELIVERY

Therapeutic Gene	Extent of Potential Efficiency *In Vivo*	Relative Obstacles
Immunogene, *ex vivo* transfer	Systemic	Requires tissue procurement and cell culture
Immunogene, *in vivo* transfer	Systemic	Vector-specific immunity may interfere with the induction of tumor-specific immunity
Cytotoxicity/apoptosis	Local-regional	Requires highly efficient gene delivery *in vivo;* possibility of cytotoxic injury to normal cells
Antioncogene/antisense	Local-regional	Requires highly efficient gene delivery *in vivo* and durable expression of therapeutic gene
Tumor suppressor	Local-regional	Requires highly efficient gene delivery *in vivo* and durable expression of therapeutic gene

Adapted from Sanda MG. Biological principles and clinical development of prostate cancer gene therapy. *Semin Urol Oncol* 1997;15:43, with permission.

TABLE 33.46. CHARACTERISTICS OF GENE THERAPY STRATEGIES

Studies confirming the potential utility of adenovirus vectors to deliver therapeutic genes to prostate cancer targets are proliferating. A library of human prostate cancer cell lines has been transfected with *the recombinant adenovirus vector (AdWTp53) expressing wild-type p53* resulting in severe growth inhibition with evidence of apoptosis and

death in comparison to untreated or control adenovirus vector-infected cells (959). Introduction of the gene for wild-type human p53 or p21 into a p53-deficient mouse prostate cancer cell line using *a recombinant adenoviral vector (AdSCMV-p53 or Ad5CMV-p21)* revealed significantly higher growth suppression after Ad5CMV-p21 infection. *In vivo* studies in syngenic male mice with established subcutaneous prostate tumors demonstrated a greater reduction in growth rate and final tumor volume in mice receiving intratumoral injection of the Ad5CMV-p21 construct.

In vitro and *in vivo* observations with a *recombinant adenovirus carrying the epithelium specific cell adhesion C-CAM gene*, the recombinant adenovirus AdCAM902, or its antisense construct, AdCAMIOI (control) using human PC-3 cells as the target demonstrated that C-CAM expression in viral-infected PC-3 cells is a long-lasting event; a single dose of C-CAM adenovirus is capable of repressing the growth of PC-3–induced tumors in nude mice for at least 3 weeks (513).

Many other promising gene therapy approaches are being developed. For example, *naked DNA* can be introduced into target cells using plasmid–liposome complexes obviating the need for a complex vector system (862). Other intriguing approaches involve the selective transfection of cellular toxin genes (429) or the *gene transfer of dominant apoptosis-inducing genes* (175). *The direct intratumoral injection of suicide genes* without the aid of the PSA promoter also can achieve target-specific, antitumor activity.

The use of antisense oligodeoxynucleotides as therapeutic agents has stimulated significant interest. DNA has a coding and a complimentary noncoding strand with the same sequence. When the noncoding strand is induced to transcribe, it produces antisense RNA molecules that combine to target mRNA in a fashion similar to the complimentary DNA double helix. Once attached, the RNA molecules cannot be "read" and the production of protein is blocked (684). Early antisense strategies involved the direct injection of short antisense oligonucleotides (974). More recently, recombinant vector systems have been used to deliver longer antisense and dominant negative mutation constructs (862).

Solid tumors cannot grow without the generation of new blood vessels. Tumor blood vessels are leaky and aberrantly organized, demonstrating unusual fan and spiral motifs, forming right angles and AV shunts (523). Upregulation of the avP3 integrins is also a feature of new blood vessel formation in tumors, a biologic process thought to be critical for the survival and differentiation of vascular cells undergoing angiogenesis (102). Because adenovirus vectors use VB3 integrins as an internalization signal, it may be possible to design such vectors specific for actively proliferating tumor vessels. In all likelihood, *antiangiogenesis gene therapy* strategies will be most effective in a state of low tumor burden. In this regard, gene therapy approaches that target the common signaling cascades in the endothelial cells, rather than specific angiogenic mediator or their receptors, may be more effective approaches to impart vasculogenesis.

Successful "vaccination" is contingent on several critical factors. The first involves the activation of antigen presenting cells (APCs), particularly *dendritic cells*, with uptake of antigen and its presentation in association with class I and/or class II MHC. This feature is a prerequisite for the initiation and propagation of an effective cell-mediated immune response. Dendritic cells are highly motile, widely distributed antigen presenting cells capable of producing interleukin-12 and actively forming clusters with T cells. A second requirement is the stimulation of both cytotoxic and helper T cells that recognize various different epitopes. Figure 33.94 illustrates the potential interactions between dendritic cells and T cells. The latter feature is important so that the tumor cell cannot escape immune detection because of antigenic drift or altered antigen presentation. Another prerequisite of successful gene therapy is the stimulation of the appropriate subpopulation of the CD4′ helper T cells (Thi subset), which provide adequate cytokine support in the local microenvironment to maintain the antitumor immune response (587). The ultimate identification of tumor-associated antigens (TAAs) would greatly facilitate this endeavor. Zhang and associates (1130) screened both primary and metastatic prostate cancers for their expression of 30 potential tumor-associated antigens. Their study provides the basis for selecting GM2, TF, Tn, sTn, hCGp, MUCI, KSA, and PSMA as target antigens for specific immunotherapy of CaP. They postulate that these nine antigens could be used to generate a polyvalent prostate cancer vaccine.

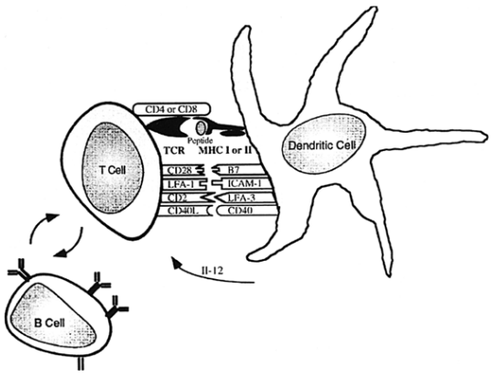

FIGURE 33.94. Potential interactions between dendritic cells and T cells. Dendritic cells can engage T-cell receptors *(TCR)* on CD4+ T cells with peptide presented in the context of MHC class II molecules or on CD8+ T cells, in the context of MHC class I molecules. Costimulatory and adhesion molecule interactions increase cell adhesion, prolong cell contact time, and enhance T-cell activation. (From Hsu FJ, Engleman EG, Levy R. Dendritic cells and their application in immunotherapeutic approaches to cancer therapy. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: principles & practice of oncology,* 5th ed. Philadelphia: Lippincott-Raven Publishers, 1997:1, with permission.)

Early clinical trials of monocyte-derived dendritic cells included patients with prostate cancer who were vaccinated with *dendritic cells pulsed with 2HLA-A2.1 restricted peptides from PSMA* (686,689,856,1017). In a phase II trial of 37 patients, peptide-pulsed dendritic cells were infused intravenously at 6-week intervals in patients who had locally recurrent or metastatic prostate cancer. Fourteen patients exhibited a CR or PR by AUA criteria (595). However, the investigators could not conclude there was an association between augmented CD8 responses to PSMA peptides and clinical benefit. Burch and associates (109) treated 13 patients with two infusions, 1 month apart, of *autologous dendritic cells pulsed with PA2024. The latter is a fusion protein of human GM-CSF and human prostatic acid phosphatase*. The infusions were followed by three subcutaneous monthly doses of PA2024. Circulating PSA levels dropped in 3 of 12 patients (1082).

Finally, Weichselbaum and associates (1086) *linked the radiation-responsive DNA sequences of the early growth response (EGR-I) gene promoter to a TNF-*α *cDNA*. They

transfected this construct into the HL525 human leukemia cells so that radiation activation of an exogenous inducible promoter could be used to control TNF-α gene activity in an experimental animal system. HL525 cells containing the EGR-TNF construct were injected into human xenografts of the radioresistant human squamous cell carcinoma cell line SQ-20B. They demonstrated an increase in tumor cures compared with animals treated with radiation alone. Of importance, there was no increase in local or systemic toxicity in these and other tumor-targeted therapies. Preliminary studies (400) suggest that targeted gene therapy radiation is capable of preferentially radio-sensitizing tumor cells.

Assessment of Treatment Efficacy

The quest for truly effective therapy in the treatment of HRPC is a critically important clinical and scientific endeavor. The pursuit of this goal has been hampered by various factors, including (a) the nature of the patient population at risk, (b) the patterns of metastasis common to prostate cancer, and (c) the difficulty in establishing response criteria to systemic chemotherapy in this disease (878).

The effectiveness of hormonal therapy as compared with the relative ineffectiveness and risk of systemic chemotherapy in patients with CaP is currently a major deterrent to early initiation of the latter in this disease. Similarly, once the patient has evolved to the stage of hormonal unresponsiveness, the impact of multisystem organ disease, general inanition, and reduced bone marrow reserves as a result of osseous metastases may likewise mitigate against the effective use of systemic cytotoxic therapy. At present, it seems appropriate to consider those patients with symptomatic disease progression for such therapy.

The standard patterns of metastasis in CaP preclude the existence of easily demonstrable and measurable tumor foci in the vast majority of patients. In patients receiving chemotherapy

for CaP, approximately 85% or more have demonstrable osseous metastases, and pulmonary, liver, and regional lymph node involvement is documented in 10% to 20%, 10% to 15%, and 10% of patients, respectively (760).

Accurate and repetitive analysis of tumor volume in the primary lesion is difficult, although precise volumetric measurements performed via TRUS may aid in such future endeavors. TRUS has been used to monitor local tumor response to various treatment modalities. Fujino and Scardino (323) noted maximal reduction in prostatic size 9 months after radiotherapy and 3 months after chemotherapy. Studies by Resnick and associates (823) and Carpenter and associates (121) noted a 20% to 30% decrease in prostatic volume within 3 to 6 months of androgen-ablative therapy. TRUS can detect some local recurrences following radical prostatectomy (823).

A similar assessment of changes in tumor volume within obturator and hypogastric lymph node groups is fraught with great difficulty and frustration. Measurable superficial adenopathy is a rare occurrence. The majority of bony metastases are blastic or contain a mixed blastic and lytic component. When the latter undergo healing in response to therapy, a blastic reaction may occur and be misconstrued as evidence of disease progression, despite the use of MRI and CT scans. Pulmonary involvement tends to be of the diffuse lymphangitic variety, rendering accurate measurements of tumor volume all but impossible. It is apparent that few patients present with tumor burdens in such locations as to permit accurate bidimensional or unidimensional measurement. More often, the clinician must rely on evaluable parameters such as bone scans and various tumor markers, including serum acid phosphatase, PSA, alkaline phosphatase, the LDH isoenzyme pattern, D-dimer and carcinoembryonic antigen (CEA) determinations. With regard to the last-named, approximately 60% of patients with soft tissue lesions secondary to metastatic prostate cancer will have demonstrable elevations of this tumor marker. Obviously, such patients represent a unique subset of those with disseminated prostate cancer. The advent of RT-PCR for PSA/PSMA mRNA present in circulating tumor cells represents the latest addition to this “library” of tumor markers (457,492). Recent studies have questioned the utility of RT-PCR for the detection of PSA mRNA for the preoperative staging and follow-up of patients with CaP (272). For example, before radical prostatectomy a positive test was obtained in 13 of 75 patients (17.3%) with pT_2 disease and 10 of 46 (21.7) with pT_3 disease. There was no significant difference in serum PSA, Gleason score, or tumor volume in men with positive or negative results. With a median follow-up of 8 months, 6 of 7 patients in whom surgery failed had a negative result before radical prostatectomy. Of patients with known metastatic disease (or failed primary treatment), a positive result was noted in 32% to 75%. Although increasing tumor burden increases the likelihood of a positive result, a significant sampling error is associated with the use of this test in the peripheral blood.

These observations are in concert with those of other investigators who noted a poor correlation between RT-PCR results and pathologic/clinical stage (897,946). In contrast, other investigators have shown a correlation between RT-PCR results and clinical staging (350,464,733). Some potential reasons for these discordant results include (a) differences in assay methodology, (b) varied patient populations, and (c) the probability that CaP tumor cells are intermittently present in the peripheral circulation. The magnitude of tumor shedding is increased concomitant with expansion of the tumor volume. Preferential sequestration in the bone marrow may account for the observation that bone marrow aspirates may be RT-PCR positive when a similar analysis performed on peripheral blood may be negative (638,1105).

In this respect, several recent observations *regarding PSMA* are of interest. Studies conducted by Pinto and associates (778) have identified that PSMA is a pteroyl poly-γ-glutamyl carboxypeptidase (folate hydrolase) and is expressed strongly in human prostate cancer. Of importance, those cancer cells that express this enzyme are resistant to methotrexate. The recent observations of Wright and associates (1108) further emphasize the potential importance of PSMA as a marker for the androgen-resistant phenotype. Following androgen ablation, PSMA reactivity was increased in 55% of posttreatment primary tissues and 100% of posttreatment metastatic specimens. In contrast, PSA expression was decreased in 70% of posttreatment primary and 100% posttreatment metastatic specimens. The significantly amplified expression of PSMA in metastatic tissues suggests that PSMA may constitute a clinically viable target for antibody and gene therapy of prostate cancer that recurs following androgen ablation. PSMA is a type II membrane protein that shares a 54% sequence homology with the transferrin receptor. Normal prostate cells produce a shorter alternative spliced variant, which encodes for a cytosolic form of the protein. With the onset of malignancy, transmembrane variant predominates (by a factor approaching 100-fold). The other tissues in which the membrane antigen form of PSMA is highly expressed include the duodenal mucosa and a subset of proximal renal tubules (418). Of note, intense PSMA staining also can be detected in the endothelial cells of capillary vessels in peritumoral and endotumoral areas of certain tumors (renal cell, transitional cell, and colon cancers). The high level of transmembrane PSMA expression in the vast majority of prostate cancers and within the capillary beds of some cancers suggests that PSMA can be used for the activation of cytotoxic prodrugs.

The assessment of treatment efficacy becomes all the more difficult to interpret because there is no universal agreement among different cooperative groups and individual

investigators with regard to the response criteria used in various treatment protocols (1112). For example, the term “objective response” is usually construed to note the achievement of complete response or partial remission. Because of the scarcity of measurable metastatic foci, the term “stabilization of disease” has been introduced to describe apparent absence of active progression. Slack and associates (923) considered the use of the stable category as a valid means to evaluate patient status in clinical trials assessing the efficacy of systemic chemotherapy. Other investigators question the validity of this concept (173). Further controversy exists regarding the association of fluctuations in levels of serum PSA/PAP and therapeutic response. Finally, many current studies use quality-of-life parameters as subjective indices of treatment efficacy.

Palliative Care

At present, there are no curative therapies for patients with metastatic HRPC. Although promising, none of the new and emerging treatments described in the preceding sections are likely to achieve this endpoint. For that reason, it is imperative to emphasize that the physician managing such patients must be ever-attentive to quality-of-life issues, particularly the relief of intractable pain.

The somatic and visceral pain associated with advanced-stage malignancy is optimally managed using the *analgesic “stepladder”* officially promoted by the World Health Organization in 1986 (282) (Fig. 33.95). Nociceptive (pain) signals are transmitted over peripheral nerves to the CNS, where farther ascending transmission and modulation occur at spinal and supraspinal levels. Both a human thalamic nucleus specific for pain and widely distributed cerebral cannabinoid receptors have been identified. A newly identified orphan opioid receptor also has been identified. The latter is widely distributed in the brain and its natural ligand “nociceptin or orphanin FQ” also may be involved in learning and memory (846).

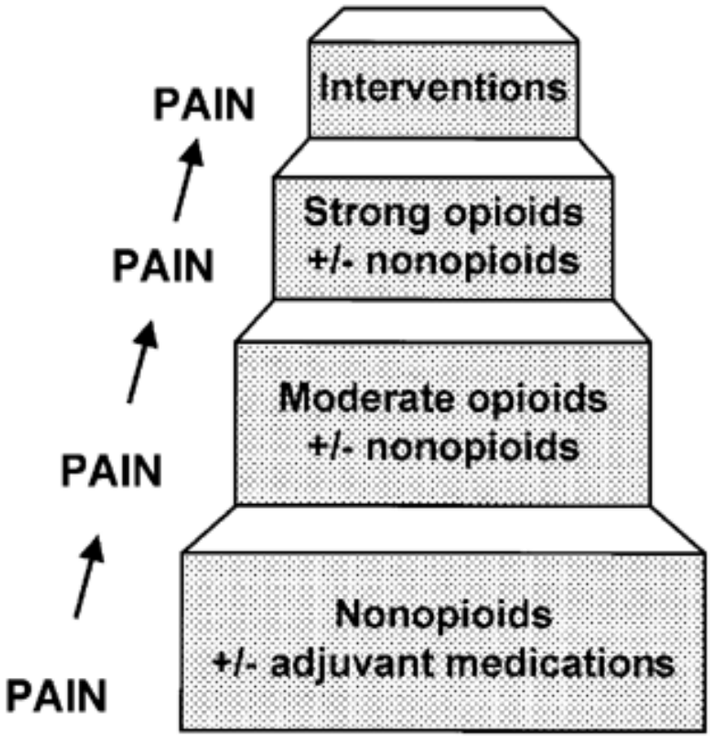

FIGURE 33.95. World Health Organization analgesic stepladder. In the event that cancer is not relieved using the first three steps of this approach, a fourth step should be considered and includes appropriate interventions, such as a simple nerve-blocks, spinal cord stimulation, spinal analgesia, and neuroablation. (From Krames ES. Practical issues when using neuraxial infusion. *Oncology* 1999;13:37, with permission.)

Pain may be classified as nociceptive (ongoing tissue damage) and nonnociceptive (neuropathic). Cancer patients usually suffer from pain due to more than one pathophysiologic mechanism (281). Chemical mediators of pain include substance P, prostaglandins, purines, norepinephrine, neuropeptide Y, endothelin, and nitric oxide.

Acetaminophen or NSAIDs may be sufficient for the management of low-intensity intermittent pain. This constitutes *step I* in the analgesic “ladder.” Although effective for mild pain, many of these agents will possess dose-limiting side effects. For moderate pain, *step 2* of the ladder is activated and involves the use of lower-potency opiate derivatives (i.e., codeine, hydrocodone, and oxycodone), alone or in combination with a step 1 agent. Severe and unrelenting pain should prompt the activation of *step 3,* which involves the use of high-potency opiates (i.e.,

morphine sulfate sustained release, fentanyl transdermal patch, hydromorphone, methadone). Once again, step 3 agents can be used in combination with an NSAID. In general, each medication should be given in maximum tolerated doses before advancing to medications of greater potency. Of great importance, *the analgesic regimen should be administered around the clock and not on an as needed basis*. The standard regimen may need to be augmented to treat breakthrough pain, which is best managed by the "as needed" use of short-acting medications (i.e., morphine sulfate elixir). *Neuropathic pain* may require the administration of a tricyclic antidepressant or gabapentin (Neurontin).

For patients with *insomnia*, the use of amitriptyline or doxepin may be particularly advantageous. The latter agent is also useful for the treatment of intractable narcotic-associated pruritus because of its antihistaminic properties. Conversely, desipramine and nortriptyline are less sedating and possess fewer anticholinergic side effects. The concomitant use of stool softeners and senna frequently obviate narcotic-associated *constipation*. If the latter does occur, magnesium-based laxatives are generally effective. When properly used, the WHO three-step analgesic ladder has been demonstrated to be effective in relieving 75% to 90% of cancer pain (1039).

External beam radiation therapy has a definite role in the management of pain associated with skeletal metastasis from CaP. Androgen-ablative techniques, particularly orchiectomy, can produce a rapid and profound improvement in such painful sites. Consideration of radiation therapy is warranted in those patients who fail to show an adequate response to androgen withdrawal, particularly those with lesions in the spine or weight-bearing areas. In the study by Benson and associates (54), 42% of patients had complete relief of pain following the completion of 3,000 to 3,500 cGy delivered to the painful site. Another 35% exhibited partial relief of symptoms. In addition to the prompt initiation of androgen ablation (usually orchiectomy), the emergency treatment of malignant extradural spinal cord compression has traditionally involved radiotherapy plus the use of moderate-dose (16 mg per day) dexamethasone. Some evidence suggests the steroid component of this regimen can be eliminated in patients who are nonparetic and ambulatory pretreatment. Radiation therapy also may be reasonable in patients with subclinical spinal cord compression (594). Patients with painful multifocal skeletal metastases may be benefited by the *technique of half-body or whole-body irradiation* (494,847). This technique involves the administration of a 600 cGy dose to the upper body followed by a 4- to 6-week hiatus, after which time approximately 800 cGy is delivered to the lower body half. The side effects of the treatment are not trivial and include severe nausea, vomiting, and the expected consequences of bone marrow suppression. Pain relief can be rapid and complete in 28% of patients, with another 70% demonstrating some improvement. As with the use of external beam therapy for focally painful lesions, the lumber spine seems to be a difficult area in which to provide effective palliation (143).

Robinson and associates (835) administered the calcium analog *strontium-89* to patients with prostate cancer who had painful multifocal skeletal metastasis. Response rates in excess of 80% were noted following the IV infusion of 50 to 60 Ci/kg. *Sr-89* ß-emitting isotope that possesses a 50.5 day half-life and follows the biologic pathways of calcium; in theory this provides access to all sites of osteoblastic metastases. Sr-89 is available as a stable isotonic solution for IV administration as a single outpatient injection. Each vial contains a single dose of Sr-89 chloride (4.0 mCi) in saline solution. More recent studies have demonstrated pain relief in approximately 70% of patients (195,791). In general, pain relief is not immediate but begins within 10 to 20 days postinjection, with relief maintained for a mean of 6 months (range of 4 to 15 months). The treatment may be repeated at 3-month intervals contingent upon the patient's peripheral blood count. Therapy is well tolerated except for hematologic toxicity (especially thrombocytopenia), which may become manifest at higher dosages and following repeat dosing. Currently, the primary use for Sr-89 is for the treatment of symptomatic, multifocal skeletal metastases in patients with hormone-refractory prostate cancer who would otherwise be considered for hemibody radiation. Of interest, clinical trials using Sr-89 in conjunction with other antineoplastic regimens (estramustine-based chemotherapy; doxorubicin; suramin) are in progress. The ultimate utility of this novel combination of agents awaits results of multiinstitutional clinical trials.

New bone-seeking agents have been developed that combine more favorable nuclear properties (shorter half-life and lower-energy particle emissions) with chelating agents to form metal complexes that preferentially localize to sites of osteoblastic metastases. *Samarium-153 (Sm153) lexidronam (EDTMP)* (Quadramet) is rapidly cleared from the blood following IV injection and is deposited in the skeleton and excreted as the intact complex in the urine. Patients with metastatic bone cancer who received I.OrnCi/kg of active drug achieved pain relief in 62% to 72% of cases (903). Pain relief was observed within 1 week of administration and persisted until at least week 16 in the majority of responding patients. γ-Ray images obtained after administration of this agent have shown uptake in skeletal lesions are indistinguishable from that obtained with diagnostic bone-scanning agents. Hematologic toxicity, primarily leukopenia and thrombocytopenia, is dose-related, reversible, and occurs most often in patients with comprised marrow reserves.

More recently, *tin-117m (Sn-117m DTPA)* has been evaluated for the treatment of metastatic bone pain (958). This agent is an avid bone seeker and its biodistribution

is virtually identical with that of the routinely used bone imaging radiopharmaceutical Tc-99m MDP. Sn-I 17m DTPA is theoretically attractive because the presence of low-energy electrons (γ-emitter) should result in the relative sparing of the bone marrow while delivering a high radiation dose to sites of skeletal metastases. In contrast, p-emitters (e.g., Sr-89, Sm-153) tend to induce more marrow toxicity. In one study, 47 patients with bony metastatic disease were assigned to five different dose levels [ranging from 2.64 to 10.58 Mbq (71 to 286 inCi) per kg of body weight], with an overall response rate of 75%. The relief was complete in 30%. The time of onset of pain relief was 19 ± 15 days with doses ≤5.29 Mbq/kg and 5 ± 3 days with doses ≥6.61 Mbq/kg (958). Myelotoxicity was minimal and less than that associated with Sr-89 and Sm-153.

Larger doses of radiation (5,000 to 6,000 cGy) may be required to relieve ureteral obstruction refractory to androgen withdrawal therapy. Although some authors have reported good results (120), others have been less enthusiastic about its efficacy (653). Satisfactory resolution of the obstruction may take many weeks, suggesting the wisdom of using double-J stents in the interim.

Radiation therapy to treating bladder neck obstruction due to locally aggressive CaP is a reasonable option in some patients. Androgen ablation (with or without tube decompression) can successfully relieve bladder neck obstruction in most patients within 3 to 6 months and may obviate the need for channel TURP in high-risk patients.

It is beyond the scope of this section to discuss every potential problem confronted by patients with advanced-stage HRPC. Nonetheless, brief consideration of a few additional supportive care issues is appropriate. *Anorexia and cachexia* have been observed in more than 60% of patients with advanced malignancy (239). The etiology of this problem is generally multifactorial and includes (a) the elaboration of tumor necrosis factor, cytokines, and small peptides produced by the tumor; (b) local side effects of the cancer itself; and (c) iatrogenic or treatment-related complications (282). Occasional benefit is derived from the use of corticosteroids (i.e., prednisone 10 to 20 mg per day), high-dose megestrol acetate (500 mg per day), or dronabinol (2.5 mg two to three times daily).

Anemia is commonly observed in patients with end-stage prostate cancer. The tumor cells have a high affinity for the red marrow sinusoids and selectively target those sites. Uncontrolled tumor proliferation ultimately leads to replacement of normal hematopoietic stem cells. Other potential causes of anemia include the myelosuppressive effects of external beam radiation, the use of Sr, and systemic chemotherapy. The resulting side effects can adversely affect quality of life. The first consideration is control of active bleeding, regardless of the source. In most instances, the anemia is chronic and insidious. Administration of epoetin alfa (Epogen) and/or transfusions of packed RBCs should be considered for any patient who is overtly symptomatic and in patients whose hemoglobin level is less than 8.0 g/dL (282).

Approximately one-fourth of patients with advanced malignancy experience clinically significant *depression*. Some of these patients will already be taking tricyclic antidepressants to control neuropathic pain. In such individuals, continuation of that therapy and cautious dose escalation is reasonable. Some potential drawbacks with respect to the use of these agents includes the obligatory 2- to 4-week period required to achieve therapeutic blood levels and GU/GI side effects due to their anticholinergic properties. The selective serotonin reuptake inhibitors (fluoxetine and sertraline) are very useful for the treatment of depression in this setting. In general, the latter agents are taken once daily, are generally well tolerated, and provide a favorable degree of psychostimulation. In addition, they possess a more rapid onset of action and have fewer anticholinergic side effects. It is important to emphasize that tricyclic antidepressants and selective serotonin reuptake inhibitors should not be administered concomitantly for fear of precipitating the “serotonin syndrome,” which is associated with flushing, elevated blood pressure, rapid heart rate, muscle spasms, diarrhea, and mental status changes.

Finally, it is particularly challenging and exceptionally rewarding to participate in the care of those patients with terminal prostate cancer during the final months of life. The doctor–patient relationship takes new meaning in this context. It is imperative that the physicians involved in the care of such patients have an unhurried attitude and encourage patients to speak about their lives, current or past relationships, and their immediate future concerns. Physical contact with the patient should not be discouraged, and the physician should manifest genuine concern for the patient and the grieving family. *Hospital and community-based hospice units* are invaluable to the patient, family, and managing physicians.

Conclusion

Sophisticated scientific approaches are beginning to yield significant insights into the genetic and biochemical aberrations associated with the uncontrolled proliferation and dissemination of HRPC. It seems likely that such advances will ultimately translate into the development of novel therapies whose impact will be well tolerated, effective, and durable. It is also highly probable that these treatments will be cytostatic rather than cytotoxic. Multimodality cytostatic approaches using treatments possessing diverse mechanisms of action may supplant traditional cytotoxic regimens, whose goal is the ultimate elimination of every tumor cell clone (Fig. 33.96). Providing such elderly patients with a

number of good quality years would be tantamount to cure in many instances.

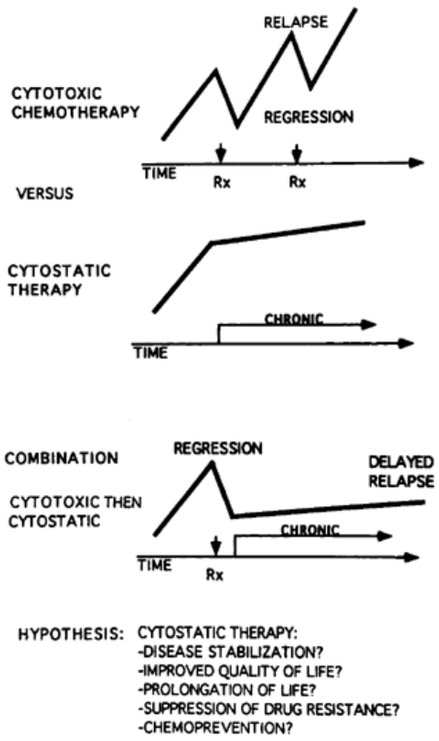

FIGURE 33.96. Cancer treatment paradigms. Cytotoxic therapy–induced regression is generally followed by relapse. Multimodal cytostatic therapy probably will be administered over a prolonged period of time. Indeed, the combination of these two treatment strategies could conceivably extend the time to recurrence and prolong survival. (From Kohn EC, Liotta LA. Molecular insights into cancer invasion: strategies for prevention and intervention. *Cancer Res* 1995;55:1856, with permission.)

Treatment of Unusual Primary Tumors of the Prostate

Although no well-established guidelines exist for the management of the unusual prostate cancers briefly described in the pathology section of this chapter, an analysis of sporadic case reports does permit certain generalizations.

Approximately 160 cases of primary and secondary intraductal prostatic adenocarcinoma have been reported in the literature. Available evidence suggests that when such lesions are localized to the prostate gland, their treatment should parallel that of the more common acinar tumors. Despite the fact that distant dissemination is often associated with osteoblastic skeletal metastases and elevated serum PSA and PAP levels, the response of these prostatic duct adenocarcinomas to androgen-ablative therapy is disappointing. Dube and associates (244) reported 5-year survival rates of 42.8% and 24% for primary and secondary prostatic duct adenocarcinomas, respectively.

Endometrioid carcinomas probably represent a variant of prostatic ductal tumor. Recent electron microscopic and

immunohistochemical data support this contention and seem to negate the likelihood of utricular origin (1124). Of interest, these lesions appear biologically less aggressive than other ductal carcinomas. Various treatment options have been reported for locally contained tumors. Because these tumors are typically located in a periurethral distribution, small lesions are potentially amenable to TUR. Most cases, however, have been treated with radical prostatectomy, cystoprostatectomy, or external beam radiation therapy (526,1075). Despite early reports to the contrary, most of these tumors are androgen-dependent, and some form of androgen-ablative therapy is certainly warranted in the presence of metastatic disease (277,1070). Indeed, of the 72 reported cases, 61 demonstrated positive staining for PSA, PAP, or both (765). It has been proposed that the PSA-negative tumors may represent a unique variant of endometrioid carcinoma, one derived from müllerian epithelium, which is PSA- and Leu 7-negative (970). Although these lesions tend to be refractory to currently available chemotherapy regimens, transient partial tumor regression was reported with the combination of 5-FU and doxorubicin (554).

Approximately 200 cases of transitional cell carcinoma of the prostate (TCCP) have been cited in the literature. Three distinct clinical subsets of TCCP are recognized and include (a) primary tumors arising in the absence of synchronous or metachronous urothelial cancers (25%), (b) secondary tumors that may be contiguous or noncontiguous with other urothelial lesions (65%), and (c) mixed tumors consisting of TCCP and prostatic adenocarcinoma (10%) (41,298,764,1099). In general, these tumors are very aggressive and often are associated with diffuse retrograde involvement of the prostatic ductal system, urethra, and bladder. The presence of a histologic continuum ranging from transitional cell hyperplasia with atypia to frank carcinoma *in situ* within the prostatic ducts would suggest a primary prostatic origin for the neoplasm in many instances (1030). Conservative treatment options such as TURP and the intravesical administration of BCG is feasible in a very small subset of patients with *in situ* disease (1075). Radical cystoprostatectomy is required for most tumors invading the fibromuscular stroma of the prostate owing to the presence of contiguous bladder neck and urethral involvement. If the latter can be excluded with certainty, radical prostatectomy might constitute a legitimate therapeutic alternative (298). Combined systemic chemotherapy and radiation therapy should be considered in those patients with gross disease beyond the prostatic capsule and in those patients with compromised surgical margins (or positive nodes) following anterior exenteration. Modifications of the CISCA [cisplatin, cyclophosphamide, adriamycin (doxorubicin)], and MVAC (*m*ethotrexate, *v*inblastine, *a*driamycin, *c*isplatin) regimens seem to be most effective coupled with sequential or concomitant radiation therapy (4,500 to 5,000 cGy). Salvage cystoprostatectomy should be considered in patients who respond to such combination drug treatment (298,385,848). It is hoped that these approaches will improve the average survival, which ranges from 17 to 23 months following radical surgery with or without preoperative radiation therapy (385). Androgen-ablative therapy seems to play little role in the presence of overt metastases because these tumors are uniformly androgen resistant. In this group, combination chemotherapy has been associated with complete (35%) and partial (22%) responses, some of which are sustained for significant periods (298). The interested reader will find the review of this subject by Matzkin and associates (623) very helpful.

Approximately 66 cases of squamous cell carcinoma of the prostate have been reported. This aggressive, androgen-resistant tumor probably represents a metaplastic variant of transitional cell carcinoma of the prostate, and the therapeutic options exercised should parallel those cited for the latter neoplasm (765). Consideration should be given to adjusting the chemotherapy regimen to include agents such as mitomycin C, 5-FU, bleomycin, or MTX, which tend to be more effective against squamous cell cancers. Again, most patients succumb to the disease, with a mean survival of 14 months (680). Although both PSA-positive and PSA-negative tumors have been reported, the observed skeletal metastases were osteolytic (765).

Mucinous (colloid) carcinoma and adenoid cystic carcinoma are rare neoplasms. Consequently, definitive statements regarding therapeutic options and survival are not available. It would seem that tumors confined to the prostate should be treated in a manner similar to that used for acinar tumors. The impact of other therapeutic modalities on locally aggressive or metastatic lesions cannot be ascertained at present. Although these tumors appear to be predominantly androgen resistant, a trial of androgen-ablative therapy would seem warranted in the presence of distant dissemination.

With regard to malignant mesenchymal neoplasms of the prostate, the treatment of rhabdomyosarcoma is thoroughly discussed elsewhere in this book. Carcinosarcomas and leiomyosarcomas of the prostate are similarly aggressive neoplasms that have most often been treated by multimodal approaches (296). This has included preoperative radiation therapy followed by anterior pelvic exenteration and systemic chemotherapy. Ahlering and associates (7) reported the results of their multimodal approach to the treatment of patients with leiomyosarcomas of the bladder (seven patients) and prostate (four patients). Anterior pelvic exenteration was performed for most patients with nonbulky disease. Postoperative external beam radiotherapy (4,500 to 5,000 cGy) and chemotherapy (cisplatin and doxorubicin) were administered in cases of compromised surgical margins or positive lymph nodes. Patients with bulky disease underwent cytoreduction with two to three cycles of preoperative chemotherapy, with or without radiation therapy, followed by salvage cystoprostatectomy. The preoperative therapy

induced a striking degree of cystic necrosis within the tumor, resulting in an increase in size appreciated on follow-up CT scans. Of note, 9 of the 11 patients were without evidence of disease with a mean follow-up of 61 months. In the past, these neoplasms have been associated with a 5-year survival rate of approximately 10% (765). These figures are likely to improve with the advent of carefully orchestrated multimodal therapy.

The treatment of small-cell carcinomas of the prostate generally involves the use of regimens with demonstrated efficacy in the management of small-cell cancers of the lung. A typical protocol for tumors not amenable to initial surgical resection is concomitant radiotherapy and cisplatin/etoposide chemotherapy (with or without vincristine). Alternatively, sequential radiotherapy can be used in concert with cyclophosphamide, adriamycin, and vincristine (1012). A median survival of 17 months has been reported (726). Information regarding the more exotic tumors involving the prostate gland is based on anecdotal case reports, and their treatment, of necessity, must be highly individualized.

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34

PROSTATITIS

J. Curtis Nickel

J.C. Nickel: Department of Urology, Queen's University, Kingston General Hospital, Kingston, Ontario, Canada.

Contents

Prostatitis is diagnosed in adult men of all ages, and symptoms of prostatitis have been said to affect up to 50% of men at some point in their life (258). Data from the National Center for Health Statistics (163) showed that in the United States in 1965, there were actually more physician visits for prostatitis than for benign prostatic hyperplasia (BPH) or prostate cancer. In fact, for 1 year in the late 1970s, approximately 25% of outpatient visits for genitourinary complaints were for prostatitis symptoms (163). Prostatitis is the most common urologic diagnosis in men younger than 50 years of age and the third most common diagnosis in men older than 50 years of age (137). It is the most common urologic diagnosis encountered in the armed forces during peacekeeping deployment (60). In 1991, approximately 5% of visits to U.S. urologists were reported to be for inflammatory diseases of the prostate (240). Urologists in Canada see an average of 22 prostatitis patients per month (median of 11) (180), while urologists in Wisconsin saw an average of 173 (median of 99) prostatitis per patients per year (155). From the latter study, the prevalence of prostatitis in Wisconsin was estimated to be approximately 5% (155). In young men (younger than 50), independent researchers found that 4% to 5% of responders reported a history of prostatitis (44,153). Data from the Olmsted County study of urinary symptoms and health status among men (227) were used to estimate the prevalence of medically diagnosed prostatitis (based on a review of 2,113 men with a medium of 50 months of follow-up).

The investigators noted the overall prevalence of a physician's diagnosis of prostatitis was 11%. A population-based study using a recently validated chronic prostatitis symptom index, reported the prevalence of prostatitis-like symptoms in men younger than 70 years old to be approximately 10% (59).

It is clear that recent studies have confirmed that prostatitis is an extremely common and important diagnosis and the symptoms associated with the diagnosis of prostatitis have significant prevalence within the male community at risk. But what is prostatitis? What causes the symptom complex that describes this clinical entity? How can we properly diagnose and classify these patients? And most important, how can we use the accumulated knowledge of a century of research in this clinical syndrome to rationally treat patients diagnosed with this clinical entity?

KEY INFORMATION

Epidemiology

- Five to ten percent of men are at risk (have either diagnosis or symptoms) for prostatitis.
- Prostatitis is the most common diagnosis made by urologists in men younger than 50 years of age.
- Prostatitis has a significant impact on quality of life.

CLASSIFICATION

Part of "34 - PROSTATITIS "

Traditional Classification System for Prostatitis Syndromes

The four traditional categories of prostatitis were formally introduced to the urologic community in a letter to the editor published in the *Journal of Urology* in 1978 (61). This classification system primarily depended on analysis of prostatic fluid [expressed prostatic fluid (EPS)]. Purulent prostatic fluid was defined as having more than 10 to 20 white blood cells (WBCs) per high-power field (HPF) (the original authors could not decide on a significant level of WBCs in EPS) associated with WBC clumps, mucous debris and occasional lethicin and oval fat bodies, and large macrophages. The categories were further differentiated by culture of prostatic fluid or a urine specimen after prostate massage.

Acute bacterial prostatitis was diagnosed when bacteria were cultured from prostatic fluid, prostatic fluid was clinically purulent, and systemic signs of infectious illness were present. If prostatic massage was considered contraindicated during acute bacterial prostatitis, the diagnosis could be made on recovery of bacteria from the urine and detection of a “hot,” swollen, tender prostate on rectal examination. Chronic bacterial prostatitis could be diagnosed when pathogenic bacteria were recovered in significant numbers from a purulent prostatic fluid in the absence of concomitant urinary tract infection (UTI) or significant systemic signs. Nonbacterial prostatitis could be diagnosed when significant numbers of bacteria could not be cultured from prostatic fluid, but the fluid consistently revealed microscopic purulence. Prostatodynia or “pain in the prostate gland” was the diagnosis for those remaining patients who had persistent complaints similar to the previous two categories but no significant bacteria or purulence in the prostatic fluid.

This traditional classification system depended in large part on the rigid and standardized Meares-Stamey four-glass technique described to evaluate the lower urinary tract inpatients with prostatitis (140). However, many urologists (and most primary care physicians and internists) did not routinely use this Meares-Stamey technique, and the routine practice of examining and culturing prostatic fluid became an uncommon practice (136,137,155,180). Therefore the classification of chronic prostatitis into the three traditional chronic categories became problematic because it relied wholly on examination and culture of the EPS. Further complicating this classification system was the realization that standard culture techniques may not be identifying possible pathogens in the so-called nonbacterial categories.

NIH Definition/Classification System for Prostatitis Syndromes

The urologic community generally recognized that significant confusion surrounded the diagnostic and treatment strategies in chronic prostatitis and many believed this was directly related to the poor definition, diagnostic criteria, and classification system used to date in this clinical syndrome. North American and International urologic researchers interested in prostatitis met at the 1995 Workshop on Chronic Prostatitis, convened by the National Institutes of Health/National Institute of Digestive, Diabetes and Kidney Diseases (NIH/NIDDK) to discuss this problem. A new definition of chronic prostatitis/chronic pelvic pain syndrome was incorporated into the 1995 NIH classification system for prostatitis (111,164). This new classification system divided the prostatitis syndromes into four main categories (Table 34.1). Categories I and II are similar to the traditional classification of acute and chronic bacterial prostatitis respectively. The new category, category III or chronic pelvic pain syndrome (CPPS), was based on the “presence of genitourinary pain in the absence of uropathogenic bacteria detected by standard microbiological methodology.” This new definition/category addresses the concern that we do not understand the etiology of the syndrome in the majority of patients diagnosed with a chronic prostatitis syndrome. CPPS was further categorized into category IIIA or inflammatory CPPS (based on the presence of inflammatory cells in expressed prostatic secretion, postprostatic massage urine or semen) and category IIIB or noninflammatory CPPS (no inflammatory cells in similar

prostate-specific specimens). A fourth category, category IV (asymptomatic inflammatory prostatitis), addresses a major omission in the original traditional classification system. This category includes asymptomatic patients without any demonstrable prostate disease as well as patients with potentially related conditions of the prostate (BPH, prostate cancer, infertility). Patients would be classified into this category based on histopathologic/culture examinations of EPS, postprostatic massage urine specimens (VB3), prostate biopsies, transurethral resection of the prostate (TURP) specimens, semen analyses, and radical prostatectomy specimens. The 1st International Prostatitis Collaborative Network met in Washington, DC, in 1998, and although the limitations of the new classification system were evident after 3 years of use, it was universally acknowledged that the NIH classification system was an improvement over the traditional classification system and was effective in both clinical practice and research protocols (181).

Category I: acute bacterial prostatitis	Acute infection of the prostate gland
Category II: chronic bacterial prostatitis	Chronic infection of the prostate gland
Category III: chronic pelvic pain syndrome (CPPS)	Genitourinary pain without uropathogenic bacteria localized to the prostate gland using standard methodology
Category IIIA: inflammatory CPPS; Nonbacterial prostatitis	Significant number of white blood cells in expressed prostatic secretions, postprostatic massage urine sediment (VB3), or semen
Category IIIB: noninflammatory CPPS; Prostatodynia	Insignificant number of white blood cells in expressed prostatic secretions, postprostatic massage urine sediment (VB3), or semen
Asymptomatic inflammatory prostatitis (AIP)	White blood cells (and/or bacteria) in expressed prostatic secretions, postprostatic massage urine sediment (VB3), semen, or histologic specimens of prostate gland

TABLE 34.1. CLASSIFICATION SYSTEM FOR THE PROSTATITIS SYNDROMES

KEY INFORMATION

Classification

- Traditional classification systems have limitations.
- The new National Institutes of Health classification system of prostatitis is an improvement over traditional systems but is still unvalidated.

LOWER URINARY TRACT EVALUATION

Part of "34 - PROSTATITIS "

Background

To adequately classify the patient according to either the traditional classification system or the more recently introduced NIH classification system for prostatitis, an evaluation of lower urinary tract specimens is required. Meares and Stamey originally described the four-glass urine collection technique as a method to distinguish urethral, bladder, and prostate infections in men (140). Although it is readily acknowledged that many urologists and primary care physicians do not carry out the four-glass procedure, it is still recognized as the premiere diagnostic test and classification tool, or in other words, the gold standard in all prostatitis/chronic pelvic pain syndrome evaluations. However, new, simpler modifications that are more cost-effective may be adequate for clinical practice.

Meares-Stamey Test

The Meares-Stamey four-glass technique provides samples for both microscopic analysis and bacterial culture. The background for this test was provided by researchers in the second and third decades of the twentieth century (169,271,272) who carried out careful culturing of the lower urinary tract in prostatitis patients. Meares and Stamey (140) extended this concept by adding a urethral specimen to the sampling technique. The voided bladder 1 (VB1) specimen includes the first 10 mL of urine. This specimen represents the cells and bacteria from the urethra and was believed to be important in the diagnosis of urethritis. The voided bladder 2 (VB2), or midstream urine specimen, represents the bladder urine. Expressed prostatic secretion (EPS) should be collected directly in a sterile container while the examiner digitally massages the prostate. EPS may not be obtainable in all patients. The voided bladder 3 (VB3) specimen is the first 10 mL of urine voided after massaging the prostate and includes any EPS that may be trapped in the prostatic urethra. An aliquot of VB1, VB2, EPS, and VB3 specimens should be quantitatively cultured (it may be difficult to quantitatively culture the EPS in most urologic clinical situations). The urine specimens (VB1 to VB3) should be centrifuged for 5 minutes and the sediment examined at high-power microscopy for leukocytes, macrophages, erythrocytes, bacteria, oval fat bodies, and fungal hyphae and their numbers recorded (per HPF or more accurately in a hemocytometer). The presence and density of WBCs (Fig. 34.1) and the quantitative

bacteriologic cultures of the urethral, bladder, and prostate specimens are used to diagnose urethritis, cystitis, and bacterial and nonbacterial prostatitis. The quantification of bacterial cultures allows for this localization of infection to a specific segment of the lower urinary tract (i.e., urethra, bladder, or prostate). Traditionally, a tenfold or greater increase in the number of WBCs or colony forming units per cubic centimeter (culture results) in a specific specimen indicated the area of inflammation/infection. A description and interpretation of the four-glass test is shown in Fig. 34.2 and Fig. 34.3 and Table 34.2, respectively.

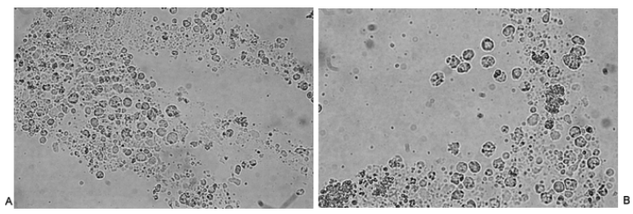


FIGURE 34.1. Photomicrographs showing individual white blood cells, clumps of white blood cells, and lipid-laden macrophages in the expressed prostatic secretion (EPS) of a patient with category IIIA CPPS. (**A:** 250× magnification; **B:** 400× magnification.)

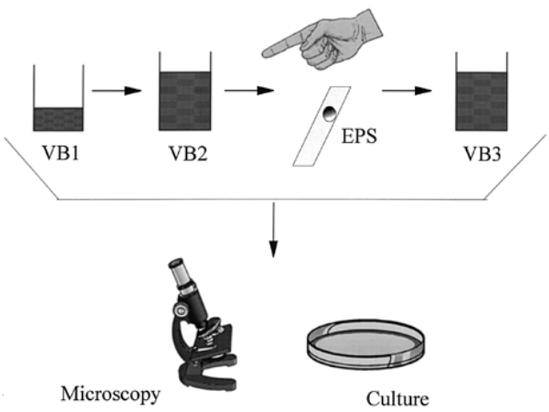


FIGURE 34.2. Meares-Stamey four-glass test. In the four-glass test, initially voided urine *(VB1)* and midstream or second-voided urine *(VB2)* represent urethral and bladder specimens, respectively. During prostate massage, expressed prostatic secretion *(EPS)* is collected and subsequently a voided bladder specimen after prostate massage *(VB3)* specimen is produced. Specimens are all cultured and a microscopic examination of the sediment of VB1, VB2, and VB3 and a wet mount microscopy of EPS is undertaken. See Table 34.2 for interpretation.

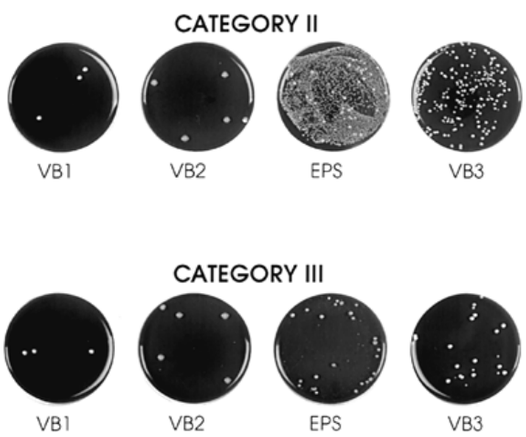


FIGURE 34.3. Culture plates from a representative Meares-Stamey four-glass test undertaken in a patient with category II prostatitis and category III chronic pelvic pain syndrome. Note the light background of Gram-positive bacteria in all specimens but the heavier growth of Gram-negative colony-forming units in the prostate-specific specimens (expressed prostatic secretion and VB3) from the category II patient. Note the light growth of Gram-positive colony forming units in all specimens from the category III patient.

Test		Meares-Stamey				PPMT	
SPECIMEN		VB1	VB2	EPS	VB3	Pre-M	Post-M
Category II	WBC	–	±[a]	+	+	±[a]	+
	Culture	–	±[a]	+	+	±[a]	
Category IIIA	WBC	–	–	+	+	–	+
	Culture	–	–	–	–	–	–
Category IIIB	WBC	–	–	–	–	–	–
	Culture	–	–	–		–	

CAT, National Institute of Health Classification Category (Table 34.2); EPS, expressed prostatic secretion; Pre-M, urine specimen before prostate massage; Post-M, urine specimen after prostate massage; VB1, first-voided urine specimen; VB2, second-voided urine specimen or midstream specimen; VB3, third-voided urine specimen; WBCs, white blood cells.
[a]Cystitis can coexist with chronic bacterial prostatitis. If confirmation is required, repeat after 3 days of nitrofurantoin therapy.
Adapted from Nickel JC. Prostatitis: evolving management concepts. *Urol Clin North Am* 1999;26:737, with permission.

TABLE 34.2. INTERPRETATION OF THE FOUR-GLASS TEST (MEARES-STAMEY) AND TWO-GLASS PREMASSAGE AND POSTMASSAGE TEST (PPMT)

The many limitations of this test include (a) the fact that EPS cannot be obtained all the time in all patients, (b) quantification of bacterial counts in the EPS may be difficult

for many urologists, (c) interpretation of WBC counts varies widely, (d) most laboratories do not routinely attempt to culture chlamydia or ureaplasma or other difficult-to-culture organisms, and (e) significant controversy remains regarding the role of Gram-positive staphylococci and corynebacterium that may be localized to a specific (i.e., prostate) specimen (184,186).

Two-glass Test (Premassage and Postmassage Test)

The two-glass test originally was suggested by Weidner (277) and later was popularized by Nickel (187) to streamline and simplify lower urinary tract evaluation in the majority of patients presenting to the clinical urologic clinic. A description and interpretation of the two-glass test is shown in Fig. 34.4 and Table 34.2, respectively. It is based on two primary premises. The first is that significant urethritis usually can be diagnosed clinically without the employment of an expensive time consuming lower urinary tract evaluation. Asymptomatic urethritis (i.e., no significant urethral pain, urethral itchiness, or urethral discharge) is considered rare and not clinically significant. In a recent report of lower urinary tract evaluations in men presenting with chronic prostatitis/chronic pelvic pain syndrome, Krieger and co-workers (114) demonstrated that “significant” urethral inflammation is rare and did not appear to affect clinical diagnoses and treatment. The second premise

is that postprostatic massage urine (the first 10 mL of urine voided after a vigorous prostatic massage) accurately reflects the microscopy and culture results of the expressed prostatic secretion. Krieger and others (114) demonstrated that postprostatic massage urine was as accurate as examination of EPS in determining prostate-specific inflammation. Ludwig and associates (127) further confirmed that examination of postprostatic massage urine accurately reflected the degree of inflammation detected on expressed prostatic secretion. Although not as accurate as the gold standard four-glass test, the two-glass or premassage and postmassage test results in the same diagnosis in more than 90% of patients tested (187). The premassage and postmassage tests are cost-effective and quick and easy to perform in classifying the patients presenting to the urologic clinic with a chronic prostatitis syndrome.

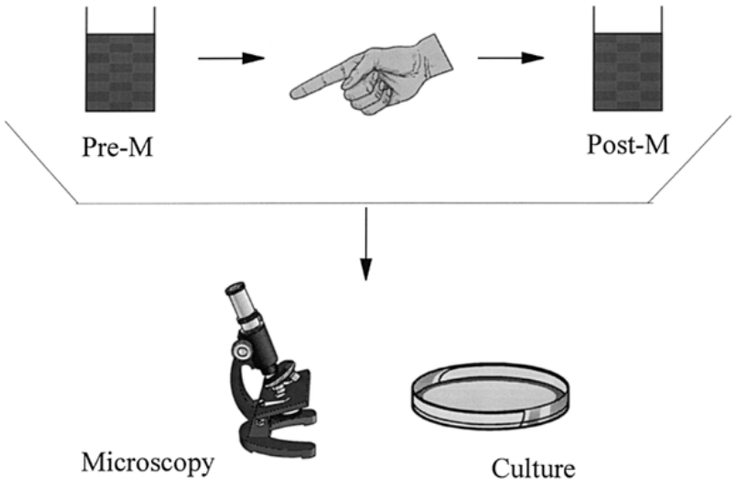


FIGURE 34.4. Premassage and postmassage two-glass test (PPMT). In this much simpler and cost-effective (compared with the Meares-Stamey four-glass test) screening, premassage and postmassage urine specimens are taken before prostate massage *(pre-M)* and after prostate massage *(post-M).* Specimens are sent for culture and microscopy of the sediment. See Table 34.2 for interpretation.

KEY INFORMATION

Diagnosis

- The Meares-Stamey four-glass test remains the gold standard for lower urinary tract localization evaluation.
- For those who cannot or will not do the four-glass test, the simpler premassage and postmassage two-glass test is a reasonable screening evaluation of the lower urinary tract.

CATEGORY I: ACUTE BACTERIAL PROSTATITIS

Part of "34 - PROSTATITIS "

Etiology

Category 1 prostatitis or acute bacterial prostatitis is defined as an acute bacterial infection of the prostate gland. The bacteria are typically uropathogenic fecal flora, very similar to the spectrum of bacteria associated with lower UTIs in females. As with simple lower UTIs in females, the route of infection in the typical case is likely an ascending urethral colonization by potentially pathogenic organisms. The most common organism found in acute prostatitis is *Escherichia coli* (58,145) with other Gram-negative organisms such as *Proteus* species, *Klebsiella* species, *Pseudomonas* species, and *Serratia* species accounting for 10% to 15% of cases (146). Gram-positive organisms are rare in acute prostatitis syndromes but *Enterococcus faecalis* may be an uncommon pathogen (146). Rarely, *Staphylococcus aureus* and other rare Gram-positive and Gram-negative organisms may cause an acute prostatic infection from either a blood-born or catheter-associated route. Coagulase-negative Gram-positive organisms such as *Staphylococcus saprophyticus* do not appear to cause an acute infection of the prostate gland.

Although most male patients develop acute bacterial prostatitis spontaneously, several host risk factors must be considered. Uncircumcised males (269), unprotected penetrative anorectal intercourse, acute epididymitis (17), Lewis Blood Group antigens (123), specific urethral antigens (49,165),

meatal and urethral stricture disease (24), and patients who have undergone urethral manipulation and catheterization (212) are predisposed to acute prostatitis. Urovirulence factors may play a significant role in the pathogenesis of acute prostatitis. For instance, bacterial P-fimbria binds to urothelial receptors, which subsequently facilitates ascent into the urinary tract and establishes deep-seated tissue infections such as acute prostatitis (49,165). Numerous reports indicate that P-fimbriated *E. coli* is commonly isolated from the urinary tract in men with prostatitis (7,268). Colonization of the lower urinary tract by *E. coli* also is facilitated by the presence of type 1 fimbria, also known as *mannose-sensitive fimbria.* The receptor is a common moiety of the uroepithelial uromucoid and this association has been shown to be important in the development of cystitis in humans, and its presence in prostatitis also has been documented (40). Phase variation of type 1 pili during the establishment of acute bacterial prostatitis also has been postulated to occur in the setting of lower UTIs (239).

Confronted by bacterial presence within the prostatic ducts, the prostate gland mounts both a local and systemic immune response (73,116,142,147). Serum and prostatic fluid antigen-specific IgG are both present immediately after onset of infection and decline over the 6 to 12 months after successful antibiotic therapy to normal values. Antigen-specific IgA in prostatic secretion also becomes elevated immediately after inflammation and begins to decrease after 12 months, whereas serum IgA disappears after 1 month following successful antibiotic therapy. Prostate-specific antigen (PSA) can be significantly elevated during an episode of acute bacterial prostatitis (42,168), likely secondary to disruption of the prostatic epithelial cell membrane (152), and slowly resolves to normal levels over the course of 6 weeks (168), provided there is no recrudescence of the infection.

Clinical Presentation

The patient with acute bacterial prostatitis presents with a sudden clinical syndrome of lower UTI, specifically dysuria, frequency, urgency, and suprapubic pain in combination with systemic symptoms associated with generalized infection such as fever, chills, malaise, nausea, and vomiting. Most patients complain of significant obstructive voiding with decreased force and caliber of the urinary stream, dribbling, hesitancy, and in many cases, acute urinary retention.

Diagnosis

In most cases, the astute clinician can make the diagnosis of acute bacterial prostatitis by history and focused physical examination. The history of local and generalized symptoms of infection associated with irritative and obstructive voiding symptoms suggests the diagnosis. Suprapubic tenderness (or even distended bladder by palpation or percussion) in a patient with pyrexia, tachycardia, and perhaps even tachypnea and hypotension corroborates the diagnosis. The prostate examination discloses an exquisitely tender (tense and perhaps edematous and enlarged) prostate. Prostate massage is not necessary and is even discouraged because of the possibility of exacerbating the problem of urosepsis.

Urinalysis and midstream urine culture complete the initial evaluation. The diagnosis is more or less confirmed with the presence of significant pyuria (more than 10 leukocytes per HPF of a centrifuged specimen on microscopy) combined with an eventual urine culture revealing more than 10^5 uropathogenic organisms per cubic centimeter (191). The original traditional classification (61) of the prostatitis syndromes required an examination and culture of the EPS, even in acute bacterial prostatitis. No data in the literature substantiate the fears that prostatic massage causes serious morbidity (such as exacerbating urosepsis), but this procedure is now generally discouraged and is not necessary to make the diagnosis of acute prostatitis. If expressed prostatic secretion is obtained, it should disclose many WBCs and bacteria on microscopy and subsequent cultures should be positive for uropathogens.

Management

The following four major considerations must be taken into account when treating acute bacterial prostatitis (166):

1. *Antimicrobial use:* class, route of administration, and duration of therapy
2. *Urinary drainage:* need for bladder drainage and subsequent mode of bladder catheterization
3. *Hospitalization:* decision whether the patient must be hospitalized or whether he or she can be safely treated as an outpatient
4. *Ancillary measures:* other diagnostic and therapeutic maneuvers to enhance ultimate treatment outcome

Patients presenting with acute bacterial prostatitis are usually very ill. The culture and antibiotic sensitivity results are not available at the time a decision regarding treatment should be made. Therefore wide-spectrum antibiotics that achieve both adequate urinary and prostatic tissue levels are required as initial therapy. In ill patients, the parenteral route of antimicrobial therapy is preferred (even if it is only a single dose if outpatient therapy is warranted). Becopoulos and others (15) suggest that netilmicin (followed by aztreonam, cefuroxime, and the ticarcillin-clavulanic acid combination) is the agent of choice, but in most cases, a combination of aminoglycoside and ampicillin (and/or cephalosporin) provides adequate wide-spectrum coverage of the most likely organisms. This combination should provide coverage against the most common Gram-negative uropathogens as well as *E. faecalis.* This combination of

antibiotics is highly concentrated in the tissue and urine (81), but once the acute and inflammatory phase resolves in the prostate gland, the concentrations in the prostate tissues do not remain at optimal levels. Once the patient has shown some initial improvement on intravenous antibiotics (or if it is planned to treat the patient as an outpatient), antimicrobial therapy should be switched to oral antibiotics. The most extensively studied antibiotics for the treatment of prostatic infection are trimethoprim-sulfamethoxazole and the fluoroquinolones (particularly norfloxacin, ciprofloxacin, ofloxacin, and levofloxacin). The advantages, disadvantages, and pharmacokinetics of these two classes of antimicrobial agents are specifically covered in the treatment section for category II chronic prostatitis. Both of these antibiotics are well absorbed, achieve reasonably high prostatic tissue levels, and have an extremely broad spectrum, especially for the Gram-negative uropathogens associated with acute bacterial prostatitis. These antibiotics achieve almost universal cure rates in patients who have been treated for susceptible bacteria in acute prostatitis. No evidence in the literature substantiates a claim for a specific duration of therapy for acute bacterial prostatitis. However, antimicrobial therapy must be continued long enough to completely eradicate all bacteria because some believe that inadequately treated acute bacterial prostatitis can progress to chronic bacterial prostatitis (although this has never been proven in any clinical study). The length of therapy should be not so long as to cause an increased risk from adverse reactions or drug toxicity. Most writers suggest treatment should be continued for 2 to 4 weeks (193,195).

Significant obstructive voiding symptoms with subsequent development of acute and painful urinary retention are common in patients with acute bacterial prostatitis. The actual incidence of acute urinary retention in these patients is unknown. Most experts have advocated the insertion of a suprapubic catheter (usually accomplished by a simple percutaneous route under local anesthesia) in patients with urinary retention or extreme voiding difficulty. Many clinicians believe that this prevents the development of prostatic abscesses, which may result from the blockage of prostatic ducts with a urethral catheter (41,206,282). Although chronic urethral catheterization is associated with the development of prostatic abscesses (282), an increased risk of developing a prostatic abscess from short-term urethral catheterization in patients with acute bacterial prostatitis has never been substantiated. A single in-and-out catheterization to effect an initial bladder drainage may be all that is necessary. It is not unreasonable to consider the insertion of a small caliber Foley catheter and leave it indwelling for 12 to 24 hours, if reasonably tolerated by the patient. Although the use of α-blockers has become accepted in the treatment of the chronic prostatitis syndromes, its beneficial effect in treating the obstructive voiding symptoms associated with acute bacterial prostatitis has not been demonstrated.

Consideration for hospitalization of patients presenting with acute bacterial prostatitis is necessary if the patient has significant sepsis with an associated need for fluid replacement, cardiopulmonary monitoring, vasopressors, or other conditions requiring inpatient intervention. In many cases, the patient only needs to be observed (while on parenteral antibiotics, intravenous fluid, and so on) for a 24-hour or less interval. Ancillary measures to improve treatment outcomes include the previously mentioned urinary drainage procedures, intravenous fluid replacement, antipyretics, the administration of stool softeners, and even warm sitz baths (226,237,238). If the patient fails to improve with appropriate antibiotic therapy (i.e., continues to have fluctuating fever, pain, and urinary obstruction) the development of a prostatic abscess should be considered (41,91,144,206,282). Transrectal ultrasonography or pelvic computerized tomography establishes the diagnosis (228). In most cases, surgery is necessary to drain the pus, which has accumulated in the abscessed cavity. Transurethral drainage is probably the best treatment when the abscess has not penetrated beyond the prostatic capsule (206). Perineal incision and drainage might be used whenever the abscess has reached or is peripheral to the levator ani muscle (79,206).

A proposed treatment plan for category I acute bacterial prostatitis is illustrated in Fig. 34.5 .

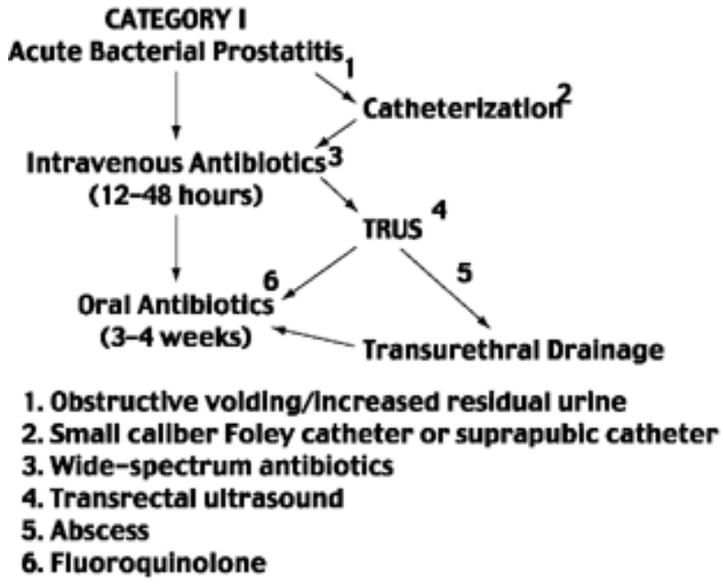


FIGURE 34.5. Proposed treatment plan for category I acute bacterial prostatitis.

CATEGORY II: CHRONIC BACTERIAL PROSTATITIS

Part of "34 - PROSTATITIS "

Etiology

The diagnosis of category II chronic bacterial prostatitis depends on localizing bacteria to prostate-specific specimens using a multiple-glass test for bacterial localization described in the previous section. Most authors and researchers agree

that chronic bacterial prostatitis is an important but rare prostate disease (125). Gram-negative pathogens, usually *E. coli,* are the most common organisms and are identified in 65% to 80% of chronic bacterial prostatic infections (279). *Pseudomonas aeruginosa*, *Serratia* species, *Klebsiella* species, and *Enterobacter aerogenes* comprise the isolated organisms in approximately 10% to 15% of cases (279). Although most chronic prostatic infections are caused by a single organism, multiple organisms associated with chronic bacterial prostatitis have been reported (146). The role of Gram-positive bacteria as pathogens in prostatitis remains controversial (94). Most authors agree that *Enterococci* may cause bacterial prostatitis and associated recurrent UTI (22,62,94,125,258,279), but the role of other Gram-positive bacteria such as coagulase-negative staphylococci, diphtheroids, and corynebacterium are thought by many to represent commensals of the anterior urethra (146,256). However, investigators have questioned the potential etiologic role of these bacteria in chronic prostatic inflammation (21,172,266). The etiologic role of these controversial potential pathogens is discussed in more detail in the etiologic section of category III.

How do the bacteria eventually reside in the prostate and cause the development of chronic inflammation? It is believed that reflux of urine into prostatic ducts, associated with high pressure and perhaps turbulent voiding is an important cause of both bacterial-induced and non–bacterial-induced prostatic inflammation (25,26,103). The ductal drainage of the peripheral zone of the prostate gland is more anatomically predisposed to facilitate reflux of urine (and any potential uropathogen present in that urine) into the peripheral zone (26). In fact, most prostatic infections are found in the peripheral zone. Challenged by host defenses and inadequate antimicrobial therapy, the bacteria may develop focal bacterial microcolonies (or biofilms) deep within the prostate protected by an endogenous glycocalyx or exopolysaccharide “slime” that makes them even more resistant to further therapeutic maneuvers (171,189). Prostatic calculi have been shown to be composed of constituents found only in urine (not in prostatic secretions) (220,263) and are present in patients with and without prostatic inflammation. These prostatic calculi may further protect pathogens, which have taken up residence in the interstices of the crystalline matrix, leading to recalcitrant and recurrent infections (69).

The composition of prostatic secretions in patients with chronic bacterial prostatitis is protective against bacterial colonization (71,131) but is altered and can even be diagnostic in chronic bacterial prostatitis. Fructose, citric acid, acid phosphatase, cations (zinc, magnesium, calcium), and the zinc-containing prostatic antibacterial factor (PAF) are decreased, whereas pH, the ratio of isoenzymes LDH5 to LDH1, and inflammatory proteins such as ceruloplasmin and complement C3c are increased (146,147). Although these changes may be nothing more than a consequence of subsequent inflammation, the secretory dysfunction can adversely affect the normal antibacterial nature of prostatic secretions.

In contrast to the immunologic situation that develops following acute bacterial prostatitis, in chronic bacterial prostatitis, no serum immunoglobulin elevation has been detected, whereas prostatic fluid IgA and IgG are both increased (116,244). If chronic bacterial prostatitis is cured by antibiotic therapy, IgG levels return to normal after months but IgA in prostatic secretions (particularly secretory IgA) is elevated for almost 2 years (73,247). In cases of antibiotic failure, persistently elevated levels of IgG and IgA have been measured (117,142,154). Antibody-coated bacteria are also another prominent feature of chronic bacterial prostatitis (222,223). Bacteria cultured from the ejaculate of patients with chronic bacterial prostatitis demonstrated a positive antibody-coated bacteria test compared with patients with nonbacterial prostatitis, prostatodynia, or control patients. Other immunologic alterations such as cytokine production, altered phagocytic activity, mast cell degranulation, increased sensory nerve density, and recurrence of autoantibodies in T-lymphocyte–mediated autoimmunity in the eventual development of inflammation has been described (154).

Clinical Presentation

The most important clue in the presentation of a patient with category II chronic bacterial prostatitis is a history of recurrent UTI. From 25% to 43% of patients with chronic bacterial prostatitis have had periods of recurrent UTI (281,284). The patients may have the typical genitourinary pain (perineal, suprapubic, penile, dysuria, or ejaculatory pain discomfort) and/or the irritative and obstructive voiding symptoms commonly associated with category III chronic pelvic pain syndrome patients (191,193). However, many patients are relatively asymptomatic between episodes of recurrent UTI (238). If the patient is suffering from a UTI at the time of initial presentation, the diagnosis of chronic bacterial prostatitis is difficult and hampered by the high bacterial count in the midstream urine. In these cases, 3 days of treatment with an antimicrobial agent such as nitrofurantoin before the performance of the lower urinary tract evaluation tests has been recommended (175,185). Nitrofurantoin can clear pathogens from the midstream urine (bladder specimen), but the number of bacteria in the expressed prostatic secretion is not affected because nitrofurantoin does not penetrate prostatic tissue.

Diagnosis

Men presenting with recurrent UTIs and/or symptoms of chronic pelvic pain syndrome (see Clinical Presentation) must undergo a rigorous evaluation of their lower urinary tract as described in the lower urinary tract evaluation

section of this chapter. The microscopic findings of the EPS and/or postprostatic massage urine (VB3) will show numerous leukocytes and lipid-laden macrophages (140,277,281,284). In principle, it is best to perform sequential quantitative bacteriologic cultures of the urethra, bladder, prostatic secretions, and prostatic massage urine as described in the Meares-Stamey four-glass test (140); however, the simpler and more cost-effective two-glass test (187) is almost as conclusive in making the diagnosis. The diagnosis is confirmed when pathogenic bacteria can be clearly localized to the prostate gland (EPS and/or postprostatic massage urine). The growth of only small numbers of bacteria from prostatic fluid is pathognomonic of chronic bacterial prostatitis when the preprostatic massage specimens are sterile and no absolute count exists in terms of number of colony forming units per milliliter in the prostate-specific specimens to diagnose chronic bacterial prostatitis. Demonstration of more bacteria in the urine after prostatic massage (or in EPS) or postmassage urine specimen than in the midstream or premassage specimen is highly suggestive of chronic bacterial prostatitis. A significant increase (a log or more) in bacterial count in the prostatic specimens compared with the preprostatic massage specimens is considered diagnostic (140,281,185).

Management

Once the diagnosis of chronic bacterial prostatitis has been made, the role of therapy is to eradicate the pathogens associated with infection with appropriate antimicrobial therapy. In many cases, this proves to be impossible, and in those cases, inhibition of the bacteria residing in the prostate may be all that can be accomplished with therapy.

Several animal models (dogs and rats) (14,129,177,188) have been used to study the principles contributing to antimicrobial drug penetration into the various prostatic compartments. Although sound pharmacologic considerations have resulted from this particular line of animal study, the clinical implications of these results must be approached with caution. The original animal prostate studies, carried out by Stamey and others (257), discovered that acidic antibiotic drugs could not penetrate successfully into prostatic secretion even when plasma concentrations were very high while basic antibiotic drugs were found in concentrations greater than their plasma level. This was explained by the principles that govern the passage of drugs across biologic membranes, emphasizing the role of nonionic diffusion of weak acids and bases across membranes with a pH gradient. They and other researchers (130,159,242) discovered that the drug characteristics that determine simple diffusion concentrations of drugs within the prostate are lipid solubility, degree of ionization, degree of protein binding, and the size and shape of the molecule. In the dog prostate, there is a pH gradient across the prostate epithelium, with the pH of the plasma being more alkaline than that of the prostatic secretion. Most antimicrobials are weak acids or bases. The Henderson-Hasselbalch equation can be used to calculate the theoretic drug concentration ratio across a biologic membrane with different pH gradients and drug pKa once equilibrium is achieved. A more detailed review of the theoretic considerations involved in antibiotic penetration in animal models is available in the prostatitis chapter in the previous edition of *Adult and Pediatric Urology* (74).

A number of important therapeutic considerations have been defined by these important studies in animal models (159). Trimethoprim and the various fluoroquinolones concentrate well in prostatic secretions, while sulfamethoxazole, ampicillin, carbenicillin (which for many years was the only antibiotic approved by the U.S. Food and Drug Administration for the treatment of bacterial prostatitis), and amino glycosides do not concentrate in the prostatic secretion. The fluoroquinolones were also found to concentrate well in the prostate and prostatic secretions in experimental prostatic bacterial infection (177). However, it remains unknown whether the pharmacokinetic results determined in animal models (uninfected or infected) have any applicability to humans with chronic bacterial prostatitis. The pH of human prostatic secretion is not similar to a dog, and in fact, the pH of prostatic secretions in men with prostatic infection is significantly increased (27,213). Therefore this alkaline prostatic secretion in prostatitis patients is significantly different from the secretions with lower pH observed in dogs (257) or even in healthy, human, male subjects (70).

Drug diffusion studies carried out in humans have evaluated antimicrobial concentration in prostatic tissue in men with BPH or prostatic fluid in volunteers who did not have prostatic inflammation (159). The drug concentration in homogenized prostatic tissue and secretions in patients without prostatic inflammation may not be relevant to patients with actual bacterial prostatitis; however, the fluoroquinolones were found to have the best concentrations in human prostatic tissue and prostatic secretions in concentrations significantly higher than the minimal inhibitory concentrations (MICs) for most prostatitis-causing pathogens. At this time, the fluoroquinolones represent the antimicrobial class for optimal therapy in chronic bacterial prostatitis.

Researchers and urologic clinicians both agree that chronic bacterial prostatitis is difficult to treat. Naber (160) has reviewed all the clinical antimicrobial trials in chronic bacterial prostatitis. Trimethoprim-sulfamethoxazole or trimethoprim alone has been extensively used both in research trials and clinically for the treatment of chronic bacterial prostatitis with very poor results. Bacterial eradication rates range from a low of 0% to a high of 67%. Most studies using trimethoprim-sulfamethoxazole for more than 4 weeks resulted in a bacteriologic cure rate (following at least 3 months of follow-up) of 30% to 50% (160). Other antibiotic studies of chronic bacterial prostatitis, including

minocycline, erythromycin, cephalexin, and carbenicillin, did not appear to improve this clinical outcome (160). Naber (160) subsequently analyzed 36 clinical studies evaluating fluoroquinolone therapy in which the diagnosis of prostatitis was deemed to be appropriate. These studies were difficult to evaluate because of unconfirmed bacterial infection, differing outcomes (bacterial eradication, clinical cure, or improvement), short follow-up periods, mixing of acute and chronic episodes, and differing diagnostic criteria as well as a wide range of treatment durations. We must therefore interpret the results of these many studies available to us in the literature with great caution. Of these studies, only one with norfloxacin (235), four with ciprofloxacin (83,216,278,280), and three with ofloxacin (106,219,221) presented results obtained during a follow-up period of 6 months. The results of these studies seem to be comparable with bacteriologic cure rates of 60% to 80% with a follow-up of at least 6 months. In general, therapeutic results were reasonable in chronic prostatitis due to *E. coli* and other members of the Enterobacteriaceae family but not in cases of prostatitis due to *Pseudomonas aeruginosa* or *Enterococci* (158).

The optimal duration of therapy is really unknown but for chronic prostatitis caused by *E. coli,* a treatment duration of 1 month with a fluoroquinolone seems to be superior to the usual 3-month treatment with trimethoprim-sulfamethoxazole. Whether or not a longer treatment with the fluoroquinolones would achieve a higher success rate is debatable. Nickel and associates (174) showed that 4 weeks of therapy with ofloxacin did not always predict the final results (in terms of symptom relief) of 12 weeks of continuous therapy. A European Consensus Statement (23) on the role of antibiotics in the treatment of chronic prostatitis empirically suggested that a 6- to 8-week course of therapy is warranted, but further antibiotics should not be given beyond this time without an appraisal of the effectiveness of the therapy. Studies evaluating direct injection of antibiotics into the prostate gland (8,95,285) have demonstrated promise, but direct injection has never become a popular route of administration. Future studies evaluating antibiotics in chronic bacterial prostatitis must use standardized valid protocols (157,181,281) including a follow-up of at least 6 months.

KEY INFORMATION

Antibiotic Therapy for Bacterial Prostatitis

- For prostatitis secondary to confirmed uropathogens, the fluoroquinolone antibiotics appear to be the optimal class of antimicrobial therapy.
- No real evidence substantiates the superiority of one fluoroquinolone over another.
- No good clinical study data substantiate a claim regarding duration of therapy.

Unfortunately, it is a clinical reality that some patients with bacteriologically documented category II chronic bacterial prostatitis have an immediate reappearance of bacteriuria and symptoms as soon as antibiotics are discontinued (relapse), or they have recurrence of infection and/or symptoms some time after antibiotics are discontinued (recurrent prostatitis). These patients can be considered for long-term low-dose suppressive (for refractory cases) or prophylactic (for recurrent cases) antibiotics. In a number of patients with chronic bacterial prostatitis, long courses of appropriate antimicrobial therapy are successful in eradicating the documented uropathogenic bacteria, but patients fail to show clinical improvement in their symptom complex. These may be the most difficult patients to manage with this category of chronic prostatitis.

It has been suggested that for category II chronic bacterial prostatitis, the addition of α-blockers to standard antimicrobial therapy may improve treatment. Barbalias and co-workers (12) retrospectively reviewed 270 consecutive patients with prostatitis treated with either antibiotics, α-blockers, or a combination of α-blockers and antibiotics. Of these patients, 64 were classified as having category II chronic bacterial prostatitis. All of these 64 patients were treated with antibiotics, and half were treated with α-blocker therapy with alfuzosin or terazosin. The recurrence rate of chronic bacterial prostatitis appeared to be reduced by combination therapy with both antibiotics and α-blockers compared with treatment by antibiotics alone. The symptomatic recurrence rate during a mean follow-up of 22 months dropped from 84% to 41% with the addition of α-blockers to the antibiotic therapy while the culture-positive recurrence rate dropped from 75% to 16%.

The addition of concurrent repetitive prostatic massage is believed to improve prostatic ductal drainage and subsequent antimicrobial penetration into prostatic secretions, and it may improve the cure rate in these recalcitrant cases (85,86,170,178,249). The concept of repetitive prostatic massage and the available clinical and experimental data are presented in more detail in the treatment section for category IIIA.

Surgery generally has been performed by surgeons who become desperate to do something concrete for patients with recurrent UTI and/or symptoms that remain refractory to antimicrobial therapy. The role of surgery is very limited in category II chronic prostatitis, unless the urologist can confirm the presence of uropathogenic bacteria within the prostate despite protracted antimicrobial therapy. This can be accomplished by using the Meares-Stamey four-glass test culture technique (140) or, alternatively, by performing a biopsy on the prostate using a sterile transperineal approach (19,171). If calculi are present, these intraprostatic stones might provide the protected nidus for bacterial persistence (141). Radical TURP (13,233) and radical prostatectomy (74) have been advocated, but no definitive clinical series or long-term follow-up has ever been reported in the literature.

A proposed treatment plan for category II chronic bacterial prostatitis is illustrated in Fig. 34.6 .

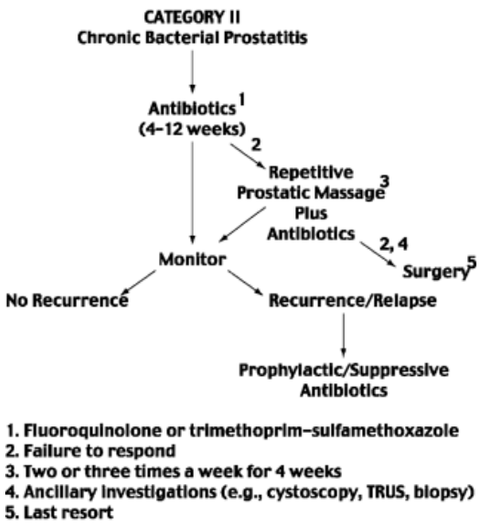


FIGURE 34.6. Proposed treatment plan for category II chronic bacterial prostatitis.

CATEGORY III: CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME (CHRONIC NONBACTERIAL PROSTATITIS/PROSTATODYNIA)

Part of "34 - PROSTATITIS "

Etiology

The diagnosis of category III chronic prostatitis/chronic pelvic pain syndrome rests on a clinical constellation of symptoms (loosely defined as genitourinary pain/discomfort) and negative cultures for uropathogenic bacteria (defined by most authorities as members of the Enterobacteriaceae Gram-negative rod family and *Enterococcus* Gram-positive bacteria) (111). Category III CPPS has been subclassified into an inflammatory category (category IIIA CPPS) and noninflammatory category (category IIIB CPPS). The definition of inflammation rests on the presence of excessive leukocytes in the prostate-specific specimens (expressed prostatic secretions or EPS, postprostatic massage urine, or VB3 and/or semen/ejaculate) compared with preprostatic massage urine specimens (i.e., VB1 and VB2). Although it is generally acknowledged that the infecting uropathogenic bacteria associated with category II chronic prostatitis are related to the subsequent prostatic inflammation, symptom complex, and history of recurrent UTIs, we do not know at this time the definitive etiology for the inflammation seen in category IIIA CPPS or the symptom complex seen in category IIIA and IIIB CPPS. A number of very attractive hypotheses are worth considering because our treatment strategies in many cases are directed towards these hypothetical pathogenic mechanisms. These proposed etiologic mechanisms are listed in Table 34.3 .

1. A microorganism-based etiology: Uropathogens (Gram-negative rods and probably enterococci, but not cultured in expressed prostatic fluid)
   - Possible prostate pathogen—coagulase-negative staphylococcus, chlamydia, ureaplasma, anaerobic bacteria
   - Acknowledged prostate nonpathogens—diphtheroids, corynebacterium sp.
   - Nonculturable organisms—"biofilm" bacteria, viruses, "cryptic" nonculturable bacteria
2. Dysfunctional high-pressure voiding
3. Intraprostatic ductal reflux
4. Repetitive perineal trauma
5. Autoimmune disease
6. Chemical irritation (urine and its metabolites, i.e., uric acid)
7. Neurogenic (neuropathic)
8. Neuromuscular
9. Interstitial cystitis (similar mechanism?)

TABLE 34.3. POSSIBLE ETIOLOGIES DESCRIBED FOR THE PATHOGENESIS OF PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

Studies have suggested the possibility that there might be a microorganism-based etiologic mechanism in category III CPPS (19,52,63,124,132,194,225,245,246,190). The potential candidates include Gram-positive organisms such as coagulase-negative staphylococcus (21,22,35,62,172,214,274), corynebacterium (224,266), diphtheroids (55,56), anaerobic bacteria (132,196,265), chlamydia (1,37,53,80,105,108,126,133,217,251,275), ureaplasma (72,90,202,203,276), trichomonas (64,77,100,113,115), "biofilm bacteria," (171,176,189), cell wall-deficient bacteria (55,56), fungi (32,78,89), or even viruses (16,51). Krieger and others (112), using polymerase chain reaction (PCR) techniques on prostate biopsies of 135 patients with chronic prostatitis/chronic pelvic pain syndrome noted that there was molecular biologic evidence of a bacterial presence in as many as 77% of the subjects. The question remains, however, whether these microorganisms identified in patients with chronic prostatitis are pathogenically involved in the inflammation or symptom complex (194). Controversy rages in the academic community as to whether or not there is a normal commensal or autochthonous microbial flora in the prostate (194). Keay and associates (101) using similar PCR amplification studies of bacterial 16s rRNA genes in prostate biopsies in men without chronic prostatitis found a similar spectrum of bacterial flora as did Krieger and co-workers (112) in chronic prostatitis and prostatodynia patients. However, Hochreiter and others (87) in a conflicting study using similar PCR techniques failed to duplicate these

results, which led to their conclusion that bacteria are usually not present in a normal prostate gland.

Anatomic or neurophysiologic abnormalities of the lower urinary tract are hypothesized to cause a dysfunctional high-pressure voiding (10,11,25,26,28,84,97,98,156) that creates a cascade of events that begins with obstructive and irritative voiding symptoms and ends with the pain associated with the prostatitis symptoms. This could be as simple as a bladder neck problem, detrusor sphincter incoordination, or urethral stricture, or it may be a more subtle dysfunctional voiding pattern that can be picked up only by sophisticated urodynamic evaluation.

Other investigators have shown that many patients with the inflammatory type of prostatitis (category II and IIIA) have a higher frequency of intraprostatic ductal reflux (25,26,103). This has been shown to occur histologically (fine charcoal particles placed in the bladder find their way into the periphery of the prostate), radiologically (opaque dye refluxing into prostatic ducts), or chemically (urine constituents found in prostatic secretions). The ducts of the peripheral prostate appear to be more predisposed to this intraprostatic ductal reflux, and it is believed that the dysfunctional voiding described in the previous paragraph also may contribute to the subsequent phenomena. Investigators (210) have suggested that the simple reflux of urine metabolites (specifically urate) in the prostatic ducts and acini may stimulate subsequent, simple, chemical inflammation. It has been suggested (148) that the resulting inflammation, caused by whatever etiology, results in increased intraprostatic pressure, which subsequently leads to both the pain and voiding symptoms experienced by men with chronic prostatitis.

In chronic nonbacterial prostatitis, although both the total IgA and IgG immunoglobulins are elevated, they are not microorganism specific (244,245,246) as is the case in category II chronic prostatitis. Others (3,4,54,101) have described similar immunologic processes and cascades in nonbacterial prostatitis that do not appear to be associated with microorganisms. Chronic prostatitis might be associated with immunologically mediated inflammation secondary to some unknown antigen or perhaps even related to an autoimmune process (57).

The pain associated with chronic pelvic pain syndromes is neuropathic in character and many investigators (6,67,205,288,289) have hypothesized a neuromuscular etiology for both the inflammatory and noninflammatory disease processes in the chronic pelvic pain syndrome.

Most authorities think that the key to the eventual diagnosis and successful management of chronic abacterial prostatitis/chronic pelvic pain syndrome lies in our eventual understanding of the etiologic mechanisms involved. It is likely that it will turn out that this clinical syndrome either has an underlying multifactorial pathogenic mechanism or represents an evolving (or progressive) pathogenic spectrum (Fig. 34.7).

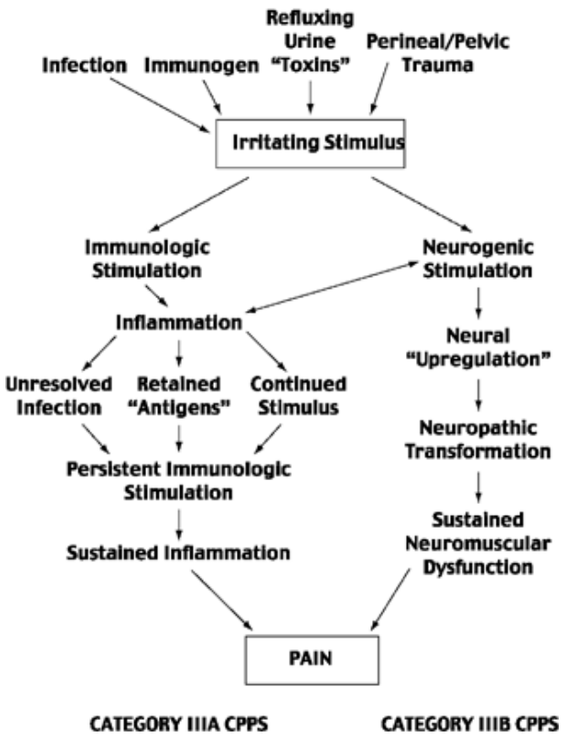


FIGURE 34.7. Proposed etiology and pathogenesis of chronic pelvic pain syndrome (category III CPPS). An initiating stimulus such as infection, reflux of some "toxic" or "immunogenic" urine substance or perineal/pelvic "trauma" starts an interrelated cascade of events, beginning with either inflammation or neurogenic injury (or both). Immunologic or neuropathic mechanisms sustain the chronicity of the initial (or ongoing) event resulting in the clinical manifestation of chronic perineal/pelvic pain.

KEY INFORMATION

Etiology

- Current state of knowledge has not confirmed the etiologic factors in the pathogenesis of the majority of cases of prostatitis.
- Candidates include microorganisms, anatomic variations, and immunologic and neurogenic causes.

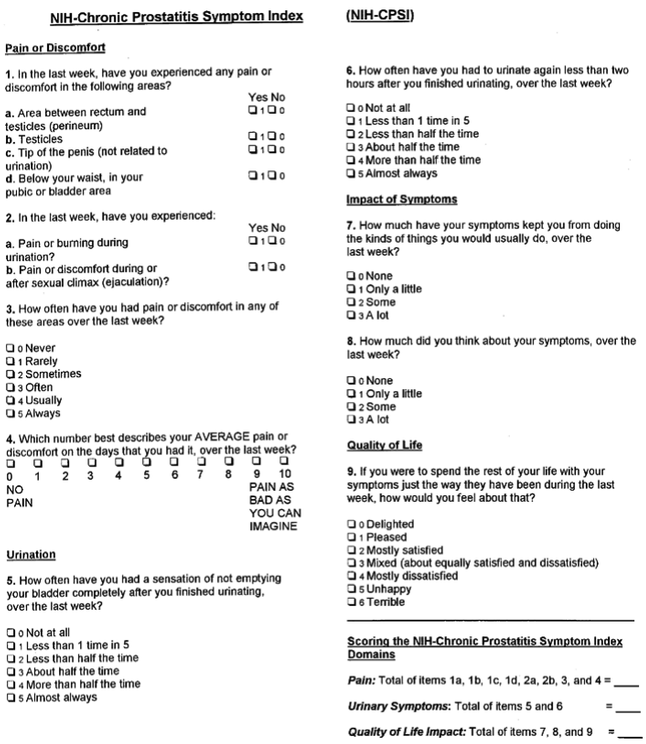
Clinical Presentation

Men with chronic prostatitis/chronic pelvic pain syndrome are distinguished by a rather specific symptom complex. These patients do not have a history of typical recurrent UTIs. The symptom best able to discriminate this prostatitis population in the symptom instruments devised by Nickel and Sorensen (173) and the most common severe symptom described by patients in a prostatitis clinic (67,110) and in a large Internet survey (2) was pain or discomfort. The pain is

usually present in the pelvic region (perineum, suprapubic), but other common complaints include discomfort localized to the external genitalia, low back pain, and pain with or after ejaculation (2,67,110,173). Irritative and obstructive voiding symptoms, while not necessarily discriminatory, were found to be an important factor in all the early symptom questionnaire/indices devised to evaluate prostatitis patients (29,110,167,173). Complaints of sexual dysfunction, which seems to occur in association with the pain, are common, but significant sexual dysfunction (other than pain on ejaculation) has not been confirmed in clinical studies.

The symptom complex associated with chronic pelvic pain syndrome has severe implications for the quality of life of patients with the condition. It has been estimated that the quality of life of a patient with chronic prostatitis is equivalent to that of a patient with active Crohn's disease, unstable angina, or recent acute myocardial infarction (283). Although the physical domain of quality of life is impaired in men with chronic pelvic pain syndrome, the mental health impact is more profound (138). It is believed that this can lead to profound personality problems, rather than the personality variables causing the symptoms associated with the prostatitis syndromes (48,68). Optimal care of these patients requires attention to individual quality-of-life issues.

The development of the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) (Fig. 34.8), published in 1999 by the NIH Chronic Prostatitis Collaborative Research Network (122), is described in more detail in the next section. In summary, however, this large, prospective study, which compared the presenting symptoms of hundreds of patients with chronic prostatitis to asymptomatic controls and men with BPH, confirmed that pain (including the number of locations, frequency, and severity of pain/discomfort), voiding symptoms (including irritative and obstructive symptoms), and quality of life/impact of symptoms on a patient's life are the predominant features associated with the clinical presentation of a patient with chronic prostatitis/chronic pelvic pain syndrome.



NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	❑ 1	❑ 0
b. Testicles	❑ 1	❑ 0
c. Tip of the penis (not related to urination)	❑ 1	❑ 0
d. Below your waist, in your pubic or bladder area	❑ 1	❑ 0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination?	❑ 1	❑ 0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑ 1	❑ 0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑ 0 Never
❑ 1 Rarely
❑ 2 Sometimes
❑ 3 Often
❑ 4 Usually
❑ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑ 0 NO PAIN ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10 PAIN AS BAD AS YOU CAN IMAGINE

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

8. How much did you think about your symptoms, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

Quality of Life

9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

❑ 0 Delighted
❑ 1 Pleased
❑ 2 Mostly satisfied
❑ 3 Mixed (about equally satisfied and dissatisfied)
❑ 4 Mostly dissatisfied
❑ 5 Unhappy
❑ 6 Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains

Pain: Total of items 1a, 1b, 1c, 1d, 2a, 2b, 3, and 4 = ____

Urinary Symptoms: Total of items 5 and 6 = ____

Quality of Life Impact: Total of items 7, 8, and 9 = ____

FIGURE 34.8. National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) captures the three most important domains of the prostatitis experience: pain, voiding, and quality of life. This index is useful in research studies and clinical practice. [From Litwin MS, McNaughton-Collins M, Fowler FJ, et al. The NIH Chronic Prostatitis Symptom Index (NIH/CPSI): development and validation of a new outcome measure. *J Urol* 1999:162;369-375, with permission.]

Diagnosis

The diagnosis of chronic prostatitis/chronic pelvic pain syndrome rests on an arbitrary definition of chronic genitourinary pain (of at least 3 months' duration) in the absence of uropathogenic bacteria detected using traditional culture techniques (111,164,181). The differentiation between the inflammatory subtype (category IIIA) and the noninflammatory subtype (category IIIB) relies on the determination of the number of leukocytes in the prostate-specific specimens. Therefore, to properly diagnose and differentiate category III CPPS, some form of lower urinary tract localization technique (either the four-glass test or the simpler two-glass test) must be performed.

What constitutes excessive leukocytosis in patients with no cultured uropathogenic bacteria? Normal individuals do possess leukocytes in their EPS and the suggested upper limit of normal varies from 2 (5) to as high as 20 (27) leukocytes per HPF (Fig. 34.4). However, most investigators (140,213,236) have reached a consensus that 10 leukocytes per HPF within the EPS is the upper limit of normal. But leukocytes are not the only cells seen in the EPS. The relationship between leukocytes and other inflammatory cells such as macrophages and lymphocytes is not clear (197,198). EPS is not always obtained and diagnosis then rests on the finding of excessive number of leukocytes in the VB3 specimen. In centrifuged urine, the presence of 4 leukocytes or more per HPF is highly suggestive of prostatitis, whereas a figure of 10 is pathognomonic (277). However, to further confuse the issue, inflammatory cell density in the prostate-specific specimens appears to fluctuate over time (5,236) and with frequency of ejaculation (92).

Some patients with obstructive voiding symptoms or a history of stones, trauma, sexually transmitted diseases, flank or abdominal pain, or hematuria need further urologic investigations. This could include upper urinary tract evaluation (ultrasound, intravenous pyelogram, computerized scan), prostate assessment (PSA, transrectal ultrasound, and occasionally biopsy), and endoscopy (urethroscopy and cystoscopy). Urodynamic assessment (including videourodynamics) appears to be the most useful ancillary test in evaluating patients with category III prostatitis (98,99,156,267) to assess bladder outlet obstruction, although some investigators have not found this to be a problem in this particular cohort of patients (134). Transrectal ultrasound is the most useful imaging evaluation, and some investigators believe that it can be helpful in making the diagnosis or at least excluding other local diseases (43,46,50,128).

Once the diagnosis has been made based on a history of the symptom complex, focused physical examination, negative uropathogenic cultures, and an assessment of the degree of leukocytosis in the prostate-specific specimens and other related medical conditions have been ruled out, the most important evaluation then becomes an accurate assessment of the patient's symptoms. The National Institutes of Health (NIH) Chronic Prostatitis Clinical Research Network (CPCRN) has developed a reliable, valid index of symptoms and quality of life/impact in men with chronic prostatitis/chronic pelvic pain syndrome (122). A structured literature review and extensive focus group, patients' and experts' evaluation was followed by cognitive and validation studies in more than 500 men to finalize this prostatitis specific NIH-Chronic Prostatitis Symptom Index (NIH-CPSI). This new index of nine questions addresses the three most important domains of chronic prostatitis: (a) pain (location, severity, and frequency), (b) voiding (irritative and obstructive symptoms) and (c) impact/quality-of-life issues (Fig. 34.8). In the first report of the International Prostatitis Collaborative Network in which guidelines were suggested for prostatitis research (181), the NIH-CPSI was acknowledged as an appropriate outcome measure for

clinical and research studies in chronic prostatitis. It also is a valuable assessment instrument for the evaluation and follow-up of patients with prostatitis in routine clinical practice (193).

Management

Although the differentiation between category IIIA and category IIIB CPPS has not been definitely validated, until it has been shown otherwise, it seems clinically appropriate to develop a best evidence approach for management of each category (109,186). As research trials that are presently in progress mature, it is likely that many therapies will be appropriate for both categories of CPPS, while some specific therapies may be more effective in one subtype compared with another (190).

KEY INFORMATION

Treatment

- The majority of patients cannot receive a truly “evidence-based” approach to therapy.
- Our present state of knowledge allows for a “best-evidence” approach to therapy.

Category IIIA: Inflammatory Chronic Pelvic Pain Syndrome (Nonbacterial Prostatitis)

A number of medical approaches to the treatment of category IIIA CPPS have been suggested and are currently being used in clinical practice. Most of these treatment modalities are based on anecdotal experience; case reports; and small, short, poorly designed pilot studies. Large, multicenter, randomized, placebo-controlled trials evaluating many of these therapeutic approaches are presently under way, and the urologist managing prostatitis must be ready to assess the results of these clinical trials once they are completed. Until the results of these ongoing trials are known, the urologist must use a best-evidence approach to managing category IIIA CPPS.

Antibiotics are not recommended for the treatment of chronic nonbacterial prostatitis by the well-known traditional experts in the field (143,215,237,258). However, evaluation of practice patterns by urologists shows that most patients with the diagnosis of prostatitis are treated with antibiotics, regardless of culture results (137,155,180). Antibiotics appear to be universally used in all categories of prostatitis because of the lack of other efficacious modalities of therapy, the rare use by urologists of appropriate quantitative segmented cultures of the lower urinary tract, and most important, clinicians' clinical perception that a significant number of patients do in fact improve while receiving antimicrobial therapy (184). Uncontrolled clinical trials do indicate that as many as 40% or more patients with a diagnosis of prostatitis (particularly the inflammatory categories) have a favorable response to antimicrobial therapy (18,22,23,45,174,203,266,281).

Antibiotics may be effective in “culture-negative” chronic prostatitis for three reasons. The definition of culture-negative prostatitis does not exclude the possibility of a bacterial cause, but rather simply means that a bacterial cause cannot be identified using our current standard microbiologic methodology and knowledge (194). Antibiotics appear to have a defined antiinflammatory effect independent of their antibacterial action. A number of researchers (76,287) have clearly demonstrated that antibiotics, especially the quinolones, have an immunomodulatory action on inflammatory cytokines that is independent of their antimicrobial activity. Finally, this “perceived” beneficial effect could be just a very significant “placebo” effect, and the reality might turn out to be that no evidence supports that antimicrobial therapy is superior to placebo for the treatment of category IIIA or, for that matter, category IIIB CPPS.

However, it is not unreasonable to suggest that patients with category IIIA chronic prostatitis/chronic pelvic pain syndrome be subjected to one 2- to 4-week course of antibiotics because of the real possibility that other organisms such as chlamydia, ureaplasma, nonculturable bacteria (e.g., “biofilm” bacteria, particularly in patients with a history of documented UTI), and Gram-positive organisms may be implicated in the pathogenesis of the prostate inflammation (194). A report by Tanner and others (266) suggests that patients with the presumed nonuropathogen, corynebacterium, localized to the urinary tract using molecular biologic techniques (PCR), improve while receiving specific antimicrobial therapy. Only one controlled clinical study examined antibiotic therapy in patients with category IIIA CPPS (nonbacterial prostatitis). Simmons and Thin (252) randomized 41 patients with chronic nonbacterial prostatitis to either minocycline or diazepam and found that there was no significant difference in symptom improvement or leukocyte count between the two groups. A European Consensus group evaluating the role of antibiotics in the treatment of chronic prostatitis (23) suggested that antibiotics should be considered empirical treatment for category IIIA CPPS, but the benefits should be appraised after 6 to 8 weeks of therapy.

KEY INFORMATION

Antibiotic Therapy for Category IIIA Inflammatory Chronic Pelvic Pain Syndrome (Nonbacterial Prostatitis)

- A 2- to 4-week trial of wide-spectrum antibiotic therapy appears to be justified.
- Long-term use of sequentially different antibiotics in refractory patients does not appear to be justified.

Therapy with α-blockers, particularly those that are not specifically prostate selective, appear to improve the voiding and discomfort associated with the prostatitis syndromes. In controlled clinical trials, Osborne and co-workers (205) and Dunzendorfer and others (66) demonstrated the superiority of phenoxybenzamine, a nonspecific α-blocker, in ameliorating several symptoms associated with prostatitis (although subjects were primarily prostatodynia patients or category IIIB CPPS) compared with placebo. De la Rosette and associates (47) randomized 20 patients to either alfuzosin or placebo, and although the patients treated with the α_1-blocker showed improvements in symptom score and although it was only just significantly better than placebo (p = .01), the change in maximal flow rate was significant in the treated group. In an uncontrolled open label study, Neal and Moon (167) treated 25 patients with nonbacterial prostatitis or prostatodynia with terazosin, another α_1-blocker for 1 month. Three-fourths of the patients indicated some form of symptomatic improvement (confirmed with a new recently developed prostatitis symptom score), and 2 months later, more than 50% of the responders remained asymptomatic (although 42% required reinitiation of therapy to relieve recurrent symptoms). This study suffered from the lack of a placebo control arm.

Barbaralias and associates (12) evaluated the effects of combining α-blockers and antibiotics in the treatment of chronic prostatitis syndromes. They retrospectively reviewed 270 consecutive patients who had been divided into three groups, 134 patients with chronic nonbacterial prostatitis (category IIIA), 72 patients with “painful male urethral syndrome” (prostatodynia or category IIIB), and 64 patients with chronic bacterial prostatitis (category II). All patients with chronic nonbacterial prostatitis were treated with α-blocker therapy, and half were treated with antibiotics. Overall, 47% of the nonbacterial prostatitis patients had resolution of their symptoms after 1 month; however, the study was not controlled with a placebo arm and in this category (IIIA) there did not appear to be any difference in combining antibiotics and α-blockers.

Repetitive prostatic massage has been the main therapeutic approach for the treatment of prostatitis for most of the twentieth century (170,201). Following the landmark paper by Meares and Stamey in 1968 (140), this therapy more or less fell out of favor with both patients and urologists. However, reports of spectacular success rates of repetitive prostatic massage (usually combined with antimicrobial therapy) (85,86) has led to the reemergence of this traditional older therapy as a potentially effective treatment modality. There are no controlled clinical trials on the use of repetitive prostatic massage, with or without antibiotics, for the treatment of prostatitis, and although many “prostatitis experts” have developed experience and expertise in the technique, no consensus on its value has been reached (170). In prospective clinical trials, one-third (178) to two-thirds (249) of patients realize some degree of symptom amelioration. Some think that frequent ejaculation (286) will accomplish the same improvement in symptoms or at least a decrease in recurrence once it has been treated.

Nonsteroidal antiinflammatory medication such as nimesulide (33,34) and indomethacin appear to alleviate the pain and discomfort in some patients with prostatic inflammation. Because of severe gastrointestinal side effects experienced with long-term high-dose administration, many patients cannot tolerate the dose and duration of therapy that may be required. The introduction of the new COX-2 inhibitors (rofecoxib and celecoxib) may provide significant benefit to some patients, and the results of large clinical trials will soon be available.

Prostate growth and development (including inflammation) are affected by the local hormonal milieu (162). It has been hypothesized that regression of ductal and glandular tissue in the prostate with 5α-reductase inhibition would improve flow parameters, reduce intraprostatic reflux, and perhaps even influence the degree of inflammation itself (192). Anecdotal case reports (88) and a randomized, placebo-controlled trial by Leskinen and others (120) would appear to support this hypothesis. However, a critical evaluation of this study (120) in which 31 patients were randomized to finasteride and 10 patients to placebo, shows that although symptom scores dropped significantly in the finasteride group, there was no significant difference in pain or symptoms between the two groups, perhaps because the treated and placebo groups were not similar in baseline characteristics. The results of a multicenter, randomized, controlled trial comparing finostende to placebo should be available in 2002.

Plant extracts (phytotherapy) are being used extensively by prostatitis patients and two such compounds, a pollen extract (30,229) and quercetin (250), both show some early promise. Shoskes and co-workers (250) used the NIH-Chronic Prostatitis Symptom Score in a randomized, controlled trial comparing 15 patients treated with quercetin to 13 patients treated with placebo. Twenty percent of patients taking placebo and 67% of patients taking the phytotherapeutic agent had an improvement of symptoms of at least 25%. Although the clinical importance of a 25% change in a symptom score that measures pain, voiding symptoms, and quality of life/impact is debatable, this study is provocative and should stimulate larger trials.

The clinical similarities between interstitial cystitis and chronic prostatitis have led many clinicians to use pentosan polysulfate (PPS), an oral exogenous glycosaminoglycan that has demonstrated modest symptom improvement in interstitial cystitis patients. Anecdotal reports and one small, randomized, controlled trial (273) of 30 patients (15 patients treated with PPS and 15 patients with placebo) demonstrated improvement of symptoms, particularly myalgia and arthralgia (with PPS compared with placebo). A prospective clinical pilot study (96) of men with category IIIA CPPS using validated symptom questionnaires to assess response were treated with PPS 100 mg three times a day for 6 months was encouraging enough

(approximately 40% of patients had clinically significant improvement) to justify a large, multicenter North American randomized, controlled study evaluating PPS 300 mg three times a day compared with placebo (study initiated in 2000).

The authors of a randomized, placebo-controlled study comparing allopurinol with placebo (211) suggested that a 3-month trial of allopurinol to potentially control the inflammatory response caused by refluxing urate was appropriate. However, further evaluation of the results of this trial (183) did not confirm the beneficial effects of allopurinol, and the widespread adoption of this particular treatment modality may be premature.

Heat therapy applied to the prostate in the form of transrectal hyperthermia (151,243,261,270) and transurethral thermal therapy (173) consistently demonstrated symptomatic improvement of symptoms in men with CPPS. Although the previously noted studies were all controlled clinical trials, only three studies (173,243,270) used a sham or placebo control. The studies were also very small, the inclusion criteria varied, and the outcome measures were not always validated. The possible explanations for benefit in these patients include effecting an “intraprostatic” sympathectomy (209), accelerating the chronic fibrotic process that may be an end result of chronic prostatitis (173) or killing noncultured bacteria deep within the prostate gland (230). However, until a large, multicenter trial is completed, this mode of therapy should be reserved as a “last resort” therapeutic intervention for this category of CPPS.

Surgery is not recommended for most cases of category IIIA CPPS. If specific indications such as bladder neck hypertrophy or urethral stricture disease is discovered on specific diagnostic testing (i.e., videourodynamics or cystoscopy), treatment tailored to the specific abnormality may improve the patients voiding symptoms and perhaps even the pain and/or discomfort (98,104). Although prostatectomy has been advocated (75), long-term data and properly designed prospective trials have not been done to confirm that either radical transurethral resection of the prostate (TURP) or radical prostatectomy achieve any long-term beneficial response. Certainly these surgical therapies have the potential to cause considerable morbidity. It has been suggested that minimally invasive surgical procedures such as retrograde balloon dilation (119), transurethral radiofrequency hot balloon thermal therapy (182), transurethral balloon laser hyperthermia (264), transurethral needle ablation (TUNA) (36), and neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (241) may benefit some patients. These and other innovative modalities of minimally invasive therapy must be evaluated in rigorous clinical trials before they can be recommended.

A proposed treatment plan for category IIIA chronic prostatitis/chronic pelvic pain syndrome is illustrated in Fig. 34.9 .

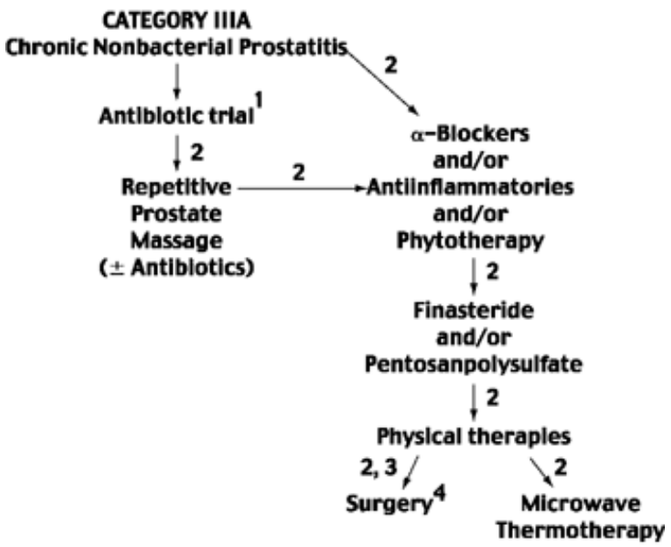


FIGURE 34.9. Proposed treatment plan for category IIIA chronic pelvic pain syndrome.

Category IIIB: Noninflammatory Chronic Pelvic Pain Syndrome (Prostatodynia)

Successful therapy for category IIIB CPPS appears to be more problematic than the treatment of the other prostatitis syndromes that have more specific characteristics (i.e., evidence of infection and/or inflammation) (186). There are few significant controlled clinical or randomized controlled trials specifically evaluating therapy in category III CPPS (prostatodynia patients). Many of the clinical trials described in the previous section (treatment of category IIIA CPPS) included patients with category IIIB characteristics as well. It is from these trials that we obtain some of the best evidence we have on appropriate therapy in this category.

Antibiotics are generally considered not indicated in this category (23); however, a number of trials (174,266) did not note any significant correlation between symptomatic results and degree of leukocytosis in prostate-specific specimens.

α-Blockers do appear to produce symptomatic improvement in patients with category IIIB CPPS. Osborne and others (205) noted symptomatic improvement in 48% of patients treated with phenoxybenzamine compared with 8% with placebo. Patients experienced significant retrograde ejaculation and 10% discontinued the drugs secondary to lethargy and asthenia. The study by Dunzendurfer and co-workers (66) with phenoxybenzamine, the study by de la Rosette and associates (47) with alfuzosin, and the

study undertaken by Neal and Moon (167) with terazosin (reviewed in the previous section on treatment of category IIIA CPPS) did include patients with category IIIB CPPS/prostatodynia. In these studies, the response obtained in the inflammatory category (IIIA) could not be differentiated from the response obtained in the noninflammatory category (IIIB). In the study reported by Barbalias and others (12) described in the previous section, 72 of the 270 patients were classified as prostatodynia or category IIIB. In this retrospective study (which was complicated with the addition of antibiotics in many patients), 58% of these patients had resolution of their symptoms with terazosin or alfuzosin therapy.

Muscle relaxants such as diazepam and baclofen appear to be helpful in patients with category IIIB CPPS, especially if sphincter dyssynergia or pelvic floor/perineal muscle spasm is confirmed. Osborne and co-workers (205) showed a satisfactory symptomatic response in 37% (10 of 27) of prostatodynia patients treated with baclofen compared with an 8% placebo response (4/10).

A significant proportion of the patients in the various controlled microwave hyperthermia and thermotherapy trials (reviewed in a previous section—category IIIA CPPS) included patients with prostatodynia (category IIIB CPPS). It is difficult to determine a differential effect of this therapy in patients with category IIIA and IIIB classification; however, it appears that some category IIIB patients obtained potential benefits compared with sham therapy (particularly with transrectal microwave hyperthermia).

Clinicians use analgesics for treating chronic pain and category IIIB CPPS is no different. While there is no doubt that analgesics, particularly the class of narcotic analgesics, can reduce pain, the long-term consequences of chronic analgesic use, particularly narcotics is unknown. There is no research available to determine an evidence-based approach for criteria to determine the type, dose, or duration of analgesics in category IIIB CPPS. A referral to a comprehensive multidisciplinary pain clinic may assist the urologist in long-term pain control in refractory category IIIB CPPS patients. Anecdotal evidence only supports the addition of tricyclic antidepressants such as amitriptyline in this syndrome, but it does appear to provide significant improvement in similar chronic pelvic pain syndromes such as interstitial cystitis in women.

Although variations of physical therapy may be one of the most poorly studied and evaluated modes of treatment, this therapeutic field actually may turn out to be the most effective in this particular syndrome. Various forms of physical therapy, including biofeedback (39,97), perineal and pelvic floor massage therapy, and pressure therapy for specific pelvic/perineal trigger points (6), have all been described as potentially beneficial to the patients. Other physical therapies that have been suggested include relaxation exercises, acupuncture, chiropractic therapy, and the use of ring or donut cushions when sitting. Controlled clinical studies will determine the ultimate benefits of these various modes of physical therapy.

Finally, most clinicians have the perception that supportive therapy, which includes reassurance and suggestions for lifestyle changes, benefits many patients. This supportive therapy could include reassurance that the patient does not have a prostate cancer, development of coping skills, advice regarding sports such as bicycle riding, and diet changes (e.g., avoidance of caffeinated and alcoholic beverages, spicy foods). At the very least, this approach causes no harm and may assist in helping patients live and cope with their disease.

A proposed treatment plan for category IIIB chronic prostatitis/chronic pelvic pain syndrome is illustrated in Fig. 34.10 .

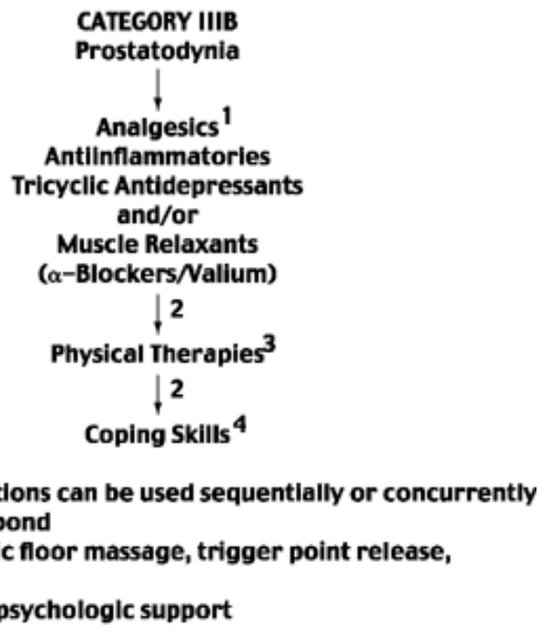


FIGURE 34.10. Proposed treatment plan for category IIIB chronic pelvic pain syndrome.

KEY INFORMATION

Therapy for Chronic Pelvic Pain Syndrome

Clinical evidence indicates that the following treatments (alone or in combination) may provide substantial improvement in symptomatology in some patients:

- Antibiotics
- α-Blockers
- Antiinflammatories
- phytotherapy
- 5α-reductase inhibitors
- Pentosan polysulfate
- Muscle relaxants
- Physical therapies
- Heat therapies

CATEGORY IV: ASYMPTOMATIC INFLAMMATORY PROSTATITIS

Etiology

Category IV prostatitis or asymptomatic inflammatory prostatitis (AIP) is defined as the presence of inflammation and/or infection in prostate-specific specimens such as expressed prostatic secretion, postprostatic massage urine, semen (or ejaculate specimen), BPH TURP chips, or radical prostatectomy specimens. Prostatic inflammation is an extremely common finding in patients with BPH symptoms who do not have symptoms of prostatitis (107,179), but there does not appear to be any correlation between the degree and pattern of inflammation, catheterization, presence of bacteria, serum PSA or PSA density, or even symptoms. A number of studies have examined the association of prostatic inflammation and prostate cancer (135,218,290). However, no clear relationship has been shown to exist between the histologic evidence of prostatic inflammation and prostate cancer or BPH. Acute bacterial prostatitis reveals a significant serum PSA elevation in the majority of patients (42,207), but the connection between PSA levels and patients with asymptomatic prostatic inflammation remains unclear (82,161,179,254).

Men with infertility (as many as 1 in 5) have evidence of an inflammatory process of the reproductive tract, usually detected with high concentrations of leukocytes in the semen, even when bacterial cultures fail to reveal any pathologic organisms (93). Although antibiotic therapy appears to improve some patients' semen parameters and may improve the possibility of fertility, the actual relationship remains unclear.

Category IV prostatitis also can occur in asymptomatic men without any genital urinary problems or pathology. Inflammation in autopsy series (many of whom did not have any prostate disease) is reported in 44% of adult prostates obtained at autopsy (139). The relevance of prostatic inflammation in these asymptomatic men, particularly those without evidence of BPH, infertility, or prostate cancer, is unknown.

Clinical Presentation

Since by definition, category IV asymptomatic inflammatory prostatitis is asymptomatic, the diagnosis is made incidentally in men being evaluated for prostate disease (BPH or prostate cancer) or infertility.

Diagnosis

Leukocytosis and/or bacteria are demonstrated in prostate-specific specimens such as expressed prostatic secretion, postprostatic massage urine, semen specimens, or histologic examination of BPH TURP chips or prostate cancer specimens (111,164).

Treatment

Because men diagnosed with category IV prostatitis are asymptomatic, no definitive therapy is required for amelioration of any symptom complex. Antimicrobial therapy may be indicated in men being evaluated for an elevated PSA, infertility, or in those men with BPH and prostate cancer in whom urinary endoscopy is being contemplated.

OTHER RELATED CONDITIONS

Part of "34 - PROSTATITIS "

Granulomatous Prostatitis

Granulomatous prostatitis, characterized by heavy lobular mixed inflammatory infiltrates, which include abundant histiocytes, lymphocytes, plasma cells, and small discrete granulomas, is usually diagnosed during evaluation for possible prostate malignancy. On digital rectal examination nonspecific granulomatous prostatitis often exhibits induration, which varies from focal to diffuse and raises the concern of malignancy. Serum PSA levels can be mildly to significantly elevated (204,255), and a transrectal ultrasound pattern may simulate carcinoma (31,255). The patients' typical clinical manifestation of nonspecific granulomatous prostatitis includes dysuria and frequency, which may be associated with fever (260). In the majority of cases, differentiation of nonspecific granulomatous prostatitis from adenocarcinoma can be made readily using morphologic criteria. Granulomatous prostatitis also can occur as a complication of treatment of superficial transitional cell carcinoma of the urinary bladder with bacille Calmette-Guérin (BCG) immunotherapy (118,150,200). Mycobacterial prostatitis also can occur as a rare event in the setting of systemic tuberculosis (234).

Seminal Vesiculitis

Seminal vesiculitis can be a concomitant clinical entity to prostatitis and is probably diagnosed (and potentially cured) along with prostatitis. It is difficult to distinguish between the two diagnoses without detailed investigation because the signs and symptoms of seminal vesiculitis include genitourinary pain, painful ejaculation (± decreased ejaculate volume), hematospermia, irritative and obstructive voiding complaints, back and lower abdominal pain, and impotence. Some authorities think that seminal vesiculitis is a separate clinical entity and is not always associated with prostatitis. Stearns (259) estimated that 13% of the patients referred for prostatitis actually have primary vesiculitis. Most studies on seminal vesiculitis in the literature actually describe patients with seminal vesicle abscesses (102).

Patients with abscesses present clinically with fever, chills, irritative voiding symptoms, dysuria, hematuria, testicular pain, and a palpable mass above the prostate on physical examination. Like prostatitis and lower UTIs, *E. coli* is the predominant organism. Historically, the seminal vesicles were evaluated with seminal vesiculography (9,65), but this particular examination has limited value. Computed tomography (208), magnetic resonance imaging (262), and transrectal ultrasonography (121) are favored means of imaging the seminal vesicle in patients suspected of having seminal vesiculitis. The findings of seminal vesicle cysts containing calculi and/or debris or significantly dilated seminal vesicles with thickened walls suggest the diagnosis is seminal vesiculitis (38).

Diagnosis not only relies on clinical symptomatology, careful digital rectal examination, and lower urinary tract localization tests (as described for prostatitis), but also includes an ejaculate culture followed by transrectal ultrasonography (probably the most cost-effective diagnostic maneuver). This can be followed by cytologic and culture verification using needle aspiration under transrectal ultrasound control. A vesiculogram using a nonionic contrast material can be contemplated to determine whether the specific vesicle is obstructed. If the ejaculatory duct is obstructed then a transurethral resection of the ejaculatory duct can be performed. Most patients can be adequately treated with a course of appropriate antibiotics, much the same way as patients with chronic bacterial prostatitis are treated. If the patient fails to respond, an operation to remove the affected seminal vesicle can be considered as a last resort.

Interstitial Cystitis in Men

Chronic prostatitis and interstitial cystitis are both chronic pelvic pain syndromes with very similar etiologic and clinical considerations. Microbiologic, immunologic, neuromuscular (or neurophysiologic), and anatomic etiologic mechanisms have been proposed for the pathogenesis of both these syndromes. Difficulties in definitions, categorization, diagnosis, and treatment continue to plague the fields of chronic prostatitis and interstitial cystitis. Certainly the symptom complex of chronic prostatitis overlaps that of interstitial cystitis occurring in men (149,199,232). This includes the irritative voiding and suprapubic pain symptoms, petechial hemorrhages on hydrostatic dilation (20), and urodynamic findings (253). This has led a number of authors to conclude that many cases of chronic prostatitis are misdiagnosed interstitial cystitis (231). Therapies that have demonstrated a modest improvement in interstitial cystitis (e.g., analgesics, antiinflammatory agents, amitriptyline, PPS) show similar benefit in patients with chronic prostatitis. These similar syndromes may in fact be related along the spectrum of chronic pelvic pain syndrome produced by multifactorial etiologic mechanisms.

SUMMARY

Part of "34 - PROSTATITIS "

Prostatitis is an extremely common and clinically important urologic condition, rivaling prostate cancer and BPH in terms of prevalence, cost to society, impact on quality of life, and the time and effort the urologic community spends in dealing with this clinical condition. The urologist must have an understanding of the potential etiologic mechanisms involved in this disease, a commitment to properly diagnose and categorize these patients, and a sound and evolving knowledge of the results of therapeutic interventions so that patients with chronic prostatitis will not be relegated to the wastebasket of urologic practice.

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35
Male Infertility

Edward D. Kim

Larry I. Lipshultz

Stuart S. Howards

E.D. Kim: Departments of Urology and Urologic Surgery, University of Tennessee, Graduate School of Medicine, Knoxville, TN 37920.

L.I. Lipshultz: Scott Department of Urology, Baylor College of Medicine, Houston, TX 77030.

S.S. Howards: Departments of Urology and Physiology, University of Virginia, Charlottesville, VA 22908.

Contents

The evaluation and treatment of male infertility have changed significantly with the introduction and widespread use of intracytoplasmic sperm injection (ICSI) in the 1990s. Men with testicular failure, who were considered hopelessly infertile, now have the opportunity to initiate their own biologic pregnancy. The most important changes in the field since the last edition of this text have been the genetic evaluation of azoospermic men and refinements in sperm retrieval procedures for ICSI. Despite the high-technology nature of these important advances, an in-depth knowledge of the basics of male reproductive physiology and the standard evaluation and treatment of the infertile male remains necessary.

PHYSIOLOGY

Part of "35 - Male Infertility "

Anatomy and Embryology of the Testicle

The normal adult testes are a pair of ovoid structures measuring 4.0 to 5.5 cm in length, 2.5 cm in width, and 3 cm in the anteroposterior dimension. Their weight ranges from 20 to 30 g. The testes lie in the scrotum with the long axis upright and tilted forward and slightly lateral; the left testis generally is slightly lower than the right. The posterior aspect of the testis is attached to the spermatic cord with the epididymis lying on the posterolateral margin. The remainder of the testis is covered by the tunica vaginalis.

Scrotum

The layers covering the testis, starting from the outside, are the scrotal skin, dartos, external spermatic fascia, cremasteric fascia, internal spermatic fascia, and tunica vaginalis. With exposure to cold or exercise, the scrotal skin contracts, becoming thickened and highly folded and wrinkled. The dartos muscle is deep to the skin and is continuous with the scrotal septum. This septum divides the scrotum into a pair of separate compartments, the walls of which are formed by fusion of the tunica vaginalis, internal spermatic fascia, cremasteric fascia, and external spermatic fascia.

Fascial Investments of the Testis

Beneath the dartos lie three fascial layers, which are derived, during the descent of the testis, from the fascial components of the abdominal wall. These fascial coverings lie one within

another in a saclike fashion and are continuous with the abdominal fascial structures from which they are derived. Most superficial is the external spermatic fascia derived from the external oblique aponeurosis. Beneath this lies the cremasteric muscle and fascia originating from the internal oblique muscle and its fascia. Innermost is the internal spermatic fascia, which is derived from the transversalis fascia.

Tunica Vaginalis

The processus vaginalis, an outpouching of fetal peritoneum from which the tunica vaginalis originates, precedes the testis in its descent into the scrotum. During normal development, the portion of the processus vaginalis that extends inferiorly from the internal inguinal ring to a point near the upper pole of the testis becomes obliterated. The lower portion, the tunica vaginalis, remains as a closed pouch folded around the testis and epididymis, which project into it from behind. The inner layer, known as the *visceral layer,* is reflected forward from the posterior wall of the scrotal chamber to cover the testis, epididymis, and lower portion of the spermatic cord. On the lateral margin of the testis, the tunica invaginates deeply as it passes from the testis to the epididymis, creating a pocket known as the *sinus* of the epididymis. The outer or parietal layer of the tunica vaginalis lines the walls of the scrotal chamber and is fairly well attached to the other coverings of the testis. The sac formed between the two layers of the tunica vaginalis contains a small amount of serous fluid. During development, the processus vaginalis may fail to be obliterated. Peritoneal contents that thus pass down the patent processus constitute a congenital hydrocele or hernia.

Testis

The outermost layer of the testis contains a dense, white, inelastic covering composed of interlacing bundles of fibrous tissue known as the *tunica albuginea.* The innermost aspect of the tunica albuginea gives off a number of thin septula, which converge posteriorly in a mass of fibrous tissue called the mediastinum testis. The mediastinum is a direct continuation of the posterior aspect of the tunica albuginea and supports the vessels and ducts of the testis as they pass to and form the gonad. As they proceed posteriorly from the tunica albuginea, the septula form a number of wedge-shaped lobules that are broader at their bases near the tunica albuginea and become narrower as they converge on the mediastinum. The estimated number of lobules in a single testis varies from 250 to 400 (148). The arteries (185), veins, and lymphatics enter the testis at its posterior margin, traverse the mediastinum, and spread out on the deep surface of the tunica albuginea to form the tunica vasculosa.

Within the framework formed by the mediastinum, septula, and tunica albuginea exists the parenchyma of the testis, which is light brown in color and composed of tiny convoluted tubules known as the *seminiferous tubules.* These tubules, estimated to number 840 per testis, have an average length of 70 to 80 cm with diameters varying from 0.12 to 0.3 mm (148). Cross-sectional examination shows that the seminiferous tubules are composed of a complex germinal epithelium resting on a thin basement membrane. This basement membrane is surrounded by a layer of fibrous tissue and contractile cells, similar to smooth muscle cells, which are thought to promote the movement of the spermatozoa and fluid toward the rete testis. In the cortex of the testis, the seminiferous tubules are very tortuous and convoluted. As they converge on the mediastinum, they become less convoluted and follow a nearly straight course, joining with other seminiferous tubules to form 20 to 30 larger ducts, approximately 0.5 mm in diameter, referred to as the *tubuli recti.* The tubuli recti enter the mediastinum testis, where they progress to form a network of epithelium-lined channels in the stroma known as the *rete testis.* At the superior portion of the mediastinum, the rete terminates in 12 to 20 ductuli efferentes. These ducts perforate the tunica albuginea and carry the seminal fluid from the testis to the epididymis.

Epididymis

The epididymis is a curved structure slightly greater than 5 cm in length that is commonly referred to by one of its three portions and is located at the posterolateral aspect of the testis. The large upper portion, termed the *globus major* or *head (caput),* of the epididymis is firmly attached to the posterior upper pole of the testis by the efferent ductules. The corpus, or body, lies on the posterior part of the lateral margin of the testis but is separated from it by the sinus of the epididymis, an infolding in the tunica vaginalis.

The globus minor or tail (cauda) of the epididymis is loosely attached by areolar tissue to the lower portion of the testis. After the tunica albuginea of the testis is perforated, the ductuli efferentes proceed to the head of the epididymis. Initially assuming a straight configuration, they become enlarged and highly convoluted, forming a group of conical masses, the coni vasculosi. These combine to form the head of the epididymis, each cone being composed of a single convoluted duct 15 to 20 cm long. Within the head of the epididymis, these ducts open into a single, exceedingly convoluted duct that constitutes the greater bulk of the epididymis.

Arterial Supply of the Testis

The arterial supply of the testis consists primarily of the internal spermatic (gonadal) artery and is augmented by the deferential and cremasteric (external spermatic) arteries. The internal spermatic artery originates from the aorta just below the renal artery and crosses the ureter, sending a branch to that structure as it does so, and proceeds through

the inguinal canal with the spermatic cord, arriving at the posterior aspect of the testis. On reaching the testis, the artery branches to form a network of vessels on the inner aspect of the tunica albuginea and sends terminal arteries backward along the septula to converge on the mediastinum. Within the proximal inguinal canal, two arteries are typically encountered (193). The deferential artery originates from the inferior vesical artery and travels in close contact with the vas deferens until it reaches the tail of the epididymis, where it branches into a capillary network. The cremasteric artery originates from the inferior epigastric artery and passes through the inguinal canal in the sheath of the cord. Thereafter, the artery continues to the parietal surface of the tunica vaginalis and anastomoses with capillary networks of the other arterial structures.

Blood Supply to the Testis

Artery	Origin
1. Internal spermatic artery	Aorta
2. Deferential artery	Inferior vesicle artery
3. Cremasteric artery	Inferior epigastric artery

Venous Drainage of the Testis

Venous drainage of the testis occurs along a major and minor route. The major route of drainage is the internal spermatic vein. The right internal spermatic vein usually drains directly into the inferior vena cava, whereas the left internal spermatic vein enters the left renal vein. The left internal spermatic vein follows a vertical course and is therefore 8 to 10 cm longer than the right. This is significant in that it produces increased hydrostatic pressure within the vein and contributes to the pathogenesis of varicocele formation.

The minor venous drainage routes of the testicle consist of the deferential vein, which follows the vas deferens and drains into the superior vesical vein and ultimately into the hypogastric vein and the cremasteric (external spermatic) vein, which leaves the spermatic cord at the external inguinal ring and empties into the pudendal vein and thereafter into the saphenous vein. The minor venous drainage system provides adequate drainage to permit preservation of testicular function after varicocele ligation involving the internal spermatic vein. The major and minor drainage systems communicate freely with one another and are subject to substantial anatomic variation.

Nerve Supply of the Testis

The nerve supply of the testis originates from approximately the lower three thoracic and the first lumbar segments. The testicular plexus is derived from the aortic plexus at the level at which the gonadal vessels originate and accompanies these vessels to the testis. Pain originating from the testis, therefore, is usually referred to the lower thoracic or upper lumbar region.

Developmental Sexual Differentiation

In the human, the gonadal anlage appears during the fourth week of embryonic life as a raised ridge on the posterior abdominal wall on either side of the dorsal midline. Covered by coelomic epithelium, it develops with time in a caudal direction and parallels the laterally developing mesonephric kidney. These two structures make up the urogenital ridge.

Initially, the gonad is a mass of mesoderm that eventually differentiates into the somatic elements of the testis (or ovary). The germinal elements (primordial germ cells or gonocytes, as they are usually called) have an extragonadal origin. They arise in the fourth week of embryonic life from the endoderm, which lines the posterior aspect of the yolk sac. These newly formed gonocytes migrate by ameboid movement up the side walls of the developing gut, through the dorsal mesentery, and move laterally into the adjacent genital ridges (Fig. 35.1) (108). The impetus for this directed migration is unknown, although some studies have suggested that the genital ridges contain a substance chemotactic to germ cells. This seems reasonable in terms of what is known about directed migration of somatic cells along a chemotactic gradient. The migratory process is remarkably efficient, and primary gonadal agenesis in males is rare. During migration, the gonocytes actively proliferate so that the cell population is greatly increased by the time the cells have reached the genital ridges. Although quantitative figures are not available for the human, in the mouse only 100 gonocytes differentiate primarily from yolk sac endoderm; however, 2 days after differentiation, migratory proliferation results in the approximately 5,000 gonocytes that enter the gonadal ridges (112,280). In humans, migration is completed by the sixth week of development.

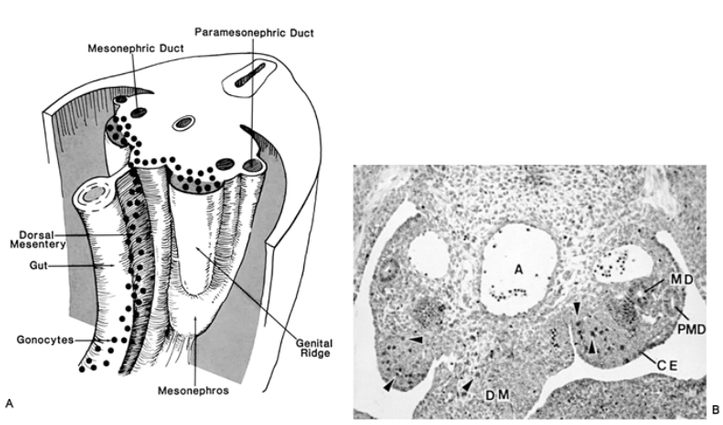

FIGURE 35.1. A: Diagrammatic cross section through an embryo showing the migratory route of gonadocytes into the genital ridges. **B:** Cross section through an embryo showing dark-staining gonocytes *(arrowheads)* arriving in the genital ridges. A, aorta; CE coelomic epithelium; DM, dorsal mesentery; MD, mesonephric duct; PMD, paramesonephric duct. (From Lipshultz LI, Howards SS. Development of the testes and establishment of spermatogenesis. In: Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 3. St. Louis: Mosby, 1997, with permission.)

Gonadal Differentiation

Differentiation of the testis from the bipotential gonadal ridge is initiated by the SRY gene (the sex-determining region located on the short arm of the Y chromosome) (385). Under the influence of the SRY gene, embryonic Sertoli cells align into cordlike structures and begin to secrete müllerian inhibiting substance (MIS), which causes regression of the müllerian duct. In the absence of MIS, the müllerian duct develops into the uterus, fallopian tubes, and upper vagina. It was previously thought that the histocompatibility-Y (H-Y) antigen was this testis determining factor (TDF), until deletions of the Y chromosome removing the H-Y antigen but maintaining the male-determining function of the Y chromosome were identified (398).

Initially, blood vessels and accompanying mesenchymal cells invade the hilum of the future testis. Subsequent

growth occurs in such a way that, beginning at the cranial pole of the testis, a series of arched, branching, and anastomotic sex cords are carved out of the gonadal blastema (79). Most of the gonocytes are sequestered within these newly forming sex cords along with mesenchymal elements, which will ultimately differentiate into Sertoli cells. A basal lamina and mesenchymal cells gradually define the newly formed cords within a tubular wall. Those mesenchymal cells, which are not part of the sex cords themselves, will form the interstitium of the testis, including the Leydig cells. At their extremities the sex cords are continuous with a network of smaller cords located in the future mediastinum of the testis. The latter will eventually cavitate to form the rete testis (79) Those gonocytes that remain in the interstitium or are trapped in the rete cords eventually perish. While these events are occurring, the mesenchyme at the periphery of the gonad condenses to form a capsule, the tunica albuginea. By the eighth week of development, a recognizable testis exists.

The mesonephros, in lateral proximity to the developing testis, begins to regress during the second month of development (201). Most mesonephric tubules degenerate completely. However, 12 to 15 tubules that abut on the hilum of the testis grow toward and establish continuity with the network of rete cords. These will become the ductuli efferentes (Fig. 35.2). At their other extremities, the tubules maintain contact with the mesonephric (wolffian) duct, which will differentiate into the epididymis proximally and the vas deferens distally.

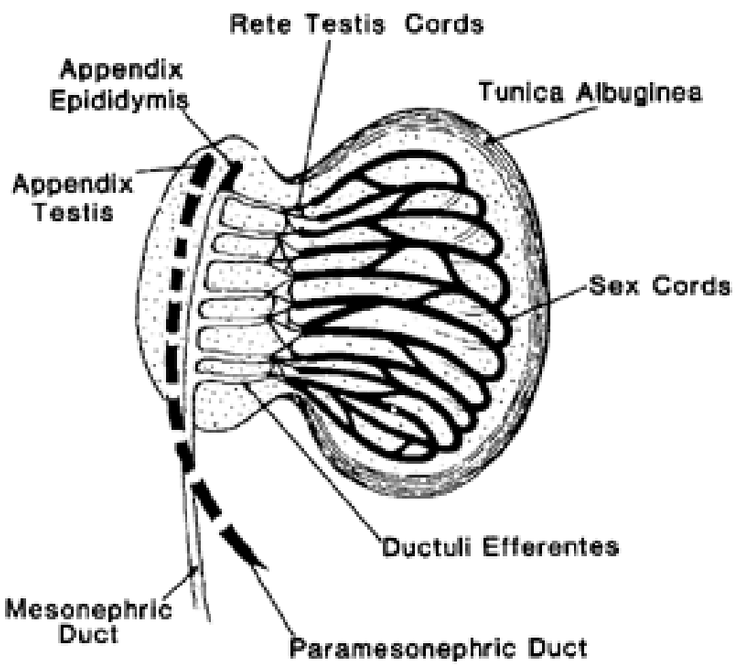

FIGURE 35.2. Diagrammatic representation of the developing testis and excretory duct system. (Modified from Langman J: *Medical embryology,* ed 4. Baltimore: Williams & Wilkins, 1975, with permission.)

Although there are reports that some mesonephric cells invade the gonad to contribute to the Sertoli cell population and to form the rete testis, there is little experimental evidence for this view (455). Serial reconstructions of the developing testis and mesonephros show that a solid rete

testis is formed well before the mesonephric tubules establish contact with it (Fig. 35.3) (79).

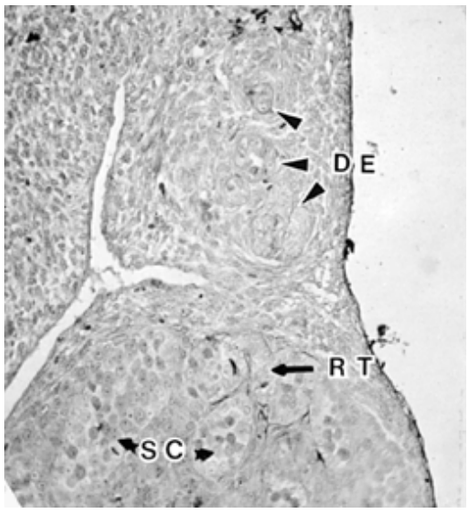

FIGURE 35.3. Cross section at the hilum of a developing testis showing mesonephric tubules, the presumptive ductuli efferentes *(DE),* growing toward the still-solid rete testis *(RT).* SC, sex cords. (From Lipshultz LI, Howards SS. Development of the testes and establishment of spermatogenesis. In: Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 3. St. Louis: Mosby, 1997, with permission.)

Conversion of the mesonephric duct into the male reproductive excretory tract appears to be regulated in two ways. A müllerian-inhibiting factor produced by the presumptive Sertoli cells causes regression of the paramesonephric (müllerian) ducts in the third month, while testosterone produced by the fetal Leydig cells concurrently promotes differentiation of the mesonephric system into a competent reproductive tract (120,404,428). The müllerian ducts persist in the female to form the uterus and fallopian tubes. Cranial portions of the mesonephric and paramesonephric ducts persist as embryonic remnants (Fig. 35.2). The appendix testis from the paramesonephric duct becomes attached by a narrow stalk to the upper pole of the testis, and the cranial mesonephric duct persists as the appendix epididymis connected to the head of the epididymis by a small pedicle.

Testicular Descent

The testis forms as a retroperitoneal organ high in the posterior abdominal wall. During the third trimester, the testis slips down the posterior wall, dragging its neurovascular “leash” (341,459). By the seventh month, it is at the level of the presumptive internal (deep) ring of the inguinal canal. Soon thereafter, the lower anterior abdominal wall is evaginated to form the scrotal sac. By birth, or shortly thereafter, the testis has moved into its extraabdominal location and is covered by the thinned-out component of the peritoneal cavity, the processus vaginalis. This pouch normally is pinched off from the parent peritoneal cavity, leaving a closed sac, the tunica vaginalis, which encloses the anterior and lateral aspects of the testis, serving as a lubricating bursa.

Endocrine Function of the Testis

The release of pituitary gonadotropins—luteinizing hormone (LH) and follicle-stimulating hormone (FSH)—is, in part, regulated by a decapeptide, LH-releasing hormone or gonadotropin-releasing hormone (GnRH) (361). GnRH is synthesized in the hypothalamus and travels to the anterior pituitary via the hypophyseal portal vessels (Fig. 35.4).

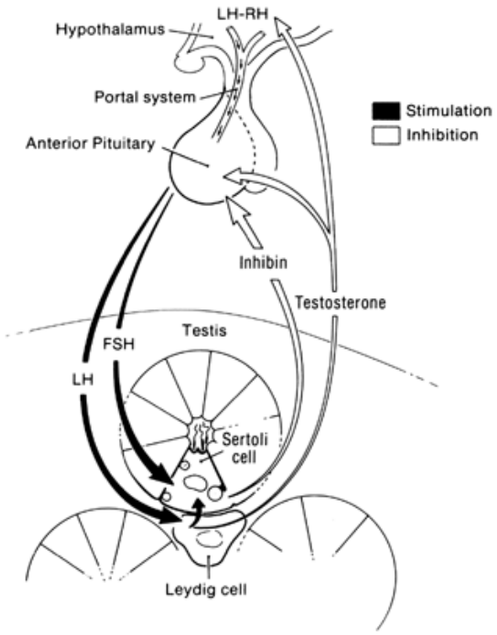

FIGURE 35.4. Hypothalamic-pituitary-testicular interrelationships. [From Lipshultz LI, Kessler DL. *Monogr Urol* 1986;7(April/May):28, with permission.]

The principal control of testosterone synthesis is mediated by LH, which stimulates the Leydig cells to produce androgen. LH binds to receptors on the Leydig cell surface and produces an increase in the activity of the enzyme adenyl cyclase. This enzyme speeds the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), which stimulates intracellular increases in the concentration of several enzymes that accelerate the biosynthesis of androgen. The Leydig cells have the capacity

to synthesize steroid hormones from either acetate or cholesterol. The process by which the androgen is released from the Leydig cell into the blood and the seminiferous epithelium is not understood. The production of androgen begins to increase in early puberty and reaches a peak of approximately 7 mg per day after puberty. Testosterone is released from the testis in episodic spikes. Other steroids, including dihydrotestosterone (DHT), 17-hydroxyprogesterone, and estradiol, are also secreted. Most of the circulating DHT and estradiol, however, are produced by enzymatic conversion of testosterone in peripheral tissues. Obese men are predisposed to increased peripheral conversion of testosterone into estrogen.

Normal peripheral plasma levels of testosterone and DHT are 300 to 1,200 ng/dL and 30 to 60 ng/dL, respectively. Approximately 98% of the circulating androgens are bound to plasma proteins, including specific ß-globulin, testosterone-binding globulin (TeBG). The free testosterone in the blood is the physiologically important fraction.

Recent studies suggest that FSH and prolactin (PRL) may contribute to androgen biosynthesis in the Leydig cells. FSH, however, binds primarily to the Sertoli cells within the seminiferous tubule (Fig. 35.4). FSH stimulates the production of an androgen-binding protein (ABP) by the Sertoli cells, an action mediated by cAMP (422). Although the precise role of FSH is not defined, spermatogenesis requires the presence of FSH and high intratesticular levels of androgen. The presence of specific androgen receptors in the seminiferous tubule supports the view that high intratesticular concentrations of testosterone are necessary for spermatogenesis. Feedback regulation of LH secretion is controlled by serum levels of testosterone and estradiol.

There appears to be specific feedback regulation of FSH secretion by the seminiferous epithelium. Inhibin, a 32-kDa protein, is secreted by Sertoli cells in response to FSH (43). Inhibin acts primarily on the pituitary to inhibit secretion of FSH. It may also act on the hypothalamus to decrease GnRH release and thereby indirectly reduce FSH levels. Interestingly, inhibin appears to have testicular effects also. These effects include stimulation of androgen production by Leydig cells and inhibition of spermatogenesis within the seminiferous tubule (440). Activin, by stimulating the production of FSH, has the opposite effect of inhibin. Although activin, which is structurally related to inhibin, is primarily thought of as a testicular product produced by Sertoli cells, evidence exists that it may be found in a variety of extragonadal tissues such as adrenal, bone marrow, spleen, and kidney. Activin is believed to influence a wide variety of functions, including release or expression of pituitary gonadotropins, as well as growth hormone, adrenocorticotropic hormone, and gonadotropin-releasing hormone.

The endocrine function of the testis is gradually altered during aging. Histologic changes occasionally appear as early as the third decade of life and are increasingly common in older men (44). The most common degenerative changes are thickening of the tubule basement membrane and tunica propria, intratubular fibrosis, and reduction in the number of germ cells in the seminiferous epithelium. Mean levels of free testosterone decline in men after age 50 years, although total circulating testosterone declines later (285). These normally occurring changes in senescent testis function become important in the assessment of the fertility potential of older men.

Spermatogenesis

Spermatogenesis begins with the primitive germ cells, the spermatogonia, and eventually leads to the production of mature spermatozoa and the renewal of production of spermatogonia. Under normal circumstances, spermatogenesis consists of an orderly progression from spermatogonium to spermatocyte, spermatid, and mature spermatozoon (Fig. 35.5). In general, spermatogenesis is a relatively inefficient process. It has been established that half of the germ cells in rodents never differentiate into mature spermatozoa secondary to mechanisms related to apoptosis (177,206,217). Studies in men also suggest that a fine balance between

proliferation and apoptotic degeneration probably results in normal spermatogenesis (242).

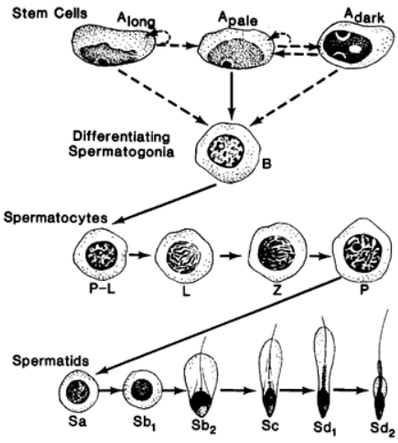

FIGURE 35.5. Individual cell types seen in the normal seminiferous epithelium. These depict the main steps of spermatogenesis in man. A_{dark}, dark type A spermatogonium; A_{pale}, pale type A spermatogonium; B, type B spermatocyte; L, leptotene spermatocyte; Z, zygotene spermatocyte; P, pachytene spermatocyte; Sa, Sb, Sb_2, Sd_2, spermatids at different stages of spermatogenesis. (From Lipshultz LI, Howards SS: Adult spermatogenesis; characteristics, kinetics, and control. In: Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 3. St. Louis: Mosby, 1997, with permission.)

In humans, sequential maturation includes the dark type A spermatogonium (Ad), the pale type A spermatogonium (Ap), the type B spermatogonium (B), the resting spermatocyte (R), the leptotene spermatocyte (L), the zygotene spermatocyte (Z), the pachytene spermatocyte (P), the secondary spermatocytes (II), and the Sa, Sb, Sb_2, Sc, Sd, and Sd_2 spermatids (Fig. 35.5) (162). In addition to Ad and Ap spermatogonia, some workers recognize a more primitive type of spermatogonium, the A_1 cell, the purported stem cell.

As germ cells mature, they move within the Sertoli cell cytoplasm from the basement membrane of the seminiferous tubule to the adluminal compartment (Fig. 35.6). Thus the Sertoli cell plays an important nutritional role in the spermatogenic process. The various spermatogonia undergo mitotic division, but the diploid primary spermatocyte undergoes a meiotic reduction division, giving rise to a haploid secondary spermatocyte containing only half the chromosomes of the primary spermatocyte and either an X or a Y chromosome. All cells up to this point have a rounded shape. As the spermatid matures, however, it elongates, develops a tail or flagellum, and assumes a configuration similar to that of a mature spermatozoon. Very few spermatozoa are present in histologic sections of the testis, because as soon as they mature, they are released into the seminiferous tubular lumen and rapidly flow out to the rete testis.

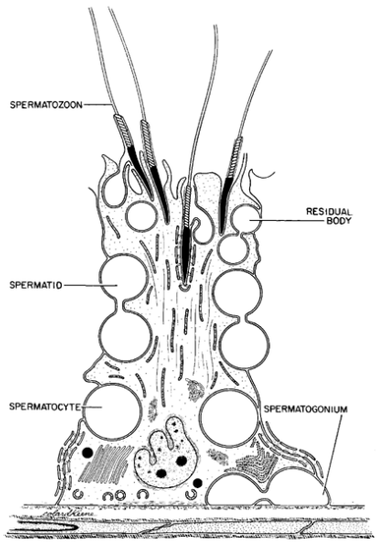

FIGURE 35.6. Compartmentalization of the germinal epithelium. Note the germ cells and their relationship to a columnar Sertoli cell. Spermatogonia are in a basal compartment, whereas the more mature germ cells are in an adluminal compartment. The adluminal compartment is separated from the basal area by tight Sertoli cell–Sertoli cell junctions at the lateral aspect of the Sertoli cell, near the base. These junctions form a blood-testis barrier, which is thought to protect the mature spermatocytes and spermatids. (Modified from Dym M, Fawcett DW. *Biol Reprod* 1970;3:308; and Dym M. The male reproductive system. In: Weiss L, Greep RO, eds. *Histology.* New York: McGraw-Hill, 1973, with permission.)

Observations of the seminiferous epithelium taken from testis biopsies reveal that specific cell types are repeatedly seen only in association with certain other cells, and that all spermatogenic cell types are not visible within one cross section of a tubule. These cell associations, or groupings, are known as stages in the cycle of the seminiferous epithelium. There are six stages or cell associations in humans (162). The cells in any given association progress together to the next cell grouping. Each stage represents a particular degree of maturation. Stages I through VI constitute one cycle of the germinal epithelium. The duration of each cycle in the human is 16 days. Approximately four cycles of the epithelium are required for an A_1 spermatogonium to mature to a spermatozoon. Heller and Clermont (162) have determined that in the human it takes 4.6 cycles, or 74 days, for a mature sperm to develop from an Ap spermatogonium.

A number of paracrine factors produced within the testis exert a local (paracrine) control on spermatogenesis (298), including cell proliferation and meiosis. These growth factors probably influence spermatogenesis by facilitating communication among various cell types within the testis (Sertoli cells, germ cells, Leydig cells, and peritubular cells). Growth factors that have been isolated from the testis, isolated testicular cell monolayer cultures, and testicular secretions include fibroblast-like growth factors, insulinlike growth factors, ß-nerve growth factors, transforming growth factor-ß, Sertoli cell–secreted growth factor, inhibin, and activin (298).

The molecular mechanisms regulating spermatogenesis are slowly being defined. This is undoubtedly one of the most exciting areas of research in male infertility. The importance of the genetic regulation of spermatogenesis has new clinical implications as a result of ICSI, which may bypass many of the previous barriers to conception and pass on abnormal genes to the offspring.

Functional Anatomy of Spermatozoa

The head of the human spermatozoon contains a nucleus that is composed of dense nucleoprotein. The nuclear

chromatin is stabilized by S-S (disulfide) cross-links between molecules. The condensation and cross-linking combine to make the mature sperm nucleus highly resistant to chemical and physical insult and thus serve to preserve the sperm during epididymal storage. The acrosome is a thin, caplike structure that envelops the anterior four-fifths of the sperm head (Fig. 35.7). It contains many enzymes that are released at the time of fertilization. The tail represents 90% of the length of the human sperm and comprises a connecting piece, a middle piece, a long principal piece, and a short end piece. The motor apparatus of the sperm tail is called the *axoneme* or the *axial filament complex.* It runs the length of the tail, within its center, and is composed of a central pair of microtubular structures surrounded by a ring of nine pairs of microtubules. The major protein of these tubules is tubulin. The major protein of the arms of the microtubules is dynein. The tubulin–dynein system is distinct from the actin–myosin system in skeletal muscle. The ring of nine microtubules is surrounded by a circle of nine noncontractile dense fibers, which are thought to serve as supportive structures. The outer dense fibers are found within a circular fibrous sheath of mitochondria.

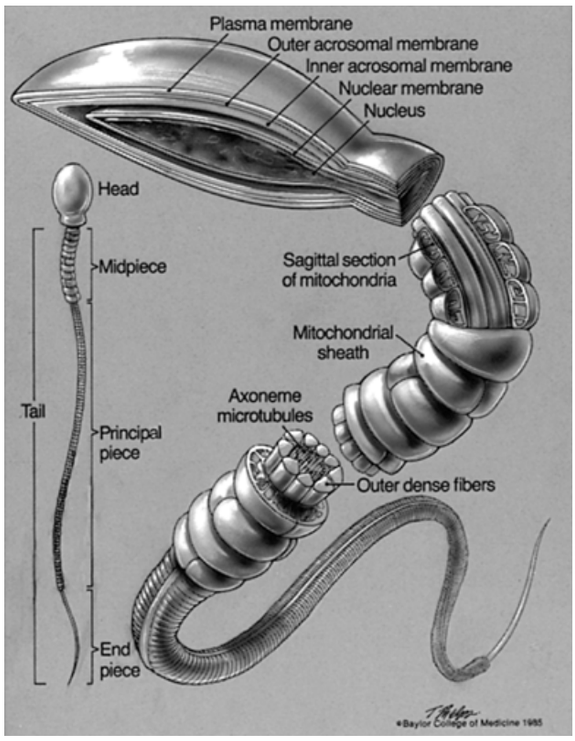

FIGURE 35.7. The illustration of the mature spermatozoon demonstrates the relationship between the head, midpiece, and other tail segments through a combination of external and sagittal section details. The insert depicts a normal spermatozoon as seen with light microscopy.

During transit through the epididymis, the spermatozoa and their milieu both undergo many dramatic changes. In addition to the changes in morphology, chemistry, motility, fertilizing potential, and metabolism, spermatozoa also undergo alterations in permeability, antigenicity, and surface membrane charge during epididymal passage (30). It is probable that in some complex yet unexplained way, these alterations are important to the sperm cell's ability to complete the fertilization process. An abnormality of any of these functions could lead to infertility in the male.

Morphologic changes in epididymal spermatozoa include changes that occur in the acrosomal membranes as the spermatozoa undergo epididymal transit. It is likely that these changes (“precapacitation events”) are necessary for capacitation, but their specific function is presently unknown.

Biochemical modifications in sperm occurring during epididymal maturation include an increase in cAMP content, loss of nonnuclear protein, shifts in free amino acid concentration, loss of palmitic acid, a decrease in the amount of most phospholipids, an increase in the amount of unsaturated fatty acids, changes in electrophoretic properties, and stabilization of the deoxyribonucleoprotein complex. Ejaculated spermatozoa meet most of their energy requirement by utilizing fructose from the seminal vesicles, although mammalian sperm can also anaerobically metabolize glucose and mannose to lactic acid. The sperm mitochondria have the enzymes of both the Embden-Meyerhof glycolytic pathway and the Krebs cycle. Therefore the metabolic function of the sperm is greatly enhanced by the epididymis.

Functional Role of the Epididymis

The epididymis is important for sperm maturation and the acquisition of sperm motility. In the unobstructed state, the best sperm motility is found in the cauda, and the least in the caput. The changing environment and physiology of the epididymis are critical to the maturation of the spermatozoa. However, with ICSI, sperm with normal fertilizing capability may be obtained from any portion of the epididymis. In addition to alterations in spermatozoa, the luminal fluid changes significantly in the epididymis. A large portion of the fluid secreted from the seminiferous tubules flows into the rete testis and is absorbed in the ductuli efferentes and proximal epididymis. Inositol, total lipid, and total protein decrease in concentration as the luminal fluid moves through the epididymis (198). In contrast, potassium concentration rises. Glyceryl phosphorylcholine (GPC), sialic acid, carnitine, hypotaurine, and acetylglucosmide are secreted in large quantities into the fluid, but their functions are not understood.

It has been known for some time that the epididymis depends on androgens for maintenance of histologic integrity (259). Subsequently, it was shown that the motility and fertility of epididymal sperm and the secretion of carnitine, GPC, and sialic acid into the fluid are androgen-dependent processes.

Vigersky and colleagues (450) have found androgens and androgen-binding protein in the fluid of the caput epididymis. Although androgen levels are higher in rete testis fluid than in the peripheral circulation, it is not clear whether most of the androgen enters the epididymal lumen from the blood or from the rete testis fluid.

Transport of Spermatozoa

Mature human spermatozoa are released from Sertoli cells into the lumen of the seminiferous tubule and then traverse approximately 6 m of duct in the male reproductive tract before they leave the urethral meatus to be deposited in the vagina. This ductal system can be subdivided into several components (Fig. 35.8). From the seminiferous tubule, the spermatozoa travel into the rete testis, a collection chamber for all the seminiferous tubules. The sperm leave the rete testis via the ductuli efferentes, which in the human are composed of 12 to 20 channels, and pass into a single, compact 3.6- to 4.6-m-long convoluted duct known as the *ductus epididymis.*

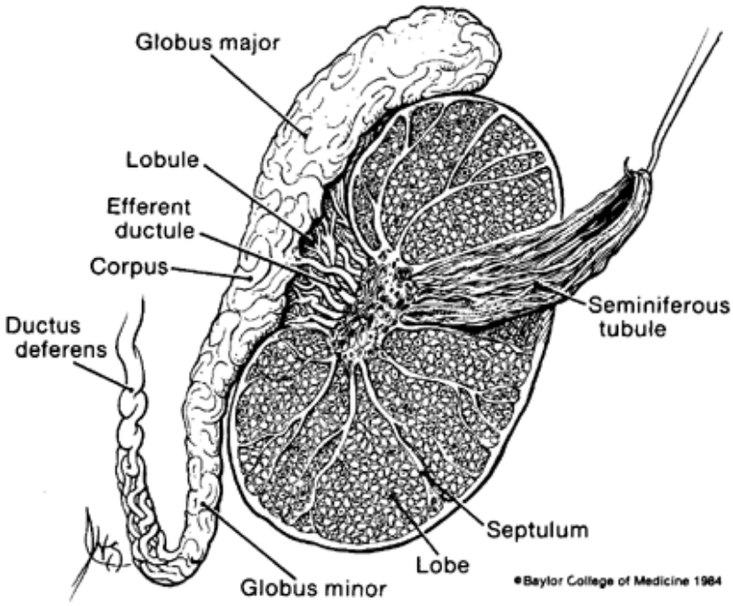

FIGURE 35.8. Cross-sectional representation of the testis and epididymis. (From Meacham RB, Huckins C, Lipshultz LI. Anatomy and embryology of the testicle. In: Javadpour N, ed. *Principles and management of testicular cancer.* New York: Thieme-Stratton, 1985, with permission.)

The epididymis has been traditionally divided into three regions: caput, corpus, and cauda epididymis. Before and during ejaculation, the spermatozoa move from the cauda epididymis into the vas deferens, which is approximately 38 cm long. The distal portion of the vas deferens is termed the *ampulla.* The ampulla terminates in the prostatic urethra after it has been joined by the duct of the seminal vesicle, forming the ejaculatory duct (Fig. 35.9).

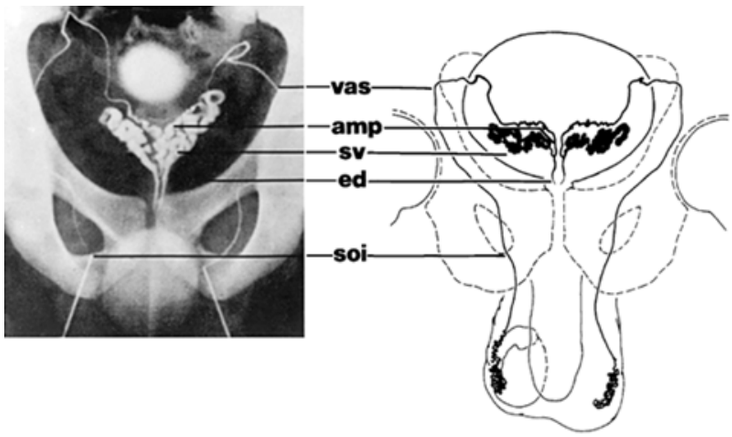

FIGURE 35.9. A bilateral vasogram *(left)* and a schematic drawing of the excurrent ducts of the male reproductive system *(right).* Amp, ampulla of the vas deferens; ed, ejaculatory duct; soi, site of injection; sv, seminal vesicles vas, vas deferens. (From Sherins R, Howards SS. Male infertility. In: Harrison JH et al, eds. *Campbell's urology.* Philadelphia: Saunders, 1978, with permission.)

The ductuli efferentes are lined with an epithelium that projects motile cilia into the lumen. In contrast, the cilia of the epididymal duct are not true cilia and possess no capacity for purposeful movement. The efferent duct's true cilia may have a role in sperm transport; the stereocilia of the epididymal duct do not. The fluid secreted in the testis flows into the epididymis. If the efferent ducts are ligated, the testis becomes tense and gains weight, and eventually pressure atrophy of the seminiferous tubules occurs (431). Because this phenomenon is not seen after ligation of the vas deferens, it is assumed that the epididymis is able to reabsorb the fluid secreted by the testicle. This absorptive capacity prevents permanent atrophy of the seminiferous epithelium after vasectomy in humans.

In the human there is a gradual proximodistal increase in the thickness of the muscle investment of the efferent ducts, epididymis, and vas deferens. Circularly arranged bundles of small, smooth muscle–like myoid cells predominate in the efferent ducts and caput epididymis, although some bundles are arranged in a spiral course. In the more distal cauda, smooth muscle cells predominate, forming the three interconnected layers of smooth muscle seen in the vas deferens

(the inner and outer longitudinal layers and the intermediate circular layer). The ratio of the thickness of muscle to lumen in the human vas deferens is far greater than in any other structure in the human. The reason for such abundant musculature is not known, but it is generally accepted that muscular contractions cause rapid sperm transport at the time of ejaculation.

The epididymal duct and the efferent ducts contract spontaneously. These contractions are thought to aid in sperm transport even during periods of sexual abstinence, whereas the contractions of the vas deferens and distal epididymis propel the spermatozoa during ejaculation. Thus sperm movement into the epididymis may be attributed to several factors: (a) positive fluid pressure from the rete testis, (b) fluid currents established by the beating of cilia along the walls of the efferent ducts, and (c) peristaltic contractions of the efferent ducts. Contractions of the seminiferous tubules and contraction of the tunica albuginea may assist in the transport of spermatozoa from the testis. Spontaneous peristalsis-like contractions of the epididymal tubules have been promulgated as the sole operative factor in the transport of spermatozoa through the epididymis. Resting hydrostatic pressure gradients may also contribute to epididymal sperm transport (205).

The transit time of sperm through the caput and the corpus is consistently 3 to 5 days and is independent of ejaculation. In young men the transit time is 2 to 4 days. Thus the variation in total epididymal transmit time is probably related to differences in the rate of passage through the cauda epididymis, which in turn are due to changes in ejaculatory frequency. Ejaculations accelerate transit through the cauda epididymis, but they probably do not affect transport from the caput to the proximal cauda. Ejaculated spermatozoa come from the vas deferens and the distal epididymis. Pabst (311a) has calculated that the human vas deferens has a capacity of 0.45 mL, which is enough to account for roughly 10% of the volume of the normal ejaculate.

In the experimental animal and in humans, the vas deferens contains large amounts of catecholamines and is richly innervated by adrenergic fibers that can cause contractions when properly stimulated (311). There is increasing evidence that parasympathetic stimulation can also cause contraction of the vas deferens; however, the sympathetic system is physiologically predominant. There is no direct evidence that the vas deferens undergoes spontaneous peristaltic contractions similar to those in the ureters and the gastrointestinal tract.

Erection, Emission, and Ejaculation

To penetrate the vagina and deposit sperm in it, the penis must be erect. Erection following local stimulation (reflexogenic erection) is mediated through the sacral spinal cord, whereas erection following psychic stimulation (psychogenic erection) is dependent on cerebral erotic centers. Psychic stimuli can augment or inhibit reflex erections. Although, classically, erection has been thought of as a simple parasympathetic function, its neurophysiology is complex. The afferent nerves for reflex erection run in the pudendal nerves, and the efferent fibers are found in the S-2 to S-4 parasympathetic outflow or in the nervi erigentes. The afferent stimuli for psychic erections travel through the thoracolumbar sympathetic outflow and the sacral parasympathetic fibers.

During erection, the vascular spaces in the corpora cavernosa and the corpus spongiosum fill with blood. The blood flows to the corpora via four branches of the internal pudendal artery: the urethral artery, the artery of the bulb of the penis, the deep artery of the penis, and the dorsal artery of the penis. There is extensive vascular communication between the two corpora cavernosa. Physiologic studies indicate that erections are the result of smooth muscle relaxation within the corpora cavernosa. As a result of sexual stimulation, cavernous nerves and the endothelial cells within the corpora cavernosa release nitric oxide (NO), which stimulates the formation of cyclic guanosine monophosphate (cGMP). This cGMP is directly responsible for the corporal smooth muscle relaxation, which enables increased arterial dilation and inflow. As the corporal bodies fill with blood and become distended, the draining venules between the external sinusoids and the tunica albuginea become compressed, thereby trapping the blood within the penis. Penile rigidity is dependent on a normal penile anatomy (e.g., elasticity of the tunica albuginea) and normal penile vasculature and nerve supply. Detumescence is initiated by the degradation of cGMP, a process that is enzymatically mediated by type V phosphodiesterase within the corpora cavernosa.

The ejaculatory process may be divided into two phases: the preejaculatory or emission phase and the ejaculatory phase. During emission, secretions from the periurethral glands, the seminal vesicles, and the prostate are deposited in the posterior urethra. In addition, sperm from the ampulla of the vas deferens, from the vas itself, and probably from the cauda epididymis are propelled by peristalsis into the posterior urethra. The emission process is primarily but not exclusively mediated through the sympathetic nervous system. At the time of ejaculation, the bladder neck (the so-called internal sphincter) closes under sympathetic control. Both emission and closure of the bladder neck can be prevented by α-adrenergic blocking agents.

The precise neurophysiologic mechanisms of emission and ejaculation are not known. The spinal center for these processes is in the lower thoracic and upper lumbar cord and possibly in the sacral cord. According to Shishito and Kimura (389), the pelvic and hypogastric nerves in the dog are involved in emission, and the pudendal and hypogastric nerves are associated with ejaculation. Fibers in the hypogastric nerve that are distinct from those stimulating emission were

found to close the bladder neck at the time of ejaculation. There is also evidence that in the human emission and bladder neck closure are stimulated from different sympathetic ganglia. Patients with postlumbar sympathectomy may have either retrograde ejaculation or failure of emission.

During the final phase of ejaculation, the external urethral sphincter relaxes and the perineal and bulbourethral muscles contract, expelling the ejaculate from the posterior urethra through the urethral meatus. This phase of the ejaculatory process is thought to be triggered by the presence of seminal fluid in the posterior urethra. The fluids secreted by the prostate and seminal vesicles constitute approximately 95% of the ejaculate volume and serve as a vehicle of transport for the sperm (480).

Capacitation and Acrosome Reaction

Spermatozoa of rabbits and rats must reside in the female reproductive tract before they acquire the capacity to fertilize ova. This phenomenon is termed *capacitation.* There are several *in vivo* and *in vitro* bioassays that measure the capacitation of sperm (175,306). They are based on the assumption that only capacitated sperm can penetrate and fertilize eggs. Under the proper experimental conditions, certain species' capacitated sperm will fertilize cross-species ova *in vitro,* whereas noncapacitated sperm will not. Therefore, as discussed later in detail, sperm must undergo capacitation to result in a positive sperm–hamster egg penetration test. Complete capacitation is also a prerequisite for successful *in vitro* fertilization (IVF).

The acrosome reaction follows capacitation. It is a progressive fusion between the plasma membrane of the sperm head and the outer acrosome membrane, resulting in the formation of a series of vesicles. Pores between the areas of fusion allow a progressive loss of the acrosomal contents. This vesiculated complex is always missing from the sperm just before it penetrates the zona pellucida. Thus the acrosome reaction is a clear-cut morphologic change that follows capacitation and precedes fertilization. The enzymes released during the acrosome reaction facilitate fertilization by allowing sperm to penetrate the vestments surrounding the ovum.

EVALUATION OF THE INFERTILE MALE

Part of "35 - Male Infertility "

Primary infertility affects 10% to 15% of married couples. In this group, about half of the men demonstrate a significant abnormality. In the last few years we have witnessed an increasing appreciation of the subtle abnormalities of gonadal and spermatozoal dysfunction that can contribute to seemingly unexplained male infertility. New diagnostic tests are emerging that may help define these previously obscure male factors. Only when these abnormalities have been clearly identified can more specific treatment regimens be introduced.

Although it has often been recommended that clinical evaluation of an infertile couple be undertaken only after 1 year of unprotected intercourse, we believe that the initial screening of the man should be considered whenever the patient has the chief complaint of infertility. This initial evaluation, however, should be rapid, noninvasive, and cost-effective. The basis of the evaluation for infertility should be a complete history, physical examination, and pertinent laboratory tests.

History

A history of specific childhood illnesses (Table 35.1) may be important in the evaluation of the subfertile man. It has been shown that in the male born with bilateral or unilateral undescended testes, regardless of the time of orchiopexy, overall semen quality is less than that found in normal men (243). In patients with a unilateral undescended testis, the defect in spermatogenesis is present not only in the undescended gonad but also in the descended contralateral gonad. Nevertheless, after orchidopexy, their fertility approaches that of men with normally descended testes. A history of testicular (spermatic cord) torsion has also been

associated with decreased fertility (29), which may be due in part to preexisting changes in the contralateral testis. Prepubertal mumps do not appear to affect the testes. However, among men who have experienced mumps after the onset of puberty, 30% have unilateral orchitis and 10% have bilateral orchitis (460). Furthermore, the testicular damage can be severe and should be readily appreciated on physical examination because the involved gonad is markedly atrophic.

History of Infertility
Duration
Prior pregnancies
  Present wife
  Another partner
Previous evaluations
Previous treatments

Sexual History
Potency
Lubricants
Timing of intercourse
Frequency of intercourse

Childhood and Development
Undescended testicles; orchiopexy
Herniorrhaphy
Y-V–plasty of bladder
Testicular torsion
Testicular trauma
Onset of puberty

Medical History
Systemic illness
Previous or current therapy

Surgical History
Retroperitoneal surgery
Pelvic injury
Pelvic, inguinal, or scrotal surgery
Herniorrhaphy
Y-V–plasty; transurethral prostate resection

Infections
Viral; febrile
Mumps orchitis
Venereal
Tuberculosis; smallpox (rare)

Gonadotoxins
Chemicals
Drugs (chemotherapeutic; cimetidine; sulfasalazine; nitrofurantoin; alcohol; marijuana; androgenic steroids)
Thermal exposure
Radiation

Family History
Cystic fibrosis
Androgen receptor deficiency

Review of Systems
Respiratory infections
Anosmia
Galactorrhea
Impaired visual fields

TABLE 35.1. INFERTILITY HISTORY

Men who have had operative correction (Y-V- plasty) of the bladder neck during childhood may have retrograde ejaculation because the internal sphincter has been ablated. This condition should be suspected in the man who gives a history of bladder surgery and whose ejaculate volume is less than 1 mL, oligozoospermic or azoospermic, and abnormally acidic. The diagnosis is confirmed by a finding of large numbers of sperm (10 to 15 per high-power field) in the uncentrifuged postejaculation urine. Another group of patients who may seek evaluation for infertility is those patients cured of testicular cancer. The infertility rate in this group has been estimated to be greater than 80%. Their infertility is secondary to the sequelae of chemotherapy, radiotherapy, retroperitoneal lymph node dissection, or a combination of all three. Frequently, the function of their contralateral “normal” testis is impaired before the institution of therapy (49). Prognosis regarding semen quality is uncertain if less than 4 years has elapsed since treatment, because the return of function to the radiated or chemotherapeutically exposed gonad may take as long as 4 to 5 years (89,275,297). The patient who has had retroperitoneal lymph node dissection with interruption of the sympathetic nodal chain or its peripheral long nerves (sacral plexus, hypogastric nerve) may show either aspermia with lack of emission or, less frequently, retrograde ejaculation (226).

The history should also include a review of past and present medical diseases. Cystic fibrosis is associated with a high percentage of abnormalities of the vas and epididymis. The population of males suffering from congenital bilateral absence of the vas deferens has also been found through DNA genetic testing to carry cystic fibrosis trait in a significant proportion of cases. Such individuals generally show none of the stigmata of cystic fibrosis and potentially are treatable by microsurgical retrieval of epididymal sperm in combination with IVF and ICSI (301).

A history of recurrent upper respiratory tract infections or bronchiectasis may lead to the diagnosis of the immotile-cilia syndrome or Young's syndrome. In Young's syndrome, inspissated material in the epididymis produces an obstructive azoospermia. Spermatozoa proximal to this lesion, however, are normal and motile (115). The immotile-cilia syndrome (115,156) is a heterogeneous group of disorders characterized by ultrastructural defects of cilia. In this syndrome the spermatozoa have the same structural defect as the cilia and are immotile. Individuals with Kartagener's syndrome have the same ciliary defect but also have situs inversus (156).

Precocious sexual puberty may indicate endocrinologic dysfunction such as congenital adrenal hyperplasia (CAH), which has historically been cited as a cause of decreased fertility potential (95). It should be noted, however, that Urban and colleagues (437) described five untreated adult men with CAH whose fertility was normal. A history of anosmia, galactorrhea, impaired visual fields, or a marked or sudden decrease in libido along with infertility may indicate a pituitary tumor. A familial history of diabetes mellitus may be relevant, because diabetes may cause a lack of emission or retrograde ejaculation. A history of decreased ejaculate volume can be a clue to this disease (149) There may be a familial history of end-organ androgen insensitivity (i.e., partial androgen receptor defect) as seen in Reifenstein's syndrome. A history of delayed sexual maturation or anosmia can lead the alert clinician to a diagnosis of Kallmann's syndrome, with its associated hypogonadotropic hypogonadism. Information about trauma to the genitourinary organs or previous scrotal or inguinal surgery including pediatric herniorrhaphy should be obtained. Prior venereal disease may be associated with urethral strictures or vasal or epididymal obstruction. Tuberculosis can lead to scarring of the epididymis and vas deferens as well.

The history should also include a detailed inquiry into exposure to drugs and environmental toxins that may interfere with spermatogenesis, either directly or through alterations in the endocrine system (Table 35.2). A reversible effect of specific pesticides on gonadal function has been reported (247). However, once azoospermia has occurred, return to a normal state is highly unlikely. Medications such as sulfasalazine, calcium channel blockers (166), cimetidine, and high-dose nitrofurantoin and ingestants such as nicotine, alcohol, and marijuana have also been implicated as gonadotoxic agents. Elimination of these substances should enable return of normal spermatogenesis. Exogenous androgens, mistakenly thought by some clinicians to improve gonadal function, actually act as a “male contraceptive,” depressing gonadotropin secretion and interfering with normal spermatogenesis. The growing use of anabolic steroids by athletes makes this area of concern increasingly important. Consequently, if a patient is taking any of these medications at the time of initial interview, the medication should be stopped and the patient's semen reevaluated in approximately 3 to 4 months.

	Observed Effects			
Type of Exposure	Decreased Sperm Count	Abnormal Morphology	Altered Sperm Transfer	Altered Hormones/Sexual Performance
Lead	+	+	+	+
Dibromochloropropane	+			
Carbaryl (Sevin)		+		
Ethylene bromide	+	+	+	
Plastic production (Sterene and acetone)		+		
Ethylene glycol monoethyl ether	+			
Welding		+	+	
Mercury vapor				+
Heat	+		+	
Military radar	+			
Radiation (Chernobyl)	+	+	+	+
Carbon disulfide				+

TABLE 35.2. DRUGS AND ENVIRONMENTAL TOXINS THAT MAY INTERFERE WITH SPERMATOGENESIS

Any generalized metabolic insult (e.g., fever or viremia) can cause impaired testicular function. However, the effects may not appear in the ejaculate for 1 to 3 months after the gonadotoxic event because of the time required for spermatogenesis. Approximately 74 days pass between the initiation of the type B spermatogonia and the appearance of mature spermatozoa in the ejaculate. Including transit time in the ductal system, the duration from the beginning of spermatogenesis to ejaculation is approximately 2.5 to 3 months. The actual time lapse between the injurious event and the appearance of abnormal cells in the ejaculate varies, depending on which stage of the spermatogenic process is

affected. For that reason, if a patient gives a history of significant medical problems in the 3 months before the first office visit and if the analysis shows subnormal semen quality, the evaluation should be repeated at monthly intervals for 4 to 6 months before a decision is made regarding the quality of sperm production.

The subject of sexual habits and coital factors must also be addressed during the initial history. Improper timing of intercourse is the most common coital factor responsible for the infertile couple's failure to conceive. Many couples do not understand the female cycle as to the ideal time for conception. Because sperm are viable for approximately 48 hours, and ova for 12 to 24 hours, intercourse should be planned at least every other day for approximately 1 week before ovulation and for several days thereafter to maximize the chance of placing viable sperm in contact with the ovum in the fallopian tube during the egg's period of viability, as suggested by Wilcox and colleagues (461). Precise prediction of ovulation may be accomplished via commercially available urine assay kits, such as OvuQUICK and ClearPlan-Easy, that measure the preovulatory LH surge. Artificial lubricants may result in a diminished motility and should not be used. One should also ask about the use of common vaginal lubricants, such as K-Y Jelly, petroleum jelly, saliva, skin lotions, and Astroglide, which all may have spermatotoxic effects (128,376,411). If lubricants must be used, light vegetable oils are the least spermatotoxic. Too-frequent periovulatory masturbation, which can deplete the sperm reserve, should be avoided.

Lifestyle Factors

These factors are important to identify because they are under the direct control of the patient. Although specific further treatments may not overcome their adverse effects, avoidance of continued exposure may improve sperm production or function.

Smoking

Although the results of individual reports vary, cumulative evidence suggests that cigarette smoking can be detrimental to male fertility. Studies by Vine and Hughes have demonstrated decreased sperm density in smokers as compared with nonsmokers (179,447). Elevated serum prolactin and estradiol levels have been noted in smokers, and both have been proposed as a contributing cause for the subfertility noted in this population. The seminal plasma from smokers has been shown to have a prominent adverse effect on the spermatozoa from nonsmokers (482). Smoking has also been reported to exacerbate the effect of other causes of infertility, such as varicocele (223). Clearly, cessation of smoking is a simple, specific step that may enhance the fertility potential of male and female patients.

Alcohol

Although chronic alcoholics can demonstrate testicular atrophy, diminished serum testosterone levels, and subfertility, moderate alcohol consumption has not been shown to deleteriously affect semen parameters (444).

Stress

The biochemical relationship between infertility and emotional stress is not well defined. Schenker and colleagues (364) postulated that emotional stress may impair the function of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in gonadotropic dysfunction. It is important for the urologist treating the subfertile male to realize that the stress of infertility itself may be particularly troublesome. Ragni and Caccamo (339) noted a fivefold increase in the number of men with abnormal semen parameters

3 months after enrollment in an IVF program, suggesting that the emotional stress these men were experiencing had a negative impact on the quality of their semen. Similarly, Clarke and colleagues (78) found a significant decline in semen quality of male IVF patients on the day of egg retrieval compared with baseline semen analyses. Therefore it is reasonable to reduce emotional stress in the subfertile couple, especially through a team approach employing physicians, nurses, social workers, and psychologists.

Exercise

Endurance training at high levels, including running more than 100 miles per week or bicycling more than 50 miles per week, has been demonstrated to result in diminished sperm concentration and motility. Moderation of endurance training is therefore a reasonable step in the management of the subfertile male; however, the true effect of extreme exercise is unclear (23).

Nutrition

Dietary derangements have been loosely linked to male subfertility (470). This is an untapped research area that needs to be explored thoroughly to identify which dietary factors play a role in the metabolic pathways involved with the development of normally functioning sperm. As an example, in animals, vitamin A deficiency causes germ cell degeneration (441). It is always appropriate to recommend a healthy diet to all patients, particularly those who may be substantially overweight. Excess fat in the body can act as a storage reservoir for estrogens in the male, thereby throwing off the normal testosterone/estradiol ratio, which may have subtle effects on sperm development and function. Excess fat also enhances the peripheral conversion of testosterone to estrogens by aromatization.

Hyperthermia

The issue of “boxer shorts versus jockey shorts” is often raised by patients. The hypothesis that jockeys cause higher scrotal temperatures and are detrimental to semen quality is theoretic and unproven. It is unlikely that underwear type has a significant effect on male fertility, and routinely advising infertility patients to wear boxer shorts cannot be supported by available scientific evidence (289). Continuous exposure to high temperature levels, however, may affect the patient who is already borderline-low in some of his semen parameters, so it would seem prudent to discontinue the use of saunas, hot tubs, and so on in the subfertile male. An extensive review of the literature demonstrated an adverse effect of occupational heat exposure on male fertility (419).

Occupational Gonadotoxins

A careful history eliciting any exposure to occupational gonadotoxins is mandatory, and minimization of exposure is essential in the treatment of the subfertile male. General categories of harmful toxin exposure include chemicals, radiation, or extreme heat (Table 35.2) (345). Aromatic solvent exposures should especially be avoided (420). A detailed description of the detrimental effect of inhaled hydrocarbon exposure in rubber factor workers was recently reported by De Celis and colleagues (98).

Declining Sperm Counts

Recent reports have suggested that sperm counts have been declining worldwide over the last 50 years (24,63,181). However, these studies are controversial and have been refuted by other authors (124,343). Saidi and Fisch have also suggested that geographic variation may be present and that the highest sperm densities may be found in New York compared with other U.S. cities (357). Most of these studies have examined trends in semen quality from sperm banks. Environmental factors, such as those having estrogenic effects, have been implicated as the underlying cause (196). Carlsen and colleagues (63) argue that a concomitant increase in the incidence of genitourinary abnormalities such as testicular cancer and possibly cryptorchidism and hypospadias suggests a growing impact of factors with serious effects on male gonadal function.

Erectile Dysfunction

Erectile dysfunction must be evaluated and treated according to its etiology. From a psychologic perspective, because difficulties with the initiation of a pregnancy are still traditionally considered a “woman's problem,” the diagnosis of a male factor abnormality may have a significant and unexpected impact on a man's self-esteem and overall sense of manhood. A focus of increasingly more attention, studies of couples with a male factor subfertility disorder have clearly demonstrated higher anxiety levels, an increase in somatic symptomatology, periods of erectile dysfunction, and even feelings of rage by the wife toward the husband. Emotional issues of guilt and depression related to feelings of a loss of self-confidence, security, self-esteem, and health are commonly encountered and often result in erectile dysfunction. Organic erectile dysfunction may also be encountered, albeit less frequently in the reproductive age group. Treatments are focused on counseling and therapy for psychogenic etiologies and noninvasive treatment options for organic erectile dysfunction.

Premature ejaculation is not uncommon in young men, but only rarely is a cause of infertility if ejaculation occurs before vaginal penetration. Treatment is most successful using a combination of methods such as reconditioning, sexual therapy, and oral medications. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, and paroxetine have shown efficacy.

Medications

Prescription Drugs

Prescription drugs can impair fertility, and when possible, an equivalent medication should be substituted for one that

causes infertility. The pharmaceuticals may be grouped according to the level at which they primarily affect spermatogenesis (Table 35.3).

Suppresion of HPG Axis	Direct Gonadotoxicity	Impaired Fertilization
Anabolic steroids	Ketoconazole	Calcium channel blockers
Cimetidine	Sulfasalazine	Colchicine
Steroidal antiandrogens (DES)	Valproic acid	Nitrofurantoin
Cyclosporine	Spironolactone	Minocycline
Phenothiazine	Allopurinol	

HPG, hypothalamic-pituitary-gonadal.

TABLE 35.3. PRESCRIPTION DRUGS THAT CAN IMPAIR FERTILITY

Chemotherapeutic Agents

Chemotherapeutic agents are another important cause of infertility. Mechlorethamine, cyclophosphamide, chlorambucil, procarbazine, and nitrogen mustard have a particularly severe effect on the testis with relatively poor recoverability. In contrast, methotrexate has a minimal effect on the testis with excellent recoverability at 6 to 12 months. Pretreatment semen cryopreservation should be offered to young male cancer patients before initiating therapy. Recent animal studies by Meistrich and colleagues (276,277) have suggested a possible beneficial effect of luteinizing hormone–releasing hormone (LH-RH) agonist pretreatment in preserving spermatogenesis, but the role of this treatment in humans is still a largely unanswered question.

Illicit Drugs

Illicit drugs, including marijuana (225), cocaine (42,49), and heroin, may also impair spermatogenesis or affect sperm motility. Their use must be eliminated in couples trying to establish a pregnancy.

Dietary Supplements

Dietary supplements have experienced increasing popularity over the last decade, but their effect on male fertility is unknown, except in artificial laboratory conditions. Ondrizek and colleagues (307) briefly exposed donor sperm to echinacea purpura and St. John's Wort, resulting in sperm DNA denaturation. In contrast, saw palmetto and ginkgo had no effect, although the long-term potential effect of saw palmetto as a 5α-reductase inhibitor may be concerning. Further study in this area is needed.

Physical Examination

Physical examination of the infertile man should include a generalized and complete evaluation. Any factor that affects overall health can theoretically be responsible for abnormalities in sperm production; for that reason the physical examination should be thorough, with emphasis placed on the genitalia. If the patient appears to be inadequately virilized (androgen deficient), as evidenced by decreased body hair, gynecomastia, eunuchoid proportions, and so on, the diagnosis of delayed maturation due to an endocrine abnormality should be considered and appropriately evaluated. Penile curvature or the presence of tunical plaques should be assessed, as should the location of the urethral meatus. Abnormalities in these factors can result in improper placement of the ejaculate within the vaginal vault. The scrotal contents should also be palpated carefully with the patient in the upright position. Testicular size and consistency must be noted, and the length and width of the testes obtained to the nearest millimeter or the volume of the testis estimated with an orchidometer. It has been shown that a decrease in testicular size is often associated with impaired spermatogenesis (244). This is not surprising, because 85% of the testis is involved in sperm production; consequently, when the germinal epithelium atrophies, loss of testicular mass occurs. Standard values of testicular size have been recorded for the normal population. These data document that in the normospermic man, the length of the testis should be greater than 4 cm and the volume greater than 20 mL.

Examination of the peritesticular area is also critical. Epididymal induration, irregularity, and cystic changes should be noted, as should the presence or absence of the vas deferens and any nodularity along its course. Congenital bilateral absence of the vas deferens is found in approximately 1.4% of the infertile male population (20). Congenital vasal agenesis is characterized by complete or partial absence of both vasa deferentia. The caput epididymis is always present and is generally accompanied by a portion of the corpus or cauda. These individuals are generally found to have absent or abnormal seminal vesicles. The patients therefore have a low-volume acidic ejaculate and are invariably azoospermic. Experience has shown that testicular size is normal, and testicular function, in terms of both androgen production and spermatogenesis, is generally intact. Varicoceles represent an engorgement of the pampiniform plexus and can cause abnormalities of gonadal function (360).

Ideally, the patient should be examined in a warm room after standing for several minutes. Palpation for asymmetry of the spermatic cords followed by a Valsalva maneuver with repalpation of the spermatic cords should be routinely performed. An “impulse” can often be felt with the increase in intraabdominal pressure. Although venography candelineate

the abnormal vessels, this is seldom necessary. Color Doppler sonography may be of some use in defining questionable lesions. Although this topic remains controversial, data exist that suggest, but do not prove, that correction of subclinical varicoceles may be beneficial in some subfertile men (272). Varicoceles can be classified according to size as follows: large, visible through the scrotal skin; moderate, easily palpable without increasing intraabdominal pressure; and small, palpable only with a concurrent Valsalva maneuver.

A scrotal varicocele is the most common surgically reversible abnormality found in the subfertile man (245) and is the most commonly identifiable abnormality in men with primary and secondary infertility (189) (Table 35.4). Whereas approximately 15% to 20% of the normal population can be found to have scrotal varices, this number approaches 40% in subfertile men (150). Not all varicoceles require surgical correction. However, if there is scrotal discomfort secondary to this lesion, if the testis ipsilateral to the scrotal varix is found to be atrophic, or if there is reasonable suspicion that impaired semen quality may be related to the presence of the varicocele, surgery should be considered. Bilateral varicoceles occur more frequently than previously reported; if the indications cited in the preceding sentence are present, bilateral varicoceles should be repaired concomitantly.

Diagnosis	Number	%
Varicocele	603	42
Idiopathic	324	23
Obstruction	205	14
Normal/female factor	113	8
Cryptorchidism	49	3
Immunologic	37	3
Ejaculatory dysfunction	18	1
Testicular failure	18	1
Drug/irradiation	16	1
Endocrine	16	1
Infection	13	1
Sexual dysfunction	4	<1
Genetic	2	<1
Total:	**425**	**100**

From Sigman M, Lipshultz LI, Howards SS. Evaluation of the subfertile male. In: Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 3. St. Louis: Mosby, 1997, with permission.

TABLE 35.4. CAUSES OF INFERTILITY: DISTRIBUTION ACCORDING TO FINAL DIAGNOSTIC CATEGORIES

A rectal examination may also be performed to evaluate the prostate and the seminal vesicles. Normally, the seminal vesicles are not palpable and the prostate is firm. Palpable seminal vesicles or a midline prostatic cyst may suggest ejaculatory duct obstruction and may require transrectal ultrasonography for verification.

Laboratory Tests

Endocrine

Although the extent of the hormonal evaluation is variable, an assessment of serum FSH and testosterone is commonly obtained. A more comprehensive evaluation would also consist of a serum LH and prolactin. In a retrospective review of a comprehensive evaluation at two infertility centers, only 99 of 1,035 men (9.6%) had abnormal endocrine studies on repetitive testing, with the majority having an isolated elevation of FSH levels (392). Only 1.7% had a clinically significant endocrinopathy that would have had an effect on disease management. The authors concluded that endocrinopathies are a rare cause of male infertility and that screening men with sperm counts of less than 10 million/mL with serum testosterone and FSH levels alone will detect the vast majority of clinically significant endocrinopathies.

The measurement of testosterone as a reflection of Leydig cell function may be especially useful if there is a history of delayed puberty, decreased libido, or impotence. Low levels of serum FSH and LH can help confirm the diagnosis of hypogonadotropic hypogonadism in an adult with incomplete sexual maturation. Gonadotropin deficiency in a sexually mature man suggests a pituitary tumor or another ablative cause of pituitary or hypothalamic damage. In these patients measurement of serum prolactin may be of diagnostic value, especially if galactorrhea is also present. However, in the routine evaluation of men with idiopathic infertility, measurement of serum prolactin is not frequently helpful. Estrogen determinations should be obtained if the patient has gynecomastia, is significantly obese, or is suspected to have end-organ resistance to testosterone. It has been suggested that a testosterone (ng/dL) to estrogen (pg/mL) ratio (T/E ratio) may help distinguish between types of underlying pathology, with a T/E ratio of 16 for normal men, 7 for men with nonobstructive azoospermia, and 4 for men with Klinefelter's syndrome (326).

A compensatory increase in FSH and LH can be found in response to testicular dysfunction, although LH changes are usually minimal. FSH, however, seems to increase progressively as the germ cells are lost and is almost always elevated when there is a marked reduction in the more mature sperm forms. An elevation of FSH greater than three times normal in the azoospermic or oligozoospermic patient strongly suggests severe spermatogenic failure. However, even azoospermic men with markedly elevated FSH levels may have sperm suitable for ICSI found on testis biopsy specimens (220).

Semen Analysis

Clinical studies of infertile patients have established limits of adequacy below which the initiation of a pregnancy

becomes statistically increasingly difficult (Table 35.5). Nevertheless, men with high-quality spermatozoa may be fertile with very low sperm densities. Even men with sperm concentrations less than 10 × 10^6/mL, when treated medically for hypogonadotropic hypogonadism, are often fertile following medical therapy (387). A semen analysis is not a definitive test for fertility. Fertility determination requires the initiation of a pregnancy and therefore is a couple-related phenomenon. Furthermore, the interpretation of the semen analysis depends greatly on how the semen is collected and analyzed and how its normal values are defined.

On *at least* two occasions:	
Ejaculate volume	1.5–5.0 mL
Sperm density	>20 million/mL or >50–60 × 10^6 total sperm
Motility	>60%
Forward progression	>2+ (scale 0–4)
Morphology (routine)	>60% normal
And:	
No significant sperm agglutination	
No significant pyospermia	
No hyperviscosity or inadequate liquefaction	

From Lipshultz LI, Howards SS, eds. *Infertility in the male*, ed 3. St. Louis: Mosby, 1996, with permission.

TABLE 35.5. SEMEN ANALYSIS: MINIMAL STANDARDS OF ADEQUACY

Collection

Two to three semen analyses should be obtained for initial evaluation, although one analysis of very high quality may be sufficient for initial screening. All specimens should be collected with a consistent abstinence period of 2 to 3 days and brought to the laboratory for evaluation of sperm motility and forward progression within 1 hour of collection. If these specimens are within 20% of one another in terms of the bulk seminal parameters to be examined, it is usually not necessary to collect more specimens. If, however, the discrepancy is greater than 20%, additional specimens are needed.

The specimen container should be clean, not necessarily sterile, and wide mouthed to minimize collection error. Collection of the semen can be by masturbation or with a special condom or sperm collection device devoid of spermicidal agents. The first technique is preferable. The bottle label should indicate the patient's name, date, time of specimen collection, and abstinence period. It should be emphasized to the patient that an incomplete collection or one obtained following a prolonged or decreased period of sexual abstinence is not only inaccurate but often misleading.

Sperm Pellet

Semen centrifugation, referred to here as “sperm pelleting,” should be performed as a first, noninvasive method of sperm recovery in all men considered azoospermic by routine semen analysis, especially those with testicular failure and for whom ICSI is a possibility. Because ICSI requires only one sperm per oocyte, the finding of even several sperm has importance. A sperm pellet may be obtained by centrifuging a semen sample in a 15-mL conical tube for 10 minutes at 1,000 revolutions per minute (200 G) (184). Hyperviscous samples may be mixed with an equal volume of sperm-washing medium before centrifugation. After discarding the supernatant, the entire pellet is removed with a glass pipette, placed on a glass slide, and covered with a cover slip. The entire slide may then inspected by starting in one corner of the cover slip under 400× power using a left-to-right, right-to-left, “zigzag” pattern to ensure adequate examination. The exact number of sperm is recorded as either motile or nonmotile.

Sperm, both motile and nonmotile, may be found in the pellets of as many as 23% of men with unobstructed azoospermia and 19% with obstructive azoospermia on routine semen analysis (184). Similarly, Lemack and Goldstein (237) reported that 10% of men undergoing a vasectomy reversal had sperm found in a centrifuged pellet. The finding of sperm after centrifugation may save the patient from a more invasive procedure if ICSI is considered.

Safety Standards

Concerns regarding the transmission of infectious diseases via contamination from contact with body secretions, including semen, has led to the development of safety measures for the andrology laboratory. Guidelines call for the consistent use of gloves when handling semen or seminal plasma, use of safety glasses when handling frozen semen vials (which may explode while thawing), and use of surgical masks when there is a high potential for creating aerosols or droplets (such as centrifugation or vortexing of open containers). Centrifuges should be covered or placed in exhaust hoods during centrifugation of biologic fluids. Mechanical pipetting devices must be used, and pipetting by mouth must never be permitted (474).

Physical Characteristics

In accordance with the standardized techniques for semen analysis that have been reported (17,173,246), we allow the ejaculate to liquefy at 37°C for 30 minutes. Volume is measured in a graduated cylinder to the nearest 0.1 mL. A small drop of semen is mounted on a microscope slide with a coverslip for evaluation of motility, forward progression, and agglutination. An aliquot of a 1:20 dilution of semen (0.95 mL of distilled water and 0.05 mL of semen using an

Eppendorf pipette) is placed on a hemocytometer for determination of sperm density and morphology.

Viscosity

Freshly produced semen is a coagulum that liquefies 5 to 25 minutes after ejaculation. The constituents of the semen responsible for coagulation originate in the seminal vesicles; the proteolytic enzymes that initiate liquefaction are found in the prostate. Following liquefaction, seminal fluid viscosity can be qualified. *Normal viscosity* is defined as occurring when the specimen can be poured "drop by drop." Impaired liquefaction and increased viscosity remain equivocal causes of infertility and cannot be considered significant in the presence of a normal postcoital test.

Motility and Forward Progression

The motility of the sperm should be evaluated within 2 hours after the specimen is produced. If the specimen is then promptly refrigerated to prevent bacterial overgrowth, sperm density determinations can be delayed. *Motility* is defined as the average percentage of sperm moving in ten random high-power microscopic fields. If the count is low, motility can be more accurately quantitated. Estimates of motility by experienced individuals are highly consistent. The quality of motile sperm (the degree of forward progression) should also be observed. Classification of the quality of sperm movement is based on the pattern displayed by the majority of motile spermatozoa and ranges from 0 (no movement) to 4 (excellent forward progression).

Several investigators have designed tests to measure the velocity of motile sperm, but these require special computerized equipment and a trained technician and are not now widely used in routine clinical practice. Although velocity tests provide interesting data, they have not, thus far, significantly altered therapy. However, it is interesting to note that the average velocity of ejaculated sperm is 75 μmm per second (129). If none of the spermatozoa are moving, the patient is said to have "necrozoospermia." This is actually a misnomer, because metabolic studies and special vital stains have revealed that the immotile spermatozoa may not necessarily be dead.

Agglutination

During the motility evaluation, any evidence of sperm agglutination should also be noted. Occasionally, clumps of agglutinated sperm are seen in semen specimens. However, increased clumping is suggestive of either an inflammatory or an immunologic process. Agglutination may be seen. In the absence of these conditions, sperm may agglutinate head to head, tail to tail, or head to tail.

Sperm Density

Spermatozoa are counted with a microscope at 400 power using the red cell section of a standard hemocytometer. Counting is faster if the spermatozoa have been allowed to settle to one focal plane. Five blocks of 16 squares each, representing one-fifth of the grid, are observed, and all spermatozoa within the area including those touching the lower and right-hand sides of each block are counted. This number is multiplied by 10^6. An average of two such readings represents the sperm density per milliliter. Alternative admixtures with corresponding changes in the calculations are suggested if the count is less than 5×10^6 (246). A Makler chamber is also commonly used with the microscope to determine density and motility (257).

Morphology

Human seminal cytology is a sensitive index of the germinal epithelium. Evaluation of the morphology of spermatozoa requires more patience and experience than determining sperm density or motility. Staining of the cells is preferable. Although a simple hematoxylin or more complicated Papanicolaou technique can be used, we prefer to use a small drop of fresh, well-mixed immobilized sperm and to observe this under the phase microscope. Using World Health Organization (WHO) criteria, cells are classified into one of five categories: normal (oval), amorphous (including large and small spermatozoa), tapered, duplicated, and immature. It has been shown that the morphologic classification of an individual's semen is remarkably consistent, and therefore a significant variation often reflects underlying testicular dysfunction.

Strict Morphologic Criteria

The morphology of human spermatozoa was first described by van Leeuwenhoek in 1677. During the last half century, various attempts have been made to enhance the evaluation of sperm morphology as part of the male fertility evaluation. Kruger and associates (230) made significant progress in defining a standardized technique for the evaluation of sperm morphology. They found that sperm located in the upper endocervical canal following intercourse were homogeneous in their morphology, and using these sperm as a reference population, they established strict criteria for morphologic evaluation (278).

The use of strict morphologic criteria for evaluating spermatozoa has found ready application in the area of IVF. Kruger and co-workers (230) performed 190 IVF cycles and evaluated their results as a function of sperm morphology. They observed a distinct threshold among patients having a percentage of sperm with normal morphology of 14% or lower. Pregnancy rates were markedly lower in this group than in couples in whom the male had exhibited 15% of sperm or greater having normal morphology. Further investigation showed that patients who have less than 4% of sperm with normal morphology are in a particularly poor prognostic group. Such individuals have achieved extremely low fertilization rates during IVF procedures (229). With use of a potentially less labor-intensive method, normal

sperm morphology as evaluated by an automated semen analyzer was also found to be a significant predictor of IVF and pregnancy (81). However, the role of strict morphology analysis in non-IVF clinical settings is not clear.

Computer-assisted Semen Analysis

Several other techniques have been used in further study of sperm function. Computer-assisted semen analysis (CASA) has been widely investigated (212,254,443). To date, there is no conclusive evidence that it adds significantly to the clinical evaluation of the infertile patient. However, its ability to look objectively at sperm movement and especially at hyperactivation (347) may give a new dimension to our understanding of change in sperm movement in association with capacitation.

Semen White Blood Cell Assays

Wolff and colleagues (469) have shown that infertile men have higher white blood cell (WBC) counts in their ejaculates compared with normal men. Compared to the WHO definition of 1×10^6 cells/mL or below as normal for WBCs in the ejaculate, 23% of 179 infertile men had white cell counts above this normal range. Along with this inflammatory infiltrate, evidence is accruing that harmful substances such as cytokines and reactive oxygen species (ROS) may be secreted by such cells and further harm sperm motility and viability (9).

In a standard semen analysis, the round cells often visible may represent immature germ cells or leukocytes. Many laboratories erroneously report immature spermatogenic cells as being "leukocytes." Monoclonal antibody assays are especially useful in the identification of leukocytes in semen, but they are expensive and not widely available (468). As an alternative, the peroxidase test is commonly used. The test is done by mixing 20 µmL of liquefied ejaculate with 20 µmL of peroxidase test working solution. This incubates for 5 minutes at room temperature. Then, 20 µmL of this solution is added to 20 µmL of saline immediately before counting. Ten microliters of the diluted specimen is loaded into a hemocytometer, and peroxidase-positive (intensely brown-stained round cells), as well as peroxidase-negative (unstained), round cells are counted at 400× magnification. Antibody-positive cells are stained red, and nonpositive cells are stained blue. The total number of WBCs per milliliter of semen is calculated by multiplying the percentage of positive cells by the total number of round cells per milliliter.

Biochemical Assays

The seminal vesicles contribute fructose and prostaglandins to the semen, and the prostate secretes zinc, magnesium, dehydrogenases, immunotransferases, citric acid, phosphate, and spermine. Several of these factors have been investigated extensively. Few, if any, of these studies have proved to be clinically useful. Production of fructose is an androgen-dependent process. Its presence should be determined qualitatively in any azoospermic patient and especially in those whose ejaculate volume is less than 1 mL, suggesting the possibility of ejaculatory duct obstruction or seminal vesicle atresia or hypoplasia. Transrectal ultrasound evaluation of the seminal vesicles adds valuable information in these patients, as discussed later in more detail. A colorimetric technique using a resorcinol reagent is best for fructose determination.

Genetic Evaluation

Genetic abnormalities related to male infertility must be considered in terms of being (a) causative for male infertility and (b) potentially transmissible to the offspring. When examining the offspring, the physician should keep in mind that abnormalities may be transmitted from either parent, or may arise *de novo,* depending on the specific defect. Present genetic screening of azoospermic and severely oligozoospermic men with testicular failure consists of Y chromosome microdeletion testing and karyotyping. In a consecutive series of 190 azoospermic men with secondary testicular failure undergoing testicular sperm extraction for ICSI, 17% had genetic abnormalities identified with screening (353). Those men with congenital absence of the vas deferens (CAVD) or unexplained bilateral obstruction should be offered cystic fibrosis gene mutation testing. Although somewhat expensive, these tests are necessary for proper genetic counseling regarding the potential for transmission of undesirable genes to the offspring. These tests are clearly only a starting point for genetic testing, as we decipher the genetic code regulating male infertility (Table 35.6).

Genetic Test	Abnormality
Cystic fibrosis gene mutation	Congenital absence of the vas deferens
DAZ gene mutations	Azoospermia, severe oligozoospermia
Karyotype analysis	Variable (e.g., Klinefelter's syndrome, XXY male)

TABLE 35.6. TESTING HUMAN GENETIC ABNORMALITIES RELATED TO MALE INFERTILITY

Cystic Fibrosis Gene Mutations

Men at risk for cystic fibrosis (CF) gene mutations have vasal or epididymal abnormalities, typically in combination with low-volume azoospermia. If the vas deferens is not palpable, CF gene mutation testing is recommended (Fig. 35.10). The most commonly encountered condition in this category is cystic fibrosis transmembrane conductance

regulator (CFTR) gene mutations. The most common presentation is congenital bilateral absence of the vas deferens, which occurs in 1% to 2% of men with infertility (150,197). The carrier status for this autosomal- recessive condition is common, being present in 1 out of 25 persons of Northern European descent and with over 550 CFTR gene mutations having been reported (96). Because of the potentially fatal nature of this autosomal- recessive disorder for the offspring, screening should now be considered routine when vasal or epididymal abnormalities are suspected.

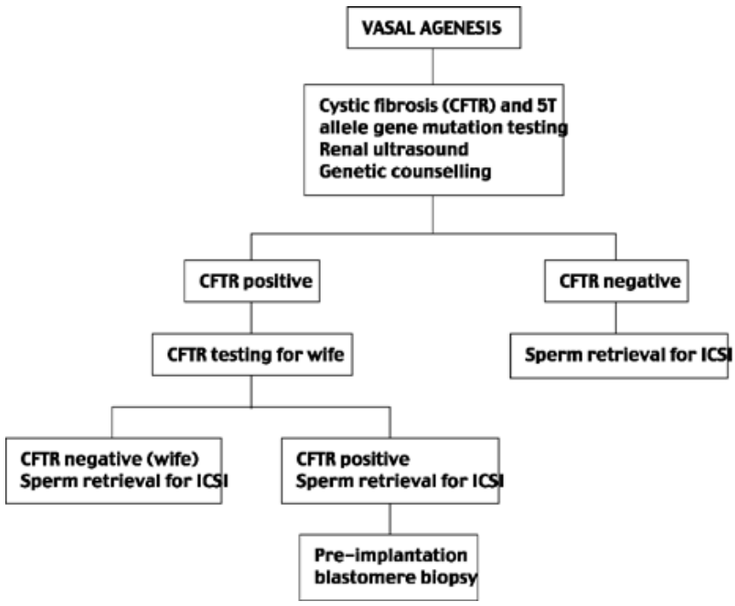

FIGURE 35.10. Algorithm for male infertility evaluation—overview.

The CF gene is located on chromosome 7 at 7q31. The CFTR is 250 kb in length and contains 27 exons. μDF508 is a three–base pair deletion in exon 10 and accounts for approximately 70% of CF alleles (216). Testing should also be performed for the 5T (thymidine) allele on intron 8 because of the high frequency of abnormal findings. Chillon and colleagues (75) characterized the mutations in the CFTR gene in 102 patients with congenital bilateral absence of the vas deferens (CBAVD) and also analyzed a DNA variant (the 5T allele) in a noncoding region of CFTR that causes reduced levels of the normal CFTR protein. Studies of CFTR mRNA in tissues from normal persons have identified various mRNA molecules that lack exon 4, 9, or 12. Whether or not CFTR mRNA contains exon 9 depends on the variable length of a stretch of thymine residues in intron 8 of CFTR. This sequence, known as a *polyT sequence*, contains 5, 7, or 9 thymines (the 5T, 7T, and 9T alleles, respectively). Because the 5T allele causes reduced levels of normal CFTR mRNA, this variant would appear likely to be involved in the pathogenesis of CBAVD. In 19 of the 102 patients, mutations in both copies of the CFTR gene were found, and none of these had the 5T allele. A mutation was found in one copy of CFTR in 54 patients, and 34 of them (63%) had the 5T allele in the other CFTR gene. No CFTR mutations were found in 29 patients, but seven of them (24%) had the 5T allele. Chillon and colleagues (75) concluded that the combination of the 5T allele in one copy of the CFTR gene with a CF mutation in the other copy is the most common cause of CBAVD. The 5T allele mutation has a wide range of clinical presentations, occurring in patients with CBAVD or moderate forms of CF and in fertile men.

These CFTR gene mutations may result in wolffian duct (epididymis, vas, secondary involvement as absence of a kidney) abnormalities as the only somatic manifestation, because sperm production is typically normal. Other clinical manifestations include unilateral renal agenesis and seminal vesicle aplasia or hypoplasia, with the latter condition often resulting in low semen volumes. We routinely obtain a renal ultrasound in men with vasal agenesis. Schlegel and colleagues (369) observed that renal agenesis is evident in about 11% of men with bilateral and 26% of infertile men with unilateral congenital absence of the vas deferens. Ipsilateral renal ectopia, crossed-fused renal ectopia, and horseshoe kidneys have also been observed. When renal anomalies coexist with CAVD, a defect in the wolffian duct at or before the formation of the ureteral bud at 7 weeks results in malformation of the entire wolffian duct and subsequent vasal agenesis.

Between 50% and 82% of men with CBAVD and approximately 43% with unilateral absence of the vas deferens will have at least one detectable CFTR gene mutation (20,107,369). Furthermore, Jarvi and colleagues (195) reported that at least 47% of otherwise healthy men with idiopathic epididymal obstruction had a CFTR gene mutation.

If the man is a carrier of a CF gene mutation and ICSI is a consideration for the couple, his partner should be tested. If the partner is a carrier of the same mutation, rules of autosomal-recessive inheritance are followed. The offspring will have a 1 in 4 chance of having full-blown cystic fibrosis, a 1 in 2 chance of being a carrier, and a 1 in 4 chance of having no gene mutations. Another viewpoint for testing for CFTR mutations is to assume that all men with CBAVD have a mutation, but that not all mutations are detected because of limited allele testing, typically for only 30 of the most common loci. Testing of the wife alone is then indicated. If both are carriers of the mutation, preimplantation blastomere biopsy analysis may be performed by several U.S. and U.K. specialty research centers under investigational protocol.

In men with CBAVD after sperm harvesting from the epididymis, pregnancy rates of up to 50% per cycle have been obtained with ICSI, in contrast to 10% with standard IVF (374,396). These excellent outcomes make genetic counseling and screening of the patient's wife important given the severity and risk of transmission (autosomal-recessive inheritance) of the classic form of cystic fibrosis. Approximate cost for this test, obtained from a peripheral blood specimen, is $300.

Y Chromosome Microdeletions

When testicular failure is manifest by azoospermia or severe oligozoospermia, we routinely screen for Y chromosome microdeletions and karyotype analysis if the couple is considering ICSI. Although the definition of severe oligozoospermia is debatable, we place a patient in this category if his sperm density is less than 5 million sperm/mL. Structural chromosomal abnormalities of the Y chromosome were initially suspected as having a role in male infertility by Tiepolo and Zuffardi (421) as early as 1976, but their findings and significance did not exert much clinical impact until the introduction and widespread use of ICSI.

It is well established that the long (q) arm of the Y chromosome is required for spermatogenesis. In the early 1990s, Ma and colleagues (253) and Chandley and Cooke (67) demonstrated that microdeletions on the Y chromosome were associated with infertility. The specific region of the Y chromosome implicated in male infertility based on mapping studies is called the azoospermia factor locus (AZF), present in band q11.23 (28). Four distinct interstitial deletions causing azoospermia or severe oligozoospermia occurring in nonoverlapping subregions of Yq11 are called AZFa, AZFb, AZFc, and AZFd (453). These subregions appear to regulate different stages of spermatogenesis. Testicular biopsies in these men have demonstrated a range of spermatogenic defects from Sertoli cell–only syndrome (no sperm-forming elements) to maturation arrests (sperm-forming cells present, but not mature sperm) at the spermatid stage (344). Deletions of the AZFb region especially have been correlated with the absence of mature spermatozoa and presence of round spermatids in testis biopsy specimen (53). AZFc coincides with the DAZ gene (deleted in azoospermia), which is a novel transcription unit that is usually present in the AZF region in men of normal fertility. Deletions of the DAZ gene result in severe impairments of spermatogenesis, but not always. AZFd, associated with mild oligozoospermia or even normal sperm counts associated with abnormal sperm morphology, has also been recently described (215).

Deletions in the DAZ gene are present in 10% to 15% of otherwise normal 46,XY men with nonobstructive azoospermia (295,344,452). (Table 35.7). This defect is clearly phenotypically diverse, because approximately 6% to 10% of men with severe oligozoospermia (sperm density less than 5 million sperm/mL) have this deletion (337,407). In contrast, DAZ deletions are found in only approximately 2% of normal men.

Reference	*N*	Status	DAZ Deletions (*N*)	% Deletions
Qureshi, et al. (1996)	100	Azoospermia or oligozoospermia	8	8
Reijo, et al. (1996)	89	Azoospermia	12	13
Stuppia, et al. (1996)	33	Azoospermia or oligozoospermia	6	18
Najmabadi, et al. (1996)	60	Azoospermia	7	12
Vereb, et al. (1997)	69	Azoospermia	6	9
	33	Severe oligozoospermia	1	3
	106	Oligozoospermia	0	0
Foresta, et al. (1997)	16	Azoospermia	6	38
	22	Severe oligozoospermia	5	23
Shirakawa, et al. (1997)	25	Azoospermia	4	16
van der Ven, et al. (1997)	204	Oligozoospermia	2	1
Pryor, et al. (1997)	26	Azoospermia	2	8
Simoni, et al. (1997)	168	Azoospermia and severe oligozoospermia	5	3
Kremer, et al. (1997)	111	Oligozoospermia	7	6
Oliva, et al. (1998)	50	Azoospermia	8	16
	136	Oligozoospermia	2	2
Rucker, et al. (1998)	183	Azoospermia	17	9
Silber, et al. (1998)	51	Azoospermia	10	20
	30	Severe oligozoospermia	4	13
Kim, et al. (1999)	40	Azoospermia	8	20
Krausz, et al. (1999)	134	Azoospermia and severe oligozoospermia	3	2
Kent-First, et al. (1999)	278	Azoospermia and severe oligozoospermia	57	20.5

TABLE 35.7. MICRODELETIONS IN DAZ IN PATIENTS WITH OLIGOZOOSPERMIA AND AZOOSPERMIA

The immediate concern of this DAZ gene microdeletion is that transmission to the offspring may occur (68,224). The male offspring may have a similar infertility-type problem, but the answer may not be apparent for at least another decade. Interestingly, some fathers of infertile men with microdeletions have been found to have the identical deletions as their sons, whereas other microdeletions appear to arise *de novo* (214,312,337). Furthermore, it is unknown whether the male offspring may have other, presently unidentified, potential for increased abnormalities such as malignancies. Thus far, no untoward effects have been observed. Interestingly, after genetic counseling, the decision to proceed with ICSI remains unchanged for the overwhelming majority of couples (296). Approximate cost for this testing is $250 to $300.

Karyotyping

Karyotyping can uncover genetic abnormalities, including structural chromosomal disorders such as Klinefelter's (classic 47,XXY), mixed gonadal dysgenesis, chromosomal translocations, and XYY syndromes. For example, Klinefelter's syndrome is relatively common, with an incidence of 1 in 500 live male births, and the XYY male syndrome occurs in about 1 in 1,000 live births. These conditions are easily assessed from a peripheral blood smear for karyotyping. Identification of these disorders is important because with the advent of ICSI, men with abnormalities such as mosaic (118,231) and nonmosaic (300) Klinefelter's syndrome can have sperm harvested from testis biopsies and initiate a

pregnancy with resultant genetically normal embryos (316). The incidence of these abnormalities is markedly increased above baseline population levels (267,279). The approximate cost for this analysis is $300.

It has been suggested that all men with severe male factor infertility have this cytogenetic analysis performed because of an increased risk for chromosomal translocations. In a study of 261 couples with male factor infertility, abnormal karyotypes were found in 4.2% of the men and 1.2% of the women (415). Five of eight fetuses from the 14 involved couples were found to have inherited a structural chromosomal abnormality. Meschede and associates (279) from Germany found a 2.1% chromosomal abnormality rate in men. Similarly, Pandiyan and Jequier (319) found that 3.6% of 1,201 men with abnormal semen analyses had either autosomal or sex chromosomal aberrations. Other ICSI series having a predominant male factor have similar findings (Table 35.8).

Reference	Men Screened	Abnormal Karyotype Rate (%)
Baschat (1996)	32	6.2
Peschka (1996)	200	3.0
Testart (1996)	261	4.2
Pandiyan (1996)	1,201	3.6
Mau (1997)	150	12.0
Stuppia (1998)	126	13
Rucker (1998)	101	21
Meschede (1998)	432	2.1

TABLE 35.8. ABNORMAL KARYOTYPE RATES IN MEN WITH SEVERE MALE FACTOR INFERTILITY

Chromosomal abnormalities detected in the offspring of male factor couples undergoing ICSI may be inherited from the father or mother, or may arise *de novo* in a nonfamilial fashion. In a very small series, In't Veld and colleagues (180) raised concerns in 1995 when they reported four (27%) cytogenetic abnormalities in 15 pregnancies initiated by ICSI. However, these pregnancies were screened because of advanced maternal age, and the series was small. Wisanto and colleagues (465), in contrast, studied a younger population and identified only six (1%) chromosomal abnormalities using chorionic villus sampling or amniocentesis from 585 prenatal diagnoses.

Algorithms for Evaluation of the Infertile Male

After performing a detailed history, a physical examination, and several semen analyses, hormonal testing may be obtained. Although it is difficult to summarize all facets of the evaluation of the infertile male, the following algorithms will help in providing a framework. After the initial evaluation, male factor infertility may be generalized into the following

groups: azoospermia; decreased sperm density, motility, or morphology; hypogonadism; and no abnormality (Fig. 35.11). This categorization allows the clinician a method for obtaining pertinent information, to translate this information into a useful therapeutic plan, and to convey this information in a meaningful fashion to the patient.

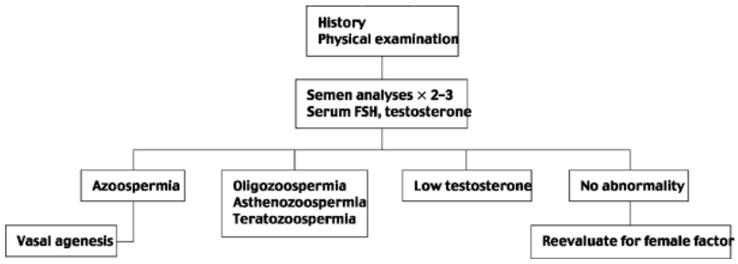

FIGURE 35.11. Algorithm for evaluation of azoospermia. FSH, follicle-stimulating hormone.

Evaluation of the Azoospermic Male (Fig. 35.12)

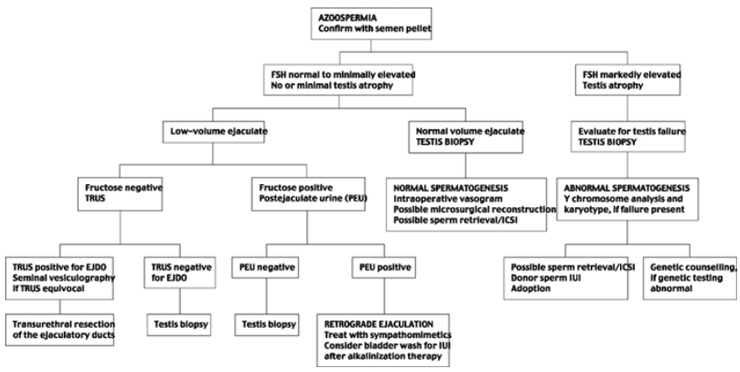

FIGURE 35.12. Algorithm for evaluation of impaired semen parameters. FSH, follicle-stimulating hormone; EJDO, ejaculatory duct obstruction; ICIS, intracytoplasmic sperm injection; IUI, intrauterine insemination; TRUS, transrectal ultrasound.

Azoospermia on a routine semen analysis should be confirmed by examining a sperm pellet after centrifugation of the specimen. Even the finding of rare sperm has significance with ICSI. Consideration should be given to whether an obstruction or spermatogenic failure is present. A markedly elevated serum FSH level and testicular atrophy suggest spermatogenic failure. If spermatogenic failure is suspected, a testicular biopsy will be diagnostic and potentially therapeutic when sperm harvesting is successful. If the couple is considering ICSI, a Y chromosome analysis for microdeletions and a karyotype analysis may identify an underlying genetic defect in up to 17% of men (353). Genetic counseling should be offered to those couples with abnormal genetic testing. If sperm can be identified on testicular biopsy or in the semen pellet, ICSI is an option. Other couples may choose donor sperm intrauterine inseminations or adoption based on financial and personal preference.

If an obstruction is suspected, the volume of the ejaculate and perhaps a fructose determination will determine the direction of the evaluation. If the volume is normal, an obstruction within the vas deferens or epididymis may be present. A testis biopsy will confirm the presence of active spermatogenesis. The site of the obstruction may be identified with a vasogram performed at the same time as microsurgical reconstruction. If sperm are identified, the couple should be offered cryopreservation.

If the ejaculate volume is low, an ejaculatory duct obstruction or retrograde ejaculation may be causative. A postejaculate urine (PEU) will definitively determine the presence of retrograde ejaculation, which may be initially treated with sympathomimetic agents. Sperm within the bladder may be used for intrauterine insemination. If the PEU contains no sperm, a testis biopsy will be necessary to determine the underlying problem.

If the semen volume is low or the semen fructose (produced by the seminal vesicles) is absent, an ejaculatory duct obstruction should be suspected. Transrectal ultrasound (TRUS) is the method of choice for evaluating the prostate for an obstruction. Dilated seminal vesicles are typically present with an obstruction. If the TRUS findings are equivocal, seminal vesicle aspiration and vesiculography will provide a definitive answer. Ejaculatory duct obstructions may be successfully treated with a transurethral resection.

Vasal agenesis is diagnosed with physical examination and can usually be confirmed with TRUS of the seminal vesicles. Other clinical clues include azoospermia and a low-volume ejaculate. Further details are provided in the section on genetic evaluation.

Abnormal Density, Motility, and Morphology (Fig. 35.13)

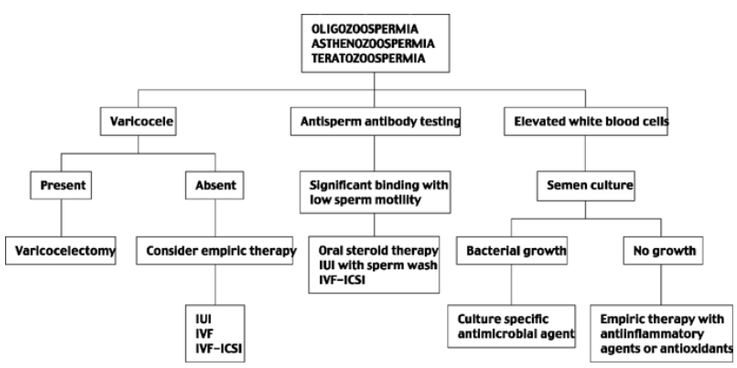

FIGURE 35.13. Algorithm for evaluation of a low serum testosterone level. IUI, intrauterine insemination; IVF, *in vitro* fertilization; IVF-ICIS, *in vitro* fertilization with intracytoplasmic sperm injection.

The differential diagnosis of abnormal semen quality includes the presence of a varicocele, presence of antisperm antibodies or WBCs, or no identifiable cause. The varicocele represents the most commonly identifiable anatomic abnormality associated with impaired semen parameters. In the absence of other significant causative factors, varicocele repair may be offered to the patient. If a varicocele is not present and the semen quality cannot be otherwise improved, intrauterine insemination (IUI), IVF, and IVF with ICSI (IVF-ICSI) may be offered to the couple. For IUI, the semen specimen is first processed using one of a variety of sperm-washing techniques. In general, best results for pregnancy outcome are obtained if the total number of motile sperm inseminated is greater than 5×10^6 and if the woman is

treated with controlled ovarian hyperstimulation (62,105,176). A minimum of 500,000 to 1,000,000 motile sperm are necessary. As a general rule of thumb, sperm-washing procedures will remove approximately 50% of motile sperm from the semen specimen. IVF is optimal for female factor infertility, when the male factor is relatively normal. The indications for IVF-ICSI are discussed in detail later in this chapter.

The presence of antisperm antibodies can be determined in serum or semen by a variety of techniques (288). The immunobead test (IBT) is currently the antibody assay of choice in most laboratories and is considered positive when the antihuman Ig second antibody (bound to a bead) attaches to its target antibody on the surface of a swimming sperm as noted by bead attachment to the sperm on a microscopic slide. The percentage of motile sperm with visibly bound beads is then scored by IgG or IgA binding and by location of bead binding (58). Although each laboratory has its own criteria of percent binding necessary to achieve clinical significance, most consider clinically positive levels to be greater than 15% to 20% bound. Fertility potential declines as the antisperm antibody titer in the seminal plasma increases or if there are any antisperm antibodies in the seminal fluid (264). Measurement of antisperm antibody titers in the man's serum, the indirect method, is not routinely performed because it is the seminal plasma levels that are significant. Treatment of significant antisperm antibodies is most effectively addressed with IVF-ICSI.

When elevated seminal WBCs are present, a semen culture should be obtained. It is important to distinguish round cells, which may represent immature germ cells, from WBCs. Culture-positive semen may be treated with antimicrobial agents. Culture-negative WBC elevations may be treated with antiinflammatory agents and antioxidants, although demonstration of a clear benefit is still being determined.

Isolated abnormal seminal parameters occur in 37% of all patients with infertility and include low or high volumes, hyperviscosity, impaired motility or forward progression, and low sperm density. Patients may have an isolated disturbance or a combination of abnormalities in any of these parameters. Motility disorders are the most common (26%) isolated abnormality (Table 35.9) (247).

Azoospermia	8
Predominance of single abnormal parameter	37
Motility	26
Agglutination	2
Asthenospermia	24
Volume	2
Morphology	1
Oligozoospermia	8
All parameters normal	55

Lipshultz LI. Infertility and sterility. In: Kaufman JJ, ed. *Current urologic therapy.* Philadelphia: Saunders, 1980: 454, with permission.

TABLE 35.9. DISTRIBUTION OF SEMEN ABNORMALITIES IN 200 PATIENTS (%)

When isolated bulk parameters are being evaluated, a simple first step is to measure the semen volume. When

semen volume exceeds 5.5 mL, sperm washing and concentration followed by IUI can be considered. If, however, the ejaculate volume is less than 1 mL, a collection error or retrograde ejaculation and the possibility of ejaculatory duct obstruction must be ruled out. Low volumes may also represent a rare hypoandrogenic state in which endocrine replacement therapy may be of benefit. Decreased ejaculate volumes may also be treated with IUI following seminal fluid washing. If viscosity is abnormally high, sperm processing with chymotrypsin should be considered.

Hypogonadism (Fig. 35.14)

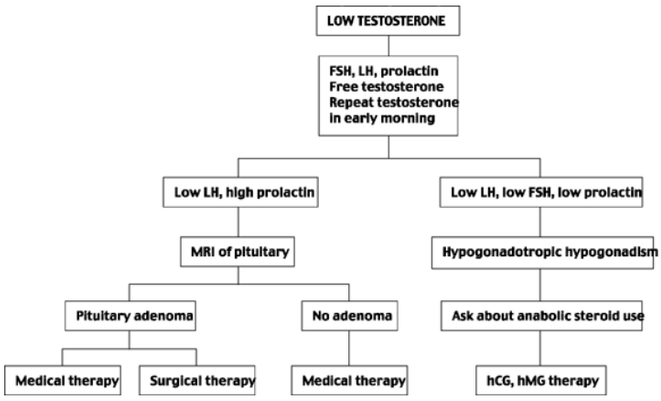

FIGURE 35.14. Algorithm for evaluation of vasal agenesis. FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging.

A low testosterone level should be reconfirmed with a testosterone level in the early morning, when testosterone levels are the highest. To minimize the effect of GnRH pulsative activity on testosterone secretion, a common method is to obtained a pooled sample over 30 minutes. A free testosterone, FSH, LH, and prolactin should also be drawn. When FSH and LH are both decreased, this pattern is consistent with hypogonadotropic hypogonadism and may be associated with deficiencies in other pituitary hormones (panhypopituitarism) or as an isolated impairment in GnRH secretion. A history of anabolic steroid abuse should be identified. Replacement therapy with human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG) should be initiated (see section on medical therapy). The decrease in gonadotropins may also be secondary to a pituitary tumor with an associated increase in serum prolactin. If the prolactin level is elevated or if there is clinical evidence of a pituitary tumor, further pituitary evaluation is indicated. This should include evaluation of serum levels of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and growth hormone (GH) and magnetic resonance imaging (MRI) of the sella turcica.

No Abnormality

Some infertile men have “normal” bulk parameters in the routine semen analyses. If careful evaluation of their wives has revealed no abnormalities, or if problems adequately treated do not result in a pregnancy, more sophisticated testing of sperm function is in order. These men may then be evaluated through such tests as the sperm penetration assay (SPA) (hamster test) (475) or *in vitro* sperm migration through cervical mucus (13). If the sperm penetration assay is “normal,” further evaluation of the female factor is in order; if the sperm penetration assay is “abnormal,” reevaluation of the male factor should be undertaken.

Diagnostic Procedures

Transrectal Ultrasonography and Ejaculatory Duct Obstruction

Men with ejaculatory duct obstruction typically seek treatment initially because of primary infertility and azoospermia or severe oligoasthenozoospermia. Perineal pain and discomfort, hematospermia, pain with ejaculation, and epididymal pain have also been reported (458). Absolute indications for performing TRUS include low-volume azoospermia in the absence of testicular atrophy and low-volume severe oligoasthenozoospermia, when retrograde ejaculation is not present. A caveat is that although low-volume ejaculates are often present, a low normal-volume ejaculate does not exclude an ejaculatory duct obstruction (65). Another absolute indication for performing TRUS is the presence of a midline cyst or asymmetry palpated on digital rectal examination.

When an ejaculatory duct obstruction is suspected, TRUS should be the initial diagnostic modality (471). Previously, vasography, which is still considered the gold standard test, had been the only reliable way to evaluate a distal ductal obstruction. The invasive nature of vasography, with its attendant risk for vasal scarring, makes TRUS the ideal screening test. Although endorectal coil MRI can provide a highly detailed anatomic depiction of the pelvis, because of lesser costs and wider availability, TRUS remains the procedure of choice for imaging the ejaculatory ducts and prostate.

The ejaculatory duct measures approximately 4 to 8 mm in diameter with a 2-mm lumen (338) and may be difficult to image in its typically nondilated state. The ejaculatory duct is formed by the confluence of the seminal vesicle and the terminal ampullary portion of the vas deferens. The ampulla of the vas deferens can be imaged in both the transverse and sagittal planes. They appear as a pair of oval, convoluted, tubular structures medial to the seminal vesicles and cephalad to the prostate. The obstructed lumen of the ejaculatory duct may be best appreciated in sagittal images as a hypoechoic tubular structure entering the urethra at the level of the verumontanum. When dilation is evident, imaging for possible causes of obstruction is advisable (338). Ejaculatory duct cysts, ejaculatory duct calcification, ejaculatory duct dilation, and seminal vesicle dilation visualized on TRUS are all consistent with ejaculatory duct obstruction (Fig. 35.15 and Fig. 35.16).

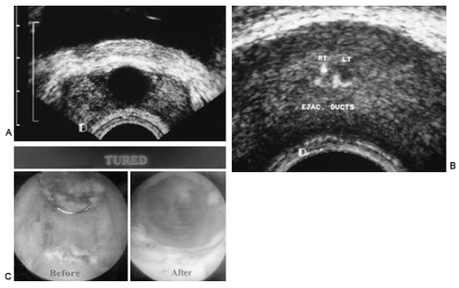

FIGURE 35.15. A: Large ejaculatory duct cyst. **B:** Ejaculatory duct calcifications, more extensive on the right. **C:** *Left panel*– the midportion of the verumontanum and the floor of the prostate distal to the bladder neck have been marked with loop cautery. This area represents the roof of the ejaculatory duct cyst. *Right panel*– after transurethral resection of this ejaculatory duct cyst, a smooth-walled cavity is identified. With further observation, efflux of milky white fluid may be observed.

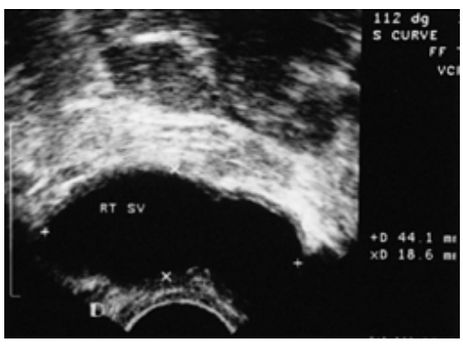

FIGURE 35.16. Seminal vesicle dilation in a patient with an obstructing ejaculatory duct cyst. If the width, 18.6 mm in this case, is greater than 15 mm, ejaculatory duct obstruction should be suspected.

Intraprostatic cysts causing obstruction of the ejaculatory duct may be of müllerian duct, wolffian duct, or prostatic origin. Also known as *utricular cysts,* müllerian duct cysts are midline in location and do not contain sperm. In a series of 150 consecutive infertility patients, Jarow (186) demonstrated an 11% incidence of müllerian duct cysts in contrast to 0% in the control group. Wolffian duct cysts, also known as *ejaculatory duct diverticula,* are also located in the midline. These cysts do contain sperm and may be produced by a distal obstruction of the ejaculatory duct. Prostatic retention cysts are located in the periphery of the prostate and do not contain sperm. Jarow (186) found these cysts in 4 of 150 infertility patients.

The seminal vesicles, which are paired, symmetric, saccular, elongated organs that lie cephalad to the prostate and

posterior to the bladder, should be carefully examined. Best visualized with transverse imaging and having a typical “bow-tie” appearance, they are homogenous with a few fine internal echoes. Serving as reservoirs of seminal fluid, the seminal vesicles have mean dimensions of 3.0 ± 0.8 cm in length, 1.5 ± 0.4 cm in width, and 13.7 ± 3.7 mL in volume (250,338,412). No significant change in volume has been demonstrated after ejaculation (164). The vasal ampulla have a mean diameter of 0.4 ± 0.1 cm and are best visualized in transverse section just medial to the seminal vesicles. Ejaculatory duct obstruction often, but not always, is associated with seminal vesicle dilation. Although obstruction should be suspected in patients with a transaxial seminal vesicle width of greater than 1.5 cm (65,250,274), seminal vesicle dilation does not occur in every patient. Asymmetry, however, should raise suspicions for ejaculatory duct obstruction.

As many as 90% of men with unilateral CAVD will have aplasia of the ipsilateral seminal vesicle, and as many as 20% may have aplasia of the contralateral seminal vesicle (154). In one series of men with CBAVD, 16% had bilateral aplasia of the seminal vesicles, and 21% had unilateral seminal vesicle aplasia and contralateral seminal vesicle hypoplasia (232).

TRUS is indicated in men with severe oligozoospermia and a low-volume ejaculate because a partial ejaculatory obstruction may be present (354). Although a partial ejaculatory duct can cause a low-volume, severe oligozoospermia, a functional ampullovesicular seminal tract disorder must also be considered (84). Patients with partial ejaculatory duct obstructions treated with transurethral resection of the ejaculatory ducts (TURED) had improvement in semen quality in 72% of cases, with 54% of improved men initiating a pregnancy (274).

Ejaculatory Duct Obstruction and Seminal Vesiculography

A recent advance has been TRUS-guided seminal vesiculography for those patients with suspected ejaculatory duct obstruction. The previous test of choice was vasography, an open surgical technique carrying a risk of iatrogenic vasal scarring. An alternative was cystoscopic cannulation of the ejaculatory ducts with retrograde infusion of contrast, a relatively difficult technique. TRUS-guided seminal vesiculography combined with seminal vesicle aspiration can effectively diagnose ejaculatory duct obstruction with substantially lower risks of vasal scarring.

The seminal vesicles may be aspirated using a 35-cm-long, 21-gauge Williams needle (or a 30-cm-long, 17-gauge oocyte retrieval needle). The patient should receive an enema and fluoroquinolone antibiotics before the procedure, in similar fashion to a prostate biopsy. The presence of numerous motile sperm in the seminal vesicles is highly suggestive of obstruction at the ejaculatory duct in men with azoospermia or severe oligozoospermia (187). Because numerous motile sperm are not typically observed in the seminal vesicle aspirate from a normal patient, it is believed that in a complete ejaculatory duct obstruction, sperm can reflux into the seminal vesicles. One report suggests that aspiration should be performed immediately after ejaculation (within the same day), because small numbers of sperm may be found in the seminal vesicles in normal men with just 5 days of abstinence (188). After aspiration, seminal vesiculography using methylene blue and a dilute nonionic contrast may be performed. Fluoroscopy, combined with radiographs after instillation of 5, 10, and 20 mL of contrast, provides ideal imaging. We have found the use of intraoperative flexible cystoscopy helpful in visualizing the egress of methylene blue from the ejaculatory duct. The pelvic and inguinal portions of the vas deferens may be seen in some patient (346).

Vasography

The primary indication for vasography is the assessment of vasal obstruction within the inguinal vas deferens. An inguinal vasal obstruction should be suspected in an azoospermic patient with normal spermatogenesis and a history of prior inguinal or scrotal surgery. In this situation, vasography should be performed only at the time of a potential microsurgical reconstruction.

Another situation in which we perform vasography is during a vasovasotomy or vasoepididymostomy. In these cases, we do not typically use contrast, but, rather, flush 10 mL of saline

toward the prostate. If resistance is encountered, raising suspicions for an obstruction, methylene blue may be added to the irrigating solution, or formal vasography may be performed. Alternatively, a 0 Prolene suture may be gently threaded within the vas deferens toward the prostate. The length of suture passed is used to estimate the site of obstruction.

The open vasogram is performed by creating a hemivasotomy, or partial transection, at the junction of the straight and convoluted portions of the vas deferens. A 25-gauge, 0.5-inch angiocath sheath is gently placed into the prostatic end of the vas deferens and a dilute nonionic contrast injected. One should never inject the contrast toward the epididymis because of the potential for damaging the delicate epididymal tubules. Tilting the table approximately 15 degrees caudally (reverse Trendelenburg) allows the best-quality radiographs to be obtained because the potential blocking effect of the symphysis pubis is avoided. For normal criteria, the reader is referred to a study by Banner and Hassler (25). The presence of obstruction is confirmed by identifying the site of blockage, as well as evidencing resistance to the injection of the contrast. If methylene blue has been added to the nonionic contrast, a small urethral catheter may be placed into the bladder to assess for the blue discoloration if the diagnosis is still in doubt.

If an epididymal obstruction is suspected based on the finding of dilated epididymal tubules and the lack of distal obstruction, an epididymovasostomy should be performed at the same operative setting. If an inguinal vas deferens obstruction is diagnosed, one should proceed with a vasovasostomy. If an ejaculatory duct obstruction is diagnosed, the hemivasotomy site should be closed with standard microsurgical technique. We use interrupted 10-0 nylon sutures for the inner layer, and interrupted 9-0 nylon sutures for the outer layer.

Alternatively, the puncture technique employs a 30-gauge lymphangiogram needle placed through the wall of the vas deferens in the direction of the prostate. Contrast or saline may then be injected distally. In less experienced hands, one risks creating submucosal false passages within the vas deferens if the lumen is not entered properly. The puncture technique and a partial-thickness vasotomy have been compared in a rat model with the findings that fertility studies, vasal patency, sperm granuloma formation, and flow characteristics were roughly equivalent (336).

Sperm Penetration Assay and Mucus Migration Tests

The sperm penetration assay takes advantage of the fact that most of the species' specificity in hamster ova is determined by the zona pellucida, which is easily removed by enzyme digestion. Since its initial description, the SPA (hamster test) has become popular in many clinical research laboratories as an *in vitro* test of sperm function and as a research tool for investigating the mechanism of fertilization. A survey of the available literature, however, reveals wide variability in the techniques and subsequent results reported from individual laboratories (282,303,309,348). Consequently, controversy persists as to what constitutes a negative assay and therefore a truly infertile patient. Although some investigators have arbitrarily set limits of less than “10% penetrated ova” to define an abnormal and, hence, infertile state, a disturbing number of false-negative findings have been detected when this level of discrimination has been used. Optimization of the SPA with very few false-negative results has been reported from our laboratory (202,203 and 204). Whereas other investigators define fertility in the SPA with respect to the percentage of total ova penetrated, our optimized assay conditions provide a more sensitive analysis, which we report as the sperm capacitation index (SCI), or sperm penetrations per hamster ovum. Of those patients who had a favorable IVF cycle (fertilizing at least 31% of the human ova), only 4 of 53 had an SCI less than 5, yielding a false-negative rate of 7%. In addition, of those patients who had a poor IVF cycle (fertilizing less than 31% of the human ova), none had an SCI greater than 5, yielding no false-positives in this group. Furthermore, no pregnancies have resulted from patients with an SCI less than 5.

Although the SPA may furnish important information as to the processes that occur once the sperm reaches the zona-stripped ova, abnormalities that affect migration of the sperm along the female reproductive tract are not taken into consideration. The postcoital test, or Sims-Huhner test, has been used for more than 60 years to measure the ability of sperm to migrate through the cervical canal (299). Unfortunately, because no standards have been established for this type of evaluation, the results may be difficult to interpret. Variations in human cervical mucus such as quantity, pH, or viscosity may impede the ability of sperm to progress through the cervical canal. The discovery that bovine cervical mucus closely resembles human cervical mucus in its biochemical and physiologic properties has allowed the creation of a uniform cervical mucus system, the Penetrak test, for analyzing this aspect of human sperm function. Liquefied semen was placed in a sample cup, and Penetrak tubes were inserted vertically in the cup and incubated for 90 minutes. The distance traveled by the farthest-moving sperm was recorded in millimeters.

Although the Penetrak assay provides reproducible information regarding the ability of sperm to penetrate bovine cervical mucus, it provides no information about the status of the cervical mucus of the patient's partner. The Tru-Trax system is similar in concept, but it can use human cervical mucus. The distance traveled by the farthest-traveling sperm is then evaluated after a 30-minute incubation (299).

Hemizona Assay

The hemizona assay provides a means of assessing the ability of sperm to bind to the zona pellucida of the human egg, a critical step in fertilization (27). This test is of historical significance because of the requirement of human ova and the availability of ICSI. In this assay, the divided halves of an oocyte

are incubated separately with donor and patient sperm. A hemizona index is derived by dividing the number of bound donor sperm by the number of bound patient sperm. Researchers have found that hemizona assay results correlate with IVF rates.

Hypoosmotic Swelling Test

Jeyendran and colleagues (199) reported that under hypoosmotic conditions (150 mOsm/L), a normal spermatozoon will absorb fluid resulting in bulging of the plasma membrane and curling of its tail. This test is based on the principle that a living spermatozoon can maintain an osmotic gradient whereas a dead cell cannot. This curling is readily detected by using phase-contrast microscopy. This simple test measures the physical and functional integrity of the plasma membrane and therefore viability. In an abnormal sample, less than 50% of spermatozoa swell; in a normal one, more than 60% of spermatozoa react. These investigators believe that when performed properly, this test provides functional information independent of other fertility tests and is particularly useful when no swelling is seen, correlating in this instance with very poor IVF results. This assay can differentiate immotile but viable spermatozoa from necrospermia. A practical protocol for performing this test has been described in the WHO manual and by Jeyendran and colleagues (200). This test is now being used with increasing frequency to evaluate the viability of nonmotile frozen sperm that have been thawed (66,251,399) and nonmotile testicular-extracted sperm before selecting specific sperm for IVF-ICSI.

Venography

Venography, if properly performed, offers an objective diagnosis of testicular venous reflux. In experienced hands, venograms nearly always show reflux if a varicocele is clinically present (472). Some series have shown venous reflux in as many as 95% of left spermatic veins and 61% of right spermatic veins (146,380). The fact that many of these men did not have palpable varicoceles raises questions regarding the significance of “subclinical” varicoceles. Venograms are especially useful in the diagnosis of testicular reflux in a patient with ectatic scrotal vessels and persistent infertility after a surgical varicocele repair. In these patients delineation of the venous anatomy can explain the reason for recurrence or unsuccessful primary repair. Embolization of patient veins can provide therapy, as well as diagnosis.

Venography has a relatively low morbidity (284) and can be performed on an outpatient basis, but it is an invasive study. Therefore, until the significance of the subclinical varicocele is further defined, venograms should be employed selectively (i.e., for patients with suspected postsurgical recurrence).

Color Doppler Sonography

In 1991, Petros and associates (330) described the use of color Doppler sonography in the detection of varicoceles and found it to be more sensitive than physical examination in the detection of this lesion. Color-flow Doppler ultrasonography defines the anatomic and physiologic aspects of varicoceles by employing real-time ultrasonography and pulsed Doppler in the same scan. We consider a varicocele significant when it has a diameter of 3 mm or greater and retrograde flow on Doppler ultrasound examination. McClure and colleagues (271) defined a varicocele as the presence of three or more veins, with one having a minimum resting diameter of 3 mm, or an increase in venous diameter with the Valsalva maneuver. Others studies have used 2 to 3 mm as a cutoff (134,145). The reversal of flow characteristic of varicoceles is confirmed by prolonged flow augmentation within a colored flow area depicted as reversing (i.e., changing color) on real-time imaging.

Controversy continues about the clinical significance of varicoceles that can be identified with scrotal sonography but are too small to detect by routine physical examination. The use of high-resolution scrotal sonography, especially color Doppler sonography, may be helpful, however, when the physical examination is equivocal or when patients are suspected of having recurrent varicocele following surgical correction. Color Doppler ultrasonography is superior to the pencil-probe Doppler stethoscope because of a significant false-positive rate with the latter technique (168). The presence of a prolonged venous flow augmentation or reflux, usually detected as a venous rush during the Valsalva maneuver, is considered diagnostic with the pencil Doppler.

TREATMENT

Part of "35 - Male Infertility "

Medical Treatment of Infertile Males

Previously, pharmacologic manipulation was employed empirically and often irrationally for all infertile males for whom there was no surgical remedy or in whom surgical remedies had failed. Today, attempts are first made to identify specifically treatable causes of male infertility (Table 35.10); based on these diagnoses, a specific therapy with a greater likelihood for success can then be chosen. Advances in biochemical and hormonal research in the area of male reproduction and improved methods of artificial insemination with IUI and IVF may be combined with medical therapy to improve a couple's fertility outcome.

Specific Areas of Concern	Empiric Therapy	Drugs of No Proven Use
Inaccurate timing of intercourse	Testosterone rebound	Lithothyronine sodium (Cytomel)
Exposure to gonadotoxins	Gonadotropins (hCG, hMG)	Arginine
Gonadotropin deficiency	Clomiphene citrate	Vitamin E
Congenital adrenal hyperplasia	Tamoxifen	Selenium or zinc
Hypothyroidism	Gonadotropin-releasing hormone	Low-dose oral androgens (fluoxymesterone)
Hyperprolactinemia	Kallikrein	
Genital tract infection	Testolactone	Low-dose corticosteroids
Abnormal ejaculation		
Immunopathology		
Hyperviscosity of semen		

hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin.

TABLE 35.10. MEDICAL THERAPY

Specific Therapy

Endocrine Derangements

Hypogonadotropic Hypogonadism.

This condition is present in fewer than 1% of all infertile males and represents a treatable form of male factor infertility. Hypogonadotropic

hypogonadism may be congenital or acquired. Congenital forms include Prader-Willi syndrome (obesity; hypotonic musculature; mental retardation; small hands, feet, and stature), Laurence-Moon-Bardet-Biedl syndrome (retinitis pigmentosa, polydactyly, hypomentia), and Kallmann's syndrome (delayed pubertal development, anosmia). Acquired etiologies include radiotherapy, pituitary adenoma, and pituitary infarct. Treatment depends on the specific goals of therapy (Table 35.11).

Condition	Treatment Goal	Therapy	Dosage
Adult hypogonadism	Virilization; normal sexual function	Testosterone enanthate or cypionate	200 mg IM q10–14d (androgen replacement)
		Transdermal testosterone (Androderm; Testoderm CIII)	4 or 6 mg testosterone patch on scrotum daily
	Initiation and maintenance of spermatogenesis	hCG	1,000–1,200 IU IM or SC 2–3 times weekly for 12 mo
		Followed by combined administration of hCG plus:	
		hMG or hFSH	75–150 IU IM or SC 3 times weekly for 6–18 mo
		GnRH	2–40 μg SC q2h by infusion pump
Prepubertal hypogonadism (delayed puberty)	Stimulation of growth and puberty	Testosterone enanthate or cypionate	50–100 mg IM monthly, then increase to 50–100 mg IM q2wk, and then to adult replacement
		hCG	1,000–2,000 IU IM or SC weekly initially, then increase to adult replacement
		GnRH	2–40 μg SC q2h by pump infusion

GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; hFSH, human follicle-stimulating hormone; hMG, human menopausal gonadotropin.

TABLE 35.11. TREATMENT OF HYPOGONADOTROPIC HYPOGONADISM

Nachtigall and colleagues (290) have shown that men with adult-onset hypogonadotropic hypogonadism may have fertility restored with long-term therapy with GnRH alone. Fuse and colleagues (131) have similarly demonstrated the efficacy of hCG alone or in combination with GnRH therapy in restoring fertility, especially if severe atrophy was not present. With use of hCG for 3 to 6 months followed by the subcutaneous administration of highly purified urinary FSH in combination with hCG for 18 months, successful induction and maintenance of spermatogenesis was achieved in 25 of 28 men (89%) with primary, complete isolated hypogonadotropic hypogonadism (119).

Hyperprolactinemia.

Although not a common finding, hyperprolactinemia can contribute to male factor infertility. Segal and colleagues (379) reported that 4% of subfertile men in their series had elevated prolactin levels. All individuals noted to have significant hyperprolactinemia should undergo computed tomography or MRI evaluation of the pituitary to rule out the presence of a pituitary tumor. Elevated serum prolactin levels impair reproductive function via a negative influence on the hypothalamic secretion of GnRH and by disrupting LH binding to the Leydig cells in the testes. Causes of hyperprolactinemia include pituitary tumors, hypothyroidism, liver disease, and central nervous

system–acting drugs such as the phenothiazines and the tricyclic antidepressants. Normally, the release of prolactin is inhibited by the catecholamine dopamine. Thus the dopamine agonist bromocriptine may be administered to restore normal gonadal function in these patients. The usual dosage is between 2.5 and 10 mg per day, usually given in two to four divided doses. Although bromocriptine, introduced in 1971, is the reference preparation against which newer dopamine agonists are compared, up to 12% of patients cannot tolerate the drug at therapeutic dosages.

The newest medication used in the treatment of hyperprolactinemia is the long-acting dopamine agonist cabergoline, which requires administration only once or twice weekly. Ferrari and colleagues (122) have shown that cabergoline at a median dose of 1 mg weekly is an effective and well-tolerated form of therapy for patients with a prolactin-secreting macroadenoma. Normalization of prolactin levels was achieved in 82% of newly treated patients.

Congenital Adrenal Hyperplasia.

Although CAH usually manifests in childhood, several cases of infertility secondary to CAH have been reported in adult men (46,438). However, men with untreated CAH may be normally fertile. This disorder is most commonly due to a deficiency in the enzyme 21-hydroxylase, resulting in decreased cortisol secretion and increased production of ACTH. Diagnosis in the normal, sexually mature male can be difficult and depends on the demonstration of elevated levels of serum 17-hydroxyprogesterone and urinary pregnanetriol, as well as a high index of suspicion. Infertility secondary to documented CAH is rare and may be treated with corticosteroids (95,290).

Anabolic Steroid Abuse.

Anabolic steroids act as male contraceptives and are becoming more widely abused by athletes. Although little is known about anabolic steroid–associated male infertility, this is a treatable form of drug-related testicular failure (191). Turek and colleagues (435) reported on an azoospermic bodybuilder with a 5-year history of steroid use who underwent successful gonadotropin replacement and conception 3 months after therapy was initiated. This particular patient's sperm density, despite having markedly atrophic testes, around the time of conception was 26×10^6 sperm/mL with 60% motility. After discontinuation of all anabolic steroids, a suggested regimen is hCG, 2,000 units three times weekly for 4 weeks, followed by hCG, 3,000 units three times weekly for 3 months, based on the gonadotropin and testosterone response. Human menopausal gonadotropin may be added after 1 month of hCG therapy. Tamoxifen (10 mg orally twice a day) may be used to minimize hCG-induced gynecomastia.

Hypothyroidism.

Hypothyroidism is a very rare cause of male infertility. Thyroxine replacement therapy generally restores fertility (69). Hyperthyroidism can also alter spermatogenesis and cause infertility. These conditions are usually obvious clinically, and screening of asymptomatic infertile men for thyroid dysfunction is not currently recommended.

Pyospermia

The significance of elevated concentrations of leukocytes within the semen is that their presence indicates infection or inflammation within the male reproductive tract. Based on the seminal leukocyte concentration, 10% to 20% of male infertility patients may have leukocytospermia. WBCs are deleterious because of their ability to stimulate the release of ROS, thereby inhibiting sperm motility and sperm function. The WHO (473), in its *Laboratory Manual for the Examination of Human Semen,* states that concentrations greater than 1×10^6 WBCs per cubic centimeter are considered elevated, and the ejaculate is termed *leukocytospermic.* However, despite an apparently abnormal threshold level for leukocytes within the semen, a wide range of conflicting evidence exists as to the significance of seminal leukocytes and infertility (12). Once suspected, appropriate leukocyte-specific testing, preferably with a monoclonal antibody technique, should be undertaken.

We evaluate leukocytospermia by obtaining a semen culture and a urethral swab for *Chlamydia, Ureaplasma,* and *Mycoplasma.* Unfortunately, the yield of these diagnostic modalities is low. Wolff and Anderson (468) summarized the semen microbiology in 100 consecutive leukocytospermic ejaculates, and almost 80% of these samples were microbiologically negative. Thus, although it is important to exclude genitourinary pathogens by culture, leukocytospermia appears to be infrequently associated with a positive seminal culture. Although many patients with pyospermia do not have documented infection, Yoshida and colleagues (476) suggested that *Chlamydia trachomatis,* but not *Ureaplasma urealyticum,* infection, as detected with *in situ* hybridization, in the male genital tract correlated well with evidence of inflammation. In the absence of urethritis, most inflammatory cells (granulocytes, lymphocytes, and macrophages) originate from the epididymis, prostate, and seminal vesicles. Clinically silent prostatitis and epididymitis may exist in men without overt symptoms. If either of these conditions is suspected, a bacterial origin must be excluded.

Treatment.

Specific genital tract infections should be identified and treated to prevent scarring to the seminiferous tubules or obstruction of the epididymis. The most common causes of epididymitis in males under age 35 are the sexually transmitted pathogens *Chlamydia trachomatis* and *Neisseria gonorrhoeae.* The treatment of choice for *Neisseria gonorrhoeae* is ceftriaxone 250 mg intramuscularly once plus doxycycline

100 mg orally twice a day for 10 days. When *Chlamydia trachomatis* is present, doxycycline 100 mg orally twice a day for 10 days or ofloxacin (Floxin) 400 mg orally twice a day for 10 days should suffice. An alternative regimen for treating *Chlamydia trachomatis* is tetracycline 500 mg orally four times daily for 10 days. Spectinomycin 2 g intramuscularly may be used in patients who are allergic to cephalosporins. An erythromycin-based product, 500 mg orally four times daily, may be given to patients who are allergic to or intolerant of tetracyclines.

Many clinicians believe that empiric therapy with doxycycline may be warranted in idiopathic infertility characterized by isolated motility impairment. Support for this concept is provided by a study of the effects of doxycycline therapy on men with idiopathic infertility and an abnormal SPA (40). Thirty-two such men were given 100 mg of doxycycline twice daily for 10 days, followed by 100 mg for 10 more days. The pregnancy rate for responders was 33% (6 of 18), and the nonresponders had a pregnancy rate of 7% (1 of 14). However, no controlled studies demonstrate improved pregnancy rates following tetracycline therapy for idiopathic infertility.

Culture-specific antimicrobial agents should be used if routine bacterial cultures indicate significant bacterial growth. Standard course of a fluoroquinolone or trimethoprim-sulfamethoxazole DS for 2 to 12 weeks should be adequate for most infections. Longer treatment courses when a chronic prostatitis is present result in higher eradication rates. Branigan and Muller (54) concluded that antibiotics combined with frequent ejaculation helped provide durable responses at 3 months. Antimicrobial therapy may be used even when cultures are negative, although results are variable. Sperm processing techniques (e.g., the swim-up, swim-down, sedimentation, Sephadex gel filtration) and density gradients have been used to separate the seminal plasma from sperm, as well as associated cellular contaminants from seminal plasma.

Antisperm Antibodies

The presence of semen antisperm antibodies is often associated with impairments of sperm function. However, not all antisperm antibodies interfere with reproduction. The detrimental effect of antisperm antibodies on sperm function is related to impaired penetration of the zona pellucida of the oocyte and to decreased sperm motility, depending on the site of sperm binding. Because of scientific limitations regarding the identification and isolation of distinctly pathogenic sperm antigens, a common initial approach has been to treat the male partner with systemic corticosteroids in an effort to decrease antibody production (382). Admittedly, this approach is highly controversial. Our regimen has been to use prednisone 20 mg orally every day for weeks 1 to 3, then 10 mg orally every day during week 4.

The risks of mood changes, altered glucose metabolism, aggravation of peptic ulcers, acne, and aseptic necrosis of the hip must be discussed with the patient and prescribed cautiously by an expert. However, with a short course of therapy in typically healthy young men, the risks are small. A second monthly course of prednisone is administered to those who fail to demonstrate a decrease in the quantity of antibodies or an improvement in the semen analysis. Large, placebo-controlled studies using corticosteroid therapy are lacking. Alexander and colleagues (14) administered 60 mg of prednisone for 7 days and observed a decrease in antisperm antibodies and a pregnancy rate of 37% (7 of 19) versus 25% (3 of 12) in the placebo group. Similarly, Haas and Manganiello (152) found a pregnancy rate of 15% (3 of 20) with methylprednisolone 96 mg per day for 7 days, versus 7% (1 of 15) in the control. Failure of corticosteroid therapy may lead to the recommendation of sperm-washing techniques for IUI. However, given only limited success in published series of IUIs in the presence of antisperm antibodies, proceeding directly to ICSI with IVF may be most efficacious.

Retrograde Ejaculation

The backward propulsion of seminal fluid from the urethra into the bladder, or retrograde ejaculation, results from failure of the bladder neck to close during ejaculation. Any condition that disrupts the normal sympathetic innervation of the bladder neck, such as retroperitoneal lymph node dissection, diabetes mellitus, previous bladder neck surgery, or spinal cord injury, can cause retrograde ejaculation. Rarely, urethral stricture disease may also be responsible for retrograde ejaculation. Medications used to treat psychoses (e.g., haloperidol) and certain antihypertensive medications (e.g., phenoxybenzamine) may result in retrograde ejaculation. The diagnosis of retrograde ejaculation is suggested by an abnormally low-volume ejaculate and is made by examination of the centrifuged postejaculatory urine specimen.

The strategy for treatment of retrograde ejaculation is the use of sympathomimetic agents orally to increase bladder neck tone (Table 35.12) (381). If a single agent is not successful, two agents may be combined. A popular regimen is to start with ephedrine sulfate or pseudoephedrine beginning 1 week before the woman's expected day of ovulation and for 3 days beyond. Intermittent dosing seems to prevent the tachyphylaxis seen in continuous dosing.

Medication	Dosage
Phenylpropanolamine	75 mg b.i.d.
Pseudoephedrine	60 mg q.i.d.
Ephedrine sulfate	50 mg q.i.d.
Imipramine HCl	50 mg q.h.s.

TABLE 35.12. MEDICATIONS USED IN THE TREATMENT OF RETROGRADE EJACULATION

Gilja and colleagues (137) reported on 17 diabetic men who were treated with ephedrine or imipramine (for ephedrine failures) during a 4-week period. Positive results were obtained in 5 of 17 patients (29.3%), specifically, in three

(17.6%) and two (11.7%) patients taking ephedrine and imipramine, respectively. In the group with retroperitoneal lymphadenectomy, after treatment with ephedrine, only one patient (12.5%) had retrograde ejaculation, and the remaining seven patients continued to lack semen emission. These seven patients were treated with imipramine, and three of them (42.8%) achieved antegrade ejaculation. Depending on the agent used and the studies cited, success rates in correcting retrograde ejaculation may be as high as 40% (143).

If these medications fail to reverse the condition, sperm may be harvested from the bladder for use in IUI. Sperm function may be optimized by alkalinizing the urine with sodium bicarbonate, 650 mg four times daily for 1 day before and the day of sperm recovery, and by prewashing the bladder with an appropriate buffered solution [human tubal fluid (HTF)] just before ejaculation.

Empiric Therapy

Treatment of Idiopathic Oligozoospermia

There is no proven effective medical therapy for idiopathic oligozoospermia, although many different drugs have been tried. Many, such as liothyronine (Cytomel), low-dose androgens, zinc, and vitamin C, are clearly ineffective and irrational. However, there are several drugs for which there is a hint of efficacy in selected patients. This therapy is indicated if the male partner in an infertile couple has suboptimal semen quality, no known reversible causes for his subfertile state, and normal gonadotropins and if the female partner has been completely evaluated and optimally treated (260).

Clomiphene Citrate.

Clomiphene citrate is an antiestrogen that causes increased gonadotropin production and, in turn, increased circulating and intratesticular levels of testosterone. Theoretically, clomiphene should not be successful in men with elevated gonadotropin levels. Evaluation of various reports of the efficacy of the drug is difficult because of differences in dosage and treatment intervals and because of associated female pathology. In addition, few studies have been placebo controlled (126,351). Similar limitations apply to the studies of the other drugs discussed in the following sections. Nevertheless, reviews by Sorbie and Perez-Marrero (402) and Allag and Alexander (15) afford certain observations regarding the effects of clomiphene citrate on semen quality and make recommendations regarding optimal dose, duration of treatment, and selection of patients.

Dose Greater Than 100 mg. Dosages of 100 mg per day or more for durations of 1 to 12 months have generally yielded no consistent change in sperm concentration (126,163,241,318) and may decrease sperm density (163) by testicular hyperstimulation. The pregnancy rate was reported as 17% (126).

Dose of 50 mg. A generally favorable effect on sperm density has been noted at this dose given for intervals ranging from 1 to 12 months. Although improved sperm densities were noted in 25% to 60% of oligozoospermic patients (82,153,209,318,363), some investigators report either diminished response or no change in sperm density after administration of clomiphene citrate (19,287). At 50 mg per day for 3 months, Ronnberg and Tuimala (352) achieved a highly significant increase in sperm density in 33 normogonadotropic oligozoospermic males compared with response in a group with elevated serum FSH. Ronnberg (351) noted an overall pregnancy rate of 10%. Charny (70) observed no response to clomiphene citrate in patients who showed multiple abnormal semen parameters and an elevated serum FSH level. At present, there is no firm evidence that this high dose is superior to 25 mg per day.

Dose of 25 mg. Clomiphene citrate 25 mg given cyclically for 25 days with a 5-day rest period, has provided significantly improved results, although a 5-day “rest period” seems difficult to justify scientifically. Studies using this regimen for 6-month intervals have achieved sperm quality improvements in 72% to 92% of patients and have achieved pregnancy rates of 35% to 40% (72,207,322,324,325). Check's 1980 study (72) included patients whose semen parameters failed to improve after varicocele ligation. We have reviewed all available data for clomiphene therapy. Sokol and colleagues (400) have completed a controlled, double-blind study that showed no significant difference in semen parameters, sperm penetration assays, or fertility between the treated group and the placebo group. They concluded that clomiphene citrate is not a useful drug in the treatment of male infertility. Controlled and noncontrolled collated series are presented here for review (Table 35.13 and Table 35.14).

Author(s)	Journal/Date	Dose	Duration	No. of Patients	Favorable Response[a]
Halim, et al.	*Proc R Soc Med,* 1973	50 mg q.d.	2 mo	25	No
Reyes and Faiman	*Int J Fertil,* 1974	1 mg q.d.	3–9 mo	16	Yes
Schellen	*Int J Fertil,* 1974	50 mg q.d.	40–90 days	101	Yes
Paulson, et al.	*Fertil Steril,* 1975	25 mg × 25 days	2–6 mo	22	Yes
Paulson and Wacksman	*J Urol,* 1976	25 mg × 25 days	9 mo	35	Yes
Paulson	*Fertil Steril,* 1977	25 mg × 25 days	6–12 mo	67	Yes
Paulson	*Urology,* 1977	25 mg × 25 days	2–12 mo	32	Yes
Check	*Fertil Steril,* 1977	25 mg × 25 days	2–7 mo	10	Yes
Epstein	*Fertil Steril,* 1977	100 mg × 3/wk	2–9 mo	16	Yes
Homonnai, et al.	*Gynecol Obstet Invest,* 1978a	25–50 mg q.d.	35–60 days	60	No
Paulson	*J Urol,* 1979	25 mg × 25 days	6–12 mo	20	Yes
Emperaire	*Arch Androl,* 1979	50 mg q.d.	100 days	54	No
Ronnberg and Tuimala	*Infertility,* 1979	50 mg q.d.	3 mo	46	No
Charny	*Fertil Steril,* 1979	25–50 mg × 5/wk	1–9 mo	54	No
Ronnberg	*Andrologia,* 1980	50 mg q.d.	3 mo	76	Yes
Ronnberg	*Int J Androl,* 1980	50 mg q.d.	3 mo	30	Yes
Jones, et al.	*J Urol,* 1980	25 mg × 21 days	6 mo	20	Yes
Check	*Fertil Steril,* 1980	25 mg × 25 days	3–16 mo	28	Yes
Ross	*Fertil Steril,* 1980	100 mg × 3/wk	3–15 mo	53	Yes
Newton	*Fertil Steril,* 1980	25 mg × 25 days	—	92	No
Ronnberg	*Int J Androl,* 1981	50 mg q.d.	3 mo	44	Yes
Ronnberg	*Andrologia,* 1981	50 mg q.d.	3 mo	11	Yes
Abel	*Br J Urol,* 1982	50 mg q.d. × 25 days	6 mo	93	No
Ibrahim	*Andrologia,* 1983	50 mg q.d.	2–3 mo	25	Yes
Wang	*Fertil Steril,* 1983	25 mg q.d.	6–9 mo	18	Yes
		50 mg q.d.	6–9 mo	18	Yes
Wang	*Fertil Steril,* 1985	25–50 mg q.d.	6 mo	24	No
Micic	*J Urol,* 1985	50 mg q.d.	6–9 mo	56	Yes
Homonnai, et al.	*Fertil Steril,* 1988	25 mg q.o.d. × 25 days	4 mo	45	Yes
		25 mg q.d. × 25 days	4 mo	44	Yes
Hammami	*Arch Androl,* 1996	25 mg q.d.	7 mo	17	Yes

[a]Favorable response: (a) significant ($p < .01$) increase in mean sperm density (in two cases, mean total count), or (b) 50% or more of patients in a study showed an increased sperm density as defined by the study, or (c) 20% or greater pregnancy ratio.

TABLE 35.13. CLOMIPHENE CITRATE THERAPY

Author(s)	Journal/Date	Dosage	Duration (mo)	No. of Patients	Favorable Response[b]
Halim, et al.[c]	*Proc R Soc Med,* 1973	50 mg q.d.	2	25	No
		Vitamin B_{12}	1.5	16	No
Paulson	*J Urol,* 1979	25 mg × 25 days	6–12	20	Yes
		Cortisone	6–12	20	No
Ronnberg	*Int J Androl,* 1980	50 mg q.d.	3	30	No
		Placebo	3	(Crossover study)	No
Abel	*Br J Urol,* 1982	50 mg × 25 days	6	93	No
		Vitamin C	6	86	No
Wang	*Fertil Steril,* 1983	25 mg q.d.	6–9	11	Yes
		50 mg q.d.	6–9	18	Yes
		Placebo	6–9	7	No
Micic	*J Urol,* 1985	50 mg q.d.	6–9	56	Yes
		No therapy	6–9	45	No
Sokol, et al.	*Fertil Steril,* 1988	25 mg q.d.	12	23	No
WHO	*Int J Androl,* 1992	25 mg q.d.	6	—	No
		Placebo	6	—	No

[a]Conclusion: positive response in 4 of 6 (66%).
[b]Favorable response: (a) significant ($p < .01$) increase in mean sperm density, or (b) 50% or more of patients showed increased sperm density, or (c) 20% or greater pregnancy rate.
[c]Patient population included many with azoospermia.

TABLE 35.14. CLOMIPHENE CITRATE: CONTROLLED STUDIES[a]

Tamoxifen.

As a treatment for male infertility, tamoxifen has been studied only since the late 1970s (462). Because success rates with this agent apparently equal those with clomiphene but without the potential side effects of clomiphene, tamoxifen at a dose of 20 mg per day may be the drug of choice for idiopathic oligozoospermia if use of a pure antiestrogen is desired (368). Although some studies have noted increases in sperm density in 11% to 100% of patients, none has reported a significant increase in motility. Pregnancy rates have ranged from 11% to 40% (61,462). Some reports, however, have refuted the effectiveness of tamoxifen in the treatment of male factor infertility (227,406). Another attractive feature of tamoxifen is that it does not provide even the weak estrogen receptor stimulation noted with clomiphene.

Human Chorionic Gonadotropin

Human Chorionic Gonadotropin Alone. Human chorionic gonadotropin has been used empirically in the treatment of oligozoospermia. The rationale for its use is based on the intrinsic LH-like activity, which may increase the intratesticular concentration of testosterone that is thought to be deficient in these patients. Although the lack of uniform dose and treatment intervals may obviate conclusions regarding its optimal administration, its effect on semen parameters and pregnancy rates is less favorable than that seen with low-dose clomiphene. Overall experience regarding hCG therapy in a number of studies shows a 29% improvement in sperm density, a 42% increase in motility, and a pregnancy rate of 18% (74,169,260,281) (Table 35.15). Of note, Margalioth and colleagues (260) observed deterioration of sperm density and motility in 40%, probably secondary to high levels of estradiol caused by high-doses hCG. Therefore hCG should not be given at high dosages. Human chorionic gonadotropin has been said to be useful in patients with sperm densities of less than 10 × 10^6/mL following varicocele ligation, significantly increasing sperm density and pregnancy rates in this severely oligozoospermic group (111). However, this study was uncontrolled and has not been confirmed by a controlled study.

Author	Journal/Date	Dosage	Duration (wk)	Number of Patients (*N* = 655)	Favorable Response[b]
Glass	*Fertil Steril,* 1963	5,000 2–3 × wk	4–6	20	Yes
Polishuk	*Fertil Steril,* 1967	Variable	Variable	14	No
Futterweit	*Fertil Steril,* 1968	5,000–10,000 2–3 × wk	10	27	Yes
Dubin	*Fertil Steril,* 1975	8,000/wk	10	50	Yes
Diejomaoh	*Int J Obstet Gynecol,* 1975	10,000 2 × wk	10	50	Yes
		5,000 2 × wk	10	24	Yes
Szollosi	*Int Urol Nephrol,* 1978	1,500 2 × wk	8–12	160	No
Mehan	*J Urol,* 1982	5,000 1–3 × wk	6	128	Yes
Margalioth, et al.	*Fertil Steril,* 1983a	5,000 2 × wk	12–15	47	No
Yamamoto, et al.	*Arch Androl,* 1995	5,000/wk	10	135	Yes

[a]Conclusion: favorable response in 7 of 10 (70%).
[b]Favorable response: (a) significant (p <.01) increase in mean sperm density, or (b) 50% or more of patients showed increase in "semen quality," or (c) 20% or greater pregnancy rate.

TABLE 35.15. HUMAN CHORIONIC GONADOTROPIN THERAPY, 1960–2000[a]

Human Chorionic Gonadotropin Plus Human Menopausal Gonadotropin. Human menopausal gonadotropin has been incorporated in different dosages with hCG in the treatment of idiopathic oligozoospermia. Whereas Schill (367) achieved an increased sperm density in 60% of patients, an increased motility in 40%, and a pregnancy rate of 30%, others (169,386) have noted only a moderate improvement in sperm density and no improvement in pregnancy rates. The total experience of combined hCG–hMG therapy shows improvements in sperm density in 41%, improvement in motility in 34%, and a pregnancy rate of 17%. These data indicate no benefit from the addition of hMG to hCG in the therapy for idiopathic infertility.

Follicle-stimulating Hormone Alone. Acosta and associates (1,2) noted marked improvement in fertilization rates following FSH administration in the treatment of men who were participating in an IVF treatment program and who had severe seminal abnormalities or fertilization failure. It should be noted that this reported improvement in fertilization rates occurred in the absence of an improvement in bulk semen parameters. Similarly, Ben-Rafael and colleagues (38) observed improved fertilization rates in eugonadotropic men who had previous IVF fertilization rates of less than 30% when FSH was administered at least 60 days before the IVF cycle. However, others have found no such improvements (210).

Testolactone.

Testolactone (Teslac), an aromatase inhibitor, prevents the conversion of testosterone to estradiol and thereby minimizes the negative effect of the latter on spermatogenesis. Vigersky and Glass (449) treated ten idiopathic oligozoospermic patients with 100 mg of testolactone daily for 6 to 12 months, noting a significant increase in the ratio of serum testosterone to estradiol, no change in serum gonadotropins, a marked improvement in sperm density in 80% of patients, and a 33% pregnancy rate. Encouraging results were also reported by Vance and Thomer (439) in four oligozoospermic men. Although the exact role of testolactone cannot be determined from this limited experience, the most effective use may be in combination with antiestrogens and other drugs that simulate gonadotropins, because it would limit the downregulatory effect of testosterone aromatization on spermatogenesis. Vigersky and Glass (449) combined testolactone with tamoxifen in

15 oligozoospermic patients for 6- to 12-month periods. Although improvement in sperm density was noted in more than 70% of patients and four pregnancies (27%) resulted, the authors concluded that combination therapy was no more effective than the use of testolactone alone. Clark and Sherins (77) investigated 25 oligozoospermic men in a double-blind, placebo study and found no effect on semen quality or fertility. This study has been questioned because there also was no effect on endocrine parameters, and the average pretreatment total sperm counts were 7.5 million.

Anastrazole (Arimidex, Astra-Zeneca), an oral nonsteroidal aromatase inhibitor used for the treatment of advanced breast cancer, has been used in men with spermatogenic failure and decreased testosterone-to-estrogen ratios. Unpublished preliminary reports suggest benefit, but further study is clearly necessary.

Gonadotropin-Releasing Hormone.

More recently, GnRH has been studied in the treatment of idiopathic oligozoospermia (22). This appears to be a more physiologic agent for increasing the pituitary's production of FSH and LH. However, investigation of GnRH as a therapeutic agent for infertility is still in its early stages, and data are limited. In preliminary studies, increases in sperm count and motility of 67% and 71%, respectively, have been noted, as well as pregnancy rates of 24% (22,439). GnRH has been given using postoperative programmable, portable mini-pumps to men with hypogonadotropic hypogonadotropism (45), and it has been recommended for the treatment of idiopathic oligozoospermia. Thus far, results are inconclusive.

Testosterone Rebound.

Rebound spermatogenesis has been shown to occur after testosterone-induced azoospermia at what has sometimes been described as “an improved level.” Numerous types of preparations and routes of administration have been explored in an effort to supply androgen to the target organs before inactivation by the liver. However, the incidence of failure to return to pretreatment sperm counts following this therapy may be as high as 4% (71). Increases in sperm density have been reported to range from 20% to 70%, with pregnancy rates between 14% and 41% (71,439). The 4% risk of worsening the patient's condition and failure to provide better results than other empiric forms of therapy strongly suggest that this should no longer be considered an effective therapy.

Corticosteroids.

Attempts have been made to stimulate spermatogenesis in idiopathic oligozoospermic patients using corticosteroids. The results of these efforts have been unrewarding: either no change in semen parameters has been noted, or sperm counts have been depressed even further. Mancini and colleagues (258), using 30 mg per day of prednisolone for 1 month, observed decreased sperm counts and spermatogenic arrest on testicular biopsy. McDonald and Heckel (273) noted no change in semen parameters or testis histology in 11 patients receiving 75 mg per day of cortisone for an interval ranging from 23 to 334 days. Uehling (436) reported no change in sperm density or motility in 38 patients treated with 2.5 mg of cortisone four times daily during a 6-month interval. Moreover, cortisone compared unfavorably with clomiphene citrate in patients with idiopathic oligozoospermia (323).

Kallikrein.

Kallikrein, a tissue hormone–releasing polypeptide, causes the release of kinins in male and female genital secretions. In addition to vasodilator effects secondary to smooth muscle relaxation, kinins have been noted to enhance sperm motility (365). Although kallikrein is not available in the United States, European studies have noted that oral administration of the agent resulted in a 67% increase in sperm motility and pregnancy rates of 17% to 38% (170,366). A review of five randomized, placebo-controlled studies of oral kallikrein therapy indicated a statistically significant increase in pregnancy rates among the patients treated with kallikrein (302). Side effects are rare, but kinins may exacerbate epididymal or prostatic inflammation (368).

Pentoxifylline.

Pentoxifylline, a methylxanthine derivative, is in the same pharmacologic class as caffeine and theophylline. Pentoxifylline is more useful clinically than caffeine, because it has a longer half-life and greater water solubility. Used to treat peripheral vascular disease, pentoxifylline has properties that decrease blood viscosity and improve impaired microcirculation. Agents in this class act via the inhibition of phosphodiesterase, generating an increase in intracellular cAMP, which in turn increases intracellular ATP production. It has been proposed that this increase in ATP may enhance sperm motility. Pentoxifylline has been used empirically in treating idiopathic oligozoospermia but has resulted in only a 17% pregnancy rate (369). Perhaps more clinically relevant is the use of pentoxifylline in the treatment of sperm *in vitro.* Treatment of washed sperm with this agent has been noted to increase hyperactivation of sperm among both normospermic and oligozoospermic men (214,270). The actual benefit of the use of pentoxifylline on the fertilization and cleavage rates achieved during IVF procedures remains unclear (425,477). (See Table 35.16 for a comparison of representative studies of the effects of empiric medical therapy on idiopathic infertility.)

Study (Year)	Agent, Dosage	Duration of Therapy (mo)	No. of Patients	Increase in Sperm Count (% of Patients)	Increase in Motility (% of Patients)	Pregnancy Rate (% of Patients)
Paulson, 1977	Clomiphene, 25 mg 25–30 days	6–12	32	NR	NR	41
Charny, 1979	Clomiphene, 25–50 mg/day	3–9	54	8	8	8
Ross, et al. 1980	Clomiphene, 100 mg 3 × wk	3–15	53	66	45	26
Willis, et al. 1977	Tamoxifen, 10 mg/day	6	9	11	NR	11
Buvat, et al. 1983	Tamoxifen, 20 mg/day	4–12	25	100	0	40
Vigersky and Glass, 1981	Testolactone, 1,000 mg/day	6–12	9	89	0	25
Homonnai, et al. 1978a	hCG, 2,500 IU 2–3 × wk	1.0–1.5	117	11	22	9
Chehval and Mehan, 1979	hCG, 5,000 IU/wk	1.5	64	69	69	36
Aparicio, et al. 1976	GnRH, 100–500 mg/day	1.0–4.5	21	67	71	24
Charny and Gordon, 1978	Testosterone enanthate or cypionate, 200 mg/wk	6–12	255	52	NR	25
Schill, 1979	Kallikrein, 600 KU/day	2	90	NR	NR	38
Schill and Michalopoulos, 1984	Pentoxifylline, 1.2 g/day	3–6	29	NR	NR	17
Comhaire, 1990	Testosterone undecanoate, 240 mg/day	6	25	NS	NS	4
Gerris, et al. 1991	Mesterolone, 150 mg/day	12	52	NR	NR	26

GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; KU, kallikrein units; NR, not reported; NS, no significant change.
Modified from Lipshultz LI, Kessler DL. Evaluation and treatment of male infertility. *Monogr Urol* 1986;7(April/May):46, with permission.

TABLE 35.16. REPRESENTATIVE STUDIES OF THE EFFECTS OF EMPIRIC MEDICAL THERAPY ON IDIOPATHIC MALE INFERTILITY

Antioxidants

Because high levels of ROS have been identified in the semen of up to 40% of infertile patients (183) but are not typically detectable in normal volunteers and azoospermic men, they have been implicated as a cause of idiopathic infertility (6). ROS have been linked with reduced fertility in men with varicoceles (8,238,269), spinal cordinjury (100),

and immunologic infertility (479). Elevated ROS levels have been correlated with abnormal sperm concentration, motility, and morphology (4,8,342).

Ros are produced by sperm as a normal physiologic process and are important mediators of normal sperm function, capacitation, and the acrosome reaction (99). However, pathologic states associated with a positive oxidative stress are created when an increased production of ROS occurs, rather than a decreased degradation of the ROS. It is likely that a significant amount of ROS-scavenging activity is provided by seminal plasma. The principal sources of ROS production are spermatozoa and leukocytes, which are capable of producing massive amounts of ROS (6). ROS damage spermatozoa by attacking the sperm membrane and causing lipid peroxidation by a chain reaction mechanism. Aitken and colleagues (10) have provided evidence that ROS may cause DNA damage in spermatozoa, thereby potentially causing problems in offspring conceived through ICSI.

Similarly, sperm-washing techniques, especially those involving repeated centrifugation, can result in significantly higher ROS levels. When centrifugation speeds of 200 to 500 G are used, ROS-negative specimens may become positive (384). More important, prolonged centrifugation time can increase ROS generation. The most effective techniques to minimize ROS generation appear to be Percoll washes and sperm swim-up methods.

The use of antioxidants in men with elevated ROS levels is an area of active investigation. During sperm preparation for IUI or IVF, steps such as using an antioxidant-supplemented culture medium (54) and removing contaminating leukocytes (55) appear to be beneficial. The use of oral antioxidants such as α-tocopherol (vitamin E) and ascorbic acid (vitamin C) also have shown mixed results (409). In a double-blind, randomized, placebo crossover–controlled trial using oral vitamin E or placebo for 3 months, Kessopoulou and colleagues (218) determined that although semen analyses were unchanged, the zona binding test, a functional assay, was significantly improved with vitamin E administration. In a randomized, placebo-controlled, double-blind study, Rolf and colleagues (349) investigated whether high-dose oral treatment with vitamins C (1,000 mg per day) and E (800 mg per day) for 56 days was able to improve semen parameters of infertile men with asthenozoospermia. No difference was found in semen profiles, and no pregnancies were initiated.

Glutathione also has antioxidant activity by its actions as a free radical scavenger. In a 2-month, placebo-controlled, double-blind, crossover trial of 20 infertile patients with dyspermia associated with unilateral varicocele or germ-free genital tract inflammation, patients received either glutathione (group 1) or placebo (group 2) for 2 months, then crossed over to the alternative treatment for an additional 2 months (238). The authors found that glutathione therapy demonstrated a statistically significant positive effect on sperm motility and morphology.

Carnitine

The introduction of proXeed has stimulated widespread interest in the use of carnitine for oligoasthenozoospermic men.

L-carnitine and acetylcarnitine are highly polar, water-soluble, small quaternary amine vitamin-like compounds. Acetylcarnitine is important for membrane stabilization. L-carnitine and acetylcarnitine play a fundamental role in intracellular energy metabolism through the transportation of activated acyl groups and helps balance fatty acid oxidation and synthesis. In epididymal fluid, L-carnitine is present at a concentration 2,000-fold greater than that present in blood plasma. In normal human seminal plasma, approximately 50% of total L-carnitine exists as acetylcarnitine.

Uncontrolled clinical studies have demonstrated that L-carnitine (3 g per day) and acetylcarnitine administered orally for up to 6 months significantly increased sperm motility, sperm count, median sperm velocity, and rapid linear sperm progression in patients with idiopathic asthenozoospermia. Costa and colleagues (87) studied 100 patients receiving 3 g per day of oral L-carnitine for 4 months. Sperm parameters were studied before, during, and after this treatment. The results of the study indicate that L-carnitine is able to increase spermatozoal motility, quantitatively and qualitatively: percent motile spermatozoa increased from 26.9% ± 1.1% to 37.7% ± 1.1% (p<001); percent spermatozoa with rapid linear progression increased from 10.8% ± 0.6% to 18.0% ± 0.9% (p <.001); and linearity index increased from 3.7 ± 0.1 to 4.1 ± 0.1 (p <.001). An increase in spermatozoal output was also observed: total number of ejaculated spermatozoa increased from 142.4 ± 10.3 × 10^6 to 163.3 ± 11.0 × 10^6 (p<.001).

Similarly, Vitali and colleagues (451) observed a favorable effect on sperm motility and rapid linear progression in 37 out of 47 patients treated. Moncada and colleagues (283) administered acetylcarnitine at 4 g per day for 60 days and found no effects on sperm density and total motility, but a significant increase in progressive sperm motility (21.7% ± 3.2% versus 38.2% ± 4.7%). This parameter returned to basal value 4 months after therapy discontinuation. Five pregnancies occurred during treatment and only two during the 4-month follow-up after therapy discontinuation. Both L-carnitine and acetylcarnitine have been well tolerated. At present, placebo-controlled studies are being performed.

Surgical Treatment of Male Infertility

Varicocele Repair

The etiology of a scrotal varicocele is related to the specific and unique venous drainage of the testis, a mechanism that also allows for alternative drainage routes following varicocele ligation. The major draining route of the left testis, where varicoceles are more commonly found, is via the left internal spermatic (gonadal) vein, which directly enters the left renal vein. The left internal spermatic vein is 8 to 10 cm longer in its vertical course than the right internal spermatic vein, which enters the inferior vena cava below the right renal vein. The result is greater hydrostatic pressure in the left drainage system, especially in a person in an upright position. In conjunction with the absence or incontinence of venous valves in the proximal left spermatic vein, this increased pressure head predisposes the patient to left-sided varicocele formation. Secondary venous drainage routes of effluxing blood from the testis are via the deferential vein to the superior vesicle vein and via the cremasteric (external spermatic vein) to the pudendal vein. These systems provide for venous drainage after varicocele repair but may also be involved in recurrent varicocele formation after a standard varicocele ligation if refluxing alternate venous pathways are missed.

Abnormal testicular function in patients with varicoceles has been variously attributed to elevated testicular temperature, hypoxia secondary to venous stasis, hormonal imbalances, or reflux of renal or adrenal metabolites or both. Research is available, however, to both support and disprove most of these theories. The work of Saypol and colleagues (359) gives support to the theory that increased heat leads to reversible pathophysiologic changes in the testes of animals with surgically created varices. The most common indications for varicocele repair in the adult are impaired semen parameters and the presence of testicular atrophy. Varicocelectomy may also be helpful for the painful varicocele (329). The indications for adolescent varicocele repair are discussed in the pediatric section.

There are three basic surgical approaches to ligation of the internal spermatic vein: scrotal, retroperitoneal, and inguinal. We do not favor the scrotal approach, because the spermatic veins in the scrotum are multiple (pampiniform plexus); the procedure consequently requires more time, and it is difficult to be certain that all of the involved tributaries have been interrupted. In addition, it is possible to damage all three major sources of blood to the testis and epididymis: the spermatic, the deferential, and the cremasteric arteries. On the other hand, proponents of this approach believe that it offers the possibility of a more complete operation by permitting ligation of veins that may not anastomose with the internal spermatic vein and thus may reduce the failure rate. This procedure does not seem rational when compared with alternative techniques.

The two eponyms usually associated with the higher division of the scrotal veins are the Ivanissevich procedure (182) and the Palomo procedure (317). Palomo originally took a high retroperitoneal approach. Subsequently, the techniques have been modified so that in some descriptions the only difference between the “modified Ivanissevich approach” and the “modified Palomo approach” is in the name. To avoid eponyms, we will describe the “high ligation” versus the “low ligation” (inguinal approach) for varicocele correction. A mini-Doppler probe and a topical vasodilator (papaverine or lidocaine) aid in the identification of the spermatic artery. Use of an operative microscope can be helpful for precise identification of arteries, lymphatics,

and the dilated spermatic veins (142), but magnifying loupes should be used at a minimum. Microsurgical varicocele repair results in lower rates of recurrence and hydrocele formation.

For the high retroperitoneal approach, a short transverse incision is made just medial to the anterior superior iliac spine approximately at the level of the internal ring (Fig. 35.17). This approach is commonly used by pediatric urologists for the repair of the adolescent varicocele. The procedure can be performed under local, regional, or general anesthesia. The external oblique fascia is incised in the direction of its fibers; the internal oblique muscle is retracted caudad with an abdominal retractor. The dilated vein is usually adherent to the reflected peritoneum and is often easily identified without any further dissection. The vein is then freed from the surrounding fat by blunt or, preferably, sharp dissection. The dissection is taken up toward the renal vein, as high as is convenient, so that anastomosing collaterals can be found. The vein is then ligated, and a segment may be removed. The area is inspected for additional veins, with care taken not to divide the artery. The vas deferens can often be found at the lower medial aspect of the incision as it curves into the pelvis. The internal oblique is tacked back in position, and the external oblique is closed with nonabsorbable sutures. A subcuticular skin closure is performed for aesthetic reasons and to eliminate the need for suture removal. The procedure is done on an outpatient basis.

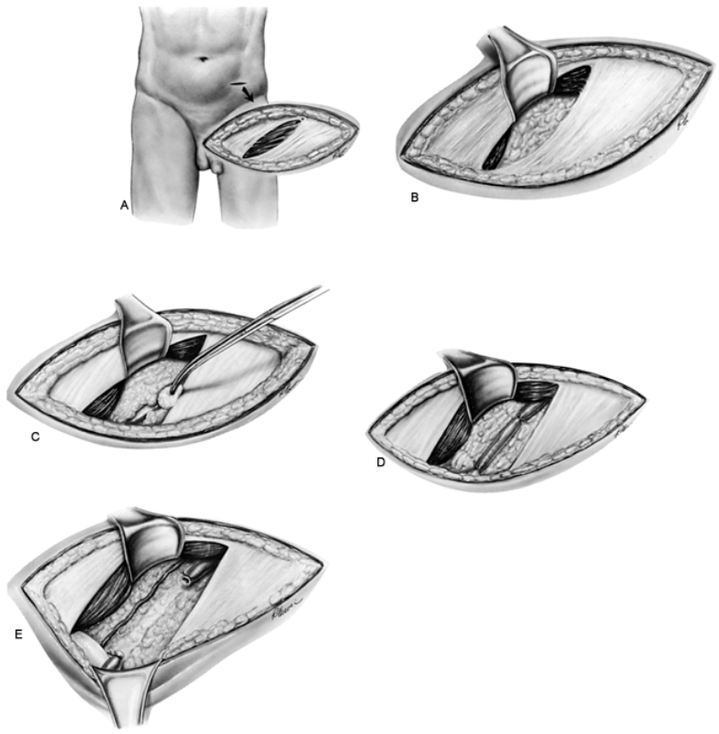

FIGURE 35.17. The high retroperitoneal approach to varicocele repair. **A:** Incision for abdominal approach: a short transverse incision is made just medial to the anterior superior iliac spine approximately at the level of the internal ring. **B:** The external oblique fascia has been incised. The internal oblique muscle is retracted with a Richardson retractor. **C:** The dilated internal spermatic vein, adherent to the reflected peritoneum, is teased away with a Kitner. **D:** The vein is freed from surrounding fat and ligated nonabsorbable suture. **E:** A segment of vein may be removed for identification. (From Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 3. St. Louis: Mosby, 1997, with permission.)

The incision for the inguinal approach (Fig. 35.18) is made two fingerbreadths above the symphysis pubis. The medial aspect of the incision should coincide with the lateral edge of the scrotum. The patient is placed in the reverse Trendelenburg position to fill the veins. The skin incision is carried down to the external oblique aponeurosis, which is divided in the direction of its fibers. After the cord is mobilized, the external spermatic fascia is then incised and the dilated vessels are identified. Each vein is then isolated and doubly ligated with nonabsorbable suture. Excision of a vein segment is not necessary, especially with the placement of a double ligature. Two to three veins are commonly found in the inguinal canal, although four or five may be encountered. It is also important to look for an enlarged cremasteric vein as it courses from the cord at the level of the external ring toward its juncture with the pudendal vein and, ultimately, the saphenous vein. When enlarged, this vein should likewise be ligated and incised, because it may contribute to varices in a small proportion of patients. The external oblique aponeurosis is then closed with interrupted 2-0 polyglactin 910 (Vicryl) or permanent suture, the subcutaneous tissue reapproximated with 3-0 plain catgut, and the skin closed with either a subcuticular or interrupted skin closure using Steri-Strip reinforcements.

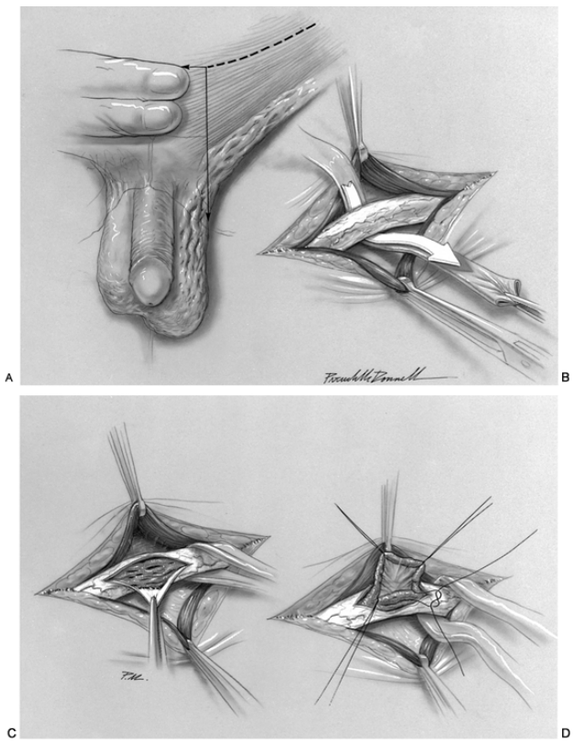

FIGURE 35.18. The inguinal approach to varicocele repair. **A:** An inguinal incision is made two fingerbreadths above the symphysis pubis with the medial aspect in line with the lateral edge of the scrotum. **B:** The external oblique aponeurosis is incised and the spermatic cord isolated with a Penrose drain. **C:** The internal spermatic fascia is stripped from its location surrounding the cord and the veins visualized. **D:** The dilated veins are isolated with vascular forceps and ligated with nonabsorbable suture. (From Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 3. St. Louis: Mosby, 1997, with permission.)

The subinguinal approach is also commonly used. Using this technique, a transverse incision is made at the level of the symphysis pubis so that the spermatic cord may be mobilized just distal to the external ring (263). Complications of these open techniques are minimal but include hydrocele formation, persistence or recurrence of the varicocele, and testicular atrophy (142).

In recent years, percutaneous venographic occlusion has been promoted in the treatment of varicoceles. Once radiographically identified, refluxing internal spermatic veins may be occluded with sclerosing solutions (380), wire coils, or detachable balloons (284). Proponents of this technique support its use as a time- and cost-effective outpatient procedure. Although the cost of outpatient surgery is actually quite comparable, the morbidity of venography is reported to be from 0.5% to 9.0% (284), whereas the reported surgical morbidity is 1% to 3%. However, there is a risk of peripheral migration or embolization of a coil or balloon, as well as the disadvantage of increased radiation exposure. A collection of data from five large series indicated that of 1,894 attempted percutaneous occlusions, 1,469 (78%) were successful (123).

Laparoscopy has been used to correct varicoceles (463,464). However, Hirsch and colleagues (167) showed no superiority of laparoscopic techniques over the standard open subinguinal technique with respect to hospital stay, analgesic requirements, or return to work. Furthermore, laparoscopic techniques require excessive operative time and carry an increased risk of damage to major vascular or abdominal structures. The laparoscopic approach is infrequently used and unlikely to gain in popularity.

Results of surgical varicocele correction are varied. Review of many collated studies indicates that 50% to 70% of surgically treated patients may show some improvement in semen quality, and 30% to 50% may initiate pregnancies within 6 to 9 months after surgery (Table 35.17 and Table 35.18) (248). Although many of these studies have been retrospective, a randomized, prospective, controlled study confirmed that varicocelectomy is an effective treatment for male subfertility (256). In group A of this study, 20 couples with a varicocele were observed for 1 year, and only two pregnancies (10%) were initiated. Those men who were not able to initiate a pregnancy had a varicocele repair, and within 2 years, 12 (66%) were successful in initiating a pregnancy. Meanwhile, 25 men in group B had a varicocele repair immediately. Within the first year, 15 (60%) initiated a pregnancy, and by 3 years, an additional four (16%) were able to father a child. Semen parameters improved in all men who had varicocele repair, regardless of pregnancy occurrence. Semen parameters were unchanged for those men in group A during their 1 year of observation. This important study concluded that the varicocele is associated with reduced fertility and reduced testicular function and that correction improves sperm parameters and fertility rates.

Author (Journal and Year)	No. of Subjects	Improved Semen (%)	Pregnancy (%)
Tulloch (*Br Med J,* 1955)	30	66	30
Davidson (*Practitioner,* 1954)	12	92	41
Scott (*Fertil Steril,* 1962)	93	78	29
Charny (*Fertil Steril,* 1962)	36	64	39
MacLeod (*Fertil Steril,* 1965)	77	74	42
MacLeod (*Fertil Steril,* 1969)	108	74	41
Dubin and Hotchkiss (*Fertil Steril,* 1969)	88	68	30
Dubin and Amelar (*Fertil Steril,* 1971)	111	81	48
Dubin and Amelar (*J Urol,* 1975)	504	71	55
Brown (*Fertil Steril,* 1967)	251	58	41
Glezerman, et al. (*J Urol,* 1976)	51	53	26
Dubin and Amelar (*Urology,* 1977)	986	70	53
Lipshultz, et al. (*Kimbrough Urol Semin,* 1977)	32	70	42
Greenberg, et al. (*J Urol,* 1978)	68	65	
Cockett, et al. (*J Urol,* 1979)	56		25
Cockett, et al. (*Fertil Steril,* 1984)	130	80	46
Hendry, et al. (*Br J Urol,* 1973)	32	69	16
Charny and Baum (*JAMA,* 1968)	104	61	24
Rodriguez-Rigau, et al. (*J Urol,* 1978)	24	54	46
Total:	***N* = 2,793**	***X* = 71**	***X* = 37**

Modified from Lipshultz LI, Kessler SL. Evaluation and treatment of male infertility. *Monogr Urol* 1986;7(April/May):42, with permission.

TABLE 35.17. VARICOCELE STUDIES

Author	No. of Subjects	Mean Preop Sperm Concentration ($\times 10^6$/mL)	Mean Postop Sperm Concentration ($\times 10^6$/mL)	$p < .05$
Laven, 1992	27	47.4	68.9	Yes
Goldstein, 1992	271	37	46.9	Yes
Marmar, 1994	466	16.7[a]	27.3[a]	Yes
Steckel, 1993				
Grade 1	22	38	46	No
Grade 2	44	33	41	Yes
Grade 3	20	18	32	Yes

[a]Median value.

TABLE 35.18. VARICOCELE STUDIES SHOWING PREOPERATIVE AND POSTOPERATIVE SPERM CONCENTRATION

In general, infertile men with a large varicocele have poorer preoperative semen quality, but repair of the large varicocele in those men results in greater improvement than

repair of a small or medium-sized varicocele (403). Varicocele repair may also have demonstrable benefits for azoospermic men with spermatogenic failure. Two recent series have identified improvements in spermatogenic function as evidenced by the presence of sperm in the ejaculate in approximately 50% of men (222,265). Those men most likely to benefit had either severe hypospermatogenesis or maturation arrest at the spermatid stage. Although these couples will still probably require ICSI, varicocelectomy may be considered to produce motile sperm in the ejaculate; avoid more invasive procedures such as testicular sperm extraction, which risk loss of testicular tissue; and allow the possibility that natural, spontaneous pregnancy may occur.

Ductal Obstruction

Occlusion of the excretory ducts of the testis is an important diagnostic entity because of its potential reversibility. The incidence of ductal obstruction among infertile men has been reported as 7.4% (110). The causes of ductal obstruction include congenital absence of the ductal system, ductal stricture following infection, vasectomy, iatrogenic injury, and functional obstruction.

The ductal system may be congenitally absent. Usually, there is an associated absence of the seminal vesicles, ampulla, vas deferens, and a major portion of the epididymis. In males, cystic fibrosis is almost always associated with congenital hypoplasia or absence of these excretory ducts. Because of the absence of seminal vesicles, these patients have, in addition to azoospermia, a low ejaculate volume, semen that does not coagulate at the time of ejaculation, and absence of fructose in the seminal plasma (454).

Stricture of the excretory ducts acquired following infection of these structures may be remediable. Before the antibiotic era, gonorrheal urethritis frequently progressed to an obstructive epididymitis. Currently, gonorrhea is an

unusual cause of male infertility. Vasoepididymal anastomoses may successfully bypass the obstruction and restore normal fertility potential to men with this lesion. Currently, vasectomy is the leading cause of infertility secondary to ductal obstruction.

Classically, the most important hallmark of men with obstruction of the excretory ducts is azoospermia in association with a normal testicular examination. Usually, testis size, Leydig cell function, and serum FSH and LH levels are in the normal range following obstruction of the ducts, although subtle alterations do occur. Ligation of the ductuli efferentes directly adjacent to the testis in rats invariably induces loss of germinal elements within the seminiferous tubules (161). Thus men with complete, longstanding, proximal obstruction may have testicular atrophy.

Vasovasostomy

Technique.

There are many recognized methods for performing a vasovasostomy; none has definitely proved to be superior. The experience of the surgeon is obviously the most important component. We present two techniques for vasal reanastomosis: the first employs a microscope and the second employs optical loupes. The technique of microscopic vasovasostomy was introduced by Owen (310) and popularized by Silber (393). The following equipment is helpful, although significant variations in instruments and technique are present between microsurgeons: an operating zoom microscope with foot pedals to control focus, magnification, position, and zoom; a standard plastic surgery instrument tray; microsurgical instruments, including a 5.75-inch curved Heifetz nonlocking needle holder, two Castro-Viejo suturing forceps with teeth (0.12 mm), two 4.5-inch straight-smooth number 3 jeweler's forceps, and 4.6-inch curved Westcott pointed microscissors; lacrimal duct dilators; a vas deferens approximator clamp; Dermalon 10-0 double-swedged suture on TE-100 needles and Dermalon 9-0 suture on an LE-100 needle (Davis and Geck); an operating table that allows the surgeon to sit comfortably with the knees under the field; biopolar microdiathermy; and a small syringe and needle for irrigation. Alternatively, many experienced microsurgeons prefer to stand during surgery.

With the patient under general, epidural, or local anesthesia, a vertical scrotal incision is made (Fig. 35.19), and the testicle, epididymis, and proximal vas deferens are delivered with the tunica vaginalis intact. A platform of towels can serve as a rest for the surgeon's hands to stabilize them during the microsurgical phases of the operation. The site of the vasectomy is identified. Healthy vasal tissue adjacent to this scarred area is placed on an empty knife blade slot as a groove director and is sharply divided with a scalpel. Alternatively, a nerve cutter can be used. This scarred vasal remnant may be sharply excised or left *in situ.*

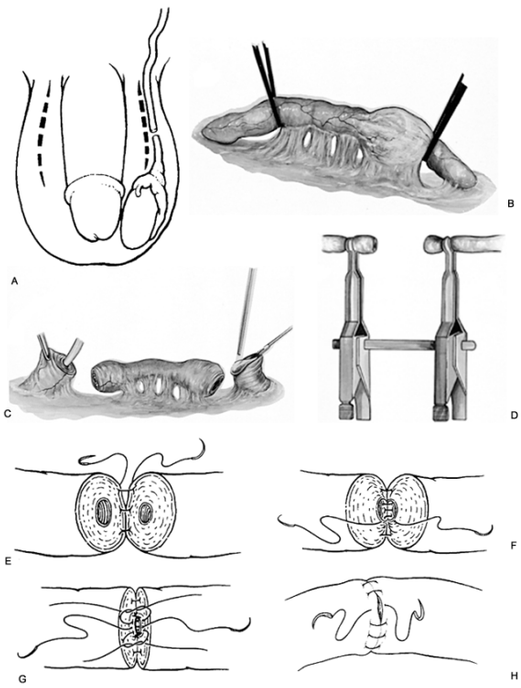

FIGURE 35.19. The microscopic technique for vasovasostomy: strict two-layer anastomosis. **A:** A longitudinal, upper scrotal incision is made. The testis is delivered into the operative field without opening the tunica vaginalis. **B:** The site of vasectomy is identified and isolated. **C:** The proximal end *(right)* of the vas is then incised until fluid is seen. The distal end *(left)* is irrigated with saline via a 25-gauge angiocath sheath to ensure patency of the abdominal end of the vas deferens. **D:** A vasal clamp may be used for approximating the vasal ends. Alternatively, 7-0 PDS sutures in the perivasal tissue may be used for reapproximation of the vasal ends (not shown). **E:** Three 9-0 nylon sutures are placed on the posterior aspect of the outer, serosal layer. **F:** The initial 10-0 mucosal suture is placed at the 6 o'clock position. Another two inner (mucosal) layer 10-0 nylon sutures may then be placed and tied. **G:** The last three “anterior” sutures are tied one at a time after all have been placed. **H:** The outer (serosal) layer is begun anteriorly and requires two to three 9-0 sutures between each of the mucosal sutures. (From Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 3. St. Louis: Mosby, 1997, with permission.)

The fluid is then milked from the proximal (testicular) end of the vasal lumen. The fluid is aspirated using a 25-gauge angiocath and a small syringe, and fluid is immediately transferred by a direct-touch technique to a sterile glass slide and viewed in the operating room. The decision making for whether to perform a vasovasostomy or epididymovasostomy is based on the quality of the fluid (Fig. 35.20). The most desirable finding is actively motile sperm. Any sperm elements found in the fluid indicate patency from the testis to the proximal vas. The finding of fluid without sperm does not mean that an effective vasovasostomy will not eventually occur, but the chances are significantly impaired. The presence of thick, creamy fluid without sperm or the total absence of fluid is a poor prognostic finding and usually indicates an epididymal or efferent duct obstruction, either functional or anatomic. Such individuals are best served by the performance of microsurgical vasoepididymostomy.

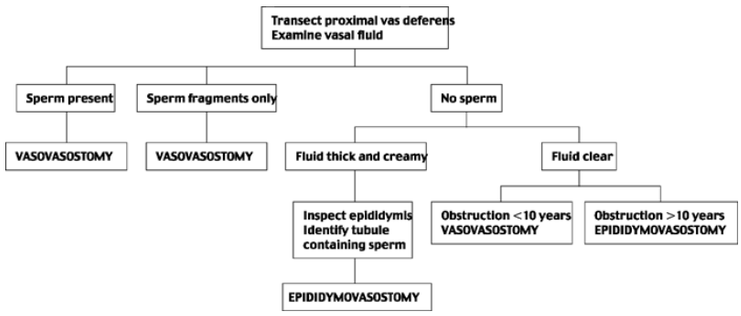

FIGURE 35.20. Algorithm for decision making during vasovasostomy or epididymovasostomy.

The distal (abdominal) end of the vas is prepared in a similar fashion until a normal lumen and a well-vascularized wall are seen. The distal lumen is very gently dilated with jeweler's forceps. The patency of the distal segment may be confirmed quickly and easily by irrigation with saline via a 25-gauge angiocath sheath. Bleeding is carefully controlled with microbipolar cautery. Care should be taken to avoid excessively devascularizing the outer wall of the vas. The two ends of the vas are then placed in a vas deferens approximator clamp. Alternatively, a suture of 7-0 PDS or Maxon can be placed through the perivasal tissue of each end of the vas to bring and hold the two ends in proximity to each other. A strict two-layer anastomosis may then be performed.

Initially, three approximating and stabilizing 9-0 nylon sutures are placed posteriorly through the serosa to include only the most superficial portion of the muscularis (Fig. 35.19). Three 10-0 nylon sutures are placed through the mucosa of the testicular vas at the 6 o'clock position. If using double-armed sutures, the needles may be placed in inside-out fashion on both sides. The sutures are then tied, with care taken to place the knot outside the lumen. These sutures do not enter the lumen and serve to decrease tension on the mucosal sutures. A total of six to eight inner mucosal layer 10-0 sutures should be present at the completion of the inner layer. It is easiest to leave the “anterior” mucosal sutures to be tied at one time, after they have all been placed. The mucosal anastomosis is reinforced with a layer of seromuscular 9-0 sutures that do not enter the lumen. This second layer begins anteriorly and requires two to three sutures between each of the mucosal stitches. The anastomosis is carefully examined to verify the absence of leaks. The testis and epididymis are then replaced within the scrotum, and the dartos muscle and skin are closed in separate layers.

The procedure is done on a day-surgery basis. Patients are able to return to work within a few days but are advised to wear a scrotal support and to avoid heavy lifting and ejaculation for 2 weeks. Three months postoperatively, the semen analysis often reveals a good sperm count with poor

motility. After 6 months, the count is usually stable or slightly improved, and the motility is significantly improved.

Although a strict two-layer anastomosis is preferred by some surgeons (393), there is no convincing evidence that it yields results superior to those of a modified two-layer microscopic anastomosis. An important benefit of the strict two-layer technique is that the discrepancy in luminal diameters between the testicular and abdominal ends of the vas may be minimized. Some surgeons still use optical loupe magnification and a single-layer anastomosis with 8-0 polypropylene, but experts rarely use this approach (Fig. 35.21). In the macroscopic approach, however, both the first and second layers are anastomosed with 8-0 suture, whereas in the microscopic approach, 9-0 suture may be employed for the first layer of the anastomosis.

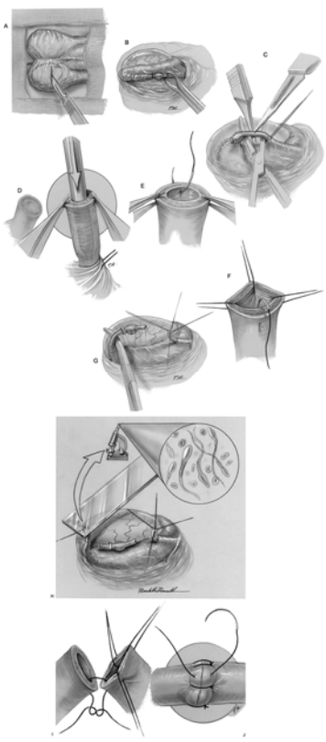

FIGURE 35.21. The macroscopic technique for vasovasostomy: modified two-layer anastomosis. **A:** A transverse scrotal incision is made. **B:** The site of previous vasectomy is identified and isolated with a towel clip. **C:** The vas is incised sharply with a no. 11 blade using the groove of an empty knife handle as a director. **D:** The abdominal vasal stump is dilated progressively with lacrimal duct dilators. **E:** A through-and-through suture of 8-0 polypropylene is placed first in the 6 o'clock position. **F:** Four 90-degree sutures of 8-0 polypropylene are ultimately placed, thus opening the vasal lumen symmetrically. **G:** The testicular vas is likewise isolated. **H:** After the testicular vas is incised, effluent fluid is immediately transferred to a glass slide and checked for the presence of sperm. **I:** Sutures from the abdominal vas are then passed to their corresponding positions in the testicular vas, again creating a four-quadrant (90-degree) anastomosis using a total of four luminal stitches. **J:** Serosal-muscularis sutures of 8-0 polypropylene are also placed between the original four-quadrant stitches to ensure a watertight closure. (From Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 2. St. Louis: Mosby, 1991, with permission.)

The Vasovasostomy Study Group series is the largest multiinstitutional report of vasectomy reversal outcomes (35). During a 9-year period, 1,469 men who underwent microsurgical vasectomy reversal procedures were studied at five institutions. Of 1,247 men who had first-time procedures, sperm were present in the semen in 865 of 1,012 men (86%) who had postoperative semen analyses, and pregnancy occurred in 421 of 810 couples (52%) for whom information regarding conception was available. Important predictive factors for success included time elapsed since vasectomy and quality of fluid from the testicular end of the vas deferens. If the interval had been less than 3 years, patency was 97% and pregnancy 76%; 3 to 8 years, 88% and 53%; 9 to 14 years, 79% and 44%; and 15 years or more, 71% and 30%. The patency and pregnancy rates were no better after two-layer microsurgical vasovasostomy than after modified single-layer microsurgical procedures, and they were statistically the same for all patients regardless of the surgeon. When sperm were absent from the intraoperative vas fluid bilaterally and the patient underwent bilateral vasovasostomy rather than vasoepididymostomy, patency occurred in 50 of 83 patients (60%) and pregnancy in 20 of 65 couples (31%). Neither presence nor absence of a sperm granuloma at the vasectomy site nor type of anesthesia affected results. The length of the testicular end of the vas deferens appears to be another significant predictor of outcome and correlates with the intraoperative status of the vasal fluid. Witt and colleagues (467) reported that testicular vasal remnant length greater than 2.7 cm predicted the presence of fluid with whole sperm present in 30 of 32 testicles (94%), whereas a testicular vasal length of less than 2.7 cm predicted the presence of fluid without whole sperm in 17 of 20 testicles (85%). These fluid findings determine whether a vasovasostomy or vasoepididymostomy should be performed.

The option of sperm cryopreservation at the time of surgery should be offered to all men undergoing microsurgical reconstruction. Motile sperm harvested from the testicular end of the vas deferens or from the epididymis (during an epididymovasostomy) may be used for IVF-ICSI at a later time if the couple is unable to initiate a pregnancy by natural intercourse. Pregnancy and delivery rates using these cryopreserved sperm are comparable with other indications for ICSI (140). Approximately 35% of men undergoing vasectomy reversals will have motile sperm found that can be cryopreserved (31). In general, if only nonmotile sperm are identified, the surgeon should not search more proximally in the vas deferens or epididymis, unless sperm cryopreservation is a primary goal of the surgery. Consideration should also be given to cryopreserving ejaculated sperm after microsurgical

reconstruction because of delayed failure rates. Approximately 10% to 21% of men with sperm appearing in the ejaculate after surgery may have subsequent azoospermia (194,266).

After a failed vasectomy reversal, repeat vasectomy reversals may provide patency and pregnancy rates of 67% to 79% and 30% to 43%, respectively (35,165,266). The likelihood of performing at least a unilateral epididymovasostomy approaches 75% (165,265). It has been recognized that the complete failure of vasectomy reversal usually is due to unrecognized epididymal obstruction at the time of the initial procedure, whereas late failure following initial patency suggests a compromised anastomosis.

Epididymovasostomy.

Epididymal obstruction may require an epididymovasostomy. This obstruction can be iatrogenic, following a vasectomy in which an epididymal tubular rupture (“blowout”) occurs, or due to a congenital lesion in which the distal epididymis is no longer patent and a bypass procedure is needed to circumvent the area of obstruction.

Inflammatory disease of the distal epididymis can also result in epididymal occlusion but is surgically a rare finding. Epididymovasostomy should be performed using a direct epididymal tubule–vasoluminal approach, which requires a microscope and an end-to-side technique. Because the decision to perform a vasovasostomy or epididymovasostomy can only be made intraoperatively, the surgeon must be capable and prepared to perform an epididymovasostomy at the time of microsurgical reconstruction.

The equipment and incision for microscopic epididymovasostomy are the same as for a microscopic vasovasostomy. Because even the slightest patient movement can jeopardize the procedure, we prefer a general anesthesia. If the patient is undergoing vasectomy reversal, the need for epididymovasostomy is indicated by thick, inspissated, vasal fluid with no sperm or the absence of vasal fluid. In the case of a patient who is azoospermic in the absence of previous vasectomy, testis biopsy may be indicated to confirm intact spermatogenesis. After the scrotal contents are exposed and the tunica vaginalis is incised, the epididymis is examined for gross evidence of obstruction. Next, patency of the distal (abdominal direction) vas deferens is confirmed by injecting 5 to 10 mL of saline via an angiocath sheath. Only rarely is a formal vasogram performed with either chromotubation and dye recovered from the catheterized bladder or with contrast material (Renografin 30) diluted 1:2 with saline.

Microscopic anastomosis of the vas deferens to a single epididymal tubule in end-to-side fashion is our preferred approach (Fig. 35.22). The site of probable epididymal obstruction can often be identified by careful inspection of the epididymis under 20× magnification. Dilated epididymal tubules filled with thick, inspissated material contain cellular debris and sperm fragments and are characteristic of an obstructed tubule. A portion of the epididymis just cephalad to such tubules is generally the most appropriate location for the performance of vasoepididymostomy. An appropriate site is identified, and a small portion of the tunica vaginalis is meticulously excised using fine microsurgical scissors, or an ellipse can be excised creating a larger lumen for the end-to-side anastomosis (261). To facilitate the subsequent anastomotic procedure, a minimal amount of tunica vaginalis should be excised. Exposure of approximately two to three loops of epididymal tubule is appropriate. Once a tubule has been selected, it is incised longitudinally using either a microsurgical blade or fine microsurgical scissors. Alternatively, an 11-0 suture may be placed at the apex of the tubule. This suture is gently lifted to tent up the tubule, which is then excised with microdissection scissors. The fluid emerging from the tubular lumen is then sampled and inspected under the microscope for the presence of sperm. The presence of intact sperm indicates epididymal patency and signifies an appropriate location for epididymovasostomy.

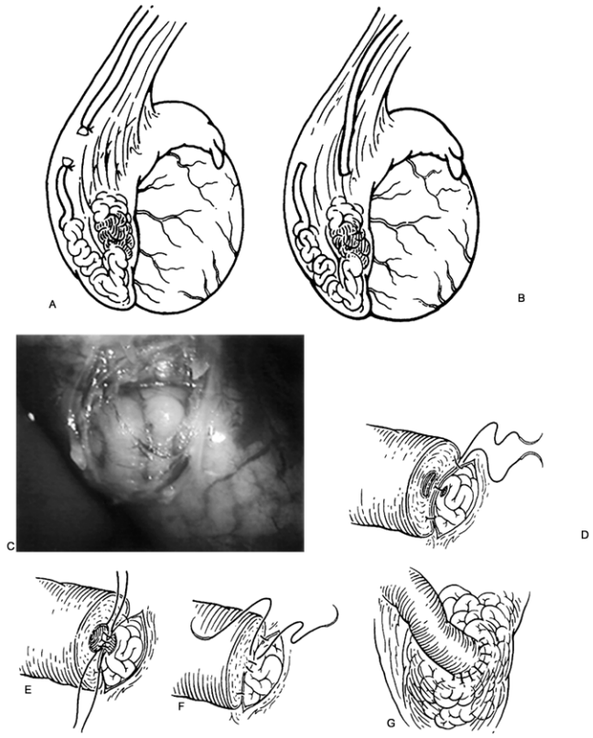

FIGURE 35.22. The microscopic end-to-side technique for epididymovasostomy. **A:** A secondary obstruction in the epididymis may develop after a vasectomy. This blockage may also occur after trauma, infection, or inflammation. **B:** The abdominal portion of the vas deferens must bypass this epididymal obstruction by being approximated proximal to the blockage. **C:** The epididymal tunic must be carefully opened to identify dilated tubules. **D:** The outer (serosal) layer of the vas deferens is secured to the epididymal tunica using interrupted 9-0 nylon sutures. The fluid from the opened epididymal tubule has been sampled for the presence of whole sperm. **E:** Two to three 10-0 nylon sutures are placed posteriorly between the inner layer of the vas deferens and the epididymal tubule. These sutures are tied down. **F:** Two to three more 10-0 nylon sutures are placed anteriorly and tied. **G:** The outer layer of the vas deferens is sutured with interrupted 9-0 nylon sutures to the epididymal tunica to complete the epididymovasostomy.

The vas deferens is then mobilized adequately to allow approximation to the selected portion of the epididymis. During this procedure, it is important to avoid devascularization of the vas deferens, which may contribute to future scarring and failure of the reconstructive procedure. The vas deferens is anchored to the most superficial aspect of the visceral layer of the tunica vaginalis with a 7-0 monofilament suture. This approximation is critical to avoid undue tension on the subsequent sutures. During this portion of the procedure, great care must be taken not to injure or compromise the underlying epididymal tubule. A two-layer microsurgical anastomosis is then performed. One or two 9-0 nylon sutures are placed at the 6 o'clock position to approximate the serosal component of the vas deferens to the visceral layer of the tunica vaginalis. Four to six 10-0 double-arm nylon sutures are placed to approximate the luminal aspect of the vas deferens to the incised epididymal tubule. Once the luminal closure has been accomplished, multiple interrupted 9-0 nylon sutures are placed to approximate the serosa of the vas deferens to the visceral layer of the tunica vaginalis. During the performance of the anastomosis, it is often helpful to place a few drops of methylene blue or indigo carmine on the epididymal tubule, as well as the lumen of the vas deferens. This will selectively stain the muscularis a bright blue and facilitate proper mucosal identification and suture placement.

The initial experience with microscopic epididymovasostomies used the end-to-end technique. The present-day standard of care is the end-to-side technique (418) because of its many advantages, including a relatively bloodless field from less dissection of the epididymis, a larger epididymal lumen for anastomosis, no need to search for the “single tubule” leaking the sperm-containing fluid, and anatomic and physiologic continuity of the entire epididymal tubular lumen proximal to the level of the obstruction. This last advantage may be the most important, because preservation of more “epididymal function” should enhance sperm “maturation” and the acquisition of the ability to fertilize an egg. Pregnancy rates for microsurgical epididymovasostomy may be as high as 30% to 40%, whereas macrosurgical pregnancy rates average 17% (418).

The triangulation vasoepididymostomy is a modification of the traditional end-to-side technique and has enjoyed increasing popularity over the last several years (39). The vas and epididymis are approximated in similar fashion, except that the epididymal tubule is not opened initially. Three double-armed 10-0 nylon sutures are placed in triangular fashion at the most prominent portion of the epididymal tubule (Fig. 35.23). The fluid that leaks from around the needle entry sites is sampled for the presence of sperm. If sperm are found, an opening is created using a microknife or the tip of a 9-0 cutting needle between the 10-0 nylon sutures. The three sutures are placed into the vasal lumen in inside-out fashion to create six points of fixation. This technique creates an intussusception of the epididymal tubule into the vasal lumen. A second layer is then completed using 9-0 nylon sutures in interrupted fashion. Using a

modified two-suture invagination technique, Marmar (262) reported patency in seven of nine men (77.7%) having a bilateral vasoepididymostomy.

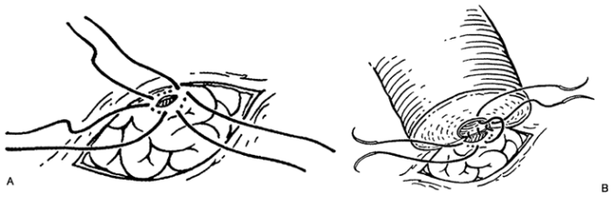

FIGURE 35.23. The Berger modification of the microscopic end-to-side epididymovasostomy: **A:** Three 10-0 nylon sutures are placed 120 degrees apart in an epididymal tubule. An epididymotomy is then carefully created between the sutures. The fluid is sampled for the presence of sperm. **B:** The six ends of the epididymal sutures are then placed in inside-out fashion to the inner layer of the vas deferens. The sutures are then tied to create an intussuscepted anastomosis. The outer layer is completed in similar fashion to the traditional end-to-side technique.

If there is a solitary functioning testis with an ipsilateral, irreparable excurrent ductal obstruction or agenesis, a crossover transseptal vasovasostomy or vasoepididymostomy can restore patency in most men, provided the contralateral vas deferens is patent (356). Contralateral testicular atrophy may be associated with prior hernia repair, varicocele, severe orchitis, cryptorchidism, testicular torsion, and trauma. Vas deferens pathology is associated with congenital absence of the vas deferens, pediatric inguinal surgery, hernia repair, and idiopathic causes.

The return of motile sperm in the ejaculate following a vasovasostomy or epididymovasostomy is time dependent. Motile sperm in the ejaculate appear on average 6 months following vasoepididymostomy and 2 months following vasovasostomy (266). The delayed appearance (mean delay 6 months) of sperm following an initially azoospermic sample is common, especially when an epididymovasostomy is performed (194). With a series of 200 vasectomy reversals, Matthews and colleagues (266) recommended that intervention for azoospermia is appropriate 6 months after vasovasostomy and 1 year after epididymovasostomy.

Repeat epididymovasostomy after failed initial epididymovasostomy is also feasible with modest success rates. In a series of 18 men with a variety of causes of epididymal obstruction, patency was demonstrated in 66% and pregnancy in 25% of patients with follow-up (321). An important surgical consideration when performing a primary or repeat epididymovasostomy is the effect of the level of anastomosis on pregnancy outcome. In the unobstructed epididymis, the sperm with the best motility and fertilizing capabilities are located distally in the cauda. The “inverted motility” present in the obstructed epididymis indicates that the sperm from the cauda have poorer motility but better fertilizing capability than sperm from more proximal sources. The outcomes of epididymovasostomy to the corpus and cauda epididymis are roughly equivalent and superior to the caput (192,220,394).

Sperm Retrieval Techniques

Microsurgical Epididymal Sperm Aspiration

In microsurgical epididymal sperm aspiration (MESA), a vertical scrotal skin incision is made and the testis and epididymis are exposed. A “mini-MESA” procedure using a 2-cm incision and leaving the intrascrotal contents *in situ* has also been described (432). With use of an operating microscope, a single epididymal tubule is opened and sperm are aspirated into a sperm-washing medium (Fig. 35.24). The general strategy is to work from the cauda toward the caput in order to spare as much functional epididymis as possible. However, in the obstructed epididymis, sperm of better quality are usually found more proximally toward the caput (373,383). Although we prefer to aspirate the sperm into a 1-mL tuberculin syringe and a shortened 25-gauge angiocath sheath, special apparatuses have also been described (139). This procedure may be performed with a general anesthetic or a local anesthetic with a spermatic cord block and intravenous sedation.

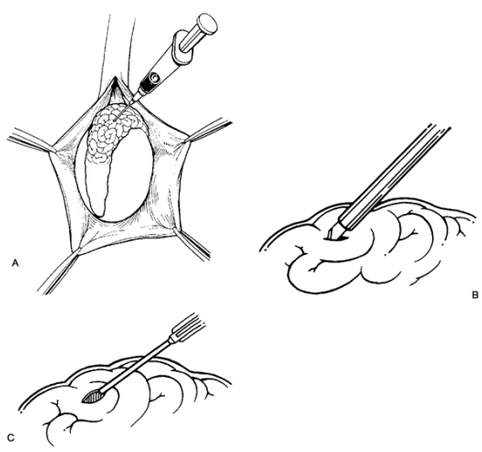

FIGURE 35.24. Microsurgical epididymal sperm aspiration (MESA). **A:** After the tunica vaginalis is opened, the epididymis is inspected for dilated tubules. A site is identified for tubule incision. **B:** The tubule is opened with a microknife. Alternatively, microdissection scissors may be used. **C:** Sperm are aspirated with a shortened 25-gauge angiocath sheath into a 1-mL tuberculin syringe containing sperm-washing medium. The fluid is examined under a microscope to ensure that motile sperm are present.

MESA has the ability to retrieve large numbers of sperm, which may be cryopreserved (frozen) and used in future cycles. Thus the need for future procedures is minimized and the amount of epididymal damage is limited. Many men may be candidates for a reconstructive epididymovasostomy

(connection of the vas and epididymis, thereby bypassing a blockage) at the same time of sperm harvest, thus increasing the chances of having sperm appear in the ejaculate. Recovery time from this operative procedure is only a few days.

Although it is considered a minimally invasive procedure, MESA is more invasive and results in greater patient discomfort than percutaneous methods. Because of the need for an operating microscope and possibly a general anesthetic, costs are greater than office-based procedures. Complications such as infection or excessive bleeding are rare.

Percutaneous Epididymal Sperm Aspiration

Percutaneous epididymal sperm aspiration (PESA) is the aspiration of sperm from the epididymis using a small (21- to 23-gauge) needle. After immobilizing and isolating the specific portion of the epididymis between the thumb and forefinger, passes of the needle with negative pressure are made until sufficient numbers of sperm are obtained. No skin incision is required, and the procedure may be performed using intravenous sedation and a local cord block. The aspirate is then immediately placed in a warmed sperm buffer before analysis. Craft and colleagues (90,91) reported obtaining sperm suitable for ICSI in most of their patients with obstruction.

PESA has the main benefits of being successful in most of the cases while avoiding a skin incision. Costs are lower because an operating microscope, the skills of a microsurgeon, and the possibility of a general anesthetic are not necessary or likely. A series by Tsirigotis and colleagues (430) involving 59 cycles of IVF-ICSI demonstrated equivalent results with MESA procedures by revealing normal fertilization in 52.6% (274 oocytes), embryo transfer of more than one embryo in 91.5%, and a pregnancy rate of 30.5% per cycle.

The blind nature of PESA with potential damage to the delicate epididymal tubules represents its main risk. If multiple cycles of ICSI with PESA are required, the epididymis may be irreparably scarred, precluding a microsurgical reconstruction and possibly reducing the likelihood of further PESA. Hematoma formation may result from damage to

the vascular supply to the epididymis; compression for several minutes may minimize this risk.

Testicular Sperm Extraction

Testicular sperm extraction (TESE) is the performance of an open testicular biopsy for sperm harvesting purposes. TESE is most applicable for men with testicular failure, but it may also be used for men with vasal obstruction. Using a local anesthetic with cord block, or a general anesthetic, a small incision is made on the anterior surface of the midportion of the scrotum. After the tunica vaginalis is opened and an eyelid retractor placed, the tunica albuginea is exposed.

When TESE is performed, the practical questions of how many biopsies to obtain and how to determine when enough tissue has been obtained arise. The amount of testicular tissue required is dependent on whether obstruction or testicular failure is the primary underlying disorder. In the case of normal spermatogenesis, only a single small biopsy from one testis is required. When testicular failure is present, however, a larger sampling of tissue is necessary. One approach is to take a single large biopsy (375). In contrast, Tournaye and colleagues (426) obtained smaller individual samples from multiple sites, averaging 2.8 ± 2.5 biopsies (range of 1 to 12) in Sertoli cell only, 4.2 ± 4.5 biopsies (range of 1 to 20) in maturation arrests, and 1.5 ± 0.8 biopsies in hypospermatogenesis. The need for several testicular specimens, often from both testes, increases the likelihood of successful sampling due to intratesticular histologic variability. If one testis appears to be healthier (i.e., larger and firmer) than its counterpart, it is preferable to biopsy the better testis. The surgeon must realize and inform the patient that multiple biopsies or a single large biopsy may potentially, although rarely, damage the subtunical arterial supply to the testis, risking further testicular atrophy.

The ability to find sperm in the testis biopsies of men with testicular failure is clearly related to the heterogeneous nature of spermatogenesis and sampling error inherent in the procurement of the small, standard biopsy specimen. Small, focal areas of spermatogenesis may be identified even in the presence of overwhelming testicular failure. As an example, the pattern of Sertoli cell only with a small focus of normal spermatogenesis in an adjacent tubule has now been frequently observed, but it may be missed if a single small biopsy is obtained (Fig. 35.25). Perhaps even more important, the ability to find sperm requires extreme patience, diligence, and tissue preparation expertise on the part of the person processing the tissue (445).

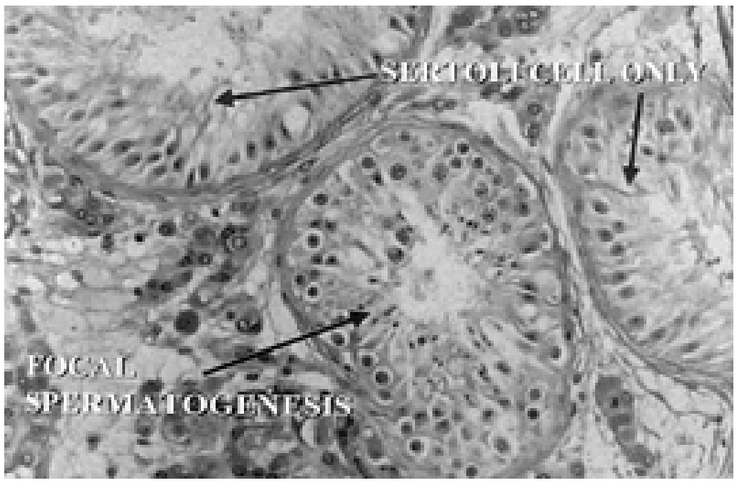

FIGURE 35.25. The heterogeneous nature of spermatogenesis is evident in this photomicrograph, which demonstrates a tubule with complete spermatogenesis surrounded by tubules with a Sertoli cell–only pattern (400×). A small, single biopsy may easily miss this small focus of sperm production. Although this patient is azoospermic, sperm may be recovered from this testis using TESE in preparation for ICSI.

When testicular failure is present, whether for diagnostic or therapeutic purposes, bilateral biopsies will increase sperm yield. Plas and colleagues (334) evaluated differences in bilateral testicular biopsies in azoospermic patients with regard to testicular histology and focal spermatogenesis. Histopathologic results of 100 testicular biopsies from 50 azoospermic patients were reviewed. After bilateral biopsy, a difference in testicular histology was found in 28% and identical histopathology was noted in 70% of patients. Testicular symmetry determined by a Prader orchidometer was noted in 54.8% of patients, whereas 45.2% had asymmetric testes. Bilateral biopsies increased the detection of focal spermatogenesis to 68%. If only unilateral diagnostic testicular biopsies had been performed, in 20% of patients focal spermatogenesis in the contralateral testis would have been missed. The study concluded that bilateral diagnostic testicular biopsies are recommended in the evaluation of patients with azoospermia.

Even more successes are evident using sperm harvested from the testis biopsies of men with an obstruction and normal spermatogenesis. However, procuring sperm from the epididymis is advisable because of a higher yield of motile sperm, unless severe epididymal scarring is present. Tournaye and colleagues (426) successfully recovered sperm in all 70 (100%) TESE procedures and had a normal fertilization and pregnancy rate of 62.5% and 43.5%, respectively. Instead of the standard open testis biopsy, percutaneous needle biopsy or percutaneous fine-needle aspiration may also be used with high sperm recovery rates (47,456). Because pregnancies have also been reported using frozen testicular sperm in men with obstructive azoospermia (174,219), an increasing practice is to cryopreserve a portion of the biopsy specimen for potential later use with ICSI. The long-term results of using sperm from frozen tissue aliquots remain to be reported.

During TESE, performance of a wet preparation or testicular touch preparation cytology intraoperatively is necessary to judge whether sperm are present (208,221) (Fig. 35.26B). Once sperm are identified, the procedure

may be terminated with a reasonable degree of certainty that more sperm will be found with further tissue extraction. Because these analyses take time, especially if no sperm are initially found, consideration should be given to providing adequate sedation or general anesthesia for patient comfort. Testicular biopsies have also been obtained percutaneously using Tru-Cut and ASAP 14-gauge channel-cut biopsy system needles. Proponents of multiple core biopsies of the testis, rather than a single superficial sampling, argue that their deeper sampling may have a better yield by providing a greater cross-sectional tissue core.

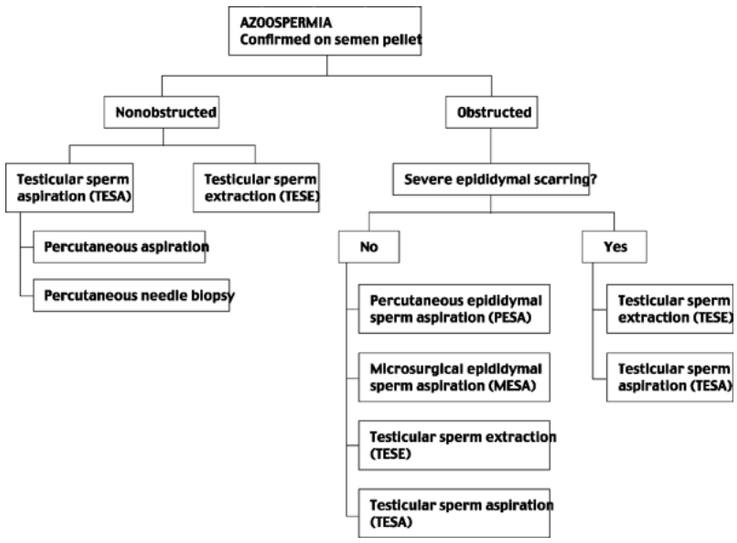

FIGURE 35.26. Algorithm for sperm retrieval techniques for intracytoplasmic sperm injection (ICSI).

A TESE microdissection technique to further assist in identifying tubules with active spermatogenesis was developed by Schlegel (372). With use of an operating microscope, identification of spermatogenically active regions of the testicle is possible by direct examination of the individual seminiferous tubules. The underlying concept for this technique is simple: seminiferous tubules containing many developing germ cells, rather than Sertoli cells alone, are likely to be larger and more opaque than tubules without sperm production. In a sequential series of TESE cases for men with nonobstructive azoospermia, the ability to find spermatozoa increased from 45% (10 of 22) to 63% (17 of 27) after introduction of the microdissection technique. Microdissected samples yielded an average of 160,000 spermatozoa per sample in only 9.4 mg of tissue, whereas only 64,000 spermatozoa were found in standard biopsy samples that averaged 720 mg in weight (p <.05 for all comparisons). For men in whom microdissection was attempted, successful identification of enlarged tubules was possible in 56% (15 of 27) of cases.

Tournaye and colleagues (426) have the largest reported series of TESE in men with nonobstructive azoospermia. In 54 TESE procedures, sperm were recovered in 81% of attempts with a sperm recovery rate of 84% in patients with incomplete germ cell aplasia and maturation arrest, 76% with complete germ cell aplasia or maturation arrest, and 100% with hypospermatogenesis. There was a normal fertilization rate of 45% with overall pregnancy rates per TESE procedure, per ICSI procedure, and per transfer of 33%, 41%, and 44%, respectively. Although follow-up on the offspring is limited, no increased incidence of congenital abnormalities has been noted in these children (104).

Su and colleagues (408) and Gil-Salom and colleagues (138) have confirmed the ability to find sperm in testis biopsies from men with testicular failure and azoospermia. Su and colleagues (408) were able to harvest sperm from 79% of men with hypospermatogenesis (31 biopsied),

47% with a maturation arrest (19 biopsied), and 24% with Sertoli cell only (21 biopsied). Of note, the testicular biopsy technique in this series involved 8× to 10× optical magnification and use of a generous incision in the tunica albuginea with a 15-degree ophthalmic knife. This magnification may be helpful for the avoidance of tunical blood vessels and identification of full tubules, which may contain mature sperm. Similarly, Gil-Salom and colleagues (138) had success rates for sperm retrieval of 54% of men with a maturation arrest (24 biopsied) and 33% with Sertoli cell only (61 biopsied).

The specifics of tissue processing are beyond the scope of this review but generally involve mechanical separation of the sperm from the seminiferous tubules using mincing and vortexing procedures (90,445). If a small biopsy is required, complications are minimal but may include bleeding and temporary discomfort. Complications such as bleeding and testicular atrophy related to vascular injury may increase if a large biopsy is required. Caution should be exercised when performing a spermatic cord block because of evidence that in an animal model, a testicular atrophy rate of 5% was reported after needle puncture of the spermatic cord (141).

Testicular Sperm Aspiration

Testicular sperm aspiration (TESA), also known as *testicular fine-needle aspiration* (TFNA), may be performed under local anesthesia with cord block. With the testis immobilized and using a fine 21- to 23-gauge needle attached to a 10- to 20-mL syringe in a Franzen syringe holder, multiple passes with gentle negative pressure are made. The aspirate is then placed into a sperm-washing solution for analysis and preparation for ICSI.

Similar to PESA procedures, TESA has the main benefit of being successful in most of the cases while avoiding a skin incision. Also, costs are reduced because an operating microscope, the skills of a microsurgeon, and a general anesthetic are not necessary. Turek and colleagues (434) described the technique of testicular mapping of sperm using percutaneous fine-needle aspiration. Using matched testicular fine-needle aspirates and open testicular biopsy specimens, the authors found that 4 of 12 men with nonobstructive azoospermia had localized “patches” of sperm detected in areas distant from sperm-negative biopsy sites. They concluded that for sperm detection, fine-needle aspiration can localize areas of sperm production within the testis and accurately guide sperm extraction procedures in men with nonobstructive azoospermia. This technique has not gained widespread acceptance.

Because the ability to cryopreserve sperm with TESA is limited, repeated sperm retrieval procedures are required for each ICSI attempt. TESA and TFNA should be limited to patients with obstructive azoospermia, although a live birth has been reported using TFNA with testicular failure (240). In a series by Friedler and colleagues (127), TFNA was compared with TESE for sperm retrieval. Whereas TFNA allowed for the performance of ICSI in 4 of 37 patients (11%), TESE enabled ICSI in 16 of 37 patients (43%). Complications associated with TESA may include hematocele and hematoma formation.

Decision Making for Sperm Retrieval

Sperm harvested from the male reproductive tract in azoospermic men are used for ICSI. The method of sperm retrieval is dependent on whether obstructive or nonobstructive azoospermia is present (Fig. 35.26). When testicular failure (nonobstructive azoospermia) is present, the testis is the site of choice for retrieval. When an obstruction is present, sperm may be harvested proximal to the site of the blockage.

Obstructive Azoospermia

Obstructive azoospermia is the absence of sperm in the ejaculate secondary to a blockage within the male reproductive tract. In this situation, the testicular production of sperm is typically normal. Although the obstruction may be at any level from the rete testis to the ejaculatory duct, the most commonly observed sites of blockage are the epididymis and vas deferens. Conditions causing obstructive azoospermia for which ICSI may be appropriate include failed vasectomy reversal (vasovasostomy and epididymovasostomy), acquired or congenital epididymal and vasal blockages, and congenital bilateral absence of the vas deferens. Other causes of obstructive azoospermia such as previous vasectomy and ejaculatory duct obstructions may be surgically treated without the need for ICSI, depending on the specifics of the clinical situation.

Most commonly, these sperm are recovered from the testis or epididymis, but procurement may also be possible from the vas deferens or seminal vesicles, depending on the location of the obstruction. When the obstruction is in the vas deferens, such as after a vasectomy, sperm are most appropriately harvested from the epididymis or vas deferens. If the patient is considering microsurgical vasal reconstruction (i.e., a vasovasostomy), sperm may be harvested from the testicular end of the vas deferens at the time of surgery with a procedure called vasal aspiration of sperm. If no sperm are found in the testicular end of the vas deferens and the fluid quality is thick and unfavorable, an epididymovasostomy is required. In this latter situation, sperm may be harvested from the epididymal fluid using MESA, followed by microsurgical reanastomosis to the opened epididymal tubule.

If the patient does not desire reconstructive surgery, sperm may be harvested using MESA alone (374) or with PESA (91,396). Alternatively, sperm may be obtained directly from the testis using a percutaneous or open procedure. We choose to obtain sperm from the testis in obstructive

azoospermia only if the epididymis is severely scarred and not amenable to a sperm extraction procedure.

Testicular Versus Epididymal Sperm

When obstructive azoospermia is present, high fertilization and pregnancy rates with ICSI are possible with either epididymal or testicular-derived sperm. This observation suggests that the complex mechanisms affecting sperm maturation during epididymal passage may not have a significant role when testis-derived sperm are used with ICSI (395). However, because significantly better fertilization and pregnancy rates have been observed using fresh ejaculated sperm compared with epididymal and testicular sperm (397), epididymal maturation of sperm probably has an important but incompletely understood role. In 1993, Schoysman and colleagues (377) described the first pregnancy using testicular sperm.

The largest experiences with testicular-derived sperm have been with fresh specimens. In a retrospective series, Silber and colleagues (395) reported that there was no difference in fertilization, cleavage, pregnancy, or take-home baby rates between fresh epididymal, frozen epididymal, and testicular sperm. In this early series, the fertilization and take-home baby rates for fresh MESA cases were 46% and 42%, respectively. Although the transfer rate was lower with TESE (84% versus 96%) and the spermatozoa could not be frozen and saved for use in future cycles, the results were not affected by whether the obstruction was caused by vasal agenesis or failed vasoepididymostomy (397). The only significant factor affecting results appeared to be the age of the woman.

Pregnancies have also been reported using frozen testicular sperm in men with obstructive azoospermia (174,219,335,350). Although most published accounts are only case reports and truly large series for comparison are unavailable, the success of this approach has prompted many centers to routinely cryopreserve a portion of testicular tissue at the time of a diagnostic testis biopsy before IVF-ICSI. Although the ideal technique for processing of the testis tissue and subsequent sperm isolation techniques have not yet been defined, many laboratories choose to freeze the tissue initially and focus on individual sperm isolation at the time of IVF-ICSI.

Nonobstructive Azoospermia

When nonobstructive azoospermia is present, the search for sperm is focused on the testis, rather than the epididymis. Sperm may be recovered using an open testicular biopsy method (TESE) or by percutaneous biopsy or aspiration (PESA) techniques. Several approaches with regard to timing may be used. Although there is no consensus as to the need for a prior diagnostic biopsy or the best method for sperm retrieval, the decision-making process must be highly individualized.

We have preferred to use a conservative approach of performing a diagnostic open testicular biopsy well in advance of an IVF-ICSI cycle for a patient with clinical evidence of testicular failure. At the time of this testis biopsy, a portion of the specimen is cryopreserved in case sperm are identified. A repeat testis biopsy for sperm extraction (TESE) is performed at the time of the actual ICSI cycle. The cryopreserved specimen may be used if sperm are not found on the TESE biopsy. By using this approach, the couple are better aware of the likelihood of identifying sperm at the time of ICSI and have time to contemplate the likelihood for requiring donor sperm backup.

Another approach is performing a TESE or TESA procedure on the day of IVF-ICSI without a prior diagnostic biopsy. The primary advantage is minimizing the need for a prior testis biopsy. The main disadvantage is the uncertainty on the couple's part about the chances of requiring donor sperm backup. If a couple is willing to use donor sperm without hesitation, this latter approach may be acceptable.

Testicular Biopsy

The indications for obtaining a testis biopsy have expanded significantly over the last several years as a result of ICSI. As a result, the testis biopsy now has new and important diagnostic and therapeutic implications for the infertile male. The urologist previously used the testis biopsy for diagnostic purposes only, that is, to distinguish testicular failure, also known as *nonobstructive azoospermia,* from obstruction in the azoospermic patient (80). Testis biopsies are now commonly being performed for therapeutic purposes, and finding even a rare mature spermatozoa has new importance. Because the majority of patients with clinically apparent testicular failure may harbor sperm within the testis, a testis biopsy should be offered to these men if ICSI is an acceptable alternative for the couple. The pivotal role of the biopsy in differentiating normal spermatogenesis from hypospermatogenesis, maturation arrests, and the Sertoli cell–only states remains the most common and important indication for obtaining a testis biopsy. Much less commonly, testis biopsies may also be considered in the severely oligozoospermic (less than 1 million sperm/mL) male, if testicular size is relatively normal, to exclude a partial obstruction within the male reproductive tract, such as at the ejaculatory duct.

Before ICSI, the patient with testicular failure was told that adoption and the use of donor sperm were the only options available. For those men with azoospermia, testicular atrophy, and an FSH level greater than three times normal, a testis biopsy was considered unnecessary because nonobstructive azoospermia was certainly present (190). The finding of mature sperm in the testicular biopsy of 30%

of such men demonstrates that even men with severe disorders are potentially capable of fathering children with ICSI (220). A current controversy is whether these men with obvious spermatogenic failure should have a diagnostic testis biopsy performed if they are intent on trying TESE with IVF-ICSI at a later time. Although several centers with extensive experience in harvesting sperm from biopsies of men with spermatogenic failure argue that a diagnostic biopsy is unnecessary and exposes the patient to additional morbidity, many couples prefer knowing the likelihood of obtaining sperm or requiring donor sperm backup at the time of IVF-ICSI and opt for a diagnostic biopsy. An interval of 3 to 6 months between a diagnostic biopsy and TESE has been recommended to allow for optimal healing of the testis.

Testicular biopsy can be performed with local or general anesthesia. If local anesthesia is used, either the spermatic cord or the area of the incision is infiltrated with lidocaine (Xylocaine). We prefer to anesthetize both areas. When vasography is also indicated, general anesthesia is suggested. If there is good reason to believe that there is no epididymal abnormality (e.g., the presence of testicular atrophy), a simple “window technique” can be employed as follows. With the scrotal skin stretched tightly over the anterior testicle and the epididymis carefully positioned posteriorly, a 1- to 2-cm incision is made and carried down to the tunica vaginalis. Commonly, when the tunica vaginalis is opened, a small amount of straw-colored fluid is observed. Before the tunica albuginea is cut, the conscious patient is warned that he may feel momentary lower abdominal pain when the tunica albuginea is incised and the parenchyma of the testis protrudes. Gentle pressure on the testis will cause additional extrusion of the stroma. A biopsy is then taken with a “no touch” technique, using a scalpel or very sharp scissors (Fig. 35.27).

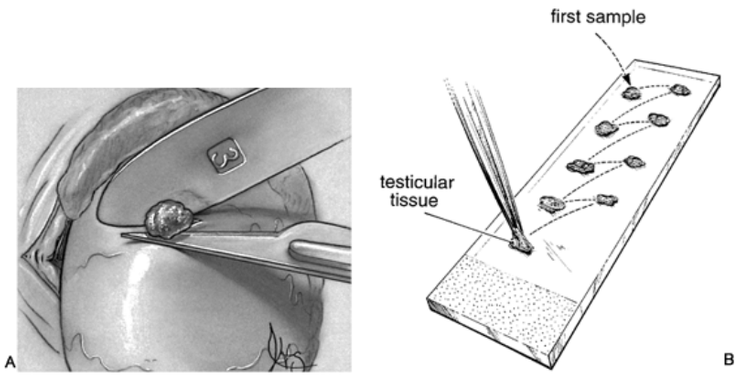

FIGURE 35.27. A: Tubules are shaved with a “no touch” technique using a no. 11 blade and an empty knife handle for support. **B:** A touch preparation cytology can identify mature sperm at the time of biopsy and aid in the decision regarding number of biopsies to obtain (**A:** From Lipshultz LI, Howards SS, eds. *Infertility in the male,* ed 3. St. Louis: Mosby, 1997, with permission. **B:** From Kim ED et al. Testicular touch preparation cytology. *J Urol* 1996;156:1412, with permission.)

The specimen is first touched gently at multiple sites on a sterile microscope slide, which is then passed quickly off the field, sprayed with fixative, and sent for hematoxylin-eosin staining for a touch preparation cytology (221). The specimen is then placed in Bouin's solution for formal paraffin embedding and staining. Formaldehyde should not be used because it distorts and partially digests the delicate germinal epithelium. The incision is closed in layers with resorbable sutures. The patient is encouraged to use a scrotal support for several days.

The testicular touch preparation cytology, also known as a “touch imprint,” allows for quick and reliable differentiation between normal spermatogenesis and a maturation arrest at the spermatid stage at the time of potential microsurgical correction of ductal obstruction. In the azoospermic

patient, we also have found touch imprint cytology to be more rapid and informative than the frozen section technique in confirming intraoperatively that mature sperm are present in the biopsy. Although hematoxylin-eosin and Papanicolaou staining typically have been used after sending the cytofixed specimen to the frozen section pathology laboratory, the Diff-Quik staining method has recently been described (33). The advantages of this stain over hematoxylin-eosin and Papanicolaou stains are that slides are allowed to air-dry first, without a need for fixative, and that the skills of a histologic technician are not required because this method can be performed in the operating room by circulating staff. Similar to the other staining methods, simple and rapid identification of spermatozoa and spermatids is possible.

Jow and colleagues (208) described the technique of wet preparation analysis. Wet preparations are performed by placing a small sample of fresh testicular tissue on a slide, adding a drop of Ringer's lactate, and compressing the specimen under a glass coverslip. The finding of motile versus nonmotile sperm on a wet preparation has positive predictive values of 100% versus 81% for the presence of reproductive tract obstruction and 94% versus 86% for complete spermatogenesis, respectively. When any complete sperm with tail is found in a testis biopsy wet preparation, obstruction is likely. When used with TESE, the finding of sperm indicates that an adequate sampling of testicular tissue has been performed.

Transurethral Resection of the Ejaculatory Ducts

Transurethral resection of the ejaculatory ducts (TURED) is the treatment of choice for men with ejaculatory duct obstruction (144) (Fig. 35.15C). With use of regional or general anesthesia, a resectoscope loop is used to unroof the ejaculatory ducts just distal to the verumontanum. Intraoperative usage of TRUS may be helpful in identifying the location of an obstructing cyst and in determining the depth of resection, which may require an incision 5 to 10 mm in depth (34). After resection, there is a communication between the ejaculatory duct and the urethra. The latter will require a microscopic epididymovasostomy.

In a retrospective review of 46 cases, Turek and colleagues (433) reported significant and durable semen quality improvement after TURED. Sixty-five percent of the patients had improved semen quality (greater than a 50% increase in total motile sperm count), and 20% initiated a pregnancy an average of 6.1 months postoperatively. Statistically significant increases in total motile sperm count were achieved in men with azoospermia, as well as those treated for oligoasthenozoospermia. Persistent azoospermia after TURED may be a result of scarring at the site of the resection or in the epididymis from a “blowout” following long-term ejaculatory duct obstruction. Complications including watery, high-volume ejaculate (due to retained urine in the cyst cavity), urinary tract infection, and chronic epididymitis occurred in 20% of the men.

Adjunctive Therapy

Vibratory Stimulation and Electroejaculation

Although a small percentage of patients with spinal cord injuries maintain the capacity to ejaculate, this capacity tends to be unpredictable and is rarely effective in the initiation of a pregnancy. Because most of these spinal cord–injured patients are young at the time of their injury, many have not had the opportunity to start a family. Between 85% and 97% of these men experience permanent loss of ejaculatory function (114). Many other causes of neurologic injury such as multiple sclerosis, peripheral neuropathies such as diabetes mellitus, and retroperitoneal surgical damage to sympathetic nerves may result in similar anejaculatory states.

Recent successes with inducing ejaculation by means of rectal probe electrostimulation or vibratory induction combined with assisted reproductive techniques have enabled these affected couples to produce their own biologic offspring. Unfortunately, the often inherently poor quality of the sperm generated has contributed to relatively poor fertilization and pregnancy rates. With the introduction of ICSI, many of the problems associated with poor sperm penetrating abilities may be overcome.

Vibratory Stimulation

Vibratory stimulation, which appears to initiate an ejaculation reflex and usually produces an antegrade ejaculation, is most effective in patients with upper cord lesions. However, we suggest that all patients have an initial trial before electroejaculation (EEJ) because the lesion may be incomplete. When vibratory stimulation is unsuccessful, EEJ often works well (56).

After standard bladder preparation, a handheld, electrically or battery driven vibrator is applied initially to the dorsum of the glans and then to the frenulum and penoscrotal area. These commercially available devices cost approximately $350. Slow movement of the vibrator often identifies a “trigger” point, which is often found to be reproducible from one cycle to another. The selection of a frequency of 100 Hz and a peak-to-peak amplitude of 2.5 mm may be important for successful ejaculation (401). Patients who ejaculate using this form of stimulation usually do so within 5 to 10 minutes, and these patients will usually exhibit tumescence and pelvic floor contractions before ejaculation. In the absence of contractions, we stimulate for only 2 to 3 minutes before proceeding with EEJ. Most patients who respond to vibratory stimulation will exhibit antegrade ejaculation, but catheterization must also be performed because these patients frequently have incomplete closure

of the bladder neck and may also have a significant retrograde component.

Brindley (56) achieved successful ejaculation using penile vibratory stimulation in 48 of 81 men (59%) with spinal cord injuries of more than 6 months duration (mostly complete). In a more recent series of 653 trials of penile vibratory stimulation in 211 men with spinal cord injury, successful ejaculations were achieved in 54.5% using high-amplitude stimulation versus 39.9% using low-amplitude stimulation (51). Success rates were highest in men with injuries at C-3 to C-7, followed by T-1 to T-5, T-6 to T-10, and T-11 to L-3. Ejaculation was reliable, because most men who ejaculated did so during 100% of the trials and within 2 minutes of stimulation onset.

Electroejaculation

In rectal probe electroejaculation, seminal emission depends on the sinusoidal electrical stimulation of sympathetic efferent fibers and smooth muscle. The best site for inducing seminal emission is in front of the bifurcation of the aorta and between the rectum and obturator nerves, where both preganglionic and postganglionic sympathetic fibers reside. Unfortunately, because electroejaculation does not stimulate the somatically mediated events of ejaculation or coordinate bladder neck closure essential to antegrade emission, pulsatile expulsion of seminal fluid does not occur. Rather, semen either dribbles from the meatus or is deposited retrograde into the bladder.

Electroejaculation is performed using a rectal probe containing a built-in thermistor for recording rectal mucosal temperature to prevent rectal burns resulting from unmonitored overheating. If the urine is sterile, the patients are prophylactically given ciprofloxacin 500 mg on the evening before their procedure and for 48 hours after the procedure. If a positive culture is found, culture-specific antibiotics are prescribed for 1 week before electroejaculation. Because the acidic pH of urine is highly toxic to spermatozoa, 600 mg of sodium bicarbonate is given orally, beginning the day before the procedure. Those patients who have had a poor response to either vibratory ejaculation or electroejaculation may be given Sudafed, 60 mg orally four times a day, beginning 2 weeks before the procedure, in an effort to augment emission and ejaculation through stimulation of adrenergic innervation. All patients are instructed to use their routine bowel preparation the evening or morning before the procedure.

The patient for EEJ is positioned in either the lateral decubitus or lithotomy position. General anesthesia is used in those patients with normal sensation or in those with incomplete lesions who are unable to tolerate electroejaculation. Initially, all patients are catheterized with a buffer-rinsed catheter (standard lubricant can potentially harm sperm motility) and the bladder is washed with a buffered phosphate solution. Approximately 30 mL of washed solution is left in the bladder, and the catheter is removed.

A preliminary digital rectal examination and anoscopy are performed to rule out any preexisting pathology, and the sphincter is dilated briefly before insertion of the probe. Once the probe has been placed in the rectal vault with the electrodes oriented anteriorly, upward pressure parallel to the prostate is used to ensure probe contact with the anterior rectal wall. Stimulations lasting approximately 2 to 4 seconds at increasing voltages are applied. Most patients exhibit a small amount of dribbling antegrade ejaculate when electroejaculation is successful, but this is unpredictable, and catheterization is always done to collect any retrograde semen. Because significantly impaired sperm motility and viability are commonly noted in the retrograde ejaculate, efforts should be directed toward maximizing the antegrade portion of the electroejaculate and optimizing the technique of preserving functional sperm in the intravesical compartment (167). After the probe is removed, anoscopy is again performed to confirm that no injury has occurred.

Most often, semen specimens are washed and subsequently used for IUI or IVF with ICSI. It is important that the female partner be properly evaluated and monitored for ovulation and reproductive tract abnormalities before EEJ. Adverse effects of the procedure are uncommon and usually consist only of a transient increase in extremity spasms. Rectal injury has been reported, but we have seen no significant injuries in more than 180 procedures using the previously described technique. Although autonomic dysreflexia and its attendant consequences are potentially serious complications, the use of nifedipine just before the procedure in patients at risk has significantly diminished these problems (404).

Results.

The results of electroejaculation in terms of sperm harvesting have been excellent, with recent data suggesting that an ejaculate of sufficient quality to use in intrauterine insemination or IVF can be obtained in approximately 80% of individuals (378). Most patients tend to have good sperm concentrations, with averages of 180 to 300 million sperm recovered per ejaculate. The major problem has been that sperm motility has averaged only 11% to 22% with poor functional characteristics (60,101).

The poor sperm quality that has been a consistent finding in patients with spinal cord injury is probably due to a number of factors: chronic urinary tract infections and epididymitis, testicular hyperthermia as a result of sitting in the wheelchair and the loss of vasculogenic tone, infrequent ejaculations, stasis of sperm within the seminal vesicles (305), possible antisperm antibodies, and chronic long-term use of various medications. Repeating ejaculation procedures on successive days may improve sperm motility, but we have not found this to be a predictable occurrence. In addition, it has been suggested that the electroejaculation procedure itself may be detrimental to sperm because of the thermal and electrical effects of the procedure (340). However, *in vitro* studies using a simulated rectal model have

failed to confirm this suspicion (466). Semen quality from vibratory stimulation may be superior to that obtained through EEJ (52).

The level of the spinal cord injury and the type of bladder management clearly affect the quality of the recovered sperm. Two studies reported that men performing intermittent catheterization, in contrast to all other forms of bladder management, had higher total sperm counts and motility (304,305). The reason for this beneficial impact is probably related to the maintenance of a lower-pressure bladder with resultant diminished risks of serious infections and reflux of urine into the ejaculatory ducts. Ohl and colleagues (304) also demonstrated that thoracic paraplegics and those with complete injuries had better overall semen parameters. The duration of time since spinal cord injury does not appear to affect semen quality (51). Several studies have also suggested that up to 50% of patients with spinal cord injury have histologic abnormalities on testicular biopsy (116,328,405).

To initiate a pregnancy following electroejaculation, IUI or IVF is required. Although the lower limits of acceptability vary, a minimum of 1 million total motile sperm is usually required for IUI. With other forms of assisted reproductive techniques, conception can occur with a much lower sperm density—as few as 50,000 sperm per oocyte for IVF and 1 sperm per oocyte with ICSI. Although results with these techniques have been encouraging, an accurate assessment of pregnancy rates has been difficult because of the lack of large published series.

Semen Processing

Impaired sperm activity or function (motility, forward progression, ovum penetrability), in the absence of antisperm antibodies, may be attributed to the presence of as yet poorly understood “seminal fluid factors.” Several reports in the literature attest to enhancement of sperm function achieved with a variety of *in vitro* manipulations, which in part may be related to the removal of these so-called seminal fluid factors (40,169,239). The ultimate objective of any sperm-processing procedure is to expose the oocyte to an optimal concentration of high-quality, motile sperm. The various methods for selection of motile spermatozoa for inseminations can be grouped into density centrifugation, swim-up, and sperm washing (41,308).

Density centrifugation of sperm using Percoll had been a standard procedure of preparing semen samples until its withdrawal in 1997. The removal of Percoll was related to difficulties in meeting U.S. Food and Drug Administration standards for clinical use. Isolate sperm separation medium, a colloidal suspension of silica particles, has gained in popularity. Processing semen with ISolate in a density centrifugation has been shown to provide an increased yield of motile sperm compared with Percoll (3). OptiPrep, iodixanol, is another alternative for density centrifugation (76,160).

Similar methods with albumin gradients have also been used for “sperm enhancement.” The albumin “swim-up” technique is performed by layering semen beneath 2 mL of Hamm's F-10 solution and incubating at room temperature for 60 minutes. The upper layer is then carefully aspirated, washed twice in Hamm's solution, and resuspended to produce a concentration of 1×10^7 motile sperm per milliliter. After an additional 60 minutes, the upper interface is again aspirated and resuspended for later use.

Comparative evaluation of these techniques has demonstrated distinct differences in the final sperm preparations. A significant increase in progressive sperm motility has been reported for sperm separated by Percoll and albumin gradients when compared with controls (320). In addition, there are several reports in the literature describing pregnancies in previously infertile couples when variations of the aforementioned sperm-processing procedures were used (228). Despite differences in sperm recovery rates, whether fecundity rates vary is controversial when comparing methods (64,106).

Artificial Insemination

The development of artificial insemination of either the husband's semen or of donor semen (therapeutic insemination donor) has been closely linked with technical advances in semen processing and storage. Also known as *sperm banking,* semen cryopreservation should be offered to all men before chemotherapy if they desire to have future offspring (155,481). Cryopreservation of sperm for artificial insemination purposes is also performed before vasectomy and in donor programs. Sperm cryopreservation may also be offered to men at the time of vasectomy reversal and at the time of sperm retrieval procedures, but these sperm are destined for used with IVF-ICSI. Guidelines for anonymous donor sperm banking practices have been established by the American Society for Reproductive Medicine, and standards have been established by the American Association of Tissue Banks (AATB) (93). Donor sperm is widely available from a number of commercial sperm banks.

Intracytoplasmic Sperm Injection

Background

The origins of gamete micromanipulation can be traced to 1979 with the birth of the first IVF “test tube baby.” In IVF, human oocytes harvested from hyperstimulated ovaries are incubated in a culture dish with sperm. The successfully fertilized oocytes are termed *embryos* and are transferred into the uterus. The applicability of this assisted reproductive technology (ART) was initially directed at women with tubal occlusion or endometriosis, conditions

that may physically impair the successful union of sperm and egg. Despite its successes, the limitations of IVF became apparent in couples with a severe male factor characterized by abnormal semen analyses and poorly functioning spermatozoa (478). Although highly variable, minimum criteria considered suitable for standard IVF include greater than 500,000 progressively motile sperm with a frequency of normal forms of greater than 3% using stict morphology criteria (314).

Interest in the initial types of micromanipulation procedures, such as zona drilling, partial zona dissection, and subzonal insertion of sperm, evolved because of the disappointing results of standard IVF for the male factor patient. One particular problem with these techniques, which was finally overcome with ICSI, was the high rate of polyspermy (up to 25%), a lethal condition involving the entrance of more than one sperm into the egg (413). Initially reported by Palermo and colleagues in 1992 (313), ICSI is now considered standard by major IVF centers and has made these other micromanipulation techniques obsolete.

Indications for Intracytoplasmic Sperm Injection (Table 35.19)

Female Factor
Failed routine IVF
Day 2 ICSI after failed IVF (rescue ICSI)
After failed previous trials of IVF
Male Factor
Severe oligozoospermia (decreased sperm concentration)
Severe asthenozoospermia (decreased sperm motility)
Abnormal sperm morphology (teratozoospermia)
Immunologic infertility
Obstructive azoospermia requiring MESA
Congenital bilateral absence of the vas deferens
Failed vasectomy reversal
Acquired epididymal or vasal obstruction
Abnormal sperm function
Defective acrosome reaction or capacitation
Abnormal sperm penetration

ICSI, intracytoplasmic sperm injection; IVF, *in vitro* fertilization; MESA, microsurgical epididymal sperm aspiration.

TABLE 35.19. INDICATIONS FOR INTRACYTOPLASMIC SPERM INJECTION

1. “Rescue” ICSI is the microinjection of mature oocytes that have failed to fertilize on the first day of egg retrieval using standard IVF. Complete fertilization failure after successful oocyte retrieval can occur in 10% to 27% of couples undergoing IVF (73). ICSI can then be performed on day 2, especially considering the poor results of second-day routine IVF insemination. As an example of outcome, Morton and colleagues (286) reported a fertilization rate of 45% and a pregnancy rate of 15% per cycle initiated. The generally poor results with rescue ICSI may be related to decreased oocyte quality 24 hours after retrieval or the presence of inherently abnormal oocytes (293,423,429). Thus “rescue” ICSI can only be considered a relative indication for micromanipulation.
2. The failure to fertilize in a previous cycle of IVF is an indication for ICSI because it suggests impaired sperm penetrating capabilities (211). Palermo and colleagues (314) demonstrated successful ongoing pregnancy rates of 37% in a large series of 227 couples who had previously failed IVF or had too few spermatozoa for conventional IVF. The success of ICSI is further confirmed by the report of a delivery rate of 47% per cycle in 25 couples experiencing unexplained fertilization failure with conventional IVF (36). However, ICSI is unlikely to overcome inherent oocyte defects, if present (133).
3. Antisperm antibodies, implicated in approximately 10% of infertile couples, have traditionally been treated with corticosteroid therapy, sperm washing, and routine IVF. Because of impaired sperm binding and decreased penetration of the zona pellucida when antibodies are present, these therapies have poor fertilization rates varying in the range of 30% to 40% (233). In contrast, a study of 55 ICSI cycles with sperm having positive antisperm antibodies demonstrated a normal fertilization rate of 75.7% and fetal sac formation rates of 26.4% (293). Based on this study's excellent results, ICSI should be the primary choice of treatment for this condition when high quantities of antisperm antibodies are present.
4. Poor results with conventional IVF have also been reported in the presence of severe teratozoospermia (abnormal sperm morphology). ICSI should be the treatment of choice after failed IVF when a severe decrease in normal sperm morphology is a reproducible finding (332,410).
5. Severe oligoasthenozoospermia (decreased sperm density and motility) is the most common indication for ICSI. Definitions regarding what constitutes “severe” are not precise; but from a practical standpoint, when sperm densities are less than 5 million sperm/mL, fertilization rates with standard IVF drop significantly (478). Men with diminished sperm motility also have poor fertilization rates with IVF (446). In these patients, as well as those couples who have failed previous IVF cycles, fertilization and pregnancy rates of 65% to 76% and 30% to 32% per cycle, respectively, have been published (396).
6. Obstructive azoospermia, accounting for about 7% of male subfertility (417), is now potentially treatable with ICSI (292). In this condition, testicular production of sperm is normal, but, because of a blockage within the male reproductive tract, spermatozoa are not present in the ejaculate. These sperm may be recovered from the testis or epididymis and used very successfully with ICSI. Conditions causing obstructive azoospermia for which ICSI may be appropriate include failed vasectomy reversal, acquired or congenital epididymal and vasal blockages,

and congenital bilateral absence of the vas deferens. Other causes of obstructive azoospermia such as previous vasectomy and ejaculatory duct obstructions may be surgically treated without the need for ICSI. When ICSI is used for this indication, sperm must be retrieved using a variety of techniques previously described.

7. Nonobstructive azoospermia, also known as *testicular failure* and responsible for about 59% of azoospermia (190), describes a condition in which sperm production is markedly abnormal. These men were previously considered hopelessly subfertile and referred to adoption agencies. Sperm retrieval rates as high as 81% have been reported from testis biopsy specimens of men with azoospermia and testicular failure (103,426). Using TESE with ICSI achieved a fertilization rate of 47.8% and ongoing pregnancy rates of 25% to 31% for these men with testicular failure. TESE is the extraction of sperm that have been harvested from a testis biopsy. These men are not candidates for standard IVF because of the extremely low number of sperm recovered and their poor motility.
8. Anejaculation is a condition often associated with impairment of sperm function, especially in spinal cord–injury patients, who have preserved ejaculation in only about 20% of cases. Although experience is still somewhat limited and large-scale studies are unavailable, the poor fertilization rates with EEJ using IUI or standard IVF suggest an important role for ICSI.

Patient Selection

Proper patient selection, as determined by a comprehensive male evaluation, should be performed before proceeding with ICSI. Many men may have reversible or otherwise treatable etiologies, such as varicoceles, infection, and ductal obstruction, for their subfertility and may not need ICSI. The temptation to omit a male evaluation as a result of the erroneous thought that the success of ICSI bypasses the need for a urologic evaluation must be avoided for several reasons:

1. ICSI has a significant cost burden to the couple per “take-home” baby. Recent analysis by Schlegel (370) has demonstrated that after factors such as average number of cycles, multiple births, time lost from work, and costs directly applicable per cycle are factored, each live birth cost approximately $72,000 to $89,000 in 1994. In comparison, the costs per take-home baby with a varicocele repair for varicoceles and vasovasostomy or vasoepididymostomy for vasal obstruction are approximately $26,000 and $25,000, respectively. These figures were derived from results available from institutions with published or above average delivery rates. The costs, which are representative for a single child, are further accentuated if more than one child is desired.
2. ICSI with IVF exposes the female to potential significant complications of ovarian hyperstimulation syndrome and multiple gestation. Although this syndrome is not common, serious life-threatening maternal complications may occur. The most recent Society for Assisted Reproductive Technology data found that of reported IVF-related deliveries in 1996, a multiple gestation rate of 34.8% was observed (358).
3. Although uncommon, significant underlying medical illnesses may be discovered with subfertility as the presenting complaint. Potentially life-threatening abnormalities, including testicular, spinal cord, and brain tumors, were discovered in 1.1% of 1,236 new male infertility patients treated at two busy infertility clinics (172).

Technique

ICSI begins with oocyte retrieval using ultrasound-guided transvaginal puncture at the time of optimal follicular development following appropriate hormonal stimulation for an IVF cycle. After the oocyte has been stabilized by a holding pipette in a micromanipulator, an injection pipette with an outer diameter of 7 µmm and an inner diameter of 5 µmm is used to penetrate the thick zona pellucida of the oocyte (Fig. 35.28). After a brief incubation, those oocytes that have extruded the first polar body (now metaphase II) are candidates for ICSI. Sperm sources include fresh and frozen specimens from routine ejaculates, microsurgical epididymal sperm aspirates, testis biopsy specimens, and electroejaculated specimens. The micromanipulation procedures are then performed using an inverted phase-contrast microscope at 400×. Although costs of an IVF-ICSI cycle vary significantly, a rough current estimate per cycle is $7,000 to $12,000 in the United States.

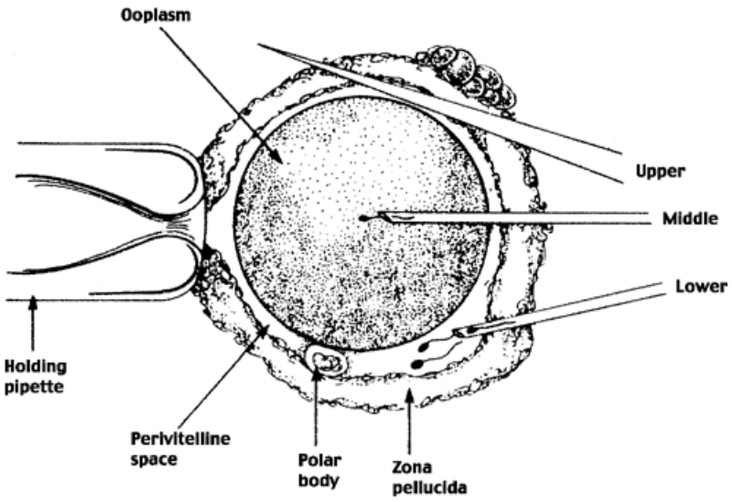

FIGURE 35.28. Intracytoplasmic sperm injection (ICSI). The oocyte is held in place using a microholding pipette in a micromanipulation apparatus. The polar body is positioned away from the site of sperm injection into the oocyte. A microinjection pipette is injected directly into the ooplasm *(middle).* Older methods, which are no longer being used, include subzonal insertion of sperm *(lower)* and partial zona dissection *(upper)*.

Results

The most recent data from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry are from cycles completed in 1996 (358). This registry represents data collected from 300 programs across the United States. Overall for all indications, 14,049 cycles, representing 31.5% of all IVF cycles, of IVF-ICSI were reported. A delivery rate per retrieval of 25.9% was reported, with a 62.2% singleton pregnancy rate. The birth defect rate was 1.8%, identical to routine IVF.

An important trend observed with the 1996 data was that the presence of a male factor diagnosis had a much less significant impact on success rates than in previous years, suggesting that ICSI may mitigate the effects of male factor infertility. In fact, those couples with a male factor diagnosis had a higher rate (24.0%) of delivery per retrieval than those with other diagnoses (21.8%). In previous years' data, those couples with a significant male factor uniformly had poorer outcomes per female age grouping than when a male factor was absent.

Because it appears that even the most severe sperm defects are treatable with ICSI, female factors such as age and oocyte quality are being examined more closely and will probably prove to be the main determinants of success.

The results of ICSI are best examined for the specific indication performed. The results and pertinent studies are discussed throughout the text of this review.

Genetic Concerns

Although ICSI is one of the most significant advances in the treatment of the otherwise untreatable subfertile male, significant concerns exist regarding the potential for transmission of abnormal genes to the offspring because many of the natural barriers to conception have been bypassed. Although these abnormal genes may result in similar types of infertility problems in the offspring (as in the father), an unanswered question is whether these genes may result in other disease states or systemic problems (234). The long-term genetic consequences in these offspring are largely undefined at this time. ICSI bypasses natural barriers to conception because sperm no longer need to penetrate the oocyte. With natural intercourse or standard IVF, in general, only the best sperm are able to penetrate the tough barrier provided by the zona pellucida of the oocyte.

A retrospective study by Palermo and colleagues (315) provided valuable insight regarding clinical outcome parameters of ICSI versus IVF. A total of 751 couples undergoing 987 ICSI cycles for male factor infertility were studied and had an overall clinical pregnancy (fetal heartbeat) rate of 44.3% and a resultant delivery rate per ICSI cycle of 38.7% (n = 382). In 8 of 11 miscarriages for which cytogenetic data were available, an autosomal trisomy was found, and 7 additional pregnancies were terminated because of a chromosomal abnormality after prenatal diagnosis. Of the 578 neonates resulting from treatment by ICSI, 15 (2.6%) had congenital abnormalities (9 major and 6 minor abnormalities). However, this frequency of malformations was lower than that observed in offspring born after standard IVF at their institution. Furthermore, when pregnancy outcome of ICSI versus IVF was analyzed in terms of semen origin, no differences were found in the frequency of miscarriages or in the rate of congenital malformations. This study concluded that the chromosomal abnormality rate was not higher in ICSI than in IVF. However, the true effect of ICSI on the offspring cannot be determined without long-term follow-up. Similarly, several reviews have concluded that ICSI does not appear to cause any significant increase in known genetic-based diseases or infertile males (117,252,371). This topic will remain controversial until much longer-term follow-up in larger groups of patients is obtained.

Future Directions

On the distant horizon is the micromanipulation procedure called round spermatid nuclear injection (ROSNI), presently considered experimental, but already described in several reports of viable human pregnancies (125) and live births (414). This technique is similar to ICSI, except that less mature, immediate sperm precursors are injected into the oocyte. Although this technique may be potentially a major advance for the future, similar significant and justified concerns regarding genetic transmission are being raised, especially because of the more severe nature of the male

infertility. With each advance in the treatment of male infertility, ethical and genetic questions are raised and must be scientifically and socially addressed.

Preimplantation genetic diagnosis (PGD) may be performed on IVF- or ICSI-derived embryos as a form of prenatal diagnosis aimed at eliminating embryos carrying serious genetic diseases before implantation (151,158,159). In PGD, a single cell is removed from an early eight-cell embryo and tested for various genetic disorders typically using *in situ* hybridization (ISH) or the polymerase chain reaction (PCR). ISH techniques allow the direct visualization of single genes and can be applied to single cells. The first clinical application of PGD was described in 1990 by Handyside and colleagues (157), who amplified Y chromosome–specific sequences using PCR to determine the sex of embryos from couples at risk of X-linked diseases. PGD may be used clinically for the detection of disease states associated with male infertility such as cystic fibrosis and numeric chromosomal abnormalities. PGD has also been used for detection of numerous other disease states, including Duchenne's muscular dystrophy, Tay-Sachs disease, fragile X, and Marfan syndrome.

The use of PGD in men with severe male factor infertility with additional adverse contributors such as advanced maternal age, repeated IVF failures, and altered peripheral blood karyotype was addressed by Gianaroli and colleagues (136). In this series of 40 men and 28 normal controls, no increase in chromosomally abnormal embryos was detected. With regard to translocations, Pierce and colleagues (331) demonstrated the use of PGD for the diagnosis of reciprocal translocations within the chromosomes 5 and 8 and Conn and colleagues (86) for couples with robertsonian translocations.

Germ cell transplantation may have clinical utility for patients undergoing gonadotoxic treatments for malignancy. As an example, a young gentleman receiving chemotherapy for testicular cancer could potentially have testicular germ cells removed before chemotherapy, then replaced afterward. Pioneering work by Brinster and Nagano (57) in mouse models has already demonstrated success.

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36

STRICTURES OF THE MALE URETHRA

George D. Webster

Suzie N. Venn

G.D. Webster: Department of Surgery, Division of Urologic Surgery, Duke University Medical Center, Durham, NC 27708.

S.N. Venn: Senior Lecturer and Consultant, Institute of Urology, UCLH, London, and St. Richard's Hospital, Chichester, UK.

Contents

The result of urethral injury, regardless of etiology, is the formation of scar tissue that may reduce the caliber of the urethral lumen and result in stricture. Such strictures were referred to in the writings of the ancient Greeks and Hindus, who reported the passage of various catheters to effect bladder drainage; indeed, pharaohs were entombed with brass dilators by their side lest their stricture problems recur in the hereafter (5). Historically, the major cause of stricture was gonococcal urethritis, but in modern communities, increased awareness and the availability of effective early treatment have lessened its impact on the urethra, and indeed in developed nations, trauma is now the leading cause.

The modern surgical era has seen a significant change in the management of urethral stricture disease, with the time-honored urethral sound playing a lesser role as an array of open surgical techniques, often utilizing tissue transfer, have become more successful. This chapter discusses the concepts germane to the successful management of this disease, identifying a rational approach based on the location, etiology, extent, and complexity of the stricture, and it describes the surgical techniques most commonly used and results achieved.

ANATOMIC CONSIDERATIONS

Part of "36 - STRICTURES OF THE MALE URETHRA "

The male urethra is divided into anterior and posterior portions. The anterior portion comprises the glans meatal, the penile, and the bulbar urethras, and the posterior portion includes the membranous and prostatic urethras. The glans meatal urethra, contained within the glans penis

and surrounded by spongy tissue, is a unique, vertically oriented, slit-shaped orifice that perfectly confines and directs the urinary stream. The penile or pendulous urethra extends from the glans to the suspensory ligament of the penis and is centrally located within the corpus spongiosum. Proximal to the suspensory ligament and surrounded by more developed spongy tissue is the bulbar portion (Fig. 36.1). The urethral lumen lies eccentrically (anteriorly) within this spongy tissue and is further enveloped by the bulbospongiosus muscles. Proximal to the bulbar urethra is the posterior urethra comprising the sphincter-active membranous portion and the prostatic portion. The membranous urethra is relatively unfixed to the surrounding structures, whereas the prostate is fixed to the pubis by the puboprostatic ligaments. The prostatic and membranous urethras are lined with transitional epithelium that gradually changes to squamous epithelium in the bulbar urethra and continues as such until changing to stratified squamous epithelium in the glans meatal urethra. As noted previously, the degree and distribution of spongy tissue envelopment of the anterior urethra vary according to location, with abundant posteriorly located spongy tissue in the bulbar urethra and relatively minimal and symmetrically surrounding spongy tissue in the pendulous urethra. This has some importance in stricture management because visual urethrotomy carries little success in the pendulous urethra, where there is little spongy tissue into which an incision can be made, as compared with the bulbar portion.

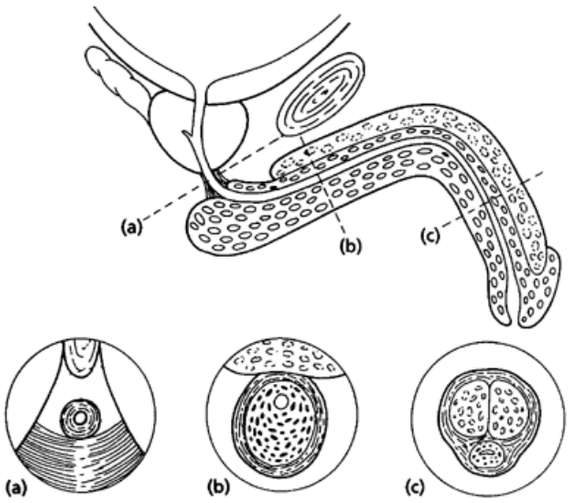

FIGURE 36.1. Anatomic divisions of the urethra. The envelopment of the urethra by spongy tissue differs from the membranous urethra *(a)* where there is none, to the bulbar urethra *(b)* and pendulous urethra *(c).* (From Webster GD, Khoury JM. Acute urethral trauma. In: Webster GD, Kirby R, King LR, et al., eds. *Reconstructive urology.* Oxford: Blackwell Scientific Publishers, 1993, with permission.)

The arterial supply of the male urethra has important therapeutic implications. It is supplied primarily by the bulbar arteries, which are proximal branches of the internal pudendal artery. Distally, it is supplied by the dorsal artery of the penis, which is a terminal branch of the internal pudendal artery. This dual blood supply allows the urethra to be detached at either end without compromise to its viability, a fact frequently used in urethroplasty (Fig. 36.2). Dartos fascia loosely envelopes the penis and connects with the superficial Scarpa's fascia at the abdominal wall at the base of the penis. In the scrotum and perineum, the Dartos' fascia continues as Colles' fascia and attaches posteriorly to the central tendon of the perineum, and laterally to the ischium and inferior ramus of the pubis. Deep to this continuous fascial plane is the superficial perineal pouch. A condensation of Colles' fascia at the base of the penis forms the suspensory penile ligament. Buck's fascia is a dense but elastic layer deep to Dartos' and Colles' fasciae, and it envelopes the erectile bodies in the penis and extends into the perineum, where it separately envelopes each crus of the corporal cavernosa and splits to envelope the bulbar urethra. These fascial layers are important in urethral injury because extravasation will be contained and will migrate within the layers, depending on the degree of injury (Fig. 36.3).

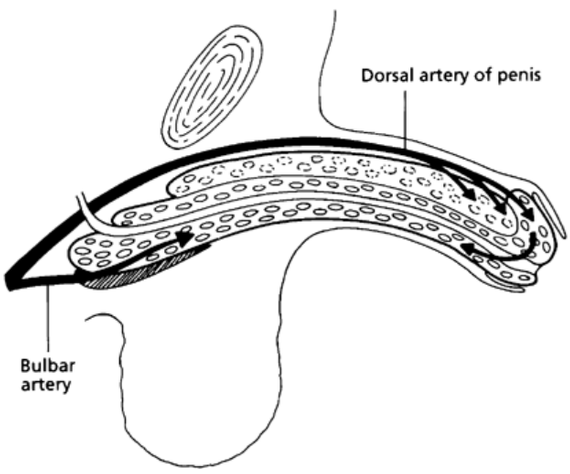

FIGURE 36.2. The urethral vascular supply is both proximal (bulbar arteries) and distal (collaterals from corporal bodies and dorsal penile arterial supply to glans penis). This allows the urethra to be transected proximally and mobilized as a "flap" on its distal blood supply. (From Webster GD, Khoury JM. Acute urethral trauma. In: Webster GD, Kirby R, King LR, et al., eds. *Reconstructive urology.* Oxford: Blackwell Scientific Publishers, 1993, with permission.)

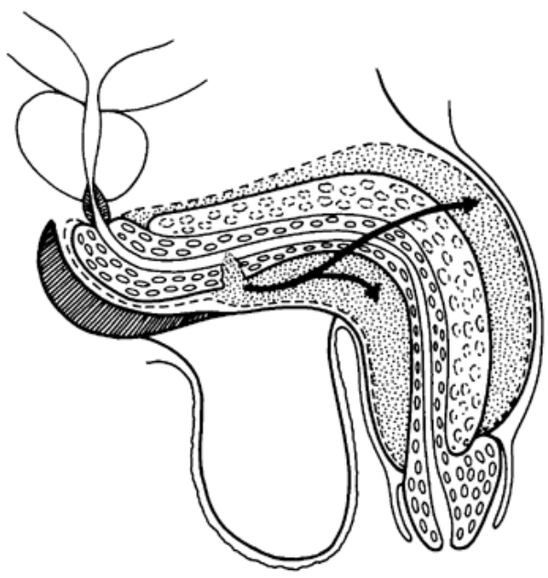

FIGURE 36.3. Fascial layers of the genitalia will determine the direction and extent of urinary and blood extravasation after urethral injury. Illustrated here is urethral injury with Buck's fascia remaining intact, directing extravasation along the penile shaft. (From Webster GD, Khoury JM. Management of acute urethral trauma. In: Webster GD, Kirby R, King LR, et al., eds. *Reconstructive urology.* Oxford: Blackwell Scientific Publishers, 1993, with permission.)

The entire posterior urethra in the male is sphincter-active, and any injury in this area will alter sphincter function to some degree. The proximal (bladder neck) and distal (external) sphincter mechanisms may be considered to function independently. Under normal circumstances, continence is maintained at the bladder neck level, with this mechanism only opening when the detrusor contracts, voluntarily or involuntarily (82). However, if rendered nonfunctional by prior surgery or injury, perfect continence can be maintained by the distal sphincter mechanism. This is confined to the 3- to 5-mm thickness of the wall of the membranous urethra from the level of the verumontanum down to the distal part of the membranous urethra where it merges with the bulbospongiosus tissue (Fig. 36.4A). The

distal mechanism comprises an inner layer of slow-twitch, striated muscle fibers capable of the sustained contraction necessary for continence, and it is the distal two-thirds of this intrinsic mechanism that is most functional. Contrary to most anatomic descriptions, it has been shown that a urogenital diaphragm comprising a musculofascial "sandwich" does not exist (87). There is virtually no muscle anterior and anterolateral to the membranous urethra, and the only periurethral muscle directly related to this part of the urethra is that which inserts into the perineal body attached to the posterior surface of the bulbomembranous urethra (15) (Fig. 36.4B). These posterior periurethral muscles are capable of momentarily interrupting the voided stream by compressing the urethra from behind, but they are totally incapable of maintaining continence in the absence of a functional intrinsic mechanism.

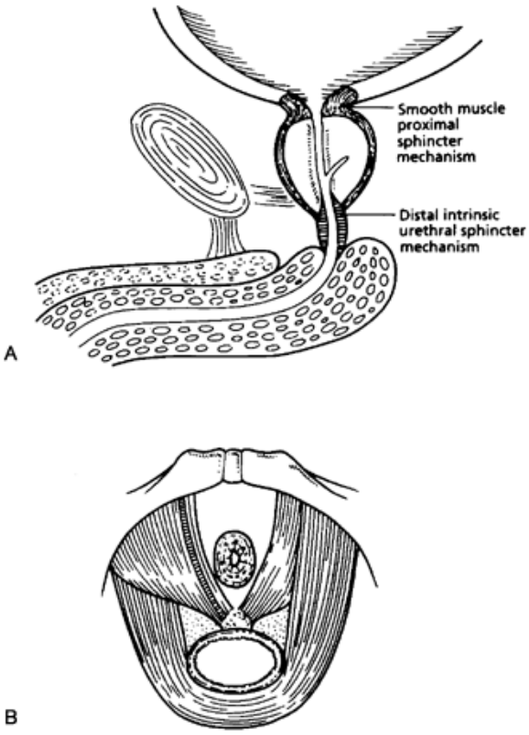

FIGURE 36.4. Male urethral sphincter mechanism. **A:** Smooth muscle proximal (bladder neck) mechanism, continuous with periprostatic musculature. Distal intrinsic sphincter mechanism resides within wall of membranous urethra. **B:** Distal extrinsic urethral sphincter mechanism (periurethral striated pelvic floor musculature) abuts on the urethra posteriorly and laterally only.

ETIOLOGY

Part of "36 - STRICTURES OF THE MALE URETHRA "

The etiology of the stricture is not only of academic importance, but also it has considerable bearing on the type of stricture that will result, and hence on the type of repair that will be most appropriate. The urethral epithelium is extremely thin, and along the majority of the urethral length, it is based on underlying spongy tissue. In the membranous urethra, the mucosa is applied to the musculature of the intrinsic urethral sphincter. Thus for the majority of the urethra, any event that damages the epithelial lining immediately exposes a spongy bed through which infection or urinary extravasation may spread with resultant spongiofibrosis. The eventual stricture then will arise partly because of cross-healing of the denuded portions of the urethra at the site of trauma and partly because of cicatrization of the damaged spongy tissue. Spongiofibrosis may extend for a considerable distance proximal and distal to the actual stricture, surfaced by normal epithelium; failure to appreciate the true extent of the urethral stricture may be one of the main reasons for failure of stricture surgery. Urethroplasty therefore should encompass not only the definitive stricture, but also should include the spongiofibrotic urethra and extend for up to 2 cm into normal urethra proximal and distal to the limits. All urethral surgeons have encountered the thickened and often cornified mucosa proximal to a tight stricture. This cornification and underlying spongiofibrosis may be caused by extravasation of urine as a result of the pressure of urine behind this obstruction.

Congenital

Although congenital strictures undoubtedly do occur, they are rare. An embryologic explanation for their occurrence in the bulbomembranous region suggests that the epidermal distal urethral anlage does not totally join the prostatic endodermal anlage just distal to the bulbomembranous junction, and thus a stricture represents incomplete rupture of the cloacal membrane. However, it is likely that their incidence is vastly overestimated because strictures occurring in patients who deny previous infection or trauma frequently are ascribed to a congenital etiology. Blandy (10) has alluded to these strictures, noting that, histopathologically, their wall shows smooth muscle rather than collagen-fibrous tissue, which would be expected were they of inflammatory or traumatic etiology. These strictures often are described as being soft, and because teleologically they should not be associated with spongiofibrosis, they should respond to careful endoscopic management. Cobb and associates (17) reported 26 such cases in children ranging from the newborn period to 16 years of age, none of whom had been instrumented previously, nor had they incurred trauma or urethritis.

Inflammatory

Inflammatory strictures usually are associated with gonorrhea or nonspecific urethritis, which often is caused by chlamydial organisms. Single infections, particularly if appropriately and rapidly treated, should resolve without significant injury to the urethral epithelium. However, repeated and incompletely treated infections cause severe local inflammation, particularly of the bulbar urethra, with resolution by scarring. Unlike traumatic strictures, which are frequently short and discreet, inflammatory strictures often involve a considerable length of the urethral epithelium and underlying spongy tissue, a fact of great importance in subsequent management. It is this degree of involvement of the underlying spongy tissue that will dictate the natural history of the stricture and its response to therapy. Superficial mucosal injury will result in strictures that probably result from cross-healing of the raw mucosal edges, and they will be diaphanous and soft and easily broken down by urethral bouginage, with low likelihood of recurrence. When infection causes deep and extensive spongy tissue fibrosis, the stricturing is because of narrowing of this deep scar, and urethroplasty management will likely become more necessary. The former superficial stricture may be converted to the latter dense one by traumatic management, allowing urinary extravasation or infection that will further injure the spongy tissue. Chronic specific inflammatory diseases are now uncommon, although tuberculosis and schistosomiasis rarely may have urethral manifestations.

Balanitis xerotica obliterans (BXO) also is associated with inflammatory strictures, particularly in the penile urethra. BXO is accepted as a cause of phimosis and meatal stenosis, but its extension to the penile urethra was thought to be caused by high-pressure voiding against an obstruction or as a result of the trauma of repeated dilations. This may not be true, and it may well be that the BXO process is locally extensive down the urethra. It appears that it may be a more

common cause of penile urethral stricture disease than previously thought (90), and its recognition as the cause is very important because it affects the selection of technique for successful repair (see subsequent discussion).

Ischemic

Urethral strictures have been reported following cardiovascular surgery, and following extracorporeal circulation may occur in up to 22% of cases. The proposed mechanisms have included the type of catheter used and the duration of trauma of catheterization, but urethral strictures are thought by most to be caused primarily by ischemia (25). These strictures typically have been in the penile urethra and have varied in length and severity. The use of suprapubic catheters or small-caliber silicone urethral catheters has been suggested to reduce the risk of this complication (13,42).

Traumatic

The more common causes of trauma to the urethra include blunt perineal injury, penetrating injury resulting from gunshot or stab wound, iatrogenic injury resulting from urethral instrumentation, and injuries following pelvic fracture.

Blunt Perineal Injury

Most blunt perineal injuries are a result of straddle injuries where the urethra is trapped or compressed against the underlying symphysis. The force of the injury determines its extent, and in severe cases it may be transected completely, but in many cases it is partial and continuity is maintained. If Buck's fascia is ruptured, extravasated blood and perhaps urine will be contained within the confines of Colles' fascia with a resulting perineal and scrotal hematoma, often in a typical butterfly distribution. If Buck's fascia remains intact, extravasation will occur along the shaft of the penis and will result in edema and discoloration (Fig. 36.3).

Penetrating Urethral Injury

Penetrating urethral injuries are becoming more common as a result of violence in our society. The low muzzle velocity of most handguns means that bullet penetration leads only to local damage. However, high-velocity military weapons cause considerable damage distant from the bullet path. In the former, immediate debridement and repair is simple, whereas in the latter, subsequent death of unrecognized nonviable tissue may lead to poor results.

Iatrogenic Urethral Injury

Iatrogenic urethral injury is the leading cause of urethral trauma, the culprit being inept urethral catheterization or instrumentation. Common sites are the penoscrotal junction and the urethral meatus. Rigid instrument trauma often is to the bulbar urethra. Most modern endoscopic systems include a forward-viewing telescope, allowing for the placement of the endoscope under vision, and there is no reason for blind insertion of a cystoscope. Similarly, the practice of blind urethral calibration by the passage of urethral sounds in patients with voiding difficulty is not recommended. Such practices frequently result in urethral laceration at the site of the stricture, with the formation of false passages and failure to gain access proximally. A urethrogram performed at this juncture shows an “extravogram,” further confusing the issue. A retrograde urethrogram or endoscopy with stricture negotiation using a filiform is the optimal practice.

Urethral Injury Following Pelvic Fracture

Most pelvic fractures result from motor vehicle accidents, but they are also an occupational hazard among miners, lumberjacks, construction workers, and those working with heavy equipment and machinery. The prostatomembranous urethra is injured in approximately 10% of patients sustaining pelvic fracture, and the magnitude of the injury will determine the extent of the initial vesicourethral dislocation. At one end of the spectrum, only urethral contusion may result; in more severe distraction injuries, the urethra may be partially torn but continuity maintained; and in severe injuries, total disruption and separation of the torn urethra results (Fig. 36.5). The incidence of partial tears varies in

reported series but averages 34%. The degree of injury is pertinent to management and outcome. Urethral elongation injuries generally are managed by urethral stenting, and will heal stricture-free, although there may be some distal-sphincter compromise. Partial tears also have the potential for stricture-free healing, if they are not aggravated by instrumentation or local infection, and a case is made for their management by temporary urinary diversion by suprapubic cystostomy in the acute phase. Total urethral distraction injuries will require realignment or reanastomosis, and philosophies regarding their management are presented subsequently.

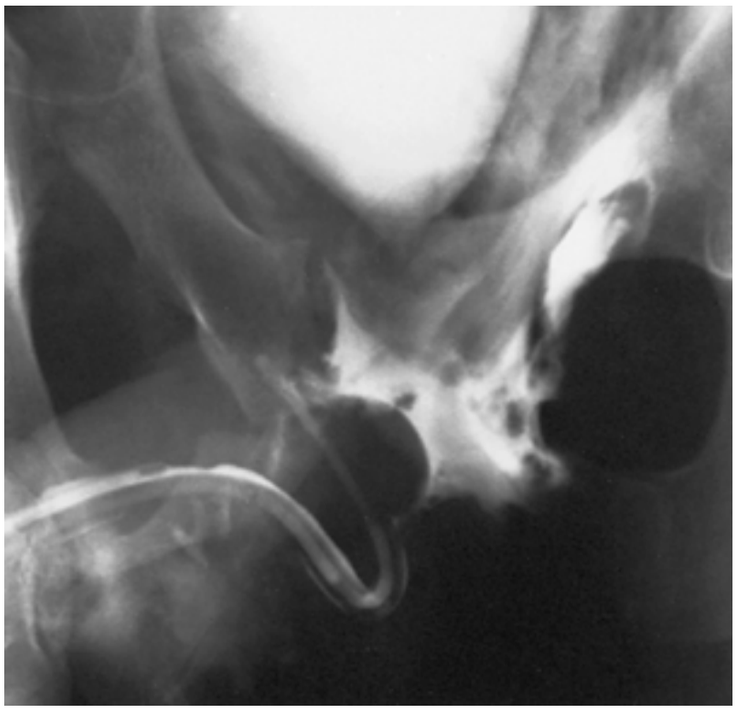

FIGURE 36.5. Total urethral disruption following pelvic fracture. A Foley catheter has been inserted and the balloon inflated in the retropubic space. Contrast injection shows the lack of urethral continuity, confirming total urethral separation.

Any pelvic fracture sufficient to damage the urethra generally will cause significant vascular and neural injury in the pelvis also, and this accounts for the high incidence of impotence in such cases. The cavernous nerves course in close proximity to the membranous urethra, and if not injured by the fracture itself, are at jeopardy during subsequent urethroplasty (71). The pattern of pelvic fracture has significant bearing on the likelihood of postinjury erectile dysfunction, and Crasweller and coauthors (20), as well as Mark and associates (49), have shown that fractures of both pubic rami are most likely to injure neurovascular structures bilaterally and lead to impotence. Obviously, every attempt must be made to avoid injury to remaining intact neurovascular structures at the time of surgical repair; however, it is important to recognize that there is a very high incidence of impotence attributable to the injury itself.

DIAGNOSIS

Part of "36 - STRICTURES OF THE MALE URETHRA "

Urethral strictures generally present with the symptoms of obstructed voiding. Because the process of urethral cicatrization may be very slow, the slowing of the stream may be insidious, and delayed recognition is not uncommon. In some cases, the process is rapid and readily recognized, such as in the postmeatal stricture that occurs following transurethral resection of the prostate (TURP). Other presentations of urethral stricture include urinary tract infections, urethral bleeding, epididymitis, and in some communities, periurethral phlegmon or urethrocutaneous fistula. In older men, there is occasionally some difficulty in deciding whether the symptoms are caused by the stricture or prostate enlargement. It is well known that prostate size on rectal examination, or the appearance of occlusive lobes on endoscopy, do not dictate that prostate outlet obstruction exists. It is judicious to reassess the patient after urethral dilation to determine which of the two pathologies is the cause of the voiding difficulty.

Radiologic Studies

Excretory urography or renal ultrasonography ideally is performed at the time of diagnosis of significant and longstanding urethral strictures. Bladder and upper tract changes are uncommon but may be important in the overall care of the patient, and sometimes the excreted contrast can be voided as a “poor man's” cystourethrogram to delineate the urethra proximal to the stricture.

Retrograde urethrography is the mainstay of the radiographic investigation of stricture disease. A variety of techniques exists, but each emphasizes the need for sterility and the avoidance of further trauma to the urethra. Retrograde urethrography may be confusing and generally is avoided within 3 to 4 weeks of traumatic urethral instrumentation, because residual urethral epithelial injury may allow startling extravasation of contrast into the spongy tissue and into lymphatics and veins of the pelvis. Ideally, liquid contrast medium suitable for intravenous urography is used. Injection techniques utilize various clamp devices. However, the use of a syringe with a catheter irrigating tip, which is impacted in the urethral meatus, or the use of a small Foley catheter, the balloon of which is gently distended just proximal to the fossa navicularis to plug the urethra, are optimal. This latter method is attractive because it avoids contrast leakage around the genitalia and also allows the investigator to keep his or her hands well clear of the field of radiation.

The urethrogram not only should delineate the stricture but also should show the urethra proximal and distal to it (Fig. 36.6). The length, caliber, location, multiplicity, and proximity of the stricture to the sphincter all should be identified. This is best done by the gentle injection of a large bolus

of water-soluble contrast medium with the patient in the half-lateral position with the top hip extended. If the caliber of the stricture is so small that contrast cannot be introduced in the retrograde manner, the more proximal urethra may be evaluated by voiding cystourethrography. This may be performed as part of the excretory urogram; however, the excreted contrast often is not sufficiently dense to give interpretable films. If the urethral stricture is not totally obliterative, a small feeding tube may be negotiated past the stricture, the bladder filled in this manner, and the contrast voided. In patients who have obliterative strictures, suprapubic cystostomy will have become necessary because of urinary retention, and voiding cystourethrography can then be accomplished by suprapubic tube filling of the bladder. If this study is not performed, a distal stricture may inadvertently be repaired and additional proximal disease may not be recognized.

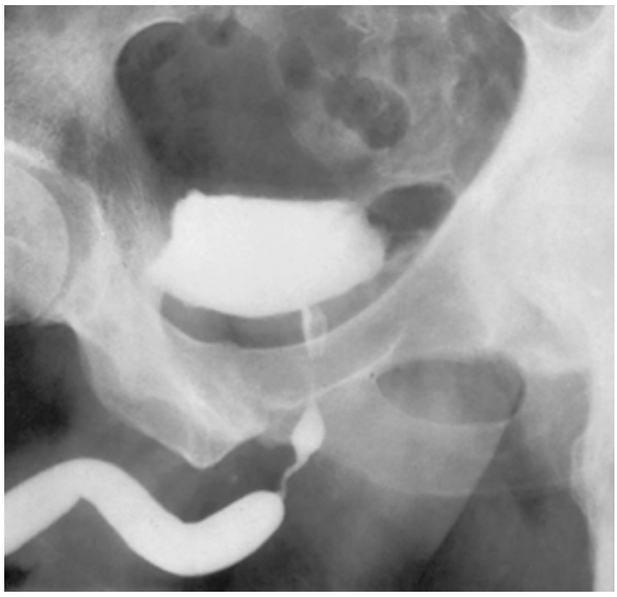

FIGURE 36.6. A dynamic retrograde urethrogram showing a healthy anterior urethra up to a long proximal bulbar stricture. The sphincter-active portion of the urethra and prostatic urethra are delineated. Proximity of the stricture to the sphincter mechanism is demonstrated adequately.

Combined retrograde urethrogram–voiding cystourethrogram is indispensable in the evaluation of the obliterative urethral defect that follows pelvic trauma (Fig. 36.7). This study generally can be performed with the patient awake; however, in the face of total obstruction of the urethra, many patients are unable to generate a detrusor contraction to open the bladder neck and thus fail to fill the proximal urethra. Fortunately, the majority of patients will accomplish this if the bladder is filled under anesthesia, so the study can precede the urethroplasty should adequate radiography not have been obtained preoperatively. This combined urethrogram and voiding cystourethrogram will demonstrate the length of the obliterated segment, a point of great importance in obliterative posttraumatic defects such as those that follow straddle injury or pelvic fracture. Because misalignment of the urethral ends is not uncommon following pelvic fracture, films with differing obliquities may be necessary. The sonographic urethrogram has been reported to be equally efficacious and in some ways superior as a diagnostic modality when compared with the standard retrograde urethrogram. The stated advantages include the identification of the extent and thickness of periurethral fibrosis and spongiofibrosis, accurate measurement of urethral luminal size, and the noninvasive nature of the study (30,53). In addition, color Doppler can demonstrate the urethral arterial supply (16), which may have a role in the evaluation of impotence. Sonography has failed to replace retrograde urethrogram in clinical practice, probably because of the difficulties in interpretation and the lack of a permanent image.

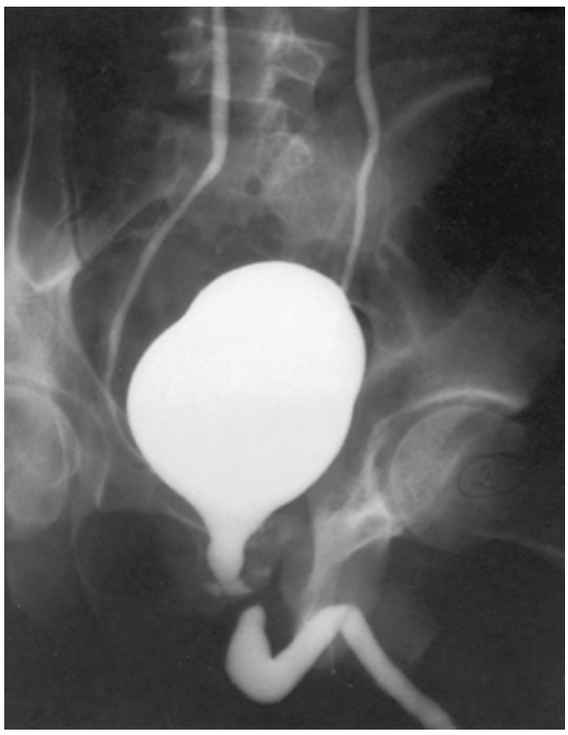

FIGURE 36.7. A combined retrograde urethrogram and voiding cystourethrogram in a patient with a pelvic-fracture urethral-distraction defect. This film demonstrates the length of the defect and the healthy appearance of the anterior urethra. Competence of the bladder neck, essential for continence after repair, is demonstrated by radiographic exposure before the “voiding” film.

Magnetic resonance imaging (MRI) also has been described for the evaluation of pelvic-fracture urethral distraction defects before surgery (23).

Endoscopy

Although urethrography is the mainstay of investigation and identifies the important characteristics necessary for treatment selection, endoscopy is still valuable. “Grey” urethra, where spongiofibrosis extends beyond the limits of the definitive stricture, may not be apparent radiographically, but it often is evident urethroscopically and will inform the surgeon of the limits of the repair.

In patients with obliterative posterior urethral defects following pelvic fracture, retrograde urethroscopy and antegrade cystourethroscopy through the suprapubic cystostomy site give valuable information. Anastomotic repairs of such defects rely on a healthy distal urethra, and this may be confirmed urethroscopically. These patients usually have had a suprapubic tube in place for some time, and bladder stones are not uncommon and should be managed before or at the time of urethroplasty. The bladder neck will be the main source of continence in such men, because the distal sphincter mechanism usually is ablated by pelvic fracture injury of the urethra. Although the bladder neck's competence may be assessed by cystography, confirmation of its competence by antegrade cystoscopy is valuable. If a flexible cystoscope is used, further visualization of the prostatic and sphincteric portion of the proximal urethral stump is possible, thereby confirming its patency.

In rare instances, urethral carcinoma may masquerade as benign urethral stricture, but endoscopic finding of an exuberant or ulcerated urethral lesion should raise the clinician's suspicion and lead to biopsy.

MANAGEMENT

Part of "36 - STRICTURES OF THE MALE URETHRA "

Urethral strictures are treated by a variety of techniques, including urethral dilation, urethrotomy, urethral stenting, and a repertoire of operative techniques. Philosophic differences among urologists exist regarding the role of each of these techniques in urethral stricture management; certainly the most commonly used methods continue to be dilation and urethrotomy. Surgical management, aiming at “cure,” has gained momentum in recent decades; however, the techniques are somewhat unforgiving, and the occasional urethroplasty surgeon with a limited repertoire of techniques may not achieve optimal outcomes.

No single operative procedure is appropriate for all strictures. Procedure selection is determined by many factors, including the location of the stricture, its etiology, its length, its multiplicity, proximity to the sphincter mechanism, and the presence or absence of such local adverse factors as fistula, false passage, or diverticulum. With these variables in mind, it is evident that no single surgical technique will be adaptable to all eventualities, and the surgeon managing stricture disease should be versed in a wide array of techniques, and in most instances, the appropriate procedure may be selected only at the time of surgery.

The operative procedures available for the repair of urethral stricture disease may be classified broadly based on three principles. These are regeneration procedures, excision and anastomotic repairs, and substitution urethroplasty. In some cases, repairs rely on a combination of these principles, and repairs may be performed in single or multiple stages, depending on individual requirements.

Regenerative Procedures

Regenerative procedures rely on reepithelialization of the urethra once the lumen has been restored. This technique tends to be the most successful for superficial strictures with little spongiofibrosis, where reepithelialization can occur on a virgin bed. Obviously, epithelialization on an underlying scar will result in restenosis, and this is generally the case following simple urethral dilation and accounts for the high failure rate. Urethrotomy attempts to circumvent this problem by incising the ring of underlying scar, in the hope that the cleft created will epithelialize and remain open. Although this does occur in a good percentage of cases, in many the cleft heals across and stricture occurs.

Indwelling urethral stents are a more recent innovation in the management of urethral stricture disease, using the principle of regeneration.

Anastomotic Repairs

Anastomotic repairs are the most successful techniques for stricture repair and are used primarily for the management of traumatic bulbar and membranous urethral stricture. To ensure success, the stricture must be excised circumferentially and a spatulated overlapping anastomosis of the healthy ends accomplished. This obviously will require urethral mobilization proximal and distal to the excision site, and will incur a degree of urethral shortening that potentially could result in penile shortening or chordee. This limitation generally contraindicates their use for the management of pendulous urethral stricture. This is also the primary limiting factor in the application of this repair for the management of bulbar urethral stricture where, in the adult, it is believed that only 2 cm of urethral shortening can be tolerated before penile chordee is possible. Accepting that 1-cm spatulations will be required to achieve an overlapping anastomosis, this leaves only 1 cm available for stricture excision. The principle of urethral reanastomosis can be used for longer repairs in the bulbar urethra by augmenting the anastomosis with a graft or flap, a technique called an *augmented anastomotic repair* (see subsequent discussion). Obviously, in the aged impotent male these limitations may be ignored.

On the contrary, anastomotic repairs invariably are applicable for the management of the pelvic-fracture distraction defect regardless of length, both because of the extensibility of the uninjured, surgically mobilized, bulbar urethra and the fact that a number of surgical maneuvers may be used to relieve tension on the anastomosis, as will be discussed later.

Substitution Urethroplasty

When anastomotic urethroplasty is not possible, substitution of the urethra is required. All techniques appear to suffer the same shortcoming, which is progressive restenosis in the long term in a significant number of cases. Mundy (63), reporting a series of 73 substitution urethroplasties, noted an attrition rate after 4 years of 5% per annum, with an ultimate 10-year successful outcome of 60%. This report did include a variety of techniques and substitution sources. This is in sharp contrast with the results for anastomotic repairs, where the majority of failures occur within the first year and the subsequent restenosis rate is very low. This emphasizes the fact that there is no ideal substitute for the urethra. In addition, it has been demonstrated that tube grafts are not as successful as patch grafts, and indeed, full circumference repair of the urethra rarely is ideal (95).

In an attempt to reduce the shortcomings of substitution urethroplasty, Turner-Warwick (84) described a variety of procedures applicable to a wide range of stricture situations, called *combination procedures.* The goal of these staged repairs was to create a fixed flat urethral roof strip, the remainder of the urethral lumen being reconstructed by substitution. This reduced the portion of substituted urethra to only approximately 50% of the total neourethral circumference. Recently, a number of authorities (32,33,96) have redefined this procedure to allow for transfer of tissue on to a urethral plate using a graft or a flap of penile skin in one stage, with success rates of approximately 85% being reported (96). This technique has been further modified by Barbagli (7), who creates a *floor* strip of native urethra, augmenting the urethra on its dorsal surface (the *dorsal onlay repair*). This technique is conceptually superior because the graft is spread-fixed to a well-vascularized, secure graft bed on the overlying corporal body (38).

Staged repairs currently are regaining in popularity, particularly in the penile urethra, and especially when the stricture etiology is BXO or when it is not possible to substitute onto a urethral plate, as in salvage hypospadias repairs. This change in philosophy has resulted from the poor results of tubed grafts and also from the ability to achieve improved cosmetic results with staged repairs.

Tissue Transfer

The "ideal" urethral substitute is moisture-resistant, hairless, in plentiful supply, easy to harvest leaving no visible scar, and has the ability to "take" easily in its new environment with little shrinkage. No one tissue has all of these characteristics. Over the years, various urethral substitutes have been used. Penile skin has been considered to be the ideal donor site for graft or flap repair of the urethra, because it has a characteristic moisture-resistant quality and, in most locations, is relatively hairless. However, it is not always available, particularly in patients who have had previous surgery. Scrotal skin was used extensively in the past, but with prolonged exposure to moisture tended to develop an eczematous change and this lead to restenosis. It now is considered to be a poor urethral substitute. Other problems related to the use of scrotum for urethral substitution include the fact that it is hair-bearing and has a tendency toward pseudodiverticulum formation, partly because of difficulty with operative sizing of the substitute. Extragenital skin may be used as graft, and the postauricular skin fulfills a number of the ideal criteria and has a more predictable take than other skin. Recently bladder, and now buccal, mucosa have gained in popularity. Both are water resistant, but bladder mucosa is difficult to harvest. It requires suprapubic incisions and is difficult to handle, and desiccation leads to hypertrophic change. However, buccal mucosa is easy to harvest, is tough and thick, leaves a concealed scar, and is plentiful. It currently is enjoying considerable popularity, with good reported results, although these are all of relatively short duration.

It is likely that in the future, cultured urethral epithelial tissue will be available, with the potential to totally revolutionize the approach to this problem.

Flap Versus Graft

Logic would imply that flaps have a natural advantage over grafts because the success of the procedure does not rely on graft take. However, full-thickness skin grafts, particularly those obtained from the foreskin, and buccal grafts, do enjoy a comparable high success rate when used for the onlay repair of urethral strictures, particularly when the graft can be supported by a healthy, well-vascularized bed. However, the longer the graft, the higher the potential rate of failure; thus in long strictures or when it is likely that good vascular support for the graft cannot be ensured, flap repair may be desirable or a staged repair may be considered. In preparing a full-thickness graft, the removal of its subepithelial tissue is important, because this will facilitate the diffusion of nutrients from the graft bed into the epithelial cells during the period before vascular ingrowth (i.e., inosculation). Full-thickness skin graft has approximately a 20% shrinkage rate and this should be taken into account in sizing the initial graft. The shrinkage rate for buccal grafts remains unknown, and it also remains unknown whether the spread-fixation of the graft to the surface of the corporal body may reduce graft shrinkage. Any factor reducing the diffusion of nutrients will reduce the chance of graft take, and one of the common avoidable factors is hematoma developing beneath the graft. To avoid this, good bed hemostasis should be ensured; the graft should be fenestrated to allow any accumulated serum or blood to escape, and the graft should be sutured (quilted) to its underlying bed. Supportive dressings should maintain the graft-to-bed apposition without excessive compression. The stenting urethral catheter generally is fenestrated or ribbed, also to facilitate the drainage of the urethra at the graft site and to prevent the accumulation of urethral secretions and debris that might promote infection and jeopardize graft take. Premature voiding over the graft will jeopardize its survival; however, prolonged stenting may abrade or introduce infection to the graft site. Full-thickness graft repair most often is used in the bulbar urethra, in which situation stenting for 13 to 20 days is ideal and catheter removal and voiding are always preceded by a pericatheter urethrogram that ensures an absence of extravasation at the graft site. A suprapubic catheter placed at the time of repair will simplify the postoperative course because it will allow for timely stent removal but avoid premature voiding.

Split-thickness skin graft is inappropriate for the one-stage repair of urethral stricture because it has a high

shrinkage rate (approaching 50%). It has been used for the staged reconstruction of complex strictures where thick split-thickness skin (0.02 of an inch), obtained from an extragenital source and meshed to a 1.5-to-1 ratio, is used (see subsequent discussion). (77)

As previously implied, flaps with an already established blood supply have been suggested (although unsubstantiated) to have a more predictable outcome, but flaps are not always available (12,70). Islands of appropriately sized and shaped penile skin, based on a subcutaneous random vascular pedicle, may be used for repair of pendulous, bulbar, and posterior urethral strictures, their use being limited only by skin availability and pedicle length. In the majority of cases, the subcutaneous penile tissue provides an adequate vascular pedicle; however, the fasciocutaneous pedicle may lend a degree of certainty to flap survival, as has been stressed by McAninch (52). In these repairs, the dissection of the subcutaneous pedicle is deep to Buck's fascia. This type of repair lends itself quite successfully to the repair of pendulous urethral stricture. In most previously unoperated patients, penile skin is sufficient to allow for the construction of an island of skin for urethroplasty, leaving sufficient penile skin for tension-free primary skin closure. In rare unoperated cases and in some previously operated cases, penile resurfacing may require the inventive rotation of scrotal skin flaps. Pedicled grafts of extragenital skin are uncommonly necessary and generally are indicated in cases of major urethral loss, such as those that may follow blast injury, burn, or local infective necrosis. Myofasciocutaneous gracilis flap, urothelial island–bladder wall flap, and even rectal mucosal flaps all have been described.

NONSURGICAL MANAGEMENT OF URETHRAL STRICTURE

Part of "36 - STRICTURES OF THE MALE URETHRA "

Urethral Dilation

Although most strictures can be dilated, some may be inappropriate for such management. These include strictures requiring frequent dilation (more often than twice a year), which should be managed by one of the alternative methods, because their rapid recurrence generally is caused by surrounding spongiofibrosis. Safe dilation of multiple or long strictures often is difficult, and the risk of producing false passage and confluent scarring is high. Obliterative strictures also are inappropriate for dilation, and the practice of “breaking through” the obliterated segment blindly with a urethral sound is hazardous and generally leads to the formation of false passages. Strictures associated with false passages, periurethral phlegmon or inflammation, urethral fistula, and urethral calculus also may render dilation inappropriate. Strictures associated with false passage simply may be impossible to negotiate using the blind technique and require endoscopic passage of a filiform. Other complications of dilation are urethral hemorrhage and bacteremia. Hemorrhage usually is not prolonged, but can be quite startling. Bacteremia generally occurs following dilation in the patient with urinary infection, but may occur in its absence, and it can be hazardous. Patients predisposed to this event should undergo urethroplasty. Unless a child's stricture can be resolved by a single or very infrequent dilation, management by this technique also is inappropriate. It is inhumane to repeatedly dilate a young boy's urethra without anesthesia, and repetitive anesthetics are ill advised.

Despite these many relative contraindications, most strictures can be managed successfully by occasional bouginage. To ensure the appropriateness of this management, initial dilation always should be preceded by a retrograde urethrogram and endoscopy to ensure that none of these contraindications exist. Once assured, the physician should have available a variety of instruments, which should include a set of curved steel bougies (e.g., van Buren sounds) and filiform bougies with a screw fitting adaptable for either curved steel followers (e.g., Le Forte sounds); plastic, gum-elastic, or woven flexible followers; and a Council-Foley–type catheter with threaded guide.

Regardless of the instrument used, the process of dilation ideally should be a gradual one, because forcible disruption of the stricture simply incurs further mucosal and spongy injury, allowing extravasation of urine and subsequent inflammation, predisposing to further fibrosis. Hence, whether filiforms or steel bougies are used, the stricture should be dilated only until resistance to dilation is sensed. This usually will allow the patient to void, and he then may be redilated using the same technique on subsequent weekly occasions until a lumen of no more than 24-French (Fr) is achieved. Dilation over 24-Fr caliber has no advantage. Once full-caliber dilation has been achieved using this technique, longer dilation-free intervals are likely to be encountered, and the likelihood of the urethra being further damaged by the process is lessened.

Small-caliber metal sounds have extremely sharp tips and may inadvertently perforate the urethra and create a false passage; thus commencement should begin with a larger-caliber bougie, which has a more blunt tip. If this cannot be negotiated through the stricture, then a filiform and follower are a better option than the small-caliber sound. Should the preliminary retrograde urethrogram show a particularly long or tight stricture, the blind passage of metal sounds should not even be attempted, but rather the need for filiforms and followers should be accepted. When passing sounds, the urethra should be well-lubricated by filling it with lidocaine (Xylocaine) lubricating jelly. Recognizing the normal anatomic curvature of the urethra, the lubricated metal sounds initially are inserted with the penis extended vertical to the abdomen and the sound allowed to almost fall under its own weight until the tip reaches the curve at the bulbous urethra. At this point, as the sound is steadied, the penis is depressed gently in a caudally directed arc, negotiating the tip of the sound naturally around the curve of the

posterior urethra and into the bladder. Almost the entire act can be accomplished by the weight of the sound itself, and there is little place for “probing” with the tip of the sound. At the point at which the stricture is encountered, gentle pressure alone usually suffices.

Filiforms are used for all difficult strictures and may be inserted blind or under endoscopic vision. A 5- or 6-Fr blunt-tipped spiral filiform is preferable. Should blind passage be unsuccessful, the filiform may be passed along the working channel of the urethroscope or, alternatively, may be passed down the urethra outside the lumen of the instrument. Once the filiform has been negotiated across the stricture into the bladder, either a flexible or a steel follower (Le Forte sound) is attached by screwing it to the male throat of the filiform and the stricture is then dilated without fear of inadvertently getting out of the urethral lumen.

On occasion, the stricture is so tight, and previously formed false passages so confusing, that the surgeon fails to find the urethra channel even under vision. Although this may be an indication for surgical repair by urethroplasty, the true urethral channel may be identified by percutaneously inserting a suprapubic cystotomy, filling the bladder with methylene-blue dye solution, and using Credé's compression of the bladder to force some of the blue solution down the urethra so that the stricture channel may be located by visualization of the wisp of blue.

Should the physician fear that the patient may be unable to void following initial dilation, or should a false passage have been created or excessive urethral bleeding encountered, a small suprapubic catheter may be inserted percutaneously for a few days. A Council catheter is designed for insertion over a filiform as a guide. This Foley-type catheter with a hole in its tip is negotiated over a flexible guide screwed onto the end of a filiform that has been passed across the stricture into the bladder. Once a Councill catheter has been slid along the length of the urethra guided by the filiform, its retaining balloon is inflated in the bladder and the catheter guide and attached filiform are removed. Balloon-catheter dilation of strictures is favored by some and may have potential advantages, and its advocates suggest that it reduces local trauma (28).

The natural history of the stricture will declare itself during the weeks and months following initial dilation. Those that recur rapidly probably should undergo either direct vision urethrotomy or definitive urethroplasty. A retrograde urethrogram may be performed approximately 6 weeks following the initial dilation, because by this time the natural history of the stricture may be apparent, and the future management of the patient can be planned.

Self dilation on an “increasing interval schedule” is always an option to avoid an imminent urethroplasty. The majority of men can be taught to self-catheterize, and after dilation they are instructed to pass a 12- to 16-Fr catheter through the stricture (but not necessarily into the bladder) initially each day for 1 week, then every second day for the next 2 weeks, then every third day for 3 weeks, and so on, until either no longer required or a comfortable interval is reached.

Internal Urethrotomy

In the nineteenth century, Otis developed the Otis urethrotome; however, this more recently has been superseded by the direct vision, or optical urethrotome, which enables the operator to more definitively incise the stricture alone. The rationale behind urethrotomy is that the incised cleft created in the stricture should epithelialize in the open position. Unfortunately, cleft epithelialization is unpredictable, and maneuvers to promote it are unsuccessful. These have included prolonged catheterization and hydrostatic dilation performed by voiding into the urethra that is obstructed by pinching the glans. This maneuver causes extravasation.

Optical Urethrotomy

The optical urethrotome permits endoscopic incision of the stricture. Both adult- (approximately 20 Fr) and shorter pediatric- (approximately 14 Fr) size instruments are available, and both use a forward-viewing telescope. General, spinal, and local anesthesia all may be used for this procedure, but instillational anesthesia is appropriate for the majority of cases (45). Antibiotic prophylaxis may be given at the start of the procedure, and the patient may continue on prophylactic urinary antiseptics for the duration of postoperative catheterization, if a catheter is used.

With the instrument in the distal urethra and the urethra compressed around the sheath so that the inflow of fluid distends the urethra, the instrument is advanced until the stricture is seen. In some cases, the anatomy of the stricture is such that safe incision can be accomplished without further ado. If the stricture is of narrow lumen or if there is any question concerning where the correct lumen is, a filiform catheter can be negotiated along the working channel of the instrument or alongside the instrument itself and through the stricture. With this filiform as a guide, safe incision through the entire stricture length can be accomplished. The knife blade of this instrument is sharp and the scar tissue customarily is incised at the 12 o'clock position to avoid the main vasculature of the urethra. In the pendulous urethra, incision at the 12 o'clock position often fails to adequately open the stricture, because in this location the spongy tissue surrounding the urethra is thin and the urethra is broadly adherent to the overlying corporal bodies. Therefore bilateral (3 o'clock and 9 o'clock) position incisions may give a more satisfactory result. When the incision is in the dorsal position, it is carried through the entire thickness of the stricture often to, but not into, the corporal tunica. It is important not to cut too deeply in this dorsal position because fibrosis or inflammation of the elastic tissue

may result in a Peyronie's-like plaque and eventually in ventral penile chordee. Similarly, the incision should not encroach upon the normal urethra proximal and distal to the stricture, particularly when incising posterior bulbar strictures that abut on the intrinsic urethral sphincter mechanism.

There is no consensus regarding the duration of catheterization following direct vision urethrotomy (1,21,67). It should be dictated by the degree of stricturing, with superficial mucosal strictures often requiring no stenting or stenting long enough for bleeding to subside, whereas dense strictures with full-thickness spongiofibrosis may require stenting for up to 3 weeks. For moderately dense strictures, 3 to 7 days' catheterization with an inert 18-Fr catheter usually is adequate.

Other methods that have been used to try to improve the success rate of direct vision urethrotomy include the injection of steroidal agents, such as triamcinolone, into the stricture at the site of incision (44). This is performed using a purpose-made endoscopic needle passed along the working element of the endoscope. Self-calibration or self-dilation by the patient with a lubricated soft catheter is probably the best method to avoid restricturing following either initial dilation management or urethrotomy (75). Optical urethrotomy also has been popularized using laser technology (68); it is proposed by some to have significant advantages over the cold knife, although this opinion is by no means universal and its use certainly adds considerably to treatment cost (78). Both neodymium:yttrium-aluminum-garnet (Nd:YAG) and argon laser treatment are reported (2).

Although urethrotomy is not complication free, problems are uncommon. The most common immediate problem is of local hemorrhage or extravasation of irrigating fluid or urine. Earlier, the possibility of erectile difficulties were alluded to, with ventral penile chordee and erectile impotence both having been reported rarely (31). Despite their rare occurrences, the possibility of such complications should be included in the preoperative counseling.

Stricture of the sphincter-active membranous urethra may follow pelvic-fracture urethral injury, extension of inflammatory disease from the bulb, or prostatectomy. In the former two events, urethrotomy may still be appropriate, recognizing that the incision will compromise the sphincter-active mechanism but that continence may still be preserved by the bladder neck. However, following prostatectomy, be it transurethral, retropubic, or radical, urethrotomy may be injudicious because it certainly will compromise continence (Fig. 36.8). In such circumstances, urethral dilation may be optimal because, although it also may compromise continence, this generally is short lived (65).

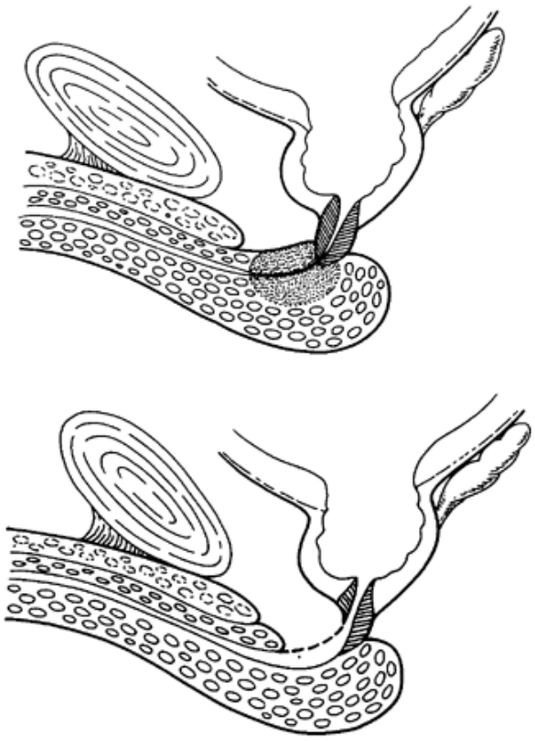

FIGURE 36.8. Following prostatectomy the bladder-neck sphincter is ablated, and continence resides in the distal sphincter mechanism. Urethrotomy or urethroplasty of a stricture at this distal site *(stippled)* may compromise continence. (From Webster GD, MacDiarmid SA. Posterior urethral reconstruction. In: Webster GD, Kirby R, King LR, et al., eds. *Reconstructive urology.* Oxford: Blackwell Scientific Publishers, 1993, with permission.)

Anastomotic contracture following radical prostatectomy occurs in approximately 5% of cases. A number of etiologies are possible. The most frequently cited causes of anastomotic contracture are distraction of the anastomosis attributable to insecure suturing, nonwatertight anastomosis with resultant local urinary extravasation, excessive local dissection and electrocautery, traumatic suture technique causing local tissue necrosis, excessively snug closure of the vesical neck, and local infection. Careful optical urethrotomy is used for such contractures should dilation fail, but extreme caution is needed to avoid compromising the remaining sphincter mechanism.

Results of Optical Urethrotomy

The published long-term results of internal urethrotomy and urethral dilation make their role in the management of stricture disease clearer. A comparison of internal urethrotomy and urethral dilation has shown no difference between the two (81). Recurrence rates after urethrotomy are in the region of 30% to 50% (3,72). Risk factors for recurrence are long inflammatory strictures and those in the penile urethra. In addition, further dilation or urethrotomy in strictures that reoccur early are of limited value (36). A rational

approach to a new stricture would be to perform a single dilation or urethrotomy, and if this fails, consider urethroplasty before the stricture extends due to spongiofibrosis resulting from repeated dilations or urethrotomy. For patients who do not wish to or are unfit to undergo surgery, a program of self-dilation may reduce the need for frequent dilations or urethrotomy.

Urethral Stents

Indwelling urethral stents are a relatively new development in the management of urethral stricture and currently are used primarily for patients with short strictures located in the bulbar urethra. Manufactured from stainless steel, titanium, or other alloys, these stents are placed endoscopically across the stricture following its dilation or optical incision. Initially exposed to the urethral lumen, the stent is covered rapidly by epithelium, the process being completed in 6 to 12 months. Endoscopic placement proves quite simple using the purpose-made deployment tool, and catheterization and hospitalization generally are not required. Since the initial report of its use by Milroy (54), the short-term success rates are in the range of 80% to 100% (97). Milroy reported results in 27 patients with follow-up over 5 years, with more than 90% patient satisfaction (55). However, nine patients had required a second overlapping stent. A recent study of 99 patients in Europe reported good results in 50% (58).

Of the problems that have been reported with the use of stents, recurrent stricturing occurs in approximately 30%, generally at the proximal or distal limit of the coil. In this circumstance, a further coil may be placed in continuity with the first. In the aforementioned report, hypertrophic scarring obliterates the lumen within the coil in 44%, and this is more common in cases where the patient has undergone prior urethroplasty and is very common when the device is used to treat obliterative strictures, such as those that follow pelvic-fracture urethral distraction injury. Too proximal placement of the coil may splint open the distal sphincter mechanism and potentially compromise continence (14%), particularly if the patient has undergone prior prostatectomy; there also may be some terminal dribbling caused by pooling of urine in the stented portion of the urethra. Compromise to erections is always a consideration and occurred in 44%, but provided the stent is not placed in the pendulous portion of the urethra, any such risk should be minimized. Although stent migration may occur during the early postinsertion phase, it is unlikely once epithelialization has commenced. Recurrent stricturing within the coil may be managed by TURP, but recurrent problems might require stent removal and urethroplasty, and to achieve this requires a complex staged repair. Urethral stents may have a role in bulbomembranous strictures, provided the patients is aware of the complications and difficulties that can arise with its use.

It is evident from the previous discussion of results that problems may outweigh the advantages at this time, and urethroplasty remains the optimal management for most strictures requiring more than urethrotomy or dilation.

SURGICAL REPAIR

Part of "36 - STRICTURES OF THE MALE URETHRA "

Surgical urethroplasty is necessary for those patients in whom instrumental management is inappropriate or impossible. A wide array of operations is available and, although most operations can be adapted for use with any stricture in any location, this is unwise and there is a more logical approach to procedure selection. Accepting that the surgeon is versed in most techniques, it has been advocated that procedure selection should be dictated by the location, etiology, length, multiplicity, and presence of local adverse factors. Most believe that no single procedure is appropriate for the management of all strictures.

General Surgical Principles

Before surgery, it should be ensured that the patient's urine is uninfected; however, in those cases with an indwelling suprapubic tube, this may not be achieved. In this event, such patients should have had a recent tube change and appropriate broad-spectrum antimicrobials prescribed. Bowel preparation is not necessary, but an empty rectum is optimal. General anesthesia may be preferred if buccal mucosa is to be harvested, and also is preferred for the repair of pelvic-fracture urethral distraction defects, but for most other urethroplasties spinal anesthesia is acceptable. The patient should be positioned in lithotomy with the legs supported such that pressure areas and nerves are well padded and safe. Exaggerated lithotomy rarely is necessary and certainly carries a higher risk of neural injury and compartment syndrome. Uncommonly, in the repair of pelvic-fracture urethral distraction defects, access to the abdomen also is required, and patient positioning and draping should be varied appropriately. Methylene blue instilled per urethra differentially stains the urethral scar from healthy urethral mucosa, helping determine the limits of the stricture. The operation should be conducted with the surgeon seated, and a headlight is optimal, particularly for the deep perineal dissections required for the repair of pelvic-fracture defects. Ring retraction is ideal for urethroplasty in the bulbar or posterior urethras, and the “table-fixed” design is optimal (Bookwalter or Omni), although the Turner-Warwick perineal ring retractor also is successful. Absorbable polyglycolic acid (PGA) suture material has highly acceptable tensile strength, absorption rate, and tissue reactivity, and 4-0 and smaller generally is used. Wound drainage may be indicated, and an appropriate-sized suction drain is optimal. Surgical dressing should be supportive and not constrictive, the latter being particularly important

following penile flap repairs. Urethroplasty requires urethral stenting using as small a catheter as will support the repair and accomplish urine drainage. In practice, a 12-Fr urethral catheter generally suffices. In bulbar and posterior urethral repairs, catheter fenestration or the use of a ribbed catheter that promotes the drainage of periurethral secretions is optimal. The placement of a suprapubic catheter at the time of urethroplasty facilitates urethral stent management later, allowing for urethral catheter removal without necessarily allowing the patient to void. The duration of urethral catheterization/stenting is determined by the type of repair, and is shortest for anastomotic repairs and most lengthy for one-stage repairs using full-thickness skin graft. Stent removal and, particularly, voiding per urethra always should be preceded by a retrograde urethrogram around the stenting catheter to ensure that healing is complete. Customarily, a retrograde urethrogram is performed at 3 and 12 months following repair. Uroflowmetry is inadequate for follow-up because reduction in urethral caliber to approximately 10 Fr is required before the urine flow rate will deteriorate. Because of the incidence of late failure, particularly following substitution urethroplasty, prolonged follow-up is indicated.

MEATAL STRICTURES

Part of "36 - STRICTURES OF THE MALE URETHRA "

Meatal strictures are infrequent but may occur in young boys who have undergone circumcision, in which case they commonly will respond to occasional meatal dilation, and meatotomy occasionally is indicated (46). In adult males, postmeatal strictures commonly follow endoscopic procedures such as TURP; these strictures also generally respond to periodic dilation, often performed by the patient himself.

BXO is the most common condition resulting in meatal stenosis requiring surgical intervention. The condition affects not only the glans penis and meatus but also may involve the prepuce, the penile skin, and the distal urethra. In some cases, the urethral involvement may go as far back as the urethral bulb, leading to the need for a complex repair. The condition rarely responds to urethral dilation, and meatal reconstruction usually is necessary. The risk of BXO recurrence in the urethra substituted with local penile skin appears to be significant, and it recently has been suggested that excision of the diseased urethra and the use of extragenital skin for substitution in BXO strictures may have a lower recurrence rate (89). This has lead to enthusiasm for the use of buccal mucosa in this endeavor (90).

A variety of procedures have been described for the repair of meatal strictures, each of which gives excellent results when used in appropriate circumstances, including those by Cohney (19), Blandy and Tresidder (11), Jordan (40), and DeSy (22). These procedures are appropriate only for the repair of meatal strictures of non-BXO origin. Figure 36.9 illustrates the technique that reconstructs the terminal urethra with an onlay or full-circumference pedicled island of distal penile skin. The size of the skin island is tailored to the individual requirements and is based on a subcutaneous vascular pedicle in a fashion similar to that described for the transverse preputial island hypospadias repair. The lateral glans flaps can be developed so that they can be reapproximated ventrally over the neourethra, giving a normal glanular appearance and enhancing the chances of establishing a directable flow.

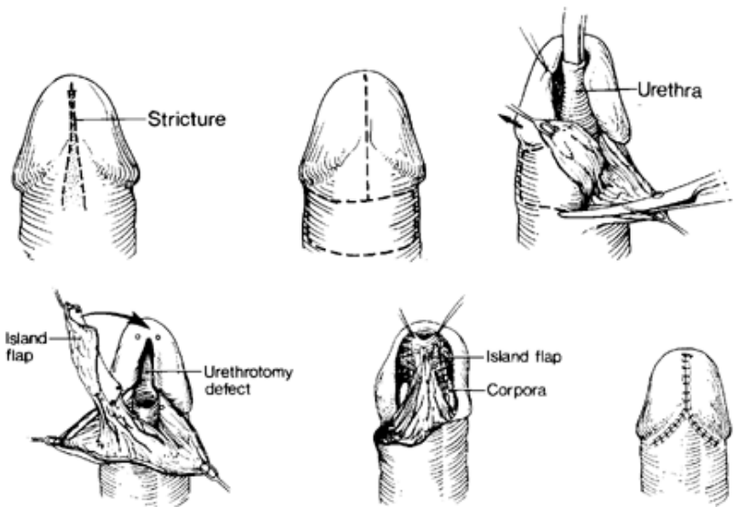

FIGURE 36.9. Repair of meatal and distal penile urethral stricture using a pedicled island of distal penile skin. This procedure allows for reapproximation of glans tissue around the neourethra, giving an excellent cosmetic and functional result. (From Webster GD, Khoury JM. Urethral stricture disease. In: Krane RJ, Siroky MB, Fitzpatrick J, eds. *Clinical urology.* Philadelphia: JB Lippincott, 1994, with permission.)

Strictures of the glanular urethra resulting from BXO are best excised and repaired in two stages. This may seem excessive for such limited pathology, but the results of single-stage repair using penile skin flaps or grafts are wrought with failure. These authors prefer to excise the

BXO-afflicted portion of the urethra by opening the glans and laying a buccal mucosal graft into the defect created. The graft is tubularized, and the glans is reconstituted in a second stage 4 to 12 months later.

STRICTURE OF THE PENDULOUS URETHRA

Part of "36 - STRICTURES OF THE MALE URETHRA "

For the purpose of this discussion, the pendulous urethra describes that portion between the glans meatus and the suspensory ligament of the penis, at which point the bulbar urethra commences. Strictures in this location may result from proximal extension of BXO, from infection, or from catheter or instrument trauma; in the latter event, they are usually short and located at the penoscrotal junction somewhat opposite the suspensory ligament of the penis. Although very accessible to dilation or urethrotomy management, these techniques do not tend to be curative for reasons discussed previously. The cause of penile urethral strictures have changed in recent years, with those caused by BXO making up a higher proportion, in part as a result of more frequent recognition of the condition. BXO is the genital form of lichen sclerosis, and this may be the preferred terminology to bring us in line with dermatology and gynecology (73). In the male, it is a frequent cause of phimosis and, in the majority of cases, circumcision is curative. However, it may involve the urethra locally or extensively (80).

Anastomotic urethroplasty generally is inappropriate in this location because excision and spatulated reanastomosis of even the shortest penile urethral stricture will incur at least 1 cm of urethral shortening, which is sufficient to cause ventral chordee. Hence, anastomotic repairs should be reserved for the patient in whom sexual function is no longer a consideration. Substitution repairs employ either graft or flap. Full-thickness skin graft repairs in the pendulous urethra may use either preputial or extragenital skin and carry good results. They may be used as onlays to augment the strictured urethral lumen, and almost never should be used as a full-circumference urethral replacement. Graft take is good, and cosmetic resurfacing of the penile shaft can be accomplished using penile skin or a local scrotal skin flap. Recently, Barbagli and associates (6,7) have described a dorsal graft technique, with the graft bed being the undersurface of the adjacent corporal body. Full-thickness skin graft repairs generally maintain their caliber well (other than the approximately 20% expected graft shrinkage); however, they appear to exhibit poor longitudinal elasticity and hence have a tendency to produce ventral penile chordee, a major consideration when this repair is used in the sexually active male. This problem is more apparent when full-circumference or long skin-graft repairs are used.

For the aforementioned reasons, the optimal management for the one-stage repair of pendulous urethral strictures appears to be the use of a pedicled island of penile skin, generally as an onlay. A number of variations of the operation have been reported by Orandi (69), Quartey (74), Turner-Warwick (85), and Mundy and Stephenson (59). In the uncircumcised male, a pedicled island of foreskin may be used with excellent cosmetic outcome, also allowing the use of the moisture-resistant inner face skin to an advantage. Even after circumcision, there is invariably sufficient penile shaft skin to allow the island to be fashioned with its long axis along the shaft of the penis and with its pedicle based laterally (i.e., laterally pedicled island of penile skin). As mentioned previously, McAninch (52) has described such a repair with the skin island based on a fasciocutaneous rather than a subcutaneous vascular pedicle, improving its vascularity; he has used this technique to repair long strictures. In these circumstances, the skin island has been a distal penile circumferential island obtained by parallel circumcising incisions.

Most commonly, the island of skin is used as an onlay to increase urethral caliber at the stricture site (Fig. 36.10 and Fig. 36.11). The appropriately sized and shaped island skin is sutured to a roof strip of “native” strictured urethra and two-layer cover is achieved, trying to avoid overlapping suture lines. A small stenting catheter is used, and its removal approximately 14 days later is preceded by a pericatheter urethrogram. Postoperative dressings should be supportive and not constrictive, and when necessary, a microsuction drain may be placed along the shaft beneath the skin closure flap. The width of the pedicled island should be sufficient to create a urethra of at least 25 Fr. In practice, allowing for a small amount of shrinkage, and accepting that the native urethral roof strip adds some to the circumference, the island of skin needs to be between 2 and 3 cm in width. In the event the penile urethral stricture extends into the fossa navicularis, the distal part of the flap should be tunneled into the glans after the meatus, and the glandular urethra have been incised on the ventral surface. The flap then resurfaces the created glans cleft, with the tip of the flap being sutured to the edges of the glans at the meatus. This maintains the normal glans appearance and also avoids retrusion of the meatus. In the event the stricture extends into the scrotal urethra, the skin island needs to be planned inventively to avoid the use of hair-bearing penoscrotal skin. This usually is accomplished by raising the skin island along the ventral shaft of the penis at the required width and proximally coursing the island around the distal shaft of the penis in a circumcising fashion. In this manner, “J” flaps with lengths of up to 15 cm can be obtained, and in most, primary, tension-free skin closure is possible. In the event penile skin cover is not possible, a rotation flap of scrotal skin can be mobilized from the anterior scrotum to resurface the ventral shaft of the penis. Although hair-bearing, its ventral location will render it unobtrusive, and of course, epilation is a possibility.

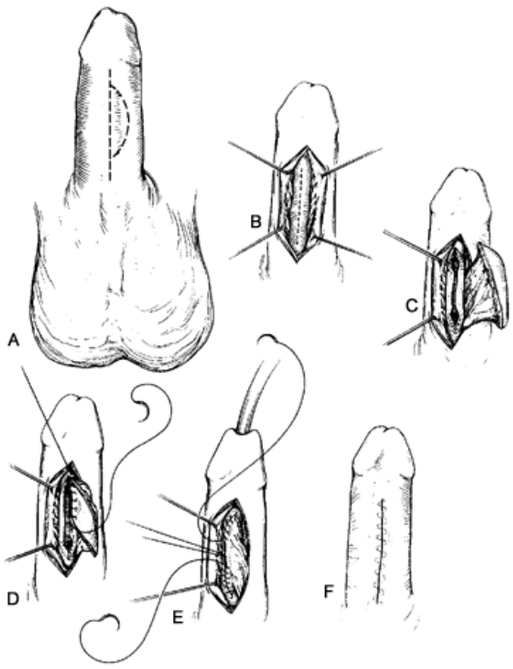

FIGURE 36.10. Onlay urethroplasty of a pendulous urethral stricture (Orandi repair). **A:** The stricture is approached through a ventral penile incision. The outline of the skin island to be used for onlay is marked once the stricture has been opened and its length and caliber determined **(B and C).** The skin island is raised on a subcutaneous vascular pedicle **(C).** The skin island is rotated inward and sutured as an onlay to augment urethral caliber **(D and E).** Skin closure is in at least two layers to avoid fistula formation **(F)**.

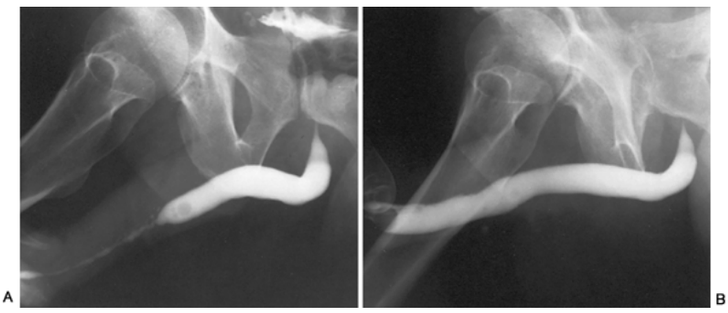

FIGURE 36.11. A: A long, tight pendulous urethral stricture. **B:** The same patient following tube replacement of the strictured urethra using a laterally pedicled island of penile skin. The island of skin was obtained in the vertical axis of the penis, and penile skin closure was accomplished primarily.

Staged repair of the pendulous urethra is necessary in complicated cases, including patients who have had multiple

prior procedures where there is considerable local scarring and skin shortage, where onlay of a flap is not possible, or where BXO is the cause. In the latter circumstances, a full-thickness graft from an extragenital source will be introduced to resurface the ventral penis after the strictured portion of the urethra has been excised. This source may be either buccal graft or postauricular skin, or combinations of the two when the extent of the replacement is extensive. Interim revision of the proximal urethrostomy may be required if there is any evidence of narrowing. At the second stage, at least 6 months later, the neourethra is tubularized from the graft, with the native penile skin being used to resurface the penis. Although simple in concept, this repair relies on full-thickness graft take on the ventral shaft of the penis, and this is not always predictable. The recent introduction of buccal mucosa has lead to renewed interest in the free grafts in the anterior urethra. As previously mentioned, buccal mucosa is easy to harvest from either the inner cheek or the lip. Some prefer to infiltrate with 1 in 100,000 epinephrine to aid the dissection, and an ellipsoid incision is made avoiding the salivary duct. Even without epinephrine bleeding is minimal, and the graft dimensions may be as high as 3 cm × 6 cm at the largest axis. Discomfort or problems with the donor site are minimal and large grafts can be taken. The graft take with buccal mucosa has been excellent thus far, but results are still very short term.

STRICTURES OF THE BULBAR URETHRA

Part of "36 - STRICTURES OF THE MALE URETHRA "

Strictures of the bulbar urethra generally occur as a result of inflammatory disease or urethral trauma from straddle injury. Trauma generally leads to a short, dense stricture with

healthy adjacent urethra, whereas infection results in a long, irregular stricture, often with diffuse proximal and distal spongiofibrosis and mucosal damage. These differences dictate the different optimal surgical approaches for strictures that have failed more conservative management.

Most surgical techniques for urethroplasty can be adapted for use in the bulbar urethra; however, optimally, the repair chosen should be dictated by a variety of factors. These include stricture length; the extent of local spongiofibrosis proximal and distal to the stricture; other local factors that may influence outcome, such as false passage, fistulae, or excessive scarring; and the availability of penile skin for urethral substitution. The available repairs are discussed in the following sections, and the surgical techniques are presented thereafter. As noted previously, stricture excision and reanastomosis are appropriate for short strictures of less than 1 cm with healthy adjacent urethra, typified by the stricture resulting from a straddle injury (Fig. 36.12 and Fig. 36.13). In those cases in which the stricture is longer than 1 cm, primary anastomosis may cause penile chordee, and onlay substitution repairs are suggested. Strictures between 1 and 2 cm in length may be handled by a combination urethroplasty, which includes excision of the stricture (less than 2 cm) and anastomosis of the spatulated ends as an open floor or roof strip. The anastomosis is then augmented (patched) by a diamond-shaped–full-thickness skin graft or pedicled island of penile skin. Because less than 2 cm of bulbar urethra is excised and provided adequate mobilization of the proximal and distal urethras is accomplished, little or no penile chordee or retraction results. This approach, originally described by Turner-Warwick (84), was called an *augmented anastomotic repair* (see subsequent discussion). The advantage of this procedure is that healthy urethra is anastomosed to healthy urethra, albeit

only as a floor (or roof) strip. Hence, in the event of graft or flap failure, continuity is still maintained. In circumstances where it is evident that the urethral defect remaining following stricture excision would preclude tension-free urethral floor or roof strip reanastomosis, a number of other options remain. Most commonly, the repair selected would be an onlay repair. In this procedure the urethra is incised or opened along the length of the stricture and for 1.5 to 2 cm proximally and distally into healthy urethra. The native strictured urethra remains as a floor or roof strip and an onlay repair using a pedicled island of penile skin or graft of penile skin or buccal mucosa is then used to augment urethral caliber. More recently, dorsal onlay urethroplasty has gained in popularity. Originally described by Barbagli (7), the stricture is opened longitudinally on the dorsal surface and the graft spread-fixed on the surface of the corpora cavernosa overlying the opened portion of the urethra. This technique achieves a number of goals, including the apposition of the graft to a secure, well-vascularized surface; the avoidance of the possibility of sacculation; and the fact that spread-fixation likely deters shrinkage. In the majority of circumstances, full-circumference urethral replacement using full-thickness skin graft or flap carry unpredictable results because graft or flap failure will be followed by urethral obliteration and thus are uncommonly recommended.

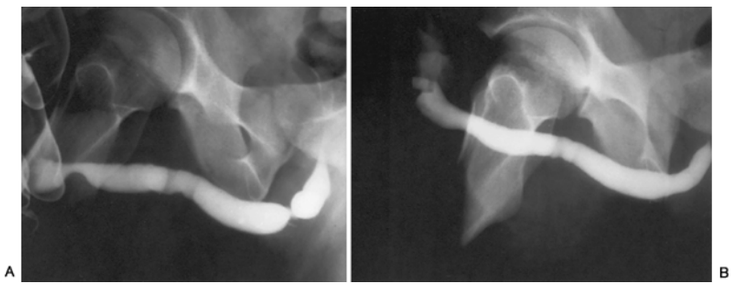

FIGURE 36.12. A: A short midbulbar urethral stricture following straddle injury. **B:** Urethrogram following stricture excision and spatulated anastomotic repair. This repair was appropriate in view of the short length of the stricture.

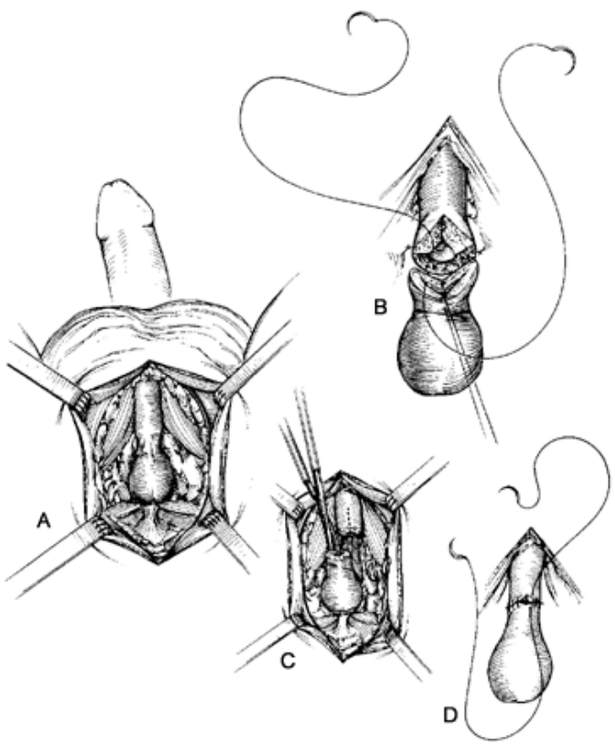

FIGURE 36.13. Anastomotic repair of bulbar urethral stricture that may follow straddle injury. **A:** The urethra is exposed through a midline perineal incision, and the stricture site is identified and excised. **B:** Following stricture excision, opposing spatulations of 1 cm are accomplished. **C:** The distal urethral opening is spread-fixed to the underlying corporal body and spatulated anastomosis performed with interrupted sutures. **D:** The anastomosis is completed and additional tension-relieving sutures are placed between urethral adventitia and adjacent corporal bodies to avoid anastomotic tension during erection.

Staged bulbar urethral reconstruction is used in circumstances in which the success of a one-stage procedure seems in jeopardy; it is particularly applicable to lengthy complex strictures with associated local adverse features, such as extensive scarring, inflammation, fistulae, false passage, and diverticulum. The staged repairs allow for the supervision and continued surgical access to the region during the interim phase, facilitating local revision procedures or adjustments of the roof strip and hair-follicle destruction in the neourethral area of the inlay. It is only when healing of the inlay or roof strip is seen to be satisfactory, and both proximal and distal urethral ostia remain stable and stenosis free, that the ultimate urethral tubulization can be performed. This entire process often requires more than two stages, and it is a misnomer to call these procedures two-stage repairs. The originally described procedures all marsupialized the strictured urethra to scrotal skin, the various techniques differing only according to the manner in which the flaps were constructed and deployed to the urethra (9,14,29,34,47,85). The major disadvantage of these repairs was that the ultimate neourethra would be constructed from scrotal skin, although sometimes the skin would be epilated before neourethral construction. As noted previously, scrotal skin is a poor urethral substitute with a high incidence of dermatitis from exposure of the skin to urine, often resulting in later restenosis. Currently performed staged repairs generally combine urethral marsupialization with the introduction of a full-thickness or split-thickness skin graft, or buccal mucosal graft into the area around the marsupialized urethra, so that the neourethra subsequently will be formed from it rather than the scrotum. Chapple and Turner-Warwick (14) have described elaborate combination-staged repairs where the urethral roof strip is reconstructed from available urethra or full-thickness skin graft and is left accessible by scrotal drop back so that its healing can be supervised and revised as necessary. Schreiter and Noll (77) describe a less elaborate technique in which meshed split-thickness or full-thickness preputial skin, when available, is transplanted adjacent to the native urethral plate after the stricture has been incised or excised. This technique is described later in the chapter.

Anastomotic Bulbar Urethroplasty

Recognizing the surgical principles and selection criteria discussed previously, this urethroplasty is used primarily for the repair of short (less than 1 cm) posttraumatic strictures, as identified by the preoperative urethrogram, and confirmed at the time of surgery. The salient surgical features are that the perineum is incised in the midline, with the incision being bifurcated posteriorly to improve access. The bulbospongiosus muscles are mobilized from the underlying bulbar urethra, which is then dissected circumferentially for a few centimeters proximal and distal to the stricture site, which is identified by the passage of a catheter. The urethra is transected at the distal limit of the stricture, and the strictured portion of the urethra is opened dorsally until healthy urethra is again encountered. If the stricture length proves to be less than 1 cm, the strictured portion of the urethra is excised. The proximal healthy urethra is then spatulated on the contralateral–ventral side so that opposing 1-cm urethral spatulations are created (Fig. 36.13). The ventrally spatulated proximal urethral opening is then spread-fixed to the overlying corporal body, the distal (dorsally spatulated) urethra then being anastomosed to it with interrupted 4-0 and 5-0 polyglycolic acid (PGA) sutures. To relieve tension, the proximal and distal urethras may be further mobilized, but the latter should not be mobilized beyond the suspensory ligament of the penis, to avoid penile chordee or retraction. Stenting is with a fenestrated 12-Fr inert catheter, and perineal closure is in layers, a suction drain being optional. This procedure currently is performed as an outpatient in most cases, and catheter removal (preceded by a urethrogram) usually is anticipated at 7 to 10 days following surgery.

Augmented Anastomotic Repair

The augmented anastomotic repair combines stricture excision and urethral floor (or roof) strip reanastomosis with augmentation of the anastomotic area using either a penile skin flap or a full-thickness graft. The urethra is approached as for a standard anastomotic repair, being transected at the distal limit of the stricture and the strictured portion of the urethra is then opened proximally on its dorsal surface. Strictures appropriate for this repair are those that are too long for a tension-free anastomosis without risking chordee by

excessive distal urethral mobilization. The urethral ends are spatulated proximally and distally for 1.5 cm at the 12 o'clock position (Fig. 36.14 and Fig. 36.15). After appropriate and judicious urethral mobilization to relieve tension, the floor of the urethra is anastomosed with interrupted 4-0 PGA sutures. In this fashion, a healthy, wide floor strip of urethra is created, but the lumen now needs to be completed by either a full-thickness graft or flap of penile skin. In general, the island of buccal mucosa or skin will be approximately 2 cm in width, and its length and shape will be determined by the length of the spatulations at the anastomosis. The urethra is stented with a fenestrated catheter.

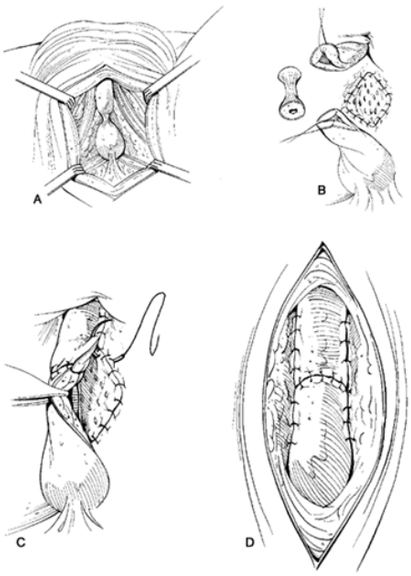

FIGURE 36.14. The augmented anastomotic bulbar urethroplasty includes short-segment stricture excision and dorsal onlay graft. **A:** Strictured urethra is approached through a perineal incision. **B:** After circumferential mobilization of the urethra at the stricture site, the short stricture is excised and the urethral ends are spatulated dorsally. The appropriately sized and shaped graft is sutured to the corporal bodies overlying the spatulation. **C:** The floor strip of the urethra is anastomosed and margins of the spatulation are sutured to the margins of the spread-fixed graft. **D:** Completed repair.

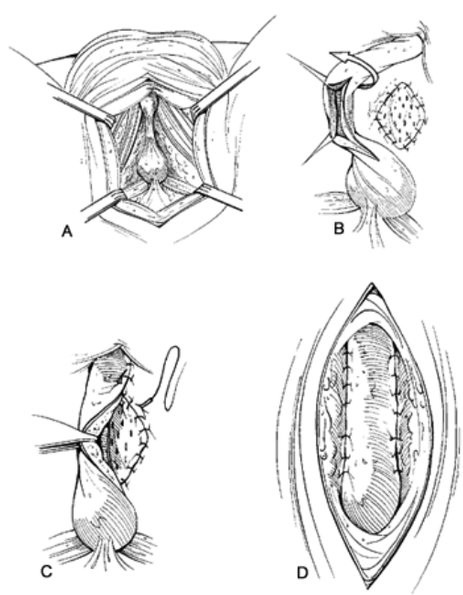

FIGURE 36.15. The dorsal onlay bulbar urethroplasty. This repair is used for bulbar strictures in which stricture length precludes excision. **A:** Bulbar urethra exposed through perineal incision. **B:** Urethra is circumferentially mobilized at stricture site and rotated to allow dorsal urethrotomy through the stricture. Appropriately sized and shaped graft is sutured to the corporal bodies overlying the stricturotomy. **C:** Margins of the urethra are sutured to the margins of the spread-fixed graft, thereby augmenting the size of the urethral lumen. **D:** Completed suture.

In the event an adequate graft bed cannot be ensured, the anastomotic area is best augmented with a pedicled island of penile skin. The appropriately sized island is outlined on the ventral non–hair-bearing surface of the shaft of the penis and the skin is incised. The subcutaneous pedicle to the island is developed proximally, with the deep layer of dissection being on the surface of Buck's fascia and the superficial being just deep to the penile and scrotal skin blood supply. In practice, a triangular-shaped pedicle (based posteriorly) results, and the island of skin then can be transferred or tunneled to the perineum, through the scrotum (Fig. 36.16). Dissection of the pedicle is critical; it must be adequate to avoid tension but must be limited to avoid compromise. The penile skin defect is closed primarily, and the island of penile skin is sutured into the urethral anastomotic area, augmenting it appropriately. Drainage, stenting, and catheter management are similar for those described for the graft repair.

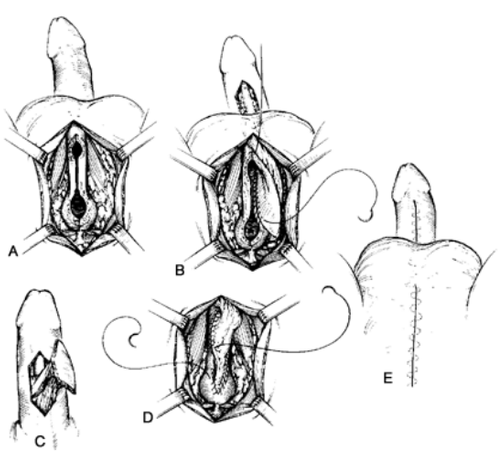

FIGURE 36.16. A: The urethra at stricture site is exposed to the perineum and the urethral incision opens the stricture and 1 cm of healthy proximal and distal urethra. The stricturotomy may be ventral (as shown) or dorsal following circumferential urethral mobilization. The advantage of dorsal onlay is lesser chance of pseudodiverticulum. **B–D:** An appropriately sized and shaped island of ventral penile skin is raised on a vascular pedicle and transferred through the scrotum to be onlayed over the urethral defect, augmenting the urethral caliber at the stricture site. **E:** Closure.

Bulbar Onlay Graft

Longer strictures of the bulbar urethra, particularly those of inflammatory origin, that cannot be managed by excision are best treated with an onlay repair (6,38,89). The onlay

may be graft or flap, although the former is currently preferred by most, and the graft source may be either penile skin or buccal mucosa. The selection of graft versus flap for the onlay depends on the nature of the graft bed, and to some degree on the philosophy of the operating surgeon. Graft survival is surprisingly predictable; although the longer the stricture, the greater the chance of graft failure, and graft survival is enhanced by the quality of the graft bed. The urethra is approached as described for the aforementioned procedures, with the strictured portion being circumferentially mobilized and then opened longitudinally through the stricture by dorsal (or ventral) incision. The incision should be carried proximally and distally into healthy urethra for 1.5 cm (Fig. 36.15). The appropriately sized and shaped graft is then sutured to the corporal body overlying the dorsally opened, strictured urethra using 5-0 Vicryl sutures. The graft is spread-fixed so that the graft is secured to its corporal-body bed, enhancing the probability of graft take. The margins of the opened urethra are then sutured to the margins of the graft, thereby augmenting its lumen by the width of the graft. The repair is stented for approximately 3 weeks with a 12-Fr fenestrated catheter, and catheter removal is preceded by a urethrogram to ensure absence of extravasation. An additional suprapubic tube is favored by some.

Staged Bulbar Urethral Reconstruction

The indications for staged bulbar urethral reconstruction were detailed previously. Although these were the standard techniques in the past, they were superseded by one-stage procedures that often were elaborated beyond their true applicability. The current role of staged repairs has gelled to their more frequent use, particularly for pendulous urethral stricture resulting from BXO, and for extensive stricture involving the full length of the urethra. Staged repairs are performed either with marsupialization of the strictured portion of the urethra to scrotal skin margins, or by the application of a graft (split-thickness skin, full-thickness preputial skin or buccal mucosa) to the margins of the opened urethra. The latter is preferable so that it will be the graft and not scrotal skin that is tubularized at the second stage, to form the new urethra. Every attempt should be made to ensure that the neourethra is not constructed from scrotal skin, which has a poor history of success because of long-term restricture, pseudodiverticulum formation, neourethral hair growth, and stone formation.

In the past, the application of a meshed split-thickness skin graft to the periphery of the marsupialized urethra has been reported when a multistage approach is indicated. Patient position and surgical draping should facilitate access to the thigh from which the split-thickness graft may be obtained using a pneumatic dermatome. Perineal approach to the strictured urethra is through a midline incision bifurcated posteriorly, the distal limit of the incision being dictated by the distal extent of the stricture; in uncommon instances, the scrotum may be bivalved and the entire urethra laid open. Once the ventral incision has been made through the entire length of the stricture and proximally and distally into good urethra, the skin graft is raised generally from the inner thigh (which is close to the operating field) to a thickness of 0.02 inch. The skin is meshed to a ratio of

1.5-to-1, using the meshing roller. An adequate width (3 cm or more) of meshed graft is then sutured in place to surround the marsupialized urethra, interposed between it and the skin edges (Fig. 36.17). It is sutured in place with 4-0 or 5-0 PGA sutures and bolstered with moist dressings (Xeroform and cotton balls soaked in Bunnell's solution) for 5 to 7 days. Graft take generally approaches 100%, and urethral catheter removal is at approximately 10 days, with voiding being avoided by continuing suprapubic drainage for approximately 2 weeks. In the interval stage before final closure, the patient must be seen frequently, with cross-bridging of the graft and exuberant granulation being appropriately managed. Careful perineal toilet is essential and, ideally, closure should be deferred until graft stability and softening is obvious. Closure has been reported as early as 8 weeks following initial grafting, but 6 months is ideal. Shrinkage of the split-thickness graft is considerable, particularly in areas where the graft is laid onto nonsupportive tissue, such as fat. Fortunately, neourethral tubulization requires only a thin strip of grafted skin around the marsupialized strictured urethra to create a 24- to 28-Fr sized lumen. At the time of urethral closure, the strip of skin around the marsupialized urethra is demarcated, incised, and tubularized over a stenting catheter using lengths of continuous 4-0 or 5-0 PGA suture. Layered perineal closure supports the repair, and a suction drain may be placed. Stenting is continued for 14 to 20 days, and voiding is deferred until a retrograde urethrogram shows an absence of extravasation.

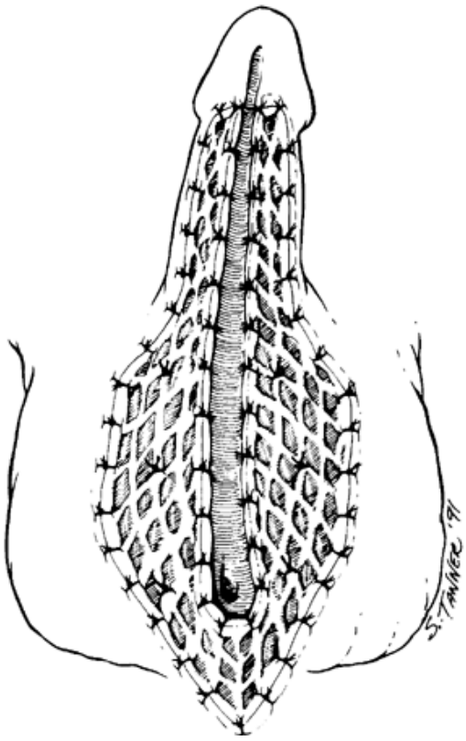

FIGURE 36.17. Staged urethroplasty for full-length stricture disease using meshed split-thickness skin graft. The meshed graft is laid alongside the marsupialized urethra so that the neourethra will be tubularized from the graft rather than from hair-bearing scrotal skin. Tubulization of the neourethra is delayed for 2 to 6 months. (From Webster GD, Khoury JM. Urethral stricture disease. In: Krane RJ, Siroky MB, Fitzpatrick J, eds. *Clinical urology.* Philadelphia: JB Lippincott, 1994, with permission.)

In the uncircumcised male, the foreskin may be harvested and inlaid around the marsupialized strictured urethra in place of the split-thickness graft. This may provide a superior quality skin, but full-thickness graft take is not as predictable and preputial skin may be insufficient to surround a lengthy stricture. In the latter circumstance, the graft may be meshed to increase graft surface area and possibly to enhance graft take. Schreiter and Noll (77) reported 96 patients with long and complicated strictures managed with this technique. Full-thickness penile skin was used in 76 patients and split-thickness skin graft was used in 23. In addition, postauricular skin or buccal mucosa may be used in this situation, and the graft origins may be mixed if availability is a problem.

Technically, these procedures are time-consuming, and in the event the stricture extends proximally into the membranous urethra, the suture fixation of the graft in the deep perineal funnel is difficult. Despite these technical difficulties, the results appear superior to those of simple scrotal inlay repair using scrotal skin.

Results of Anterior Urethroplasty

Expectations of a successful outcome are the greatest in anastomotic repairs of the bulbar urethra for traumatic strictures, and failures generally present within the first year (39). Mundy (62,63) has shown that in patients undergoing substitution urethroplasty, full-circumference tubed repairs fare less well than onlay (i.e., patch) repairs; Mundy suggests that, unlike anastomotic repairs, there is a steady annual attrition rate after approximately 4 years of approximately 5% per annum. He also noted that scrotal skin repairs do much worse. Mundy concludes that in the long term (more than 10 years), all skin inlays have a tendency to deteriorate. Nonetheless, this may be an acceptable situation considering the alternatives (dilation or urethrotomy management), and providing patient selection is appropriate. Others have reported good long-term results even from repairs using scrotal skin (76). Blandy's group (9) followed 194 patients undergoing a one-stage scrotal patch repair who were followed from 3 to 20 years, and noted stricture recurrence in only 7%, but some were as late as 15 years. The results using the aforementioned combined approach of onlay techniques, grafts when penile skin is unavailable, and a staged repair with grafting in complex cases and when circumferential substitution is required, is reported to give an 85%

overall success rate (96). Newer techniques such as the dorsal onlay urethroplasty and the use of buccal mucosa show promise and conceptually seem to be superior, but long-term results are needed before their place in urethral stricture management can be confirmed (6,33,38,51).

One of the concerns of bulbar urethroplasty is postoperative impotence. In the past, an incidence as high as 15% had been suggested; however, this is no longer the case with current practice, and Mundy (62) reported a 33% temporary and a 0.9% permanent (more than 3 months) rate.

STRICTURES OF THE POSTERIOR URETHRA

Part of "36 - STRICTURES OF THE MALE URETHRA "

Stricture or obliteration of the posterior or membranous urethra most commonly result from urethral disruption at the time of pelvic fracture, although they also may follow prostatectomy.

Prostatomembranous urethral injury occurs in approximately 10% of patients sustaining pelvic fracture, the majority being the result of automobile or occupational injury. The magnitude of the initial trauma will determine the amount of prostatovesical displacement on which the degree of urethral injury will depend. In the majority of pelvic fractures, the urethra either is not injured or is simply contused and/or elongated with minimal residual sequelae. If urethral disruption does occur, it may be partial or complete, and retrograde urethrography will diagnose the extent. Patients with contusion and/or elongation injury require a temporary urethral Foley catheter; however, in those with a partial tear in whom retrograde urethrography will show continuity but some extravasation, optimal management is by suprapubic cystostomy alone until the urethra heals. Urethral catheterization is considered injudicious in this scenario because it is considered that it may convert the partial tear into a complete tear. Often, however, an attempt has been made during the resuscitation of the patient before the urethral injury has been suspected or assessed.

Once the diagnosis of total prostatomembranous urethral disruption is made by retrograde urethrogram, excretory urography also should be performed to evaluate the upper tracts and the bladder, because bladder rupture occurs simultaneously in up to 10% of cases. A small percentage of cases demand immediate surgical intervention (Fig. 36.18) (92). These include the patient with an associated rectal injury in whom early exploration is needed to evacuate the contaminated hematoma and to perform a colostomy. Urethral realignment over a stenting catheter is appropriate in such cases. Patients in whom both the prostatomembranous urethra and the bladder neck are injured by the fracture also should undergo exploration so that the bladder neck can be debrided and repaired. This is to improve the chance of continence.

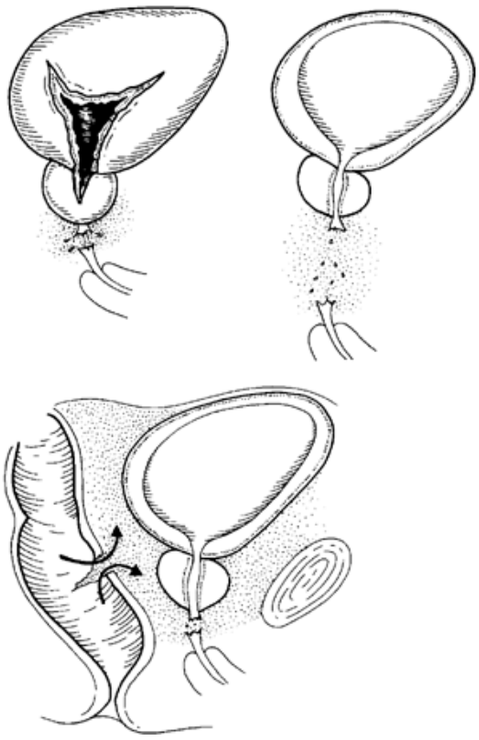

FIGURE 36.18. Primary indications for “early” intervention in cases of posterior urethral injury after pelvic fracture. These include associated rectal tear, associated injury to the bladder neck, and excessively long distraction defects. (From Webster GD, Khoury JM. Management of acute urethral trauma. In: Webster GD, Kirby R, King LR, et al., eds. *Reconstructive urology.* Oxford: Blackwell Scientific Publishers, 1993, with permission.)

The management of patients other than these is controversial. The debate centers on the timing of intervention and the use of endoscopic or open surgical repair. Repair can be immediate, delayed (within 1 to 2 weeks), or late (after 3 months). At each of these times, the urethra can be repaired by endoscopic or open surgical techniques. The outcomes debated with the use of these different approaches are the incidence of strictures, impotence, and incontinence. For a number of decades, placement of a suprapubic catheter and open surgical repair at 3 to 6 months has been the gold standard, with successful outcome reported in more than 95% of patients. Numerous reports advocating the use of endoscopic techniques to reestablish urethral continuity are currently appearing. The difficulty in defining the role of endoscopy is that the numbers are small, follow-up is short, and the variety of different techniques used make comparison with open surgical repair difficult.

Immediate Urethral Realignment

Advocates of immediate urethral realignment stress the advantage of the immediacy of managing the problem, thereby avoiding the need for prolonged suprapubic catheterization while awaiting secondary repair. In this approach,

the injury is explored at the time of presentation, the pelvic hematoma is evacuated, and the urethra is realigned over a stenting catheter using one of a variety of techniques. Unfortunately, conditions rarely are ideal for cautious surgery soon after pelvic fracture, and early exploration often results in catastrophic new bleeding. An historic review of 15 reported series encompassing 301 patients managed in this fashion showed that only 69% of them had stricture-free healing of the urethra in any event (92). Of these patients, 40 of 201 (20%) were incontinent, and 102 of 252 (40%) were impotent. This is in sharp contrast to the results of accumulated series of 236 patients managed by delayed intervention in whom only 4 (1.7%) were incontinent and 26 (11%) were impotent. Although these results do reflect the results of surgery performed in a prior surgical era, the discrepancy in outcomes still leads one to view aggressive early intervention with caution.

Instances in which patients who have been catheterized using endoscopic techniques within the first few hours of injury have been reported. Herschorn and associates (35) reported on immediate catheterization, with a concluding comment that careful urethral catheter realignment (either immediately or within 5 weeks of injury) is safe and obviates total urethral closure. Their method of catheterization was retrograde or antegrade, primarily using the linked-catheter technique; they comment that 54% of patients managed in this fashion subsequently developed a stricture in follow-up and required urethrotomy or dilation, and no patients developed incontinence. They also suggest that the rate of impotence was related to the extent of injury rather than injury management. Elliot and Barrett (26) recently reported a historic series with results of immediate realignment of complete urethral disruption in 56 patients. Although the risk of incontinence and impotence in this series is similar to that of other methods, postrealignment strictures that required further treatment occurred in 68%. In addition, many patients with pelvic-fracture urethral disruption have other injuries, and the urethral injury is not a priority in their management at this stage. A further consideration is that urethral catheterization may introduce infection and cause further bleeding, and in the long term, two-thirds of the patients will still be left with a urethral stricture.

Delayed Primary Repair

Delayed primary repair requires that the patient with prostatomembranous urethral disruption from pelvic fracture be managed by suprapubic catheter placement at the time of injury, and that the disruption then be realigned endoscopically over a stenting catheter or repaired surgically at the next opportunity (usually within the first 10 days) when the patient's general condition has stabilized. The advantage of this technique is purported to be an avoidance of the high risk of pelvic exploration during the immediate postinjury period.

Mundy (64) reported 17 men with pelvic-fracture urethral distraction defect in whom he performed abdominal exploration with pelvic hematoma evacuation and sutured anastomotic repair over a stenting catheter. In 12 cases, the site of injury was immediately subprostatic, but he noted that in 5, the rupture was as much bulbar as it was membranous urethral, but in all cases he was able to place six anastomotic sutures. Follow-up was not long at the time of publication, but thus far no patients have required subsequent urethroplasty, and four have required dilation or urethrotomy (61). Of the 13, 5 are potent and none are incontinent. Chapter author, George Webster, has had similar unreported experience with delayed primary repair, performed per perineum rather than abdominally. The advantage of the perineal approach is the simplicity of the anastomosis and the lesser operative morbidity as compared with the laparotomy approach. However, a disadvantage is that many patients cannot be placed in the lithotomy position so soon after pelvic-fracture injury.

Delayed endoscopic realignment is being reported increasingly. The techniques used are evolving, and currently include combinations of antegrade and retrograde endoscopy, fluoroscopy, and magnetic interlocking sounds. Cohen and colleagues (18) reported on five cases with complete posterior urethral disruption following pelvic fracture managed by endoscopic realignment 7 to 19 days following injury. This was performed using a flexible endoscope passed through a suprapubic tract and a rigid or flexible cystoscope negotiated per urethra. Once a guidewire was negotiated across the injury, a catheter could be guided over the wire and left indwelling for 5 to 10 weeks. Their patients performed intermittent self-catheterization for up to 6 months following catheter removal. They had a successful outcome in four; one patient was unable to perform the self-catheterization and ultimately required urethroplasty because of obliteration. Two patients were potent and none were incontinent. One criticism of their technique is their use of Foley-catheter traction, presumably to facilitate healing at the realigned injury, and the use of traction has now been largely abandoned because of the risk of damage to the bladder neck. Indeed it is probable that intraabdominal pressure will force the bladder and prostate back to the pelvic floor without traction, the direction of descent being simply guided by the stenting catheter. Further reports of these different realignment techniques have been published and it may be that they have a role in management, but at present the numbers are small and the follow-up has been short.

A recent literature review (43) compared all immediate realignment with late repair and found a similar risk of incontinence, but half the risk of stricture. The risk of impotence in this review was doubled with early realignment; however, this may reflect the severity of the injury rather than the results of the intervention. They concluded that the various procedures complement each other in the management of these patients. The reported results need to

be evaluated with care, because success after endoscopic procedures often includes those patients who require outpatient dilation, which in open surgical repairs would be considered a failure.

Secondary Repair of the Distraction Defects Following Pelvic-Fracture Urethral Injury

The delayed management of membranous urethral injuries again falls broadly into two categories: (a) endoscopic procedures, including direct vision internal urethrotomy and urethral dilation and (b) open surgical procedures, including anastomotic and substitution urethroplasties. Procedure selection is dictated by the nature of the urethral defect (obliterative or nonobliterative); the length of the defect; the presence of complicating factors, such as urethral cavitation, fistulae, or bladder neck injury; and to some degree, by the treatment philosophy of the surgeon.

Delayed Endoscopic Management of Posterior Urethral Strictures and Distraction Defects

The role of urethral dilation and direct vision internal urethrotomy has been well-established for the treatment of nonobliterative membranous urethral strictures following partial urethral tears. Although recommended as first-line therapy in these cases, it must be recognized that few strictures are cured, with most requiring long-term, periodic dilation management and many requiring eventual open urethroplasty.

More controversial is the use of visual urethrotomy, better known as *cut-for-the-light technique,* in the management of obliterative membranous urethral defects. Variations of this technique have been described by Barry (8) and Marshall (50) and many other small series. A more recent report by Spirnak and co-workers (79) presented five patients with distraction defects less than 3 cm in length, which were managed an average of 4 months following injury. Once urethrotomy had been accomplished through the obliterated segment, a stenting catheter was left for 3 to 7 days, and after removal, the patient was placed on a 3-month regimen of urethral self-dilation. They noted three totally successful outcomes an average of 31 months following treatment, whereas two, who failed to perform self-dilation, required repeat urethrotomy. Of the latter patients, one is now a success, but the other has required urethroplasty. El-Abd (24) reported a series of *core-through* procedures performed in 79 patients. Strictures longer than 2.5 cm were treated by open urethroplasty. Half of the patients were considered a success but still required an average of two procedures to achieve stability. Although if successful, this procedure may spare the patient an open urethroplasty, it may result in a number of complications, and often requires multiple anesthetics. False passages may be created that bypass the sphincter, and fistulae may be established between urethra and rectum. At best, if the procedure is successful, urethral continuity is reestablished, but the channel created lies in dense scar tissue, and generally requires long-term dilation and often, eventual surgical urethroplasty.

The role of this technique in the management of pelvic-fracture urethral distraction defects remains to be established by long-term follow-up of larger series of cases. Optimal techniques (e.g., radiographic versus stilette directed versus endoscopically guided) need to be established, as do patient-inclusion criteria for the technique (length of defect) and appropriate timing (from time of injury). It is likely that until these questions are answered, the procedure cannot universally replace the surgical management of these defects, and enthusiasm for this nonoperative approach must be tempered with caution.

Delayed Surgical Repair of Pelvic-Fracture Urethral Distraction Defects

There is no panacea for the management of posterior urethral distraction defects, but Webster and colleagues believe that the optimal repair is by a one-stage anastomotic procedure, preferably performed through the perineum alone (94,95). This repair has proven to be remarkably versatile and durable, and has been used successfully for distraction defects as long as 7 cm. It also is the opinion of these authors that only extremely complex strictures will require an abdominoperineal approach or a substitution urethroplasty. Experience proves that fewer than 5% of cases will be classified as complex because of associated adverse local features impacting upon repair selection, and these features are noted in Table 36.1 . Certainly, those reconstructive urologists dealing primarily with war rather than automobile injuries will have a higher incidence of such complicated cases.

Long urethral defect	Associated anterior urethral stricture
Chronic periurethral cavity	Factors limiting surgical access
Rectal, cutaneous, and peri-urethral bladder base fistula	History of prior failed repair
Incontinence	

From Webster GD. Urethral injuries. In: Whitfield HN, Hendry WF, Kirby RS, et al., eds. *Textbook of genito-urinary surgery.* Oxford: Blackwell Scientific Publishers, 1995, with permission.

TABLE 36.1. FEATURES ASSOCIATED WITH *COMPLEX* POSTERIOR URETHRAL STRICTURES

Progressive Perineal Approach for the Repair of Posterior Urethral Distraction Defects

A 3-month delay before embarking on repair generally is sufficient. Longer delays have not proven advantageous, and

the proposal that the length of the distraction defect reduces with time is not borne out by experience. A combined cystogram–retrograde urethrogram will have evaluated the complexity and length of the defect, the competence of the bladder neck, and the normality of the anterior urethra. In addition, antegrade and retrograde cystoscopy will have been performed to verify the radiographic findings and also to rule out bladder stones, which are present as a result of the long-term catheterization.

The patient is placed in the lithotomy position, and both the abdomen and perineum are prepped in case combined retropubic access is required intraoperatively. Excellent exposure of the posterior urethra is obtained by a midline perineal incision bifurcated posteriorly, and the bulbospongiosus muscle is divided in the midline (Fig. 36.19A). The bulbar urethra is then mobilized circumferentially as far proximally as the obliterated segment where it is transected, and distally to a few centimeters distal to the crura (Fig. 36.19B). The anterior urethra in essence becomes a urethral flap depending on collateral retrograde blood supply from the corpora cavernosa and glans. Previous anterior urethral surgery or strictures and significant hypospadias may jeopardize the blood supply to the flap, precluding this mobilization and dictating an alternative repair. In addition, this blood supply seems less well-developed in prepubertal boys. The blood supply can be assessed using Doppler ultrasound.

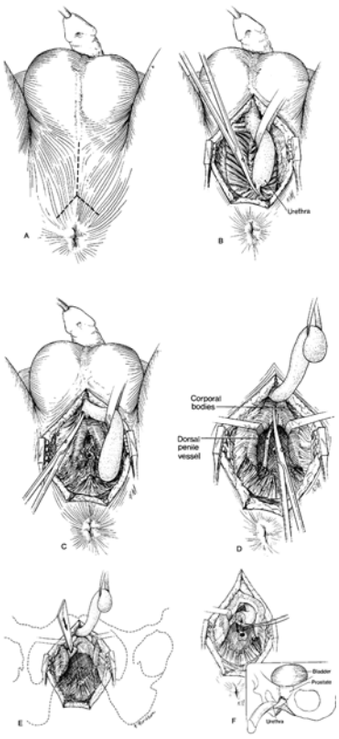

FIGURE 36.19. Perineal repair of pelvic fracture urethral distraction defects. **A:** A midline perineal incision is bifurcated posteriorly. **B:** After dissecting the bulbospongiosus muscle from the bulbar urethra, it is circumferentially mobilized proximally to the obliterative defect. Incision of the posterior urethral attachments *(scissors)* facilitate mobilization. **C:** Once transected posteriorly, the urethra is mobilized distally as far as the suspensory ligament of the penis, if necessary. **D:** Penile corporal bodies are separated, right from left, from the crus distally for 5 to 7 cm. The dorsal penile vessels dorsal to the corpora lie beneath the inferior ramus of the pubic above. **E:** A channel is excised from the inferior ramus of the exposed pubis between the separated corporal bodies using bone osteotome and/or bone rongeur. **F:** The corporal body is dissected circumferentially and the mobilized urethra rerouted around it and through the resected bony defect. The mobilized bulbar urethra is spatulated dorsally for anastomosis to the posteriorly spatulated prostatomembranous urethra. *(Inset)* Supracrurally rerouted urethra shown traversing resected inferior bony defect to facilitate bulboprostatic anastomosis. (From Webster GD, MacDiarmid SA. Posterior urethral reconstruction. In: Webster GD, Kirby R, King LR, et al., eds. *Reconstructive urology*. Oxford: Blackwell Scientific Publishers, 1993, with permission.)

Through the suprapubic tract, a urethral sound is then negotiated carefully through the bladder neck and into the prostatic urethra until its tip can be palpated in the perineum, then a vertical incision is made through the perineal scar onto its tip. Adequate exposure is obtained with a nasal speculum inserted retrogradely into the membranoprostatic urethra (replacing the antegrade sound), allowing the membranous urethra to be spatulated at the 6 o'clock position as far proximally as the verumontanum. The bulbar urethra is spatulated on its opposite side to ensure an ultimate 40-Fr–sized bulboprostatic anastomosis.

At this point, it will become apparent whether a simple tension-free anastomosis is possible or whether further lengthening procedures are required. These further maneuvers are carried out in a progressive, stepwise fashion as the need for further lengthening is required (95). In order, these maneuvers are performed as follows:

1. *Further circumferential mobilization to the suspensory ligament.* Careful dissection is required to avoid dissection into the spongy tissue, which could jeopardize the blood supply of the flap. If mobilization is taken beyond the suspensory ligament, penile chordee may result (Fig. 36.19C). Up to 2 cm of lengthening can be obtained by this maneuver because of the elasticity of the healthy bulbar urethra.
2. *Separation of the proximal corporal bodies.* If the urethra is allowed to course between the separated corporal bodies rather than over them, at least 1 or sometimes 2 cm of apparent urethral lengthening can be achieved. The proximal 4 to 5 cm of the corporal bodies can be separated by careful sharp dissection along a relatively avascular plane in the midline (Fig. 36.19D). Beyond this point, the corporal bodies are connected more intimately making further separation too difficult.
3. *Inferior pubectomy.* The two aforementioned maneuvers achieve a tension-free anastomosis in approximately 50% of cases. A further 1 to 2 cm can be gained by redirecting the urethra through a bony channel excised from the inferior pubic bone now exposed between the separated corporal bodies. A small wedge of bone only is removed using an osteotome and bone rongeur (Fig. 36.19E), facilitating the anastomosis in an additional 28% of cases. In an attempt to preserve the more laterally situated neurovascular bundle along the inferior surface of the pubis, excision of bone must be limited to the midline.
4. *Rerouting the urethra around the corporal body.* As a final maneuver, the urethra can be rerouted laterally around the corporal body and through the tunnel created by the inferior pubectomy (Fig. 36.19F). A tunnel is created in the soft tissue around the corporal body, taking care to avoid the corporal body, thereby preventing damage to the neurovascular bundle close to its surface. This supracorporal rerouting achieves at least a further centimeter of urethral lengthening and is required in approximately 23% of cases.

It is difficult to predict preoperatively which patients will require these final two maneuvers, because urethrograms only estimate the length of the distraction defect in one radiographic plane and give little information about associated spongiofibrosis and urethral elasticity. Subsequent transurethral instrumentation or insertion of a penile prosthesis has not been affected adversely by the new course of the urethra.

The Anastomosis.

The anastomosis can be difficult, particularly when the prostate is riding high and all four maneuvers were needed to reduce anastomotic tension. A long nasal speculum is inserted retrogradely into the prostatic urethra, and under direct vision a spatulated end-to-end bulboprostatic anastomosis is performed using interrupted 4-0 PGA sutures. The verumontanum is an important landmark, and identification of the prostatic urethral mucosa also is important. Using needles bent into a "J" shape (Fig. 36.20), each suture is inserted before being individually tied. The needles are advanced through the prostatic urethral edge from outside to inside; the point of the needle being retrieved within the prostatic urethra and advanced until the hub of the needle clears, and then withdrawn. Approximately eight sutures are inserted commencing at the 12 o'clock position and proceeding clockwise before each is tied in the same order as they were inserted.

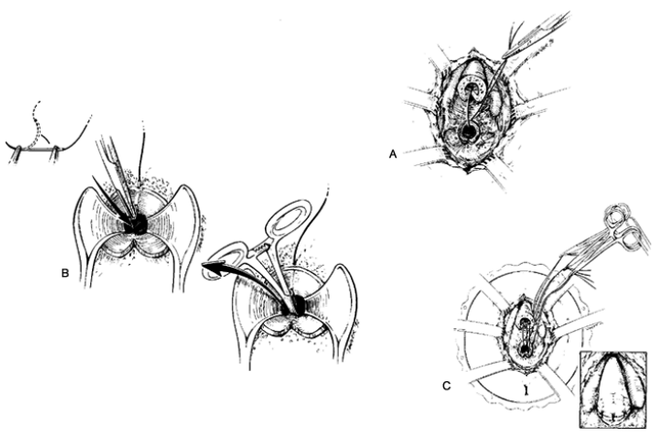

FIGURE 36.20. A: Bulboprostatic anastomosis is facilitated using a standard suture needle bent into a "J" shape. The needle is advanced through prostatic urethral edge and the needle tip is retrieved in the prostatic lumen. The needle is advanced through the bladder neck to clear needle, and then is withdrawn. **B:** Suture placement is commenced with the 12 o'clock suture in the prostatic urethra. **C:** Sequential sutures are then placed in a clockwise direction around the prostatic urethral opening but are not tied. Hemostats placed on the end of each suture are stacked sequentially on an Allis clamp. After approximately eight sutures have been placed, they are then individually tied, commencing with the 12 o'clock suture proceeding clockwise. A catheter is inserted following suture placement and tying. (From Webster GD, MacDiarmid SA. Posterior urethral reconstruction. In: Webster GD, Kirby R, King LR, et al., eds. *Reconstructive urology*. Oxford: Blackwell Scientific Publishers, 1993, with permission.)

A 12-Fr fenestrated silicone catheter is inserted once the anastomosis is complete, together with a suprapubic cystostomy tube. A periurethral Jackson-Pratt drain may be inserted for wound drainage and, in most cases, is removed the following day.

Urethral stenting with an indwelling Foley catheter is required for approximately 2 to 3 weeks, and the stent is removed only after a retrograde urethrogram around the catheter proves no extravasation. The suprapubic catheter usually is removed on the same day after a successful trial of voiding. A retrograde urethrogram is performed 3 and 12 months postoperatively.

Results of Anastomotic Urethroplasty of Posterior Urethral Injury

In the chapter authors' experience with this technique, in 113 cases of pelvic-fracture distraction defects, the overall stricture-free success rate was 97%. Patient ages ranged from 9 to 69 years (mean 36 years), and the causes of injury were automobile related in 71 and occupational in 42. Obliterative defects ranged from 1.5 to 7 cm (only three cases were strictures) and the maneuvers used to facilitate the tension-free anastomosis are shown in Table 36.2 . Complications were uncommon and included temporary peroneal nerve dysfunction in four and persistent incontinence attributable to preexisting bladder neck dysfunction in two (see subsequent discussion). Other authors have reported similar success rates (60).

Urethral mobilization	9	(8%)
Corporal separation	46	(41%)
Inferior pubectomy	31	(28%)
Supracorporal rerouting	27	(23%)
	113	(100%)

From Webster GD. Urethral injuries. In: Whitfield HN, Hendry WF, Kirby RS, et al., eds. *Textbook of genito-urinary surgery.* Oxford: Blackwell Scientific Publishers, in press. Used by permission.

TABLE 36.2. MANEUVERS TO FACILITATE ANASTOMOSIS

Impotence is a frequently reported complication in this group of patients. Often debated is whether impotence is caused by the injury itself or is a consequence of the surgery. This has become more controversial as the endoscopic procedures have been noted to have a high rate of impotence (43). In a group of 92 patients in whom follow-up data could be obtained, it was noted that 57 (62%) patients remained potent in the long term, with a median follow-up of 48 months; importantly, the operation did not render impotent any patient who was preoperatively potent. Self-injection with vasoactive agents was successful in 24 of 27 (89%) impotent patients, suggesting a predominant neurologic etiology. Of 30 patients in whom original postinjury radiographs could be examined, the pattern of bony injury was able to be correlated with incidence of impotence. The authors found that bilateral pubic rami fractures correlated with impotence, with 13 of 15 being impotent, whereas 11 of 15 with unilateral fractures or no fractures remained potent (49). It is likely that disruption of the cavernous nerves lateral to the prostatomembranous urethra behind

the symphysis pubis is the most likely etiology of impotence in this injury.

Factors Complicating Perineal Anastomotic Repair

As noted previously, a number of uncommon complicating factors may render perineal anastomotic repair inappropriate, but in recent experience they account for fewer than 5% of cases (Table 36.1).

Long urethral defects may be avoidable by early intervention following the initial pelvic fracture. In those cases with massive pelvic hematoma and resulting “pie-in-the-sky” appearance of the bladder on the early cystogram, some consideration should be given to early hematoma evacuation and urethral realignment over a stenting catheter. This

may be performed endoscopically, as noted previously. In the event the defect is long (more than 5 cm), a perineal approach is not negated but all of the tension-relieving maneuvers likely will be needed. The tubed perineoscrotal flap procedure or a tubed full-circumference substitution urethroplasty has been suggested for such cases, but certainly gives suboptimal results and generally is resorted to only as a salvage maneuver.

Chronic periurethral cavity occurs in those cases in which the pelvic hematoma liquefies and evacuates through the urethra, leaving cavities within the pelvic floor that may become epithelialized and ultimately may be a source of chronic infection and stone formation. These epithelialized pelvic floor diverticula may become infected and discharge into the rectum, creating fistulae, or may be associated with pelvic osteomyelitis. When identified, these cavities suggest the need for an abdominoperineal repair so that the pelvis can be cleaned out and omentum brought into the pelvis to facilitate absorption and healing.

Rectal, cutaneous, and periurethral bladder-base fistulae may occur from the injury itself, from the aforementioned complication of pelvic floor abscess, or from inept urethral instrumentation, particularly at the time of cut-for-the-light endoscopic urethroplasty. These fistulae do not necessarily preclude an anastomotic repair.

Incontinence is uncommon following pelvic-fracture injury. The urethral injury itself or the subsequent urethroplasty are likely to compromise the distal sphincter mechanism, but fortunately the bladder neck remains competent and functional. However, any prior bladder neck surgery or injury obviously may adversely affect continence. In Webster and Venn's experience, and as reported by others, incompetence of the bladder neck on the preoperative cystogram does not necessarily translate into postoperative incontinence, and for this reason, these authors hesitate to perform bladder neck reconstruction at the time of the urethroplasty (37,48). Webster reviewed 15 patients with open bladder necks on cystography who had undergone posterior urethroplasty, and of these, six were continent and eight were incontinent posturethroplasty. Of the eight, six were managed successfully by bladder neck reconstruction, one underwent artificial sphincter implantation, and one was improved with collagen injections. Individualized management is needed in such cases, and in some, simultaneous or staged bladder neck reconstruction may be justified. Cystoscopy is helpful in the evaluation of the bladder neck, and the patient who has an obvious sector scar is the best candidate for bladder neck reconstruction.

Associated anterior urethral stricture may complicate significantly the management of postpelvic-fracture membranous urethral strictures both by interfering with the retrograde urethral blood supply after urethral mobilization and by reducing urethral elasticity. In this scenario, substitution repairs may find their place.

Factors that limit surgical access may complicate the repair because of an inability to achieve the degree of lithotomy position needed to gain exposure. It does not necessarily preclude a perineal approach; however, it may dictate that the urethra be circumferentially mobilized perineally, but the anastomosis be performed abdominally.

Once prior repair has failed, the subsequent salvage repair has a number of additional problems to contend with, not the least of which is the fixation of the bulbar urethra in perineal scar. Surprisingly, however, anastomotic repairs as described previously are still possible in the majority of cases (93). In the event these are not possible, a one-stage substitution urethroplasty using a pedicled island of penile skin mobilized from the penis on its subcutaneous vascular pedicle, or a staged scrotourethral inlay-type procedure, may be performed.

Combined Abdominoperineal Transpubic Approach for More Complex Injuries

In the past, abdominoperineal transpubic repairs have been used extensively; however, they now are used most often in a limited fashion, when circumstances necessitate (51). Some of the aforementioned features indicate a need for this repair, the chief of which are fistulous tracts, inability to achieve the lithotomy position, and pelvic floor cavities. Bladder neck incompetence, as noted previously, is not in itself an indication for abdominoperineal repair, and its management should be deferred to a secondary procedure.

If this deferred approach is required, a lower midline abdominal incision is made after the perineal dissection of the anterior urethra has been completed (as previously described), and the bulbar urethra has been transected at the level of the obliteration. Indeed, the further steps of corporal-body separation and wedge excision of the inferior pubis may have been performed. Through the abdominal incision, the prevesical and retropubic spaces are dissected carefully down to the level of the apex of the prostate, staying close to the periosteum of the retropubis, until communication with the perineal dissection is made. To avoid injury to the bladder neck, it is wise to open the bladder high on its anterior wall so that an intravesical finger can help direct the retropubic dissection. It rarely is necessary to excise the entire anterior wedge of pubis as previously described by Waterhouse and colleagues (91), because equally good access is achieved by partial removal of the posterior surface of the pubis using a Capener gouge (82). This wide access anterior to the prostate will facilitate the anastomosis of the mobilized bulbar urethra to the spatulated prostatic urethra. In addition, the retropubic bone removal will improve access to the pelvic floor to deal with the complicating features, which, as previously discussed, are the indication for this approach. Most important is that the omental wrap be fashioned into a pedicle and placed

around the anastomosis and bladder neck, filling the space resulting from bony excision.

Substitution Urethroplasty

In the past, this approach was the preferred technique of many surgeons, particularly after Morehouse and associates (56) reported good outcomes in 1972. Now, these repairs should be used only when associated anterior urethral stricture disease is compromising the retrograde urethral blood flow and hence precluding anastomotic repair, and in rare complex salvage situations (57). Substitution procedures may be performed in one or two stages. The one-stage repairs include pedicled skin island and free full-thickness skin graft repairs; two-stage procedures include a variety of scrotourethral inlay operations sometimes combined with full-thickness or meshed split-thickness skin graft inlay. The complexities of the individual situation dictate which repair is most appropriate, but in general, graft repairs do poorly in pelvic-fracture cases because of the lack of a well-vascularized bed.

Postprostatectomy Strictures of the Posterior Urethra

Strictures of the posterior urethra following open prostatectomy or TURP are not uncommon. The mechanism for injury during a TURP is multifactorial and includes mucosal denudation caused by the tight gripping of an inadequate urethra over a poorly lubricated over-sized sheath, overaggressive distal resection and electrocoagulation involving the membranous urethra, and Foley-catheter irritation. During open prostatectomy, the membranous urethra can be injured during finger or sharp transection at the prostatic apex.

Prostatectomy ablates the proximal sphincter mechanism, and therefore continence is threatened by any injury and stricturing of the distal urethral sphincter. Fortunately, the majority of these strictures are superficial and are best managed by periodic urethral dilation. Direct vision internal urethrotomy is absolutely contraindicated as discussed previously. Urethroplasty also threatens the distal sphincter mechanism, although an elaborate continence-preserving, push-in bulbourethral-resleeving procedure was described by Turner-Warwick (83). Wallstent placement across the stricture has been successful, but requires the implantation of an artificial sphincter at a more distal site to salvage continence.

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37

URETHRAL CARCINOMA

Jeffrey C. Applewhite

M. Craig Hall

David L. McCullough

J.C. Applewhite, M.C. Hall, and D.L. McCullough: Department of Urology, Wake Forest University School of Medicine, Wake Forest University Baptist Medical Center, Winston-Salem, NC 27157.

Contents

Urethral carcinoma is an uncommon disease. Although it was first described in men and women in the early 1830s, through 1980 the number of reported cases in men was approximately 600, and approximately 1,200 cases had been reported in women (54). Thus urethral carcinoma is the only shared genitourinary malignancy that is more common in women than in men. This fact has been confusing to students of the disease because the male urethra is longer and more complex. Because urethral carcinoma is uncommon, no single institution has a sufficient number of patients to define clearly the natural history of the disease or to examine prospectively the different treatment options. As a result, there is no standardized approach to managing primary urethral carcinoma.

ANATOMY

Part of "37 - URETHRAL CARCINOMA "

The male urethra is an epithelium-lined tubular structure that is surrounded by connective tissue, smooth muscle, elastic fibers, and the richly vascular corpus spongiosum. There are several glands of Littré along the length of the urethra and the paired Cowper's glands, which empty into the posterior aspect of bulbar urethra. The urethra has an average length of 21 cm. The mucosa of the urethra consists of transitional epithelium in the prostatic portion; stratified or pseudostratified columnar epithelium in the pendulous, bulbous, and membranous portions; and nonkeratinized stratified squamous epithelium at the meatus and fossa navicularis (Fig. 37.1). By anatomic convention, the prostatic and membranous urethra make up the posterior urethra, and the more distal segments are considered to be the anterior urethra. However, when discussing urethral carcinoma, previous authors considered the bulbous urethra with the posterior segment because of differences in

treatment and prognosis of tumors of this segment as compared with those in the penile or pendulous urethra. Therefore, in this discussion, posterior urethral carcinoma includes lesions that arise in the prostatic, membranous, and bulbar urethra.

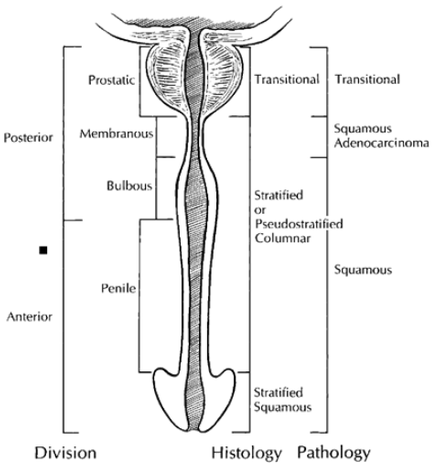

FIGURE 37.1. Divisions, histology, and pathology of the male urethra.

The lymphatic drainage of the anterior urethra parallels that of the glans and corpus spongiosum into the superficial and deep inguinal nodes, which then drain to the external iliac nodal chain (Fig. 37.2). Tumors of the prostatic, membranous, and bulbar urethra drain along three pelvic lymphatic channels: one parallel to the dorsal vein of the penis to the external iliac chain, one to the obturator and internal iliac group along the pudendal artery, and one into the presacral nodes (16).

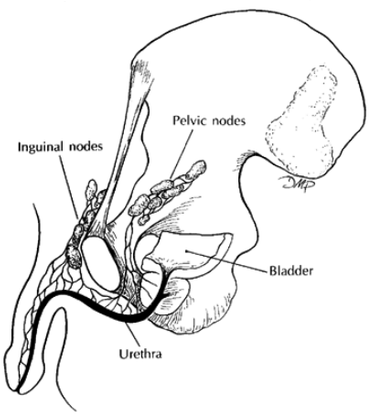

FIGURE 37.2. Lymphatic drainage of the male urethra.

The female urethra is also an epithelium-lined tube supported by submucosal connective tissue, elastic and muscle fibers, and a rich venous network. The average length is 4 cm.

The epithelium of the distal two-thirds consists of stratified squamous epithelium, which is continuous at the meatus with the epithelium of the vulva. The proximal one-third is lined by transitional epithelium, which is continuous with the mucosa of the bladder (Fig. 37.3). As in the male urethra, several small glands lie along the urethra and open into the urethral lumen. The periurethral glands of Skene are concentrated near the meatus but extend along the entire urethra (3,4). Although no definite anatomic divisions exist for the female urethra, Grabstald (41) described carcinoma as anterior when limited to the distal third, and entire (posterior) when the proximal two-thirds is involved. Again, this arbitrary division reflects the differences in treatment and prognosis associated with the location of the tumor in the urethra.

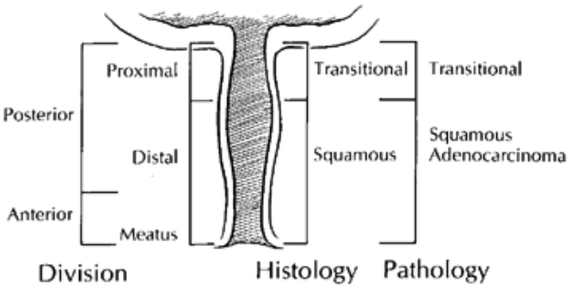

FIGURE 37.3. Divisions, histology, and pathology of the female urethra. (Adapted from Droller MJ, Nyberg L. *Urethral carcinoma.* AUA Update Series, 1983, vol 2, lesson 19, with permission.)

The lymphatic drainage of the female urethra follows two courses. As in the male urethra, the drainage of the distal urethra is to the superficial and deep inguinal nodes, and the drainage of the proximal urethra is to the external iliac, obturator, and presacral nodes (Fig. 37.4).

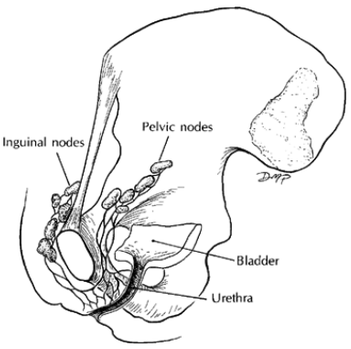

FIGURE 37.4. Lymphatic drainage of the female urethra.

URETHRAL CARCINOMA IN MEN

Epidemiology and Etiology

The peak age of incidence for primary urethral carcinoma in men is in the sixth decade, although it has been reported in both teenagers and men in their nineties (63). There are no racial predilections. The exact cause of urethral carcinoma in men is unknown, but chronic inflammation and the presence of the human papillomavirus (HPV) have been identified as causal factors. Approximately 35% to 88% of men with urethral cancer have an antecedent history of stricture, and 37% to 44% have a history of sexually transmitted diseases (57,63,101). The association between urethral carcinoma and urethral stricture is further strengthened by the fact that the bulbomembranous urethra is the most common location for both disease processes. In addition, squamous metaplasia commonly occurs at the site of urethral stricture in epithelium that is normally columnar (11).

Significant evidence also links the presence of HPV with the genesis of urethral carcinoma in men. The HPV-16 and HPV-18 genotypes are implicated in 70% to 90% of invasive cervical carcinomas, and they are also the genotypes most strongly implicated in urethral cancer. Using polymerase chain reaction (PCR), HPV-16 DNA exclusively was found to be associated with squamous cell carcinoma (SCC) of the male urethra in 4 of 14 (29%) patients (122). Tissue from metastatic sites revealed HPV-16, and metastatic deposits in the ten patients with primary tumors negative for HPV-16 were found to be negative as well. Thus complete concordance of HPV-16 status in primary and metastatic specimens was demonstrated, strongly supporting HPV as an etiologic factor in SCC of the male urethra.

The presence of HPV-16 has been specifically associated with cancer in the pendulous portion of the urethra as opposed to bulbar urethral tumors. Cupp and colleagues (21) detected HPV-16 DNA by PCR in all 6 patients with SCC of the pendulous urethra, whereas none of 12 control urethral tissue specimens were positive. Furthermore, no patients with SCC of the bulbar and posterior urethra tested positive for HPV, suggesting a possible etiologic difference between SCC of the distal and proximal urethra.

Signs and Symptoms

The signs and symptoms of urethral carcinoma can be vague and nondescript, but they may also mimic those of urethral stricture and its complications of abscess and fistula formation. In the series by Kaplan and associates (63) of 232 patients, 47% had symptoms of obstruction, 39% had a palpable mass, and 31% had a periurethral abscess. Grabstald (41) reported that in many instances skin ulceration is the primary finding on physical examination. Other less common symptoms, in descending order of frequency, included urethral discharge or hematuria, fistula, retention, inguinal mass, priapism, penile gangrene, and incontinence (63). The possibility of urethral carcinoma should be considered in the setting of perineoscrotal abscess or fistula and stricture disease in men without a history of trauma.

Diagnosis and Staging

Because of a much higher incidence of benign urethral strictures, it is understandable that this diagnosis often is made initially. Only after the “stricture” is noted to warrant much more frequent dilation or to bleed excessively after dilation is a malignant process considered and the proper diagnosis made. Biopsy is essential for the diagnosis of urethral carcinoma. Usually, urethroscopy with transurethral biopsy of suspicious, friable, or necrotic-appearing tissue is adequate. In many instances, however, repeated deep biopsies must be taken in areas of abscess or phlegmon. Transcutaneous needle core biopsy of a palpable urethral mass is at times a useful diagnostic maneuver. The index of suspicion must be high.

Careful staging of urethral carcinoma is very important in planning proper therapy and predicting prognosis. The extent and location of the primary lesion are more closely associated with treatment and prognosis than is the cell type. Historically, several staging systems have been reported. Ray and associates (101) proposed a staging system that has been used by many authors (116,120). Although this staging system is common in the older literature, the tumor, node, and metastasis (TNM) classification is the standard staging system for both male and female urethral cancer

(Table 37.1) (3). This classification is based on the depth of invasion of the primary tumor and the presence or absence of regional lymph node involvement and distant metastases.

TABLE 37.1. STAGING OF MALE AND FEMALE URETHRAL CARCINOMA

Male and Female TNM[a]		Male (adapted from Levine, 1980)[b]		Female (adapted from Grabstald et al., 1966)[b]	
Primary tumor (T) (male and female)		Stage 0	Confined to mucosa only *(in situ)*	Stage 0	Confined to mucosa only *(in situ)*
T_X	Primary tumor cannot be assessed	Stage A	Into but not beyond the lamina propria	Stage A	Into but not beyond the lamina propria
T_0	No evidence of primary tumor	Stage B	Into but not beyond the substance of the corpus spongiosum or into but not beyond the prostate	Stage B	Muscle (infiltrating periurethral muscle)
T_a	Noninvasive papillary, polypoid, or verrucous carcinoma	Stage C	Direct extension into tissues beyond the corpus spongiosum (corpora cavernosa, muscle, fat, fascia, skin, direct skeletal involvement, or beyond the prostatic capsule)	Stage C	Periurethral
T_{is}	Carcinoma *in situ*	Stage D_1	Regional metastases, including inguinal or pelvic lymph nodes (with any primary tumor)	C_1	Infiltrating the muscular wall
T_1	Tumor invades subepithelial connective tissue	Stage D_2	Distant metastases (with any primary tumor)	C_2	Invading vaginal mucosa
T_2	Tumor invades corpus spongiosum, prostate, or periurethral muscle			C_3	Infiltrating adjacent structures (bladder, labia, clitoris)
T_3	Tumor invades corpus cavernosum, beyond prostatic capsule, anterior vagina, or bladder neck			Stage D_1	Regional metastases, including inguinal or pelvic lymph nodes (with any primary tumor)
T_4	Tumor invades other adjacent organs			Stage D_2	Distant metastases (with any primary tumor)
Regional lymph nodes (N)					
N_X	Regional lymph nodes cannot be assessed				
N_0	No regional lymph node metastases				
N_1	Metastases in a single lymph node, 2 cm or less in greatest dimension				
N_2	Metastases in a single node more than 2 cm in greatest dimension, or in multiple nodes				
Distant metastases (M)					
M_X	Distant metastases cannot be assessed				
M_0	No distant metastases				
M_1	Distant metastases				

[a]From American Joint Committee on Cancer. *AJCC cancer staging manual*, 5th ed. Flemming ID, Cooper JS, Henson DE, et al., eds. Philadelphia: Lippincott-Raven, 1997, with permission.
[b]From Droller MJ, Nyberg L. *Urethral carcinoma*. AUA Update Series, 1983 (vol. 2, lesson 19), with permission.

Adequate staging includes cystourethroscopy and bimanual examination. Preoperative bimanual examination under anesthesia helps determine the local extent of tumor, including infiltration of adjacent organs and structures, associated prostatic abnormalities, or pelvic sidewall adherence (126). Thorough palpation of the inguinal region is important because, unlike penile carcinoma, inguinal adenopathy usually indicates metastatic disease rather than infection (63,101). In the setting of organ-sparing surgery, urethroscopy is critical with biopsy of the proximal urethra to ensure adequate margins.

Computed tomography (CT) helps define the extent of the disease and often is useful in evaluating the regional lymph nodes. However, its accuracy is limited by the size of the nodes and the presence of inflammation and induration of the soft tissues secondary to abscess or extravasated urine. All patients should undergo a CT of the abdomen and pelvis as part of their metastatic evaluation. Magnetic resonance imaging (MRI) appears to offer no advantage over CT in the evaluation of lymphadenopathy. Fine-needle aspiration of suspicious lymph nodes should be considered to confirm metastatic disease.

CT has very limited accuracy in defining local tumor extent because of poor soft tissue discrimination. When the extent of local tumor infiltration is questionable after cystourethroscopy and bimanual examination under anesthesia, MRI may provide useful additional information. MRI appears to be the best option for evaluating the local extent of the primary lesion. It provides superior soft tissue contrast imaging in any plane and therefore is better at assessing local invasion of the corpus spongiosum or corpora cavernosa as well as adjacent soft tissue, organs, or bone (Fig. 37.5) (62).

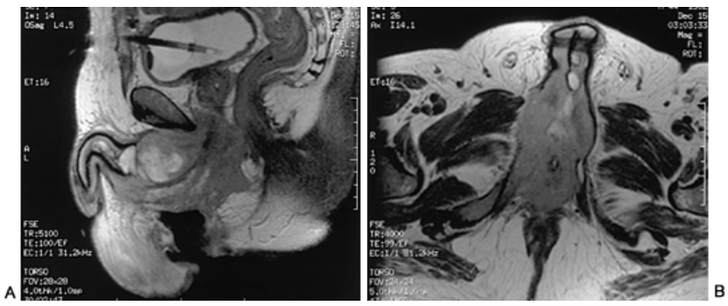

FIGURE 37.5. Magnetic resonance imaging scan of male urethral carcinoma: **A:** Sagittal T_2-weighted image demonstrates extension to the prostatic capsule, pubic symphysis, and anus and invasion of corpora cavernosa. **B:** Axial T_2-weighted image of the same lesion demonstrates possible involvement of the right pectineus, adductor longus, and adductor brevis muscles.

Other imaging studies may be necessary depending on the clinical situation. A chest radiograph is routinely obtained to rule out pulmonary metastases, and bone scans are obtained selectively when the possibility of osseous metastases is considered. The entire urothelium is assessed with either intravenous pyelography or retrograde pyelograms in patients with transitional cell carcinoma (TCC). Retrograde urethrograms suggested urethral carcinoma in 60% of the patients in one series (101). Although these studies may show long, irregular strictures with extravasation, fistula formation, or obstruction, the utility of urethrography is limited in the era of urethroscopy and typically delineates only luminal defects (119).

With TCC of the prostatic urethra, the prostate may be nodular and indurated on digital rectal examination if there is invasion of the prostatic stroma. Lesions that invade the stroma, ejaculatory ducts, and periprostatic tissues appear hypoechoic on transrectal ultrasound imaging; however, a lesion confined to the prostatic urethra usually is not detected in this manner (117). Unlike in the much more common adenocarcinoma of the prostate, the serum acid phosphatase level and prostate-specific antigen (PSA) are normal, skeletal metastases typically are osteolytic rather than osteoblastic, and there is no response to hormonal manipulation. Transurethral biopsy of the prostate is necessary to assess the ducts and stroma for the presence of invasion or limitation to the epithelium. Furthermore, bladder tumors originating in the trigone or bladder neck with local extension to the prostate and prostatic urethra may be erroneously considered primary urethral carcinoma unless careful examination and biopsy exclude the bladder as the site of origin.

Histopathology

Male urethral carcinoma occurs in the bulbomembranous, penile, and prostatic urethra in approximately 60%, 30%, and 10% of cases, respectively. Histologically, approximately 80% of these tumors are SCCs, 15% are TCCs, and 5% are adenocarcinomas or other rare cell types including neuroendocrine, lymphoma, sarcoma, and myeloma.

Natural History

Male urethral carcinoma spreads by direct extension into adjacent structures, and metastases occur largely by the lymphatogenous route to regional nodes which are palpable in 20% to 40% of patients at the time of diagnosis. Ray and associates (101) reported that at presentation 26% of patients had stage C disease and 43% had stage D disease. Advanced disease at the time of diagnosis is especially common in patients with posterior lesions, which were stage C or D in 86% of patients. In contrast, stage A or B disease was identified in 55% of patients with anterior carcinoma. Earlier presentation is attributed to an earlier onset of symptoms in patients with anterior lesions. However, symptoms of carcinoma of the prostatic urethra are more often confused initially with a more benign process. The median time period between development of symptoms and presentation for treatment was 5 months in one large series, with a range from 1 day to 15 years (63). This delay in diagnosis has also been reported by others and would be expected to contribute to the significant proportion of patients with advanced disease at diagnosis (41,76).

Most patients have only locally advanced disease or regional lymph node metastases when they die, with death occurring secondary to sepsis or bleeding (63). Distant hematogenous spread is unusual and is reported in less than 15% of patients (64,83). Of these patients, 62% had involvement of the corpora cavernosa when the diagnosis was made (63). The most common sites of distant metastases are the lungs, liver, and bones (63,101).

Survival rates are related to the clinical stage at the time of presentation. In general, lesions of the distal urethra tend to have a lower clinical stage than tumors of the

proximal urethra. Five-year survival rates for men with tumors of the anterior urethra regardless of stage are approximately 40% compared with 5% for invasive bulbomembranous tumors (6).

TCC of the prostate behaves differently, with a propensity for lymphatogenous and hematogenous dissemination. Carcinoma *in situ* begins in the prostatic urethra or ducts and is believed to be the precursor of invasive carcinoma (32,84,118). Stromal invasion is a poor prognostic indicator, with metastatic disease reported in up to 100% of patients (123). Thus treatment and prognosis for TCC of the prostatic urethra also depend on local tumor extent.

BOX 37.1 MALE URETHRAL CARCINOMA: ETIOLOGY, DIAGNOSIS, STAGING, AND NATURAL HISTORY

Chronic inflammation and the presence of human papillomavirus have been identified as causal factors in male urethral carcinoma.

Maintaining a high index of suspicion for urethral carcinoma in patients with urethral stricture and its complications is crucial for prompt diagnosis.

Careful staging, including examination under anesthesia, cystourethroscopy, and selected imaging studies, is important in planning therapy and determining prognosis.

With the exception of prostatic urethral transitional cell carcinoma, male urethral cancer spreads by direct extension and to regional lymph nodes; distant metastases are uncommon.

Surgical Treatment

Surgery with or without radiation therapy has been the treatment of choice in managing urethral carcinoma in men. Although local tumor control has been reported with radiation therapy, in practice, it is largely reserved for low-stage anterior urethral tumors in patients who refuse surgery or are not surgical candidates. Although potentially phallic preserving, definitive radiation therapy for urethral carcinoma in men is associated with significant morbidity, including chronic penile edema and urethral stricture. The extent of surgery depends on both tumor stage and location in the urethra. In general, anterior urethral tumors are more amenable to surgical control, have a better prognosis, and more often warrant less radical surgery than posterior urethral tumors.

Anterior Urethral Carcinoma

Carcinoma of the anterior urethra accounts for approximately 30% to 40% of all urethral carcinomas (63). These tumors often are amenable to less radical forms of therapy than those of the posterior urethra. Cure depends on adequate local control (63,70). Surgical treatment options include transurethral resection (TUR), local excision, partial penectomy, or radical penectomy with or without emasculation (70).

For the uncommon carcinoma *in situ* and papillary noninvasive T_a lesion involving the distal urethra, local excision may suffice. Konnak (67) described five patients with low-grade stage T_a TCC or SCC who underwent local

resection and fulguration. Although three patients developed local recurrence, they were treated conservatively, and all five patients were free of tumors 18 months to 14 years after initial therapy. Dalbagni and associates (22) also reported successful management of superficial or *in situ* tumors of the anterior urethra with periodic TUR and fulguration. In 30 such patients with long-term follow-up, none progressed to invasive disease despite a high recurrence rate. The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is an additional therapeutic option for these low-stage lesions. It has been useful with similar lesions in the bladder and can be applied transurethrally. Such therapy may result in less scar formation than use of the resectoscope (113).

Invasive tumors of the anterior urethra often can be controlled by partial penectomy with a proximal 2-cm margin (63). For more proximal or extensive anterior urethral tumors, total penectomy with perineal urethrostomy usually is necessary (63,101). In addition, emasculation should be considered when there is tumor involvement of the scrotal skin or genitalia.

In the Memorial Sloan-Kettering Cancer Center series reported by Dalbagni and associates (22), 7 of 8 patients with invasive distal urethral cancers were cured with partial penectomy with or without ilioinguinal lymphadenectomy. This included one patient with completely resected inguinal metastases. After more than 5 years of follow-up, 4 of 7 patients with more proximal or extensive anterior urethral carcinoma were alive without disease after total or partial penectomy with ilioinguinal lymph node dissection. Three died with lung metastases at a mean of 24 months postoperatively. The overall survival at 5 years was 36%.

Bird and Coburn (10) advocated subcutaneous penectomy as an alternative between limited local excision and formal amputation in patients with larger tumors. This mode of phallus preservation reportedly provides an acceptable cosmetic, psychologic, and reconstructive outcome without apparently compromising cancer control in three select patients followed for an average of 12 months.

Posterior Urethral Carcinoma

Carcinoma of the proximal or bulbomembranous urethra makes up 50% to 60% of male urethral carcinomas (72). The difficulty in managing posterior tumors is the location of adjacent organs and structures and extent of proximal invasion. Most patients have bulky tumors infiltrating adjacent structures at the time of diagnosis, and overall survival of these patients is poor despite aggressive radical exenterative surgery (13,101). However, multiple series document favorable long-term survival when local tumor control can be achieved.

Local resection, TUR, or laser photoirradiation may be feasible for the very unusual finding of early superficial tumors of the bulbomembranous urethra. However, the presence of extensive local disease necessitates wide radical excision to offer any hope for disease control. Despite seemingly adequate radical surgery, local recurrences are common and have always been associated with eventual death (13,101).

Previous authors recommended radical cystoprostatectomy with pelvic node dissection and en bloc penectomy and scrotectomy (13,41,46,63,101,107,116). Pubic resection has also been recommended to facilitate exposure and complete resection (74,111). Marshall (78) reported success in the treatment of bulbomembranous carcinoma in 1957 with anterior exenteration and total emasculation. He was able to achieve 5-year survival in 4 of 5 patients. The one death in this group was a result of sepsis and uremia, and autopsy performed 58 days after surgery revealed no residual cancer. In contrast, less extensive surgery or radiation therapy with an attempt at bladder preservation failed in three out of four patients so treated. Farrer and Lupu (35) reported the UCLA series with deep male urethral carcinoma. They combined their series with others between 1957 and 1983 and cited a 5-year disease-free survival rate of 30% (9 of 30) with radical surgery. Only 1 of 33 patients treated without radical surgery was disease free at 5 years.

Radiotherapy alone has yielded poor results (13,63,101). However, the role of planned preoperative radiotherapy is unclear but does have support (13,41,70,116). Preoperative radiation may downstage the tumor and permit excision of lesions that otherwise would be unresectable or make it possible to obtain tumor-free margins. Hopkins and associates (55) reported on a series of 16 male patients with proximal or distal urethral carcinoma. Although the mean survival of patients was only 15 months, the authors concluded that a combination of radiation therapy and radical extirpative surgery was the best therapy for proximal carcinomas. A Memorial Sloan-Kettering experience in 12 patients with invasive (T_3) disease in men and women treated with en bloc radical excision and inferior pubic rami resection coupled with preoperative radiation therapy suggests an advantage over less extensive surgery in terms of local control and survival (66). At a mean follow-up of 40 months, the overall local control rate was 83%. Postoperative complications were common, including pelvic abscess, intestinal fistulae, and superior pubic rami fractures.

Although recent literature reports an improvement in prognosis, it remains very poor for patients with bulbomembranous disease (27,63,78,101). Therefore investigators recently advocated a multimodality approach integrating chemotherapy, radiation therapy, and surgery. In a series of 46 men (40 treated with surgery alone) treated between 1958 and 1996, the overall 5-year disease-specific survival was 50% (83% for low-stage and 45% for high-stage tumors) (22). No difference in outcome was found for patients treated before or after 1975. The authors argued that surgery alone is suboptimal management of male urethral carcinoma, and they propose chemoradiation and surgery for high-stage disease.

Dinney and colleagues (27) recently reported the experience from the M.D. Anderson Cancer Center demonstrating better outcomes over the last decade than in their earlier series reported in 1980. Using primary surgery, the authors reported that 52% of patients had no evidence of disease over a mean follow-up of 50 months (27). However, those with bulbomembranous disease still had only a 25% 5-year disease-free survival rate. Emphasizing the importance of locoregional control, they concluded that radiotherapy was largely ineffective and that local control was achieved only with radical surgery. They attributed the improved outcome in their patients to a combination of factors including earlier intervention, use of adjuvant chemotherapy, and refinement in surgical technique.

In a series reported by Gheiler and associates (40), patients with low stage (T_{a-2}) disease experienced excellent outcome after treatment with surgery or radiation therapy. Furthermore, in patients with higher-stage disease, their data suggest higher survival rates for patients treated with multimodal therapy than for those treated with surgery or radiation monotherapy.

Management of Lymph Nodes

Palpable lymph nodes generally indicate the presence of metastatic disease in 80% to 100% of patients. Inguinal lymphadenectomy can be curative if nodal spread is confined to the inguinal nodes (13,27,55,63,78,87,101,126). Thus palpable inguinal nodes are an indication for ilioinguinal node dissection at the time of cystoprostatectomy. However, lymphadenectomy is indicated only for palpable nodal disease because there is no evidence of clinical benefit from prophylactic lymphadenectomy in the setting of clinically normal nodes (8). However, with improved techniques associated with less morbidity, prophylactic dissection may be warranted in patients at high risk for nodal disease (17,126). The proper management of the pelvic nodes in the setting of positive inguinal nodes is not entirely clear because most patients with pelvic adenopathy die of their disease. Radical surgery in this situation probably is unwarranted because long-term survival is very unlikely. These patients probably are best approached with chemotherapy and further locoregional therapy depending on the response.

Radiation Therapy

Data on the role of radiation therapy alone in managing male urethral cancer are limited. In general, radiation therapy has been reserved for low-stage distal urethral carcinomas in patients refusing surgical management. The primary advantage of radiotherapy is potential organ preservation. However, complications are common and include woody penile edema, penile atrophy, and urethral stricture (120).

Chemotherapy and Chemoradiation

Existing data on chemotherapy for urethral cancer are difficult to assess reliably because of insufficient sample sizes and variability of patient selection factors and primary treatments (31). The best-studied single-agent drugs are cisplatin, bleomycin, and methotrexate. All are inadequate as single agents. Trials with multiple-agent chemotherapy have led to organ-sparing management of anal and head and neck cancers. These regimens include cisplatin with fluorouracil; cisplatin, methotrexate, and bleomycin; cisplatin, fluorouracil, and leucovorin; fluorouracil, mitomycin, and radiation therapy; and cisplatin with vindesine (31). Few data exist regarding combination therapy for urethral cancer, but future efforts to improve outcomes in advanced disease and possibly allow organ preservation in selected cases are warranted.

Concomitant external beam radiation with fluorouracil and mitomycin C has been shown to provide effective treatment for locally advanced SCC of the esophagus and anal canal, with increased local control, increased control of nodal disease, increased survival, and preservation of anal function, and has become the standard of care in these patients (8,72). Chemotherapy given concomitantly with radiation acts as a radiosensitizer and interferes with cell repair after a sublethal dose of radiation.

Recently, there have been encouraging results with these multimodality approaches in urethral cancer (8,61,72,73,91,110). Oberfield and associates (91) reported on two men with locally advanced SCC of the proximal urethra treated with chemoradiation. Forty-five Gy in 25 fractions over 5 weeks was delivered to the penis, perineum, and regional lymphatics in addition to mitomycin C (10 mg/m^2) and 5-fluorouracil (1 g/m^2 per day) for 4 days at the start of the cycle and 28 days later. Both patients were free of tumor at 1.5 and 4 years. Furthermore, Baskin and Turzan (8) treated a patient with high-stage SCC of the penile urethra with a similar protocol followed by partial urethrectomy and perineal urethrostomy. The pathologic specimen demonstrated no evidence of residual tumor. Further research in this area is warranted.

BOX 37.2 TREATMENT OF MALE URETHRAL CARCINOMA

The possibility for cure of urethral carcinoma depends on adequate local control.

The extent of surgery necessary to obtain local control depends on tumor stage and location in the urethra.

Despite aggressive surgical resection in the setting of bulky posterior tumors, local recurrence is common and prognosis is poor.

Encouraging preliminary results suggesting improvements in outcome have been reported using a multimodality approach combining surgery, radiation, and chemotherapy.

TRANSITIONAL CELL CARCINOMA OF THE PROSTATE

Primary TCC of the prostate implies no preexisting or concomitant bladder cancer and is a rare entity. In the Mayo Clinic experience, only 37 of 5,700 men with prostate cancer had primary TCC (127). The etiologic factors for TCC of the prostate are considered to be the same as those for bladder TCC (79). Primary prostatic TCC makes up approximately 9% of the total number of urethral carcinomas, and very little information is available about the most effective treatment options (116). Usually, stromal invasion is present at diagnosis, and the prognosis is poor (104). Patients often present with hematuria and the irritative voiding symptoms of frequency, urgency, and dysuria.

TCC of the prostate is most commonly associated, either synchronously or metachronously, with bladder TCC. The increasing use of intravesical therapy to treat bladder cancer has altered the natural history of the disease and may be contributing to an increasing incidence of prostatic TCC (79).

Prostatic urethral neoplasms arising from the prostatic urethral epithelium or the periurethral portion of the prostatic ducts are considered urethral neoplasms distinct from those arising elsewhere in the prostate (3). Previous attempts at staging primary TCC of the prostate used staging systems for adenocarcinoma of the prostate. These methods are unsatisfactory because of differences in the natural history and pathologic features of the disease processes. The current American Joint Committee on Cancer TNM staging system for primary TCC of the prostate is depicted in Table 37.2 . Accurate staging is vital because patients with carcinoma *in situ* or ductal involvement have a very different prognosis from those with stromal invasion (80).

Primary Tumor (T)	
T_{is} pu	Carcinoma *in situ,* involvement of the prostatic urethra
T_{is} pd	Carcinoma *in situ,* involvement of the prostatic ducts
T_1	Tumor invades subepithelial connective tissue
T_2	Tumor invades any of the following: prostatic stroma, corpus spongiosum, periurethral muscle
T_3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, bladder neck (extraprostatic extension)
T_4	Tumor invades adjacent organs (invasion of the bladder)
Regional Lymph Nodes (N)	
N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastases
N_1	Metastases in a single lymph node, 2 cm or less in greatest dimension
N_2	Metastases in a single node more than 2 cm in greatest dimension, or in multiple nodes
Distant Metastases (M)	
M_X	Distant metastases cannot be assessed
M_0	No distant metastases
M_1	Distant metastases

From American Joint Committee on Cancer. *AJCC cancer staging manual,* 5th ed. Flemming ID, Cooper JS, Henson DE, et al., eds. Philadelphia: Lippincott-Raven, 1997, with permission.

TABLE 37.2. STAGING OF TRANSITIONAL CELL CARCINOMA OF THE PROSTATE

Wood and associates (125) conducted a prospective study to determine the most effective means of diagnosing TCC of the prostate in a group of 25 patients with bladder carcinoma, all of whom underwent radical cystectomy. Precystectomy prostate needle biopsy, fine-needle prostatic aspiration, and TUR biopsies of the prostate were performed in all 25 patients. Ten patients were found to have prostatic involvement upon examination of the cystectomy specimen. The accuracy of the three detection methods was 20%, 40%, and 90%, respectively. All patients with prostatic involvement were identified correctly using a combination of the three methods. Therefore TUR biopsy should be performed in patients at high risk for TCC of the prostate or in patients with a positive urine cytology and normal bladder urothelium proven by cystoscopy and biopsy. It should be performed with generous sampling of the tissue between the bladder neck and verumontanum at the 5 and 7 o'clock positions. Because isolated TCC of the prostate is very uncommon, careful exclusion of concomitant bladder disease is imperative (85).

As previously noted, there is very little information about the efficacy of various treatment modalities for TCC of the prostate. Intravesical bacille Calmette-Guérin (BCG) has been used with excellent results to treat prostatic TCC *in situ.* However, as it extends deeper into the prostate along the ducts, the ability of BCG to come in contact with the cancer may be inconsistent (85). TCC of the prostate may be treated with BCG in the setting of minimal ductal involvement, but posttreatment TUR biopsies of the prostate must be performed to ensure adequate response (85).

Treatment of carcinoma *in situ* of the prostatic urethra probably is best achieved by TUR followed by intravesical BCG, although excellent and similar results have also been reported without TUR (79,93,96). The resection is believed to allow better contact between BCG and the prostate, and this belief has been supported by multiple series (15,52,112). If this approach fails in patients with carcinoma *in situ* or there is disease progression with extensive ductal invasion or stromal involvement, cystoprostatectomy with urethrectomy is indicated.

Prostatic stromal invasion portends a very poor prognosis because these tumors have a tremendous propensity for lymphatic and hematogenous dissemination. Therefore exenterative surgery has been recommended historically. Radical cystoprostatectomy is recommended over radical prostatectomy because TCC often is a multifocal disease with frequent involvement of the bladder and urethra (41). Definitive radiotherapy as the sole form of treatment is unpredictable and generally not used (76). It should be reserved for select patients who are not surgical candidates.

Investigators at Memorial Sloan-Kettering Cancer Center used a multimodal approach with chemotherapy and TUR and preservation of urinary function in selected patients with prostatic TCC. This approach includes four cycles of methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC) chemotherapy followed by extensive TUR of the prostate. If there is no tumor in the resection specimen, these patients may be observed with surveillance biopsy at regular intervals. If there is residual disease or a recurrence during surveillance, radical prostatectomy is performed with preservation of urinary function (44).

In a report by Cheville and colleagues (19) on 50 patients with TCC of the prostate without invasive bladder cancer, locoregional spread was the strongest predictor of patient survival. Their study demonstrated a 5-year disease-specific survival rate of 100% for patients with carcinoma *in situ* compared with 45% for urethral submucosal and stromal invasion. The anatomic barrier to extension of tumor was the basement membrane of the urethra, periurethral glands, and prostatic ducts and acini.

Wishnow and Ro (123) studied 23 men with TCC of the prostate detected in radical cystoprostatectomy specimens. They found that radical surgery was curative in 89% of 18 patients with carcinoma *in situ* or ductal involvement, with 11% developing metastases. All five of the patients in their series with stromal invasion developed metastatic disease.

TCC of the prostate in patients with preexisting or concurrent TCC of the urinary bladder has received substantial attention in recent years because of the popularity of orthotopic continent urinary diversion. Prostatic involvement of TCC, especially stromal invasion, is a clearly defined risk factor for urethral recurrence after cystectomy. Wood and associates (124) demonstrated that 43% of 84 cystectomy specimens for bladder cancer contained TCC of the prostate.

Esrig and colleagues (34) compared the natural history of patients with bladder cancer and prostatic stromal involvement occurring via direct extension through the bladder wall with that of stromal invasion arising intraurethrally. Based on data from 143 patients with prostate involvement after cystoprostatectomy, they proposed a staging classification that distinguishes between these two groups. Previous reports in the literature and staging systems did not address the two completely different natural histories. The authors determined that patients with P_1 bladder tumors with prostatic stromal invasion arising intraurethrally clearly had a higher overall 5-year survival rate (65%) than those with P_{4a} tumors with prostatic stromal invasion from a bladder primary tumor invading through the bladder wall (21%). Furthermore, they determined that TCC of the prostatic urethra confined to the mucosa or ducts and arising separately from a concomitant bladder tumor did not alter survival after cystectomy based on the primary bladder tumor stage. However, stromal invasion that arises intraurethrally places patients with P_1 bladder cancer into a higher-risk group with prognosis similar to that of muscle-invasive bladder cancer. Thus to precisely categorize the disease and the response to adjuvant therapy protocols, a designation of prostatic stromal invasion arising intraurethrally should be made along with the primary bladder stage.

BOX 37.3 DIAGNOSIS AND MANAGEMENT OF PROSTATIC TRANSITIONAL CELL CARCINOMA

Primary prostatic transitional cell carcinoma (TCC) implies no preexisting or concomitant bladder cancer and is rare.

The presence and extent of prostatic TCC are best determined by deep transurethral biopsies between the bladder neck and verumontanum at the 5 and 7 o'clock positions.

Initial management of prostatic TCC confined to the mucosa or prostatic ducts generally is transurethral resection and adjuvant bacille Calmette-Guérin.

Stromal invasion of prostatic TCC portends a poor prognosis and usually is treated with cystoprostatectomy.

Further experience with multimodality therapy and possible preservation of urinary function is warranted.

URETHRAL CARCINOMA IN WOMEN

Part of "37 - URETHRAL CARCINOMA "

Epidemiology and Etiology

Although the source of urethral carcinoma in women is not entirely known, there have been weak associations with both urethral caruncle and chronic irritation caused by infection, coitus, and childbirth (116). Marshall and colleagues (77) reviewed 376 cases of urethral caruncle and found carcinoma in 9 patients (2.4%). Another series reported less than a 1% incidence of a positive history for urethral caruncle in women with urethral carcinoma (82). It is possible that early urethral carcinoma may have been mistaken for caruncle, and only after the lesion failed to respond to therapy was the correct diagnosis made. This underscores the need for a biopsy of any urethral lesion that does not respond promptly to conservative therapy, is associated with persistent bleeding or symptoms, or enlarges.

Another potential origin of urethral carcinoma is the urethral diverticulum. Sixty-eight cases of carcinoma in urethral diverticula have been reported in the English literature (100).

The major cell type of these diverticular carcinomas is markedly different from that of urethral carcinoma. Adenocarcinoma accounts for approximately 60% of these lesions, followed by TCC (27%) and SCC (12%). The most common symptoms reported in one series were irritative voiding (67%), followed by hematuria (49%) (100). Infection and urinary stasis may contribute to the malignant change. Reported cases of malignancy are few in contrast to the more common incidence of urethral diverticulum; therefore the relationship between the two is unclear. Many cancers that

may have originated in a diverticulum are seen at an advanced stage with tissue destruction to the extent that the diverticulum is not observed. The presence of a diverticulum and bleeding should arouse suspicion of carcinoma.

As in male urethral carcinoma, an association with HPV has been reported. In one series, PCR-based analysis demonstrated HPV (types 16 and 18) genotypes in 59% of cases (121).

Signs and Symptoms

The symptoms of urethral carcinoma in women are nondescript. In most reports, the most common symptom is urethral bleeding or spotting, which occurs in more than half of the patients (26,40,41 and 42,70,116). Other symptoms are commonly associated with bladder irritation and include urgency, dysuria, frequency, pain, dyspareunia, and incontinence. However, in the series by Grabstald and associates (42), 38% of patients had a palpable mass, 4% had a vaginal fistula, and 4% were asymptomatic. Two recent series reported obstructive symptoms in approximately 50% (14,60).

Diagnosis and Staging

When the previously mentioned signs and symptoms occur, one must have a high degree of suspicion and include urethral carcinoma in the differential diagnosis to avoid delays in therapy. The symptoms of urethral carcinoma are shared by more common benign urethral lesions, including caruncle, polyp, erosion, urethral prolapse, hemangioma, fibroma, diverticulum, and urethrovaginal fistula. The liberal use of biopsy of any suspicious urethral lesion and endoscopy to evaluate lower tract symptoms will result in earlier initiation of appropriate therapy with a potential increase in survival.

Careful clinical staging is important because therapy depends more on stage, location, and size of the tumor than cell type or grade. The meatus, labia, clitoris, vagina, and groin must be inspected to detect areas of local infiltration or induration. Bimanual examination under anesthesia allows evaluation of extent and fixation of the mass as well as assessment of inguinal and pelvic lymph nodes. Biopsies of the vulva, vagina, and bladder should be obtained as suggested by findings on bimanual examination and cystourethroscopy. CT is helpful in evaluating local extension and especially the status of the pelvic lymph nodes. The intravenous urogram, bone scan, liver profile, and chest film with tomography as indicated by findings will help detect distant metastases.

MRI has become the standard modality to evaluate local extent of disease because CT has poor soft tissue contrast (Fig. 37.6) (58). The normal female urethra on T_2-weighted or gadolinium-enhanced T_1-weighted images demonstrates a characteristic targetlike appearance (58). The outer ring of low signal intensity probably corresponds to the outer muscular layer, the middle layer of high signal intensity probably corresponds to submucosa, and the central low-intensity layer probably represents mucosa. There is accurate size assessment with MRI and excellent sensitivity and negative predictive value in assessing tumor extent. However, there is potential for overestimation caused by inflammation and edema. Local coils may be used to further improve imaging resolution in MRI (98). Lymphadenopathy is underestimated with MRI, and CT remains the study of choice for nodal assessment (58).

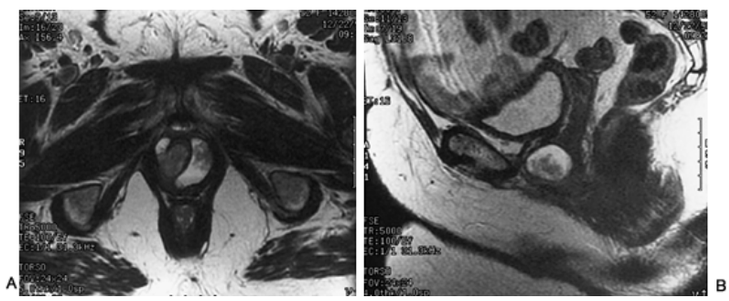

FIGURE 37.6. Magnetic resonance imaging scan of adenocarcinoma of the female urethra involving a urethral diverticulum. **A:** Coronal T_2-weighted image demonstrates a polypoid soft tissue mass within a left urethral diverticulum. **B:** Sagittal T_2-weighted images of the diverticulum and soft tissue mass.

The clinical staging system proposed by Grabstald and colleagues (42) has been widely used in the past (Table 37.1) (42). Therapy and prognosis are closely related to stage and location of the tumor. Although this staging system is still common in the older literature, the newer TNM classification is currently the standard staging system for both male and female urethral cancer (Table 37.1) (3).

Histopathology

The three predominant cell types are SCC, TCC, and adenocarcinoma. SCC accounts for approximately 55% of cases, adenocarcinoma and clear cell adenocarcinoma for 15%, and TCC for 15% (89). The remaining approximately 10% of cases are rare cell types including neuroendocrine tumors, sarcomas, lymphomas, and melanomas. Lesions are equally distributed between the proximal and distal urethra.

In the recent literature, there is an increasing experience with clear cell carcinoma, a distinctive tumor primarily of the female urethra that has generated interest with respect to prognosis and relationship to urethral diverticula (4). One review of 19 cases describes the clinical and pathologic features of this now widely accepted subtype of urethral carcinoma (92). Rarely described in men, the majority of these tumors are papillary and typically arise in dilated paraurethral glands more commonly called diverticula. These tumors may include areas that microscopically appear to be nephrogenic adenoma, but evidence that these tumors arise from malignant transformation of nephrogenic adenoma is inconclusive (4). There appears to be a more favorable prognosis associated with clear cell adenocarcinoma (4,29,75,92).

Immunostaining of female urethral adenocarcinoma for PSA and prostatic acid phosphatase has been described for both clear cell and non–clear cell types (30,92,114). However, in more recent series, clear cell adenocarcinoma was not found to be positive for PSA and prostatic acid phosphatase immunostaining and thus is unlikely to originate in Skene's glands (4,29,75,92). Drew and associates (29) suggest a müllerian derivation for clear cell adenocarcinoma based on a histologic pattern similar to other tumors of the female genital tract and positive reactions with the CA-125 antigen. The histogenetic origin of this subtype of adenocarcinoma remains to be determined.

Natural History

The natural history of urethral carcinoma in women is very similar to the natural history of the disease in men. Although urethral carcinoma has been reported in patients as young as 4 years, more than 75% of patients are in the postmenopausal age group, with a mean age of 61 years (103,116). There is a higher incidence among white women (88%) than African American women (12%) (89). The average delay in diagnosis after the appearance of symptoms has been reported to be 5 months (116). Eighty-four percent of patients already have muscular invasion or involvement of regional lymph nodes at the time of diagnosis (14).

Spread occurs by local extension to adjacent structures and to regional lymph nodes. Early invasion may involve the periurethral connective tissue, urethrovaginal septum, vagina, bladder neck, or vulva. Large, fungating meatal lesions may be difficult to differentiate from primary vulvar carcinoma. Surprisingly, involvement of the pubic bone is unusual (103). Carcinoma of the entire urethra tends to be more locally advanced at initial presentation, possibly because of a delay in diagnosis (7,14). In one series, 13% of patients with an anterior lesion had metastases to lymph nodes, in contrast to 30% of patients with posterior tumors of the urethra (7).

Lesions of the anterior urethra tend to metastasize to the inguinal nodes, whereas lesions of the posterior or entire urethra spread to the pelvic lymph nodes (Fig. 37.4). Clinical evidence of inguinal adenopathy is seen in 35% to 56% of patients, but pathologically proven metastasis occurs in only 12.5% to 35% of the total number of patients seen with this disease (14,26,41,42,116). This has created controversy as to whether adenopathy usually represents metastatic disease rather than secondary infection. Whereas Grabstald (41) found histologic evidence of cancer in 24 of 25 patients with enlarged nodes, Desai and associates (26) reported that only 2 of 6 patients with adenopathy had positive biopsies. However, most authors consider inguinal adenopathy to represent metastatic disease (41,42,70,116). In patients who underwent pelvic lymphadenectomy, 50% were found to have positive nodes (42).

As is the case with urethral carcinoma in men, distant metastatic spread is uncommon at the time of diagnosis. In the original series of Grabstald and associates (42), 11 of 79 patients (14%) had distant metastases, but metastases were present in only 5 patients initially. Patients with adenocarcinoma were more likely to have distant spread. Lung, liver, bone, and brain are the most common areas of involvement (41). Untreated female urethral carcinoma has a dismal prognosis, with a mean survival of 12 months (81). The most important prognostic parameter is location of tumor and stage of the disease. Dalbagni and associates (23) report a 5-year disease specific survival of 89% for low-stage and 33% for high-stage disease and 69% and 18% for disease of the anterior and entire urethra, respectively.

Surgical Treatment

In the treatment of low-stage disease, mucosal lesions can be treated effectively with TUR and fulguration or laser ablation. Local excision for anterior lesions that are externally visible may be sufficient. Tumors involving a greater length of urethra but still restricted to mucosa or submucosa can be

effectively treated with TUR. Partial urethrectomy may be performed for low-stage lesions localized to the distal urethra as long as an adequate proximal surgical margin can be obtained and urinary continence is not compromised.

In selected patients with stage T_2 or T_3 disease, total urethrectomy may occasionally be an alternative with bladder preservation. This is seen primarily with anterior lesions in which adequate margins cannot be obtained by local excision (89). Bladder-sparing surgery may be a reasonable surgical option in the properly selected patient. Hedden and colleagues (49) describe a small series of patients with locally advanced stage C disease without bladder involvement treated with wide local excision with or without neoadjuvant radiation, bladder preservation, and either ileovesicostomy or continent catheterizable stoma. Local control was achieved in all patients with a median follow-up of 42 months, suggesting that bladder-sparing surgery is possible and feasible.

In high-stage disease (as most proximal tumors are), which includes involvement of the entire urethra with extension to bladder and vagina, a multimodality approach probably is most appropriate (89). Radiation alone or surgery alone generally results in poor survival rates, with a 5-year survival of 0% to 17% (14,26,42). Surgically, these patients are treated with anterior exenteration along with en bloc resection of the pubic symphysis and inferior rami. A somewhat better prognosis may result from treatment with preoperative irradiation followed by anterior pelvic exenteration (14,41). The amount of recommended radiation varies from 20 Gy in 5 days to 50 Gy over 5 weeks (14,41). One radiation–surgery protocol involves preoperative interstitial irradiation delivering 60 Gy for 4 days followed by anterior exenteration 2 weeks later (56). The rationale for preoperative irradiation is an attempt to decrease the rate of local recurrence, which has occurred in 66% to 100% of patients treated with one form of therapy only (20,41).

Tumors arising from urethral diverticula are most commonly adenocarcinoma (61%), followed by TCC (27%) and SCC (12%). Aggressive surgical treatment consisting of anterior exenteration with total urethrectomy and wide excision of vaginal wall is the standard of care in these patients because local recurrence has been documented in 44% of those treated by diverticulectomy or radiation (100).

Treatment and prognosis depend primarily on location, stage, and size, not cell type. Five-year survival has been reported as 40% for anterior carcinoma, 13% for carcinoma of the entire urethra, and 26% for the group as a whole (120). Bracken and colleagues (14) found that 5-year survival was 45% for lamina propria invasion, 41% for periurethral muscle invasion, 26% for extension beyond the urethra, and 18% for metastatic disease in a series involving 64 patients. The 5-year survival of patients with tumors that were less than 2 cm in size was 60%, and that for patients with lesions greater than 5 cm in size was 13%.

As in male urethral cancer, local recurrences are common, and failure to achieve local control of the disease most often results in death. Bracken and co-workers (14) report local recurrence in 33 of 71 patients (46%); only 3 of these patients survived after additional forms of therapy were administered.

Inguinal lymphadenectomy has been recommended only in cases of palpable lymphadenopathy. However, Foens and associates (36) demonstrated a 10% inguinal failure rate in patients who received groin treatment (surgical or radiation) at the time of diagnosis and a 52% failure rate in patients who did not initially receive groin treatment. Their retrospective study included 42 patients seen over a 47-year time frame. Indications for prophylactic inguinal treatment surgically or with radiotherapy must be evaluated further (17).

Radiation Therapy

Radiation techniques include external, interstitial, and intracavitary radiation and combinations of external beam with interstitial or intracavitary radiation. Early lesions can be treated effectively with interstitial radiation. In larger tumors, implants rarely can deliver adequate dosages without excessive tissue toxicity, so external beam with interstitial boost is recommended. In very advanced tumors, external beam radiation alone is used (37).

Radiation may be a reasonable alternative to local surgery for patients with low-stage urethral cancer, with cure rates averaging about 75% (45,69,105). Dosages in various series range from 50 to 60 Gy for brachytherapy alone to 40 to 50 Gy of external beam with a 20- to 25-Gy brachytherapy boost. The rate of complications in women ranges from 0% to 49%, with strictures being the most common, followed by fistulae, incontinence, urethral necrosis, and cystitis (39,105).

Two recent series of the use of modern radiation therapy techniques to treat female carcinomas stress the combined use of external and interstitial irradiation (2,105). In the series by Ali and associates (2), three patients with muscle invasive tumors did well without recurrence at up to 30 months with a combination of external and interstitial radiation. In addition, Sailer and colleagues (105) report 5-year survival rates of 60% to 80% for low-stage disease treated with combination radiation therapy. They used 45 Gy external radiation plus interstitial and intravaginal radiation sufficient to achieve a total dosage of 65 to 70 Gy. These authors recommend a combination of surgery and radiation therapy for advanced disease.

Grigsby (43) recently reported a series of 44 women treated by radiation or preoperative radiation and surgery. On multivariate analysis, tumor size was the most important prognostic factor. This author recommends treating women with tumors less than 2 cm with surgery or radiation. If radiation is the chosen modality and the lesion is less than 1 cm, interstitial radiotherapy at dosages of 30 to

65 Gy may be given. If a lesion is 1 to 4 cm, the radiotherapy regimen may include combination external radiation and intracavitary or interstitial radiation to dosages of 70 to 85 Gy. If a lesion is greater than 4 cm, patients may be more effectively treated with preoperative radiation to dosages of 45 to 50 Gy (43). Ten-year cause-specific survival in this series for lesions less than or equal to 2 cm, 2 cm to 4 cm, and 4 cm or more were approximately 90%, 30%, and 20%, respectively.

Foens and associates (36) compared the roles of surgery and radiation therapy in managing female urethral cancer. Only 36% of those treated with radiation alone and 60% of those treated with surgery alone had local recurrence, and the best results were those of combined interstitial and external beam radiation. There was also a significantly lower inguinal failure rate of 10% in those who received inguinal radiation compared with 52% in those who did not.

Garden and associates (39) presented their results with radiation therapy for female urethral cancer and reported that patient prognosis had remained essentially unchanged since 1976. Patients presenting early with only partial urethral involvement had a 74% local control rate and 48% 10-year overall survival rate. The length of urethra involved was an independent factor affecting overall survival, disease-free survival, and local control. The results for advanced disease were very poor, with only a 16% 5-year survival for fixed lesions. Based on their results they drew a number of conclusions about radiation therapy. First, early distal lesions can be treated with radiation only, which usually consisted of interstitial brachytherapy alone using 60 to 66 Gy. A reasonable surgical candidate may benefit from preoperative external beam radiation of 45 to 50 Gy. If the lesion is not amenable to surgery or the patient is not a surgical candidate, then 45 to 50 Gy external beam radiation followed by 20 to 30 Gy interstitial therapy is a reasonable approach. Even though histologic type did not affect outcome, it did affect natural history. Nodal disease was more common with SCC, and it was recommended that the inguinal nodes receive external beam radiation. Finally, these authors suggest that radiation is reasonable for palliation, although any potential benefit generally is of short duration.

Chemotherapy and Chemoradiation

Cisplatin, bleomycin, methotrexate, and 5-fluorouracil have demonstrable activity in urethral carcinomas. However, studies are limited to small series, often with widely variant treatment regimens and inconclusive results (31). Because of the small number of cases in any particular series and the wide variations in treatment modalities, it is difficult to evaluate with any certainty the various forms of therapy. There are no well-controlled studies comparing different approaches.

As discussed in male urethral cancer, a number of recent case reports and small series have demonstrated excellent results with chemoradiation consisting of 5-fluorouracil, mitomycin C, and external beam radiation as primary therapy for advanced SCC of the female urethra (69). Regimens similar to those used with head and neck and anal malignancies may be promising for female urethral cancer in improving efficacy and potentially allowing organ preservation. Licht and co-workers (72) reported on two men and two women receiving 5-fluorouracil and mitomycin C with 30 to 50 Gy pelvic irradiation. Three had complete responses and one had a partial response, whereas none of 15 other patients with advanced disease treated with surgery with or without radiation therapy had a durable complete response. Johnson and associates (61) demonstrated successful treatment of a bulky advanced stage SCC of the entire female urethra using low-dose preoperative radiation therapy with concomitant chemotherapy. At the time of report, this patient was free of disease 28 months after therapy completion.

BOX 37.4 DIAGNOSIS AND TREATMENT OF FEMALE URETHRAL CARCINOMA

As for male urethral carcinoma, a high index of suspicion with biopsy of any urethral lesion worrisome for carcinoma or not responding to conservative therapy is important for prompt diagnosis.

Careful clinical staging is important in determining appropriate therapy and prognosis.

Natural history of urethral carcinoma in women is similar to that in men; spread occurs primarily by local extension and to regional nodes.

Radiation therapy plays a more important role in the management of urethral carcinoma in women than in men.

Further experience with multimodal approaches is warranted based on encouraging initial results.

MANAGEMENT OF THE URETHRA AFTER CYSTECTOMY

Part of "37 - URETHRAL CARCINOMA "

Male Urethra

TCC often is a multicentric disease, and although it is most common in the bladder, it may occur anywhere along the urothelium. This has led to controversy about the need for prophylactic urethrectomy in men who undergo radical cystoprostatectomy (1,108). Approximately 4% to 15% of these patients develop neoplasms in the urethra at some time in the course of their disease (47,101,109). Prophylactic urethrectomy adds length to an already time-consuming operation and increases overall morbidity (108). In one series of 110 patients undergoing a prophylactic urethrectomy at the time of radical cystectomy, a 12%

complication rate as a result of the additional urethrectomy was reported (108).

Urethral recurrence is a significant threat to survival, especially when associated with invasion into the richly vascular corpus spongiosum. Ahlering and associates (1) reported four deaths attributed to urethral carcinoma occurring after cystectomy. All four patients had invasive lesions, with a mean interval between cystectomy and urethrectomy of 46.5 months. This emphasizes the importance of identifying risk for urethral recurrence early.

Many patients are asymptomatic, even though they have epithelial changes, carcinoma *in situ,* or invasive tumor in the urethra. Urethroscopy and urethrograms have a low degree of accuracy (108). Cytologic changes may be the first sign of epithelial dysplasia or carcinoma before the development of overt tumor. In the series of Schellhammer and Whitmore (108) of men undergoing delayed urethrectomy, washings for cytologic analysis were positive in 14 of 15 patients, with the false-negative result occurring in a patient from whom only one specimen was collected.

Hickey and colleagues (51) reported on a group of patients who had undergone radical cystoprostatectomy for carcinoma of the bladder. Seventy-two patients underwent urethral surveillance consisting of urethral wash cytologies every 6 months. Seven (10%) had positive findings and underwent urethrectomy, and all were found to have carcinoma *in situ.* At the time of reporting, 6 of 7 were free of disease. There were no false-positive findings, and no patient has had a local recurrence without a positive finding. After cystoprostatectomy, urethral cytology should be performed semiannually for the remainder of the patient's life (106). It is important that normal saline washings be done without lubrication of the catheter because the lubricant may interfere with the cytologic examination.

Hermansen and associates (50) demonstrated the usefulness of flow cytometry to detect urethral recurrence after cystectomy. They reported on four patients, all of whom had positive flow cytometry that demonstrated perfect concordance with wash cytologies. All of the tumors were aneuploid. No data are available regarding ability to detect diploid tumors. Flow cytometry is less subjective than cytology but is more expensive. Its true diagnostic information over cytology awaits further studies with larger groups of patients.

The most common symptom in men with a urethral recurrence is a bloody urethral discharge (1,108). This has been seen in up to 80% of cases (1). Other symptoms include pruritus at the meatus, perineal pain, and fullness or mass along the urethra. It is imperative to counsel patients after cystectomy to promptly report the onset of bloody urethral discharge, which in itself is an indication for urethrectomy.

In this era of orthotopic neobladder reconstruction, the indications for prophylactic urethrectomy at the time of cystectomy must be clarified. For many years, debate has occurred as to which patients are at high enough risk for urethral recurrence to warrant prophylactic urethrectomy. Historically, prophylactic urethrectomy has been recommended for patients with diffuse carcinoma *in situ,* multifocal tumors, and tumors involving the bladder neck and prostatic urethra. This broad grouping may limit the pool of patients for whom orthotopic reconstruction may be an option. Recent data are beginning to shed light on which of these patients are likely to be at highest risk for urethral recurrence (33,38,47,71,115).

Levinson and associates (71) documented prostatic involvement as the most important risk factor, with urethral recurrences occurring in 4 of 24 patients (17%) who had disease extending into the prostate, including 3 of 10 (30%) of those with stromal invasion. They also noted recurrence in only 1 of 22 (4.5%) with either carcinoma *in situ* or multifocal tumors not involving the prostate and in none of the 9 patients with tumors at the bladder neck alone. Hardeman and Soloway (47) reported similar results in a group of 86 men monitored with urethral washings for a mean of 40 months after radical cystectomy. They found urethral recurrences in 1 of 27 (3.3%) with solitary tumors not at the bladder neck and 1 of 29 (3.6%) with multifocal tumors, carcinoma *in situ,* or tumors near the bladder neck but not involving the prostate. Of 30 patients with tumors in the prostate, 11 (37%) suffered urethral recurrence. When this group was further broken down according to degree of prostatic involvement, none of the 8 with disease confined to the urethra, 2 of 8 (25%) with ductal involvement, and 9 of 14 (64%) with stromal involvement experienced urethral recurrence. Tumor characteristics in the bladder or distal ureters do not seem to be nearly as strong a predictor of urethral recurrence as disease involving the prostate. Erckert and co-workers (33) found a 6.1% overall incidence of secondary urethral tumors in 910 men managed conservatively and there was a significant difference between the occurrence in patients with an initial solitary TCC of the bladder (2.6%) and those with recurrent multi-focal cancer (10.1%). In addition, they did not see an increased risk for urethral tumors with bladder carcinoma *in situ.*

Freeman and associates (38) compared the urethral recurrence rate after cystectomy in men with an orthotopic ileal neobladder and men with a cutaneous diversion. In their study population of 436 men, carcinoma *in situ* and multifocal tumors of the bladder were not individually associated with a significant risk of urethral recurrence, whereas prostatic involvement was. Interestingly, they found that patients with an ileal neobladder were at a significantly lower risk for urethral recurrence at 5 years (2.9%) than those with a nonorthotopic urinary diversion (11.1%). More specifically, in patients with prostatic urethral involvement, the 5-year probability of recurrence was 5% and 23.7% for orthotopic and nonorthotopic diversion, respectively. They hypothesized that this difference may be

attributed to physiologic, biochemical, genetic, or immunologic characteristics of the ileum, continued exposure to urine, or unknown systemic effects of orthotopic diversion.

Current data support the conclusion that patients with no evidence of prostatic involvement on preoperative staging and negative intraoperative frozen section of the urethral margin can safely be offered a continent diversion to the urethra. It may even be possible to stratify patients with prostatic involvement based on the extent of prostatic disease when an orthotopic neobladder is being considered. Men with extensive prostatic ductal or stromal invasion or TCC involving the bulbomembranous urethra should undergo en bloc urethrectomy at the time of radical cystoprostatectomy.

All men with a urethral remnant after cystoprostatectomy should undergo periodic urethral washings, and urethrectomy should be performed if cytologic findings are positive. Furthermore, a bloody urethral discharge is an indication for urethrectomy. Urethrectomy should also be considered after cystectomy in men who are found on pathologic analysis to have positive margins at the prostatic urethra or prostatic ductal or stromal invasion. This should be performed within 2 to 3 months of the cystoprostatectomy. When performing urethrectomy, it is advisable to include the fossa navicularis and meatus with the specimen. Schellhammer and Whitmore (109) reported that 7 of 27 patients (26%) who previously had undergone urethrectomy developed a tumor in the meatal remnant.

Female Urethra

Stenzl and colleagues (115) evaluated the long-term risk of urethral involvement in women with bladder cancer and the indications for orthotopic reconstruction of the urinary tract. Historically, a high incidence of urethral involvement in women with bladder cancer has been reported, so urethrectomy has been routine at the time of radical cystectomy in women (25). However, these reports did not examine the relationship between the site of the bladder primary and urethral involvement. Recently, Stenzl and co-workers (115) reported only a 1% incidence of secondary urethral cancer in 104 women with localized, invasive disease. More importantly, there was no urethral involvement without concomitant involvement of the bladder neck. There was a marginally significant correlation with trigone involvement and no correlation with any other bladder regions. These authors concluded that in women without tumor at the bladder neck and with a negative intraoperative proximal urethral frozen section, a portion of the urethra can be preserved for orthotopic reconstruction with minimal risk of urethral recurrence.

Another study by Chen and associates (18) of women undergoing radical cystectomy also evaluated the risk of urethral as well as vaginal and cervical involvement. Their results were consistent with prior studies in that only bladder neck involvement was predictive of urethral involvement, with 7 of 21 (33%) patients with bladder neck involvement having urethral involvement. However, 2 of 9 patients with secondary urethral involvement had no evidence of tumor at the bladder neck. Therefore they recommended that women who are candidates for orthotopic neobladder undergo examination under anesthesia, bladder neck and urethral biopsies, and frozen section of the proximal urethra. Patients with palpable masses on bimanual examination should also undergo transvaginal biopsies if considering orthotopic diversion.

Hollier and colleagues (53) reported that bladder neck and trigone involvement in women represented a 33% and 20% risk of urethral involvement, respectively. Furthermore, higher tumor stage (T_3 and T_4) also correlated with a 20% risk. Based on their data, they concluded that any woman with higher stage tumors or involvement of the bladder neck and trigone is at high risk for urethral involvement and should not be considered a candidate for orthotopic diversion.

As in men, there is growing evidence that a significant segment of the female urethra can safely be left intact in carefully selected women to permit orthotopic urinary reconstruction. The appropriate method of surveillance for both men and women with continent diversions via an intact urethra is not known. Whether a voided urine cytology or an endoscopic observation is optimal remains to be seen.

BOX 37.5 MANAGEMENT OF THE URETHRA AFTER CYSTECTOMY

Urethral recurrence occurs in 4% to 15% of patients after radical cystoprostatectomy.

Close follow-up of the urethral remnant with interval cytology is important. Positive urethral wash cytology findings and bloody urethral discharge are indicators for urethrectomy.

The most important risk factor for urethral recurrence is prostatic stromal invasion in men and involvement of the bladder neck in women.

Men without prostatic stromal invasion and women without tumor involvement of the bladder neck may undergo orthotopic neobladder reconstruction if intraoperative frozen sections of the urethral margin are negative. The risk of urethral recurrence is low in this setting.

RARE AND BENIGN URETHRAL TUMORS

Part of "37 - URETHRAL CARCINOMA "

Male Urethra

Primary sarcoma, melanoma, and adenocarcinoma occur rarely in the male urethra (12,95). Metastases to the male urethra from prostatic, colonic, rectal, bladder, renal, ureteric, and testicular sources have been identified (86).

The presenting signs and symptoms of sarcomas, arising from the supportive tissue of the corpus spongiosum, include the presence of a mass, pain, or obstruction. Aggressive surgical therapy must be used for potential cure.

Primary malignant melanoma of the urethra has been reported in 36 cases, with a much higher predilection in white men (99). Patients typically present in the sixth to eighth decades with symptoms including palpable mass, hematuria, bloody urethral discharge, fistula, persistent dysuria, and obstructive symptoms. However, melanuria is more specific for this disease. Delays in diagnosis are common, with the interval from onset of symptoms to diagnosis averaging 24 months (99). Tumors may be multifocal and occur in any portion of the urethra but are most common in the fossa navicularis (approximately 50%). Only 20% of malignant melanomas occur in the proximal urethra (97). Treatment has ranged from partial or total penectomy to emasculation with cystoprostatectomy with or without bilateral inguinal or pelvic lymph node dissection. Multimodality therapy, including radiotherapy and immunotherapy, may be useful adjuncts to surgery or as palliation. Despite these efforts, dissemination is common and occurs by direct extension, lymphatics, or hematogenous routes. Survival is poor, and most tumor-related deaths occur within 3 years of diagnosis (9,94,97). Only three patients have been reported to survive longer than 5 years after diagnosis (97). Ander and co-workers (5) reported an additional patient who survived 8 years after local excision, radiation, and chemotherapy. The rarity of this lesion and the great variability in applied therapy make an assessment of the most beneficial therapy difficult.

Adenocarcinoma is a very rare urethral cancer thought to arise in Cowper's gland. However, local necrosis and tissue destruction may prevent exact localization of the site of origin in many cases. All patients have demonstrated obstructive symptoms, and 52% had pain with defecation or constipation. Most have also had a palpable perineal mass. In 13 reported cases there were no 5-year survivors, despite therapy (12).

Congenital cysts occur in the urethral meatus or Cowper's gland and are rare. Excision is curative in meatal cysts. Transurethral unroofing is effective with small Cowper's gland cysts. Open excision may be necessary for large ones.

Urethral polyps are congenital lesions that occur most often in the prostatic urethra with an attachment to the verumontanum. They have been described in the anterior urethra as well. Presentation usually occurs in the first decade of life, with obstruction the most common symptom. Other symptoms include hematuria and enuresis. Diagnosis usually is by cystourethroscopy, although ultrasound has been described as diagnostic in a recent report. This lesion also has been reported in adults (90). Transurethral or suprapubic excision is curative.

Angiomas rarely occur in the urethra, with only 13 cases described in the literature (102). They may cause hematuria or bloody urethral discharge. Invasion has not been noted, but recurrences are typical unless adequate margins are obtained. Although fulguration may suffice in the small lesion, radical surgery has been necessary at times. Cure has been achieved with excision and reconstruction of the urethra (84).

Although they may involve the entire urethra, the most common meatal and parameatal neoplasms in men are papillomas and condylomata acuminata (59). Condyloma acuminatum makes up approximately 30% of all primary tumors of the male urethra (41,84). Patients with squamous papillomas may have hematuria, dysuria, pressure sensation, or pruritus. A typical reddish-purple, mulberry-like lesion often is visible on physical examination (59). Many times, simple eversion of the meatus is sufficient to demonstrate the presence of papillomas. Condylomata acuminata may show similar symptoms and may be difficult to distinguish from papillomas on gross examination. They more commonly involve the skin of the penis or perianal region in men 20 to 40 years old. Condyloma acuminatum is autoinoculable, and, like squamous papillomas, the lesions tend to be multiple. Histologically, both are composed of squamous epithelium in a papillary configuration, but condyloma acuminatum has a thin supporting stalk, a keratinized superficial layer, and an abundant infiltration of lymphocytes at the base of the lesions. The squamous papilloma has a prominent central vascular stalk and no keratinization of the superficial cell layer and has been considered the male analogue of the urethral caruncle in women (59,84). Treatment with excision and fulguration of the base usually suffices for lesions located at the meatus.

Intraurethral condylomata acuminata occur in 5% of patients with disease of the external genitalia. The lesions may occur anywhere along the course of the urethra but are typically intrameatal. Symptoms include hematuria, pyuria, and urethral discharge. TUR with fulguration of the base has been used, but condyloma lesions often are multiple, and this form of therapy carries a significant risk for scarring and stricture formation. Of the various therapeutic agents used, topical fluorouracil has been effective and has no injurious effects on the uninvolved areas of the urethra (28). Side effects usually consist of urethral irritation and burning in one quarter of patients and typically respond well to local application of 2% lidocaine jelly (68). The Nd:YAG laser may also be effective and may result in less urethral scarring than TUR and fulguration (113). It has been suggested that both squamous papillomas and condylomata acuminata are caused by HPV (24,88). This viral agent has also been linked to cervical dysplasia in women, resulting in speculation of carcinogenic potential (24,88).

Female Urethra

Malignant melanoma is one of the most unusual tumors of the female urethra, with only 48 cases reported (65).

However, the urethra is the most common site for primary melanoma of the genitourinary system in men and women, usually occurring in the distal urethra (64). This tumor often is in an advanced stage at presentation; thus survival is poor. Only six 5-year survivors are known (65).

Twelve cases of lymphoma presenting in the urethra have been reported, and 10 of these 12 were in women. One case of primary urethral large cell lymphoma, B cell subtype in which the patient presented with obstructive voiding symptoms was reported by Hatcher and Wilson (48). The patient was treated with an outpatient chemotherapy regimen with complete resolution of the mass.

Ovarian, uterine, pulmonary, and lymphoma metastases to the female urethra have been reported (86).

CONCLUSIONS

Part of "37 - URETHRAL CARCINOMA "

Carcinoma of the urethra is an uncommon disease characterized by extensive local invasion in both sexes. Although it is often advanced at presentation, distant metastatic spread beyond regional lymph nodes is unusual. It is thought to result from chronic irritation, stricture, infection, and diverticulum formation. Signs and symptoms are nondescript for carcinoma and are typical of the more common benign conditions of the urethra, often resulting in a delay in diagnosis. Despite aggressive therapy using radiation, chemotherapy, surgery, or a combination of modalities, local recurrence is common with proximal lesions, resulting in death. Only with early recognition and prompt initiation of appropriate therapy can improvement in survival be seen. Novel, more effective therapies clearly are needed. The diagnosis of urethral carcinoma should be considered in any patient of either sex who has lower genitourinary tract or urethral symptoms.

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38

GYNECOLOGIC ASPECTS OF UROLOGY

Edward J. McGuire

Queena Chou

J. Quentin Clemens

Marko Gudziak

Helen O'Connell

Vaseem Ali

E.J. McGuire: Department of Urology, University of Michigan, Ann Arbor, MI 48109.

Q. Chou: Department of Obstetrics and Gynecology, University of Western Ontario, St. Joseph's Health Care London, London, Ontario, Canada.

J.Q. Clemens: Department of Urology, Northwestern University Medical School, Northwestern Memorial Hospital, Chicago, IL 60611.

M. Gudziak: Department of Urology, Royal Melbourne Hospital, Melbourne, Victoria, Australia.

H. O'Connell: Department of Surgery, University of Melbourne; Department of Urology, Royal Melbourne Hospital, Melbourne, Victoria, Australia.

V. Ali: Department of Obstetrics and Gynecology, University of Texas Medical School at Houston, Herman Hospital, Houston, TX 77030.

Contents

PELVIC FLOOR RELAXATION DISORDERS

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

As the population ages, more women are seeking care for pelvic organ prolapse. Treatment of prolapse makes up approximately 20% of gynecologic surgical workload (295). Olsen and colleagues (229) found an 11% lifetime risk of surgery for pelvic organ prolapse or urinary incontinence by age 80 years and a 29% reoperation rate for failed procedures. Pelvic organ prolapse is a protrusion of the pelvic organs into or out of the vaginal canal (7). According to Nichols and Randall (223), genital prolapse may result when normal pelvic supports are subjected to chronic increases in intraabdominal pressure or when congenitally defective genital support responds inadequately to normal intraabdominal pressure (223). However, the relationship between pelvic organ support and pelvic organ function is complex and not completely understood (275).

Pelvic Floor Anatomy

The pelvic diaphragm consists of passive and active support structures (301). The passive support structures are the bony pelvis and connective tissue, including visceral and parietal fascia, the arcus tendineus levatoris ani, and the arcus tendineus fascia pelvis. Active support structures are the muscles (the levator ani, iliococcygeus, and pubococcygeus) and the nerves (pudendal and sacral plexus). The pelvic floor lies at the bottom of the abdominal cavity and acts as a supportive layer to prevent the abdominal and pelvic organs from falling through the opening within the bony pelvis (80).

Connective Tissue

Organized, dense collagen form ligaments or tendons. Loosely arranged collagen, smooth muscle, elastin, adipose tissue, blood vessels, lymphatics, and nerves contiguous with the pelvic organs have been controversially called *endopelvic fascia* (323). Parametrium and paracolpium "fascial" attachments form the uterosacral and cardinal ligaments (300).

The attachments of the arcus tendineus fascia pelvis and arcus tendineus levatoris ani consist of dense connective tissue originating from the obturator and levator ani fascia and provide anterolateral support of the vaginal wall. They insert anteriorly at the pubic rami bilaterally and extend posteriorly to the ischial spines (Fig. 38.1) (300). The urethra lies on a hammocklike supportive layer composed of the endopelvic fascia and anterior vaginal wall (83).

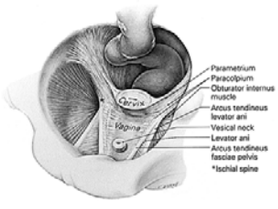

FIGURE 38.1. Cervix, vagina, and supportive structures drawn from dissection of a cadaver of a 56-year-old woman after hysterectomy. The bladder has been removed above the vesical neck. The paracolpium extends along the lateral wall of the vagina. (From DeLancey JOL. Anatomic aspects of vaginal eversion after hysterectomy. *Am J Obstet Gynecol* 1992;166:1717, with permission.)

DeLancey (79) initially described the concept of dividing the pelvic supports system into three levels. Levels I, II, and III represent apical, midvaginal, and distal vaginal supports, respectively. Level I defects are associated with uterine prolapse, enterocele, and posthysterectomy vaginal vault eversion. They are caused by a loss of support of the paracolpium and parametrium (uterosacral and cardinal ligaments). Level II defects affect the fibromuscular integrity of the vagina and its lateral supports (arcus tendineus fascia pelvis and arcus tendineus levatoris ani) and may appear clinically as cystocele, rectocele, or paravaginal defects. Level III defects correspond to loss of perineal body integrity or fusion of the distal urethra to the pubic bone at the perineal membrane. The perineal membrane is the triangular sheet of dense fibromuscular tissue spanning the anterior half of the pelvic outlet (318). It is also called the *urogenital diaphragm.* Loss of level III supports results in descent or separation of the perineal body or urethral hypermobility (Fig. 38.2).

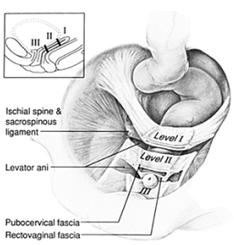

FIGURE 38.2. Levels of support of the upper and midvagina. In level I (suspension), the endopelvic fascia suspends the vagina from the lateral pelvic walls. Fibers of level I extend both vertically and posteriorly toward the sacrum. In level II (attachment), the vagina is attached to the arcus tendineus fascia pelvis and superior fascia of the levator ani. (From DeLancey JOL. Anatomic aspects of vaginal eversion after hysterectomy. *Am J Obstet Gynecol* 1992;166:1717, with permission.)

Muscles

The levator ani muscle and associated connective tissue attachments to the pelvis form the hammocklike pelvic diaphragm, which extends between the pubes anteriorly and the coccyx posteriorly. The levator ani consists of two parts, the diaphragmatic part (coccygeus and iliococcygeus muscles) and the pubovisceral part (pubococcygeus and puborectalis muscles). The coccygeus muscles extend bilaterally from the coccyx and sacrum to the ipsilateral ischial spine. The iliococcygeus muscle extends from the lateral pubic symphyses, over the pelvic sidewall (obturator internus muscle), attaching to the arcus tendineus levatoris ani laterally and meeting in the posterior midline at the anococcygeal raphe and coccyx. This forms the levator plate (Fig. 38.3). The pubovisceral portion of the levator ani arises from the inner pubic bones, attaching to the lateral vagina and rectum, and extends bilaterally to the anococcygeal raphe and coccyx (318). Understanding of pelvic

floor anatomy has been greatly enhanced using magnetic resonance imaging (MRI) (Fig. 38.4).

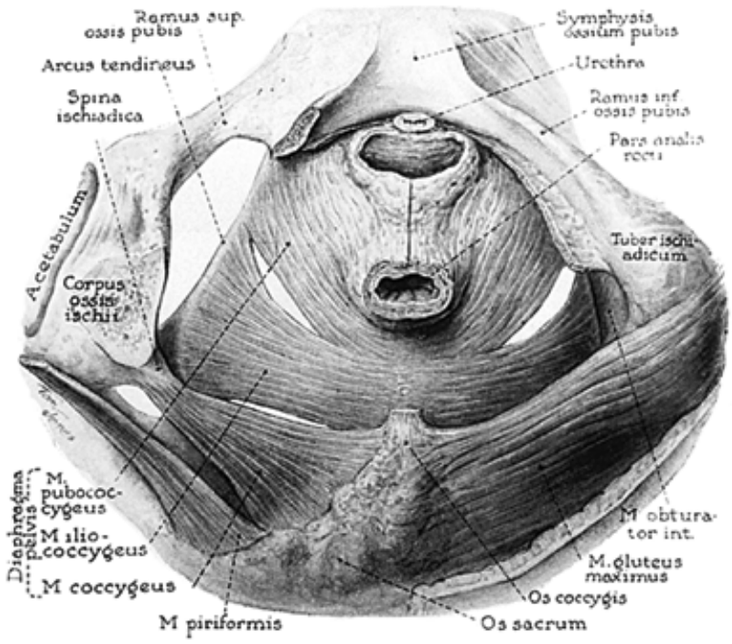

FIGURE 38.3. The levator ani muscle as seen from below. (From Anson BJ. *An atlas of human anatomy.* Philadelphia: WB Saunders, 1950:366, with permission.)

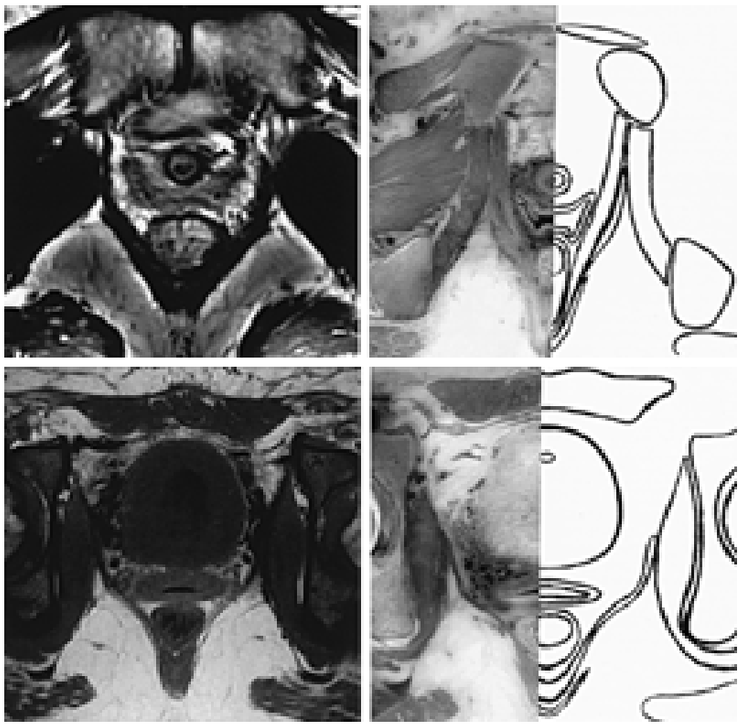

FIGURE 38.4. Axial views of the pelvis near the pubic symphysis. Proton density magnetic resonance image of 28-year-old living patient using a pelvic phased-array coil (repetition time 3,800 ms, echo delay time 18 ms, field of view 20 cm, scan time 8:59 minutes). **A:** Cross-sectional anatomy of the right hemipelvis. **B:** Corresponding diagram of the left hemipelvis. Axial view of the pelvis 3 cm cephalad to above. **C:** Cross-sectional anatomy of right hemipelvis. **D:** Corresponding diagram of the left hemipelvis. (From Strobehn K, Ellis JH, Strobehn JA, et al. *Obstet Gynecol* 1996;87:277, with permission.)

The levator ani muscle consists of slow twitch (type I) fibers, which maintain constant tone, and fast twitch (type II) fibers, which are responsible for reflex and voluntary contraction (318).

Nerve Supply

Innervation is supplied by sacral nerve root S-2, S-3, S-4, with possible contributions from pudendal nerve branches.

Etiology

Multiple factors contribute to the development of genital prolapse and urinary incontinence. Although the inherent strength of the muscles and connective tissue is important, they may deteriorate with age, prolonged lifting, or chronic cough causing long-term increase in intraabdominal load (81), decreasing estrogen with menopause (7), and pelvic support damage caused by vaginal birth (6,236). Previous gynecologic surgery, such as hysterectomy, predisposes to vaginal prolapse (79). Native connective tissue quality may play a role in isolated breaks in fascial attachments

of the pelvic organs when subjected to chronic wear and tear (248).

Vaginal Birth

Delee (84) described the anatomic injuries associated with vaginal birth. The vagina is detached from its fascial anchors as the fetal head passes through the genital hiatus. Posteriorly, the levator ani muscles and connective tissue are torn from the rectum, and muscle separation occurs with tearing or overstretching. Anteriorly, vaginal attachments to the bladder may be torn, causing weakness of the attachment of the levator ani to the pubic symphysis. Factors associated with weakness of the pelvic floor include forceps delivery (247,302), episiotomy (143,247), prolonged second stage of labor, and increased fetal size (6,247). Levator ani muscle denervation has been detected in 50% of women with symptomatic pelvic organ prolapse (272). Parous women demonstrate more obvious histologic and electromyographic evidence of denervation (272). Cesarean delivery is considered protective against pudendal nerve injury (114). In 20 nulliparas, vaginal birth was associated with significant loss in pelvic muscle strength, whereas cesarean delivery was not (262).

Signs and Symptoms

Women with symptomatic genital prolapse complain of pelvic pressure, a feeling of heaviness, and often a visible protrusion of tissues. Sacral backache may be caused by traction on the uterosacral ligaments (81). They may also report a sensation of perineal wetness, vaginal bleeding caused by vaginal wall ulceration and atrophy, and difficulty with sexual intercourse.

Women with anterior wall prolapse also complain of urgency, urge incontinence, and frequency. Loss of support of the urethra and lower vaginal wall is associated with stress urinary incontinence. Loss of support of the upper anterior vaginal wall and bladder base can cause urinary retention and difficulty voiding. Apical prolapse may be associated with similar symptoms (81). Posterior wall prolapse has been associated with difficulty emptying the rectum, sometimes necessitating manual depression of the posterior vagina for defecation. Weber and Walters (323) found that there was no correlation between bowel symptoms and the presence of a rectocele. It is important to consider other causes of constipation, especially in older women.

Multiple sites of prolapse commonly are present simultaneously (Fig. 38.5). Therefore prolapse, bowel, bladder and sexual function are dynamically related (275).

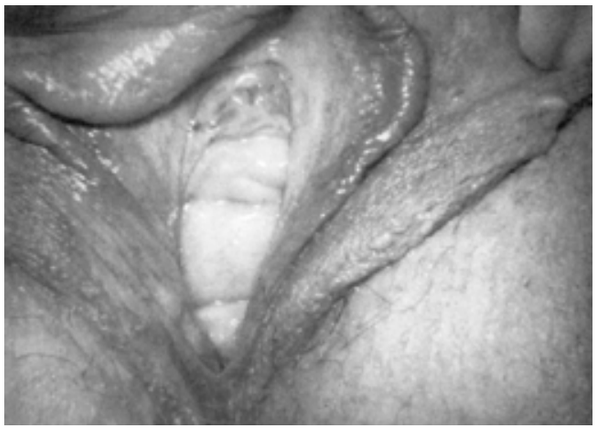

FIGURE 38.5. Prolapse of the anterior, superior, and low position vaginal walls associated with a cystocele.

Prolapse and Urinary Tract Dysfunction

Fifty percent of women with genuine stress urinary incontinence have clinically important prolapse of the anterior vaginal wall (295). In as many as 80% of previously continent women, stress urinary incontinence can develop as a new condition after repair of severe prolapse (30). Occult or potential incontinence is defined as unmasked stress urinary incontinence, which may be caused by a mobile urethra after prolapse reduction (306). When the urethra is mobile or there is leakage when a cystocele is reduced during evaluation, an appropriate urethral suspension should be done with the cystocele repair (190).

Procidentia may occasionally imprison the ureters, leading to hydroureter and hydronephrosis. The diagnosis is made by intravenous urography with the patient upright.

Evaluation and Diagnosis

Pelvic organ prolapse is a clinical diagnosis based primarily on the physical examination. Traditionally, prolapse is subclassified according to pelvic organ. At physical examination, areas of prolapse should be assessed initially with and without Valsalva maneuver in the lithotomy position. It may be necessary to examine the woman in the sitting or standing position to reproduce maximal conditions (7). Each area of weakness in pelvic support must be graded individually according to maximal degree of descent to or beyond the introitus during maximal straining. Rectovaginal examination may assist in evaluation of the posterior vaginal wall (46). In the presence of a history of vaginal bleeding, investigations to rule out malignant or premalignant sources may be necessary, especially in the menopausal woman.

The simplicity of Baden's (18) system of classification and grading of pelvic organ prolapse severity has greatly contributed to its wide usage for many years (Table 38.1). Although it is easily amenable to clinical practice, this system has been associated with variable interobserver reproducibility and the inability to definitively ascertain the

organs behind the visualized vaginal bulge. Therefore, in 1996, Bump and associates (46) proposed the International Continence Society standardization of terminology for female pelvic organ prolapse. This is a descriptive system of site-specific measurements of the pelvic supports. It attempts to objectively assess six defined points along the uterovaginal axis and includes measures of the genital hiatus, perineal body, and total vaginal length (Fig. 38.6). The complete quantitative description corresponds to specifically defined overall stages of prolapse. The system attempts to quantify prolapse and improve precision, although it is not organ specific. It has become a useful research tool.

Cystocele
First degree: The anterior vaginal wall, from the urethral meatus to the anterior fornix, descends halfway to the hymen. Second degree: The anterior vaginal wall and underlying bladder extend to the hymen. Third degree: The anterior vaginal wall and underlying urethra and bladder are outside the hymen. This cystocele is often part of the third-degree uterine or posthysterectomy vaginal vault prolapse.

Uterine or Vaginal Vault Prolapse
First degree: The cervix or vaginal apex descends halfway to the hymen. Second degree: The cervix or vaginal apex extends to the hymen or over the perineal body. Third degree: The cervix and corpus uteri extend beyond the hymen or the vaginal vault is everted and protrudes beyond the hymen.

Rectocele
First degree: The saccular protrusion of the rectovaginal wall descends halfway to the hymen. Second degree: The sacculation descends to the hymen. Third degree: The sacculation protrudes or extends beyond the hymen.

Enterocele
The presence and depth of the enterocele sac, relative to the hymen, should be described anatomically, with the patient in the supine and standing positions during Valsalva maneuver.

From Walters MD, Karram MM, eds. *Urogynecology and reconstructive surgery.* St. Louis: Mosby, 1999:38, with permission.

TABLE 38.1. CLASSIFICATION OF THE SEVERITY OF PELVIC ORGAN PROLAPSE AS DESCRIBED BY BADEN (1968) AND MODIFIED BY BEECHAM (1980) ACCORDING TO MOST DEPENDENT POSITION OF THE PELVIC ORGAN DURING MAXIMAL STRAINING OR STANDING.

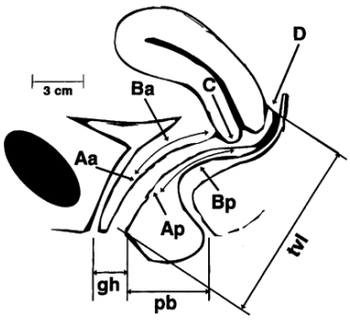

FIGURE 38.6. Six sites (points *Aa, Ba, C, D, Bp,* and *Ap*), genital hiatus *(gh),* perineal body *(pb),* and total vaginal length *(tvl),* used for pelvic organ support quantitation from the International Continence Society. (From Bump RC, Mattiasson A, Bo K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:10, with permission.)

Other tools for assessing genital prolapse include imaging procedures such as ultrasonography, contrast radiography, computed tomography (CT), and MRI. Techniques to assess urethral hypermobility include videocystourethrography, Q-Tip test, and ultrasonography. Videocystourethrography may also demonstrate central and lateral defects of the anterior vaginal wall (Fig. 38.7). Ultrasonography displays dynamic descent of the urethrovesical junction in real time.

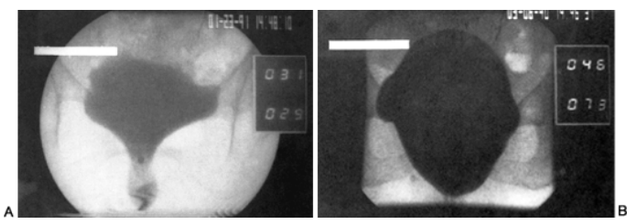

FIGURE 38.7. Videourodynamic study with the patient upright showing anterior wall defects. **A:** A cystocele with a narrow central defect in the pelvic floor is shown. Despite equal pressures in the bladder (31) and urethra (29), no leaking occurs because of the protective effect of the cystocele on the urethra. **B:** A large cystocele descends because of a defect in the vaginal support laterally at the arcus-ischial junction. This is a lateral defect.

Treatment

Issues such as future fertility, future sexual function, severity of symptoms, impact on quality of life, and the presence of medical complications affect treatment choices. Because genital prolapse usually is a quality-of-life problem, the potential risks and benefits of treatment must be evaluated individually. Nonsurgical and surgical management options should be considered.

Prophylaxis

Preventive measures include managing respiratory and metabolic disorders, which cause chronic increase of intraabdominal pressure. Weight control, nutrition, smoking cessation, and avoidance of occupational and recreational activities that stress pelvic supports also are important. Changing obstetric management to minimize instrumental trauma and prolonged labor may help preserve the pelvic floor (7). Postmenopausal estrogen replacement increases skin collagen content and improves vaginal epithelialization (38). Its direct effect on preexisting genital prolapse is unclear. Pelvic muscle exercises may strengthen the pelvic diaphragm and prevent pelvic relaxation.

Nonsurgical

Treatment of chronic respiratory conditions, weight loss, estrogen replacement, pelvic floor exercises, and biofeedback may improve conditions. Vaginal pessaries may be used in women awaiting surgery, women with prolapse during pregnancy, and women with medical contraindications for surgery. These rings are individually fitted to reduce genital prolapse. Local estrogen cream may decrease discomfort and erosion. Temporary relief of symptoms by pessary reduction of prolapse may indicate amelioration of prolapse symptoms with surgery.

Surgical

Apical Support Defects

A fascial break at the vaginal apex may result in an enterocele, a hernial sac that consists of peritoneum in contact with vaginal mucosa with no intervening fascia (Fig. 38.8) (249). Therefore excising the enterocele sac and reestablishing the continuity of pubocervical and rectovaginal fascia at the vaginal apex regardless of the anchoring site is recommended (79). For women who have completed childbearing, hysterectomy usually is combined with a technique for apical support restoration. Once the uterus is removed, the vaginal apex should be fixed to a higher point in the pelvis (79).

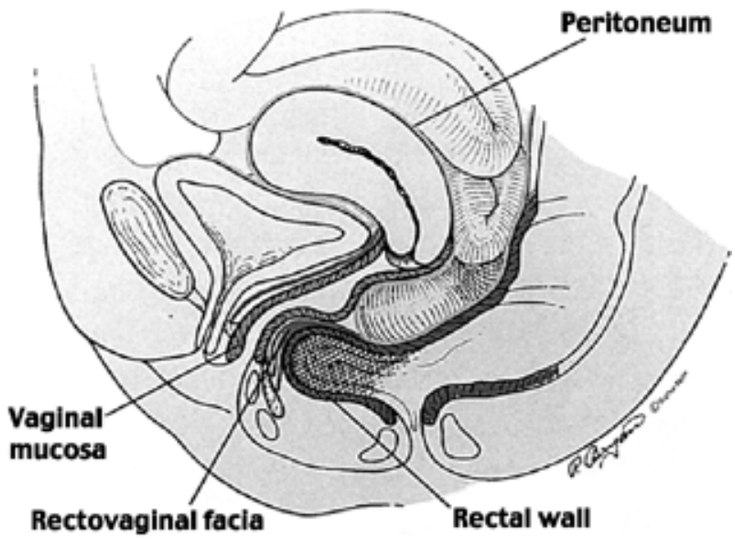

FIGURE 38.8. Posterior enteroceles. The fascial defect with the uterus in place *(left)* and with the uterus removed *(right).* (From Richardson CA. The anatomic defects in rectocele and enterocele. *J Pelvic Surg* 1995;1:214, with permission.)

Sacrospinous Ligament Suspension.

The sacrospinous ligament suspension involves unilateral or bilateral fixation

of the vaginal apex to the sacrospinous ligament and coccygeus muscle complex by a vaginal approach. The reported success rate ranges from 83% to 97% (278). An 18% recurrence rate has been cited (304). The lateral and posterior deflection of the vaginal axis associated with the typical unilateral fixation has been criticized as being not anatomic. Described complications include recurrent anterior wall prolapse (278), vaginal shortening, sexual dysfunction, pain, and hemorrhage. The notable procedure risks are related to injury to the nearby pudendal nerves and vessels, the gluteal vessels, and the sacral nerve roots.

Iliococcygeus Suspension.

Considered a less morbid procedure, the iliococcygeus suspension involves attaching the vaginal apex to bilateral iliococcygeus muscle just anterior to the ischial spine (277). In contrast to the sacrospinous ligament suspension, the point of fixation is removed from critical structures. The reported anterior wall prolapse recurrence rate ranges from 4% (207) to 19% (277). Foreshortening of the vaginal length is a drawback of this procedure.

Uterosacral Suspension.

Uterosacral suspension involves bilateral suspension of the vaginal vault from the origins of the uterosacral ligaments (214). McCall combined this with a culdoplasty, where the uterosacral ligaments are plicated and the cul-de-sac is obliterated. Currently, uterosacral suspension is more often performed by vaginal or laparoscopic approach. Reported recurrence rates range from 0% to 11% (95). Intraoperative cystoscopy is recommended because of the close proximity of the ureters to the uterosacral ligaments and the increased risk of ureteric entrapment or obstructive attenuation.

Abdominal Sacral Colpopexy.

Abdominal sacral colpopexy involves placing a synthetic bridge between the prolapsed vaginal apex and the anterior surface of the sacrum. The sacral promontory to the upper third of the sacrum is considered the safest site of fixation (2). Separate pieces of mesh material often are attached to the anterior and posterior vaginal wall. It is often accompanied by a Halban or Moschowitz culdoplasty to obliterate the cul de sac, incite scarring, and potentially reduce the risk of enterocele formation behind the posterior mesh. A 90% cure rate has been reported (2). Failure usually occurs at the vaginal fixation site. Specific risks include life-threatening hemorrhage from injury to the sacral venous plexus, bowel obstruction, and mesh erosion.

Colpocleisis.

In older women who will no longer be sexually active, a LeFort colpocleisis may be the preferred management of massive vaginal vault eversion. It is associated with less perioperative morbidity. It consists of denuding a rectangle of vagina anteriorly and posteriorly and reapproximating the underlying tissue. If left *in situ,* the uterus and the cervix remain hidden behind the new vaginal septum, and channels are left open below the cervix and lateral to the closure to allow any secretions and uterine bleeding to be noted. Endometrial carcinoma or hyperplasia must be ruled out before this procedure is performed. Stress incontinence may develop after colpocleisis because of flattening of the posterior urethral–vesical angle (223).

Anterior Wall Support Defects

Anterior wall defects have been described as lateral, superior, and midline. Specific repairs address specific defects. Some women with cystoceles may also have concomitant genuine stress urinary incontinence. In this scenario, a combined antiincontinence procedure may be needed.

Anterior Colporrhaphy.

Anterior colporrhaphy or cystocele repair addresses central anterior defects. A vaginal approach is used. The vaginal epithelium is incised and dissected from the underlying endopelvic fascia to reveal the defect. The area of dissection extends from the descending pubic rami to the bilateral pelvic sidewall. The endopelvic fascia is plicated to reinforce the anterior vaginal wall and reduce the anterior herniation. Synthetic material, cadaveric fascia, or autologous fascia sometimes is used to reinforce or substitute for endopelvic fascia (Fig. 38.9) (165).

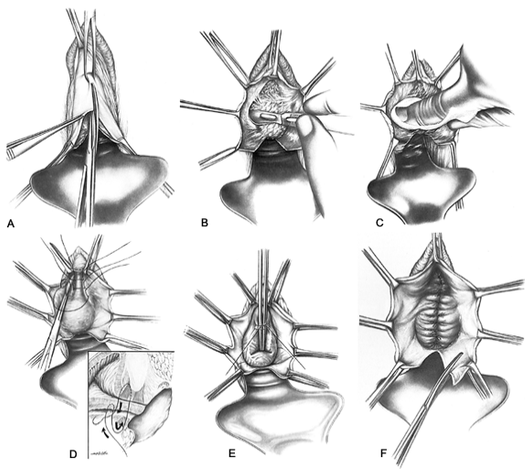

FIGURE 38.9. Technique of anterior colporrhaphy. **A:** Scissor dissection of vaginal mucosa to the region of external meatus with traction on the vagina along the course of dissection to separate bladder from vaginal mucosa. **B:** Sharp dissection of the white, avascular plane between the adherent fascia and vaginal mucosa. **C:** Blunt finger dissection with gauze sponge to free fascia from mucosa beneath the urethra and bladder. **D:** Beginning at the external meatus, successive vertical mattress sutures are placed in the mobilized paraurethral fascia (Kelly plication). **E:** Successive sutures are continued along the posterior floor of the bladder and urethra and are tied. **F:** The normal urethrovesical anatomy is restored. The excess vaginal mucosa is excised. The vaginal mucosal edges are reapproximated in the midline. (From Thompson JD. Surgical correction of defects in pelvic support: anterior compartment defects. In: Rock JA, Thompson JD, eds. *TeLinde's operative gynecology,* 8th ed. Philadelphia: Lippincott-Raven 1997: 980, with permission.)

Paravaginal Defect Repair.

Performed both by abdominal and vaginal approach, the paravaginal defect repair is an attempt to restore lateral anterior wall defects. Abdominally, the retropubic space is dissected to expose the arcus tendineus fascia pelvis, the pubic bone, and the ischial spines. The separation or detachment of the arcus tendineus fascia pelvis and lateral vaginal sulcus from the pelvic sidewall indicates a paravaginal defect. Repair involves suturing the detached fascia to the pelvic sidewall along its anatomic line of attachment between the pubic bone and the ischial spines (276). By the vaginal route, the anterior vaginal wall is opened, as in the anterior colporrhaphy, and the arcus tendineus fascia pelvis is reattached to the pelvic sidewall. Macer (195) reported a cure rate of 78% and 92% for vaginal and abdominal approaches, respectively.

Posterior Wall Defects

Posterior Colporrhaphy.

Posterior colporrhaphy remains the mainstay procedure for posterior wall defects. It involves incision and dissection of the posterior vaginal wall to expose the defect. Traditionally, as described by Nichols (223), transverse plication of the detached rectovaginal fascia separate from the vaginal mucosa has been advocated. More recently, Richardson (249) suggested site-specific reapproximation of discrete breaks in the rectovaginal fascia, without levator plication, as a more anatomic repair that

minimizes bowel symptoms and dyspareunia postoperatively. Rectocele repair often entails simultaneous perineal reconstruction to reapproximate separated superficial perineal muscles. This results in an increase in perineal body length and restores the normal caliber of the genital hiatus.

VAGINAL INFECTIONS

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

Bacterial Vaginitis (Nonspecific Vaginitis)

Gardnerella vaginalis is the organism most often associated with bacterial vaginitis. The organism was named for Gardner, who, with a co-worker, in 1955 described a vaginal infection caused by the organism *Haemophilus vaginalis* (184). More recently, the disease has been called bacterial vaginosis because the condition is characterized by vaginal discharge but the absence of true tissue invasion or local tissue inflammatory changes (97,286). In addition to *G. vaginitis,* other anaerobic organisms often are present in the vagina and vaginal discharge of patients with nonspecific vaginitis or bacterial vaginosis (200). The basic cause of the anaerobic bacterial overgrowth is not known. Whether bacterial vaginosis is a sexually transmitted disease is also unknown (283). The anaerobic overgrowth is associated with a change in the normal flora of the vagina, particularly the population of lactobacilli, the predominant organisms in a normal vaginal flora. There are 100-fold to 1,000-fold decreases in the usual bacterial counts of lactobacilli in patients with symptomatic bacterial vaginosis. In addition, unusual species of lactobacilli can be cultured from the vagina. The underlying mechanisms involved in the changes in bacterial flora are unknown. Moreover, the presence of *Gardnerella* organisms is not universally associated with symptoms or vaginal discharge (97,115,184,286,330).

Symptoms

Patients generally complain of a malodorous discharge, particularly after intercourse. On examination, there is a thin, watery, usually grayish-white discharge. Most patients with typical bacterial vaginosis do not complain of pruritus, dysuria, or true dyspareunia (211). When exposed to potassium hydroxide (KOH), amines present in the vaginal discharge volatilize and release a characteristic fishy odor. There is an increased rate of vaginal cell exfoliation, which contributes to the discharge. Typically, *Gardnerella* bacteria are attached to the exfoliated cells.

Diagnosis

The diagnosis is based on the presence of a grayish-white discharge, which is adherent to the vaginal epithelium, a vaginal pH greater than 4.5, a positive amine test in the presence of KOH (whiff test), and the detection of “clue” cells in the vaginal discharge. Clue cells are exfoliated vaginal epithelial cells covered with *G. vaginalis* organisms, which gives the cells a stippled, granulated appearance and blurs the cell borders (115,211). There are few polymorphonuclear leukocytes (PMNs) in the discharge. Generally, cultures are not useful because it is not the presence of the organism that defines the disease. Other exfoliated cells, called comma cells, are covered with adherent curved rodlike bacteria on Gram stain; they also are associated with bacterial vaginosis in the absence of true clue cells.

Treatment

Oral metronidazole, 800 to 1,100 g per day for 1 week, constitutes standard therapy. This is associated with a 90% cure rate. Oral clindamycin also can be used, 300 mg twice a day, or it can be applied as a 2% vaginal cream or used as a suppository once daily for 7 days. The latter treatment is indicated in women sensitive to metronidazole, pregnant women, or those who cannot tolerate the side effects of systemic therapy. Amoxicillin and ampicillin also have been used, particularly in pregnant women, but these drugs are less effective than clindamycin and metronidazole (58,245,287).

Treating the sexual partners of women with bacterial vaginitis has not been shown to improve outcome when compared with placebo treatment of the sexual partners (185).

Candida and Other Yeast Infections

Although only 5% of women develop recurrent yeast infections, 75% experience at least one infection, and 50% experience more than one infection (292). *Candida* species are commonly isolated in the vaginal flora of healthy asymptomatic women (115). Factors responsible for overgrowth of the yeast organism and symptoms include antimicrobial therapy, pregnancy, high estrogen levels, diabetes mellitus, corticosteroid therapy, and altered immunologic status. The role of other factors that putatively have been related to yeast infections is controversial. These latter factors include sexual activity and many other less well-established associations (110). Most symptomatic infections are caused by *C. albicans,* but *C. tropicalis* and *Torulopsis glabrata* also can be pathogenic (154). The precise cause of *Candida* infections is not established. Sexual transmission has been studied but has not been proven to be a causal factor (110,153). Altered immunologic status has been suggested as a cofactor, related to a reduction in cellular organism immunogenicity associated with secretion of a carbohydrate “mannan” by the organism, which may induce specific T-cell suppressor lymphocytes (148,153,166).

Symptoms

Vulvar pruritus and a cheesy-white vaginal discharge, together with dyspareunia, burning vulvar pain, and occasional dysuria, are typical symptoms. In diabetic patients, involvement of the vulva and intertriginous areas is common. On examination of the vagina, white adherent patches are seen, which resemble the patches seen in the throat in patients with thrush. The vaginal epithelium is inflamed, but the cervix usually is normal (246).

Diagnosis

The diagnosis is based on typical findings on examination, a vaginal pH less than 4.5, and a saline and KOH prep (10% to 20% KOH) that demonstrates budding yeasts, or hyphae with branches. Microscopic tests are valuable if positive, but they are not very sensitive. Cultures are specific, but they take at least 24 hours and often are not done in physician's offices. A rapid slide test using a latex agglutinin technique is available; it is more specific but not much more sensitive than the microscopic test (98).

Treatment

The imidazoles are the first line of therapy. Topical agents are available as over-the-counter preparations. *C. tropicalis* and *Torulopsis* species usually are not very sensitive to imidazoles. The imidazoles include butoconazole, clotrimazole, miconazole, and terconazole (212,270,285). There do not appear to be any significant differences in efficacy in this group of agents, with the possible exception of butoconazole, which may be more effective at smaller dosages.

Initial therapy fails in approximately 20% to 25% of women. This may occur because the organisms are not sensitive or for other reasons.

Culture identification of the organism is thought to be helpful when the initial trial of therapy fails. Long-term oral therapy, such as ketoconazole 100 mg daily for 4 to 6 weeks has been found effective (270). Idiosyncratic toxic reactions to the imidazoles have been reported, including hepatitis, but these are unusual. For highly recurrent infections resistant to standard therapy, painting the affected tissue with gentian violet can be effective though inconvenient and messy.

Although none of the oral agents currently available are approved by the U.S. Food and Drug Administration (FDA) for vaginal infections, almost all of them have been used as oral therapy for *Candida* infections. Oral therapy is equivalent or superior to local therapy. Ketoconazole (40 mg daily for 5 days), fluconazole (150 mg as a single dose), and triaconazole (200 mg daily for 3 days) have been found to be equally effective. Safety of the oral agents in pregnancy has not been demonstrated. Local agents are used during pregnancy, but some systemic absorption of these also may occur, with potential for fetal effects (96,270).

Trichomonas vaginalis

Infection with *Trichomonas,* a protozoan parasite, is perhaps the third most common vaginal infection. This is a sexually transmitted disease, and its incidence varies from 2% to 5% in a general gynecologic office practice to 5% in family planning clinics and 10% to 25% in gynecology clinics in university hospitals. It affects perhaps 5% of the U.S. population between ages 16 and 35 (252,307). The organism is strictly anaerobic and attaches to epithelial cells in the vagina and urethra and in Skene's glands in women and in the urethra and prostate in men as well as beneath the foreskin in uncircumcised men. Systemic therapy usually is needed for cure.

Symptoms

As many as 50% of affected women are asymptomatic. When symptoms occur, they classically include a profuse, frothy, greenish watery discharge. In fact, the discharge often is indistinguishable from that seen in patients with nonspecific bacterial vaginosis. Other symptoms include pruritus, dysuria, and dyspareunia. *Trichomonas* has a positive association with bacterial vaginosis. However, the typical vaginal discharge is different with a combined infection because all *Trichomonas* infection discharges contain large numbers of PMNs, in contrast to the discharge in patients with bacterial vaginosis.

Diagnosis

The vaginal pH generally is 5 or higher. The characteristic discharge may or may not be present. White blood cells are present in the discharge, and the trichomonal organism may be visualized on a saline prep, identifiable by its rapid flagellar movement. Often, the organism also can be identified in urine specimens. The false-negative rate for wet mounts is as high as 50%, so culture is the most reliable method. The organism grows on selective media, but identification takes 2 to 7 days, much too long for clinical utility (178). Two new monoclonal antibody stain methods are available, which are comparable in specificity to culture and nearly equal to culture in sensitivity (188).

Treatment

Primary therapy is with metronidazole (250 mg three times a day for 7 days). Single oral doses of 2 g provide comparable outcome, or a 90% to 95% cure rate at 10 days. The organism does not persist in the male genital tract, but concurrent treatment of sexual partners is recommended to

prevent the short-term risk of reinfection in women treated with short-course therapy. Treatment failure is unusual; a second course of therapy is recommended in such instances. Clotrimazole can be used as local therapy, but it is much less effective; however, it must be used during pregnancy (184,188,245,286). Side effects of metronidazole are common and include glossitis and nausea. The drug also has Antabuse-like properties, and severe, violent reactions can occur if patients drink alcohol while taking the drug.

Newer Therapy and Changing Concepts of Epidemiology

Povidone-iodine pessaries have been used for the local therapy of *Candida* and *Trichomonas* and nonspecific vaginitis. These nontoxic suppositories containing 200 mg of povidone-iodine have been shown useful in small series without placebo controls (341).

In the United States and Europe, *Trichomonal* vaginitis is much less common than it was 10 years ago, and *Candida* infections have become much more common (169). Vaginitis still is one of the 25 most common problems in clinical medicine in the United States, and with the increase in incidence of candidiasis, it has come an increase in the incidence of yeast infection caused by noncandidal organisms, which are resistant to standard therapy.

However, failure of treatment to resolve symptoms of vaginitis may be the result of a noninfectious cause. At least two studies have suggested that, rather than failure of antimicrobial therapy, failure of response simply may reflect a noninfectious problem (259,264).

Ray and co-workers (241) did vaginal cultures in 100 women with “vaginitis” and 50 age-matched “normal” controls. *T. vaginalis* was cultured from 11% of symptomatic patients, *Candida* from 31%, and *Gardnerella* from 31%. In the control group, 22% were positive for *Gardnerella,* 14% for *Candida,* and none for *Trichomonas.* These findings suggest that cultures are not specific for any diagnosis (241).

Another study, from Denmark, found no difference in the concentration of *G. vaginalis* in women with and without a symptomatic vaginal discharge. In other words, the concentration of organisms in patients without the disease was about the same as it was in patients with symptomatic vaginal discharge (40).

Furthermore, women with infrequent vulvovaginal candidiasis often have an identifiable cause for the infection, whereas those with highly recurrent or resistant infections often do not. Although noncandidal species are more common in recurrent infections, resistance to imidazoles is rarely responsible by itself for recurrent infections (284). Treatment of presumed gastrointestinal reservoirs or sexual partners is rarely effective in women with relapsing infection (270). Immunologic studies suggest the existence of an acquired *Candida* antigen–specific immunologic deficiency that is hormone sensitive (148,166).

Genital Herpes

Genital herpes is a common condition, and it is estimated that about 20 million acute and recurrent infections occur in the U.S. population annually (213). Herpes is a sexually transmitted disease, and the incubation period is 2 to 10 days. Transmission is not efficient; transmission to an infected person's sexual partner is approximately 10% annually (184).

Acyclovir therapy has reduced the severity of acute episodes and decreased the incidence of recurrence and the severity of recurrent exacerbations.

Pathogenesis

Herpes simplex virus type I and II cause infections of the oral and genital mucosal surfaces. The type II variety causes 80% of genital infections. These are DNA viruses, which can be typed using monoclonal antibodies (213).

Symptoms

A prodromal symptom complex of paresthesias precedes by 12 to 48 hours the appearance of vesicles and pustules, which usually occur in groups. The paresthesia reflects the diffuse sensory neural involvement by the virus. The vesicles rupture, leaving very painful ulcers, which are sometimes clean based and sometimes purulent. A primary infection is severe in patients who have previously been unexposed to herpes simplex virus because there are no preformed antibodies. Systemic symptoms are more common with the first episode and include fever, myalgia, headache, and malaise. Acute urinary retention may occur in acute episodes, particularly during pregnancy. With the initial episode, herpes simplex type II usually can be cultured from the cervix or the base of the ulcers if they are not secondarily infected. With subsequent episodes, positive herpes simplex cultures are less common (213,255).

Dysuria is a prominent symptom; urinary retention related to cord or root involvement may necessitate intermittent catheterization for 4 to 8 days. Rarely, with extensive neural involvement including transverse myelitis, intermittent catheterization may be needed for several weeks. The major differential diagnosis is a syphilitic ulcer (255). Herpes tissue culture or a cytologic diagnosis by a Papanicolaou smear, viral antigen, or DNA detection is the most specific methods of diagnosis. Tzanck stains also can be used. These are fresh preparations, stained with Wright's stain, of scrapings from vesicles. The technique detects the multinuclear giant cells typical of herpetic infection. Stains are 50% to 80% specific (184).

Treatment: Dosage and Route

Acyclovir is the acyclic analog of guanosine, which is a competitive inhibitor of herpes simplex virus DNA polymerase, which slows viral replication. For acute infections, the dosage is 400 mg acyclovir three times daily for 10 days. Topical treatment is much less effective but can be used (168). Recurrent episodes are treated with 200 mg acyclovir daily for 2 to 5 days or 800 mg twice daily for 5 days; 400 mg twice daily is used for prophylaxis of recurrent episodes. The usual duration of prophylactic treatment is 1 year, followed by a period of observation to see whether there is a recurrence. The incidence of side effects in patients treated for as long as 3 years has been minimal. For a severe or critical disease, as may occur in pregnancy, the intravenous route is used (5 mg/kg every 8 hours for 5 to 7 days) (103). Immunodepressed patients fare poorly with herpes simplex infections, and increased dosages of acyclovir are needed. Safety of acyclovir in pregnancy has not been determined; the drug is not used unless life-threatening infection is present.

Genital Warts

Human papillomaviruses (HPVs) that cause genital warts are ubiquitous; the true incidence is unknown but is thought to be high. There are numerous HPV types; types 16, 18, and 31 appear to be more oncogenic than others. The association between HPV and genital malignancy is fairly strong and convincing; however, the relationship is based primarily on the common finding of HPV-DNA sequences in malignant tissue (157). Patients with HPV infection should undergo regular evaluation, particularly for cervical malignancy.

Clinical Expression

Cauliflower-like lesions, called *condyloma,* arise on the external genitalia and anal regions and occasionally are present in the oral cavity. These are soft, white sessile tumors with fingerlike projections, especially on the vulva. On the skin, the lesions are more keratotic. There may be small, papillary lesions that may coalesce. Subclinical infections can be recognized by application of dilute acetic acid, which turns the lesions white.

Diagnosis

Usually, the diagnosis is obvious, but some clinical cases may be diagnosed by Pap smear, colposcopy, or acetic acid test. The acetic acid test involves soaking the skin or genital area in 3% acetic acid for 5 minutes and then examining the area under magnification. A shiny white appearance of the skin may occur on the lesions, but these findings are nonspecific. The typing of HPV is based on DNA hybridization. This is the only method that allows differentiation of the more than 60 HPV types (49).

Treatment

No satisfactory treatment exists for HPV, and no treatment eradicates the infection. Treatment is directed only at the unpleasant or unsightly lesions, and that does not get rid of the virus. Patients, treated or untreated, are infectious to their sexual partners and should be advised to use condoms. Once present in the female genital tract, HPV infection is a multicentric disease. Patients with evidence of HPV infection should have regular colposcopic examinations of the entire genital tract for malignancy.

VULVAR PAIN AND VULVAR VESTIBULITIS SYNDROME

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

One of the most frustrating problems facing gynecologists and urologists is that of chronic vulvar discomfort and dyspareunia. Terms such as *focal vulvitis, vulvar adenitis,* and *vulvar hyperesthesia* have been used to describe this condition. Friedrich (111) coined the term *vulvar vestibulitis syndrome* (VVS) in 1987. VVS is a chronic clinical syndrome or constellation of symptoms limited to the vulvar vestibule and characterized by the following criteria: severe pain on vestibular touch or attempted vaginal entry, tenderness to pressure localized within the vaginal vestibule, and physical findings confined to vestibular erythema of various degrees (111,240). It has been proposed that VVS should be differentiated from vulvodynia, which is chronic vulvar discomfort usually characterized by burning, and from pruritus vulvae, which is associated with chronic itching. The discomfort of VVS may be characterized by a sharp pain or a sensation of rawness. The *sine qua non* is introital dyspareunia, but the pain may be elicited by tight clothing, biking, or tampon insertion (202).

On physical examination, there is localized erythema of the vestibular fossa, commonly involving the fourchette. When even mild pressure is applied to the affected areas with a cotton-tipped applicator, an immediate and marked pain response is elicited.

VVS occurs predominantly in Caucasians between ages 20 and 40 (111,129,199). The cause of VVS is not known. A number of studies have documented an increased incidence of candidal and HPV infections in affected patients (111,130,199,233,240). However, other investigators have not confirmed these findings (25,113,201). Furthermore, the presence of HPV infection does not affect treatment results (35). Neither gonorrhea, chlamydia, *Mycoplasma, Gardnerella, Ureaplasma,* nor *Trichomonas* appears to be causal (25). Urine-born oxalate crystals (288) have been implicated as possible etiologic agents in some patients.

Fitzpatrick and associates (108) reported the association of VVS with interstitial cystitis in three patients and proposed that both syndromes may represent a disorder of the urogenital sinus–derived epithelium because both bladder and vestibular mucosa are derived from the urogenital sinus. Histologic and immunohistochemical analyses of affected regions demonstrate greater inflammation and nerve fiber density when compared with control tissues (33,55,240,333).

There is no consensus about the appropriate treatment for VVS. Nonspecific therapies (sitz baths, lubricants, antiinflammatory agents) are rarely successful. Mild cases of discomfort may respond to topical lidocaine jelly. Antifungal and antibiotic creams should be prescribed only in cases of documented infection. Indiscriminate use of these agents is expensive and may worsen symptoms by inducing an inflammatory reaction. Patients with concomitant HPV infections and VVS may benefit from intralesional injections of alpha-interferon (152). Other treatments that have been used include long-term oral antifungal medications, acyclovir, amitriptyline, calcium citrate with low-oxalate diet, *N*-acetylglucosamine, and topical capsaicin (112,202,288). Biofeedback with pelvic floor muscle exercises may improve symptoms in some patients (126). When medical treatment is unsuccessful, surgical excision of the tender areas (perineoplasty) is performed. Published success rates of this procedure range from 43% to 100% (29).

ESTROGEN REPLACEMENT THERAPY

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

The increasing life expectancy in women over the last 50 years has led to the fact that approximately half of a woman's adult life is spent after menopause (87). The median age of natural menopause in the United States is 51.4 years (90). Approximately 1% of women become postmenopausal before age 40, and 5% become postmenopausal after age 55 (3). With the permanent cessation of ovarian activity and a subsequent fall in estrogen levels, there is a dramatic increase in the serum levels of follicle-stimulating hormone (FSH). Most women develop some features of estrogen deficiency such as thermoregulatory dysfunctions (e.g., hot flashes, sweats), vaginal thinning and atrophy, osteoporotic changes, menstrual irregularities, changes in the endometrium, and neurologic and emotional changes (90,225).

Estrogen replacement therapy (ERT) for postmenopausal women counteracts some of the effects of estrogen deficiency. In a study of the value of ERT in a hypothetical cohort of 10,000 women, it was estimated that using estrogen for 25 years would produce a gain of 3,951 “quality-adjusted life years” compared with the same number of women not using estrogen (134). In a study of 685 women given estrogen therapy who were designated at risk for osteoporosis, only 49% were still taking estrogen at the end of 1 year. In the group of women who had undergone hysterectomy, the 1-year compliance was 59% (308). In the National Health and Nutrition Examination Survey (NHANES) I study, 50% of women sampled used estrogen therapy for more than 1 month, but only 20% continued its use beyond 5 years (37). However, ERT is not without risk, and each patient should be thoroughly examined and counselled before ERT is initiated (23,68,134,225). Postmenopausal hormone replacement therapy (HRT) is individualized, and the ultimate decision and responsibility lies with the patient.

Effects of Estrogen Replacement Therapy

Short-term Effects

Postmenopausal women may experience menstrual irregularities, hot flashes, sleep and mood disturbances, decreased libido, and vaginal dryness (8). Hot flashes may cause irritability and sleep disruption. The incidence of hot flashes increases in the presence of smoking or a maternal history of hot flashes (296). Fluctuating hormone levels are associated with an increase in emotional lability (194). Breast atrophy and dyspareunia caused by vaginal atrophy are later indications of estrogen loss (28). ERT has been shown to be the most effective therapy for treating hot flashes related to estrogen deficiency (291).

Effect of Estrogen on Bone

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, causing an increase in bone fragility and susceptibility to bone fracture (69). Twenty-eight million Americans have varying degrees of osteoporosis. Women make up 80% of this group (9). More than 40% of women over age 50 experience osteoporosis-related fractures (124). Peak bone mass in men and women is attained by age 30 years, with a subsequent 0.4% bone loss per year in both sexes. In women, there is an annual 2% cortical bone and 5% trabecular bone loss for 5 to 8 years after menopause (9). It is estimated that women hospitalized for hip fractures have an overall mortality rate of 30% within 1 year of hip fracture (9).

Estrogen therapy is the only pharmacologic approach that has been widely recommended to treat osteoporosis. It has an antiresorptive effect that decreases osteoclastic bone resorption and directly increases bone mass. It is associated with a 50% reduction in the risk of hip fractures. In women with proven osteoporosis, it the first-line therapy for fracture prevention. The effect of estradiol on bone mass probably is both dosage and time dependent (9). When estrogen is combined with progesterone for hormone

replacement, the progesterone component does not significantly increase bone mass.

For osteoporosis prevention in the menopause, early institution of ERT is recommended. Beyond 5 years of menopause, ERT is suggested if osteoporosis is established by bone densitometry. Other therapies that are effective in preventing bone loss include alendronate, sodium fluoride, and intranasal calcitonin. Adequate dietary calcium intake, vitamin D, and weight-bearing exercises also contribute to reduction in fracture risk (9).

Effects of Estrogen on the Cardiovascular System

At age 50, women have a 50% risk of coronary artery disease (CAD) and a 30% risk of CAD mortality (135). CAD is considered the leading cause of death among women beyond 65 years of age, accounting for more than 400,000 deaths per year (8). Epidemiologic and observational studies suggest a 35% to 50% reduction in coronary heart disease with postmenopausal estrogen use (24,135,293). In the Nurses' Health Study, 59,337 postmenopausal women were followed to provide 337,854 person-years of follow-up. The age-adjusted relative risk of major CAD in current estrogen users was 0.60 when compared with women who never used estrogen. The relative risk for women who used a combination of estrogen and progesterone was 0.39. Estrogen use alone or combined estrogen and progesterone was not found to be associated with stroke (294).

In the Leisure World study, estrogen users with previous myocardial infarction, stroke, or hypertension were found to have a 50% decrease in risk of death from subsequent stroke or myocardial infarction (146). This was also reinforced by the Lipids Research Clinics study, in which there was an 85% reduction cardiovascular risk in estrogen users with previous cardiovascular disease, especially in women with severe disease (48).

Estrogen has direct and indirect effects on the cardiovascular system. Estrogen increases the plasma enzyme hepatic lipase, which catalyzes the hydrolysis of phospholipase and irreversibly degrades lipoproteins (316). In the Heart and Estrogen/Progestin Replacement Study (HERS), postmenopausal estrogen use was associated with an 11% reduction in low-density lipoproteins (LDLs) and a 10% increase in high-density lipoproteins (HDLs) when compared with a placebo group (155). As an antioxidant, it elevates nitric oxide levels and directly reduces vascular wall lipid uptake (261). It also acts as a calcium antagonist, causing vasodilation (328). Other metabolic effects of estrogen include a reduction in fasting glucose and fasting insulin levels (50). However, ERT has been found to increase triglyceride levels. In general, alteration in lipid profile is thought to contribute to 25% of the total cardioprotective effect of estrogen (48).

In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (339), a randomized, controlled trial, estradiol combined with medroxyprogesterone was associated with less favorable changes in HDL than estradiol alone or estradiol combined with micronized progesterone. Observational trials show no difference in cardiovascular risk in estrogen alone versus combined estrogen and progesterone therapy.

Although observational and epidemiologic studies support a significant cardioprotective effect of ERT, the HERS (155) was the first randomized, double-blind, placebo-controlled trial that examined estrogen and progesterone use in secondary CAD prevention. A total of 2,763 women less than 80 years old with CAD were randomized to placebo or a combination regimen of continuous estrogen and progesterone. The subjects were followed for 4.1 years. The investigators reported a 50% increase in coronary heart disease events within the first year of hormone use but a significant decrease in risk in years 4 and 5 (RH 0.67). Overall, there was no difference in CAD events (RH 0.99). They concluded that oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CAD events in postmenopausal women with established coronary disease. However, they suggested that continuation of treatment in women already receiving ERT might provide protection against CAD events after several years of therapy. Although the results of this trial raise some concerns, clinicians should consider all evidence available when assessing individual patient needs.

Effects of Estrogen on the Lower Urinary Tract

The urethra and vagina are embryologically derived structures that contain estrogen receptors (158). In the menopausal state, there is a decrease in mitotic activity of vaginal and urethral mucosal epithelium, a decrease in exfoliation of surface cells, a decrease in tissue vascularity, and thinning of the mucosal layer. These changes cause vaginal dryness, dyspareunia, and atrophic vaginitis and urethritis (8). ERT causes hypertrophy and thickening of the urethral mucosa with engorgement of blood vessels in the submucosal tissue, thus increasing the efficiency of mucosal closure (319). Vaginal estrogen may increase the sensitivity of α-adrenergic receptors in the urethral musculature and thus may improve genuine stress incontinence and the urethral response to α-adrenergic medication (320). However, in a study of 83 hypoestrogenic, incontinent women, 3 months of cyclic oral HRT had no effect on clinical or quality-of-life variables associated with urinary incontinence. No significant changes in incontinent episodes, diurnal or nocturnal voluntary micturition, or fluid loss was noted (100).

Local estrogen therapy can occasionally improve the irritative symptoms of the urethral syndrome and may prevent urinary tract infections by restoring vaginal pH to

premenopausal levels, which reestablishes the normal vaginal flora (242). It has also been used in the local treatment of urethral caruncles (250). To obtain the effect on the urethra and vagina, estrogens are best administered vaginally at a dosage of half an applicator (2 g or its equivalent) every other day, with that dosage reduced by half after a response occurs. Systemic absorption does occur with intravaginal therapy and, though small, may warrant concomitant use of progesterone.

Effect of Estrogen on Cognitive Function

Estrogen promotes the growth and survival of cholinergic neurons and could decrease cerebral amyloid deposition, both of which may delay or prevent Alzheimer's disease. In a longitudinal study of aging and health in a New York City community, 1,124 older women who were initially free of Alzheimer's disease, Parkinson's disease, and stroke were assessed cognitively and followed for 1 to 5 years. In the group of women who were current or past users of ERT (12.5%), the age of onset of Alzheimer's disease was significantly later, and the risk of disease was 60% lower. Duration of use corresponded with greater risk reduction. Other studies report a risk reduction of 60% to an increase of 10%. However, these are uncontrolled studies with small sample sizes and short duration of follow-up (305).

In controlled studies, estrogen maintains short- and long-term memory. Its antioxidant nature is partially responsible for its neuroprotective actions. The effect of improved glucose transport into the brain may improve cerebral blood flow and explain acute memory enhancement (273).

Effect of Estrogen on Colon Cancer

Colon cancer is the fourth most common cancer and is the second leading cause of death in the United States (34). Meta-analysis of case control and prospective studies has shown a 20% reduction in the risk of colon cancer and a 19% reduction in the risk of rectal cancer in postmenopausal women who reported any use of ERT regardless of duration of use. The differences in health and socioeconomic factors, including frequency of medical visits between estrogen users and nonusers in these studies, suggest that women who choose to take postmenopausal hormones are characteristically different (139).

The postulated mechanism of action is related to the significant decrease in bile acid synthesis in women on ERT. Secondary bile acids are believed to initiate or promote malignant change in colonic epithelium (99). Estrogen receptors are found in normal colonic mucosa (208). Estrogen is thought to have a direct effect on the mucosa and act as a tumor suppressor (208). It has also been shown to decrease levels of insulin-like growth factor–1, which is a cell mitogen (51). Further studies are needed to better define the relationship between colon cancer and estrogen therapy.

Effect of Estrogen on Gynecologic Malignancy

Both endometrial hyperplasia and endometrial adenocarcinoma have been associated with unopposed estrogen therapy. Postmenopausal estrogen therapy is associated with a threefold to fourfold increase in the relative risk of endometrial cancer. With 5 to 10 more years of exposure, the increase is about tenfold. The incidence of endometrial carcinoma in patients who receive both estrogen and progesterone is significantly lower than in those receiving estrogen alone (90). In the PEPI trial, 875 postmenopausal women were randomized to receive estrogen alone, estrogen plus progesterone, or placebo. Endometrial histologic findings were examined. Women receiving placebo or estrogen plus progesterone exhibited a 1% incidence of atypical endometrial hyperplasia, compared with a 34% incidence in women who received estrogen alone (138). Therefore progestin administration usually is considered mandatory in women with an intact uterus (23,134). Side effects associated with progestational therapy include weight gain, fluid retention, breast tenderness, and depression. Progesterones inhibit growth of endometrial cells, decrease the number of cytoplasmic estrogen receptors, and counteract the effects of estrogen on the endometrial lining.

Although it has been shown that premenopausal progestins in the form of oral contraception decrease the incidence of ovarian cancer, the effect of postmenopausal HRT on the risk of ovarian cancer is not clear. A recent meta-analysis showed that HRT was associated

with an increased risk of epithelial ovarian carcinoma, especially when used for more than 10 years (119).

Effect of Estrogen on Breast Cancer

There is a 1 in 9 lifetime risk of developing breast cancer in the United States. The relationship between ERT and breast cancer remains unclear. Results from the Nurses' Health Study suggest that the risk depends on age and duration of exposure. In women receiving hormones for more than 5 years, increasing age was correlated with increasing breast cancer risk. In addition, longer duration of use was associated with increased relative risk (66,67). This study has been criticized for biases between the study groups. Meta-analysis continues to yield conflicting results. Three of six meta-analyses showed no overall effect, no dose-related effect, and no duration of use effect (17,65,91,135,279,298). Some studies suggest that long-term use of combined estrogen and progesterone therapy is associated with decreased risk of breast cancer. The relationship of HRT to histologic types of breast cancer is also unclear. An observational study of 37,000 women reported an association between HRT use with an increased risk for invasive breast cancer that had favorable histologic characteristics (118).

Similarly, the results of studies conducted to assess the effects of progesterone on breast cancer are conflicting and warrant further evaluation. In a recent cohort study of 46,355 postmenopausal women, 2,082 cases of breast cancer were identified. Increases in risk with regimens of estrogen only and estrogen–progestin combination were restricted to use within the previous 4 years. The investigators also reported a slight increase in breast cancer risk with the estrogen–progestin regimen beyond that associated with estrogen alone (66). Despite these findings, the protective effects of progesterone against estrogen-induced endometrial neoplasia cannot be discounted.

Dosage and Route of Administration

Women who decide to begin HRT should undergo annual physical examination, including breast and pelvic examinations. Routine assessment of blood pressure, Pap tests, lipid profile, and mammography should be performed. For perimenopausal women (45 to 50 years), it may difficult to determine whether menopause has actually occurred. Women with FSH levels greater than 40 mIU/mL can be started on HRT (291).

The generally effective daily dosage of oral conjugated estrogens is 0.625 to 1.25 mg. Equivalent dosages of other estrogens (as compared with 0.625 mg conjugated estrogen) are 1 mg oral micronized estradiol, 0.75 mg oral estropipate, and 0.05 mg per day transdermal estradiol (8). The lowest dosage that relieves symptoms and affords cardiovascular and bone protection should be used. Although there is no evidence that one form of estrogen is superior to another, most studies addressing the protective effects of ERT are based on the use of 0.625 mg oral conjugated estrogens. Whereas oral therapy is associated with immediate impact on the lipoprotein profile, transdermal administration is associated with changes in the lipoprotein profile within 6 months. The methods of administration of estrogen in current use are shown in Fig. 38.10 .

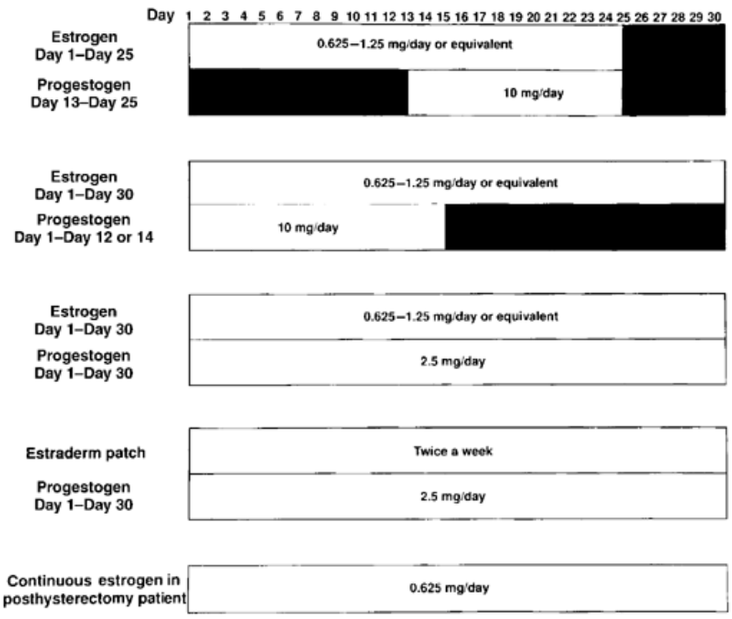

FIGURE 38.10. Diagram of estrogen replacement therapeutic plans available.

In women with an intact uterus, it is necessary to add a progestin to the estrogen to prevent endometrial neoplasia (339). With cyclic hormone therapy (5 to 10 mg medroxyprogesterone acetate for 12 to 14 days of each month), withdrawal bleeding is more common but more predictable than with continuous treatment (2.5 mg medroxyprogesterone acetate daily). Continuous combined estrogen and progesterone treatment produces a thin, atrophic endometrium, which can be associated with amenorrhea in up to 75% of women after 1 year of use (8).

In women who do not have a uterus, the addition of a progestin to ERT affords no additional advantage.

Risk Factors

Thromboembolic Disease

Recent studies have reported a twofold to fourfold increase in the risk of venous thromboembolism associated with ERT (74,137,141,163). This is thought to be related to

altered hepatic production or metabolism of coagulation factors, causing elevation of factor VII (209,220) and protein C (220) and a reduction in fibrinogen and plasminogen activator inhibitor type 1 (173). In contrast, some studies suggest that estrogen increases fibrinolytic activity.

Observational studies quote a 1 to 2 per 10,000 incidence of thromboembolic events per year in low-risk HRT users (74,137,141,163). Because the baseline risk of venous thromboembolism is low in users and nonusers, the increased risk associated with HRT must be weighed against benefits for the individual patient. Risk factors such as family history of venous thrombosis, gross obesity, and a previous episode of thromboembolism associated with immobilization should be considered (8).

Endometrial Hyperplasia and Endometrial Cancer

Endometrial hyperplasia and cancer are estrogen-dependent tumors. ERT use in women with previously diagnosed endometrial cancer should be considered carefully. Although patients with stage I adenocarcinoma of the endometrium can be treated with estrogen without fear of recurrence, data on the effect of estrogen on more advanced endometrial cancer are not conclusive. Because progestational agents have a protective effect on the endometrium, combination therapy seems indicated whenever estrogens are used. An undetected estrogen-dependent tumor may become apparent earlier with use of ERT.

Breast Cancer

Regarding estrogen use in patients with a diagnosis of breast cancer, the literature is controversial. There is concern that estrogen may stimulate residual cancer cells to proliferate. No definitive studies show the effect of estrogen on breast cancer recurrence or survival. Breast cancer survivors should undergo extensive counseling from the oncologist when considering HRT. Close surveillance is recommended in breast cancer survivors who choose ERT. In women with risk factors for breast cancer, the data remain inconclusive.

Hepatobiliary Disease

Use of ERT in women with liver or gallbladder disease and familial hyperlipidemias (elevated triglycerides) may increase the risk of gallstone formation. In the HERS, gallbladder disease was significantly higher in the hormone-treated group of women with coronary heart disease (155).

Alternative Therapy

Alternative therapies to relieve vasomotor symptoms include clonidine hydrochloride, phenobarbital, ergotamine, and belladonna alkaloids. However, none of these therapies afford the additional benefits associated with ERT. Some dietary sources of estrogen such as phytoestrogens, available from soy products, may reduce hot flashes by 45%, compared with an 80% to 90% reduction with ERT and a placebo response of 30% (5). They have been shown to decrease LDL cholesterol and triglyceride levels (13). Achieving therapeutic levels of phytoestrogens would require enormous consumption of soy products (145).

More recently, selective estrogen-receptor modulators (SERMs) have been proposed as an alternative to traditional HRT. These compounds bind with high affinity to estrogen receptors and activate them, eliciting specific agonist or antagonist activity depending on the tissues involved (196,290). Common types of SERMs currently available include triphenylethylenes (tamoxifen, clomiphene) and the benzothiophenes (raloxifene). In a large randomized trial, tamoxifen was shown to reduce the risk of breast cancer in high-risk women by 45% (105). However, tamoxifen use increases the risk of venous thromboembolism and uterine cancer (230). It has not been shown to affect osteoporosis or heart disease. A randomized trial of 7,000 women with osteoporosis showed that raloxifene decreased the incidence of breast cancer by 75% and the incidence of fractures by 50% without increasing the risk of endometrial cancer (71). It also improves LDL cholesterol levels without affecting triglyceride levels. The recommended daily dosage of raloxifene is 60 mg (8). Effects of SERMs on cognition and coronary heart disease remain unknown. Unfortunately, SERMs aggravate hot flashes. The FDA has approved the use of tamoxifen for primary prevention of breast cancer in high-risk women and for secondary prevention of breast cancer for up to 5 years. The FDA has approved raloxifene for preventing osteoporosis.

ENDOMETRIOSIS

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

Endometriosis is the presence and growth of the glands and stroma of the lining of the uterus in an aberrant or heterotopic location (315). The most common locations include the dependent portions of the pelvis, most often on the ovaries, the anterior and posterior cul-de-sac, the uterosacral ligaments, the broad ligaments, and the uterus (156). Extrapelvic endometriosis can involve the intestines, ureter, bladder, and lungs (215,221,325). Rarer sites include surgical scars, lymphatics, skin, spinal column, and nose.

Endometriosis is a benign but often progressive disease. It is an estrogen-dependent or estrogen-facilitated condition affecting up to 14% of premenopausal women (75,142). Treatment generally involves removing the ovarian source of estrogen.

Pathogenesis

Several theories have been developed to explain the histogenesis of endometriosis. The leading theories include retrograde menstruation with implantation and growth of

endometrial cells, metaplasia of celomic epithelium, hematogenous or lymphatic spread, and iatrogenic dissemination (162,228,263). Studies have demonstrated abnormalities in the cell-mediated immune system of patients with endometriosis, and a genetic predisposition with polygenic multifactorial inheritance pattern has been found. An investigation by Simpson and associates (280) demonstrated a sevenfold increase in the incidence of endometriosis in relatives of women with the disease. A higher incidence of endometriosis is observed in women with müllerian anomalies and uterine outflow obstruction. Endometriosis has been reported in men who have received treatment with estrogen for prostatic carcinoma and in postmenopausal women on ERT (238,266).

Prevalence

Endometriosis occurs in 3% to 10% of women of reproductive age and in 25% to 35% of infertile women (228). The typical age at which endometriosis is diagnosed is between 25 and 29 years. The peak incidence is between 20 and 40 years, and only 2% to 4% of all women needing laparoscopy for endometriosis are postmenopausal.

Symptoms and Signs

Approximately one-third of patients with endometriosis are asymptomatic. The most common symptoms are chronic pelvic pain and infertility. Chronic pelvic pain presents as dysmenorrhea, dyspareunia, lower abdominal pain, or low back pain. Some women with extensive endometriosis have little or no pain, whereas others with only minimal disease complain of severe pain. Infertility can result from tubal blockage by adhesions, ovulatory dysfunction, prostaglandins, disordered follicle growth, or chemical toxins produced by peritoneal macrophages. The uterus is most commonly retroverted and fixed. The ovaries may have blood-filled cysts called endometriomas. The uterosacral ligaments may be tender and nodular. Adnexal masses and parametrial thickening may be present. Cutaneous lesions may be present on the vagina, perineum, and umbilicus and within surgical scars (215).

Diagnosis

Laparoscopy is the optimal diagnostic method for endometriosis. Typical lesions have been described as red, black, white, or as having a “powderburn”-like appearance. Ultrasound, CT, and MRI are helpful only if ovarian enlargement or large masses are present. Colonoscopy, barium enema, and intravenous pyelography (IVP) are important diagnostic tests if the history and physical examination suggest advanced disease or extragenital involvement. Microscopically, endometriosis contains four major components: endometrial glands, endometrial stroma, fibrosis, and hemorrhage. Not all the components are identifiable in every case, and in postmenopausal women only hemorrhage may be present. Serum levels of cancer antigen 125 (CA-125) may be used as a chemical marker and noninvasive test for endometriosis. Serum concentration of CA-125 is elevated in most patients with advanced endometriosis (231). As a screening test, CA-125 lacks sensitivity and specificity. CA-125 may also be helpful as a marker of treatment response and of recurrence (101).

Treatment

Therapy for endometriosis is based on the patient's age, her future reproductive plans, the location and extent of disease, the patient's symptoms, and associated pelvic disorders.

Medical Treatment

Medical therapy is advised for most patients with mild to moderate disease (21). The ectopic endometrial tissue contains hormone receptors and is hormone responsive (183). Therefore the medical treatment of endometriosis consists of prolonged courses of hormone agents that suppress ovarian function or have a direct effect on endometriotic tissue. The medications used are oral contraceptives (estrogen–progesterone acetate), progestin (norethindrone, medroxyprogesterone acetate), androgens and their derivatives (danazol, gestrinone), and gonadotropin-releasing hormone agonists (leuprolide acetate, goserelin, nafarelin). Low-dose estrogen combination birth control pills produce amenorrhea by suppressing FSH and luteinizing hormone (LH). The usual dosage is one pill per day continuously for 6 to 12 months. Both oral and injectable medroxyprogesterone acetate, a progestational agent, have been effective in treating endometriosis by causing deciduation and atrophy of endometrial tissue (227). Side effects include weight gain, fluid retention, breakthrough bleeding, and depression. Danazol is a synthetic derivative of the androgen ethisterone. Dosages of 800 mg daily produce amenorrhea and inhibit ovulation. The standard length of treatment is 6 to 9 months. Adverse effects of danazol include fluid retention, migraine headaches, dizziness, fatigue, depression, oily skin, hirsutism, and deepening of voice. These side effects occur in up to 80% of women and have limited its widespread use. Gestrinone, an antiprogestational steroid, decreases FSH and LH secretion and is administered only twice a week. Side effects include androgenic and antiestrogenic sequelae. Chronic administration of gonadotropin-releasing hormone (GnRH) agonists (leuprolide and nafarelin) suppress gonadotropin secretion, producing a medical oophorectomy. They can be administered intramuscularly, subcutaneously, by vaginal pessary, or by intranasal absorption. Side effects of GnRH agonists are menopausal symptoms caused by hypoestrogenic state, including vaginal dryness, hot flushes, and a decrease in the density of trabecular bone. Recovery of

bone loss may take 6 months to 1 year after discontinuation of therapy (76). Long-term GnRH agonist use may cause osteoporosis (269). For this reason, therapy generally is limited to a single 6-month course. In response to these concerns, various hormonal add-back regimens (progestins or estrogens) have been combined with a GnRH analog. The rationale for this approach is that low levels of serum estradiol may promote normal bone metabolism while maintaining endometrial suppression (22). Preliminary studies demonstrate that these regimens appear to preserve the efficacy of GnRH analog therapy while overcoming the hypoestrogenic side effects (151,216,303).

Surgical Treatment

Definitive surgical therapy consists of hysterectomy with bilateral salpingo-oophorectomy (92,317). Conservative surgery is done in patients who want to retain fertility. This includes excision or destruction of implants, lysis of adhesions, excision of endometriomas, and sometimes an anterior uterine suspension. The use of presacral neurectomy to treat pelvic pain has proved effective for dysmenorrhea, but the effect on other pelvic pain, back pain, and dyspareunia is inconsistent. Conservative surgery can be accomplished by laparoscopy using cautery or laser, thereby reducing operating time and hospital stay and minimizing blood loss (227). Laparoscopic fulguration has limitations; ureteral injury can occur during fulguration of endometrial implants of the uterosacral ligaments.

Patients with severe disease may benefit from a 4- to 6-week preoperative course of GnRH agonists or danazol to reduce local vascularity. Postoperatively, hormonal intervention has been suggested to eliminate all endometriotic implants. ERT can be given after total abdominal hysterectomy and bilateral salpingo-oophorectomy; however, endometriosis can recur in 5% to 10% of cases (89).

Endometriosis of the Urinary Tract

Bladder

Approximately 1% of women with endometriosis have urinary tract involvement; the bladder is affected in approximately 85% of these women (85,123,170,205,274). Symptoms often closely mimic those of interstitial cystitis (suprapubic pain, frequency, urgency, and dysuria) (282). The classic finding of menstrual hematuria is present in less than 25% of cases (274). There should be a high index of suspicion for this entity in patients with a prior diagnosis of endometriosis who are referred for irritative voiding symptoms, especially if they are receiving HRT. Such therapy usually is safe in these patients, but it can reactivate previously dormant endometrial implants (131,167,180,260).

Cystoscopic findings are variable. No disease may be evident if the endometrial tissue is confined to the serosa of the bladder. Deeper lesions appear as bluish submucosal nodules that may ulcerate and bleed. These nodules usually are located behind the trigone or at the bladder dome. Disease foci may be solitary or multiple (123,221) and may almost disappear between menstrual periods. Malignant transformation of vesical endometriosis has been reported (4,312). Any lesions discovered at cystoscopy should be biopsied for histologic confirmation of the diagnosis. Treatment consists of initial hormonal therapy followed by partial cystectomy if necessary.

Ureter

Ureteral endometriosis commonly involves the lower third of the ureter and is bilateral in 15% of cases. Ureteral obstruction is most likely to occur when the cardinal and uterosacral ligaments are involved (85,123). More than 126 cases of ureteral endometriosis have been reported, with permanent renal damage in up to 30% (205). Two types of ureteral endometriosis have been described: extrinsic, in which extensive scarring and fibrosis caused by endometriotic implants lead to obstruction, and intrinsic, in which the ureteral wall is invaded by endometriotic tissue. The former is more common (170,205). Symptoms may include flank pain, dysuria, urgency, and hematuria (123,164).

Endometriosis must be considered in the differential diagnosis of unexplained ureteral obstruction occurring in any woman past the age of menarche. If there is any clinical evidence of ureteral obstruction, ultrasound or IVP should be performed (Fig. 38.11 and Fig. 38.12). A few cases of endometriosis of the kidney have been reported (123,164).

All occurred in women between 22 and 49 years of age, and the most common symptoms were lumbar pain and hematuria. The correct diagnosis was made only after surgical removal and histologic study.

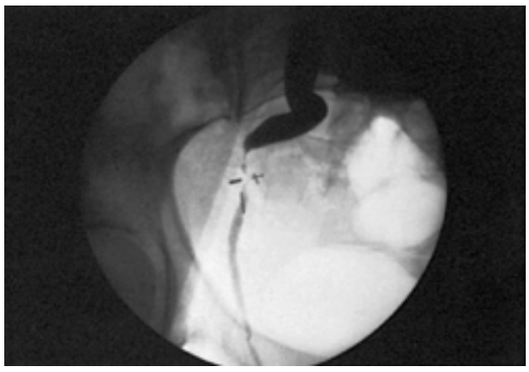

FIGURE 38.11. Antegrade pyelogram demonstrating a fixed site of ureteral narrowing in a 42-year-old woman 2 years after hysterectomy. The surgical clips and the prior hysterectomy led to a tentative preoperative diagnosis of iatrogenic ureteral fibrosis. Histopathologic analysis of the affected ureter obtained at the time of ureteral reimplantation demonstrated secretory and proliferative endometrial tissue of the invasive variety, with extensive local scarring.

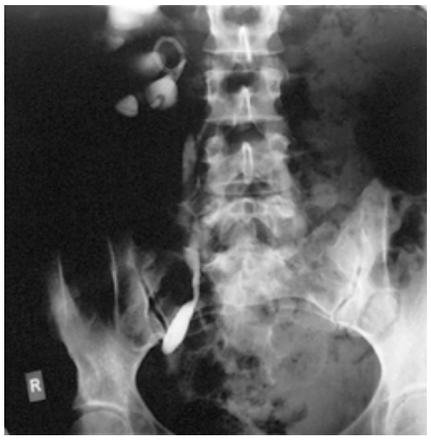

FIGURE 38.12. Typical appearance of a ureter affected by an endometrial implant, proven by tissue examination after excision.

Ureteral endometriosis has been successfully treated by medical means using danazol, GnRH agonists, progestins, and estrogen–progestin combinations (117,121,253,254). However, recurrence of ureteral obstruction after cessation of medical management is common. If medical therapy is attempted, close surveillance of renal function is mandatory. The standard therapy of ureteral endometriosis is surgical and includes ureterolysis or segmental ureteral resection with ureteroneocystostomy and castration. Renal involvement usually is treated with nephrectomy.

Tamoxifen and Endometrial Disease

Tamoxifen is a synthetic nonsteroidal estrogen antagonist and agonist that is widely used as adjuvant therapy for breast cancer in postmenopausal women. While acting as an estrogen antagonist in the breast, it has estrogen agonist activity in other tissues, including the endometrium (133). Consequently, patients who receive tamoxifen therapy are at greater risk for endometrial abnormalities. Most of these abnormalities are benign, including endometriosis (218), adenomyosis (64), and endometrial polyps (226). However, there is also a twofold to threefold higher risk of developing endometrial carcinoma (73). Any vaginal bleeding in women treated with tamoxifen should be investigated promptly and thoroughly.

RETAINED OVARY: THE OVARIAN REMNANT SYNDROME

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

The ovarian remnant syndrome occurs in women who have undergone a bilateral salpingo-oophorectomy in whom ovarian tissue remains (297,322). Usually, these patients also have had a hysterectomy. The ovarian remnant becomes a cause of chronic pelvic pain. Because of the extensive prior surgery, patients with this kind of chronic pelvic pain syndrome often are considered to suffer from “nongynecologic” disease (61). The ovarian remnant may result in ureteral obstruction, the most common urinary tract involvement, but it also can induce bowel obstruction and may be associated with painful pelvic masses and, on occasion, urinary retention (27,198,237). Generally speaking, laparotomy is needed to remove all ovarian tissue. That tissue may be extremely difficult to identify (237). More recently, laparoscopic surgical techniques have been used to treat ureteral obstruction related to residual ovarian tissue.

Diagnosis

Peripheral estrogen levels greater than expected for surgically menopausal women, after complete cessation of HRT, suggests the diagnosis of retained or residual ovarian tissue. In addition, premenopausal levels of LH and FSH in women after bilateral salpingo-oophorectomy suggest functioning ovarian tissue. Clomiphene citrate administration has been used before surgical exploration to stimulate the retained residual ovarian tissue to facilitate ultrasonic localization and complete surgical removal (177). Ovarian function may reactivate endometrial implants in patients with that problem before total abdominal hysterectomy and bilateral salpingo-oophorectomy (237).

POSTMENOPAUSAL BLEEDING

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

Postmenopausal bleeding is bleeding that occurs after 1 year of amenorrhea without HRT. Bleeding that accompanies cyclical withdrawal bleeding from progestins is not considered postmenopausal bleeding. However, new onset of bleeding after established amenorrhea or outside cyclic withdrawal bleeding while using HRT is considered abnormal and warrants assessment.

Etiology

The most important cause of bleeding is endometrial carcinoma or complex endometrial hyperplasia with atypia. It is estimated that 5% to 10% of unexplained postmenopausal bleeding is related to these serious disorders. Therefore 90% to 95% of bleeding results from benign causes such as endometrial atrophy, endometrial polyps, or simple endometrial

hyperplasia (16). However, 10% to 20% of cases involving endometrial neoplasia result from malignancy. Other sources of bleeding must be considered. Women may report bleeding that originates from various vulvar lesions, vaginal cancer, vaginal foreign bodies, cervicitis, cervical polyps, cervical ulcers, or cervical cancer. In addition, urinary tract bleeding may be mistaken for postmenopausal uterine bleeding.

Clinical Evaluation and Diagnosis

The major diagnostic consideration is to ensure that the origin of bleeding is determined. Pelvic examination, Pap smear, endocervical curettage and colposcopic biopsy, endometrial biopsy, and transvaginal sonography generally reveal a genital cause of bleeding. Test for occult blood in the stool rules out a gastrointestinal source of bleeding. Fractional curettage may be necessary to distinguish between cervical and uterine lesions. Endometrial biopsy is a crucial component of postmenopausal bleeding assessment. It is an office procedure in which a sample of endometrial tissue or cells is obtained by brushing, scraping, washing, or vacuum. The sensitivity for detecting pathologic tissue ranges from 88% to 97%, which is comparable that of to dilation and curettage (299). However, a negative endometrial biopsy is not necessarily diagnostic, and repeat sampling may be necessary, depending on the clinical situation. Histologic examination of the sampled endometrium determines the course of treatment. In some patients, dilation and curettage may be necessary to obtain an adequate histologic sample, especially in patients with cervical stenosis.

Transvaginal ultrasonography is an accurate method for assessing endometrial thickness. There is a strong correlation between increased endometrial thickness and pathologic involvement. An endometrial stripe of 4 to 6 mm is considered the threshold for an increased risk of serious endometrial disease. Suspected endometrial neoplasm detected by ultrasound must be further assessed by histologic sampling (182). The sensitivity of transvaginal ultrasonography ranges from 81% to 100%, and the specificity ranges from 61% to 100%.

In sonohysterography, the endometrial cavity is distended with 10 mL sterile saline to detect focal areas of endometrial thickening. Submucous fibroids and endometrial polyps can also be detected by this technique. Endometrial sampling is necessary in cases of increased endometrial thickening. Areas of endometrial hyperplasia and cancer often are found in endometrial polyps.

Hysteroscopy may be performed with a rigid scope using a fluid distending medium and heavy sedation. It is used for diagnosis and therapeutic procedures. Office hysteroscopy involves a flexible fiberoptic cable with a carbon dioxide distending medium. Flexible hysteroscopy allows office visualization of the endometrial lining. It is used for diagnosis and simple biopsies, directed biopsies, and polypectomy.

Cancer of the Endometrium

Adenocarcinoma of the endometrium is the most common gynecologic malignancy in the United States, accounting for 34,000 cases of invasive endometrial cancer each year. In the United States, 2% to 3% of women develop cancer of the endometrium (11). It is found primarily in postmenopausal women. The peak age incidence is seen in women in their late fifties and early sixties. The diagnosis is made by histologic evidence. The most common symptom is bleeding.

Risk factors for the low-risk subtype are related to an increase in circulating estrogens: obesity, chronic anovulation, menstrual irregularities, nulliparity, early menarche (younger than 12 years), late menopause (older than 52 years), estrogen-secreting ovarian tumors, unopposed ERT, and tamoxifen use (20). Diabetes, hypertension, and previous pelvic irradiation are also considered risk factors (39,321). Smoking and the use of oral contraceptives decrease the risk (11). Carcinoma of the endometrium is also associated with hereditary nonpolyposis colorectal cancer (HNPCC) (47). Onset of endometrial cancer in this group occurs an average of 15 years earlier than sporadic cases. Endometrial screening is recommended for patients with HNPCC (186).

Treatment

Patients with adenomatous hyperplasia without atypia can be treated with medroxyprogesterone acetate 10 mg daily for 12 to 14 days each month. A follow-up biopsy in 3 months is recommended to confirm reversal of pathologic tissue changes (257). Endometrial hyperplasia with atypia is managed surgically by a total abdominal hysterectomy and bilateral salpingo-oophorectomy because 25% of patients with atypical hyperplasia found on endometrial sampling are found to have endometrial adenocarcinoma on surgical specimen. Postoperative irradiation is given depending on surgical stage. Because postmenopausal bleeding occurs early in the natural history of estrogen-related endometrial adenocarcinoma, the diagnosis often is made at an early stage of disease.

THE ADNEXAL MASS

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

Anatomically, the adnexa encompasses the region within the pelvis that includes the ovaries, fallopian tubes, round ligaments, and structures arising from associated embryologic rests. The spectrum of disease arising from the adnexa is diverse. The annual hospitalization rate for ovarian neoplasms in the United States ranges from 160,000 to 289,000

women (72,127,331). It is estimated that 5% to 10% of women in the United States will undergo a surgical procedure for suspected ovarian neoplasm in their lifetime (219). In women with no family history of ovarian cancer, the incidence of ovarian malignancy is 1.4 per 100,000 women less than 40 years old and 45 per 100,000 more than 60 years (144).

Etiology

Adnexal masses may be physiologic, infectious, nonneoplastic, or neoplastic. They may originate from any component of the adnexa. Pedunculated uterine fibroids may mimic the clinical presentation of adnexal masses. The most common benign ovarian neoplasms are benign cystic teratomas and serous cystadenomas. The most common malignant ovarian neoplasm is epithelial carcinoma. Age is the most important predictor of malignancy (175). There is a twelvefold increase in risk of ovarian carcinoma from age 20 to 29 years to 60 to 69 years (175). During reproductive years, the most common ovarian mass is the functional cyst (Fig. 38.13). Endometrioma should be considered in the premenopausal woman. In younger patients with a solid adnexal mass, the common malignant neoplasm is the ovarian germ cell tumor.

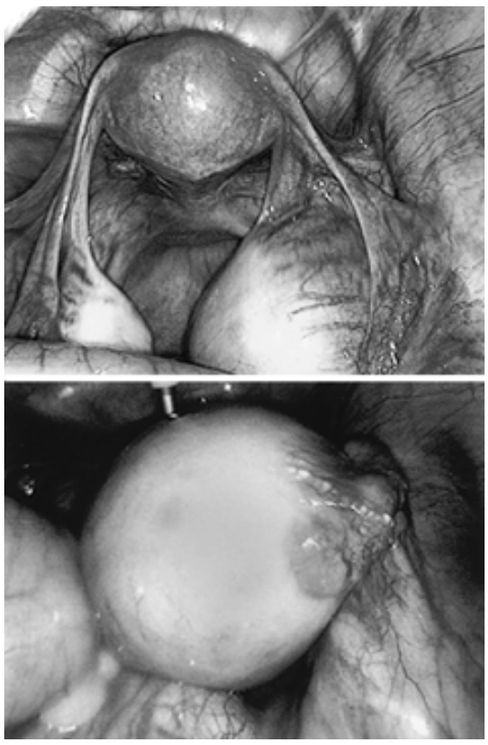

FIGURE 38.13. Large right cystic teratoma. Normal left ovary, bilateral fallopian tubes, uterus, and cul de sac are seen.

Clinical Presentation and Evaluation

The initial symptom associated with an adnexal mass may be acute onset of lower abdominal pain, which may be related to torsion of the mass at its stalk or rupture of a cystic mass with release of fluid or blood into the peritoneal cavity. The most common and important differential diagnosis is appendicitis. Chronic, intermittent pain may reflect the twisting and untwisting motion of the mass. Other symptoms include midcycle pain (Mittelschmerz pain), dysmenorrhea, and menstrual disturbances. Clinical symptoms often reflect mass compression on local pelvic organs and include nausea and vomiting, sensation of abdominal bloating, dyspepsia, early satiety, constipation and change in stool caliber, and urinary retention. Most symptoms are nonspecific.

In addition to a complete history, physical examination is important in assessing characteristics of the mass and the presence of accompanying adenopathy. Malignancy may be suspected in the presence of a palpable mass, generalized abdominal discomfort, and ascites. Endometriotic mass may be associated with a retroverted uterus, cul de sac nodularity, uterosacral shortening, and tenderness. Asymptomatic masses may be detected on routine pelvic examination.

In reproductive-age women, a serum pregnancy test is necessary to rule out an ectopic pregnancy, especially in the acute situation.

Transabdominal and transvaginal ultrasonography has become a useful diagnostic tool for assessing adnexal masses. An ovarian cause can be determined easily in most cases. Ovarian size and shape can be visualized. The normal premenopausal ovary measures 3.5 × 2 × 1.5 cm. The normal postmenopausal ovary measures 1.5 × 0.7 × 0.5 cm 2 to 5 years after menopause (147). Wall structure, septations, echogenicity, and shadowing of the mass are considered to predict malignancy (86). Current ultrasonography techniques have demonstrated improved sensitivity, specificity, positive predictive value, and negative predictive value for diagnosing adnexal malignancy. Use of color-flow Doppler to determine malignancy is controversial (41,265).

White blood cell count may indicate a tuboovarian mass secondary to pelvic inflammatory disease. Serum CA-125 level in the postmenopausal woman has improved sensitivity and specificity for predicting malignancy related to epithelial carcinomas (104). In the premenopausal woman, a mildly elevated CA-125 level is found in a variety of benign conditions. In the younger patient with a solid adnexal

mass, elevated serum ß-human chorionic gonadotropin (ß-hCG) and α-fetoprotein suggest a malignant germ cell tumor (10).

When malignancy cannot be ruled out or when symptoms resist conservative management, laparoscopic assessment of the adnexal mass may be warranted. The patient's entire clinical picture must be considered. Laparoscopic diagnosis of adnexal masses is reliable and safe, allowing immediate and adequate surgical treatment (52).

Management

In the premenopausal woman, an asymptomatic cystic mass less than 10 cm may be initially managed by observation (19); 70% of these masses resolve spontaneously (289), although the recurrence rate is unknown. Follow-up physical examination and repeat ultrasound after the next menstrual cycle should be done. In a large multicenter trial, the risk of malignancy in this group has been reported to be essentially nonexistent (268). With the persistence of findings or a change in ultrasound findings toward a more complex mass, surgical assessment is indicated. A cystectomy is preferred, but an oophorectomy may be necessary in the presence of benign disease. For women in their reproductive years, every attempt should be made to preserve ovarian function and fertility potential in the presence of benign conditions. Cyst aspiration is not recommended because 66% of cyst aspirates are read as benign when they are actually malignant (311). If a solid mass or other findings suggestive of malignancy are present, surgery is indicated.

In postmenopausal women, most adnexal masses warrant surgical assessment to determine the presence of a malignancy. The exception is the asymptomatic postmenopausal woman with a simple, unilocular cyst measuring less than 5 cm with a normal CA-125 level. In this situation, conservative management may be offered with close follow-up. When the physical examination, ultrasound findings, and serum markers suggest malignancy, more than 75% of postmenopausal women have ovarian carcinoma. When all modalities suggest a benign process, 5% of postmenopausal women have ovarian carcinoma (256).

The standard surgical approach has been laparotomy for cystectomy or oophorectomy. However, laparoscopic assessment of ovarian masses, including laparoscopic cystectomy and oophorectomy, has become acceptable. Laparoscopy allows inspection of the mass, pelvis, and abdominal cavity. This approach is indicated if suspicion of malignancy is low or questionable. However, even in this scenario, patients should be advised of possible conversion of a laparoscopic procedure to a laparotomy if probable malignancy is found and confirmed by pathologic frozen section evaluation of tissue biopsy. In the presence of a malignancy, the appropriate surgical management is a staging laparotomy and debulking of tumor burden. Because of the proximity of the adnexa to the urinary tract, care must be taken to avoid inadvertent ureteric injury. If malignancy is highly suspected preoperatively, the surgeon should proceed directly to laparotomy. Currently, the prognostic implication of intraoperative rupture of a malignant ovarian cyst has been undetermined.

CARCINOMA OF THE CERVIX

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

A dramatic increase in the early diagnosis and treatment of cervical cancer and subsequent vast improvement in survival in the United States in the last four decades are attributable mostly to the widespread use of screening cervical cytology and aggressive management of cervical intraepithelial neoplasm. However, cervical cancer continues to be a leading cause of death in underdeveloped countries. It is the third most common genital malignancy after endometrial and ovarian cancer. In 1993 the American Cancer Society estimated that there will be approximately 16,000 new cases of invasive cervical cancer and 5,000 deaths from cervical cancer each year in the United States.

Epidemiology and Etiology

Cervical cancer tends to occur in women in their forties to sixties, with a median age of 54 years. Various epidemiologic factors are associated with cervical cancer, such as sexual intercourse at an early age, multiple sexual partners, multiparity, low socioeconomic status, cigarette smoking, and sexually transmitted diseases such as genital herpes and condylomata acuminata. The rising incidence of cervical cancer in younger women is attributed to the increased incidence of cervical intraepithelial neoplasia, perhaps associated with genital viral infections. Eighty-five percent of cervical cancers are squamous cell, and 10% to 15% are adenocarcinomas. Very rare adenosquamous carcinomas also occur.

Clinical Symptoms

Cervical carcinoma usually is asymptomatic in the early stages. The most common symptoms are vaginal discharge, irregular vaginal bleeding, and postcoital or postmenopausal bleeding. Advanced cervical cancer may present with backache, hematuria, ureteric obstruction, urinary and rectal fistulae, and rectal bleeding. Cervical cancers may be characterized by gross appearance as exophytic or endophytic. Exophytic lesions protrude from the cervix and can be visualized easily. Late detection of endophytic lesions may contribute to a poor prognosis. These cancers may not be apparent on cervical cytopathologic specimens.

Staging of Cervical Cancer

The staging of cervical cancer is based on a clinical examination. The international classification of cancer of the cervix is as follows:

Stage 0	Carcinoma *in situ,* intraepithelial carcinoma.
Stage I	Carcinoma strictly confined to cervix.
Stage IA	Preclinical carcinomas of the cervix, that is, those diagnosed only by microscopy.
Stage IA1	Minimal microscopically evident stromal invasion.
Stage IA2	Lesions detected microscopically that can be measured. The upper limit of the measurement should not show a depth of invasion of more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates, and a second dimension, the horizontal spread, must not exceed 7 mm. Larger lesions should be staged as IB.
Stage IB	Lesions of greater dimension than in stage IA2, whether seen clinically or not. Preformed space involvement should not alter the staging but should be specifically recorded to determine whether it should affect treatment decisions in the future.
Stage II	Involvement of the vagina but not the lower third, or infiltration of the parametria but not out to the sidewall.
Stage IIA	Involvement of the vagina but no evidence of parametrial involvement.
Stage IIB	Infiltration of the parametria but not out to the sidewall.
Stage III	Involvement of the lower third of the vagina or extension to the pelvic sidewall. All cases with hydronephrosis or a nonfunctioning kidney should be included unless they are known to be attributable to other causes.
Stage IIIA	Involvement of the lower third of the vagina but not out to the pelvic sidewall if the parametria are involved.
Stage IIIB	Extension onto the pelvic sidewall or hydronephrosis or nonfunctional kidney.
Stage IV	Extension outside the reproductive tract.
Stage IVA	Involvement of the mucosa of the bladder or rectum.
Stage IVB	Distant metastasis or disease outside the true pelvis.

Pretreatment Evaluation of Cervical Cancer

Pap smears may be “negative” in 30% of women with invasive cancers. Biopsy of any suspicious cervical lesion is essential even if the smear is normal. All patients with cervical cancer should undergo a thorough history and physical examination. Other diagnostic tests to be done include chest radiograph, colposcopy, cystoscopy, proctosigmoidoscopy, IVP or CT scan, or barium enema.

Treatment

Microinvasive carcinoma with an invasion depth of 3 mm can be treated satisfactorily with cone biopsy if the margins of the core are free of turnover. Frequent follow-up is mandatory.

For microinvasive carcinoma 3 to 5 mm deep, radical hysterectomy with pelvic lymphadenectomy is recommended.

For invasive cervical cancer of stage IB and IIA, radical hysterectomy with pelvic lymphadenectomy or pelvic irradiation is equally effective. The treatment of stage Ill and IV cervical cancer is palliative.

COMPLICATIONS OF SURGERY FOR STRESS INCONTINENCE

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

Treatment Failure

Reported failure rates for stress incontinence surgery at 5 years or more are high (62,232,309). The success rates for slings are somewhat better than for other procedures (32,53,217). Late outcomes for needle suspensions and retropubic suspensions are roughly equal (62,309). When outcomes are studied long after a procedure, the data often are gathered by telephone or mailed questionnaire and not direct clinical assessment. The accuracy of these data with respect to a precise clinical and urodynamic diagnosis has not been determined. In studies in which tentative diagnoses established by responses to questions in standardized survey instruments were compared with a diagnosis arrived at as a result of a rigorous clinical and urodynamic assessment, poor agreement has been found (12,172). A person who reports wetting might be considered to have experienced treatment failure when that is not the case. The symptom “occasionally wet” does not differentiate those who have a recurrence of the original problem treated (e.g., intrinsic sphincter dysfunction or urethral hypermobility) from a new problem. Even more problematic is the fact that often we do not know precisely what original problem was treated other than presumed stress incontinence, which is clearly not one condition but a complex of interrelated conditions. Some degree of incontinence is reported by 15% to 30% of women in very large population surveys. Thus some incidence of incontinence in a study population obviously exists, and this should be considered in assessing the responses given by treated women to survey questions (187). That has not been done, and by inference the normal population has been considered “never wet.”

Conclusions about the value of any procedure drawn from late outcome data probably are invalid because it is usually not clear what conditions existed before the operation and what condition caused the positive response to the survey question. The mere fact that incontinence is a problem after surgery does not by itself establish failure of the operative procedure. Incontinence, even when specifically characterized as “stress, urge, or mixed,” is not equivalent to a diagnosis. Thus failure rates, although interesting, have no particular relevance to selection or nonselection of a given operation in a particular patient. In addition to problems with questionnaire-based diagnoses, there is a curious lack of agreement between patient responses to questions about incontinence and responses to the question, “Are you satisfied with the treatment that was provided to you for the condition stress incontinence?” Even though “incontinence” rates range from 12% to 53%, “satisfied” rates are much higher (217,309). Perhaps the women understand something the survey instrument does not measure.

Voiding Dysfunction

Retention

After sling procedures, retropubic suspensions, and occasionally after needle suspension, short- or long-term complete or partial urinary retention may occur. Mean hospital stays less than 24 hours are not compatible with resumption of normal voiding in many patients after urethral suspension, especially if the urethral procedure is combined with repair of genital prolapse or a hysterectomy (217). Kursh (179) reported that 81% of patients who underwent needle suspension were unable to void completely at a mean interval of 22 days after the procedure. Korda and co-workers (176) reported a mean period of catheter drainage of 10 days after a retropubic suspension, and 25% of patients still had difficulty with bladder emptying beyond that point. Morgan and co-workers (217) noted that a mean 8.4 days of intermittent catheterization was needed after a sling procedure. The prevalence of prolonged retention after sling procedures or other suspensions generally ranges from 3% to 10% (32,197,244,324). Some workers have reported higher rates after polytetrafluoroethylene sling procedures (327,340). Other workers have reported higher rates of partial and complete retention after some procedure, especially retropubic suspensions (116,343).

Treatment

There are few data on what constitutes an abnormal duration of retention. Spontaneous resumption of normal voiding as late as 10 weeks after a procedure is rare but does occur. Most authors suggest some kind of takedown procedure to relieve obstruction at or around 10 to 12 weeks, or even earlier in some cases. Foster and McGuire (109) reported a 65% success rate, or resumption of normal voiding without stress incontinence, after a urethral takedown procedure done late after the original suspension procedure. Nitti and colleagues (224) described a similar series in which 71% of patients subjected to urethrolysis and a repeat suspension resumed normal voiding. Since the latter report, most authors have not combined urethral mobilization procedures with a resuspension of the urethra. Thus Carr and Webster (54) reported resumption of normal voiding without recurrence of stress incontinence in 86% of patients subjected to a retropubic urethrolysis, 73% of those who had a vaginal approach, and 25% of those who had an infrapubic procedure. Brubaker (42), McLennan and Bent (193), Goldman and associates (132), Cross and associates (70), and Ghoniem and El-gamasy (125) all reported series in which a vaginal procedure designed to take down or modify a urethral suspension was done in an effort to restore normal voiding. None of these workers combined the procedure with a repeat urethral suspension. In general, the operative procedures that led to the takedown operation were not needle suspension procedures, and thus these patients may be different or have had a different operation than those described by Nitti and colleagues (224). Moreover, 8 to 35% of the patients in the more recent series failed to achieve normal voiding after a takedown operation. Thus a presumed obstructive process was not always relieved by an operation designed to undo the effects of a sling or suspension procedure. The imperfect outcome here may reflect a change in the type of operative procedure done for stress incontinence, a problem with detrusor function that was not recognized before the primary procedure or one that developed after that procedure, or a lack of efficacy of the procedure used to take down the suspension. From a review of the literature it is not clear which of these variables is the main cause of failure of a procedure done to undo the suspension. It does seem clear that a resuspension at the time of a takedown procedure is not needed, and the real problem seems to be related to achieving sufficient urethral mobility and function to permit resumption of normal voiding. Although most workers have settled on a transvaginal approach or rarely an infrapubic approach or abdominal approach, others have reported on a transurethral resection of the obstructive bladder neck in two planes (102). Gronbaek and associates (140) successfully used bladder neck incision at 4 and 8 o'clock. They noted that initial improvement could be followed by later deterioration, but overall they achieved a 76% success rate, which compares favorably with the results of “urethrolysis” described by most American centers. Late follow-up seems important in these cases, and a French study reported initial success in 80% that fell to 40% at 6 months, suggesting that rescarring and fixation can be a problem (258). In addition, there is no systematic study of the incidence of obstructive uropathy by operation, and there is no way to be sure that the same conditions are present in two groups of patients who are subjected to

different operations with different outcomes. None of these studies was prospective.

Uncontrolled Detrusor Contractility: Urge Incontinence

Some 12% to 65% of women with stress incontinence, where that diagnosis is made by clinical assessment or by video urodynamic testing, also have motor urge incontinence symptoms or an unstable contraction of the bladder on a cystometrogram (1,191). In the past, the diagnosis of motor urge incontinence was permissible only if an unstable bladder contraction was noted on a cystometrogram. That view is no longer tenable. As many as 50% to 60% of patients with motor urge incontinence (where urinary leakage is driven by an uncontrolled contraction of the detrusor that occurs suddenly, without warning) have a stable bladder during a cystometrogram. Urge incontinence is then a clinical diagnosis, not a urodynamic one (136). Where significant stress incontinence is objectively identified, operative therapy that cures the stress incontinence often is associated with resolution of motor urge incontinence symptoms (217). If an operation fails to cure the stress incontinence, motor urge incontinence often continues to be a problem. For example, in a 1989 study Peattie and Stanton (232) reported on 44 women with genuine stress incontinence subjected to a needle suspension operation. Before the operation 6 of these women had detrusor instability, and a larger number had urge incontinence symptoms but a negative provocative cystometrogram. Postoperatively, 27 of these patients still had stress incontinence, and 15 had detrusor instability. Thus an operation that fails often is associated with persistent urge incontinence symptoms. Most surgeons no longer regard urge incontinence as a relative contraindication to surgery for coexistent stress incontinence because outcome data in the literature suggest that stress incontinence is causally related to urge incontinence (32,53,217,342). Although this seems to be the case in 60% to 75% of patients in whom preoperatively both stress and urge incontinence exist, in 25% or more urge incontinence persists despite successful surgical resolution of the stress incontinence. In another 7% to 14%, pronounced symptoms of urge incontinence seem to occur *de novo* only after the operative procedure. The occurrence or persistence of severe motor urge incontinence after a procedure that cures stress incontinence is a real problem that is often difficult to treat successfully. Efforts to determine preoperatively which patient might not be relieved of her urge incontinence or to predict patients who might develop urge incontinence have not been successful. Most workers now regard preoperative urge incontinence symptoms or the finding of overt detrusor instability as indeterminate with respect to overall outcome of treatment of urethral dysfunction and stress incontinence (217).

Complications Related to Materials Used in Urethral Suspension Procedures

Simple needle suspension procedures often are associated with early and late failure (106,310). More complicated procedures developed to improve efficacy used bolsters of foreign material in an effort to provide better tissue purchase for the suspension sutures. Various synthetic materials has been used to enhance suture tissue purchase. These materials can be associated with draining sinus formation, fistulization, and erosion into the bladder, urethra, or vagina. Richardson and co-workers (251) reported a 5% rate of delayed reaction to Dacron buttress material used to enhance tissue purchase by urethral suspension sutures. Dwyer and coworkers (93) reported a number of complications in 1,164 women treated with a retropubic suspension or a Stamey type procedure for stress incontinence. These complications included ureteral ligation and intravesical placement of or erosion or migration of sutures and bolsters into the bladder. The latter conditions were associated with pelvic pain, urinary infection, and severe urinary irritative symptoms. Pohl (239) reported a case of abdominovaginal fistula related to a Dacron bolster that became obvious only after 12 years had elapsed from the date of the procedure. Thus late problems can occur. In addition to problems related to sutures placed in or eroding into the bladder (Fig. 38.14), which cause terrible bladder symptoms, failure of these procedures led to efforts to improve them. Appell and co-workers (14) reported on the use of percutaneous bone anchors to stabilize suture suspension and thus improve results. Appell and Leach (15) reported good results with the new technique a few months after the procedure. With time, however, failure occurred as it had with the earlier needle suspensions (267). Schultheiss and associates (267) in Hannover followed a large group of patients and compared the results of needle suspension with and without bone anchors. They found no difference, and overall results were poor. Further efforts involved use of slings of natural and synthetic material combined with bone anchor fixation. Good early results were reported by several workers (150,234). Unfortunately, it became clear that synthetic slings had a tendency to erode into the vagina, urethra, or bladder (Fig. 38.15) (63). The polypropylene sling bone anchor device was withdrawn from the market because of these problems. A number of these procedures were done, and there is a delay between the operation and the appearance of a definite erosion, so patients who have had such a procedure (and perhaps any procedure in which foreign material was used) are at risk. The rate of risk is unknown. Generally, these patients complain of pain with voiding, a vaginal discharge, vaginal bleeding, or incontinence (63). Occasionally, the site of erosion is difficult to visualize because the anterior vaginal wall is elevated and fixed in a high retropubic position. Chai and Sklar (56) described the use of a flexible cystoscope used as a vaginoscope to more

easily visualize the site of erosion. Removal of the sling and all foreign material, if possible, seems advisable because there are now several reports of osteomyelitis associated with bone anchors, especially those associated with erosion into the vagina or urethra (107,206,334).

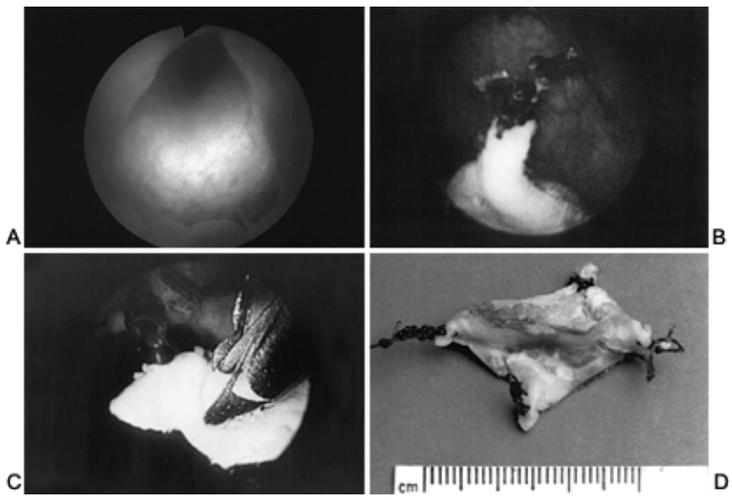

FIGURE 38.14. Recurrent urinary tract infections after pubovaginal sling in a 78-year-old woman. Cystoscopic view from urethra **(A)** demonstrates a large stone at the bladder neck. View from within bladder **(B)** shows nonabsorbable suture and sling material with stone attached. The stone was grasped and fragmented **(C),** and the sutures were cut to remove the specimen **(D)**.

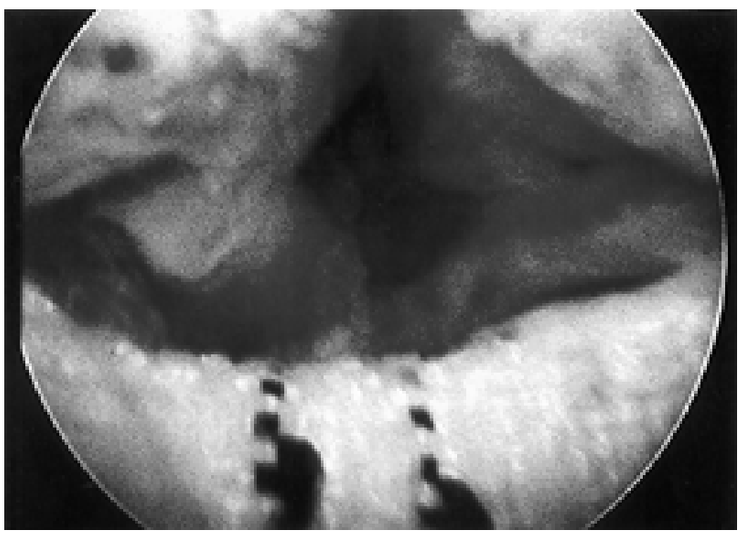

FIGURE 38.15. Cystoscopic view from urethra demonstrating entire eroded polyester sling within urethral lumen. See also Color Figure 38.15.

Other materials used for slings have been reported to cause similar problems. For example, Melnick and Lee (210) reported transsection of the urethra related to a Mersilene sling placed many years before the occurrence of the problem. Bent and colleagues (26) reported a high rate of tissue reaction and infection associated with polytetrafluoroethylene woven material used for suburethral slings. Reactive complications occurred in 23%. DeBodinance and co-workers reported that Gore-Tex slings were “rejected” or poorly tolerated in 23 of 72 consecutive patients and therefore suggested prudence in the use of such materials (78). Chin and Stanton (59) used silastic slings for stress incontinence recurrent after failure of a prior operative procedure in 74 women. They noted that 4 women needed removal of the sling for obstruction, and 10 women developed erosion of the sling into the bladder or urethra or vagina. That is an adverse event rate of 19%. Of 74 women, 29 had persistent or new detrusor instability postoperatively. Only 23 women had reached 5 years after the surgical procedures, so these results should be considered short term. Weinberger and Ostergard (326) described outcomes after use of Gore-Tex slings in 62 women who responded to a telephone survey. They noted a 40% wound complication rate, and sling removal was needed in 22%. In a later report by the same authors (327) involving the same cohort of 108 patients, a high rate of obstruction was noted with Gore-Tex slings. The mean length of postoperative catheterization was 10.7 weeks, and the authors concluded that this type of sling commonly produces voiding difficulty. The voiding difficulty was not always resolved even after sling removal. Cholhan and Stevenson (60) reported spontaneous

transection of the urethra by a polytetrafluoroethylene sling. The authors noted that sling transection was a rare complication, but that assessment may be incorrect. In view of the time course for erosion or reaction to foreign material, this problem may be with us for the foreseeable future (159,251).

Bone Anchors

Bone anchors were borrowed from orthopedics to stabilize needle suspension to prevent late failure. These devices did not improve the poor late outcome associated with needle suspension procedures, and these devices have been associated with some complications. These include osteomyelitis, displacement and migration (Fig 38.16), hernia formation through the fascial defect created to place the bone anchor, osteitis pubis syndromes, suture and sling suspension failure, and inadvertent transvesical placement (107,332). Rarefaction of the bone around the bone anchor, demonstrated on a plain film, or a positive bone scan suggests osteomyelitis and should prompt bone anchor removal (271). Erosion of foreign material into the urinary tract opens a pathway along the suture to the bone anchor, and in this circumstance it is preferable to remove the bone anchor when the sling material and the sutures are removed. If there is rarefaction of the bone, removal is very easy; if not, the anchors must be unscrewed from the bone.

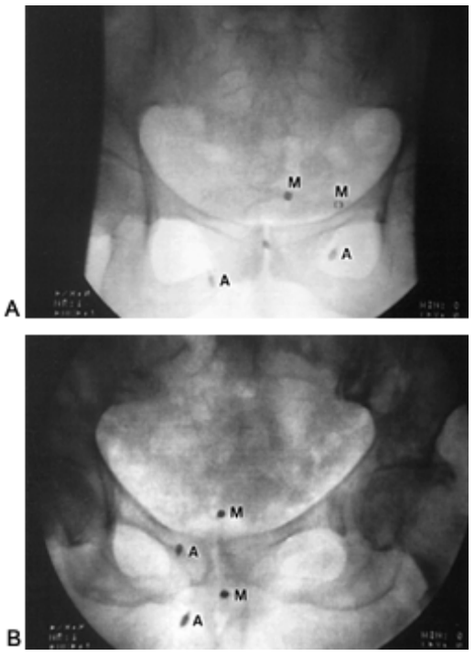

FIGURE 38.16. Displaced bone anchors after surgical procedures for stress incontinence. A, bone anchor; M, radioopaque marker on urodynamics catheter.

UROLOGIC COMPLICATIONS OF PELVIC MALIGNANCY TREATMENT

Part of "38 - GYNECOLOGIC ASPECTS OF UROLOGY "

Treatment of cervical or endometrial carcinoma by radiation therapy or radical extirpative surgery can have serious consequences with respect to urinary tract function.

Radical Hysterectomy

A small percentage of patients subjected to radical (Wertheim) hysterectomy suffer prolonged neural injury or irreversible damage to the neural apparatus controlling bladder or urethral function (57,189). Initially, urologic dysfunction is expressed as difficulty with volitional micturition, which often is treated by prolonged catheter drainage (57). That treatment in conjunction with the neural injury appears to lead to an alteration in bladder compliance. The condition is very similar to that which occurs in patients who develop bladder dysfunction after abdominal perineal resection for carcinoma of the rectum (189). In both cases, the dysfunction may be confined to transient loss of the micturition reflex, which is best managed by intermittent catheterization. In a small number of patients, a permanent neural injury is associated with complete loss of low-pressure bladder storage function, loss of reflex micturition, and an open, nonfunctional internal sphincter mechanism that resists abdominal pressure extremely poorly (337,338). This kind of urethral dysfunction results in urinary leakage associated with very minimal activity. Such a combination of conditions—an areflexive, poorly compliant bladder, and an open, nonfunctional internal sphincter mechanism—cannot be managed by intermittent catheterization alone because stress incontinence continues to be a problem despite the effect of intermittent catheterization on bladder compliance (338).

This constellation of lower tract problems also occurs in children with myelodysplasia: a nonfunctional internal sphincter and an areflexive bladder that stores urine poorly and gains pressure with filling. Because incontinence, caused by internal sphincter dysfunction, is such a problem, treatment is undertaken early. Because the areflexive detrusor gains pressure with volume, an effort to halt the gradual deterioration in compliance can be made by instituting intermittent catheterization in combination with anticholinergic agents. Bladder pressure control does not circumvent leakage driven by changes in abdominal pressure, which continues unless the internal sphincter is closed by treatment (171,337). Treating the incontinence by chronic

catheter drainage only makes bladder compliance and complications worse over time.

If normal bladder compliance has been preserved, a procedure that effectively closes the nonfunctional internal sphincter will restore continence (e.g., a pubovaginal sling, an artificial sphincter, or an injectable agent such as collagen or fat). If bladder compliance is abnormal, achieving a satisfactory urethral continence mechanism by closing the urethra must be done in conjunction with some treatment that increases bladder capacity, such as an augmentation cystoplasty (171).

Radiation Therapy

The overall incidence of serious bladder injury from radiation therapy for carcinoma of the cervix is estimated to be 3% to 5%. The actual incidence may be higher in long-term and very-long-term survivors of radiation therapy, however, and the various types of radiotherapy in use 25 years ago can be related to very late onset of lower urinary tract problems (313).

Whereas more acute problems, including radiation cystitis with bleeding and vesicovaginal fistula formation, may be apparent within 3 years after cessation of radiation, late fistula formation and serious hemorrhage or problems with incontinence related to detrusor fibrosis and urethral sphincter failure may occur as long as 10 to 28 years after radiation therapy (313).

In 1933, Dean (77) defined three phases of bladder injury by radiation therapy: acute, subacute, and chronic. The acute phase, which starts 3 to 6 weeks after treatment, is characterized by vascular congestion and mucosal and submucosal edema, as well as degenerative changes, epithelial cell death, inflammation, desquamation, and ulceration. Focal deep muscular changes also occur. Subacute changes are characterized by variable fibrosis and healing, but the tissue remains abnormal for years. Chronic changes include obliterative endarteritis, proliferation of capillaries with capillary vascular ectasia, mucosal atrophy, ulceration, fibrosis and hyalinization, bleeding, contracture, and fistula formation. The late chronic injury phase may be exacerbated by small vessel disease associated with aging or other diseases.

Symptoms

Symptoms usually are incontinence with urgency, frequency, dysuria, or bleeding in association with bladder irritative symptoms. Any patient with a history, recent or remote, of radiation therapy within the pelvis should be evaluated carefully for the most likely expressions of radiation injury. Among these are hemorrhagic cystitis, usually associated with progressive fibrosis; and a small-volume, high-pressure, noncompliant bladder with or without a nonfunctional urethral sphincter. The late effects of radiation on bladder and urethral function include loss of normal low-pressure bladder urine storage; failure of the urethra to function as a sphincter, with a lack of resistance to abdominal pressure; and failure of the urethra to act as a compliant conduit during voiding attempted by the Valsalva maneuver, caused by a loss of detrusor reflex function. Valsalva voiding is rarely efficient and often is associated with significant residual urine volumes. Despite incontinence, the total picture is that of leakage driven by high ambient detrusor pressures and residual urine (344). High bladder pressures may lead to hydroureteronephrosis, vesicoureteral reflux, and renal damage or failure. These problems that accompany urinary incontinence, which is often the presenting complaint, become progressively worse as bladder storage function deteriorates. High bladder pressure, residual urine, and infection may result in severe, intractable vesical hemorrhage. In addition to these problems, large vesicovaginal and vaginal rectal fistulae may develop, spontaneously complicating the picture of incontinence.

In patients with fistulae, occlusion of the fistula with a large-balloon catheter is useful during videourodynamic study, or fluoroscopy alone without pressures, to determine proximal urethral competence, bladder compliance, and the presence of vesicoureteral reflux. Multiple biopsies should be taken near the fistula and along its course, together with random bladder biopsies, to determine whether recurrent carcinoma, or perhaps *de novo* carcinoma development, is involved in fistula formation. The classic site of a radiation fistula is posterior, involving the area of the trigone or the area just above the trigone (43,44). In patients incontinent without fistula formation, a very careful assessment of bladder storage activity is important before any procedure on the urethra. A poorly compliant bladder may look normal if continuous leakage occurs during the study. Moreover, incontinence related to poor bladder compliance often is exacerbated by activity, and, historically, the description of incontinence related to poor compliance often is identical to that related by patients with stress incontinence. However, because detrusor pressure is the driving force for the wetting, a urethral procedure will not be effective in curtailing the incontinence. The treatment of leakage driven by detrusor pressure entails bladder enlargement (171,338).

Treating Poor Bladder Compliance

The initial treatment is by anticholinergic agents, combined with intermittent catheterization if residual urine is present. If that treatment is unsuccessful, augmentation cystoplasty may be needed. In some cases, where destruction of the trigone has occurred as a result of radiation, supravesical diversions may be the only viable option.

Treating Radiation Fistulae

Closure of a fistula related to radiation therapy usually entails interposition of vascularized tissue. The techniques

vary, but the majority of these fistulae are closed transvaginally. Elkins and colleagues (94) reported excellent results with a Martius labial fat pad interposition technique. Others have used bulbocavernosus grafts with good results; additional techniques include the use of gracilis muscle, as reported by Garloch (122) in 1928 and others (94,204).

Ureteral Obstruction After Radiotherapy

The incidence of radiation-induced ureteral obstruction has been reported to be between 0.4% and 8.0% (174). The combination of radiotherapy and radical surgery has resulted in an increased incidence of ureteral obstruction. In one series the incidence was 41.7%. In recent years, the incidence of major urologic complications has fallen markedly (235). Ureteral complications of irradiation occur later, with 80% occurring within 48 months after treatment and most occurring more than 24 months after treatment.

In 1972, Alfert and Gillenwater observed that after irradiation, ureteral obstruction is caused by recurrent tumor in two-thirds of cases and sclerotic fibrosis after destruction of malignant disease in the other third. With improved irradiation regimens, whether these proportions are still applicable is uncertain. A more recent review of urinary diversion in gynecologic malignancy reported on a series of 19 patients with ureteral obstruction (161). Only 2 patients in this series had ureteral obstruction caused by irradiation alone.

Reported ureteral complications related to irradiation include strictures, retroperitoneal fibrosis–induced ureteral obstruction, hematuria caused by ureteritis, or more rarely, ureteroarterial fistula (45). Ureteral obstruction also may be related to poor bladder compliance. The most significant determinant of irradiation injury is the dose of irradiation. With doses of irradiation less than 8,000 rads, the incidence of major complications is low. Interestingly, patients who developed irradiation-related major complications in one study had survival rates better than those who did not develop complications (45).

If ureteral obstruction is identified after irradiation for gynecologic malignancy, a cystometrogram and computed axial tomography with or without needle biopsy and other measures may be needed for accurate diagnosis and planning of effective therapy.

Radiation Cystitis

The onset of acute radiation cystitis is 3 to 6 weeks after the start of irradiation, with symptoms indistinguishable from those of bacterial cystitis. Urinalysis shows a variable combination of leukocytes, erythrocytes, unusual epithelial cells, necrotic debris, and bacteria. Secondary bacterial infection is common. Urine culture, sensitivities, and appropriate antibiotics are recommended (329). Late hemorrhage occurs in 3% to 12% of patients after pelvic irradiation (120).

A number of specific and nonspecific strategies exist to control the hematuria. Initial management includes cystoscopy with evacuation of clots, with bladder biopsy and fulguration of bleeding areas. After a cystoscopy, irrigation is continued until the drainage is clear, and management is essentially the same as that after a bladder tumor resection. Not infrequently, hematuria persists despite this management. Coagulation defects, especially disseminated intravascular coagulation and systemic hyperfibrinolysis, may be present. An intravenous urogram is necessary to evaluate the upper urinary tract, which may be the source of the hematuria.

If hematuria continues despite conservative measures, other measures can be used. These include instilling epsilon aminocaproic acid (EACA), intravesical alum, intravesical formalin, desmopressin, hyperbaric oxygen, temporary urinary diversion with ureteral occlusion catheters, arteriographic embolism, or surgical supravesical diversion (120,314,329).

EACA is a fibrinolytic agent that can be given orally, parenterally, or intravesically (120,281,329). It is contraindicated in disseminated intravascular coagulation because it may exacerbate small vessel thrombosis in this condition (120). It can be administered by continuous bladder irrigation after clot evacuation. This causes superficial protein precipitation and decreased cell permeability and stops small vessel bleeding.

Alum is instilled into the bladder as a 1% solution at a rate of 5 ml/minute (128). In the presence or renal impairment, especially with an eroded mucosal surface, serum aluminum levels should be monitored because central nervous system and bone marrow and renal toxicity have been caused by systemic absorption.

Formalin, an intravesical agent, acts by coagulating the tissues. Administration is very painful and necessitates anesthesia. In the presence of vesicoureteral reflux, it may cause renal injury. If reflux is present, formalin still may be used if ureteral occlusion balloon catheters are inserted (120). A recommended starting dosage for formalin is 0.5% to 1.0% solution given for 10 minutes. Formalin can exacerbate bladder fibrosis, further impairing storage activity.

Desmopressin is a vasopressin analog that increases levels of factor VIII and von Willebrand factor and may shorten bleeding times. It is a useful adjunct for treating intractable hematuria. Other methods for controlling hematuria include hyperbaric oxygen, administered in daily treatments for 2 months. Before supravesical diversion, control of hematuria with bilateral ureteral occlusion balloons should be tried. The patient with severely contracted, fibrotic, noncompliant bladder may need surgery, either augmentation cystoplasty or urinary diversion.

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39

URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS

John N. Krieger

J.N. Krieger: Department of Urology, University of Washington; Department of Urology, VA Puget Sound Health Care System, Seattle, WA 98195.

Contents

HISTORY

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Urethritis was recognized in antiquity and has been documented since the dawn of recorded history. According to Herodotus, Venus cursed the Scythians for pillaging her temple with “the woman's disease,” characterized by a discharge from the penis. Those attacked by this disease were looked on as accursed (133,165,166). Galen (c. A.D. 130–201) coined the term *gonorrhea,* combining the roots *gonus,* or “seed,” and *rhoea,* or “flow” (133). Thus *gonorrhea* literally means “leakage of semen.” The celebrated Arabian physician Maimonides distinguished urethral discharge from semen: “The fluid escapes without erection and without feeling of pleasure” (133).

Eventually, it was recognized that urethritis followed intercourse with an infected woman. This idea led to efforts to control venereal disease by regulating prostitution (133,165,166,327,389). According to legend, during the Middle Ages prostitutes in Paris were restricted to domiciles called *clapiers.* This explains the origin of the term *clap.* Another approach to control sexually transmitted diseases was taxation of afflicted men. For example, Elizabeth I (1533–1603), the “virgin queen,” decreed that every male attendant “who had a running from the pentle, should pay into the public treasury 40 shillings” (78).

During the nineteenth century, the predominant viewpoint of the medical community was that venereal disease was “punishment for the Lewdness of Mankind” (306). As stated by Dr. Samuel Dolly of the Royal College of Surgeons, “could the disease be eradicated fornication would ride rampant through the land,” an unfortunate (in his opinion) situation (327). Patients with sexually transmitted

diseases were ostracized and confined to institutions such as the Social Evil Hospital in St. Louis (35).

The scientific foundation for the diagnosis of urethral inflammation dates from 1879, when Neisser demonstrated the bacterium, now known as *Neisseria gonorrhoeae,* in stained smears of urethral, vaginal, and conjunctival exudates (143). Thus it was possible to distinguish gonococcal urethritis from nongonococcal urethritis (NGU). The distinction was important clinically once effective therapy for gonorrhea became available with the development of sulfonamides in the 1930s.

DEFINITIONS

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Urethritis is the response of the urethra to inflammation of any cause (52,293). Such inflammation results in the classic symptoms of urethral discharge accompanied by burning on urination or an itching sensation. Urethral discharge is the characteristic finding on physical examination. The pathognomonic laboratory finding is an increased number of leukocytes on Gram's stain of the urethral smear or first-voided urine specimen. Urethritis may be classified as infectious if a microorganism with pathogenic potential is identified or noninfectious in the absence of a recognized pathogen. Infectious urethritis is classified as gonococcal, or gonorrhea, in the presence of *N. gonorrhoeae.* If *N. gonorrhoeae* is not detected despite objective evidence of urethral inflammation, the patient has NGU. This condition was formerly called *nonspecific urethritis,* but *nongonococcal urethritis* is preferred because specific causes of NGU may be identified in most patients. *Postgonococcal urethritis* is the term used for NGU that occurs shortly after effective therapy for gonorrhea.

INCIDENCE

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Up to 50% of the U.S. population will acquire a sexually transmitted disease by age 30 to 35 (123). Urethritis is one of the most common problems in ambulatory medical practice. Despite recent declines in incidence, gonorrhea remains one of the most frequently reported infectious diseases in the United States, with approximately 600,000 cases reported per year in men from 1975 and 1991 (45,52,144). The best estimate is that approximately 40% of cases of gonorrhea are reported (30,105). In Great Britain, where infectious disease reporting is more complete and all forms of urethritis are reportable, 34% of patients with urethritis had gonorrhea (399). Less complete data suggest that NGU is also more common than gonococcal urethritis in the overall U.S. population (49,162,408). It is estimated that gonorrhea accounts for approximately 35% of cases of acute urethritis in men. This leads to an estimate of at least 4 million cases of urethritis per year among men in the United States (30,105). The estimated annual incidence is 3.7 cases of urethritis per 100 males older than age 15 years (105).

The relative proportions of gonococcal urethritis and NGU depend on many factors, including the population studied, geography, socioeconomic factors, sexual orientation, age, and race (144). For example, the reported incidence of gonococcal infection in patients attending clinics for sexually transmitted diseases was highest in inner-city populations: 90% in Lexington, Kentucky, 64% in Detroit, and intermediate in cities such as Denver, New Haven (45), and Seattle (140). College students had the lowest reported incidence (8%) of gonococcal disease in heterosexual men with urethritis (231). NGU is more common in patients from higher socioeconomic groups (292). Heterosexual black men with urethritis have a higher incidence of gonorrhea (58% to 70%) than heterosexual white men (25% to 37%) in most studies (153,408).

Although national gonorrhea rates have declined since 1986, rates for minority adolescents and young adults, especially in inner cities, continue to be high. Recent data suggest that rates were 5,715 per 100,000 for black adolescents aged 15 to 19 and 6,339 per 100,000 for black adults aged 20 to 24, compared with rates of 189 per 100,000 for white adolescents and 186 per 100,000 for young white adults (49,144). Because there is no evidence of differences in racial susceptibility to gonorrhea or NGU, these differences may reflect the willingness of patients from higher socioeconomic groups to be treated for the milder symptoms characteristic of NGU (292). Thus equating signs of acute urethritis with gonorrhea often is in error, especially in private practice.

ETIOLOGY

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Urethritis is a clinical syndrome with many causes (Table 39.1). The cause is commonly infectious, resulting from exposure to microorganisms spanning the full spectrum of medical microbiology. From a microbiologic viewpoint, these organisms have little in common other than the potential to cause urogenital tract disease and to be commonly transmitted by sexual contact (194). This mode of transmission and the epidemiological risk factors for sexually transmitted diseases imply that patients with one of these diseases are at risk for others because multiple pathogens may be acquired simultaneously. Some patients develop symptoms of urethritis that reflect infection with microorganisms acquired through means other than sexual contact, or they have symptoms without objective evidence of an inflammatory response or a recognized pathogen (196).

Sexually transmitted	
Gonococcal	
Neisseria gonorrhoeae	Bacterial
Nongonococcal	
Chlamydia trachomatis	Bacterial (chlamydia)
Ureaplasma urealyticum	Bacterial (mycoplasma)
Uncommon causes	
Trichomonas vaginalis	Protozoan
Herpes simplex virus (types 1 and 2)	Viral (DNA[a])
Human papillomavirus	Viral (DNA[a])
Rare or debatable causes	
Mycoplasma hominis[a]	Bacterial (mycoplasma)
Haemophilus ducreyi	Bacterial
Bacteroides urealyticus[a]	Bacterial (anaerobic)
Neisseria meningitidis	Bacterial
Candida albicans	Yeast
Corynebacterium genitalium[a]	Bacterial
Other organisms	
Non–sexually transmitted	
Associated with genitourinary infection or abnormalities	Bacterial
Prostatitis	
Urethral stricture	
Instrumentation	
Foreign body	
Immunologic	
Reiter's syndrome	Infection associated
Wegener's granulomatosis	
Stevens-Johnson syndrome	
Chemical allergy (rare)	
Food allergy (doubtful)	
Chronic irritation	

[a]These organisms are suggested as causes in the literature but are not established; most experts consider them possible or doubtful causes.

TABLE 39.1. CAUSES OF URETHRITIS IN MEN

The following sections consider the most significant causes of urethritis in clinical urology. We emphasize treatable, infectious causes of urethritis. For each pathogen there

is a limited discussion of microbiologic characteristics of the organism that have important clinical implications. Attention then is directed to relevant considerations of the epidemiology, diagnosis, and treatment of that pathogen. Non–sexually transmitted conditions are discussed in the differential diagnosis of urethritis. Finally, we consider specific complications of urethritis and related conditions.

DIAGNOSTIC TESTING

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Testing to establish the presence of urethral inflammation is highly desirable in any clinical setting (52). This is especially true in urological practice, where patients often are referred for evaluation of atypical or persistent signs and symptoms. Urethritis can be documented by the presence of any one of the following findings: mucopurulent urethral discharge, a Gram stain of urethral secretions demonstrating five or more leukocytes per oil immersion field, or presence of leukocytes in the first-void urine.

The Gram stain is preferred as a rapid diagnostic test for evaluating possible urethritis (52). This test is a highly sensitive and specific method for documenting both urethritis and the presence of gonorrhea in patients who have leukocytes containing intracellular, Gram-negative diplococci. In patients who refuse the urethral smear, or for screening populations at high risk for infection, the first-void urine is an alternative to the traditional urethral smear. A positive leukocytes esterase test or ten or more leukocytes per high-power microscopic field is considered diagnostic of urethritis.

If none of the criteria for urethritis is present, then treatment should be deferred pending diagnostic test results unless the patient is considered unlikely to return. Testing should be done for both *N. gonorrhoeae* and *Chlamydia trachomatis,* with arrangements for close follow-up of a positive result. Patients with positive test results for either of these organisms should have appropriate treatment, as described later in this chapter. In addition, sex partners should be referred for evaluation and treatment. Empirical treatment of symptoms without documentation of urethritis is recommended only if the patient is considered at high risk for infection and is also considered unlikely to return, such as adolescents with multiple sex partners.

Documenting presence of specific pathogens is highly desirable. Such information supports treatment compliance and partner notification. Positive test results also support the need for counseling in behavior modification and testing recommendations for both syphilis and HIV. Negative test results and poor response to previous therapy support the need for additional evaluation and etiological testing, as described later in this chapter.

GONOCOCCAL URETHRITIS

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Biology of N. gonorrhoeae

N. gonorrhoeae is a Gram-negative, non–spore-forming bacterium that usually appears as diplococci (Fig. 39.1). On light microscope examination, gonococci appear encapsulated and exhibit a characteristic “twitching” motility (336). Identifying *N. gonorrhoeae* in culture usually depends on typical appearance of the colonies, Gram stain, oxidase reaction, and carbohydrate uptake (244).

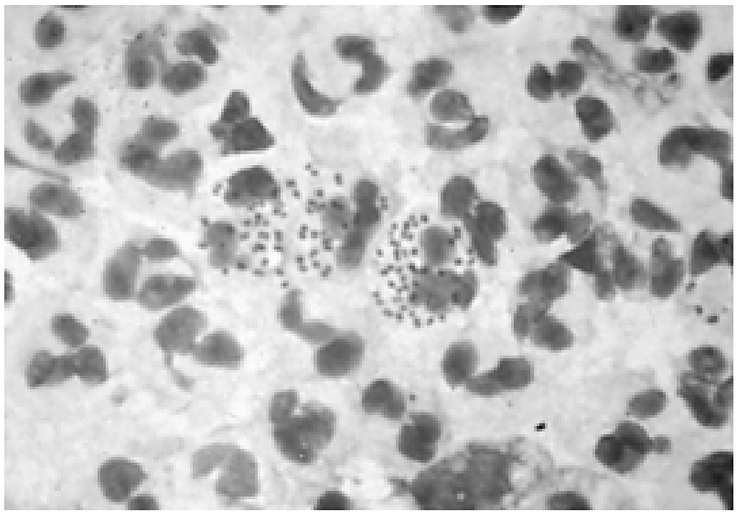

FIGURE 39.1. Gram-stained urethral smear from a patient with gonorrhea. There is a profuse inflammatory infiltrate with polymorphonuclear leukocytes containing characteristic Gram-negative intracellular diplococci.

Although *N. gonorrhoeae* does not grow on simple laboratory media such as nutrient agar, there are a variety of commercial and completely defined growth media (144,336). Most media incorporate antimicrobials, such as vancomycin or nystatin, to inhibit overgrowth of other bacteria. Gonococci are strict aerobes, but increased carbon dioxide tension (5% to 10%) is needed for growth. This is usually provided in a candle jar or carbon dioxide incubator. Specific nutritional requirements (auxotypes) vary from

strain to strain and form the basis for one classification scheme for gonococcal strains (45). There is geographic variation in the distribution of different auxotypes (143). In addition, particular auxotypes of gonococci may be associated with specific disease syndromes. For example, 88% of cases of disseminated gonococcal infection (187) and more than 90% of asymptomatic urethral infections among men in Seattle were caused by strains needing arginine, hypoxanthine, and uracil (70). In contrast, this auxotype caused only 33% of uncomplicated gonorrhea.

Although auxotyping has been used in conjunction with antibiograms to monitor outbreaks of antimicrobial-resistant gonorrhea, this method has limited usefulness for differentiating between strains (186). More sophisticated methods use serologic classification based on antigenic differences in gonococcal outer membrane protein I (144,188). Monoclonal antibodies against different outer membrane proteins can distinguish particular serotypes (188,356). The combination of auxotyping and serovar analysis proved useful for epidemiological studies of *N. gonorrhoeae* strains (143). New molecular techniques, such as fingerprinting using plasmid profiles, and restriction endonuclease analysis also have proven useful for epidemiologic investigations (372). Thus we can now monitor the dynamics of gonorrhea outbreaks on a molecular level.

Variation in the appearance of *N. gonorrhoeae* colonies becomes apparent when organisms are grown on solid media (154,277). Colonies are described as small or large, opaque or transparent. Because there is no useful animal model, human studies of gonococcal virulence factors are ongoing (55,57). Inoculation studies demonstrated that organisms from the small colonial variants were virulent, whereas the large colonial variants were avirulent (174,176). These characteristics are determined by opacity proteins. Subsequent studies demonstrated that bacteria from the small colonies had pili, but organisms from the large colonies had no pili. Gonococcal pili are believed to facilitate attachment to host cells. Gonococci of one colonial type rapidly change in both colony appearance and piliation on cultivation (336). Almost all gonococcal strains studied contain plasmids (336). Plasmids are inherited, extrachromosomal, genetic elements that are not essential to the host cell. Some plasmids, called *R-plasmids,* code for characteristics that make bacteria resistant to antimicrobials. *N. gonorrhoeae* containing R-plasmids were first isolated in 1976 (85,342,371). Biochemical evidence suggests that these R-plasmids were acquired from strains of *Haemophilus influenzae.* The R-plasmids code for ß-lactamase production, activity that confers absolute resistance to penicillin. Strains of *N. gonorrhoeae* with a ß-lactamase are called *penicillinase-producing N. gonorrhoeae* (PPNG). PPNG strains originally were isolated from patients in certain areas of Africa and the Far East. Before 1980 there was a gradual increase in the incidence of PPNG in the United States, and most cases could be traced to Far Eastern sources (143). Beginning in 1980, however, there was an increase in PPNG in the United States, and these strains have become endemic in certain areas of the (48,123,143,311,397). To date, five different ß-lactamase plasmids have been described in *N. gonorrhoeae* (156). In addition, gonococci have acquired another plasmid from streptococci that confers high-level resistance to the tetracyclines (156).

Chromosomal mutations are the second mechanism for developing drug resistance in *N. gonorrhoeae* (156,191). Such strains are called *chromosomally mediated resistant N. gonorrhoeae* (CMRNG) (48). Unlike the PPNG, the CMRNG strains do not produce ß-lactamase (92). Chromosomally mediated resistance to penicillin generally is low and has been associated with mutations at four sites (156). However, the effects of these mutations are additive. The combination of several mutations may increase penicillin resistance 100-fold or more. A second problem is that the CMRNG strains also exhibit high-level resistance to other drugs, particularly tetracyclines and most cephalosporins (156). Other *N. gonorrhoeae* strains have been described with chromosomally mediated resistance to many other classes of antimicrobials, including aminoglycosides, spectinomycin, sulfonamides, trimethoprim-sulfamethoxazole, and quinolones (156). Thus gonococci now have multiple mechanisms for developing resistance to antimicrobial drugs.

Studies of other potential virulence-associated factors are limited by the lack of an animal model for gonorrhea. Humans are the sole host of *N. gonorrhoeae,* and efforts to develop a suitable experimental model have met with limited success (57,336). Despite these problems, several lines of evidence suggest that gonococcal pili may be important in disease development (174,336). Presence of pili was associated with small colonies *in vitro* and with virulence in both human volunteers and in animal models. Pili increased the

adherence of gonococci to a wide variety of cells, including tissue culture cells, erythrocytes, polymorphonuclear leukocytes, vaginal epithelial cells, buccal epithelial cells, and fallopian tube explants (235,272,336). Because adherence is the first step in pathogenesis for many organisms, presence of pili appears to be associated with gonococcal virulence. There is distinct antigenic variation between pili isolated from different gonococcal strains. Evaluating these strain-specific and common antigens of pili is an area of active research by workers trying to develop gonorrhea vaccines (31). To date, however, none of the vaccines has proven effective in clinical trials (20). Like other Gram-negative bacteria, *N. gonorrhoeae* contain lipopolysaccharide in their cell membranes (4). Lipopolysaccharide has been associated with endotoxin activity, with toxic effects in animal models and with toxic effects in tissue culture systems (336). Gonococci also elaborate an enzyme that inactivates host immunoglobulins (Ig), specifically IgA (18). This enzyme may allow gonococci to persist at host mucosal surfaces despite a host immune response.

Epidemiology

Case-finding and contact-tracing efforts have resulted in a dramatic reduction in the incidence of gonorrhea in much of western Europe and Canada (144). However, gonorrhea remains common in the United States and the developing world. Part of the decline in incidence has been attributed to behavioral changes related to the HIV epidemic. Rates have declined in homosexual and bisexual men, in whites, and in older adults. In contrast, gonorrhea rates remain high in younger populations and in blacks.

Approximately 17% of men develop gonorrhea after a single episode of vaginal intercourse with an infected woman (145). The transmission rate increases to 60% to 80% after four exposures. Approximately 90% of women who are secondary sexual partners of infected men have gonorrhea (369), but no studies controlled for the number of exposures.

Recent reports emphasize the role of men with asymptomatic infections in the epidemiology of gonorrhea. It was believed that almost all women with gonorrhea were asymptomatic, whereas almost all men developed symptoms. The problem was that reports of carefully defined groups of patients were generalized to the overall population. For example, studies reporting that more than 80% of women with gonorrhea had no symptoms were based on surveys of sexual contacts with men with gonococcal urethritis; women evaluated because of lower genital tract symptoms generally were excluded (143,275). However, fewer than 25% of women with gonorrhea attending acute care facilities were asymptomatic (125,233). It also has become apparent that asymptomatic urethral infection in men is important in the epidemiology of gonorrhea. In one study only 2 of 81 men (2.5%) infected at a known time remained asymptomatic for 14 days (128). The problem is that asymptomatic men tend to accumulate in the general population and remain active sexually, whereas symptomatic patients tend to seek medical care (125,143,144,233). For example, an unannounced “short-arm” inspection revealed that 2.2% of a large group of military personnel had gonococcal urethritis; most were asymptomatic or had ignored minimal symptoms. It is now believed that such patients are primarily responsible for transmitting the disease. Thus most men named as source contacts of women with gonococcal pelvic inflammatory disease or gonococcal arthritis were asymptomatic or had ignored minimal symptoms of gonorrhea (89,125). Asymptomatic urethral carriage of gonococci also may represent a hazard to the patient. For example, gonococcal epididymitis has been well documented in men with no previous history of urethritis (14).

Clinical Manifestations

N. gonorrhoeae infects mucous membranes lined by nonsquamous epithelium (276). Adherence of the bacteria to mucosal surfaces appears to be the initial event in pathogenesis (144,228). Mucosal invasion occurs within 24 to 48 hours (276). This is accompanied by a marked polymorphonuclear leukocyte infiltration, submucosal microabscesses formation, and inflammatory debris exudation into the urethral lumen, resulting in the characteristic discharge (55,56,57). In untreated patients a gradual accumulation of mononuclear cells that may persist for months. Before the appearance of effective antimicrobials, urethral discharge persisted for an average of 8 weeks, and 95% of patients became asymptomatic within 6 to 8 months (141,276).

Acute urethritis is the most common manifestation of gonococcal infection in men. The incubation period was 2 to 5 days in 36 of 44 men (82%) in one study (129) and usually ranges from 1 to 14 days (143). Observations suggest that certain strains of gonococci may have unusual incubation periods. For example, some strains from the western Pacific may produce symptoms and positive cultures within 12 hours after exposure, whereas other strains may take as long as 3 months to produce symptoms (128).

Patients usually complain of dysuria and urethral discharge. The discharge initially may be slight and appear mucoid, but most patients develop purulent, milky discharge within 24 hours (144,276). On occasion, urethral discharge comes to the patient's attention as an unpleasant odor on urination or observation of mucous strands in the urine. The discomfort experienced by patients with urethritis usually manifests as dysuria. Some patients may localize this discomfort to the meatus or distal penis or along the shaft. Occasionally, patients report that dysuria increases after ingestion of irritants such as alcohol or spicy foods. This observation may lead the patient to believe that his disease is a food allergy. Other patients experience discomfort

during urination, described as pain, itching, urinary urgency, or heaviness in the genital area (234,292).

The intensity of dysuria is variable, ranging from minimal discomfort with micturition to exquisite tenderness. Similar variability also is present in the quantity of discharge. In some patients the discharge may be profuse and occur spontaneously. Other patients may have minimal discharge that presents as a crust covering the meatus or a small drop of increased moisture at the meatus that is apparent only on arising. In one review, 31% of men with gonococcal urethritis had a discharge that was mucoid in appearance, closely resembling the discharge observed in patients with NGU (30). In addition, a small group of men never develop overt signs or symptoms of urethritis (125,144). Therefore the characteristics of the urethral discharge by themselves are not sufficient for determining whether the patient has gonococcal or NGU.

Diagnosis

If possible, the patient should be examined at least 2 hours after his most recent urination and ideally before his first void of the day (292). This facilitates detection and examination of minimum amounts of discharge (353). If spontaneous discharge is not apparent, discharge may be observed at the meatus after urethral stripping or prostatic examination. Some patients with objective laboratory evidence of urethral inflammation lack physical signs of urethritis.

Laboratory diagnosis of gonococcal infections depends primarily on identification of the gonococcus in stained smears or cultures from infected sites. Microscopic examination of the urethral specimen is the first procedure for evaluating symptoms or signs of urethritis. Specimens should be obtained with calcium alginate swabs inserted at least 2 cm into the urethra and rotated gently (24,128,292). Standard cotton-tipped applicators should not be used to obtain urethral specimens because their large size makes insertion uncomfortable, and free fatty acids in the cotton fibers may be toxic to fastidious pathogens (175). Ideally, the swab should first be inoculated in culture media, then applied to the microscope slide (128). Duplicate swabs should be obtained in situations in which this procedure is impractical. The swabs should be rolled over the slide rather than “streaked” because the latter procedure may distort cellular morphology. The slide should then be air-dried, heat-fixed, and stained with one of the many Gram stain procedures.

Microscopic examination of urethral specimens is a mandatory adjunct to urethral cultures. This procedure facilitates diagnosis and immediate presumptive therapy of patients with urethritis. A small subset of men (less than 2%) with symptomatic urethritis also have typical organisms on Gram stain but negative cultures for gonorrhea. Such false-negative cultures occur because some *N. gonorrhoeae* strains are inhibited by the small concentration of antimicrobials used in standard, selective media for isolating gonococci (117,292). The Gram-stained urethral specimen should be examined with the oil immersion objective. Because the distal urethra is colonized by a variety of bacteria, observing varied extracellular organisms is of no particular importance (292). Two findings have diagnostic significance: presence of inflammatory cells and the presumptive identification of gonococci. The finding of acute inflammatory cells, particularly polymorphonuclear leukocytes, in the urethral specimen is abnormal, as discussed in the next section. Identification of typical, Gram-negative, intracellular diplococci within polymorphonuclear leukocytes (Fig. 39.1) by experienced microscopists has a 95% sensitivity and a 99% specificity for diagnosing gonococcal urethritis (161). Gonococci are not randomly distributed among polymorphonuclear leukocytes but are found in large numbers in few cells.

Two culture media are most effective for isolating *N. gonorrhoeae*–modified Thayer-Martin medium (367) and New York City medium (119,296). Both media give excellent results. Various other tests based on serologic and fluorescent antibody methods, as well as detection of bacterial endotoxin, have been developed to diagnose gonorrhea. However, the high sensitivity and specificity of the urethral Gram stain and culture combination make routine use of these diagnostic methods unnecessary (128,144).

Nonculture tests for diagnosis of *N. gonorrhoeae* have become available during the last decade. These tests are especially useful in settings where culture viability can be jeopardized by temperature variability and delays during transportation to the microbiology laboratory. These tests include both nonamplified and amplified DNA probe tests (144) that provide sensitivity and specificity comparable to culture. Some amplified DNA tests have proven useful for screening first-void urine specimens. This approach has proven useful for screening high-risk populations without the need for a urethral swab (54,271).

Treatment

Historically, gonococcal urethritis was managed by local measures, such as salves and ointments, intraurethral antiseptic solutions, and assorted instruments (128,131,165). These treatments became obsolete during the 1930s with the availability of the sulfa drugs (74). By 1943, however, most *N. gonorrhoeae* isolates were resistant to sulfadiazine. Gonococcal urethritis was first treated with penicillin in 1943, and over the next four decades the dosages of penicillin necessary for curing gonorrhea increased steadily (128). Drugs in the penicillin class are no longer recommended as first-line treatment for gonococcal urethritis.

Current recommendations for treating gonococcal urethritis are outlined in Table 39.2 (50). Each recommendation has advantages and disadvantages. Thus treatment should be individualized. Intramuscular aqueous procaine penicillin accompanied by probenecid was a time-honored regimen

that can no longer be recommended (143,144,234). Problems include the large, painful injections that limit patient acceptance and the parenteral administration of a large amount of procaine, which may be toxic. Increasing resistance of the gonococcus to penicillin also has limited the effectiveness of penicillin treatment.

Oral regimens
Cefixime 400-mg single dose *or*
Ciprofloxacin 500-mg single dose *or*
Ofloxacin 400-mg single dose
Plus
Azithromycin 1-g in a single dose *or*
Doxycycline 100 mg twice daily for 7 days
Parenteral regimens
Ceftriaxone 125 mg intramuscularly
Plus
Azithromycin 1-g single dose *or*
Doxycycine 100 mg twice daily for 7 days
Special considerations
For patients allergic to cephalosporins or fluoroquinolones, substitute spectinomycin 2 g intramuscularly

Adapted from 1998 Guidelines for treatment of sexually transmitted diseases. Centers for Disease Control, 1998. *MMWR* 1998;47(RR-1):1, with permission.

TABLE 39.2. RECOMMENDED TREATMENT REGIMENS FOR UNCOMPLICATED GONOCOCCAL URETHRITIS

Effective single-dose treatments are available. These agents include the gold standard parenteral treatment with ceftriaxone (125 mg intramuscularly). Single-dose oral treatment is an attractive alternative. Effective agents include cefixime (400 mg), ofloxacin (400 mg), and ciprofloxacin (500 mg) (52,249,285,286,357). Because treatment may be administered as a single dose under direct supervision of the physician, it is ideal for patients who are not reliable (47,128,249,285,286,357).

Possible coexisting chlamydial infection is an important consideration for all patients with gonorrhea. Such infections occur in up to 45% of patients with gonorrhea (49). Therefore all recommended regimens in Table 39.2 include treatment for possible chlamydial infections. Current recommendations are treatment with doxycycline (100 mg twice daily) for 7 days or a single (1 g) dose of azithromycin, an effective alternative that offers the advantages of single-dose treatment.

Routine follow-up evaluation is no longer recommended for patients with uncomplicated gonococcal urethritis who receive one of the recommended regimens (52). If symptoms persist and there is evidence of urethritis, patients should be recultured. Documented *N. gonorrhoeae* should be tested for antimicrobial susceptibility. Recurrent infections after treatment with one of the recommended regimens most often result from reinfection by contact with an untreated partner. This emphasizes the need for effective counseling and treatment of both the patient and his partners (128). All patients with gonorrhea should receive appropriate evaluation and treatment for other sexually transmitted diseases, including syphilis and HIV testing.

NONGONOCOCCAL URETHRITIS

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Comparison of Clinical Features of Gonorrhea and Nongonococcal Urethritis

There are differences between populations of men with gonococcal urethritis and NGU in epidemiologic studies (22,140,228). For example, comparison of 113 men with NGU and 69 men with gonococcal urethritis demonstrated that patients with NGU were more often white, better educated, more likely to be students, and of higher socioeconomic status (140). Patients with NGU were older at first intercourse, had fewer sexual partners, and were less likely to have had a previous episode of gonorrhea but more likely to have had previous NGU (22,140,153). Unfortunately, such demographic characteristics have limited value in assessing individual patients.

The usual incubation period for NGU development is 1 to 5 weeks after sexual intercourse with an infected partner, and most cases occur between 2 and 6 weeks (21,22,228). This is longer than the usual 2- to 6-day incubation period for gonorrhea, and the onset of symptoms of gonorrhea usually is more abrupt (144). However, there is wide variation in the incubation period for both infections, and a significant proportion of both groups remains asymptomatic. Gonococcal urethritis and NGU may produce similar symptoms and signs. Both conditions commonly cause urethral discharge, dysuria, and itching, whereas increased urinary frequency and urgency occur less often.

In general, symptoms are more severe in patients with gonorrhea. In one report, discharge and dysuria occurred in 71% of 185 men with gonococcal urethritis but in only 38% of 214 men with NGU (153). Discharge was apparent on physical examination of 99% of men with gonorrhea, and discharge was apparent in 81% of men with NGU. Gonococcal infections tend to be associated with more profuse and purulent discharges (30). There is sufficient overlap in the clinical characteristics of patients with gonococcal urethritis and NGU that distinction based solely on physical examination is associated with a high probability of error.

Occasionally, the discharge associated with NGU is manifest only before the first micturition of the day as meatal crusting or staining of underwear. On initial evaluation some patients may have no objective evidence of urethral inflammation. Almost 50% of such patients had objective evidence of urethritis (mainly NGU) on reexamination before voiding in the morning (332). This implies that when a discharge is suspected on clinical grounds but

not apparent on physical examination, the patient should be reevaluated in the morning after not voiding overnight.

Diagnostic Criteria for Nongonococcal Urethritis

By definition, NGU is diagnosed when microscopic examination of the urethral smear demonstrates inflammatory cells, usually polymorphonuclear leukocytes, without *N. gonorrhoeae.* Observation of more than four polymorphonuclear leukocytes per ×400 oil immersion microscopic field is abnormal and occurs in 60% to 90% of men with symptomatic urethritis (24,292,305,354). Alternative criteria used in clinical investigations of NGU include the combination of urethral discharge and 20 or more polymorphonuclear leukocytes in two or more of five random ×400 microscopic fields of the initial 10 to 15 mL of the urinary stream (21,28). Such definitions are useful in clinical investigations that are limited to evaluating patients with clear-cut disease. In everyday clinical practice, however, these criteria are too restrictive (21,292). Between 16% and 50% of men with culture-proven urethritis have fewer than four polymorphonuclear leukocytes per high-power microscopic field of the urethral specimen (75,320,342). Micturition reduces the number of urethral polymorphonuclear leukocytes (332), and there may be a marked variation in the number of inflammatory cells reported by different observers (398). Presence of even an occasional polymorphonuclear leukocyte suggests urethritis, especially in a patient with symptoms or a small amount of discharge (292). This viewpoint is supported by isolation of *C. trachomatis* from symptomatic men with little or no evidence of increased numbers of polymorphonuclear leukocytes in urethral smears or first-voided urine specimens (22,305). Therefore smears or first-voided urine may be used as a rough guide to the presence of urethral inflammation. As with gonococcal urethritis, cultures or other laboratory tests are necessary to exclude urethral infection with recognized pathogens in men with minimal objective evidence of urethritis (22).

There are few characteristic clinical features that permit distinction between the various causes of NGU (Table 39.1). The two most common causes of NGU are *C. trachomatis,* which is responsible for 30% to 50% of cases, and *Ureaplasma urealyticum,* which may be related to 25% to 35% of cases (21). Various other organisms have been implicated as less common causes of NGU. The remainder of this section considers the epidemiology, biology, diagnosis, and treatment of NGU caused by these organisms.

C. trachomatis

Biology

Although they were initially considered to be large viruses, the chlamydiae are now recognized as small bacteria with a unique growth cycle (317). Chlamydiae are complex microorganisms that have cell walls closely resembling the cell walls of Gram-negative bacteria (38,230,316). Like the viruses, chlamydiae are obligate intracellular parasites. Their genomes are among the smallest of all organisms, but unlike viruses they contain both DNA and RNA. Chlamydiae contain only enough DNA to code for approximately 1,000 ordinary-sized proteins. By comparison, bacteria such as *Escherichia coli* contain sufficient genetic material to code for roughly 3,000 proteins. Chlamydiae thus share many of the basic characteristics of other bacteria, including the presence of both DNA and RNA, a similar cell wall, ribosomes, metabolic enzymes, multiplication by fission, and susceptibility to antimicrobials (195).

The genus *Chlamydia* contains two species: *C. psittaci,* an important pathogen of birds and domestic mammals that rarely causes disease in humans, and *C. trachomatis,* now recognized as a major human pathogen (315). A newly recognized species, *C. pneumoniae* (formerly TWAR), has recently been identified as a cause of acute respiratory disease, including pneumonia (120,183,317).

The species differ in their inclusions and sensitivity to antimicrobials (317). *C. trachomatis* inclusions contain glycogen and therefore stain with iodine, whereas *C. psittaci* inclusions do not stain with iodine. Strains of *C. trachomatis* are sensitive to sulfonamides. In contrast, *C. psittaci* stains usually are sulfonamide resistant. Both species contain a variety of strains with different characteristics. The remainder of this discussion is limited to *C. trachomatis.*

Strains of *C. trachomatis* may be classified according to biologic and immunologic characteristics. *C. trachomatis* strains can infect a limited range of host cells. Non-lymphogranuloma venereum (LGV) strains infect mucosal surfaces but are inefficient at infecting host leukocytes (314,317,345). In contrast, LGV strains infect lymphoid cells and are more efficient at replication in macrophages. Differences between LGV organisms and other *C. trachomatis* strains also are apparent in experimental animals (279,316). LGV strains are not lethal after intracerebral inoculation of mice but do produce conjunctivitis in primates. Thus LGV strains are more invasive in both human hosts and animal models, whereas non-LGV strains of *C. trachomatis* tend to infect mucosal surfaces.

Immunologic studies have identified 15 serotypes of *C. trachomatis,* which can be considered in three broad groups (serovars) based on their clinical syndromes and immunologic characteristics (121,279,383,407). Strains in three serotypes, L1, L2, and L3, are associated with LGV. Serotypes A, B, Ba, and C are associated with hyperendemic-binding trachoma in undeveloped countries. *C. trachomatis* strains belonging to serotypes D through K have been associated with a wide variety of clinical syndromes, including urogenital tract infections such as NGU, epididymitis, cervicitis, and salpingitis, as

well as other conditions such as proctitis, pharyngitis, inclusion conjunctivitis (both infant and adult), and infantile pneumonia (128,195,316,343,345).

Their unique life cycle distinguishes the chlamydiae from other microorganisms (195,314,316,317,345). Like viruses, chlamydiae are obligatory intracellular parasites and thus cannot be cultured on artificial growth media. There are two distinct morphologic forms, the elementary body and the reticulate body, and both forms play essential roles in the chlamydial life cycle (Fig. 39.2) (195,315,316). The elementary body is the infectious particle that is able to survive in the extracellular environment but has limited metabolic capability. The initial step in pathogenesis appears to be attachment of the elementary body to the surface of a susceptible host cell (37,216). Phagocytosis of the attached elementary body is induced by the chlamydial particle. After penetration of the host cell, chlamydiae are contained within the phagocytic vesicle, where they specifically inhibit phagolysosomal fusion and release of the toxic products that normally defend against infection of host cells (316,317). After ingestion, the elementary body undergoes a poorly understood reorganization process to become a reticulate body. The reticulate body is the metabolically active and replicating form of chlamydiae. Reticulate bodies can use host macromolecules for synthesis of chlamydial nucleic acids and proteins but cannot make their own high-energy compounds and therefore are “energy parasites” (14). The reticulate bodies divide by binary fission, starting approximately 8 hours after infection. A second reorganization process begins 18 to 24 hours after infection, as some reticulate bodies transform into elementary bodies. The cycle ends with rupture of the host cell and release of infectious elementary bodies after 48 to 72 hours.

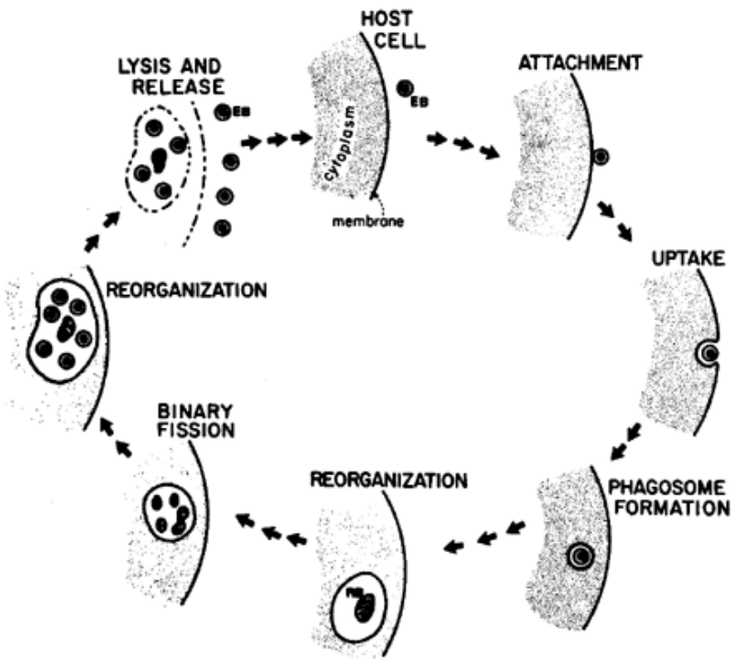

FIGURE 39.2. Life cycle of *C. trachomatis.*

Epidemiology

It has been estimated that there are 89,000,000 *C. trachomatis* infections per year worldwide (345), including 4,000,000 to 5,000,000 infections per year in the United States (51). These infections cost the U.S. health care system an estimated $2.4 billion dollars per year.

C. trachomatis is a major urogenital tract pathogen that is responsible for a significant proportion of NGU (314,345). Several types of evidence support this conclusion, including isolation rates of *C. trachomatis* from different patient populations, studies of anti- *C. trachomatis* antibody titers, and investigations of the postgonococcal urethritis syndrome. The isolation rate of *C. trachomatis* is lowest among asymptomatic men. Especially low rates of chlamydial isolation were reported in studies of asymptomatic men who were screened to exclude pyuria: Only 0% to 3% of such patients had positive urethral cultures (20,29). In other investigations, the incidence of urethral infection with *C. trachomatis* ranged from 0% to 7% of asymptomatic men seen in general medical settings to 15% to 20% of all men attending sexually transmitted disease clinics (140,261,280,314,319,404). In a military population, the 11% incidence of asymptomatic chlamydial infections of the urethra was higher than the 2% incidence of asymptomatic gonorrhea (342). Patients with gonococcal urethritis have chlamydial isolation rates ranging from 4% to 34%, usually 15% to 25% (22,25,140,261,297,365,380,404). Men with NGU had the highest incidence of urethral chlamydial infections, with reported rates ranging from 20% to 58%, usually 30% to 40% (22,140,261,280,297,305,354,365,404).

Serologic studies are complicated by the high background prevalence of antichlamydial antibodies in most adult populations (22,140,314). There is one well-controlled study of men with initial episodes of NGU and few previous sexual partners (29). In this carefully selected population, significant increases in antibody titers occurred in sera from nine of ten men who had symptoms for less than 10 days and positive chlamydial cultures. Measurements of IgM, a transiently detectable antibody that permits diagnosis of recent systemic infection in patients with preexisting antibodies, also supported a role for chlamydiae in NGU. Antichlamydial IgM antibodies were detected in 16 of 20 sera from men with positive urethral cultures but in only 3 of 39 men with NGU who had negative urethral cultures (p <.0001) (29). These findings support the idea that NGU was associated with recent acquisition of chlamydial infection rather than reactivation of a latent infection.

Postgonococcal urethritis is a syndrome of recurrent urethritis after effective treatment for gonorrhea. It is believed that postgonococcal urethritis results from a dual infection

with *N. gonorrhoeae* and another pathogen, most often *C. trachomatis.* In one study, penicillin was used to treat 14 men with dual infections with both chlamydiae and gonococci: 11 patients (79%) subsequently developed postgonococcal urethritis (297). Similar results were obtained in studies with penicillin and other antimicrobials, such as ampicillin, spectinomycin, and gentamicin, that are ineffective against chlamydiae (22,140,262). Two additional observations support a role for *C. trachomatis* in approximately 70% of men with postgonococcal urethritis (22,314). The rate of postgonococcal urethritis is much higher in men simultaneously infected with both *C. trachomatis* and *N. gonorrhoeae* than in *Chlamydia*-negative men with gonorrhea. The rate of postgonococcal urethritis is especially low if a drug such as tetracycline, which also is effective against chlamydiae, is used to treat men with gonococcal urethritis. Thus some men have simultaneous urethral infections with both gonococci and chlamydiae. Because of the shorter incubation period, such patients may develop symptoms of gonorrhea and seek treatment during incubation of their chlamydial infections. Postgonococcal urethritis develops if a drug with no effect against *C. trachomatis* is used for therapy.

Diagnosis

Many methods have been used for laboratory diagnosis of chlamydial infections. Older urologists are familiar with delayed hypersensitivity tests, such as the Frei test, that used a crude antigen preparation to diagnose LGV (316). Variability between antigen lots, cross-reactivity between common antigens of LGV and non-LGV strains of *C. trachomatis,* and availability of more sensitive and specific methods have supplanted use of delayed hypersensitivity tests. Cytologic staining procedures, such as Papanicolaou's stain, also have been used to demonstrate chlamydial inclusions in clinical specimens (316,318). Although useful in diagnosing acute chlamydial ophthalmia neonatorum (128), cytologic methods cannot be recommended to diagnose other clinical syndromes because of their low sensitivity. For example, the accuracy of cytology is only 15% to 20% for diagnosis of chlamydial urogenital tract infections (316,318). Serologic tests are another way to diagnose chlamydial infections. In routine clinical situations such tests are not useful because of the high background prevalence of antichlamydial antibodies in most populations (316,318,384). Although almost all culture-positive patients have antibodies, many culture-negative patients also have positive reactions. Thus a positive serologic test for chlamydiae has low predictive value for current infection. There are certain situations in which serologic tests may have value. A negative serologic test should have a high predictive value for ruling out past chlamydial infections (316). In patients with initial attacks of NGU and few past sexual partners, it may be possible to document seroconversion (29). Serodiagnosis is also useful in cases of chlamydial pneumonia in infants (128) and in diagnosing LGV (316).

Isolating the organisms in culture is the traditional gold standard for diagnosing chlamydial infections. Unfortunately, culture techniques are slow and take a major commitment of laboratory resources and personnel. Early studies used yolk sac isolation procedures taking up to 6 weeks and thus were not useful clinically (157,158,316). Tissue culture methods for *C. trachomatis* were a major advance that permitted screening of large numbers of specimens, with results of initial isolation attempts within 48 to 72 hours (118). Because chlamydiae are obligate intracellular parasites, highest isolation rates are obtained from specimens containing as many epithelial cells as possible (342). Optimal specimens from men with urethritis may be obtained with thin urogenital swabs on an aluminum shaft to obtain intraurethral scrapings, which are preferred to specimens of purulent discharges, secretions, or urine (342). Refrigerated specimens should be transported to the laboratory within 24 hours because inclusion counts decline rapidly after that period. The clinical specimens are inoculated onto tissue culture cell monolayers that have been treated with antimetabolites or radiation to inhibit host cell replication. Mature chlamydial inclusions then are detected in infected cells with iodine, Giemsa, or immunofluorescent stains (342,370). Widespread availability of these methods has been limited by the expense and time needed to isolate *C. trachomatis* in culture.

Automated molecular methods for detecting amplified *C. trachomatis* DNA or RNA are an important advance in chlamydial diagnostics (345). The most widely used methods depend on the ligase chain reaction (LCR) or the polymerase chain reaction (PCR). In high-risk populations, both approaches have proven effective for evaluating urethral and urine specimens. The specificity of these methods has consistently been above 99% (36,71,110,289). LCR and PCR target nucleotide sequences on the *C. trachomatis* plasmid, which is present in multiple copies within each elementary body (317,345). Among high-risk males, these methods have 87% to 100% sensitivity for testing first-void urine. Such molecular approaches detected up to approximately 40% more infections than urethral culture in some studies.(289).

Other approaches to diagnosing chlamydial infections include enzyme immunoassays and PCR and LCR assays (6,94,111,115,130,155,221,323,325,326,328). Each of these techniques offers advantages of speed and sensitivity and obviates routine tissue culture to diagnose chlamydial urethritis. The sensitivity of these new diagnostic methods can exceed that of culture under certain circumstances. Thus screening of urine specimens as an alternative to urethral swabs can be used to evaluate high-risk populations (112,130,155,325,326).

Treatment

Various techniques for *in vitro* susceptibility testing of *C. trachomatis* have been proposed, but there is no widely accepted method (246,314,318,373). The tissue culture assays are in general agreement in demonstrating that the most effective drugs against *C. trachomatis* are rifampin and the tetracyclines (317,345). The macrolides, sulfonamides, some quinolones, and clindamycin are somewhat less effective (246,298,314,316,317,342,373).

Based on clinical data, drugs in the tetracycline and azalide classes are considered the first-choice regimens for uncomplicated *C. trachomatis* infections in adults (Table 39.3) (26,47,48,316,370). Using the tetracyclines, treatment for 7 days or longer appears superior to shorter courses.

Recommended regimens
Azithromycin 1-g single oral dose
Doxycycline 100 mg orally twice a day for at least 7 days
Alternative regimens (if tetracyclines and azithromycin are contraindicated or poorly tolerated)
Erythromycin base 500 mg orally four times a day for at least 7 days
Erythromycin ethylsuccinate 800 mg orally four times a day for at least 7 days
Ofloxacin 300 mg orally twice daily for at least 7 days
Special considerations (if only erythromycin can be used but the patient cannot tolerate high-dose schedules)
Erythromycin base 250 mg orally four times a day for 14 days
Erythromycin ethylsuccinate 400 mg orally four times a day for 14 days

Adapted from 1998 Guidelines for treatment of sexually transmitted diseases. Centers for Disease Control, 1998. *MMWR* 1998;47(RR-1):1, with permission.

TABLE 39.3. TREATMENT FOR NONGONOCOCCAL URETHRITIS

Doxycycline (100 mg orally twice a day) for at least 7 days is a highly effective and inexpensive regimen (72). Azithromycin (1 g orally as a single dose) offers the advantages of a single-dose oral regimen. Treatment with erythromycin (500 mg orally four times a day) or ofloxacin (300 mg orally twice a day) for at least 7 days is an alternative for patients in whom tetracyclines are contraindicated or not tolerated (48,258,303). In contrast to ofloxacin, another fluoroquinolone, ciprofloxacin, had unacceptable failure rates when used to treat chlamydial urethritis in men (147,258,303).

Although some patients have not responded to treatment with tetracycline, the recovered organisms were susceptible *in vitro,* and resistance to tetracycline has not yet been demonstrated in clinical isolates (316). Some studies suggest that occasional isolates of *C. trachomatis* have developed resistance to erythromycin *in vitro,* but this has not reached clinically significant levels (246,316). The sulfonamides are effective both in laboratory studies and clinically for treating patients with trachoma and LGV (318,378). The sulfonamides have not been evaluated extensively for treating other chlamydial genital tract infections because they are not active against other microorganisms that cause similar diseases (47,269,316,318).

Single-dose treatment with azithromycin (1 g by mouth), a new azalide drug, proved effective for uncomplicated *C. trachomatis* infections in a number of recent studies (149,227,252,340,346,395). Single-dose treatment is attractive because such therapy can be administered under supervision to increase patient compliance. Although azithromycin is more expensive than the tetracyclines, this drug is now considered one of the first-line treatments for chlamydial infection (50).

There is no indication for treatment of chlamydial infections with other classes of antimicrobials. Drugs in the penicillin and cephalosporin groups have some activity *in vitro* against *C. trachomatis* but are not useful clinically (25,314,316). Studies in animal models imply that dosages of 20 to 30 million units of penicillin per day would be necessary for clinical efficacy. Occurrence of postgonococcal urethritis amply illustrates the ineffectiveness of suboptimum dosages of drugs in the penicillin class to treat chlamydial urethritis. Rifampin is also active against *C. trachomatis* in tissue culture assays. However, other laboratory studies indicate that chlamydiae rapidly develop resistance to rifampin. There are no current indications for this drug to treat chlamydial infections (67,179,316). Aminoglycosides have no effect against *C. trachomatis* and are widely used to prevent bacterial contamination during growth of chlamydiae in culture. Other antimicrobials, such as cephalosporins, antifungal antimicrobials, and nitroimidazoles, are inactive against chlamydiae (314,320).

Careful evaluation of men with chlamydial urethritis for simultaneous infection with other sexually transmitted pathogens is an important aspect of treatment. Particular attention also should be directed to evaluating and treating sexual partners. Women who are partners of men with NGU should be treated empirically for chlamydial infections with one of the regimens in Table 39.3 (47,52,342). At least 33% have positive cultures, and many infected women are asymptomatic. The doxycycline and azithromycin regimens described earlier are the first choice unless the patient is pregnant. Erythromycin is the treatment of choice for women who are pregnant or possibly pregnant.

U. urealyticum

Biology

U. urealyticum is one of the mycoplasmas, a diverse class of organisms isolated from numerous members of the animal kingdom (101,359). The mycoplasmas are aerobic bacteria

that may be cultivated in complex artificial media (178). The organisms are membrane bound but do not appear on Gram stain (178). Although a number of species have been isolated from humans, most attention has been directed to three species: *Mycoplasma pneumoniae,* a major cause of primary typical pneumonia; *M. hominis;* and *U. urealyticum,* commonly isolated from urogenital tract sites. *U. urealyticum* were formerly known as the *T-strain mycoplasmas* because of their characteristic "tiny" colonies when grown on standard media to isolate mycoplasmas. These organisms were renamed *U. urealyticum* because they are distinguished from other mycoplasmas by their ability to hydrolyze urea, which is a growth-limiting requirement (177,178,331), and because they are the only mycoplasmas inhibited by high concentrations of ammonium (313). The genital mycoplasmas and ureaplasmas are the smallest-known free-living microorganisms. They may be cultured with both solid and liquid media (108). On most solid media the colonies produced by *U. urealyticum* are smaller than those of the other classic mycoplasmas and have a characteristic appearance. A positive reaction for urease activity is used to confirm that colonies with characteristic morphology represent ureaplasmas (108). Because ureaplasmas can be cultured in liquid media without producing the turbidity characteristic of other bacteria, a pH indicator and urea are incorporated into the media (108,330). Breakdown of urea to ammonia results in a change in color of the indicator. There are at least 8 to 14 distinct serotypes of *U. urealyticum* (108,217). However, different systems for serotyping have been described, and there are no generally accepted methods. To date there are no convincing data that particular *U. urealyticum* serotypes are associated with distinct disease syndromes (108,359).

Epidemiology

Neonates are commonly colonized with genital mycoplasmas during vaginal deliveries, but neonatal colonization tends to be transient (108,184,359,362). Cultures of urine or genital specimens from prepubertal boys are rarely positive for the genital mycoplasmas (100,108). Similarly, sexually mature patients with no history of sexual contact are seldom colonized with ureaplasmas or *M. hominis.* Among sexually experienced people the incidence of colonization increases in proportion to the number of sexual partners. In one study of normal men the incidence of colonization with ureaplasmas was 3%, 19%, 41%, and 56% among men with 0, 1, 3 to 5, and more than 14 partners, respectively (232). Black race and lower socioeconomic status have been associated with a higher prevalence of ureaplasmas (108,361). These findings indicate that asymptomatic genitourinary tract carriage of ureaplasmas is remarkably common in adult men.

Evaluation of the importance of *U. urealyticum* as a cause of NGU must account for the high background prevalence of colonization among asymptomatic men (359). Patients and control subjects must be matched carefully for previous sexual experience; comparisons of cloistered monks and patients attending sexually transmitted disease clinics are inappropriate. In addition, laboratory evaluation must include cultures for both *N. gonorrhoeae* and *C. trachomatis,* which are clearly urethral pathogens. For these reasons it is difficult to evaluate most studies of the role of *U. urealyticum* in NGU done before the mid-1970s.

Three lines of evidence support the viewpoint that *U. urealyticum* is an important cause of *C. trachomatis*–negative NGU: isolation studies, antimicrobial treatment studies, and urethral inoculation studies. In some investigations, ureaplasmas were isolated significantly more often from patients with nonchlamydial NGU than from men with *C. trachomatis*–positive urethritis or control populations (29,287,404). However, other investigations have not supported these findings (140,361). Another approach was to compare the numbers of ureaplasmas in men with NGU and in asymptomatic men. In one study of 69 men with NGU, 11 (16%) had both *C. trachomatis* and *U. urealyticum;* 15 (22%) had *C. trachomatis* only; 35 (51%) had *U. urealyticum* only; and 8 (12%) had neither organism (28). Colony counts of *U. urealyticum* were higher in men with nonchlamydial NGU than in men with chlamydial urethritis or matched control populations without urethritis. These data are consistent with the view that larger numbers of ureaplasmas are present when ureaplasmas are urethral pathogens than when they are commensal organisms (28,29,108).

Antimicrobial treatment studies, in which ureaplasmas were selectively eliminated, support the idea that ureaplasmas may be pathogens in NGU (22,257). Some drugs, such as sulfonamides and rifampin, are effective against *C. trachomatis* but not against *U. urealyticum* (22,362). Other drugs, such as spectinomycin and streptomycin, are ineffective for treating *C. trachomatis* but active against *U. urealyticum* (257,362). *C. trachomatis*–negative, *U. urealyticum*–positive NGU responded poorly to treatment with sulfonamides or rifampin (23,67). In contrast, treating similar patients with spectinomycin or streptomycin resulted in elimination of *U. urealyticum* and good clinical responses in most instances (23). In other studies, presence of tetracycline-resistant strains of *U. urealyticum* was associated with persistent urethritis in patients treated with tetracyclines or minocycline (90,305,349).

Intraurethral inoculation was used to fulfill Koch's postulates, demonstrating that ureaplasmas may cause NGU. The authors of one study (360) inoculated themselves with *U. urealyticum* isolates from patients with NGU. Both men developed objective evidence of urethritis. Intraurethral inoculation of primates was associated with colonization with *U. urealyticum* for varying periods and with polymorphonuclear leukocytes on urethral smears from some animals (27,363).

On balance, these data support a role for *U. urealyticum* as an opportunistic pathogen in some cases of NGU (36,359). Some authors maintain that ureaplasmas may be responsible for 30% to 40% of NGU (21,22). However, these organisms also may be isolated from the urethras of many men who have no symptoms or signs of urethritis (232,362). Thus the precise proportion of NGU attributable to *U. urealyticum* is unknown. In urologic practice this proportion appears to be significantly lower than 30%. It is also apparent that isolating *U. urealyticum* from a man with NGU is not equivalent to demonstrating that ureaplasmas are pathogens in that case (108).

Diagnosis and Treatment

Culture systems for isolating *U. urealyticum* are not generally available. Thus diagnosis depends primarily on clinical recognition of syndromes, such as *C. trachomatis*-negative NGU, that can be caused by *U. urealyticum* (359).

The tetracycline and macrolide drugs are most commonly used to treat *U. urealyticum* infections (21,359,365). Because tetracyclines are also the treatments of choice for *Chlamydia*-positive NGU, many strains of ureaplasmas are eliminated simultaneously by such wide-spectrum antimicrobial therapy. Tetracycline-resistant *U. urealyticum* constitute 10% or more of strains in some studies (90,108,349). Tetracycline resistance is caused by the *tet M* plasmid, the same plasmid that codes for tetracycline resistance in *N. gonorrhoeae* (301). Isolating tetracycline-resistant strains from patients with NGU has been associated with lack of response to tetracycline therapy (90,349). Re-treatment with erythromycin is recommended for such patients. A reasonable recommendation is erythromycin stearate 500 mg orally four times daily for at least 7 days, or equivalent dosages of other forms of erythromycin (22). The newer macrolides or quinolones have also been suggested for treating tetracycline-resistant organisms (359). There is little indication for treatment of NGU with the combination of an aminocyclitol (active against ureaplasmas) and a sulfonamide (active against chlamydiae). Drugs such as trimethoprim-sulfamethoxazole or the penicillins are inactive against ureaplasmas.

If cultures for *U. urealyticum* are available, the indications for obtaining such information are not clear-cut. Obtaining routine cultures for *U. urealyticum* can be recommended only in research settings because many perfectly normal, sexually experienced men have positive cultures. Considering ureaplasmas as the primary cause of urethritis in such situations is not warranted (108,232). Obtaining cultures for ureaplasmas from men with *C. trachomatis*–negative NGU who have not responded to conventional therapy may be more reasonable, especially if sensitivity testing is available. In this situation it is more likely that ureaplasmas may be pathogens, and documenting antimicrobial resistance may direct therapy.

Chlamydia-negative, Ureaplasma-negative NGU

Clearly there are patients with NGU in whom neither *C. trachomatis* nor *U. urealyticum* is implicated as a pathogen. Crude estimates may be made about the size of this group of patients. As summarized earlier, *C. trachomatis* has been recovered from the urethras of 25% to 60% (usually 30% to 40%) of men with NGU (21,22). Several lines of evidence suggest that chlamydiae are rarely responsible for NGU in men whose initial cultures are negative. Repeated cultures in untreated men with negative cultures usually are also negative, and such patients rarely have serologic evidence of recent infection with *C. trachomatis* (28,29,124). Chlamydiae are rarely isolated from cervical specimens from sexual partners of patients with negative urethral cultures (140,213,268). Finally, men with *C. trachomatis*–negative NGU usually respond poorly to treatment with antimicrobials effective against *C. trachomatis* (23,29,67,124,148). *U. urealyticum* has been implicated as a pathogen in at most 20% to 25% of patients with NGU (22). Thus neither chlamydiae nor ureaplasmas are implicated in 20% to 50% of cases of NGU. A large number of these patients consult urologists for evaluation.

A wide variety of microorganisms are considered potential pathogens in *C. trachomatis*-negative, *U. urealyticum*–negative NGU. There is good evidence that some organisms, such as *Trichomonas vaginalis,* herpes viruses, and human papillomavirus (HPV), may cause urethritis in men, but the proportion of NGU attributable to infection with these organisms is uncertain. Many other organisms (Table 39.1) also have been associated with NGU in some studies. In the following sections we consider the varied causes of *C. trachomatis*-negative, *U. urealyticum*–negative NGU and appropriate therapy, when indicated, for these infections.

T. vaginalis

Epidemiology and Pathogenesis

The significance of *T. vaginalis* as a cause of genitourinary tract disease in men is controversial (193,206). Many European studies identify *T. vaginalis* as a major cause of morbidity (160,193). Urologic diseases attributed to trichomoniasis include NGU (69,134,392,400), prostatitis (207,209), urethral stricture disease (44,392), balanoposthitis (142), epididymitis (96), and infertility (376).

In epidemiologic studies, NGU was the syndrome most closely associated with *T. vaginalis* (142,193,206). Men with no genitourinary complaints are rarely infected with *T. vaginalis* (209,396). In other studies, *T. vaginalis* was isolated from 1% to 18% of men with gonococcal urethritis (193,388,396). Trichomonads were isolated most often from men with NGU: In one review of 12 studies, 1% to 68% of such patients were infected with *T. vaginalis,* with a mean prevalence of 11% (193). In clinical studies, approximately

16% of sexual contacts of women with trichomonal vaginitis developed NGU within 3 to 8 days (68,69). In another study, Weston and Nicol (392) evaluated 206 sexual contacts of women with trichomoniasis: 93 developed NGU within 5 days. During follow-up studies without therapy, 50% were clear of their infections within 2 weeks, whereas the remaining patients had persistent infections. The prevalence of trichomoniasis was especially high, up to 85%, in men who had not responded to multiple courses of antimicrobials and who had long-standing symptoms (142,193,209). As a rule, these studies suffer from several methodological problems. Control groups generally were inadequate or were poorly matched with cases. In addition, most studies did not investigate other potential pathogens, such as *C. trachomatis,* that may cause NGU.

The alternative viewpoint is that *T. vaginalis* rarely causes symptomatic disease in men (193). In several studies using methods for isolating multiple pathogens, *T. vaginalis* was an unusual cause of acute urethritis (21,22,140). Most of these investigations were concerned primarily with other pathogens, and evaluation for *T. vaginalis* was included primarily for completeness. Thus negative results for fastidious pathogens such as trichomonads must be interpreted cautiously. One potential explanation for the benign and apparently self-limited nature of trichomonal infection in many men is that *T. vaginalis* strains are killed rapidly by zinc salts and other components of prostatic secretions (201,202).

Current ethical standards precluded repetition of human inoculation studies performed from 1940 to 1955, a period before effective antitrichomonal therapy. These studies fulfilled Koch's postulates for *T. vaginalis* as a human pathogen in both sexes (132,212). Of particular interest is the study by Lancely and McEntegart (212), who inoculated five subjects intraurethrally with *T. vaginalis*. Three developed urethral discharge containing protozoa, whereas two had mild urethritis without cultivable organisms. Five control patients inoculated with sterile growth medium showed no abnormalities.

Several recent studies may help resolve these issues. A comprehensive investigation of 447 sexually active heterosexual men found that men with trichomoniasis were significantly more likely to complain of urethral discharge, to have discharge on examination, and to have inflammatory cells in their urethral secretions. *T. vaginalis* remained associated with nongonococcal nonchlamydial urethritis after adjustment for race, age, number of sex partners, exposure to a partner with trichomoniasis, and history of trichomoniasis, urethritis, or gonorrhea (199). Besides nonchlamydial NGU, trichomoniasis was associated with sexual contact with an infected woman and a history of treatment for trichomoniasis or NGU (203). A longitudinal study found that spontaneous resolution occurred in 36% of untreated men, but one asymptomatic man had persistence of *T. vaginalis* throughout a 4-month period (204). Nongonococcal nonchlamydial urethritis was documented in 12 of 21 men (57%) at the visit before treatment or spontaneous resolution, compared with only 2 (10%) after elimination of *T. vaginalis* ($p < .001$).

On balance, these data support the idea that *T. vaginalis* may cause NGU in some men, particularly patients with disease that is unresponsive to conventional antibacterial therapy or that is long-standing (36). It is also possible that geographic variations in antigenic composition of the parasite (197) or differences in intrinsic virulence of various strains (200,210) may explain apparent differences in clinical presentation of male trichomoniasis in various studies. Clearly, the importance of trichomoniasis as a cause of morbidity in men merits further investigation.

Diagnosis and Treatment

Routine evaluation for trichomoniasis is not indicated for men with uncomplicated, acute NGU (21,22,36,294). However, there are groups of men with NGU who merit investigation for *T. vaginalis,* particularly patients with urethritis that has been unresponsive to previous antibacterial therapy, including tetracyclines; men with long-standing symptoms; or patients whose partners have signs or symptoms suggesting trichomoniasis (36,193,292,294).

Diagnosis based solely on the clinical picture is unreliable because symptoms and signs associated with trichomonal urethritis significantly overlap the clinical picture of NGU caused by other pathogens. Diagnosis of trichomoniasis traditionally has depended on direct microscopic identification of motile parasites (142,193,292,294). Most often, a saline wet mount of urogenital secretions or freshly voided urine is examined. Best results are obtained by evaluating specimens with phase contrast or by racking down the condenser of a standard bright-field microscope (292). In expert hands, these methods have a 60% to 70% sensitivity in women when compared with culture but are much less reliable in men (193,196,310). Various staining procedures have been used by different workers. However, such techniques have few advantages over careful examination of the saline wet mount (142,193,229,352). Culture techniques using various liquid and semisolid media proved most accurate for diagnosing trichomoniasis in clinical studies (76,114,136,396). Unfortunately, reliable culture systems are unavailable in most clinical microbiology laboratories. Developing broad-spectrum monoclonal antibodies against *T. vaginalis* has promise for direct diagnosis of protozoa in clinical specimens (196,198). However, molecular detection methods are even more promising (379).

Metronidazole is the treatment of choice for *T. vaginalis* infections in both men and women (105,193,294). Metronidazole is the prototype of the 5-nitroimidazole class of antimicrobials. These drugs have selective activity against anaerobic protozoa and bacteria because the metabolic pathways in such organisms reduce the nitro group producing toxic metabolites (193,294). Aerobic and facultatively

anaerobic organisms may absorb metronidazole but do not metabolize the drug. *T. vaginalis* organisms resistant to high levels of metronidazole have been isolated from patients with refractory trichomoniasis (238,239). Unfortunately, alternative therapy has been limited to other 5-nitroimidazole drugs, which offer no particular therapeutic advantages (193,196,294).

Although some studies have been done in men (45,135,355), most studies evaluating treatment of trichomoniasis have been done in women (105,294). The conventional treatment has been metronidazole 250 mg orally three times daily for 7 days, resulting in cure rates of approximately 95% (291). Several studies using a single oral dose of 2 g of metronidazole have reported cure rates of 85% or more (83,98,204,291).

Trichomoniasis is common in sexual partners of infected women. In one study (392), *T. vaginalis* was isolated from 70% of men who had contact within the past 48 hours. At 2 weeks after the last sexual exposure, 30% remained infected. Simultaneous treatment of male sexual partners of infected women has not been shown to affect the cure rate with the long course of therapy (291). This presumably is related to spontaneous clearance of infection in many asymptomatic men. Simultaneous treatment of sexual partners increases the cure rate with single-dose metronidazole therapy (83,122,291). In addition, treatment is recommended for asymptomatic partners of infected women for epidemiologic reasons and because the long-term effects of a chronic inflammatory focus in the male genitourinary tract are unclear (294). Infected men who have symptoms of NGU, prostatitis, or other urologic conditions need specific therapy. Patients with trichomoniasis and their partners also should be evaluated for other sexually transmitted diseases and treated appropriately.

Viruses

NGU is associated with two viruses: herpes simplex virus (HSV) and HPV.

Genital Herpes Infections

Biology

The term *herpes* originated from the Greek verb meaning “to creep.” *Herpes* is the family name for a group of viruses that infect a wide range of vertebrate and invertebrate species (282,337). The herpes viruses contain linear double-stranded DNA and possess a distinctive morphology and characteristic lipid envelope (337). To date, eight human herpes viruses have been identified: varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, HSV type 1 and type 2 (HSV-1 and HSV-2), and human herpes virus types 6, 7, and 8 (282).

The herpes viruses share several characteristics, including the capacity to cause primary infection in anyone and viral latency and reactivation, with the ability to cause both asymptomatic and symptomatic infections (7). Sexual contact is a significant mode of transmission with cytomegalovirus, HSV-1, and HSV-2. Infection with HSV-1 and HSV-2 may cause urogenital lesions, and both viruses have been associated with NGU (59,60 and 61,63).

Epidemiology

Genital herpes is one of the three most prevalent sexually transmitted infections in the United States (with chlamydial and HPV infections) and, apart from AIDS, probably is of most concern to sexually active people (62). Studies suggest that the incidence of genital herpes increased during the last three decades (59,66). Current estimates suggest 270,000 to 600,000 new cases of genital herpes per year in the United States (12,250). Other estimates indicate that 31 million people in the nation are infected with genital HSV (254). Genital HSV infections are responsible for almost 250,000 initial visits to physicians' offices per year (49). Serologic studies suggest that the prevalence of antibodies to genital herpes is approximately 22% in the general U.S. population, meaning that as many as 45 million people may be infected (62).

The highest prevalence of clinically diagnosed genital herpes is in middle- and upper-class whites (59). In inner-city clinics for sexually transmitted diseases, herpes is diagnosed only one-tenth as often as gonorrhea (349). In contrast, student health clinics treating middle- and upper-class young adults report infections with genital herpes seven to ten times more often than gonorrhea (351). Similar reports from Scandinavia and Japan confirm that genital herpes infections occur most often among single, well-educated patients in their midtwenties (59,171,335).

Transmission of HSV infections usually occurs by close contact with a person who is actively shedding viral particles at a peripheral site, mucosal surface, or secretion (59,60 and 61,63). Genital infections may be transmitted during periods of both symptomatic and asymptomatic viral shedding (66,240). Asymptomatic shedders of virus appear to be important in transmitting HSV genital infections. After primary infection, herpes viruses may enter a stage of latency involving dorsal root ganglia (59,337). Subsequent reactivation may occur despite the presence of circulating antibodies and sensitized lymphocytes (65). Reactivation usually is associated with skin lesions (vesicles) that tend to occur in the same location. The intervals between bouts of recurrent disease vary widely among infected patients.

Clinical Findings

The clinical manifestations of genital HSV infections are highly variable and are determined largely by whether the infected person is experiencing an initial episode of infection or recurrent disease (59,63,65,66,394). First episodes of genital herpes infections may be considered in two

groups, depending on whether patients have clinical or serologic evidence of prior HSV infections (59,65). Patients with primary genital herpes lack evidence of previous HSV infection. Primary genital herpes often is associated with systemic symptoms involving multiple genital and extragenital sites, prolonged viral shedding, and lesions. Urethral discharge and dysuria may occur with either HSV-1 or HSV-2 infections. The best data are available for patients with primary HSV-2: 44% of men experienced dysuria, and 27% had urethral discharge, lasting a mean of 6 to 7 days (59). In such patients, HSV may be isolated from both urethral swabs and first-voided urine specimens. The discharge usually is clear or mucoid in character and has a typical appearance of NGU on Gram stain. Patients who have first clinical episodes of genital herpes but who also have clinical or serologic evidence of previous HSV infections usually experience milder disease than patients experiencing true primary genital herpes.

Approximately 80% of patients with HSV-2 infections experience recurrences after primary genital infections (66). This is higher than the 50% recurrence rate for patients with HSV-1 primary genital infections. Thus the proportion of patients with HSV-2 genital infections tends to increase with time. Recurrent genital herpes is less severe than initial infections (59,60 and 61,63,290). The disease is localized to the genital area. Symptoms are milder and of shorter duration. Dysuria or urethral discharge occurs less often, 9% and 4%, respectively, in one study (59).

NGU caused by genital herpes infections is characteristically associated with external genital lesions. Clinical differentiation of herpetic lesions from other causes of genital ulceration may be difficult (59,60 and 61,63). Patients with urethritis and genital lesions may also suffer from many possible combinations of infectious conditions. Thus laboratory confirmation of the diagnosis is recommended for patients in whom a definitive diagnosis cannot be made (59,60 and 61,63). Specific diagnosis is also helpful in certain situations, such as planning treatment with acyclovir, diagnosing atypical lesions, and educating patients about the risk of transmission (7,66).

Diagnosis and Treatment

Clinical differentiation of genital herpes infection from other genital infections can be difficult. If the patient has multiple grouped vesicles or if there is a history of previous lesions of similar size, duration, and character, then HSV is likely. However, diagnostic testing is recommended because multiple infectious pathogens may be present, to support partner notification and evaluation, and because typing of the viral isolate has prognostic implications.

Isolating HSV in tissue culture is the most sensitive and specific way to diagnose genital herpes infection (59,60,61 and 62). Improved culture methods can diagnose herpes virus infections in 24 to 48 hours (7). Cultures are especially accurate for vesicular lesions but have substantially lower sensitivity for diagnosis of crusted lesions (7). Other diagnostic techniques using antigen detection, PCR, or serologic methods may be useful in some clinical situations, as in patients with crusted lesions or in population surveys (66).

Systemic antiviral chemotherapy for genital HSV can partially control signs and symptoms of primary and recurrent infections and can reduce the frequency of recurrent episodes (52,66). Treatment does not eradicate latent virus and does not affect the risk frequency or severity of recurrences when treatment is discontinued.

Three drugs have been proven effective in randomized clinical trials: acyclovir, famciclovir, and valacyclovir (52,66). The antiviral compound acyclovir has the longest clinical record (59,247). Acyclovir is a nucleotide analog that is selectively phosphorylated by viral-directed thymidine kinase, forming acyclovir monophosphate (64,217,219). Intravenous acyclovir is useful for treating severe infections (60,61,63,312). Oral acyclovir capsules, administered in several dosage regimens, shortened the course of both initial and recurrent genital HSV infections and were effective in reducing the frequency of recurrences (33,62). Valacyclovir is a valine ester of acyclovir that has enhanced absorption after oral administration. Famciclovir, the prodrug of penciclovir, also has high bioavailability after oral administration and high efficacy. Because topical therapy with acyclovir is less effective than systemic treatment, this route of administration is discouraged. Recommended treatment regimens are summarized in Table 39.4 .

Genital herpes
First clinical episode
Acyclovir 400 mg orally three times a day for 7–10 days
Acyclovir 200 mg orally five times a day for 7–10 days
Famciclovir 250 mg orally three times a day for 7–10 days
Valacyclovir 1 g orally twice a day for 7–10 days
Special considerations
Treatment may be extended if healing is incomplete after 10 days
Recurrent episodes
Episodic recurrent infection
Acyclovir 400 mg orally three times a day for 5 days
Acyclovir 200 mg orally five times a day for 5 days
Acyclovir 800 mg orally twice a day for 5 days
Famciclovir 125 mg orally twice a day for 5 days
Valacyclovir 500 mg orally twice a day for 5 days
Daily suppressive therapy for frequent recurrences
Acyclovir 400 mg orally two times a day
Famciclovir 250 mg orally twice a day
Valacyclovir 500 mg orally twice a day
Valacyclovir 1,000 mg orally twice a day
External genital warts
Patient-applied
Podofilox 0.5% solution or gel twice daily for 3 days, then 4 days off therapy; cycle can be repeated up to four times, if necessary
Imiquimod 5% cream at bedtime, then wash off after 6–10 hours; repeat three times a week for up to 16 weeks, if necessary
Provider-applied
Cryotherapy with liquid nitrogen or cryoprobe; repeat every 1–2 weeks
Podophyllin resin 10%–25% in benzoin; repeat weekly if necessary
Trichloroacetic or bichloracetic acid 80%–90%; repeat weekly if necessary

Adapted from 1998 Guidelines for treatment of sexually transmitted diseases. Centers for Disease Control, 1998. *MMWR* 1998;47(RR-1):1, with permission.

TABLE 39.4. MEDICAL TREATMENT FOR GENITAL VIRUS INFECTIONS

Although antiviral therapy may be effective in promoting lesion healing and reducing symptoms, an effective vaccine would be the best approach (3,59,66,337). Heterologous vaccines to other viruses proved ineffective for treating patients with HSV infections. Inactivated HSV vaccines are currently in use in Europe. However, there have been no well-controlled clinical studies of these vaccines. Many authorities in this country are concerned about the oncogenic potential of viral genetic material present in the inactivated virus vaccines. Thus inactivated vaccines are unavailable in the United States. Development of purified subunit HSV vaccines is an active area of research (3,59,282).

Human Papillomavirus

Biology

Genital warts, also known as *venereal warts, gonorrheal warts, condyloma acuminatum,* and *fig warts,* are caused by HPV (224,256,259). These double-stranded DNA-containing viruses also cause warts in other locations, including plantar and palmar surfaces, skin, larynx, and oral and anal cavities (107,189,256,260). After infection of a susceptible cell, the virus stimulates rapid cell division with duplication of the virus (225). Released viral particles are

then transmitted by autoinoculation to other anatomic areas and to other people who contact the infected site (46,225,259).

There was little progress in this field until the late 1970s. Although HPV still cannot be cultivated in the laboratory (107,152,189), advances in molecular biology led to cloning of the HPV viral genetic material and logarithmic increases in our understanding of these viruses (93,152,390). Because much new information is in the general medical and gynecology literature, we briefly summarize important findings and then discuss specific urologic issues.

To date more than 80 distinct HPV types have been described. These are called *genotypes* because classification depends on DNA composition rather than structural antigenic characteristics. More than 30 HPV genotypes infect the urogenital tract predominantly (95,107,189). Genital HPV genotypes may be considered low, intermediate, or high risk for malignancy. HPV types 6, 11, 42, 43, and 44 are associated with low risk (95). Classic, exophytic genital warts usually are caused by HPV types 6 and 11. In addition, these genotypes are associated with low-grade cervical dysplasia (CIN I to II). HPV types 31, 33, 35, 45, 51, 52, and 56 are associated with an intermediate risk for genital malignancy. These genotypes usually are found in low-grade cervical dysplasia and occasionally in high-grade dysplasia and cancers. HPV types 16 and 18 are associated with a high risk of malignancy. These HPV types are seldom found in patients with obvious clinical lesions but often found in genital cancers and high-grade cervical dysplasia (CIN III). Other HPV types have been identified in the urogenital tract, but it is not yet possible to definitely assess their role in neoplasia.

Several lines of evidence support the association between HPV and genital tract cancers. Women with cervical cancer are significantly more likely to have HPV infections than control subjects. In some studies, more than 50% of cervical, vulvar, vaginal, and anal cancers contain HPV types 16 and 18 DNA (116,152). HPV DNA has been identified in cervical cancer metastatic to lung, pelvis, and lymph nodes (37,104). HPV can transform or make normal cells immortal, a critical characteristic of malignancy (107,189).

Three key points from the gynecology literature deserve emphasis. First, although cervical HPV infection is strongly associated with dysplasia and cancer, HPV DNA can be detected in up to 15% of women with normal cervical cytology. Second, HPV types 16 and 18 are the genotypes found most often in women with cervical cancer. Whether women with HPV 16 or 18 and normal cervical cytology are at risk for dysplasia and cancer is uncertain at present. Third, there is no clear evidence that treating asymptomatic male sexual partners changes the natural history of genital HPV infections in women. In fact, limited data suggest that treating subclinical HPV infections in such men makes little or no difference (300).

Epidemiology

Since 1968, there has been a substantial increase in the number of patients with exophytic venereal warts. Recent estimates indicate that there are 24 million people infected with genital HPV infection in the United States (254) and that genital HPV infections are responsible for approximately 300,000 initial visits to physicians' offices per year (49). The annual number of patient visits to physicians for this condition has leveled off at 1 million in the United States; this figure includes more than 64,000 urologic consultations (47,224,245). Epidemiologic evidence supports the idea that genital warts are transmitted sexually in almost all cases (9,109,255). Approximately two-thirds of sexual contacts of infected patients develop similar lesions (9,224,255,256). The usual incubation period appears to be

1 to 2 months but may be up to 9 months in some cases (224,256).

Clinical Findings

As a rule, condylomata occur in areas where stratified squamous epithelium is thin, or on mucous membranes, and have a characteristic appearance, as described in the chapter on skin diseases. Presence of external warts is considered an indication for internal examination by urethroscopy, anoscopy, or speculum because up to 50% of such patients also have internal lesions (224,256). Intraurethral warts often are associated with complaints of urethral discharge, dysuria, bloody spotting on undergarments, or initial hematuria (Fig. 39.3) (21,22,106,225,256,259,292). Most exophytic intraurethral warts are located in the distal urethra (237,368). Cases have been described of intraurethral spread of condylomata to involve the bladder and ureter (251,283,409). HPV viral antigen also has been described in bladder tumors (32). However, in our (unpublished) experience, NGU is an unusual presentation of intraurethral condylomata in patients without visible lesions on the external genitalia or fossa navicularis. HPV infection has been associated with carcinomas of the penis and scrotum (34,284,309).

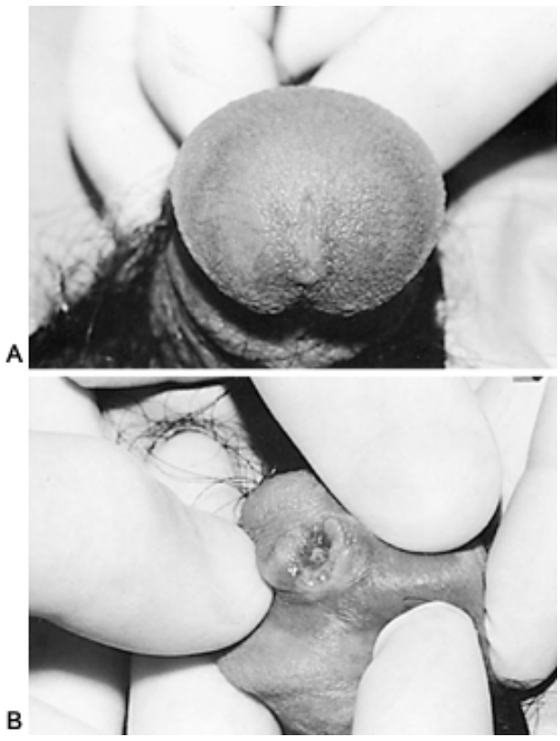

FIGURE 39.3. Normal external genitalia in patient with gross, painless hematuria. **B:** Intraurethral condyloma acuminatum visible only on careful inspection of the fossa navicularis.

Subclinical HPV infection is a new clinical problem. These infections occur in asymptomatic men who are sexual partners of women with HPV. Diagnosis of HPV infections in women is facilitated by characteristic cytologic findings and specific probes for HPV DNA (182,390). After acetic acid is applied, characteristic white areas may be identified on the external genitalia of most sexual partners (216,410). HPV DNA probes and cytology may also help identify urethral infections in such men (241,308,410). The HPV genotypes most often identified are 16 and 18, which are associated with the highest risk for malignancy. Normal tissue also may be infected with HPV (93,220). There is a strong temptation to treat such men aggressively with subclinical infections. The problems with this approach include treatment-associated morbidity, which may be substantial; difficulties in defining the necessary extent of treatment; high recurrence rates; and no evidence that aggressive treatment for subclinical disease alters the natural history of HPV infection in female sexual partners (52,300,410). Thus insufficient data are available to define optimum strategies for managing subclinical HPV infections, but most experts recommend that these men receive no treatment (52).

Medical Treatment

Various treatments for genital warts have been used, but there have been few well-controlled clinical studies (Table 39.4) (52). None of the currently available treatments is completely satisfactory. Caustic agents, such as 10% to 25% in compound tincture of benzoin, are the traditional therapies. Podophyllin has several substantial limitations: Often, several applications are needed; systemic absorption may be associated with toxicity, particularly if the drug is applied to mucosal surfaces; there is potential for stricture formation; and there is a high rate of recurrence. Currently, podofilox, an antimitotic agent, is recommended for self-administered outpatient therapy for exophytic genital warts (50). A 0.5% solution is applied to the lesions twice daily for 3 days, followed by 4 days without treatment. If necessary, the 1-week cycle can be repeated up to four times. Adverse reactions occur in most patients treated with podofilox, especially burning, pain, inflammation, and itching. Data are unavailable on podofilox treatment of warts in the perianal area or genital mucous membranes (urethra, rectum, or vagina). Alternative modes of therapy include surgical excision, cryotherapy, laser therapy, and electrocautery (16,52,109,122,192,224).

Antimetabolites such as 5% 5-fluorouracil or thiotepa may be useful for intraurethral condylomata, but neither has been evaluated adequately (224,225,381). Immunotherapy with interferons is under active investigation for treating patients with genital warts (87,102,173,224,225,322,378). To date, however, the limited efficacy of systemic interferon

does not justify the observed toxicity, and the efficacy of topical interferon is uncertain (181). Topical imiquimod (5% cream) is a new immune-enhancing agent that has proven effective for treating external genital warts (15,218,281,377). Patients apply the cream three times per week for up to 16 weeks.

Patients with genital HSV or HPV infections should be evaluated for other sexually transmitted diseases. Particular attention should be directed to patient counseling about the transmissibility of these infections and to evaluation of sexual contacts.

Cryotherapy and Surgery

Cryotherapy uses liquid nitrogen to destroy warts by thermal-induced cytolysis (16,52). Its major drawback is that without substantial training, warts often are overtreated or undertreated, leading to either efficacy or increased complications. Pain after application of the liquid nitrogen, followed by necrosis and sometimes blistering, can occur. Although local anesthesia is not used routinely, its use facilitates treatment if there are many warts or if the area of warts is large.

Surgery is most beneficial for patients who have a large number or area of genital warts. Surgical removal has the advantage or rendering the patient wart-free, usually with a single visit (16,52). Once local anesthesia is achieved, visible genital warts can be destroyed by electrosurgery, by tangential excision with a pair of fine scissors or scalpel, or by curettage. Because most warts are exophytic, treatment usually can be accomplished with wounds that extend only into the upper dermis. Carbon dioxide laser and more extensive surgery may be useful in managing extensive warts or intraurethral warts, particularly for patients for whom other treatments have failed. Biopsy should be considered for patients with atypical or extensive lesions.

Other Potential Pathogens

Many other organisms are represented as causes of NGU, including fungi, *M. hominis,* and other aerobic and anaerobic bacteria. Fungi are suggested as one cause of NGU. Although occasionally men with yeast balanitis have symptoms of urethritis, controlled studies indicate that fungi rarely are pathogens in NGU (21,28,140). *M. hominis,* the classic large-colony mycoplasma organisms, were first associated with NGU more than four decades ago. These organisms are transmitted by sexual contact and often are isolated from men with NGU (257,362). *M. hominis* may be associated with increased maternal and perinatal morbidity (40,42). However, studies of patients and control subjects who were carefully matched for past sexual experience demonstrated that *M. hominis* is isolated with similar frequency in both populations (41,257,362); thus the current consensus is that *M. hominis* is not a cause of NGU (41,257,362).

M. genitalium is a newly described mycoplasma that was first isolated from the urethras of two men with NGU (374). These organisms are fastidious, and few isolates have been cultivated. In animal models, *M. genitalium* colonization is associated with urogenital inflammation and a significant antibody response (359,375). Because optimum culture systems are unavailable, sophisticated techniques must be used to detect specific DNA sequences (359). There are conflicting data on the role of *M. genitalium* as a cause of urethritis in humans. British investigators used sophisticated molecular methods to detect *M. genitalium* in urethral samples from 24 (23%) of 103 men with acute NGU but from only 3 (6%) of 53 men without NGU ($p < .006$) (359). They also found that the mycoplasma-positive men responded to treatment with doxycycline, suggesting that the association of *M. genitalium* with NGU was causal. Other investigators could not confirm this association (146). Thus, of the genital mycoplasmas, only *U. urealyticum* is generally accepted as a significant cause of urethritis.

H. ducreyi, the cause of chancroid, causes urethritis in infected men (304). However, this disease is uncommon in the United States. Results of some antimicrobial treatment studies suggest a potential role for bacterial pathogens in patients with *Chlamydia*-negative, *Ureaplasma*-negative NGU (22,25,287). In one study 46 such men were treated with minocycline (25). Symptoms persisted or recurred in 24 patients within 6 weeks, but 23 of these "treatment failures" actually improved during therapy. Although this initial response to therapy is consistent with a bacterial cause of *Chlamydia*-negative, *Ureaplasma*-negative NGU, no organism has been established as a pathogen. To date, comparison of the aerobic and anaerobic urethral flora has revealed no significant differences between men with *Chlamydia*-positive and *Chlamydia*-negative NGU (28,354,406). A number of reports describe urethritis associated with *N. meningitidis* infection (126,163,236,400). The clinical presentation of urogenital disease associated with such nongonococcal *Neisseria* appears similar to disease caused by *N. gonorrhoeae.* Various investigators have suggested urethral organisms such as *Staphylococcus saprophyticus* (151), *Corynebacterium genitalium* (103), and *Gardnerella vaginalis* (387) as causes of NGU. However, in controlled studies these organisms were isolated more often from asymptomatic control subjects that from patients with NGU (22,28,29,292). Many other organisms have been suggested as causative agents of NGU in uncontrolled studies, including *H. parainfluenzae* (91), *H. equigenitalis, Clostridium difficile, Branhamella catarrhalis* (22,292,358), and *Bacteroides ureolyticus* (405).

In summary, despite many studies, the cause is unknown for 20% to 30% of NGU cases.

Chronic Urethritis Syndrome

Chronic urethritis can be defined as persistent urethral inflammation without *N. gonorrhoeae* or *C. trachomatis* (198).

Patients usually relate the onset to sexual activity and often to an episode of acute urethritis (22,28). Symptoms often improve during antimicrobial therapy but recur after completion of therapy. The causes and pathophysiology of this syndrome are poorly understood (198).

Several observations suggest that endoscopic examination of the lower genitourinary tract may be useful for evaluating chronic urethritis. Certain infections, such as intraurethral condylomata, may be apparent only on urethroscopy (225). Chronic urethritis may occur with stricture disease, bacteriuria, prostatitis, periurethral abscess, and presence of a foreign body (as discussed later in this chapter). The problem is that few studies have evaluated the role of endoscopy in men with clinically and microbiologically characterized urethritis.

One prospective study evaluated 36 men with chronic urethritis (198). Patients had symptoms for an average of 12 months and failed to respond to an average of five courses of antimicrobial drugs. Structural abnormalities were documented in 9 (25%) of 36 patients but were considered clinically significant in only 4 patients (11%). Physical examination and uroflow testing led to clinical suspicion of anatomic abnormalities in all four patients with significant lesions, including urethral strictures in three and benign prostatic hypertrophy in one patient. Additional abnormal findings included wide-bore strictures in three patients and developmental abnormalities of doubtful significance in two patients. This study suggests that among men with chronic urethritis, careful physical examination and uroflow testing can be used to screen for evidence of structural abnormalities that merit endoscopic evaluation.

NON–SEXUALLY TRANSMITTED URETHRITIS

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Bacterial Urethritis

Urethral discharge may be one feature of many urologic conditions such as urethral stricture disease, phimosis, bacterial prostatitis, and genitourinary tract catheterization, instrumentation, or presence of a foreign body (274). In these cases, the discharge is associated with urinary tract infection and objective evidence of inflammation (polymorphonuclear leukocytes on Gram stain). The causative agents are those commonly associated with bacteriuria. Appropriate antibacterial therapy is important, but often the condition persists until underlying anatomic abnormalities are corrected.

Noninfectious Urethritis Syndrome

Because of the psychologic importance of the genital tract, a significant proportion of patients who complain of urethral discharge or “burning” do not have organic disease. Often, such patients are concerned about the possibility of venereal infection or have feelings of guilt about masturbation or other activities. Microscopic examination of the urethral specimen reveals no evidence of an inflammatory response. An occasional patient repeatedly strips the urethra searching for a discharge that may eventually appear (292).

Infections with recognized urethral pathogens may have minimal symptoms. Some patients with urethritis have totally negative urethral Gram stains on initial examination, particularly if this study is done shortly after micturition. Thus symptomatic patients with negative examinations should be reevaluated before voiding.

COMPLICATIONS OF URETHRITIS

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Urethritis in men is associated with a wide variety of potential complications. Significant complications may result from apparently trivial or totally asymptomatic urethral infections. In this section we consider some of the potential complications of urethritis in infected men, in their sexual partners, and in children. Finally, attention is directed to several syndromes that are related to diseases considered in this chapter.

Complications of Urethritis in the Patient

Epididymitis

Epididymitis accounts for more than 600,000 physician visits per year in the United States and is responsible for more days lost from military service than any other disease (14,403). Sexually transmitted pathogens are responsible for most cases of epididymitis in men younger than 35 years (14,196). Epididymitis is a well-documented complication of gonorrhea. Before the availability of penicillin, epididymitis occurred in 10% to 30% of men with gonococcal urethritis (39,276). In recent studies, *N. gonorrhoeae* was isolated from 16% of men with acute epididymitis in the military (386) and from 21% of men in the civilian population (14). *C. trachomatis* is now recognized as the most common cause of epididymitis in younger, sexually active populations (13,14,127). Formerly, such patients were considered to have idiopathic nonspecific epididymitis. In a careful study, Berger and associates (13,14) identified chlamydiae as the cause of 17 of 34 cases of epididymitis in men younger than age 35 years but in only 1 of 16 cases of epididymitis in men older than 35 years. Other investigators reported similar findings (79,194).

Most cases of epididymitis result from retrograde ascent of urethral pathogens via the ejaculatory duct and vas deferens to the epididymis (13,14,194,195,321). Patients with clinical evidence of epididymitis usually have concomitant disease involving the testis; thus most patients really have an epididymo-orchitis (194,195,253). Inflammation of the epididymis precedes involvement of the testis, and the epididymis is the predominant site of disease. Testicular damage and infertility may persist after resolution of acute epididymitis (253,263). Some studies suggest that many

patients with epididymitis also have involvement of the prostate (79) and seminal vesicles (208).

Epididymitis usually is accompanied by a hydrocele, caused by an inflammatory exudate between the layers of the tunica vaginalis. In severe cases, vascular compromise of the terminal branches of the spermatic vessels may occur, resulting in testicular infarction with abscess formation (150,194,195,266,295,334). The abscess may rupture into the tunica vaginalis, resulting in development of a pyocele. Both grayscale (324) and color-flow Doppler (86,205,242) ultrasonography are useful for evaluating patients with complicated epididymitis.

Painful scrotal swelling is the usual complaint of patients with epididymitis. Swelling may occur over 1 to 2 days or may be more gradual in onset and is commonly accompanied by dysuria or urinary frequency. Urethral discharge is common but often is mild or asymptomatic, especially in patients with chlamydial disease (14,194,195). Initial laboratory studies should include a urethral specimen for Gram stain, urinalysis, and culture of midstream urine. Indications for additional cultures, diagnostic tests, and therapeutic measures depend on the clinical setting and results of these initial studies.

Many patients with sexually transmitted epididymitis do not complain of urethral discharge, and some patients may not have a history of recent sexual contact (14,386). These findings suggest that urethral pathogens may be carried asymptomatically for prolonged periods before the development of epididymitis. Underlying anatomic abnormalities are uncommon in young men with sexually transmitted epididymitis. Accurate diagnosis depends on a high index of clinical suspicion and laboratory evaluation for sexually transmitted pathogens. Specific antimicrobial therapy, generally with drugs active against both *N. gonorrhoeae* and *C. trachomatis,* is the most important aspect of therapy (52,194,195). As a rule, complete anatomic evaluation is not indicated for patients with uncomplicated sexually transmitted epididymitis.

The clinical considerations in older men with epididymitis contrast sharply with those for patients younger than age 35 years. In older men, most cases of epididymitis are related to infections with coliforms, species of *Pseudomonas,* or Gram-positive cocci (13,14,402). Patients with bacterial epididymitis have a high prevalence of underlying urologic disease and often have a history of recent genitourinary tract instrumentation (14,194,195,321). Epididymitis may occur weeks, or rarely months, after urologic operations or manipulations (194,195). The incidence of epididymitis may be reduced by avoiding surgery or instrumentation of an infected urinary tract, if possible, or by using appropriate antimicrobials if manipulation of the infected urinary tract is essential. Specific antimicrobial therapy, accompanied by local measures, such as bed rest, ice packs, and scrotal elevation, is adequate in most cases. Surgery may be necessary to treat complications such as testicular infarction, scrotal abscess, or pyocele of the scrotum (150,324,402). Scrotal exploration with orchiectomy and drainage usually is the treatment of choice. Patients with well-documented bacterial epididymitis also merit thorough urologic evaluation and correction of significant anatomic abnormalities.

Urethral Stricture Disease

Development of urethral stricture has long been recognized as a complication of urethritis (302). Most studies are in the older literature and do not distinguish between structures associated with gonococcal and nongonococcal infections. In 1948, Beard and Goodyear reported a group of patients with urethral strictures who had initial management before the availability of penicillin. In 190 of 211 cases (90%) the strictures were related to past episodes of “gonococcal urethritis.” The shortest time interval between the episode of urethritis and development of the urethral stricture was 18 months, and the longest interval was more than 30 years. An average of 21.5 years elapsed between the episode of urethritis and development of the stricture. These findings were confirmed in a study of patients in undeveloped countries: 91 of 643 men with gonococcal urethritis (14%) developed strictures after an average of 15 years (180). A more recent study found that urethritis was the primary etiologic factor in 45% of 120 consecutive urethral strictures (347).

Complications of stricture disease were common in older series, including acute urinary retention (59%), severe prostatitis (21%), paraurethral abscess (17%), urethral calculi (7%), and urinary extravasation (6%) (11). Inflammatory strictures still account for approximately 20% of cases in contemporary surgical series (19,248). A British study assessed the risk of stricture in 490 men with urethritis; there were 2 strictures in 113 patients with gonorrhea (2%) and 16 strictures in 328 patients with NGU (5%), with short-term follow-up (80). Although the data are incomplete, they support the idea that urethral strictures may complicate both gonorrhea and NGU. It appears that the availability of effective antimicrobials has reduced the incidence of stricture disease, but inflammatory strictures remain a significant problem in urologic practice.

Systemic Diseases

Urethritis may be significant as a cause or an effect of systemic disease. Urethritis may be one clinical feature of generalized conditions, such as Wegener's granulomatosis or the Stevens-Johnson syndrome (292). Primary urethral infections may also result in systemic diseases such as disseminated gonococcal infection or Reiter's syndrome.

Disseminated Gonococcal Infection

Disseminated gonococcal infection is one of the most important complications of gonorrhea. This syndrome occurs in approximately 1% of patients with *N. gonorrhoeae* infections of mucosal surfaces (243). The risk of disseminated

infection appears to be higher in women, particularly in association with menstruation or pregnancy; in whites; and especially in patients with abnormalities of the serum complement system (214,243). Development of septic arthritis or tenosynovitis is the most common clinical manifestation of disseminated gonococcal infection (187,243,329). Other manifestations include hepatitis, myopericarditis, meningitis, and adult respiratory distress syndrome (243). Most patients with disseminated gonococcal infection do not experience symptoms at the initial mucosal site of infection (243). A wide variety of bacterial virulence factors distinguish strains of *N. gonorrhoeae* associated with systemic infections, such as resistance to the bactericidal action of human serum, particular growth needs and colonial morphology, and specific outer membrane proteins (243). Fortunately, gonococcal isolates associated with disseminated disease are susceptible to penicillin (243).

Reiter's Syndrome

Approximately 1% to 4% of cases of NGU are followed by development of Reiter's syndrome (22,129,159,292). Other elements of Reiter's syndrome include arthritis and uveitis. Lesions of the skin and mucous membranes are common. Reiter's syndrome is the most common peripheral inflammatory arthritis in young men (5,292). The condition appears to result from an abnormal host response to a number of infectious agents (5,99,159,292). The current idea that Reiter's syndrome represents an idiosyncratic immune response is supported by the finding of histocompatibility antigen HLA-B27 in 60% to 97% of patients with Reiter's syndrome (164,215). Most cases in Europe and North America follow an episode of sexually transmitted urethritis, but some cases occur after bacterial gastroenteritis. Urethritis usually occurs first, and other features of the syndrome occur 1 to 4 weeks later (391). Arthritis tends to be the most persistent feature of the syndrome and may last 2 to 6 months after resolution of other aspects (5). The syndrome usually resolves spontaneously, but recurrent disease occurs in 35% to 70% of patients, and some patients experience permanent disability.

Urethritis as a Cofactor for HIV Infection

HIV causes AIDS and related conditions. Sexual contact with an infected person is a major mode of transmission of HIV, but the precise risk factors of HIV transmission during sexual contact are not completely understood. Because HIV preferentially infects certain classes of white blood cells, it is reasonable to expect that genital tract inflammation, as described in this chapter, might increase the efficiency of HIV transmission (43,137,341). Epidemiological data suggest that a twofold to fivefold increase in sexual transmission of HIV is associated with other sexually transmitted diseases (139,385). Postulated mechanisms include breaks in the mucosa and recruitment of inflammatory cells (82,134,401). Recent studies also show that HIV levels in seminal plasma are reduced dramatically by treatment of urethritis (58). Limited clinical observations also suggest that other sexually transmitted disease pathogens might adversely influence the clinical course of HIV infection (333).

Complications in Sexual Partners and Children

The most devastating complications of sexually transmitted urethritis occur in female sexual partners of infected men and in children. For this reason every effort should be made to evaluate and treat sexual contacts of men with urethritis.

Female Sexual Partners

Serious complications in sexual partners include development of urogenital cancer and pelvic inflammatory disease and its complications. Epidemiologically, carcinoma of the uterine cervix is a sexually transmitted disease (270). Various sexually transmitted organisms have been associated with cervical carcinoma, including *Treponema pallidum, N. gonorrhoeae, T. vaginalis, C. trachomatis,* HSV, and HPV. The closest associations are with HPV (170,270). There is also limited evidence that other gynecological cancers, such as carcinoma of the vulva, may be related to infection with sexually transmitted organisms.

Development of pelvic inflammatory disease is a consequence of ascending infection by cervical organisms (73,108,138,167,394). Most cases of pelvic inflammatory disease are associated with infection by *N. gonorrhoeae* or *C. trachomatis,* but genital mycoplasmas and a wide variety of aerobic and anaerobic bacteria may also be important (88). Salpingitis is the most common serious infection in young women. Current estimates are that the annual rate of salpingitis is 1.5 per 100 women aged 15 to 19 years, 1 per 100 women aged 20 to 24 years, and less than 0.5 per 100 women over age 25 years (393). These figures lead to estimates that 15% of American women will have had pelvic inflammatory disease by age 30 years (72,88,223,267,393). Besides the cost of caring for patients with acute infections, the social and economic impacts of pelvic inflammatory disease are immense. Tubal damage results in a risk of infertility of about 1 in 25 after a single episode of mild salpingitis. After a moderately severe episode the risk of infertility is one in seven, and after a severe episode the risk increases to one in three. After multiple episodes of pelvic inflammation, more than 60% of patients become infertile (223,394). Pelvic inflammatory disease has also been associated with a sevenfold increased risk for ectopic pregnancy and with chronic pelvic pain (88,394).

Less severe conditions develop in other women whose sexual partners have urethritis. Although dysuria, frequency, and

urgency are common complaints of women with bacterial cystitis, many women with urethral syndrome do not have conventional bacterial urinary tract infections. *C. trachomatis* is commonly isolated from women with dysuria and frequency (106,344). Other sexually transmitted pathogens such as *N. gonorrhoeae* and *T. vaginalis* also may cause irritative lower urinary tract symptoms (292). Sexually transmitted vaginitis is also a common cause of morbidity among women who are sexual partners of men with urethritis (200).

Neonatal Syndromes

Maternal infections with pathogens such as *T. pallidum* or *N. gonorrhoeae* have long been recognized as causes of neonatal disease, congenital syphilis, and gonococcal ophthalmia neonatorum. However, the full range of perinatal morbidity attributable to sexually transmitted pathogens was recognized only in recent years. Spontaneous abortion, stillbirth, premature delivery, low birth weight, neonatal pneumonia, and congenital abnormalities have all been associated with infections acquired *in utero* or during birth (278,279), especially neonatal herpes and HIV infections, which have high mortality and morbidity (62).

RELATED CONDITIONS

Part of "39 - URETHRITIS: ETIOLOGY, DIAGNOSIS, TREATMENT, AND COMPLICATIONS "

Lymphogranuloma Venereum

LGV is caused by certain serotypes of *C. trachomatis,* as discussed earlier in this chapter. The disease is also known as *climatic bubo, strumous bubo, poradenitis inguinalis, Durand-Nicolas-Favre disease,* and *lymphogranuloma inguinale* (278,279). Although common in areas of Africa, Asia, and South America, LGV is encountered only sporadically in the United States (264,278).

LGV is a chronic disease with a wide variety of clinical manifestations (264,278). Three stages of infection usually are described. The primary infection is an inconspicuous genital ulcer, most often located on the genitalia (264,278). Although urethritis may occur, most primary lesions are asymptomatic. The secondary phase is characterized by the inflammatory lymphangitis, which may be accompanied by a painful swelling and purulence in the inguinal nodes; “bubo” formation, known as *inguinal syndrome;* or acute hemorrhagic proctitis, known as *anogenital syndrome* (264,265,278,288). Constitutional symptoms may be marked during this phase. Most patients recover from the secondary phase with no sequelae. A tertiary phase occurs in a few patients. This phase is characterized by a chronic inflammatory response and development of genital ulcers, fistulae, strictures, and genital elephantiasis. In contrast to most other *C. trachomatis* infections, serologic tests are useful in diagnosing LGV. Cultures from genital sites are positive in about one-third of cases (21,278).

Doxycycline 100 mg orally two times a day for at least 3 weeks is the treatment of choice for LGV (Table 39.2) (52). Erythromycin 500 mg orally for a minimum of 3 weeks is the recommended alternative for patients who are allergic or who cannot tolerate the tetracyclines (52). Patients should be followed until all clinical signs and symptoms have resolved. Local lesions commonly warrant management. The current recommendation is that fluctuant lymph nodes be aspirated through healthy adjacent skin with a large-bore needle. More conventional procedures for incision and drainage may result in prolonged drainage and delayed healing (52,279). Surgery may be necessary to treat tertiary complications such as strictures or fistulae.

Paraurethral Gland Infections

Infection of paraurethral structures may complicate urethral or cutaneous infections with sexually transmitted pathogens (226,307,350). Such patients may show minimal symptoms of urethritis and have fluctuant lesions of the median raphe of the penis, of the paraurethral glands, or of congenital defects such as cysts and sinus tracts resulting from incomplete fusion of embryological structures (53,350). Antimicrobial therapy depends on results of appropriate cultures. Surgical excision of abnormal glandular or cystic structures may be necessary in selected cases after the acute inflammatory response resolves (53).

Fournier's Gangrene

In 1883, Fournier described a fulminating gangrenous disease of the male genitalia. Three characteristics were stressed: abrupt onset in a previously healthy young man, rapid progression, and absence of other predisposing conditions. During the twentieth century, a wide variety of alternative names were applied to this disease, including *necrotizing fasciitis of the genitalia* (8,211), *synergistic gangrene of the scrotum and penis* (97), *necrotizing infection of the scrotum* (17), *polymicrobial genital gangrene* (366), and *necrotizing perineal infection* (190). During this period the clinical definition of Fournier's gangrene was enlarged to encompass patients ranging in age from neonates to older adults, patients experiencing a more gradual onset of disease, and patients with a variety of predisposing conditions (1,2,185,212,272,348).

Typically, patients experience swelling and erythema of the genitalia accompanied by fever, chills, and malaise. Physical examination may demonstrate crepitus caused by presence of subcutaneous gas. The inflammatory process may extend along the fascial planes superiorly to the axillae and inferiorly to the perineum (160,222,338). A feculent odor usually is apparent. Predisposing conditions are present in most patients with Fournier's gangrene, including systemic diseases, particularly diabetes; genitourinary tract diseases, especially urethral stricture disease, trauma,

or infection; and gastrointestinal diseases, most often perirectal abscess (77,113,160,168,169,338,382). Aerobic and anaerobic cultures usually isolate a mixture of organisms, commonly including aerobic Gram-negative rods, aerobic Gram-positive cocci, and strict anaerobes, particularly *Bacteroides* species and occasionally clostridia (10,84,160,366).

Fournier's gangrene has a high mortality rate, up to 45% in recent series (160,272,338,348). Cases associated with perirectal disorders appear to have a higher mortality rate (272,348). Early aggressive management offers the best chance for cure. Broad antimicrobial coverage with drugs effective against aerobic Gram-negative rods, aerobic Gram-positive cocci, and anaerobes should be instituted promptly. Surgical drainage is necessary in all cases. Most authorities recommend radical debridement of devitalized tissue (97,160,338). One report of four patients has advocated more limited debridement with placement of through-and-through drains (172). Limited debridement may be effective in some cases, but our experience is that patients with the full-blown syndromes are best treated with aggressive debridement of devitalized tissues. Use of hyperbaric oxygen therapy has been recommended (299) and is reasonable if such facilities are available (1).

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40

UROLOGIC ASPECTS OF AIDS AND HIV INFECTION

John M. Corman

John N. Krieger

J.M. Corman and J.N. Krieger: Department of Urology, University of Washington; Department of Urology, VA Puget Sound Health Care System, Seattle, WA 98195.

Contents

AIDS is the most severe clinical manifestation of infection with HIV. This syndrome is defined by development of serious opportunistic infections, neoplasms, or other life-threatening conditions resulting from progressive immunosuppression caused by HIV infection. The first cases of AIDS were described in 1981, and the number of reported cases has increased rapidly. The first 100,000 AIDS cases were reported during an 8-year period, whereas the second 100,000 cases were reported in a 2-year period (70). Despite these dire statistics, dramatic progress has led to improved management of opportunistic infections, specific antiviral chemotherapy, and improvements in length and quality of life for infected people.

BIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS AND RELATED RETROVIRUSES

Part of "40 - UROLOGIC ASPECTS OF AIDS AND HIV INFECTION "

This section defines the unique properties of retroviruses and considers HIV, the causative agent of AIDS, in the context of other retroviruses.

Retroviruses

The usual flow of genetic information is from DNA to RNA, a process called *transcription,* then from the RNA to protein, a process called *translation.* In retroviruses, this flow of genetic information is different. Retroviruses contain their genetic information in RNA. During replication, a copy of the viral RNA is transcribed by the viral DNA polymerase. This process of reverse transcription is the distinctive characteristic of the retroviruses. The viral DNA is integrated into the host cell genome to establish infection (89,96). Infection with retroviruses seldom results in lysis of host cells. Thus retroviral infection tends to be permanent. Viral propagation within the infected cell can proceed either through production of new virus particles followed by infection of new cells (horizontal transmission) or by replication of infected cells (vertical transmission).

Identifying HIV

AIDS was first described based on several features that suggested an infectious cause. These features included clustering of cases and transmission by sexual contact and blood products. In 1983, Barre-Sinoussi and associates identified a retrovirus that ultimately proved to be the causative agent (4). The causative agent is now called *human immunodeficiency*

virus type 1 (HIV-1). The fact that the causative agent of AIDS is a retrovirus made it possible to predict many of the unusual virus–host relationships and the formidable difficulties that must be overcome to control a slow virus infection (45,89).

Pathogenesis of HIV-1

After the virus gains entry to the host, the first step in HIV-1 infection is binding of the virus particle to the surface of a target cell. After binding to the host cell surface, the virus is internalized and its genetic material is released into the host cell cytoplasm. The viral RNA is then transcribed by the reverse transcriptase enzyme into a linear, double-stranded viral DNA in the host cell cytoplasm. Identification of reverse transcriptase as essential for HIV-1 replication highlighted this protein as a key target for antiretroviral therapy. The viral DNA is transported to the nucleus, where it is integrated into the host cell genetic material. This process is mediated by the viral integrase protein. After integrating the viral genetic material, the host cell is persistently infected. This means that the only way to eliminate the infection is to eliminate all infected cells in the host.

Virus Production from Infected Cells

The integrated viral DNA, called *provirus,* is transcribed into messenger RNA (mRNA) by the host cell's RNA polymerase. Viral mRNAs are translated into structural polypeptide precursors. The HIV-1 viral protease is essential for proteolytic processing of these precursors. Because such processing steps are necessary for infectivity, the viral protease has become an important target for anti-HIV therapy. HIV-1 can also induce fusion of host cells with other cells, forming large syncytia. In this fashion, infected and uninfected cells can fuse. Thus HIV-1 may also be transmitted from one host cell to another without being exposed to the humoral immune system of the host.

Because the CD4 molecule is the primary receptor for HIV-1, any cell that expresses this protein is a target for HIV-1 infection (6). The CD4+ T lymphocyte is extraordinarily susceptible and is the predominant cell type targeted by HIV. However, cells of the monocyte or macrophage lineage also express CD4 and can be infected. Although the hallmark of infection with HIV is progressive depletion of CD4+ T cells, a broad array of defects also occurs in function of a variety of immune cell types.

Pathogenesis

HIV-1 infection is a chronic viral illness that results in gradual destruction of the host immune system, with the occurrence of infections, malignancies, and other signs of immune impairment. Depletion of a particular type of T cells (CD4+) is a primary manifestation of HIV-1 infection. HIV-1 can lyse cultured CD4+ T-cells, but the basis for this is incompletely understood (38,96). One aspect appears to be formation of large, multicellular syncytia in which one infected cell can account for the death of many other noninfected cells. This process appears to depend on expression of the CD4 antigen on the surface of susceptible cells.

Monitoring the total CD4+ T-cell count is the standard method for following disease progression because these levels correlate with the severity of immune suppression. The case definition of AIDS was modified to include patients with a total CD4+ T-cell count below 200/mm^3 without symptoms or any other AIDS-defining illness. The time from infection until development of AIDS can vary greatly, ranging from less than 3 years in some people to decades in others (38). Some infected people may become long-term nonprogressors, but this is rare.

An acute illness resembling mononucleosis may occur at the time of seroconversion, but HIV-1 infection is characterized by prolonged clinical latency (65), with the median period of latency estimated to be approximately 10 years (86). Viral replication continues, associated with a gradual erosion of immune competence during this clinically quiescent period. Opportunistic infections and malignancies develop as the person becomes progressively immunosuppressed.

Antiretroviral Strategies

HIV-1 has developed mechanisms that allow it to persist, spread, and cause disease in the presence of natural immunity. As summarized earlier, these mechanisms include covert infection of cells and tissues, blood, and secretions, as well as refuge in the central nervous system outside the blood–brain barrier. The second major problem is that HIV-1 can produce antigenic variants that may be freed temporarily from immune restraints. Because of these problems, many workers believe that the only way to control HIV-1 is to view it as an intracellular pathogen, seek methods to maintain dormancy of the virus, and prevent progression to disease. A second strategy is to develop means to prevent infection in the first place.

Avoiding Infection

At present, the only way to control HIV-1 infection is to avoid exposure to the virus. For this reason, education is critical to persuade people to avoid high-risk behaviors, in particular intravenous drug use and promiscuity. Current programs for screening blood for antibodies to HIV-1 have almost totally eliminated transfusion-associated infections in this country. The problem remains that many people are already infected and that others will continue to practice

high-risk behaviors. Thus additional strategies are needed for dealing with this infection.

Vaccines

Developing a vaccine to prevent infection by HIV-1 is an attractive strategy. However, many difficult obstacles must be overcome (37). First, the high degree of variability among HIV-1 strains may make development of a vaccine difficult. An effective vaccine must be active against a broad range of types of this virus. Unfortunately, very small changes in the *env* gene may produce large changes in the viral surface, limiting the ability to develop neutralizing antibodies (89,96). A second problem is that there is no good animal model system in which to test vaccines. Use of chimpanzees has been the standard to date, but these large apes are scarce and expensive to maintain, and infected animals do not develop disease. A third problem with vaccine development is that people with natural infections are known to develop antibodies against HIV-1. Such people develop AIDS despite the presence of these antibodies, suggesting that it may be difficult for many humans to mount a long-lasting, protective response against HIV-1 (96). Many investigators hope that if we can develop higher levels of antibodies before the first exposure to the virus, then protection against infection might occur.

Antiviral Chemotherapy

Treatment is necessary for people who are already infected to eliminate or limit the spread of the virus. As antiviral therapy has become more potent, many researchers and clinicians have begun initiating therapy early in the course of HIV-1 infection (38). The goal of such treatment is to reduce the HIV-1 viral load and to limit the rate of disease progression.

During the past decade, a number of agents have been developed that have proven useful (32,38). Established agents fit in one of three categories: nucleoside analog reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors. The nucleoside reverse transcriptase inhibitors have been available longest. These compounds inhibit the viral reverse transcriptase that is essential for HIV-1 replication. These drugs include zidovudine (ZDV, AZT), the first effective antiretroviral, which is an analog of thymidine. Other drugs in this group include didanosine, an analog of adenosine; zalcitabine and lamivudine, analogs of cytidine; and stavudine, also a thymidine analog. The major problem is that these drugs have low potency when used as single agents. All nucleoside reverse transcriptase inhibitors have significant side effects that complicate long-term use. In addition, resistance has been described for all available agents in this class.

The nonnucleoside reverse transcriptase inhibitors also target the HIV-1 reverse transcriptase (38). However, these agents are noncompetitive inhibitors that bind tightly and specifically. Unlike the nucleoside analogs, the nonnucleoside reverse transcriptase inhibitors do not require intracellular activation to interact with the reverse transcriptase. Thus these agents show activity against HIV-1 in resting as well as activated host cells, an important property because resting cells can serve as reservoirs for latent virus. Currently, three nonnucleoside reverse transcriptase inhibitors are approved: nevirapine, delavirdine, and efavirentz. Each of these agents has its own side effect profile. Rapid emergence of resistant HIV-1 strains is the major limitation of the nonnucleoside reverse transcriptase drugs (35,38). Thus the major use of these agents will be in combination with other antiretroviral drugs. Recent data suggest that nonnucleoside reverse transcriptase agents may also be synergistic in combination with various nucleoside analogs, interferons, and protease inhibitors.

Development of the highly active protease inhibitors is the most exciting therapeutic development during the last decade. In short-term studies, the protease inhibitors are at least ten times more potent than previously available drugs in reducing the HIV-1 viral load (88). The amino acid cleavage sites for the HIV-1 protease are specific for HIV-1 and differ from the cleavage site of human host proteases. These agents offer several advantages, particularly the ability to inhibit HIV replication in cells that are chronically infected by a mechanism that is distinct from the mechanism of action of the HIV reverse transcriptase inhibitors. Synergism between the reverse transcriptase inhibitors and the protease inhibitors has been readily demonstrated *in vitro.* Because the protease inhibitors constitute a different class of agents from the reverse transcriptase inhibitors, the toxicity profiles of these two classes of agents are very different, facilitating development of combination chemotherapy. Currently available agents are competitive inhibitors that bind to the active site of the HIV-1 protease. Available agents in this class include saquinavir, indinavir, ritonavir, nelfinavir, and amprenavir. Clinical experience suggests that the HIV-1 protease inhibitors are highly effective agents that are well tolerated by patients (30,51,88). However, each of these agents has a distinct toxicity profile (38).

Combination Antiretroviral Therapy

Clearly, the era of monotherapy for HIV infection is over, with most interest now centered on selecting optimal antiretroviral drug combinations (88). Current strategies institute therapy with a combination of agents, especially with agents that would require HIV-1 to have multiple, separate mutations to develop resistance to all agents in the combination (38). This strategy should reduce or delay the appearance of new mutations and result in substantial and long-lasting reductions in the viral load. Fewer viral replication cycles reduces the likelihood that mutants will arise that escape the immune response of the host. Other potential

advantages of combination therapy are that targeting different stages of viral replication and different tissue and cellular reservoirs of HIV-1 replication may produce synergistic effects of the antiviral agents.

Nevertheless, a number of experts caution that although we are making advances toward the goal of transforming AIDS into a chronic disease whose effects can be largely held in check by treatment, long-term studies with greater numbers of patients are needed. Such caution reflects earlier experience with zidovudine, the first effective antiretroviral drug. Initially high hopes for zidovudine arose from short-term studies showing that zidovudine appeared to extend life in HIV-infected patients. However, zidovudine proved to have only limited ability to reduce viral load. HIV, with its high replication rate, rapidly becomes resistant to zidovudine. AIDS researchers had a rude awakening in 1993. A 3-year study found that asymptomatic patients who began taking zidovudine in the early stages of HIV infection lived no longer than those who began treatment after the onset of AIDS. Researchers wary of premature enthusiasm also point to evidence that HIV can become resistant to the new protease inhibitors. Some suggest that this problem may not be inevitable if these potent drugs, in combination with other agents, can suppress virus levels dramatically, forestalling development of resistance. Other clinicians are concerned about the long-term toxicities of antiviral therapies that may be administered to asymptomatic people for decades. Other potential disadvantages of combination therapy are that treatment with multiple agents may increase the potential for patients to develop multidrug-resistant HIV-1 variants early in the course of infection. In addition, use of multiple agents means that patients must comply with complicated regimens, taking large numbers of pills with substantial side effects over long periods.

DIAGNOSIS, NATURAL HISTORY, AND CLASSIFICATION OF HIV-1 INFECTION

Part of "40 - UROLOGIC ASPECTS OF AIDS AND HIV INFECTION "

Diagnosis of HIV-1 Infection

Infected patients usually are diagnosed by serologic tests that recognize antibodies against HIV-1 antigens (31). Detecting anti–HIV-1 antibodies by enzyme-linked immunosorbent assay (EIA) is highly sensitive (greater than 99%) and specific (95% to 99%) (80). Current technology is in the second or third generation, with EIAs using polypeptide antigens of the HIV-1 core and envelope produced by recombinant DNA technology. Recently developed nucleic acid amplification tests can detect viral RNA or proviral DNA in nearly all HIV-1–infected people (31). Serum samples that are reactive should be retested and repeatedly positive specimens confirmed with a second highly specific test. The most commonly used test is the Western blot. The risk of a false-positive result is estimated to be 1 to 5 per 100,000 people screened. Perhaps more important from a clinical perspective, estimates of the false-negative rate for HIV-1 antibody testing range from 1 in 40,000 to 1 in 1 million. The median time between HIV-1 infection and confirmed seropositivity is approximately 3 months, with 95% or more of infected people positive by 6 months (31). However, the more sensitive third-generation assays have shortened the window period between infection and detection of a serum antibody response. Testing strategies such as HIV culture nucleic acid detection tests may also prove useful (31).

Natural History of HIV-1 Infection

Deficient Cell-mediated Immunity

HIV-1 infection leads to a sequential decline and finally ablation of cell-mediated immunity, eventually leading to manifestations of opportunistic diseases. Therefore HIV-1 infection results in a wide range of clinical presentations ranging from totally asymptomatic carriage of the virus to life-threatening disease (Table 40.1).

Bacterial infections, multiple or recurrent in children <13 years old
Candidiasis of bronchi, trachea, lungs, or esophagus
Cervical cancer, invasive[a]
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month duration)
Cytomegalovirus
Disease other than liver, spleen, or nodes
Retinitis (with loss of vision)
Encephalopathy (HIV related)
Herpes simplex, chronic ulcers (<1 month duration)
Bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month duration)
Kaposi's sarcoma
Lymphoid intestinal pneumonia or pulmonary lymphoid hyperplasia in children <13 years old
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary of brain
Mycobacterium avium–intracellulare complex or *M. kansasii,* disseminated or extrapulmonary
M. tuberculosis, any site (pulmonary[a] or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis carinii pneumonia
Pneumonia, recurrent[a]
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain
Wasting syndrome caused by HIV

[a]Conditions added to the 1993 AIDS surveillance case definition. From Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992; 41(RR-17):1–19.

TABLE 40.1. AIDS CASE DEFINITION

Occasional patients are repeatedly positive by EIA but indeterminate by Western blot (14). Clinically, the concern is that some of these people are in the early window period. However, approximately one-third of the people with indeterminate test results are negative on repeat testing. In general, people considered at low risk for infection who are nonreactive on repeat testing do not need further follow-up. In contrast, high-risk patients should be followed serologically for at least 6 months. Most patients who are infected and asymptomatic may not be ill, but they have a chronic progressive disease that may ultimately lead to significant immunologic impairment or death.

Clinical Spectrum and Progression

The spectrum of HIV-1 infection ranges from asymptomatic infection to severe immunodeficiency with serious secondary infections, neoplasms, and other conditions (27). Initial or primary infection with HIV-1 is associated with an acute mononucleosis-like illness in 50% to 70% of patients. This acute illness associated with seroconversion is characterized by fever, lymphadenopathy, night sweats, myalgia, arthralgia, rash, malaise, lethargy, and sore throat. The interval between exposure and development of the acute retroviral syndrome usually is 2 to 4 weeks, with the illness lasting from 1 to 2 weeks. The rate of progression from asymptomatic disease to AIDS is high and increases with the length of follow-up (66).

Effective antiretroviral therapy and widespread prophylaxis against *Pneumocystis carinii* pneumonia have substantially altered the natural history of AIDS (26). The median survival in treated patients with AIDS ranges from 2 to 3 years. Antiretroviral therapy and prophylaxis against opportunistic infections also extend the clinical incubation from infection with HIV-1 to AIDS. Prophylaxis against opportunistic infections, such as *P. carinii,* means that diseases that occur later during HIV-induced immunodeficiency, such as *Mycobacterium avium–intracellulare complex* bacteremia or cytomegalovirus (CMV) organ disease, may be the first clinical manifestation of HIV disease.

EPIDEMIOLOGY

Part of "40 - UROLOGIC ASPECTS OF AIDS AND HIV INFECTION "

The AIDS Epidemic

The AIDS epidemic usually is dated from the 1981 description of *P. carinii* pneumonia and Kaposi's sarcoma in previously healthy homosexual men. By 1992, AIDS was the leading cause of death for men and the fourth leading cause of death for women 25 to 44 years old (9). Because the surveillance system for AIDS cases relies on availability and willingness of physicians to diagnose and report AIDS cases through local regional and national agencies, there is concern that AIDS cases may be underreported. In 1998, 297,137 people were reported to be living with AIDS in the United States, a 10% increase from the previous year (20). The U.S. Public Health Service has estimated that approximately 650,000 to 900,000 are infected with HIV-1, of whom 200,000 are unaware of their infections (91). Annually, 41,000 new infections occur, and half of the newly infected patients are younger than 25 years (49,72).

Worldwide predictions indicate that the epidemic will continue to grow, with an increasing proportion of infected people living in developing countries. In 2000, an estimated 40 million people were infected with HIV-1, with more than 16,000 new infections per day and with the developing world having approximately 84% of all infected people (70,71).

Modes of Transmission and Major Risk Groups

Three modes of transmission have been described for HIV-1: direct sexual contact, exposure to contaminated blood and blood products, and perinatal transmission. These modes of transmission can occur under a variety of circumstances, and many factors influence the spread of HIV-1.

Sexual Transmission

Sexual transmission of HIV-1 infections may occur between homosexual and heterosexual people. The majority of people with AIDS in the United States are in homosexual or bisexual men. HIV-1 seroprevalence rates in homosexual and bisexual men range from 10% to 70% (22). However, the HIV-1 infection rates in selected cohorts of homosexual men in major cities have clearly declined, reflecting the efficacy of education efforts in this population (48). This has been attributed changes in sexual practices, particularly limiting sexual partners, using condoms, and other practices to avoid exchange of semen. Supporting data for such changes include the declining incidence of other sexually transmitted diseases, such as gonorrhea, in homosexual men since 1982. The increasing use of effective therapy, such as prophylaxis against *Pneumocystis* and antiretroviral therapy, has also delayed the occurrence of AIDS-defining conditions in many HIV-1–infected men.

Heterosexual transmission is now recognized as the major route for spread of HIV-1 in Africa (74). In developed countries, heterosexual transmission appears to be an increasingly common mode of infection. Since 1986, the rate of increase in this group has been higher than the rate of increase of any other exposure category. The increase has been most striking for women infected through heterosexual contact. The number of cases among women infected through heterosexual contact exceeded those infected through injecting drug use for the first time in 1992 (23). The average risk of HIV-1 infection from a single heterosexual contact may be less than 0.1% (69).

Blood-borne Transmission

Intravenous Drug Users

Intravenous drug users are the second largest category of AIDS patients in developed countries. The current seropositivity rate in this population has been estimated to be as high as 60%. Intravenous drug users also appear to be a potentially important link between the reservoir of HIV-1–infected people and the uninfected heterosexual population. For example, women who acquire HIV-1 infection by sexual contact often have partners in high-risk groups, especially intravenous drug users. Female-to-male spread of HIV-1 is commonly associated with commercial sex workers. Many of these women are intravenous drug users or the sex partners of intravenous drug users.

Blood and Organ Recipients

The probability of infection after receiving a single-donor blood product documented to be HIV-1 positive approaches 100% (27). Since the spring of 1985, essentially all units of blood collected in the United States and all organ donors have been screened for HIV-1 antibodies. The result has been near elimination of new HIV-1 infections from blood transfusions and organ donation.

Hemophiliacs

The typical hemophiliac receives approximately 70,000 units of clotting factor concentrates per year (48). Thus hemophiliacs are exposed to many blood-borne infections, particularly viruses. Current studies of hemophiliac men in the United States indicate that the seroprevalence increased from approximately 10% in 1980 to 70% to 80% in 1984. In 1984, heat treatment was found to be effective in eliminating HIV-1 from factor concentrates. This method has been widely adopted, and very few infections currently occur in people receiving factor concentrates (48).

Health Care Workers

See Protecting Yourself and Your Staff later in this chapter.

Perinatal Transmission

Children can acquire HIV infection during delivery, via breast milk, or through any of the mechanisms discussed so far, including blood or blood factor transfusion or sexual exposures. However, most HIV disease in children results from transmission from a parent who is at risk for AIDS. Pooled data from a variety of large studies suggest that infants born to infected mothers have an approximately 25% risk for acquiring HIV. Assessing infection in newborns is complicated by the presence of passively acquired maternal antibody. Thus HIV antibody tests do not reflect the infection status of the infant before clearance of maternal antibodies.

Unproved Modes of Transmission

Other potential modes of HIV spread, including casual contact, human or insect bites, fomites, food, and water, have been investigated. To date there is no proof that HIV infection can be contracted from such sources (27). Combining data from several studies (48), approximately 450 family members and household (nonsexual) contacts of patients with AIDS have been investigated. None was seropositive, although they shared eating utensils, toothbrushes, razors, and toilet articles or kissed patients with AIDS on the lips. In addition, more than 30 patients have been reported who have been bitten by people with AIDS, but none seroconverted (48). There has been some concern about transmission via mosquito bites, but this also appears unlikely. Finally, there are no reports of HIV transmission by food, water, or other articles.

AIDS AND HIV INFECTIONS IN UROLOGIC PRACTICE

Part of "40 - UROLOGIC ASPECTS OF AIDS AND HIV INFECTION "

Genitourinary Tract Involvement

The genitourinary tract may be involved in HIV infections as the site of infections or sequela of immunosuppression.

Immunodeficiency and Urology

Given the systemic nature of AIDS, it is not surprising that the genital tract is involved. This is especially true in patients who die of opportunistic infections. For example, one study (83) of 80 autopsies in patients with AIDS demonstrated that 2 of 11 cases with systemic toxoplasmosis involved the testes, 4 of 48 cases of systemic CMV infection involved the prostate and 1 involved the testes, and 1 of 27 cases of systemic candidiasis involved the prostate. The testes in most patients exhibited marked spermatogenic arrest, germ cell degeneration, peritubular fibrosis, and Leydig cell depletion, nonspecific findings that probably reflect the severe systemic disease in these patients. Other immunocompromised patients develop symptomatic genitourinary tract infections with both common and unusual organisms, such as epididymitis caused by *Candida* (90) or CMV (75).

Renal Infections

Resurgence of tuberculosis is related to the HIV epidemic. The number of new tuberculosis cases in the United States has increased each year since 1986 (27). This increase is closely associated with the HIV epidemic. More than 100,000 people in the United States are coinfected with HIV and *M. tuberculosis*. Although pulmonary findings typically are present in HIV-positive patients, it is not uncommon for genitourinary and genital tuberculosis to be the initial finding (97).

There has been a notable rise in drug-resistant tuberculosis in the United States. People with or at risk for HIV infection appear to be at greater risk for active infection with drug-resistant strains of *M. tuberculosis*. People coinfected with HIV and *M. tuberculosis* have a much greater likelihood of developing clinical tuberculosis, including extrapulmonary disease, and may be more difficult to diagnose and to treat than non–HIV-infected people (27,82). The importance of these trends is that genitourinary and genital tuberculosis are again considerations in evaluating and treating urologic patients.

Other common renal infectious manifestations of AIDS include CMV, *Aspergillus,* and *Toxoplasmosis* infections. CMV is a common opportunistic infection in immunocompromised patients. Renal infection is most commonly noted in widespread disease in association with acute tubular necrosis (57). Although it has been suggested that CMV infection of the kidney might facilitate the development of HIV-associated nephropathy (HIVAN), a recent retrospective study of 75 autopsy kidneys has suggested that the two findings are unrelated (67). *Aspergillus* and *Toxoplasmosis* are common opportunistic infections of the kidney. Both organisms are treated with systemic therapy. Profound infections, as manifest by abscesses, warrant percutaneous drainage.

Penile and Urethral Infections

Both men and women with HIV infection are at increased risk for genital tract infections (26). Genital herpes virus infections may be chronic or recurrent and are associated with increased likelihood of HIV transmission to sexual partners. Genital warts may also be severe and chronic (Fig. 40.1). Other sexually transmitted diseases, such as syphilis, may have more atypical and prolonged manifestations in people with HIV infection.

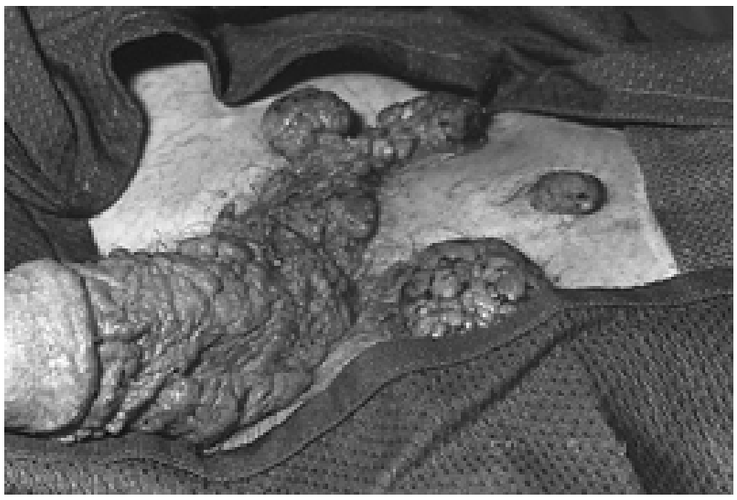

FIGURE 40.1. Extensive condyloma acuminata in a patient with AIDS and human papillomavirus infection.

The first rheumatic disease reported in HIV-positive patients, Reiter's syndrome, consists of uveitis, urethritis, and arthritis and often presents in incomplete form (84). The link between Reiter's syndrome and AIDS is poorly understood. The syndrome, particularly the urethral discharge, usually is refractive to antibiotic therapy. Pelvic inflammatory disease appears to be more common, to be more severe, and to necessitate more frequent hospitalization and surgical intervention in HIV-seropositive women.

Prostatic Infections

The prostate gland is a common site for a variety of opportunistic infections in HIV-positive patients. In one study, bacterial prostatitis was diagnosed in 17 (8%) of 209 men hospitalized for treatment of HIV infections (59). The clinical presentation varies based on the severity of the infection but includes fever, obstructive and irritative voiding symptoms, and a tender prostate on digital rectal exam with possible fluctuance. A superimposed urinary tract infection may be present in up to 22% of patients with AIDS (50). Diagnosis includes broad cultures for aerobes, anaerobes, fungi, and mycobacteria. Prostatic abscesses necessitate open, transrectal, or endoscopic drainage. Bacterial prostatitis necessitates prolonged (6-week) courses of antibiotics with high levels of prostatic penetration. Fungal prostatitis initially is treated with two-agent therapy (amphotericin and flucytosine) with long-term oral fluconazole for persistent or recurrent infections.

Testicular and Epididymal Infections

The most common testicular disorder in AIDS is testicular atrophy (58) secondary to endocrine imbalances, febrile episodes, malnutrition, toxic effects of therapeutic agents, and testicular infections. Autopsy studies have demonstrated opportunistic infection of the testicles in up to 39% of men with AIDS (36). Clinically, scrotal infections usually present as epididymoorchitis. Clinical relapse is common and may result in persistent symptoms or fulminant infection with abscess formation. Documented infection of the epididymis associated with HIV often is secondary to tubule obstruction. Treatment includes initial antibiotic treatment followed by long-term maintenance suppression.

Lymphadenopathy

Generalized lymphadenopathy is common among HIV-infected people, often beginning with the acute retroviral syndrome (26). It is now recognized that 50% to 70% of infected people develop persistent generalized lymphadenopathy and that the natural history of HIV infection associated with persistent generalized lymphadenopathy does not differ from that of HIV infection without generalized adenopathy (26). Involution of enlarged lymph nodes, reflecting degeneration of follicular germinal centers and

loss of hyperplasia, often accompanies progression of HIV infection.

Urologic Malignancies

Given the large numbers of HIV-infected people, it is to be expected that a broad range of malignancies has been described in patients with AIDS and other HIV infections (95). These malignancies include squamous cell carcinomas in various sites, malignant melanoma, testicular cancers of all histologies (1,58,98,99), Hodgkin's disease, and cervical carcinoma (27,95).

Therapy selection for neoplasms in HIV seropositive patients is influenced by several factors. The first is clinical stage of HIV infection. In general, asymptomatic or minimally symptomatic patients should receive standard therapy. Characteristics associated with an increased risk of toxicity following cancer therapy include bone marrow suppression by antiretroviral therapy, leukopenia, and significant immunodeficiency. AIDS-related life expectancy may influence the therapeutic decisions.

Although there is minimal evidence that any cancer is caused by the HIV-induced immunologic deficits, Kaposi's sarcoma, primary central nervous system non-Hodgkin's lymphoma, and high-grade peripheral B-cell lymphomas are now diagnostic of AIDS in patients with HIV infections (19). Although the cause of these AIDS-associated malignancies has not been clearly defined, most authorities believe that deficient immune surveillance is the key factor (95).

Kaposi's Sarcoma

In 1872, Kaposi's sarcoma was first described in older men with pigmented skin neoplasms (10). Classic Kaposi's sarcoma affects the feet and lower extremities of men of Mediterranean and eastern European descent. This disease, rare in the United States before 1981, ran an indolent course that was not associated with HIV. Beginning in the early 1970s, cases of Kaposi's sarcoma were described in patients with organ transplants, particularly kidneys. Kaposi's sarcoma is the most common malignancy in patients with AIDS (64) and was seen in some of the initial cases. The predominant group affected appears to be homosexual men.

In 1981, Friedman-Kien (40) described an aggressive form of Kaposi's sarcoma in 50 previously healthy homosexual men. Epidemiologic, geographic, and molecular biologic evidence suggests that development of Kaposi's sarcoma may be related to coinfection with a second infectious agent (6,24,64). The incidence of Kaposi's sarcoma in HIV-seronegative homosexual men is higher than expected, supporting the hypothesis that the etiologic agent can be sexually transmitted and distinct from HIV. Sophisticated molecular studies identified the newly described Kaposi's sarcoma–associated herpes virus (human herpesvirus 8) in lesions from patients with Kaposi's sarcoma and in some AIDS-related B-cell lymphomas (24).

The typical lesion appears as a subcutaneous, painless, nonpruritic nodule. Lesions often are pigmented and red to blue. Exophytic masses can occur, and they may present with bleeding or pain. Lymphedema is common, as would be expected from any lymphatic lesion (95). Up to 2% of patients with AIDS initially present with penile Kaposi's sarcoma (81). Eventually, up to 20% of patients with Kaposi's sarcoma develop genital lesions. Involvement of the lower extremities is common and may be associated with marked scrotal and penile edema.

Diagnosis usually is made by biopsy. However, once the diagnosis is confirmed, additional lesions can be recognized based on their characteristic clinical appearance. Three variants have been reported (spindle cell, anaplastic, and mixed), but the mixed cellular variant is by far the most common type in patients with AIDS (95). Kaposi's sarcoma is characterized histologically by proliferation of abnormal vascular structures. Three diagnostic features are vascular structures with slits lined by large malignant-appearing endothelial cells, surrounding spindle cells, and extravasated erythrocytes. Most authorities believe that the origin of the tumor is endothelial.

The natural history of AIDS-associated Kaposi's sarcoma is highly variable. Newly diagnosed Kaposi's sarcoma as an initial manifestations of AIDS warrants a multidisciplinary approach (2). Aggressive antiretroviral therapy may significantly influence the course of disease. However, because response to therapy can be highly variable, simultaneous local and systemic therapy against Kaposi's sarcoma often is initiated at presentation. Patients with constitutional symptoms such as fever, night sweats, and weight loss do poorly (95). In the usual setting of HIV infection, Kaposi's sarcoma appears to progress rapidly, often with visceral involvement. Patients who have had previous opportunistic infections, anemia, low CD4 cell counts, and gastrointestinal or pulmonary disease appear to do especially poorly (95). In contrast, patients with a few small lesions and no evidence of opportunistic infection or constitutional symptoms do well.

The optimal therapy is unclear for several reasons. First, the natural history of this tumor is highly variable. Second, no therapeutic agent has been proven to reduce the underlying immune deficit. Third, conventional cytotoxic therapy may cause further impairment of cellular immunity. Classic Kaposi's sarcoma responds well to radiation. The response to radiation is less durable in HIV-positive patients. However, radiation therapy has proven somewhat useful for symptomatic, local disease, with an optimal dosage of approximately 2,500 rads (95). An additional study demonstrated that higher dosages of fractionated radiation therapy improved local control rates (87).

Surgery usually is reserved for biopsy to confirm the diagnosis or for palliation of lesions that bleed or are uncomfortable. Cytotoxic agents also have been used to treat

HIV-associated Kaposi's sarcoma with widespread mucocutaneous disease with some durability. The most active agents include liposomal anthracyclines, paclitaxel, vinca alkaloids, and bleomycin (42,43 and 44,93). Cytotoxic agents are recommended for selected patients with favorable prognostic indicators (26). Biologic agents including α-interferon are now considered first-line therapy for cutaneous Kaposi's sarcoma. Depending on overall CD4 counts and concomitant antiviral therapy, remission rates as high as 60% have been noted.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma was first associated with HIV infection in 1982. The CDC definition for AIDS (15) now includes patients with high-grade B-cell non-Hodgkin's lymphoma in the setting of documented HIV infection. AIDS-associated non-Hodgkin's lymphoma closely resembles that associated with other immune deficiency states.

Invasive Cervical Carcinoma

Women with HIV are at greater risk for invasive cervical carcinoma. Cervical disorders are common in HIV-seropositive women (26). The incidence of cervical lesions increases as immunosuppression progresses. Human papillomavirus coinfection appears to play a major role in the development of cervical atypia and squamous dysplasia. Thus frequent evaluation, including cervical cytology, colposcopy, and other indicated studies, is recommended for women with HIV infection.

Testicular Cancer

Some evidence suggests that an increased incidence of germ cell and non–germ cell testicular tumors may be associated with HIV infection (11,57,58,98). On retrospective review of 3,000 patients enrolled in an HIV clinic, the rate of testicular neoplasms was 50 times greater than that found in the general population (99). HIV-positive patients have a greater risk of tumor bilaterality and a greater risk of developing high-grade testicular lymphoma than HIV-negative people (3,85). The therapeutic dilemma in patients with testicular tumors and HIV-1 infection is that accepted treatments for testicular neoplasms, except surveillance, may result in additional immune suppression. Furthermore, patients with AIDS often tolerate radiation and chemotherapy poorly. This may necessitate major modifications of standard treatment protocols, resulting in decreased effectiveness. Despite these limitations, most experts recommend that men with AIDS or HIV and testicular neoplasms should receive standard treatment as indicated by the tumor histology and stage (98).

Renal Disease and AIDS

Renal disease in AIDS has a varied presentation: electrolyte abnormalities, renal insufficiency, and renal failure. Whether there is a specific AIDS-associated nephropathy is debatable (26). The problem is that many patients with AIDS are at high risk for renal disease because of concomitant factors that have all been associated with renal disorders, such as hepatitis B infection, treatment with toxic drugs, fluid and electrolyte abnormalities, opportunistic infections, and malignancies.

HIV nephropathy, as described in 1984 by Rao (76), is characterized by proteinuria and elevated serum creatinine and by focal and segmental glomerulosclerosis on biopsy. These findings are noted in 5% to 10% of HIV-positive patients. Although this disorder closely resembles heroin-associated nephropathy, only half the patients had a history of drug use. In a review of 75 consecutive patients with AIDS in Miami, 43% had proteinuria (68), and among 36 autopsies, 17 people had renal disorders, including 5 with focal glomerulosclerosis and 12 with mesangial proliferation (68). This AIDS-associated nephropathy is most common in the eastern United States, where there are large numbers of patients who have AIDS associated with intravenous drug use. In contrast, patients with AIDS in San Francisco, Seattle, and other cities have much less renal involvement than those in New York and Miami.

Renal dysfunction associated with HIV disease usually is diagnosed incidentally in patients presenting with opportunistic infections and CD4+ cell counts less that 200/mm^3 (26). The clinical course of AIDS-associated nephropathy is variable. Patients with other causes of renal dysfunction, such as nephrotoxic drugs or acute tubular necrosis, may improve. Others experience rapidly progressive clinical deterioration. Activating cellular immunity through chronic dialysis may accelerate HIV pathology. Renal failure is best managed via peritoneal dialysis, despite the risk of peritonitis, secondary to an overall lower risk of exposure to infections (29). When hemodialysis is instituted, the 2-year survival rate is 50% (39).

Urolithiasis

Indinavir, the third available protease inhibitor, has important urologic toxicity. Kidney and ureteral stones are the most serious adverse effect observed so far in patients taking indinavir, appearing in about 2% to 3% (38,60), but rates as high as 12% have been reported (46,77). The stones are caused by precipitation of indinavir crystals that are nonopaque and may be associated with minimal findings on noncontrast computed tomography examination (7,41).

Our experience is consistent with recommendations for conservative treatment in most cases, consisting of hydration, analgesics, and temporary cessation of indinavir (46,52). Indications for intervention include persistent fever, intractable pain, inability to tolerate oral hydration, or the presence of a solitary kidney. Indinavir crystals, which develop at pH 7.0, can be dissolved when the pH is lowered to 4.0. This suggests that short-term urinary acidification

may be valuable for stone dissolution. After resolution of the acute symptoms and passage of the stone, indinavir therapy can be restarted with aggressive oral hydration (28).

Voiding Dysfunction

Because AIDS and HIV infection affect both central and peripheral nervous systems, voiding dysfunctions are expected. Urinary retention is the most common voiding dysfunction (54%) seen by urologists, although detrusor hyperreflexia (27%) and outflow obstruction (18%) have been documented during urodynamic evaluation of patients with AIDS and voiding symptoms (92). For patients in urinary retention secondary to bladder dysfunction, intermittent catheterization is the treatment of choice. When the patient lacks sufficient manual dexterity, indwelling urethral or suprapubic catheterization is used.

Fournier's Gangrene and AIDS

Fournier's gangrene has a propensity to occur in immunocompromised hosts (12,33,78). This aggressive, progressive, necrotizing fasciitis has been documented as the presenting finding in previously undiagnosed patients with AIDS (63). Treatment of Fournier's gangrene depends on rapid diagnosis, wide surgical debridement, hemodynamic support, and prolonged antibiotic therapy. Diverting colostomy and partial or complete scrotectomy are commonly used during operative debridement. Health care providers must exercise particular caution in the postoperative management of open surgical wounds (discussed later).

HIV, Semen, and Cervical Secretions

Direct contact with semen is important for sexual HIV transmission (34,69). HIV has been isolated by cocultivation of seminal cells and donor lymphocytes (47,100). We found that asymptomatic and minimally symptomatic seropositive men shed HIV in their semen (55,56). Clinical stage of infection, counts of CD4+ cells in peripheral blood, and zidovudine treatment had minimal impact on seminal shedding. These findings are controversial because other studies suggest that HIV shedding in semen occurs most often among men with low CD4+ cell counts in their blood and that antiretroviral therapy reduced shedding (1). In recent studies, HIV was cultured from 36 (17%) of 215 semen specimens from 56 seropositive men, and cytomegalovirus was cultured from 30% of the specimens (54). The CD8+ cell count in peripheral blood was the best predictor of HIV shedding in semen. HIV shedding was more closely associated with concomitant shedding of cytomegalovirus than with the CD4+ count, and antiretroviral therapy had minimal influence on HIV shedding. Lack of a strong relationship between CD4+ cell counts and HIV shedding may be explained in part by recent observation of large differences in virus load in the systemic compartment among subjects with similar CD4+ counts (S.A. Fiscus, R.W. Coombs, and associates, unpublished data). Differences in CD8+ cell counts may help resolve the controversy over the significance of systemic immunologic function, chiefly assessed by CD4+ counts, as a predictor for HIV shedding in semen. Recent studies suggest that treatment with a combination of a protease inhibitor and nucleoside analogs causes a dramatic decrease in cell-free HIV-1 RNA in semen (61,94). This finding could have implications for sexual HIV-1 transmission.

Contact with cervicovaginal secretions of infected women is also believed to be important for sexual HIV-1 transmission. In one study of HIV-seropositive prostitutes (53), cervical HIV DNA was detected in 40 (44%) of 92 women. Presence of cervical HIV was associated with cervical inflammation, suggesting that controlling conditions associated with cervical inflammation might reduce sexual HIV transmission.

Abnormalities on Urinalysis

Abnormalities on urinalysis are common and include hematuria, pyuria, bacteriuria, and proteinuria. One recent study suggested that hematuria occurs in 25% of people infected with HIV (25). Although hematuria may be related to many causes, genitourinary tumors appear to be uncommon, particularly in young men. Thus complete urologic evaluation can be ruled out in young men with asymptomatic microscopic hematuria (25). Proteinuria is also common in certain populations of HIV-positive patients, as considered earlier.

Protecting Yourself and Your Staff

As of June 1997, there were 52 reports of HIV seroconversion in health care workers associated with an occupational HIV exposure (73). Possible occupational transmission, cases in which transmission is likely but for which the CDC's strict criteria were not met, was reported in 114 other health care workers (16). These cases of occupational transmission included three surgeons. In a recent study of 51 seroconversions in health care workers, there was a 95% seroconversion rate within 6 months of exposure (79).

A number of studies evaluated the risk of occupational transmission to health care workers after exposure to HIV-seropositive patients (48). The risk of seroconversion after a needle-stick injury appears to be approximately 0.3% (5). The seroconversion rate after cutaneous exposures to HIV-infected blood is less than 0.09% (17). Several factors may increase the risk of seroconversion for health care workers: a visibly, grossly contaminated needle; a contaminated needle placed directly in a vein; a deep injury; or a hollow-bore needle injury (13,62).

Uniform body substance precautions (18,22) are strongly recommended because all patients are considered potentially infected with HIV. Paramount in this concept is avoiding direct contact with potentially infected body substances, especially blood, urine, semen, and tissue (e.g., during surgery).

To maximize infection control, the urologist must observe three rules. First, there should be no direct contact of blood, semen, or urine with your mucous membranes or nonintact skin. Second, extraordinary care should be used to prevent injuries by sharp instruments during invasive procedures and operations. Recapping needles is especially dangerous and should not be done under any circumstance. Refining puncture-resistant gloves and redesigning needles and other sharp instruments will further reduce injury rates (27). Third, health care workers with exudative skin lesions or weeping dermatitis should not perform invasive procedures. Disturbing case reports document the importance of these recommendations (21).

Postexposure Prophylaxis

Despite the extremely low risk of seroconversion after a health care worker's exposure to HIV-1, the issue of postexposure prophylaxis must be addressed. In deciding whether to proceed with such therapy, several factors are considered: the nature of the exposure, the volume of blood or fluid involved in the exposure, and the infectivity of the exposure source. Because HIV infection does not occur immediately after exposure, there is a chance to intervene before viral replication.

Postexposure prophylaxis must be considered by a health care site well before any potential exposure. Because animal studies suggest that prophylaxis should begin as soon as possible (8), rapid consultation with a provider expert in the field is crucial to discuss the efficacy and toxicity of the involved agents. Although zidovudine is the only agent shown to prevent HIV transmission in humans, combination therapy (including protease inhibitors) may be recommended depending on the nature of the exposure and the resistance of the involved organism.

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41

TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM

Randall G. Rowland

James R. Herman

R.G. Rowland and J.R. Herman: Department of Surgery/Urology, University of Kentucky Chandler Medical Center, Lexington, KY 40503.

Contents

The anatomy and physiology of the scrotum and its contents are discussed in detail in Chapter 1 . In this chapter, infections and benign and malignant masses of the scrotum and its contents are discussed.

INFECTIONS OF THE SCROTUM AND CONTENTS

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

Scrotal Cellulitis

Acute cellulitis of the scrotum typically causes pain and swelling and may include purulent discharge. Associated systemic signs and symptoms include fever and chills and also may reflect the presence and severity of comorbid conditions such as diabetes, malignancy, and obesity. On

physical examination, the affected scrotal skin is warm, thickened, and tender and may have areas of fluctuance or purulent discharge. Presence of necrosis or crepitus suggests Fournier's gangrene (see later discussion). A foul odor may indicate presence of anaerobic organisms in addition to the usual causative agents. In isolated cellulitis, the testes and epididymis, if they can be palpated, are normal, whereas scrotal palpation in patients with secondary skin involvement of an underlying process reveals abnormal intrascrotal findings. Unusual etiologies of scrotal abscess include presentation as a complication of ruptured appendicitis (1,79,134,173) and as urethral or scrotal squamous cell carcinoma (119). Scrotal ultrasonography often is useful when the physical findings are inconclusive.

Causative organisms are typically those associated with cellulitis elsewhere; *Staphylococcus* sp., and *Streptococcus* species, particularly group B, are isolated most frequently (12,74). Unusual organisms such as *Pseudomonas* species from hot tub exposure (55), *Haemophilus influenzae* (18), and *Candida albicans* (87) also are reported.

Therapy is dictated by the physical findings. Culture of purulent material and antibiotics are the mainstay of therapy. Control of associated comorbid conditions such as diabetes also is important. Surgical debridement, dressing changes, and hydrotherapy often are helpful. Unfortunately, infection of the scrotal wall or contents may progress to become a life-threatening, necrotizing fasciitis involving the scrotum and perineum; therefore careful follow-up is important.

Epididymitis and Orchitis

Acute infection of the epididymis and testis typically causes scrotal pain and a local mass. Timing of the onset of symptoms is variable because symptoms may not develop for weeks and, rarely, months following exposure. Often, systemic symptoms of fever, chills, and abdominal pain also are seen with an acute infection of the scrotum. Early physical findings usually allow localization of the infection; however, later in the course of the disease, development of epididymoorchitis or an inflammatory hydrocele may obscure physical findings, and in the more severe forms, testicular infarction/abscess formation also may occur (Fig. 41.1). Generally, tenderness and swelling associated with viral orchitis are localized to the testis, and the epididymis and cord structures are normal to palpation. Acute epididymitis, on the other hand, results in induration and tenderness of the affected epididymis and is often associated with thickening and tenderness of the vas deferens. Extension of the epididymal mass and tenderness that also involves the testis heralds development of epididymoorchitis. However, the epididymal component is typically both earlier and predominant in symptomatology (99,100,136).

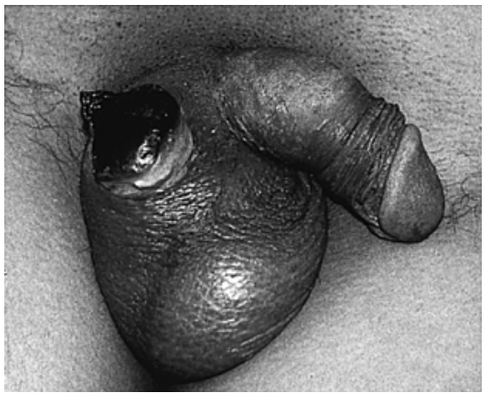

FIGURE 41.1. Testicular abscess involving the scrotal wall. Necrotic testicular tubules are present in the center of the wound in this paraplegic patient.

Other causes of acute scrotal pain and swelling of the testis/epididymis such as torsion must be excluded (see Chapter 53). Establishing the etiology of the acute scrotum is critical to appropriate management. Scrotal ultrasonography with or without Doppler flow studies often is helpful in identifying abscess formation and excluding torsion in young patients (52,103,121,171). Initial studies should include urinalysis with culture following urethral swab for Gram stain. Additional tests are directed by the history and physical examination.

The causative agent of isolated orchitis is typically viral, whereas the cause of epididymitis and the more advanced epididymoorchitis is almost always bacterial. Viral etiologies primarily include mumps in the postpubertal patient (60); however, immunization-induced orchitis and other rare viral orchitis, including coxsackie A and B virus, have been reported (104,122,208,215). Infections of the vas deferens and epididymis often are associated with infection of the lower urinary tract. As discussed in Chapter 38, in men younger than 35 years of age, the most likely pathogens are sexually transmitted bacteria (9,101,102) (Table 41.1). In fact, in the antibiotic era, *C. trachomatis* is the most commonly isolated pathogen in this younger population (9,10,73).

Cell Type	Average Incidence (%)	Range (%)
Seminoma	42	34–55
Embryonal carcinoma	26	23–34
Teratocarcinoma	26	9–32
Teratoma	5	1–6
Choriocarcinoma	1	1–4

Data tabulated from Johnson DE. Epidemiology. In: Johnson DE, ed. *Testicular tumors,* 2nd ed. Flushing, NY: Medical Examination Publishing, 1976:37.

TABLE 41.1. PRIMARY CELL TYPES OF GERM CELL TESTIS TUMORS IN 2,562 CASES FROM NINE SERIES

In the older age group and in patients with congenital or acquired defects of the genitourinary system, such as benign prostatic hyperplasia, spinal cord injury, or recent instrumentation (9,10,99,100,168), the most prevalent organisms include the coliforms, *Pseudomonas* species and Gram-positive cocci (9,10,211). Other rare infections of the epididymis and testes include tuberculosis, brucellosis, histoplasmosis, and idiopathic granulomatous epididymoorchitis (31,67,155,165). Last, in a Houston inner-city hospital, some 30% to 50% of patients with epididymoorchitis presenting in the emergency center are newly found to be HIV positive (24).

Coinfection with HIV is well documented in patients diagnosed with bacterial urethritis (82,205). Therapy includes antibiotics directed at likely pathogens, bed rest, and scrotal elevation. Surgical exploration and drainage occasionally are required to treat complications such as infarction or abscess (83,171,211). Unfortunately, testicular injury with persistent infertility following resolution of infection may occur (136,141).

Fournier's Gangrene

Fournier first described necrotizing fasciitis of the perineum in 1883 when he described five cases of an idiopathic fulminant necrotizing fasciitis in otherwise healthy young men (54). More recent series recognize a synergistic polymicrobial disease affecting the scrotum, penis, and perineum originating from genitourinary, colorectal, or idiopathic sources (5,6,7,22,76). Infection arising from penile and periurethral sources is discussed in Chapter 38 .

Clinical presentation is highly variable, and a high index of suspicion and knowledge of the clinical appearance are important for recognition and prompt treatment of this life-threatening infection. Smith and co-workers reported pain, erythema, scrotal swelling, shock, ileus, delirium, and crepitus (50% to 62%) as the most common physical findings (180). Recent series report 32% to 60% of patients are diabetic (22,76,180). Additional conditions associated with Fournier's gangrene include alcoholism, AIDS, prolonged hospitalization, malignancy, intravenous drug use, and malnutrition, all of which represent some degree of immune suppression (7,49,76,106,118,131,132,180).

This rapidly progressive infection represents a polymicrobial infection involving primarily *Escherichia coli*, *Bacteroides*, staphylococci, *Proteus*, streptococci, *Pseudomonas*, enterococci, and *Clostridium perfringens* (6,22,43,145).

Anatomically, the fascial planes of the perineum determine the extent and direction of spread. Condensation of Colles' fascia to form the perineal body with lateral fixation at the pubic rami and fascia lata tends to define the posterior and lateral extension. On the anterior abdominal wall, Colles' fascia becomes Scarpa's fascia and becomes the dartos on the penis and scrotum, allowing free progression of the disease onto the anterior-abdominal wall and thorax to the axillae. Scrotal wall and testicular sources tend to follow along these same planes. Infection arising from the periurethral glands may penetrate Buck's fascia and, rarely, the urogenital diaphragm to involve the space of Retzius. An anorectal source may follow the aforementioned planes or may spread into the space of Retzius, then down along the spermatic cord to involve the testis, scrotum, and penis. Smith and co-workers suggest that perianal involvement can be used to distinguish between an anorectal source and a urogenital source (180).

Treatment of Fournier's gangrene has not changed significantly following availability of antibiotics; it remains a surgical emergency. The infection can spread within a few hours; therefore prompt recognition; stabilization; broad-spectrum antibiotics covering Gram-positive, Gram-negative, and anaerobic organisms; and surgical debridement are indicated. Typically, a penicillin to cover Gram-positive organisms, a third-generation cephalosporin or aminoglycoside to cover Gram-negative organisms, and metronidazole to complete coverage of anaerobic organisms are used. The mainstay of treatment remains early surgical debridement. Physical findings typically under estimate the extent of the disease (Fig. 41.2A and Fig. 41.2B). The surgical team should be prepared for the possibility of laparotomy, extensive debridement, diversion of the fecal and urinary streams, and placement of enteral or parenteral access as indicated. Before debridement, proctoscopy, retrograde urethrogram, or cystoscopy should be performed. The goal of surgical debridement is to remove all devitalized tissue. The urethra and uninvolved testicles can frequently be preserved (Fig. 41.2A and Fig. 41.2B). Placement of the testes in abdominal or thigh pouches has been advocated; however, the authors prefer to cover the testes with saline soaked dressings, allowing granulation with delayed coverage with split-thickness skin grafting. Generally, areas of fascitis involvement can be identified easily and all overlying necrotic tissue should be removed until the wound borders contain viable tissue.

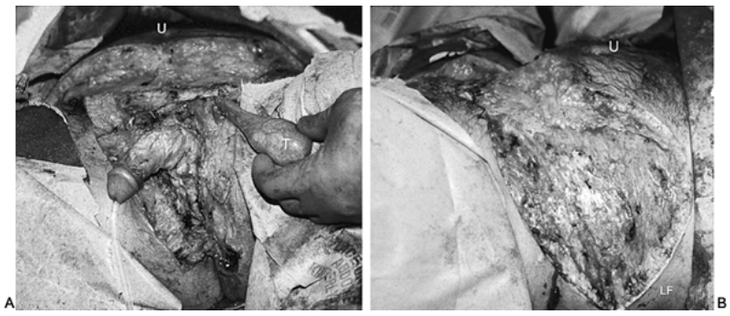

FIGURE 41.2. Fournier's gangrene arising from a right scrotal wall source in a patient with diabetes and hepatic insufficiency. The left testicle is shown with its intact tunica vaginalis in **A**. In **B,** the lateral and superior extent of disease progression is demonstrated. Before debridement, examination under anesthesia and proctoscopy confirmed a scrotal source, then all necrotic tissue was removed. Following debridement, a diverting colostomy was performed along with placement of an internal feeding tube before transfer to an intensive care unit. The urinary system was managed by Foley catheter (the urethra and its blood supply also were preserved.) LF, left flank; T, testis; U, umbilicus. (From Johnson DE, Woodhead DM, et al. Cryptorchism and testicular tumorigenesis. *Surgery* 1968;63:919, with permission.)

These patients are critically ill and commonly require correction of electrolyte abnormalities (including hemodialysis), mechanical ventilation, volume expansion with colloids, or blood products and crystalloids. Pressure support with dopamine or epinephrine is also commonly required. Of paramount importance is sufficient caloric and protein intake to allow wound healing. Some authors also have advocated use of hyperbaric oxygen (19,148,216) although it remains controversial and should not delay prompt surgical debridement (180). Local wound care should follow standard surgical principles, with wet to dry dressings, using saline in combination with hydrotherapy and sitz baths. Others have recommended peroxide, Dakin's solution, or honey during dressing changes (43).

Once the infection has cleared, the surgical defects can be allowed to close by secondary intention with skin grafting as needed. Nonmeshed skin with a ventral Z-plasty closure for the penis and meshed skin over the granulating testes and cord structures works well. Ventral Z-plasty graft closure on the penile shaft minimizes ventral chordee, and meshed graft over the testicles and cord structures simulates the rugated appearance of the scrotum.

Despite early recognition and prompt surgical debridement, Fournier's gangrene remains a disease with significant mortality. In modern series, mortality ranges from 18% to 25%, including HIV/AIDS patients who fare no worse than average (6,7,22,43). Age, extent of disease, spread onto the abdominal wall or thighs, shock or sepsis at presentation, positive blood cultures, lack of colostomy, and elevated blood urea nitrogen (BUN) (greater than 50 mg/dL) are reported as risk factors (7,43).

BENIGN LESIONS OF THE SCROTUM AND CONTENTS

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

Spermatocele

A spermatocele is a cystic structure that arises from the epididymis. It usually is located superior to the testis within the tunica vaginalis and represents aneurysmal dilation of a rete testis tubule. Infection, obstruction, and trauma have been proposed as etiologic factors. On examination, the structure will transilluminate. Spermatoceles are filled with a milky fluid that contains spermatozoa. They are found most commonly in middle-aged men.

The diagnosis usually is made easily upon physical examination. Scrotal ultrasound is very helpful in confirming the diagnosis if there is any doubt on physical examination. No treatment is needed unless the patient has significant discomfort from the mass. However, caution is advised in patients still considering fertility because either direct injury or perioperative fibrosis may affect adjacent rete testis tubular patency. Elective, simple transscrotal excision is satisfactory treatment as long as there is no evidence of a testis tumor.

Varicocele

A varicocele is a dilation of the pampiniform venous plexus and the internal spermatic vein. This condition is present in up to 20% of males. It is usually present on the left side. Incompetence of the venous valves where the left gonadal vein inserts into the left renal vein is most often cited as the cause of a varicocele. Distention of the veins is more prominent when the patient is standing and generally decreases when he is supine.

Retroperitoneal pathology such as left renal tumor with vascular invasion, retroperitoneal lymphadenopathy, or retroperitoneal sarcomas can cause venous obstruction with the formation of a varicocele. The sudden onset of a

varicocele or an isolated large right varicocele should prompt investigation of the retroperitoneum.

In most patients, a varicocele is of no clinical significance. A small percentage of patients are hypofertile. A varicocele is associated with oligospermia, decreased sperm motility, and an increase in the percentage of abnormal sperm forms (stress pattern). Brown and colleagues demonstrated venous communications between the two testes and pampiniform plexuses (14). Although several causes of the infertility have been proposed, the venous communications between sides probably accounts for the generalized changes seen in the presence of a unilateral varicocele.

Symptomatic varicoceles include a patient with infertility and stress pattern on semen analysis or if he complains of scrotal or testicular pain. Patients usually describe their pain as an ache or heaviness exacerbated by prolonged periods of standing or straining. Ligation of the ipsilateral internal spermatic vein through an inguinal incision is recommended under these circumstances. Many patients enjoy an improvement in sperm counts and quality. Scrotal ligation of the veins has been unsuccessful because of development of collaterals. Internal spermatic vein ligation also is performed for those patients who have severe local symptoms from large varicoceles. In the last several years, ligation of the internal spermatic vein has been performed with laparoscopic techniques by some urologists. Recurrent or persistent varicocele has been treated with transcutaneous embolization (194).

Hydrocele

A hydrocele is a fluid collection in a serous space, usually between the layers of the tunica vaginalis (Fig. 41.3). This space can be totally isolated around the testicle (hydrocele of the testis); it can occur as an isolated structure along the tunica vaginalis of the cord (hydrocele of the cord); or persistent patency of the tunica vaginalis can allow the sac within the scrotum to communicate with the peritoneum (congenital or communicating hydrocele). The hydrocele fluid is usually amber and translucent. Its specific gravity generally ranges from 1.010 to 1.025, consistent with an exudate. The albumin content varies between 3 and 6 g/dL. An example of a hydrocele of the testis (around a normal testis) is shown in Fig. 41.4 . *Hydroceles* may occur as a congenital abnormality where the process vaginalis fails to close. In this case, an inguinal hernia is virtually always associated with the malformation. Congenital hydroceles are most common in infants and children. In adults, hydroceles are more frequently due to infection, tumor, or trauma. Infection of the epididymis of testes often results in the development of a secondary hydrocele. Tropical infections such as filariasis also may produce hydroceles, with marked fibrous thickening of the tunica, and the hydrocele contains a milky fluid with a rather large amount of sediment. The turbidity of the fluid is due to chylous drainage caused by lymphatic obstruction (89). If the hydrocele is caused by filariasis, cholesterol and calcium deposits in the tunica are common. Tumors are a less common, although certainly more significant, cause of hydrocele development. The most common tumor is a germ cell testis tumor, followed by tumors of the testicular adnexa. Hydroceles also can result from trauma to the testis and cord structures. One additional cause of hydrocele is ipsilateral renal transplantation. It has been estimated that in up to 70% of patients with ipsilateral renal transplantation, hydroceles develop from division of the vas deferens and spermatic vessels (182).

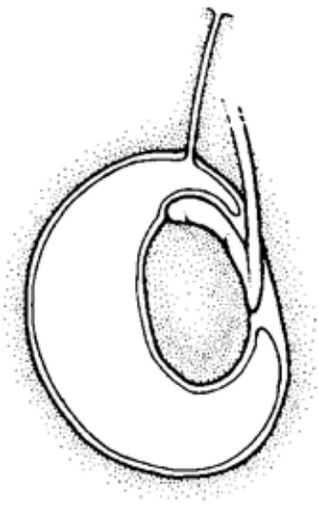

FIGURE 41.3. A hydrocele is a fluid collection in the serous space between the layers of the tunica vaginalis. The process vaginalis may or may not remain patent, allowing the hydrocele to communicate with the peritoneum.

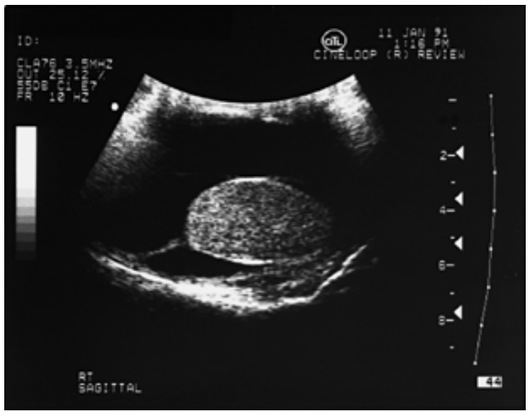

FIGURE 41.4. Ultrasonograph of a normal testis within a hydrocele.

After the cause of a hydrocele has been determined in an adult, no therapy is needed unless the hydrocele is large enough to make the patient uncomfortable or there is a significant underlying cause for the hydrocele, such as a tumor. In the past, “conservative” treatment consisted of aspiration of the hydrocele with or without the injection of a sclerosing agent to attempt to fix the tunica vaginalis to the

tunica albuginea. These treatments generally were unsuccessful and are discouraged. Andrews and Wylly described one of the first surgical corrections in 1907. They named the procedure the “bottle operation.” In this procedure, the hydrocele was opened high along its anterior aspect. The testicle was delivered through the incision, and the inverted hydrocele sac was tacked to the cord structures behind the testis. In a variant of this procedure, the hydrocele was incised anteriorly, the excess of the hydrocele sac was trimmed away, and the cut edges were oversewn with sutures for hemostasis and were tacked posterior to the testis and cord structures (Fig. 41.5). In 1964, Lord described a procedure for the repair of hydrocele that was thought to be an improvement based on the fact that the previously reported procedures often were accompanied by the development of hematomas. The Lord procedure is illustrated in Fig. 41.6 . Twenty-two consecutive cases were reported without hematoma (114).

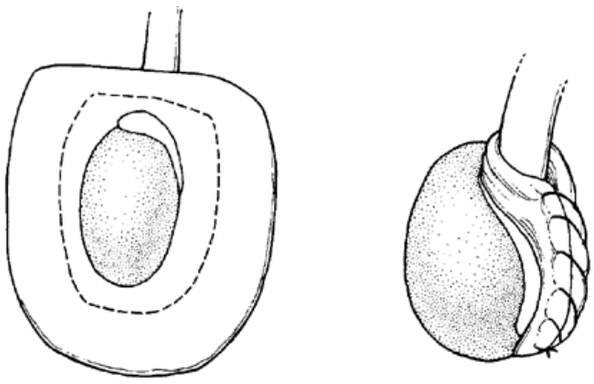

FIGURE 41.5. Jaboulay and Winkelmann modified the procedure described by Andrews and Wylly by excising the excess hydrocele sac before sewing the edges of the sac posterior to the testis.

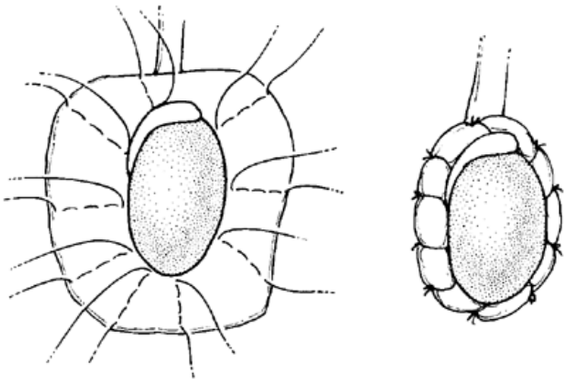

FIGURE 41.6. In the Lord procedure, radial sutures are used to gather the hydrocele sac around the posterior aspect of the testis and epididymis.

Of the various procedures, the Lord procedure seems to be the most appropriate for thin-walled hydroceles, and the excision eversion (Jaboulay-Winkelmann) procedure seems more appropriate for patients with a thickened, indurated tunica. Frequently, a scrotal drain is left for 24 to 48 hours after repair of the hydrocele.

MALIGNANT LESIONS OF THE SCROTUM AND CONTENTS

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

Testis Tumors

Epidemiology

In 2000, testis tumors will account for approximately 1.1% of all neoplasms in males (71). Historically, testis tumors are the second most common malignancy (behind leukemia) in the 20- to 35-year-old age group (143). The classic article by Dixon and Moore on testis cancer cited an incidence of 2.8 cases per year per 100,000 men in the U.S. Army between 1940 and 1947 (32). A similar incidence of 2.3 cases per year per 100,000 men in England was reported by Collins and Pugh (25). This report was from data gathered in the late 1950s and early 1960s. More recently, an incidence of 2.8 per 100,000 is reported in the Surveillance Epidemiology and End Results (SEER) database from 1992 to 1996 (71).

A longitudinal study of the incidence of testis tumors in males in Copenhagen was reported by Clemmensen (23). The incidence of tumors rose from 3.2 per 100,000 in 1943 to 6.3 per 100,000 in 1962. A similar rise was noted by Skeet in England (178). The author reported an increase in incidence from 2.3 per 100,000, as reported by Collins and Pugh from the late 1950s and early 1960s, to 3.76 per 100,000 in the period 1967 through 1971. The 2000 edition of the SEER database summary allows comparison of trends in SEER incidence over the 1975 to 1979 and 1992 to 1996 periods. The incidence rose 3.2% in the former and fell 2.8% in the latter period (71).

Dixon and Moore's publication of the Armed Forces Institute of Pathology classification of testis cancer made it possible to collect data on the various histologic types of testis cancer. Before that time, inconsistent terminology made it difficult to compare the distribution of tumor types in different series. These authors reported that 97% of all testis neoplasms were of germ cell origin, while 3% were of non–germ cell origin. Many series of testis cancers have been published since the Dixon and Moore report in 1952 (32). Johnson reported the distribution of the predominant cell type in testis in tumors in nine series (92). A total of 2,562 cases were reported. Seminoma was the most frequent predominant cell type, followed by embryonal carcinomas, teratocarcinoma, teratoma, and choriocarcinoma. Table 41.1 shows the average percentage of each tumor cell type along with the range of percentages reported for each cell type.

Testis tumors have been reported from infancy to age 89 years. Seminomas tend to appear later, and the average age of appearance in various series ranges from 30.7 to 41.9 years (142,143,193). Embryonal carcinoma is seen slightly earlier, with an age range from 26.1 to 33.0 years (95,144). For choriocarcinoma, the average age of onset is lower, ranging from 24.0 to 26.3 years (95).

The incidence of testis tumors in different racial and geographic populations has been studied and reported by many authors. Dixon and Moore reported that the incidence of testis tumor was lower in nonwhites than in whites (32). They found that testis tumors in nonwhites constituted 1.5% of their series, although nonwhites made up 6.07% to 8.5% of the total U.S. Army population, which was the source of their series. Teppo reported a set of data showing that the rate of testis tumors was less than 1 per 100,000 in nonwhite populations, while most white populations had an incidence of greater than 1 per 100,000, with the exception of Finland, which had a rate of 0.9 per 100,000 (192). A more detailed report on testis tumors in black Africans showed that the low incidence of tumor was due primarily to an exceedingly low incidence of seminoma and teratoma, while the incidences of other cell types were similar to those in white populations (191).

It also is interesting to note that there is a difference in the incidence of seminomas in rural and urban populations within the same country. An increased rural incidence was reported by Lipworth and Dayan for England and Wales during the period of 1961 through 1967 (111). The same observation was made in New York by Sharma and associates from Roswell Park Memorial Institute (174).

Testis tumors seem to be slightly higher in incidence in the right testicle than the left. Several authors propose that this can be explained by the higher incidence of cryptorchism on the right, and by the association of testis cancer with cryptorchism (107). The relationship of testis cancer and cryptorchism is discussed further in a subsequent section of this chapter.

In summary, testicular tumors are several times more common in most white populations than they are in nonwhite populations. In general, the incidence of testis cancer seems to be increasing with time (23). The existence of multiple tumor registries will make it possible to record pertinent epidemiologic data with greater detail in the future.

Etiology

Many authors have postulated chemical or viral exposure as possible etiologic agents for testis cancer; however, trauma, atrophy, and cryptorchism are the factors most commonly thought to be associated with the disease.

A history of testicular trauma has been reported in 8% to 25% of all patients with testis cancer (25,97,142). Most of these authors feel that trauma does not have a role in the history of testis cancer, but more likely provides the mechanism for the discovery of a testicular mass by the patient. From his review of patients in the literature, Gilbert promoted the role of atrophy as a possible etiologic factor in testis cancer when he reported that 80 of 5,500 patients (1.5%) with testis tumor had developed the tumors in atrophic testes (65). The cause of atrophy of the testis in these patients was not specified. A history of mumps orchitis with subsequent atrophy of the testis was present in 24 patients (0.5%) who developed testis cancer. In light of this association, although this is a small percentage of the total patients with testis cancer, Hausfield and Schrandt recommended immediate orchiectomy if any suspicious mass was noted in an atrophic testis (75). This is probably sound advice in the case of an atrophic or a normal testis. Fortunately, additional diagnostic aids such as ultrasound and tumor markers are now available to help make the diagnosis.

The potential for a cryptorchid testis to develop a tumor was first described by LeComte in 1851 (108). Data from several series indicate that even after orchiopexy is successfully performed, the testis in question has a persistently elevated risk of development of a subsequent testis tumor. Johnson and colleagues have demonstrated that the contralateral testis also is at risk, even if it was normally descended at the time of birth (93). In approximately one-fifth of patients with a history of cryptorchid testis and subsequent development of testis cancer, the tumor occurs in the contralateral, normally descended testis (81).

The general consensus at this time is that orchiopexy should be performed between the ages of 1 and 2 years. Orchiopexy before age 1 year is contraindicated because of the possibility of spontaneous descent of the testicle within the first year of life. If a cryptorchid testis is still present and has been untreated after the patient has reached puberty, the testis should be removed instead of being relocated in the scrotum. This recommendation is made on the basis of observations that the cryptorchid testis has lost the capacity for spermatogenesis. Even in patients who have undergone early orchiopexy, long-term follow-up is required because of the increased incidence of subsequent development of testis tumor in this patient population. It is critical that the patient be taught the techniques of self-examination of the scrotal contents as soon as he is old enough to thoroughly understand the procedure.

Pathology

As previously noted, primary neoplasms of the testis fall into two groups. The majority are tumors arising from germ cells; these account for 94% to 97% of cases (32,126). The remaining portion of primary testicular neoplasms is made up of tumors arising from nongerminal elements. These account for 3% to 6% of all testicular neoplasms.

Classification of testis tumors has fallen along two different lines: the American and British classifications. The early

foundations of the American classification were based on work by Friedman and Moore (59). Proposed in the 1940s, this classification was based on a study of 1,000 testicular neoplasms from the Army Medical Museum that were collected during World War II. In this scheme, each group of tumors was assumed to be a distinct histologic type. The five categories suggested were seminoma, embryonal carcinoma, choriocarcinoma, teratoma, and teratocarcinoma.

Further studies in this area by Dixon and Moore (32) and Mostofi and Sobin (127), reporting the consensus of the World Health Organization classification of testis tumors, and Teilum (190) have helped develop the current American working classification of testis tumors. This classification is based on the premise that all seminoma and nonseminomatous tumors originate from totipotent germ cells. A schematic diagram of this concept based on work by Teilum (190) and Friedman and Moore (59), among others is presented in Fig. 41.7 . Embryonal carcinomas can develop further into embryonic structures, such as teratoma, or into extraembryonic structures, such as yolk sac tumors or choriocarcinoma.

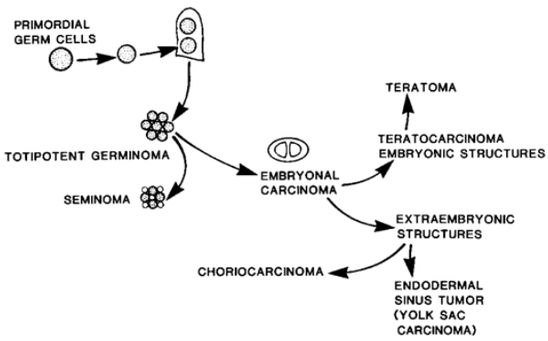

FIGURE 41.7. Schematic drawing of the origin of germ cell testis tumors and analogous germinal, fetal, or placental structures.

By contrast, the British scheme, which was presented initially by Willis (209) and modified and expanded by Collins and Pugh (25), is based on the concept that nonseminomatous tumors develop from teratoma. Embryonal carcinoma fits into this scheme as a single cell-type tumor developing from teratoma. As in the American system, the British system agrees that seminoma develops from germ cells. For the remainder of this chapter, the current American pathologic classification of germ cell testis tumors is used. This classification is given in Table 41.2 .

Precursor lesion
Intratubular germ cell neoplasia (unclassified type equivalent to "carcinoma *in situ*")
Tumors of one histologic type
Seminoma
Variant: seminoma with syncytiotrophoblastic cells
Spermatocytic seminoma
Variant: spermatocytic seminoma with a sarcomatous component
Embryonal carcinoma
Yolk sac tumor (endodermal sinus tumor)
Choriocarcinoma
Teratoma
Mature teratoma
Immature teratoma
Teratoma with an overtly malignant component
Monodermal variants
Carcinoid (pure and with teratomatous elements)
Primitive neuroectodermal tumor
Tumors of more than one histologic type
Mixed germ cell tumors (specify individual components)
Polyembryoma and diffuse embryoma

TABLE 41.2. CLASSIFICATION OF TESTICULAR GERM CELL TUMORS

Seminoma

Seminoma is the most common tumor of a single cell type. At presentation, the testis may be enlarged as much as ten times without loss of its normal shape. On cut surface, the tumor is usually solitary with distinct borders. It is pink-white, smooth, and usually homogenous (125). In addition to primary tumors in the testicle, seminoma can occur in extragonadal sites such as the retroperitoneum, mediastinum, pituitary, or pineal regions. Seminomas also are more common than nonseminomatous tumors in undescended testes. As noted earlier in the chapter, the patient's age at presentation is generally several years older than for nonseminomatous tumors.

Microscopically, the seminoma cells are uniform and have clear cytoplasm and well-defined cell borders (125). In the ovary, this tumor is called *dysgerminoma.* Three histologic types of seminoma have been described: typical, anaplastic, and spermatocytic (124). Initially, the anaplastic variety was thought to carry a graver prognosis, while the spermatocytic variety, which usually presented later in the patient's life, was thought to carry a more optimistic prognosis. Currently, the differences in prognoses of patients with these tumors are debatable.

Embryonal Carcinoma

At the time of clinical presentation, embryonal carcinoma usually is seen as a smaller, more asymmetric testicular mass than seminoma. Grossly, on the cut surface, the embryonal carcinoma is very heterogeneous (125). Microscopically, the tumor usually occurs in a solid form and does not have the lobular pattern of seminoma. Embryonal carcinoma cells tend to be larger, demonstrate more pleomorphism, have more mitoses, and have less distinctive cell membranes with nuclear overlapping than seminomatous tumor cells. Glycogen can be shown in embryonal carcinoma cells by the periodic acid–Schiff technique (126). Embryonal carcinoma

tends to metastasize early and often demonstrates other cell types in the metastatic sites.

Yolk Sac Tumor (Endodermal Sinus Tumor)

This was originally described as a rare tumor of infancy and childhood. Telium thought that the histologic findings in this tumor were similar to the endodermal sinuses present in the rodent (189). Pierce and coauthors compared the tumor to a mouse yolk sac or vitelline tumor (146). Synonyms for this tumor include *infantile embryonal carcinoma, orchidoblastoma, embryonal carcinoma of infants and children,* and *embryonal carcinoma of the prepubertal testis.* Yolk sac elements are found in 38% of adult patients with testis tumors. In 10% of patients, the yolk sac tumor is the dominant element of mixed adult testis tumors. No pure adult yolk sac tumors have been reported in series by Talerman (186) or Roth and Panganiban (161).

In gross appearance, the yolk sac tumor is very similar to embryonal carcinoma. Microscopically, four patterns have been recognized in the testis (187,190). The first microscopic pattern is the *microcystic and myxomatous pattern.* Microscopically, under low power, the tumor is similar in appearance to a honeycomb. Cysts are lined by flat mesothelium-like cells, and many mitoses are present. The second histologic pattern is called the *endodermal sinus pattern.* Perivascular formations known as Schiller-Duval bodies are present. Schiller-Duval bodies are similar to the endodermal sinuses seen in the rat placenta. The third microscopic formation is called the *solid cellular pattern.* In this group, aggregates of small polygonal cells with clear cytoplasm and frequent mitoses are present. The fourth pattern seen in testis tumors is the *alveolar glandular* or *cystic pattern.* Eosinophilic globules are noted inside and outside tumor cells and have been shown to contain α-fetoprotein. They are considered analogous to Reichert's membrane in the mouse embryo (147).

Polyembryoma

Polyembryoma is an unusual tumor composed primarily of embryoid bodies (127). The embryoid body is described as a structure containing a disk and cavities surrounded by loose mesenchymal cells simulating an embryo of approximately 2 weeks' gestation. The presence of embryoid bodies does not make the tumor a polyembryoma. Actually, embryoid bodies are found more often in embryonal carcinoma and teratoma because the polyembryoma tumor is so rare.

Choriocarcinoma

At clinical presentation, choriocarcinoma tumors are often extremely small. Despite their small size, wide metastatic spread is common. On cut surface, the tumor tends to show large areas of hemorrhage with a small rim of viable tumor. Microscopically, two cell elements must be present to qualify as choriocarcinoma: syncytiotrophoblasts and cytotrophoblasts. Pure choriocarcinoma is rare. It is found much more often in association with other tumor elements. Syncytiotrophoblasts often form the leading edge of the tumor and allow it to erode in blood vessels, which probably accounts for the large amount of hemorrhage found in the primary and metastatic tumor sites (124).

Teratoma

By definition, teratoma consists of two or more embryonic germ cell layers (endoderm, mesoderm, and ectoderm). Typical endodermal structures seen in teratoma are mucus-secreting glands as in the gastrointestinal, genitourinary, or respiratory tracts. Mesodermal elements often present in teratoma include cartilage, bone, muscle, and lymphoid tissue. The ectoderm may be represented by stratified squamous epithelial cell–lined cysts and neural tissue elements (126). Mature and immature elements of each of these germ layers may be present in the teratoma. At presentation the teratoma may vary greatly in size, and on cut surface, the gross specimen is markedly heterogeneous. Often, both solid and cystic-appearing areas are present within the same mass. In the more cystic tumors that appear to be “benign,” 30% metastasize in 5 years. Adenocarcinoma or epidermoid carcinoma can develop in the epithelial components of teratoma (126).

Simple Epidermoid Cysts

Price and Mostofi (153) described these lesions as keratinizing, stratified, squamous cell–lined cysts supported by fibrous tissue. These tumors are considered special cases of teratoma, but not truly teratoma because only a single germinal layer, not the required two layers, is represented. The simple epidermoid cyst accounts for approximately 1% of testicular tumors. The behavior appears to be totally benign; no incidences of metastasis have been reported in 69 cases found in the American Testicular Registry (151).

Carcinoid Tumor

Talerman and associates (188) reported 23 cases of carcinoid tumor of the testis. Seventeen of these tumors were primary testis tumors, three of which had elements of teratoma present as well. The remaining six tumors were metastatic carcinoid tumors of the testis. The patients may or may not have the clinical syndrome associated with carcinoid tumors. Recent reports on a total of five patients with carcinoid tumor of the testes noted that none of these patients had clinical carcinoid syndrome (96,214). However, in all of the tumors, the argentaffin reaction was noted histologically. The prognosis appears to be excellent in primary tumors; in metastatic tumors the outlook has been poor.

Mixed Histologic Germ Cell Tumors

Approximately one-fourth of germ cell tumors are composed of multiple cell types. The most common of these mixtures is embryonal carcinoma and teratoma. Together these cell elements are commonly referred to as *teratocarcinoma* (Fig. 41.7). Sixty-four percent of teratocarcinoma

tumors also contain elements of seminoma. The next most common mixture is embryonal carcinoma and seminoma, which accounts for approximately 5% of testis tumors (126). Although hundreds of other combinations are possible, no other combination presents more than 3% of the total incidence of these tumors. In general, the behavior of mixed tumors is similar to that of its most aggressive element; that is, teratocarcinoma behaves in a manner similar to embryonal carcinoma.

Stromal Tumors of Mixed Cell Type

When both Sertoli (tubular) and Leydig (interstitial) cell elements are present in a tumor, it is called an *androblastoma.* This is a "male" presentation of these structures. When thecal stroma and granulosa complexes are present, the tumor is called a *gynoblastoma* and represents a "female" manifestation of these tumors. It is often difficult to differentiate androblastomas from gynoblastomas (204). When both male and female structures are clearly present, the tumor is designated a *gynandroblastoma.* Despite the predominance of male or female structures, these tumors can produce male or female hormones or both (58). Cheville recently reviewed germ cell and sex cord–stromal tumors. A description of the use of special histologic stains employed to make the diagnosis of each of these tumors is given (21).

Mixed Germ Cell and Stromal Tumor (Gonadoblastoma)

The gonadoblastoma is a mixed cell type tumor containing large germ cells similar to seminoma, and small cells similar to immature Sertoli and granulosa cells. Elements similar to Leydig or interstitial cells also may be present. These tumors are associated with dysgenetic gonads, either a streak gonad or a testis. They also are known to occur in patients with intersex disorders (170). Chapman and others reported a case of gonadoblastoma in a genotypically and phenotypically normal, fertile man with scrotal testes (20). A careful review of 10 cases of sex cord–stromal tumors showed that 9 of the 10 cases were a combination of sex cord elements and entrapped germ cells of the testis based on inhibin staining patterns. This suggests that true unclassified mixed germ cell sex cord–stromal tumors have not yet been observed (197).

Somatic (Nongerminal) Tumors

Somatic tumors of the testis also have been known as *gonadal stromal tumors* or *sex cord mesenchymal tumors.* These designations have been used to differentiate them from germ cell tumors. The term *somatic* or *nongerminal* seems most appropriate for these tumors in light of our current understanding of their origin and structure.

Sertoli (Tubular) Cell Tumors

Sertoli (tubular) cell tumors usually have a glandular; tubular; or a fused, solid epithelium-lined structure. These formations are similar to areas found in prepubertal testicular tubules or those areas found in cryptorchid testes. Differentiation between hamartoma, hyperplasia, and neoplasia is difficult (59). Metastasizing carcinomas of Sertoli cell origin are rare (185). Sertoli cell tumors can occur in children and represent 1.3% of all testis tumors in this group. These tumors can vary greatly in histologic appearance and endocrine activity (11).

Malignant Lymphoma of Testis

Malignant lymphoma of the testis can occur as either a primary or secondary tumor. The terminology involving malignant lymphoma has been somewhat confusing. Other synonymous terms used in the literature include *lymphosarcoma, reticular cell sarcoma,* and *lymphoblastic lymphoma.* According to Gowing, malignant lymphoma is the second most common testis tumor in patients older than 50 years of age (68). The peak incidence of presentation of malignant lymphomas of the testis is between ages 60 and 80 years. The disease can be unilateral or bilateral. Bilateral tumors can occur either synchronously or metachronously. Because survival is usually good after orchiectomy alone, many of the tumors must be primary tumors of the testis.

A recent report of diffuse large-cell lymphoma of the testis, on the other hand, showed poor response to chemotherapy overall, with a median survival of 41 months in patients with limited disease (Ann Arbor stage I/II) and 16 months in patients with advanced (Ann Arbor stage IV) disease (195).

Metastatic Tumors to the Testis

Metastatic tumors to the testis are theoretically possible from any blood-borne tumor. These tumors are unusual and represent 0.9% of 2,739 testis tumors reported by Pugh (154). The most commonly reported site of the primary is the prostate, with eight cases noted; bronchus and bowel are the next most frequent sites of primary tumor spreading to the testis (15). Other reported sites include pancreas, skin (malignant melanoma), bladder (transitional cell carcinoma and sarcoma), thyroid (carcinoma), and neuroblastoma. A new report on 738 patients who died from solid malignant neoplasms noted metastases to the testes in 5 (0.68%) patients. There were three cases of bronchial carcinoma, one of melanoma, and one of pancreatic endocrine carcinoma (61).

CLINICAL MANIFESTATIONS OF GERM CELL TESTIS TUMORS

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

The most common symptom or finding associated with testicular tumors is scrotal swelling. Also identified with testis cancer is a sensation of fullness or heaviness of the scrotum, which is occasionally described as pain. On rare occasions, patients have manifestations of metastatic disease

such as hemoptysis, a mass noted in the supraclavicular area, or a large abdominal mass. Also, patients occasionally have systemic endocrine effects, such as gynecomastia.

Unfortunately, the diagnosis of testis cancer is often delayed by confusion regarding the scrotal findings and symptoms. Not infrequently, the patient is treated for presumed epididymitis. The key to success in this particular dilemma is follow-up examination. After the patient has been treated with antibiotics for the presumed epididymitis, he should be reexamined after the course of the antibiotics has been completed to make certain that no residual mass is palpable. All too often the index of suspicion of a testis tumor is too low, and the patient goes on either with no treatment for his disease or with repeated or continuous treatment for presumed epididymitis. Public awareness of testis cancer is increasing, and campaigns for testicular self-examination have had an impact on earlier detection and diagnosis of testis cancer.

Fortunately, very sensitive serum markers have been found. The most sensitive and useful markers are serum human chorionic gonadotropin (hCG) levels, serum α-fetoprotein (AFP) levels and lactate dehydrogenase (LDH) levels. hCG is measured as the ß-chain of the protein (ß-hCG). hCG is produced by the syncytiotrophoblast, whereas AFP is produced by the yolk sac cell. Syncytiotrophoblasts have been demonstrated to be present, usually as isolated cells, in up to 10% of seminomas. Syncytiotrophoblasts also are present in choriocarcinoma. Yolk sac cells are found in embryonal tumors as well as in pure yolk sac tumors. LDH is a nonspecific marker, which may be elevated in the absence of ß-hCG or AFP elevation and has been incorporated as a part of the primary node (T), regional lymph nodes (N), distant metastasis (M), and serum tumor markers (S) (TNMS) staging (TNMS) system for germ cell neoplasms in the fifth edition of the American Joint Committee on Cancer Staging (AJCC) criteria, thus adding $T_xN_xM_xS_x$ to the staging criterion. Overall, more than 70% of patients with testis tumors will have one or more of these serum markers elevated. In the case of possible testis tumor, serum markers should be obtained. A positive marker has great significance; however, a negative marker does not exclude the presence of a germ cell testis tumor.

DIAGNOSIS OF GERM CELL TUMORS

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

Any mass within the body of the testicle itself must be considered a germ cell tumor until proven otherwise. Once a testis tumor is suspected, it is advisable to have the patient examined by a trained urologist. The urologist should be able to help differentiate the physical findings between epididymitis, spermatocele, varicocele, hydrocele, and testicular cancer. One of the most important aspects of physical examination is determining the location of the mass in question. The examiner should use two hands. One hand steadies the testicle and the other grasps it, using the fingertips and the tip of the thumb to try to differentiate between a mass located in the body of the testicle and a mass located in the epididymis. Transillumination is helpful to detect solid versus fluid-filled masses. Ultrasonography has been helpful in differentiating between solid and cystic lesions and also in helping pinpoint the location of the lesion. Figure 41.8 and Figure 41.9 show examples of a normal testis and a testis with a germ cell tumor (seminoma). Epidermoid cysts of the testis usually can be diagnosed with ultrasound or magnetic resonance imaging (MRI), each showing an onion ring appearance with alternating bands of

signal intensity (105). Ultrasound also helps elucidate the status of the underlying testicle in a patient who has a hydrocele that is too tense to allow adequate examination (Fig. 41.4). Doppler flow studies often can demonstrate blood flow within an intratesticular mass, increasing the likelihood of tumor presence. The absence of blood flow in the onion ring lesion seen on ultrasound or MRI further supports these lesions being benign epidermal cysts (105). Testicular lesions may have a uniform appearance suggesting seminoma (Fig. 41.9) or a heterogenous appearance suggesting presence of a mixed tumor or a tumor with teratomatous elements. More recently, testicular microlithiasis has been associated with testicular intraepithelial neoplasia or frank carcinoma in up to 35% of cases (8).

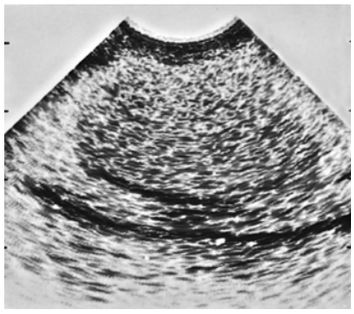

FIGURE 41.8. Longitudinal cut of an ultrasonogram of a normal testis. Note the relative uniformity of the body of the testis.

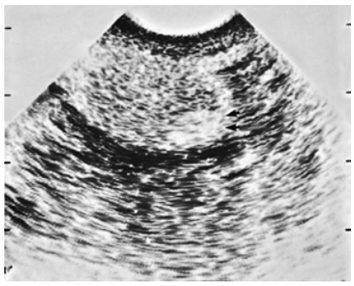

FIGURE 41.9. Longitudinal cut of an ultrasonogram of a testis with a tumor located on the posterior aspect replacing over half of the testis . Note changes in the echo pattern.

If a mass in or adjacent to the body of the testis cannot be satisfactorily identified with physical examination, transillumination, and ultrasonography, then the burden of proof is on the urologist to examine the mass further through surgical exploration. Because the lymphatics of the testis flow along the cord structures, it is important to explore the testicle through an inguinal incision to avoid contamination of the superficial inguinal lymphatics by the testicular lymphatics. Figure 41.10 indicates the location of the inguinal incision. After the incision is made, the external oblique aponeurosis is incised in the line of its fibers. The cord structures are mobilized; the easiest way to get around the cord structures is to sweep from lateral to medial at the level of the pubic tubercle. Care should be taken to make certain that the vas deferens and the testicular vessels are included in this bundle of tissue. Once the cord structures are isolated, they can be dissected more proximally, and a Penrose drain or noncrushing clamp can be placed on the cord to help prevent any spread by lymphatics (although this route of spread is only theoretic) or any blood-borne metastasis during the remainder of the surgical procedure. At this point, the testicle can be delivered into the incision by placing traction on the cord structures. Loose connective tissue and cremasteric fibers often must be mobilized from the cord structures to allow delivery of the testicle. The testicle will still be attached to the dependent portion of the scrotum by the gubernaculum of the testis.

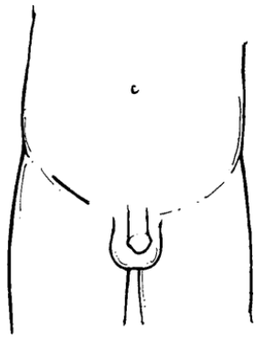

FIGURE 41.10. A curvilinear incision is made in the skin lines at a spot overlying the internal inguinal ring, which is approximately two-thirds of the way from the pubic tubercle to the anterosuperior ileal spine, just cephalad to the inguinal ligament.

At this point, direct examination of the testis should be accomplished. If the mass is clearly within the body of the testicle and is solid, an orchiectomy should be performed by ligating the cord structures at the level of the internal inguinal ring. During this part of the procedure, one should take care to separate the vas deferens from the vasculature. These should be tied separately and mobilized to allow separation of the two structures. This aspect is important, because separating these structures at the time of orchiectomy facilitates the dissection of the gonadal vessels in the retroperitoneum if a node dissection is required.

If, at the time of exploration, the location and consistency of the mass is not obvious, then the tunica vaginalis can be incised to expose the tunica albuginea of the testis. If with this level of observation, it is still not possible to distinguish the exact nature of the mass in question, a biopsy can be performed. Before performing a biopsy, however, it is recommended that the testicle be walled off with dry laparotomy pads to avoid any potential spill into the wound. If there is any doubt at the time of biopsy and frozen section, the testicle should be removed. It is an error of much greater significance if a testis with a tumor is left in place than if a testis without a malignant neoplasm is removed. If the mass is shown to be benign, the tunica albuginea of the testis can be reapproximated with an absorbable suture and the testis can be returned to the scrotum. Because noncrushing clamps are used, the blood supply of the testis should not be jeopardized.

In prepubertal males, lesions consistent with teratoma or epidermal cyst, with negative tumor markers, and a benign clinical evaluation can be excised using a testis-sparing technique. Frozen sections should be obtained at the time to confirm the benign nature of the lesion (62,201). The same is true for postpubertal males with findings consistent with epidermal cysts (105).

Serum markers (ß-hCG, AFP, and LDH) should be obtained before surgical exploration in anyone suspected of having a testis tumor. This will be helpful later in monitoring the level of markers as an indication of response to therapy.

When a non–germ cell tumor is encountered, the same inguinal orchiectomy with high ligation of the cord also is indicated. Often, simple surgical excision of these tumors is satisfactory treatment; however, because one cannot be certain ahead of time of the precise diagnosis of the tumor, it is advisable to treat it in the same manner as one would a potential germ cell tumor.

In the case of either a suspected germ cell tumor or a non–germ cell tumor, a transscrotal approach to open biopsy or needle aspiration of the mass is ill-advised. The inguinal approach is definitely recommended to avoid potential

cross-contamination of different lymphatic drainage systems.

Patients who have had previous inguinal or scrotal procedures for conditions such as cryptorchidism, inguinal hernia, or hydrocele should be approached in the same manner as a patient with no previous procedure in this area. The one exception to this recommendation is a testicular tumor encountered through a scrotal incision. In this instance, an inguinal approach for the orchiectomy should be used and a hemiscrotectomy also should be performed to excise the area of potential wound contamination. If there is obvious extension of the tumor into the scrotal wall, a combined inguinal approach along with a hemiscrotectomy should be used to achieve en bloc resection of the testis, cord structures, and scrotal wall.

When a scrotal violation has occurred, there is a possibility of metastases to the inguinal lymph nodes. The patient must be followed for evidence of inguinal adenopathy in addition to the normal follow-up. However, inguinal node involvement is rare unless there has been gross tumor spillage, which has been untreated for several months.

Orchiectomy for a metastatic lesion to a testis is rarely indicated. Normally, the primary source of tumor is recognized, and because it is often a late manifestation of disease, the precise knowledge of metastasis to the testis plays little role in management of the patient.

STAGING OF TESTIS TUMORS

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

Definition of Stages

As with most solid tumors, the AJCC has developed a TNMS system for germ cell neoplasms. Seminoma and nonseminomatous germ cell tumors (NSGCT) including teratoma, yolk sac tumor, choriocarcinoma, embryonal carcinoma, teratocarcinoma, and mixed other cell types are included. Rare non-germ cell tumors such as stromal cell tumors, Sertoli cell and Leydig cell tumors are not included in the current TNMS classification. In 1997, the AJCC in collaboration with the World Health Organization (UICC) updated the TNM classification to include presence of lymphovascular invasion and serum markers as part of the staging criterion (Table 41.3). The updated system allows more precise definition of both the clinical and pathologic stage of germ cell tumors and therefore simplification of treatment and prognosis decision-making schema. Table 41.4 provides a comparison between the updated TNMS staging schema between the 1997 fifth edition AJCC schema and its predecessors, the 1992 AJCC schema and the Indiana schema.

TABLE 41.3. AMERICAN JOINT COMMITTEE ON CANCER, FIFTH EDITION FOR TESTICULAR NEOPLASMS: SEMINOMA, EMBRYONAL CARCINOMA, YOLK SAC TUMOR, TERATOMA, CHORIOCARCINOMA, OR MIXED

Primary Tumor (pT)

pTX	Tumor cannot be assessed (e.g., no orchiectomy performed)
pT0	No tumor present (e.g., scar only)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)
pT1	Tumor limited to testis and epididymis without lymphovascular invasion, tunica albuginea invasion allowed but not tunica vaginalis
pT2	Tumor limited to testis with lymphovascular invasion or extension beyond tunica albuginea and involving the tunica vaginalis
pT3	Spermatic cord invasion with or without lymphovascular invasion
pT4	Scrotal invasion with or without lymphovascular invasion

Regional Lymph Nodes (N)

Clinical

N_x	Regional nodes cannot be accessed
N_0	No regional adenopathy
N_1	One or more regional nodes, all are <2 cm in greatest dimension
N_2	One or more regional nodes, any one node between 2 and 5 cm in greatest dimension
N_3	One or more regional nodes, any one >5 cm in greatest dimension

Pathologic

pN_x	Regional nodes cannot be assessed
pN_0	No regional nodes
pN_1	<5 total nodes, all <2 cm in greatest dimension
pN_2	Regional node between 2 and 5 cm greatest dimension, or >5 positive nodes none >5 cm in greatest dimension, or any node with extra nodal extension
pN_3	Regional node(s), any one node >5 cm in greatest dimension

Distant Metastasis (M)

M_x	Distant metastasis cannot be assessed
M_0	No distant disease
M_1	Distant disease
M_{1a}	Nonregional nodes (e.g., mediastinal) or pulmonary mass(es)
M_{1b}	Distant disease other than nonregional nodes or pulmonary disease

Serum Tumor Markers (S)

S_x	Not available or not done
S_0	All markers within normal limits
S_1	LDH <1.5xN and ß-hCG <5,000 mIU/mL and AFP <1,000 ng/mL
S_2	LDH 1.5–10xN or ß-hCG 5,000–50,000 mIU/mL or AFP 1,000–10,000 ng/mL
S_3	LDH >10xN or ß-hCG >50,000 mIU/mL or AFP >10,000 ng/mL

Stage Grouping

Stage	Tumor	Nodes	Metastases	Markers
0	pTis	N_0	M_0	S_0
I	pT1-4	N_0	M_0	S_x
IA	pT1	N_0	M_0	S_0
IB	pT2-4	N_0	M_0	S_0
IS	Any pT	N_0	M_0	S_{1-3}
II	Any pT	N_{1-3}	M_0	S_x
IIA	Any pT	N_1	M_0	S_{0-1}
IIB	Any pT	N_2	M_0	S_{0-1}
IIC	Any pT	N_3	M_0	S_{0-1}
III	Any pT	Any N	M_1	S_x
IIIA	Any pT	Any N	M_{1a}	S_{0-1}
IIIB	Any pT	N_{1-3}	M_0	S_2
	Any pT	Any N	M_{1a}	S_2
IIIC	Any pT	N_{1-3}	M_0	S_3
	Any pT	Any N	M_{1a}	S_3
	Any pT	Any N	M_{1b}	Any S

AFP, α-fetoprotein; β-hCG, β-human chorionic gonadotropin; LDH, lactate dehydrogenase.

TABLE 41.4. CLINICAL STAGES OF TESTIS TUMORS

AJCC5[a] Stage	Description	AJCC4[b] Stage	Indiana Stage
I	Tumor limited to the testis	I	A
IA	No extension or lymphovascular invasion		
IB	Local extension of tumor or lymphovascular invasion		
IS	Local tumor but with marker elevation[c]		
II	Tumor of testis and regional nodes	II	B
IIA	Limited regional nodes and modest marker elevation[c]		B1
IIB	Regional nodes 2–5 cm and modest marker elevation[c]		B2
IIC	Extensive regional nodes		B3
III	Distant tumor	III	C
IIIA	Pulmonary or nonregional nodes, modest marker elevation		
IIIB	Moderate marker elevation[c] with or without pulmonary or regional or nonregional nodes		
IIIC	Extensive marker elevation[c] or nonpulmonary metastases		

[a]AJCC5, *American Joint Committee on Cancer,* 5th ed, 1997.
[b]AJCC4, *American Joint Committee on Cancer,* 4th ed, 1992.
[c]Serum markers (lactate dehydrogenase, β-human chorionic gonadotropin, and α-fetoprotein) are new in the AJCC5 staging criteria.

Clinical Staging

Clinical staging must be accomplished to appropriately plan the initial therapeutic approach to the patient. As shown in Table 41.3, clinical stages are grouped into stage I, with tumor with or without lymphovascular invasion, with or without marker elevation limited to the testis cord structures and scrotum; stage II, with tumor confined to the retroperitoneal lymph nodes; and stage III, with tumor involving the abdominal viscera or extending above the diaphragm.

Repeated serum markers (AFP, ß-hCG, and LDH) should be obtained at intervals after the radical orchiectomy is performed. If the patient had elevated markers before radical orchiectomy, following up the serum markers is helpful in determining whether residual tumor is definitely present. The ß-hCG has a half-life of approximately 1 day, the AFP has a half-life of approximately 5 days, and the LDH half-life is approximately 3 days. Knowing the half-life, it is possible to estimate whether residual disease is still present based on the observed rate of degradation of the markers in those patients who had initially elevated markers. Unfortunately, some patients will have degradation of the markers at the normally expected rate and will still have residual tumor. Again, just as in the initial presence or absence of the marker, a positive or elevated value has significance, while a normal level value does not necessarily exclude presence of residual tumor.

Presence of pulmonary parenchymal metastases can be satisfactorily evaluated with either whole lung tomography or computed tomography (CT) scans. Numerous reports in the literature support the sensitivity and specificity of each of these modes of examination. The choice of the examination should be in the hands of the individual practitioner and should be based on the instrumentation available and the skill and experience of the radiologist at the institution. In general, chest CT scans are used rather than tomography. If retroperitoneal lymph nodes are not enlarged, conventional chest radiograph is probably sufficient. If pulmonary parenchymal lesions are evident, the patient's tumor would be classified as clinical stage III.

The abdomen is evaluated by abdominal CT scan, which allows assessment of the major viscera such as the liver, spleen, and kidneys as well as the retroperitoneal lymph nodes. The threshold of detection for an abnormal mass by CT scan is approximately 1.0 cm. When this criterion is used, sensitivity is in the range of 70%, with an approximately 30% false-negative rate. This limitation is readily explained by the presence of microscopic or small volume gross nodal involvement. The quality of CT also can be eroded by lack of retroperitoneal fat in these young, otherwise healthy, frequently thin patients. Leibovitch and co-workers have reported a sensitivity increase to 91% by decreasing the size criterion to 3 mm for nodes located within the predicted landing zones and 1 cm for all other areas. This modification yielded a 10% false-negative rate but decreased specificity to 52% (109). If one or more enlarged retroperitoneal lymph nodes are noted and all are less than 2 cm, the patient's disease is classified as clinical $T_xN_1M_xS_x$, stage IIB disease. Patients with one or more retroperitoneal lymph nodes between 2 and 5 cm are

classified as clinical $T_xN_2M_xS_x$, also stage IIB disease by the revised classification (Fig. 41.11), and any retroperitoneal lymph node larger than 5 cm is classified as clinical $T_xN_3M_xS_x$, stage IIC disease (Fig. 41.12). Presence of extraretroperitoneal lymph nodes is classified as clinical $T_xN_xM_{1a}S_x$, stage III disease, and presence of visceral, pulmonary, or other metastases are classified as clinical $T_xN_xM_{1b}S_x$, stage IIIC disease.

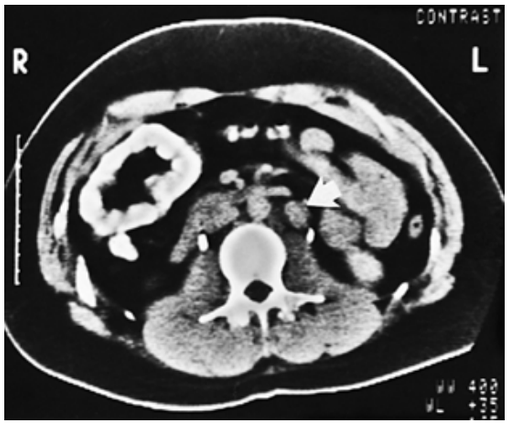

FIGURE 41.11. Abdominal computed tomogram showing a 2-cm-by-1.5-cm mass *(white arrow)* in the left periaortic area just anterior and medial to the left ureter, which is opacified with contrast *(white area).* This represents clinical stage IIB ($T_xN_2M_xS_x$) disease.

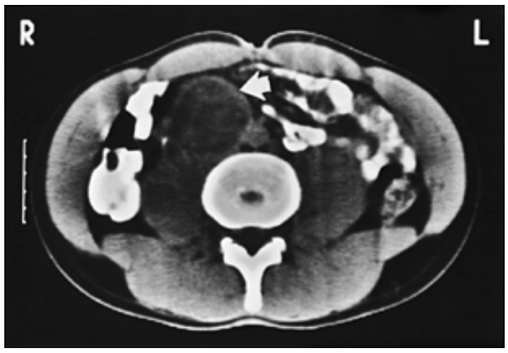

FIGURE 41.12. Abdominal computed tomogram showing a 5-cm-by-6-cm mass *(white arrow)* anterior to the right psoas muscle, which also obscures the vena cava. The 1997 revision of the AJCC staging criteria also categorizes these findings as stage IIC disease, but with $T_xN_3M_xS_x$, TNMS nomenclature.

The workup just described is performed in the case of all types of germ cell tumors. Historically, patients with seminoma also were studied with lymphangiogram (Fig. 41.13). A lymphangiogram was thought to be valuable for definition of radiation ports in the treatment of seminoma. Currently, at the authors' institution, a lymphangiogram is not used for seminoma or nonseminomatous germ cell tumors because the findings would not influence treatment.

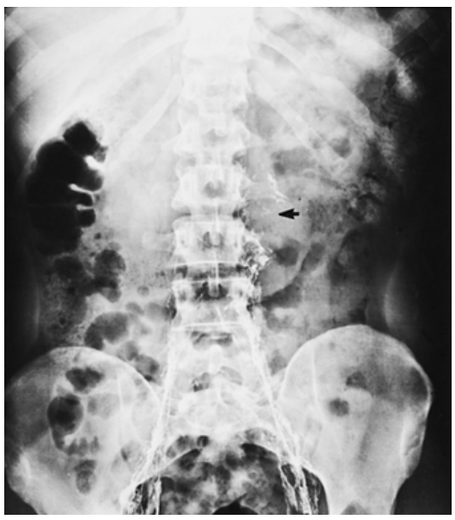

FIGURE 41.13. A bipedal lymphangiogram of a patient with left testicular seminoma. Distortion and obstruction of the lymphatics in the left periaortic area at the L-2 to L-3 level *(black arrow)* suggests stage II disease.

MRI is a promising technique for imaging the body. The technical aspects of the procedure are improving steadily. A comparison of images from some of the first-generation

MRI instruments did not show any advantage over conventional CT scans (50). The quality of the new images on the improved instrumentation may well change that status.

The 1997 revision of the AJCC staging criteria brought incorporation of two significant changes. First, recognition of the importance of lymphovascular invasion within the primary tumor was addressed by redefining clinical $T_1N_xM_xS_x$ tumors as those tumors limited to the testes and epididymis without lymphovascular invasion, and clinical $T_2N_xM_xS_x$ tumors as those that extend beyond the tunica albuginea *or* contain lymphovascular invasion. Secondly, the 1997 revision, for the first time, incorporates the serum markers ß-hCG, AFP, and LDH into the clinical staging criteria. Thus all three markers are within normal limits at diagnosis for $T_xN_xM_xS_0$ disease. Elevation of LDH less than 1.5 times normal, ß-hCG less than 5,000 mIU/mL, *or* AFP less than 1,000 ng/mL is defined as clinical stage $T_xN_xM_xS_1$ disease. For $T_xN_xM_xS_2$, any one marker is above the S_1 criterion but less than 10 times normal for LDH, *or* less than 5,000 mIU/mL for ß-hCG *or* less than 10,000 ng/mL for AFP and for $T_xN_xM_xS_3$ any one marker above 10 times normal for LDH, *or* greater than 50,000 mIU/mL for ß-hCG *or* greater than 10,000 ng/mL for AFP. Additional markers are available but are not widely used because of cost and lack of close correlation with disease stage or specificity (e.g., placental alkaline phosphatase, LDH isozymes). Numerous molecular markers also are being studied, but none are clinically applicable for general use at this time.

Combining clinical T stage, N stage, M stage, and S stage allows more precise clinical staging of germ cell neoplasms (Table 41.3).

Overall, the accuracy of clinical staging varies between 20% and 40% (159,164). The 1997 revision of the AJCC TNMS staging system incorporates improvements in clinical and radiographic staging of the retroperitoneum and chest and recognizes the importance of lymphovascular invasion within the primary tumor and the value of serum markers in this disease. This matter is discussed more fully later in this chapter; however, on a practical basis, patients with nonseminomatous, low-stage tumors (clinical stages I through IIB) undergo a primary surgical staging by retroperitoneal lymph node dissection, whereas patients with high-stage disease (stages IIC and III) undergo treatment with primary chemotherapy. At some centers, patients with clinical stage IA disease are observed without surgical staging. This point also is discussed more thoroughly later in the chapter.

Surgical Staging

Retroperitoneal lymph node dissection (RPLND) serves two purposes in the setting of low-stage disease. First, because approximately 30% of clinical stage I patients are pathologic stage II ($T_xN+M_0S_x$), RPLND serves a staging purpose in that it reliably identifies the pathologic stage II patient early in the course of his disease. Second, the removal of metastatic disease by RPLND in pathologic stage II patients is therapeutic in approximately 50% to 70% of patients. That is, in patients proven to have small- to moderate-volume retroperitoneal metastasis, RPLND can provide long-term cure to 70%, without the necessity of subsequent chemotherapy (39).

RPLND originally was perfected and described by Cooper and Leadbetter and associates (26) who used an extraperitoneal thoracoabdominal approach. The extraperitoneal thoracoabdominal approach is useful in dealing with patients who have bulky retroperitoneal disease high in the abdomen. This extraperitoneal thoracoabdominal approach is still in use in many centers for RPLND in patients with low-stage disease (Fig. 41.14).

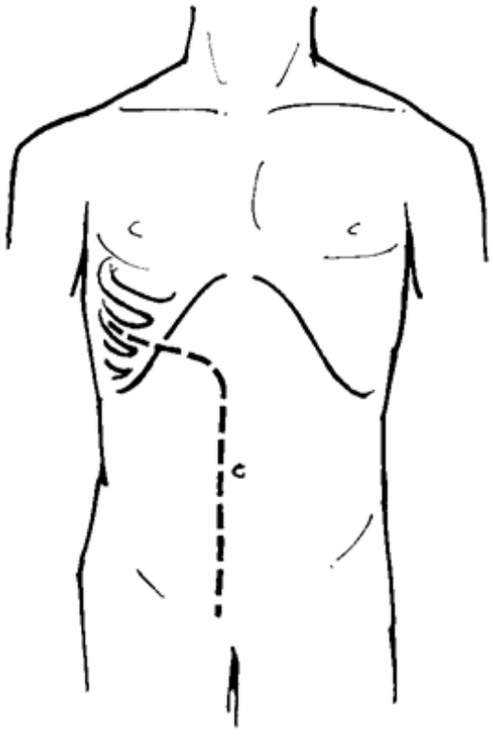

FIGURE 41.14. Thoracoabdominal approach used by some centers for a radical retroperitoneal lymph node dissection. This is an extraperitoneal approach.

Donohue perfected and popularized a transabdominal approach, which avoids a thoracoabdominal incision, does not require the incision of any muscle, and provides excellent bilateral exposure (35). The original technique uses a midline xiphoid-to-pubis incision followed by mobilization of the right colon and root of the small bowel (Fig. 41.15). An incision is performed from the foramen of Winslow to the cecum, then cephalad to the ligament of Treitz. The inferior mesenteric vein is divided, and the root of the small bowel and right colon is mobilized off the retroperitoneum and placed in a bowel bag on the patient's chest. The split

and roll maneuver, whereby lymphatic tissue is split over the aorta and the vena cava and rolled medially and laterally, is then performed. The inferior mesenteric artery is identified and divided, and the mesentery of the left colon retracted laterally. This exposure allows completion of the traditional full bilateral RPLND (Fig. 41.16). The borders of this dissection include the crus of the diaphragm superiorly, the bifurcation of the common iliac arteries distally, and the ureters laterally. After the split and roll maneuver (Fig. 41.17) is performed, the aorta and vena cava can be retracted from the posterior body wall. Lymphatic tissue is then harvested in four packages: right paracaval, interaortocaval, left periaortic, and interiliac areas. No effort is made during full bilateral RPLND to preserve sympathetic efferent fibers. Hence, virtually all patients who undergo full bilateral RPLND lose emission/ejaculation.

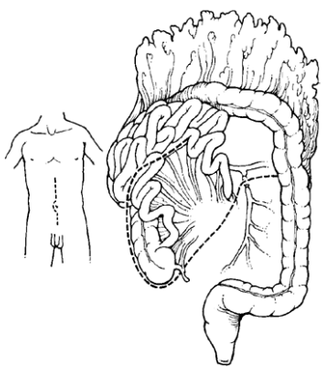

FIGURE 41.15. Surgical incision and site of peritoneal incision to mobilize the small bowel and right colon for an anterior approach for a radical retroperitoneal lymph node dissection. (From Donohue JP. Retroperitoneal lymphadenectomy: the anterior approach including bilateral suprarenal-hilar dissection. *Urol Clin North Am* 1977;4:509, with permission.)

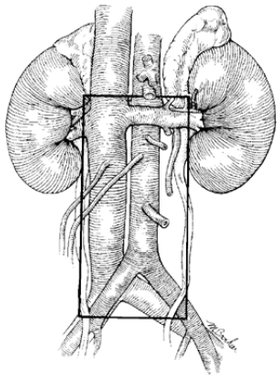

FIGURE 41.16. Margins of dissection of full bilateral retroperitoneal lymph node dissection, including right and left suprahilar areas.

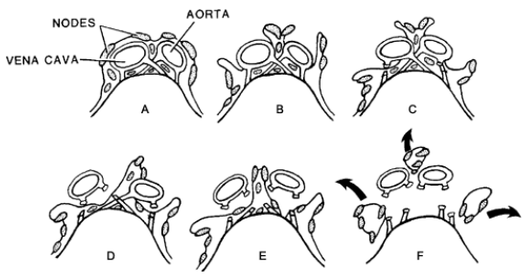

FIGURE 41.17. A–F: "Split-and-roll" technique, which has been modified such that the tissue adjacent to the aorta and vena cava is removed in three bundles: right pericaval group, interaortocaval group, and left periaortic group.

Mapping studies performed by Donohue and others subsequently proved that a full bilateral dissection was not necessary in all patients (40). These mapping studies showed that in patients with low-volume retroperitoneal disease, the site of the disease in the retroperitoneum could be predicted based on the side of the primary and the volume of retroperitoneal disease. Therefore patients with low-volume retroperitoneal disease at laparotomy underwent a modified template, en bloc dissection (Fig. 41.18). The advantage of the modified template dissection is the preservation of ejaculation in some but not all patients. In addition, because the retroperitoneum is not dissected bilaterally, the procedure requires less time in the operating room and generally a shorter period of postoperative ileus. Thus modified template dissections allow maintenance of the staging and therapeutic aspects of the procedure but eliminate some of the morbidity of the procedure, that is, loss of ejaculation.

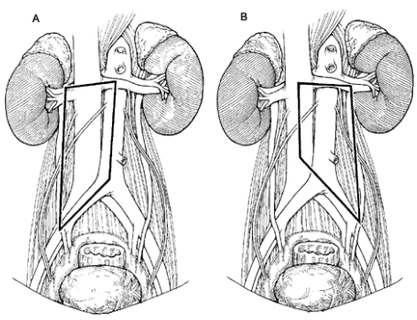

FIGURE 41.18. Templates for right **(A)** and left **(B)** modified nerve-sparing retroperitoneal lymph node dissection.

As surgeons became more experienced with the retroperitoneum, it became apparent that the sympathetic efferent fibers could be reliably identified and dissected in the course of a retroperitoneal lymph node dissection. Donohue, Jewett, and others subsequently showed that these

fibers could be dissected followed by either a full bilateral or a modified unilateral lymph node dissection (36,91). The advantage of a nerve-sparing dissection over a modified template dissection is that ejaculation is preserved at the 99% level with nerve-sparing RPLND, as opposed to 50% to 90% with modified template unilateral RPLND. In addition, it is now clear that modified template nerve-sparing RPLND maintains both the staging and therapeutic aspects of the procedure because local recurrence in the retroperitoneum after nerve-sparing RPLND is rare.

The surgical approach for a nerve-sparing dissection usually requires an incision only in the root of the small bowel mesentery, as shown in Fig. 41.19 . The zones of dissection are similar to the modified template dissection. The modified templates for nerve-sparing RPLND are depicted in Fig. 41.20 .

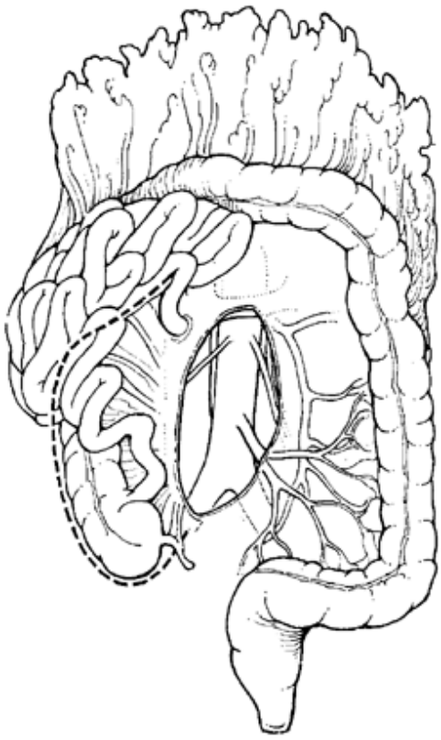

FIGURE 41.19. A retroperitoneal window is created to give exposure for nerve-sparing retroperitoneal lymph node dissection. The *dashed line* indicates the peritoneal incision needed to mobilize the remainder of the small bowel and ascending colon if more extensive exposure is required.

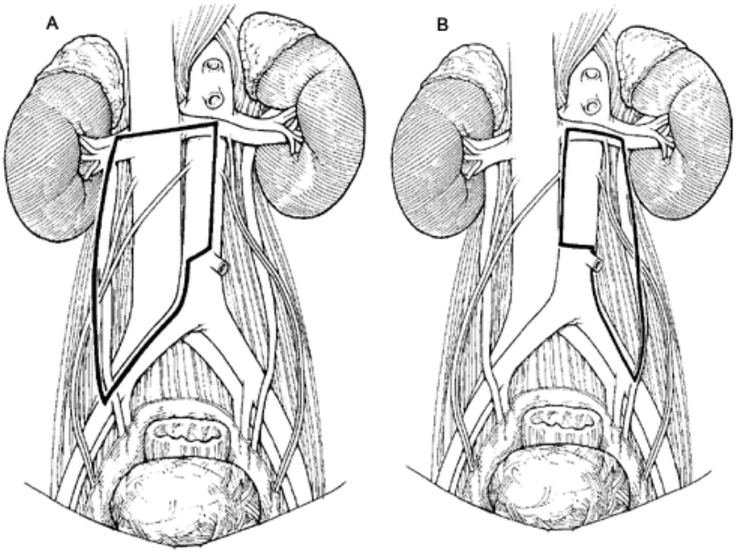

FIGURE 41.20. Templates for right **(A)** and left **(B)** modified retroperitoneal lymph node dissection.

It is well recognized that some patients with testicular cancer are hypofertile at the time of diagnosis, before any therapy. Thus the question of whether nerve-sparing RPLND is reasonable has been raised. The fertility of patients who have undergone nerve-sparing RPLND has been studied, and it is known that at least some of these patients are fertile at diagnosis. Nerve-sparing RPLND reliably preserves this fertility potential because approximately

80% of couples who attempt pregnancy after nerve-sparing RPLND are successful (56).

Therefore, as the template of dissection has evolved from full bilateral to a modified to a modified nerve-sparing approach, the staging and therapeutic aspects of the procedure have been maintained while reducing the risk of loss of emission to 1% to 2%.

Patients scheduled for nerve-sparing RPLND are admitted to the hospital the morning of surgery. Routine blood chemistries and a urinalysis are obtained the morning of surgery if the patient has not been seen recently. A type and screen is obtained; transfusion is rarely necessary during routine modified template nerve-sparing RPLND.

Standard modified template nerve-sparing RPLND requires approximately 2 to 3 hours operative time. A nasogastric or orogastric tube is placed after induction of anesthesia. After evacuation of stomach contents at the completion of the procedure, the tube is removed.

The patient is sent to a normal hospital room after the recovery room. Clear liquids are begun the following day because a significant ileus is not usually present. The diet and activity are rapidly advanced, with the hospital stay averaging 3 to 5 days.

TREATMENT OF LOW-STAGE TESTIS TUMORS

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

Stage I Nonseminomatous Germ Cell Testis Tumors

In patients who had clinical stage I nonseminomatous germ cell testis tumor as evidenced by no metastases in the chest

on radiologic evaluation, no evidence of retroperitoneal metastases as shown by abdominal CT scan, and normal serum levels of ß-hCG, AFP, and LDH, the standard treatment historically was a full bilateral radical RPLND, as originally described by Donohue (34). See Fig. 41.21 for schema. Postoperatively, if disease in these patients was truly pathologic stage I (no retroperitoneal metastases), the patients were observed without adjuvant therapy. Using this treatment regimen, 154 patients were described by the Southeastern Cancer Study Group. Of these, 15 patients (9.7%) had relapse of the tumor, and of these, 3 died (2% of patients). Two of these three patients declined chemotherapy, and the third patient received chemotherapy in what would now be considered suboptimal doses. In light of this overall cure rate in excess of 98%, adjuvant chemotherapy does not seem to be needed for pathologic stage I testis tumors as long as careful follow-up is obtained.

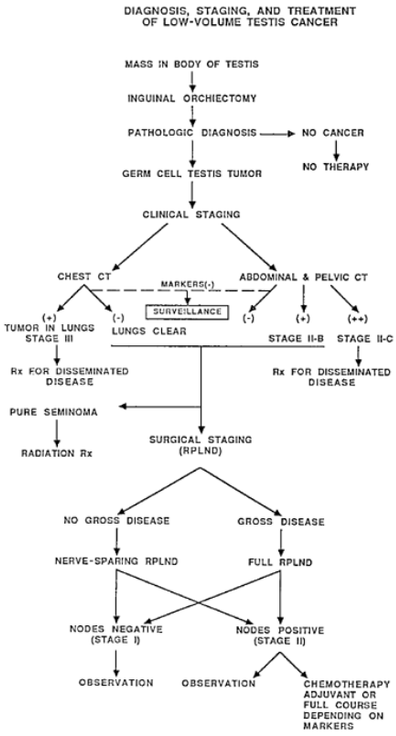

FIGURE 41.21. Algorithm for the diagnosis of testis cancer and for the treatment of low-stage disease. Note that the treatment of high-stage tumors (IIC and III) is shown in Fig. 41.22. AFP, α-fetoprotein; CT, computed tomography; ß-hCG, ß-human chorionic gonadotropin; RPLND, retroperitoneal lymph node dissection.

Because of the problems with ejaculatory impotence after a full bilateral dissection, most centers have used a modified set of boundaries for radical RPLND in patients with no gross evidence of metastatic disease in the retroperitoneum. The margins of the modified template dissections used at Indiana University are shown in Fig. 41.18A and Fig. 41.18B . These modifications were made on review of the distribution of positive nodes in patients with pathologic stage IIA disease. In this study, virtually no metastatic lesions were noted in the area lateral to the midplane of the contralateral great vessel. Also, virtually no metastases were present in the suprahilar zones. Rare metastases were noted in the presacral areas (40). By modifying the boundaries of dissection, the rate of ejaculatory impotence was reduced significantly. In one series reported by Richie and Garnick, 17 of 19 patients who underwent a modified dissection had preservation of antegrade ejaculation (158). One patient had antegrade ejaculation after taking imipramine, and 1 of the 19 patients had retrograde ejaculation. Another series of 145 patients, reported by Weissbach and Boedefeld, compared the rate of postoperative ejaculation, rate of progression, and postoperative complications of 36 patients undergoing a full bilateral radical RPLND with the same rates in 68 patients undergoing a modified RPLND (206). Ejaculation was successfully preserved in 75% of those patients undergoing a modified RPLND and in 23% of those undergoing a full bilateral radical RPLND. The relapse rates in the two groups were 22% in those who had a full bilateral dissection and 12% in those who had a modified dissection. One needs to remember that there was a selection bias in this group because this was not truly a randomized study. No significant difference was noted in the complication rate between the two groups, with a 12% rate in the full bilateral dissection group and a 17% rate in the modified dissection group.

Beginning in 1985, true nerve-sparing procedures were performed at Indiana University for those patients with no evidence of gross disease, and a desire to preserve emission. The surgical approach and boundaries of dissection have been shown in Fig. 41.19 and Fig. 41.20 . A review revealed preservation of emission in 72 of 73 patients. The recurrence rate [4 of 73 (5%)] has not been significantly different from the rate of those patients who had undergone full bilateral or modified node dissections in the past. A more recent report from Indiana University has verified the early experience with nerve-sparing RPLND (39). The recurrence rate has remained unchanged from the earlier experience in both pathologic stage $T_xN_{1-2}M_0S_x$ patients. Ejaculation is preserved in more than 98% of patients.

In light of the high success rate of treating germ cell testis cancers with systemic platinum-based combination chemotherapy, some authors have proposed conservative management of clinical stage IA testis tumors. The Medical Research Council in the United Kingdom, for example, performed a retrospective multivariate analysis that suggested four prognostic factors: vascular invasion, lymphatic invasion, presence of embryonal carcinoma, and absence of yolk sac tumor (57). A prospective study designed to test this hypothesis supported a prognostic index based on these factors (157). Subsequent studies were unable to distinguish between lymphatic and vascular invasion but confirmed its importance (63,86,90,129,135,172,181,183). Presence of embryonal carcinoma (41,86,128,129,135,181) and absence of yolk sac tumor (98) also have been confirmed as prognostic indicators in this patient population. In addition to the normal clinical evaluation—chest evaluation by CT scan, abdominal and retroperitoneal evaluation by abdominal CT scan, and measurement of serum markers—some centers that are pursuing an observation protocol also evaluate their patients with a lymphangiogram. If all of the studies are negative, then the patients are followed conservatively. The optimal follow-up schedule for patients managed by surveillance is controversial. Most groups recommend more intensive follow-up in the early years of surveillance, with lengthening of the follow-up period as the time from diagnosis increases. What is apparent, however, is that abdominal imaging is absolutely necessary in patients managed by surveillance because most of the patients whose disease recurs manifest recurrence as an abnormality in theretroperitoneum on abdominal CT scanning. It also is clear that this follow-up in patients managed by surveillance must be prolonged because recurrences in patients managed by surveillance are not rare after the second year of follow-up. In contrast, recurrences greater than 2 years after a nerve-sparing RPLND are rare. Therefore compliance with follow-up is a major consideration in a patient considered for surveillance.

The Medical Research Council group in Great Britain has reported its experience using surveillance in clinical stage I patients (157). The overall survival in the short term was 98%. Of the patients whose disease recurred in this report, 20% went on to require postchemotherapy RPLND. It is clear that surveillance done effectively with good compliance yields roughly equivalent results as RPLND for clinical stage I patients in the short term. However, because unresected retroperitoneal germ cell cancer can remain indolent for significant periods of time only to reactivate later, long-term follow-up and reporting of patients managed by surveillance is absolutely necessary. A recent report (3) confirms that unresected germ cell cancer can remain indolent for significant periods in a certain percentage of patients. Therefore lifelong follow-up is mandatory.

Because nerve-sparing RPLND and surveillance yield roughly equivalent results in properly managed patients in the short term, the morbidities of these two therapies become increasingly important as a determinate of which management scheme is appropriate in an individual patient. The morbidity of nerve-sparing RPLND is low (3) and consists of short-term management of pain and the 1% risk of small bowel obstruction secondary to postoperative adhesions. Because nerve-sparing RPLND almost always preserves ejaculation, it rarely impinges upon fertility in this group of patients.

Patients managed by surveillance whose disease does not recur have low morbidity. Although patient anxiety can be a problem, these patients incur no additional morbidity. However, the 30% to 40% of patients who do develop recurrence are given chemotherapy, which has very definite morbidity. Because chemotherapy has a definite effect on spermatogenesis, long-term reports are needed concerning spermatogenesis in patients administered current chemotherapeutic regimens for testicular cancer.

Stage II Nonseminomatous Germ Cell Testis Cancer

Historically, patients with clinical stage II nonseminomatous testis cancer have undergone full bilateral radical RPLND as their primary treatment. Fig. 41.21 also includes stage II treatment schema. The relapse rate after radical RPLND has been proportional to the bulk of disease present in the retroperitoneum. In patients with microscopic disease only ($T_xN_1M_xS_x$), the relapse rate has been approximately 25%. In pathologic stage IIB ($T_xN_{1-2}M_xS_x$), the relapse rate has been approximately 40%. In patients with pathologic stage $T_xN_3M_0S_x$ or $T_xN_xM_1S_x$ disease, the relapse rate has varied between 75% and 100%. Because the relapse rate in this group has been so high, most centers treating testis cancer believe that the appropriate initial therapy in this group should be systemic chemotherapy. The aspects of this form of treatment are discussed in a later section of this chapter.

As previously discussed, if no gross disease is noted at the time of RPLND and the patient is presumed to have clinical stage I disease ($T_xN_0M_0S_x$), a modified nerve-sparing RPLND is carried out. Again, from the distribution of positive lymph nodes in patients with stage $T_xN_1M_xS_x$ carcinoma (40), a modified dissection is satisfactory for removing disease because in the absence of gross disease, virtually no presacral, suprahilar, or contralateral (lateral to the midplane of the contralateral major vessel) metastases occur.

Many authors have addressed the issue of additional therapy after RPLND for stage $T_xN_{1-2}M_0S_x$ testis cancer over the years. One of the authors of this chapter (RGR) has participated in a study of 240 patients with stage ($T_xN+M_xS_x$) disease. Half of these patients were assigned to observation postoperatively and half were assigned to two courses of adjuvant combination platinum chemotherapy

[cisplatin (*cis*-diaminedichloroplatinum), vinblastine, and bleomycin (PVB)]. Each arm was balanced with an equivalent number of stage N_1 and N_2 cases. Forty percent of the observation cases relapsed and were treated with four courses of PVB chemotherapy. Of the 40% who suffered relapse, all but four (3%) of the patients are alive and free of disease. Four patients have died. The regimens of three constituted protocol violations, and they did not receive the normal full-dose PVB therapy.

In the patients treated with two courses of adjuvant PVB chemotherapy, only 1 of 120 has suffered relapse. This patient is now free of disease after surgical excision of the residual tumor. One other patient died of gastrointestinal complications 2 months postoperatively. Overall, survival in the adjuvant PVB group is 99.2% (38). Similar results have been reported by other institutions using a vincristine, doxorubicin (Adriamycin), bleomycin (VAB-6) protocol (199).

When stage N_1 and N_2 tumors are considered together, the overall survival rate is 98%. The difference between observation with delayed chemotherapy, if needed, and adjuvant chemotherapy is very small. One issue that needs to be settled is the difference in the two groups in terms of long-term side effects of adjuvant chemotherapy.

Currently, the authors recommend individualization of the treatment of stage N+ testis cancer. After a node dissection is performed, the bulk of the metastatic disease and the reliability and availability of follow-up to the patient are considered. If for any reason follow-up of the patient for at least 2 years would be suboptimal, two courses of adjuvant chemotherapy are recommended (Fig. 41.21). On the other hand, if one is dealing with a very reliable patient who understands the potential for relapse, observation and treatment with four courses of bleomycin, etoposide, and cisplatin (BEP), if recurrence is identified, are appropriate. Treatment with two courses of adjuvant BEP extends the period of disability only approximately 1 month. After undergoing the adjuvant chemotherapy, the patient has a very high likelihood (greater than 99%) that he will not require any subsequent therapy for testis cancer that will interrupt his ability to lead a productive life.

An alternative approach to the management of clinical stage $T_xN+M_0S_x$ testis cancer is the administration of primary chemotherapy (85). In this report, survival was comparable to the Indiana University experience with clinical stage II disease in the short term. Approximately one-third of clinical stage II ($T_xN+M_0S_x$) patients managed with primary chemotherapy will require postchemotherapy RPLND. Similar to clinical stage I ($T_xN_0M_0S_0$) patients, what is needed in clinical stage $T_xN+M_0S_x$ patients managed with primary chemotherapy is information relative to short- and long-term side effects of therapy in the entire group, and frequency of late recurrences (recurrence of disease greater than 2 years from completion of initial therapy).

It is now clear that nerve-sparing techniques can be used in patients with evident retroperitoneal disease (91). Hence, patients with clinical stage $T_xN+M_0S_x$ disease who are subjected to RPLND now may have their disease resected and maintain ejaculatory competency postoperatively. If these patients do not subsequently require chemotherapy, their fertility status has not been affected by their therapy. Therefore the necessity of reporting long-term morbidity of clinical stage $T_xN+M_0S_x$ patients managed by both nerve-sparing RPLND and primary chemotherapy is apparent in order to allow an individual patient to make a decision regarding therapy.

Low-stage Seminoma

For patients with clinical stage I pure seminoma, some centers perform lymphangiography in addition to routine staging tests. If a patient's disease is still found to be stage I (no evidence of retroperitoneal metastases), the patient undergoes radiation to the ipsilateral inguinal and iliac area and the periaortic and pericaval areas to the level of the diaphragm (Fig. 41.21, left poststaging branch). In a series of 62 patients treated this way, 59 were free of disease after a 3-year follow-up (88). The normal treatment is 2,500 rad delivered over a 3-week period. This 95% cure rate is representative for other series in the literature. Surveillance also has been used in a study setting for clinical stage I seminoma. The short-term results are good. However, long-term follow-up is necessary because seminoma may recur many years after initial diagnosis (203).

In patients with clinical stage IIB ($T_xN_2M_xS_x$) pure seminoma, which is diagnosed by grossly enlarged lymph nodes in the retroperitoneum seen on CT scan or by positive nodes seen at the time of lymphangiography, a controversy exists in terms of the fields for radiation therapy. Hussey and Doornbos recommend mediastinal and left supraclavicular radiation as well as periaortic, pericaval, and ipsilateral inguinal radiation (88). In their experience, those patients receiving only iliac and periaortic radiation had a 55% cure rate. Other centers have adopted a policy of radiation limited to the retroperitoneum below the diaphragm, based on the observation that their recurrence rates have been similar regardless of whether or not they had radiation to the mediastinum and supraclavicular area (202). Also, it has been noted that if a patient has had full radiation both above and below the diaphragm, his ability to receive full-course chemotherapy in the event of a relapse has been severely limited. In light of these findings, plus the observations that seminoma responds well to platinum-based combination chemotherapy, physicians in many centers think that stage IIB seminoma should be treated with radiation to the diaphragm only. Shipley reports a combined series of data from the literature indicating that in 164 stage IIB patients with pure seminoma, the cure rate was 85% with radiation therapy alone (176). The radiation dose to the retroperitoneum

is usually in the range of 3,000 rad, with some centers using an additional boost of up to 600 rad in areas where gross disease was shown on CT scan or lymphangiogram. Radiation to the retroperitoneum is normally well tolerated. When radiation is limited to the retroperitoneum and inguinal area, full-dose chemotherapy may be used if the patient has a relapse.

Stage III seminoma is treated in the same manner as a nonseminomatous tumor, using primary chemotherapy.

TREATMENT OF HIGH-STAGE GERM CELL TESTIS TUMORS

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

Over the last 10 to 15 years, the treatment of high-stage testis cancer has changed dramatically. The survival rates in advanced disease previously were in the range of 5% to 10%. The initial approach to high-stage disease was surgical resection or debulking, followed by chemotherapy. Although this made a dramatic advance in the survival rates over those of surgery alone, the rates at the time were considerably lower than currently are available using multimodal therapy. In 1976, Merrin and colleagues filed an initial report on 11 patients who underwent primary cytoreductive surgery followed by postoperative chemotherapy using a six-drug regimen. Although they initially reported a complete response in three patients, a follow-up report quoted the survival rate in this group as 43% (120). A similar result was noted in a small group of patients from Indiana University. Seventy-five percent of those patients treated with primary cytoreductive surgery suffered relapse (37).

The subsequent development of effective cell cycle–specific agents used in combination made it possible to reverse the order of treatment in disseminated disease. Einhorn and Donohue (45) made a milestone report in this area. In this series of patients, cytoreductive chemotherapy was the primary treatment followed by adjunctive surgery to resect any residual masses that were present. Merrin and associates also reported a satisfactory result with this new approach (120).

Another significant advance in the treatment of disseminated testis cancer was made by Samuels and associates (166), who noted that the combination of vinblastine and bleomycin produced a complete response rate in 17 (33%) of 51 patients. This complete response rate was higher than would be predicted from single-agent data, thus demonstrating a strong synergistic effect. Other reports gave similar results using the combination of vinblastine and bleomycin with the addition of actinomycin D (28,212).

The next significant advancement in cure rates for advanced testis cancer came with the use of cisplatin. This agent was reported initially by Rosenberg and colleagues to cause a significant inhibition of bacterial replication (160). Higby and associates, in a phase I trial, showed that it was active against testicular carcinoma (78).

In light of the encouraging reports about cisplatin, platinum-vinblastine bleomycin (PVB) was started in August of 1974 at Indiana University. Fifty patients were treated using the PVB regimen between 1974 and 1976 (46). Of 47 evaluable patients, 33 (70%) achieved a complete clinical remission with a combination of the three drugs. The remaining 30% experienced a partial remission. One-third of these patients subsequently were rendered disease free by surgical resection of the remaining tissue masses. In those patients who achieved a complete clinical remission by chemotherapy alone (70%), only 9% had a subsequent relapse. In the initial series of 50 patients, 4 patients died in complete remission. Two of the deaths were attributed to the side effects of chemotherapy. One died of Gram-negative sepsis and the other of bleomycin-induced pulmonary fibrosis. The other two deaths were thought to be due to preexisting conditions. The report of an additional 78 patients using PVB, with or without doxorubicin, noted no additional drug-induced mortality (47).

Although in the overall experience, the rate of mortality was relatively low, the rate of granulocytopenic fevers (38%) and sepsis (15%) was significant. To try to reduce toxicity of the primary chemotherapy, a three-arm study was undertaken by the Southeastern Cancer Study Group (47). One arm received the standard PVB treatment course using 0.4 mg/kg of vinblastine. The second group received a reduced dose of vinblastine (0.3 mg/kg). The last group received 0.2 mg/kg of vinblastine with an addition of 50 mg/m^2 of doxorubicin. All groups received cisplatin at a rate of 20 mg/m^2 each of 5 days at the beginning of each 3-week course of chemotherapy. In addition, each patient received 30 units of bleomycin intravenously weekly for the 12-week treatment course. In this study, the difference in the response rates among the three different groups was not significant. The decrease in the toxicity of the regimen in terms of granulocytopenic fevers and sepsis was significant. The group that received the smaller dose of vinblastine (0.3 mg/kg) without doxorubicin had the lowest rate of granulocytopenic fever (15%), and no sepsis was documented in the 27 patients assigned to this treatment arm. Because of the lower rate of toxic effects in the 0.3-mg/kg group, this regimen became the standard treatment.

Maintenance therapy had originally been used with patients receiving vinblastine, 0.3 mg/kg monthly for an additional 20 months. A randomized trial to study the efficacy of the maintenance therapy was performed. In 113 patients studied, there was no significant difference in the relapse rate in the maintenance group receiving monthly vinblastine (9%) versus the group with no maintenance (7%). The disease-free status also was similar (44).

In reviewing a total of 125 patients who were treated with the basic PVB combination with or without doxorubicin, the overall complete response rate was noted to be 69% (47). In this report, the response to disease was essentially

inversely proportional to the amount of disease present. If serum markers only were elevated and there was no demonstrable gross disease, the complete response rate was 100%. On the other hand, if there was advanced pulmonary disease—defined as masses greater than 2 cm in diameter or more than six pulmonary metastases per lung—the complete response rate was 55%. In advanced abdominal disease—defined as presence of masses greater than 6 cm in diameter—the complete response rate was 46%. A report by Vugrin and associates (198) at Memorial Sloan-Kettering Cancer Institute has noted a similar (68%) complete remission rate using the VAB-6 protocol, which also contains cisplatin.

The next significant development in chemotherapy was the substitution of etoposide for vinblastine. This reduced toxicity but maintained the same efficacy rate. Einhorn and his associates (48) reported a study comparing three versus four courses of cisplatin, etoposide, and bleomycin (BEP) in low-risk patients with metastatic disease. The study showed that three courses were as effective as four in this patient population.

An additional study by Loehrer and co-workers (112) looked at the possibility of deleting bleomycin in the aforementioned regimen. The results in this 166-patient study showed the need to maintain bleomycin to keep up efficacy. As a result, cisplatin, etoposide, and bleomycin are the current agents used in many centers for chemotherapy for germ cell tumors.

Progress in Diagnosis and Staging

Another significant improvement in the treatment of advanced testis cancer is the increase in the ability to accurately diagnose and stage advanced disease. As pointed out earlier in this chapter, the development of CT scans has aided greatly in the diagnosis and staging of testis cancer. Although truly massive disease is not a diagnostic dilemma in most patients, correct assignment of a patient to a low-stage approach with primary surgery versus a high-stage approach with primary chemotherapy is aided greatly by evaluation of retroperitoneal and chest masses using CT scans in the abdomen, and CT scans or whole-lung tomograms in the chest. In one series reported in the literature, the detection rate of stage IIC disease was virtually 100% (164). For low-stage disease, improvements in CT scanning technology has prompted several authors to propose modification of the staging criteria for the retroperitoneum. In 1997, Hilton and co-workers reviewed CT nodal staging criteria for 10-mm metastases and found a sensitivity of 37% and specificity of 100%; however, by decreasing the primary landing zone minimum size to 4 mm, the sensitivity increased to 93% and specificity fell to 58% (80). The false-negative rate decreased from 63% for 10-mm node size criterion to 7% using a 4-mm node size criterion. Liebovitch and co-workers proposed decreasing the size criterion located within the primary landing zones and reported a sensitivity of 91% (10% false-negative rate) and specificity of 52% (109). The value of MRI and positron emission tomography (PET) scanning for staging tumors and characterizing abnormal tissue masses is currently under study.

With questionable pulmonary metastases and without retroperitoneal masses, the use of serum markers (AFP, ß-hCG, and LDH) can be useful. If any of the serum markers are elevated, then a patient can be assigned reliably to primary chemotherapy without mass biopsy or excision.

Current Approach to the Treatment of High-stage Disease

In view of the advances in chemotherapy, diagnosis, and staging previously cited, the primary treatment of advanced testis cancer has changed from cytoreductive surgery followed by chemotherapy to primary chemotherapy followed by surgical resection of any residual disease. This approach has led to a doubling of the survival rates compared with the surgery-chemotherapy approach used initially. Figure 41.22 shows the procedure used for treatment of patients with advanced disease. When patients with advanced disease are treated with primary chemotherapy, approximately 70% enjoy a complete clinical remission. This overall 70% complete rate of remission varies inversely with the amount of tumor present at the time of initiation and treatment (44). Patients with only elevated markers had a 100% response rate to chemotherapy, whereas patients with advanced or bulky abdominal disease had a 46% complete remission. Vugrin and associates have demonstrated similar findings using VAB-6 as their primary chemotherapy treatment (199).

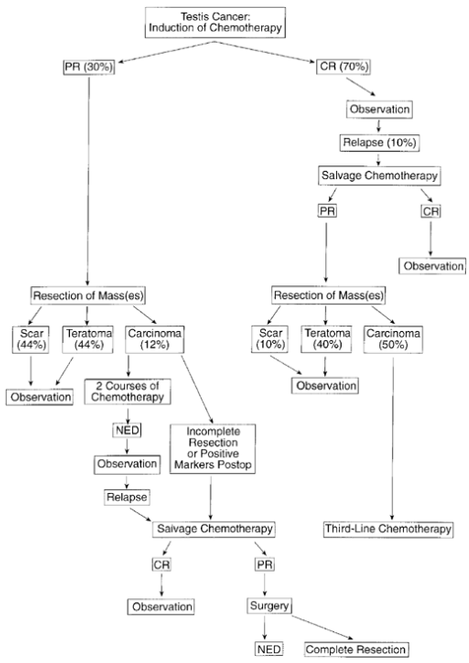

FIGURE 41.22. Algorithm for the treatment of high stage disease. BMT, bone marrow transplant; CR, complete clinical remission; NED, no evidence of disease; PR, partial clinical remission.

After patients have undergone four courses of primary chemotherapy, complete clinical reevaluation is needed. This evaluation should include serum markers (LDH, AFP, and ß-HCG), and chest and abdominal CT scans. With this testing, if there is absolutely no evidence of residual disease, then the patient can be observed. If, on the other hand, a partial remission is shown to have occurred by virtue of any of the above tests not indicating completely normal results, surgical resection of the tumor is indicated. The one exception to this rule is in patients with pure seminoma whose AFP level was never elevated (Fig. 41.21). This recommendation is based on the following observations at Indiana University: virtually all patients with disseminated seminoma that have never had an elevated AFP level have no active disease present at the time of excision of residual masses after four courses of chemotherapy. In all cases, resection of such tissue has yielded only scar or necrotic tumor. No teratomas or cases of persistent carcinoma have been observed. An exception to this scenario is the patient who has discrete residual retroperitoneal masses greater than 3 cm after chemotherapy, in contrast to sheets of residual “scar” tissue. In this case, the discrete masses yield residual

tumor in at least one-fourth of the patients. Therefore postchemotherapy RPLND is recommended if discrete masses greater than 3 cm are present.

If a patient has persistently elevated serum markers after four courses of chemotherapy, CT studies are reviewed. If findings are localized and amenable to resection, the masses are resected. However, if diffuse or disseminated disease is identified, salvage chemotherapy should be undertaken.

In patients with negative markers in whom only a partial remission of disease is achieved, based on chest and abdominal CT scan findings, surgical resection of the tumor is performed. The surgical approach used to resect the residual masses is based on the size and location of disease. Table 41.5 shows the indications of various surgical approaches used in resecting disease. Depending on the amount of disease present, the procedures for resection of residual chest disease may be separated by several weeks from the procedure for resection of abdominal disease. However, in most instances it is possible to carry out resection of both chest and abdominal disease as a combined surgical procedure.

	RPLND	Thoracotomy	Median Sternotomy
Residual abdominal mass on CT	+		
Retrocrural mass on CT	+	±	±
Unilateral parenchymal		+	
Lung mass on CT or WLT			
Bilateral parenchymal or mediastinal masses			+
Elevated AFP or β-hCG[a]	±	±	±

[a]Persistent modest elevation of markers with potentially resectable mass.
AFP, α-fetoprotein; β-hCG, β-human chorionic gonadotropin; CT, computed tomography; RPLND, retroperitoneal lymph node dissection; WLT, whole-lung tomography.
Modified from Rowland RG: Surgical management of postchemotherapy residual testis tumor. In: Catalona WJ, Ratliff TL, eds. *Urologic oncology*. Boston: Martinus Nijhoff Publishers, 1984:255.

TABLE 41.5. INDICATIONS FOR SURGICAL APPROACHES AFTER CHEMOTHERAPY FOR ADVANCED TESTIS TUMORS

In patients undergoing resection of residual masses after four courses of primary chemotherapy, approximately 44% have scar or necrotic tumor as their only pathologic finding at the time of surgery. Teratoma is found in an additional 44% of the surgical specimens, and carcinoma is present in approximately 12%. Patients having scar or teratoma are

observed carefully using a course of follow-up outlined in a later section of this chapter. It should be noted that in patients with teratoma, in addition to undergoing the standard follow-up as previously outlined, additional follow-up for at least 10 years is necessary because of the rare instance of a late recurrence of teratoma.

In patients with residual carcinoma of their resected residual masses, further therapy is determined by whether the tumor was completely resected as evidenced by persistence of negative markers and the surgeon's findings at the time of operation. If all evidence indicates that complete resection of residual tumor mass was accomplished, then patients normally are followed carefully. If complete resection was not accomplished at the time of surgery, or if markers become positive in the postoperative period, then salvage chemotherapy is given.

Of the 70% of patients who achieve a complete clinical remission after four courses of primary chemotherapy, only 10% subsequently relapse. This represents approximately 7% of the initial population who were treated with primary chemotherapy for advanced disease. In this patient population, approximately 80% will achieve a second complete clinical remission with salvage therapy. This patient population is observed carefully for recurrence for a minimum of 2 years. In patients who receive a partial remission (20%) after salvage chemotherapy, the same principles apply to the resection of residual masses as previously outlined for patients who have a partial remission after primary chemotherapy alone. One significant difference, however, is that the distribution of pathologic findings in this group is considerably different from that in patients having surgery after primary chemotherapy. As shown in Fig. 41.21, only 10% of patients undergoing surgery for residual masses after a partial remission with salvage chemotherapy have scar or necrotic tumor as the only pathologic finding. Again, approximately 40% will have teratoma in the specimen, while 50% will have residual carcinoma. Patients with scar and teratoma are observed as they would be after surgery for a partial remission after primary chemotherapy. The same caution applies to patients with teratoma: they must have long-term follow-up because of potential late recurrences. Patients with carcinoma in their surgical specimen whose markers return to normal values are followed. In patients with carcinoma in the surgical specimen and elevated markers, third-line or tertiary chemotherapy (autologous bone marrow transplantation) is given.

Salvage surgery has been performed in a series of chemorefractory patients at Indiana University (130). In a group of 48 chemorefractive patients, a total of 60% were rendered grossly disease free and achieved negative markers after surgery. Twenty-one percent have maintained a durable complete remission a mean of 46 months after salvage surgery.

Overall, emphasis in the treatment of advanced disease has switched from primary surgical cytoreduction followed by adjuvant chemotherapy to primary cytoreductive chemotherapy followed by adjuvant surgical resection of any residual masses.

Retroperitoneal Lymph Node Dissection in Patients Treated with Chemotherapy

If RPLND is indicated because of a partial response to primary or secondary chemotherapy, several additional points must be considered before the operation. In addition to routine evaluation of the patient, as would be carried out before a primary RPLND, the patient must be monitored for any potential side effects of chemotherapy that could interfere with optimal care at the time of surgery. The notable point in this area is potential restrictive lung disease due to pulmonary fibrosis caused by bleomycin. Patients who have received bleomycin as part of their chemotherapy regimen should undergo screening pulmonary function studies and blood gas analyses performed on room air. It is not uncommon for patients to have an arterial oxygen content in the range of 70 to 80 mm Hg. These patients also may have a diffusion defect and a moderate decrease in their forced expiratory volume (FEV_1). Mild to moderate diffusion and restrictive defects have not been detrimental in the management of these patients.

Another area to consider is possible renal toxic effects from exposure to cisplatin. If the patient's serum creatinine

level is elevated, a baseline evaluation with a creatinine clearance is suggested. In all of these patients, care must be exercised to avoid potentially nephrotoxic agents because they seem to potentiate the toxic effects of cisplatin. Special care must be taken in patients who have significant impairment of renal function at the time of surgery. The greatest concern is the use of potentially nephrotoxic antibiotics.

Another area of concern is potential myelosuppression in patients who have received vinblastine. Such myelosuppression is normally short lived, and because the surgical resection of residual tumor masses is not usually carried out until 5 to 6 weeks after the last course of chemotherapy, myelosuppression after chemotherapy is rarely a problem. After four or more courses of chemotherapy, the patient may still be anemic at the time of readmission for resection of residual tumor. If the hemoglobin level is less than 10 g/dL, the patient should be given a preoperative transfusion.

Usually, patients scheduled to undergo postchemotherapy resection of residual disease (RPLND with or without thoracotomy or median sternotomy) are admitted to the hospital 24 hours before surgery. In addition to standard preoperative testing, additional monitoring to look for pulmonary and renal toxic effects is carried out. The patient undergoes a mechanical bowel preparation with a clear liquid diet and citrate of magnesia as a cathartic. In the afternoon of the preoperative day, an intravenous line is established and the patient is hydrated with dextrose and 0.5 N saline at the rate of 100 mL per hour until the time of surgery. This prevents dehydration of the patient from the bowel preparation. Also, if a patient appears to be volume depleted, an additional 500 mL of 5% plasma protein can be given. This will help maintain a normal intravascular osmotic pressure, which seems to be important in terms of preventing pulmonary problems at the time of surgery. Also, to help during the postoperative period, the patient is instructed in pulmonary exercise techniques including the use of incentive spirometry and blow bottles or suction devices. The patient's prior knowledge of these techniques seems particularly helpful in enabling him to effectively exercise the pulmonary system in the postoperative period.

Surgical Preparations

Patient warming devices such as warming blankets or heat-reflective coverings should be used. This is critical because the procedures performed in these patients are frequently lengthy, and because incisions are often large, the potential for loss of body heat is considerable. Normally, the anesthesiologist should make preparations for heating and humidifying the gases used during the procedure, as well as warming intravenous fluids that are used. If an RPLND alone is planned, the patient is placed on the table in a supine position. If a combined thoracoabdominal incision is planned, the patient is placed in the appropriate torque position after induction of anesthesia. In these instances, along with the cases in which a median sternotomy is performed in combination with an RPLND, the chest portion of the procedure usually is performed first. The chest incision is left open to provide additional exposure to the upper retroperitoneum because there is often persistent bulky tumor in this area. After the RPLND is completed, the wound generally is closed using a two-team approach, with the thoracic surgeon closing the chest and the urologist closing the abdominal portion of the incision.

Technical Considerations of Postchemotherapy Retroperitoneal Node Dissection

Based on experience gained through the analysis of the distribution of scar tissue, teratoma, and carcinoma in the specimens resected from patients undergoing postchemotherapy RPLND, Donohue and associates found that, contrary to previous experience with patients undergoing primary RPLND, the distribution of the pathologic findings in this group could not be predicted (40). The histologic findings were extremely heterogeneous. Because of the heterogeneity in findings and the presence of pathologic findings in the contralateral side, suprahilar zones, and presacral areas, a full bilateral RPLND is indicated in almost all of these patients regardless of the gross findings at the time of surgery.

In most instances, the standard “split-and-roll” technique (Fig. 41.17A to F) can be used with patients having a postchemotherapy RPLND. In some instances, however, if rather massive residual disease is still present, special techniques can be applied. Figure 41.23 illustrates a technique developed by Donohue in which the bulky disease is systematically dissected away from the critical structure, such as the aorta and vena cava. Once this bulky tissue is rolled out of the way, the surgeon can return to the routine techniques of doing a systematic full bilateral RPLND, as originally described by Donohue (34). A modification of the dissection of the suprahilar zones is shown in Fig. 41.24 . This modification is based on the observation that the lymph nodes are located primarily posteriorly at the level of the crus of the diaphragm (Fig. 41.25). After completion of the procedure, the retroperitoneum is closed by replacing the bowel in its normal location and reapproximating the root of the small bowel mesentery to the retroperitoneum, as well as reapproximating the lateral attachments of the right colon to the colic gutter with running absorbable sutures. The abdominal incision usually is closed with interrupted, inverted figure-of-eight sutures of a nonabsorbable monofilament, no. 0 or 1 suture. If the patient has been particularly debilitated or had a particularly large-volume tumor, abdominal retention sutures are used as well for approximately 3 weeks.

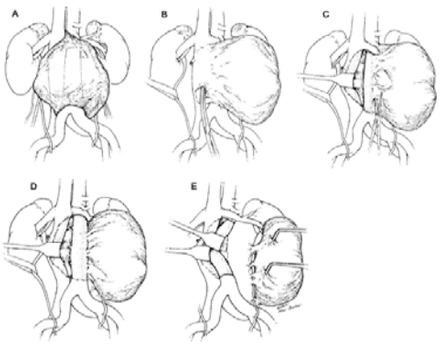

FIGURE 41.23. A–E: Technique for removing bulky tumor during a postchemotherapy retroperitoneal lymph node dissection (RPLND). The mass is removed by separating it into a bundle anterior to the midportion of each of the great vessels and the ureters. Once the bulky mass has been resected, a standard full bilateral RPLND can be performed.

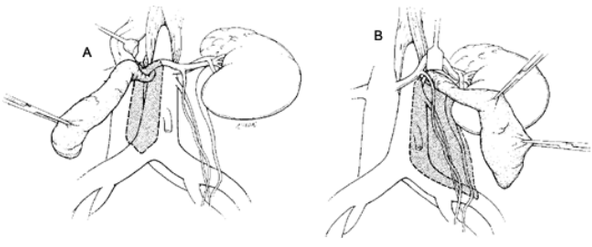

FIGURE 41.24. A: Modification of the right suprahilar dissection. In view of the posterior location of the nodes in the suprahilar zone shown in Fig. 41.23, the right suprahilar nodes are removed en bloc with the interaortocaval zone. The dissection is extended cephalad posterior to the right renal artery and left renal vein in the area of the crus of the diaphragm. **B:** Modification of the left suprahilar dissection using the same line of reasoning. The left suprahilar zone is removed en bloc with the left periaortic tissue by extending the dissection posterior to the left renal artery and vein.

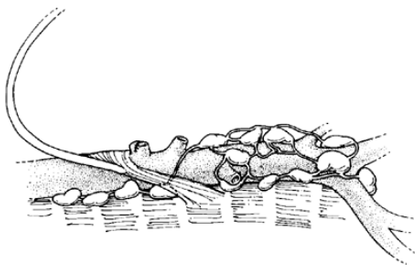

FIGURE 41.25. Lateral view of the location of the lymph nodes relative to the aorta. Note that at the level of the crus of the diaphragm, the nodes are located posterior to the vessel.

In highly select patients in whom the retroperitoneal disease has been confined to one area, nerve-sparing techniques can be applied to other zones. This allows preservation

of emission in some patients. It should be noted that even if emission is preserved by the nerve-sparing technique in the contralateral side, the patient may still be infertile based on oligospermia or aspermia from chemotherapy.

Postoperative Care

Unlike patients undergoing primary RPLND, those who have had prior chemotherapy usually are sent to a surgical intensive care unit for the first 24 hours after surgery. This allows careful monitoring of central venous pressure, arterial pressure, blood gases, and urinary output. During the first 24 to 48 hours, 5% plasma protein may be administered at a rate of 250 to 500 mL every 8 hours as part of fluid replacement. This is necessary because of high third-space loss postoperatively. Again, because of preoperative exposure of most of these patients to bleomycin, it is critical to avoid overhydration with crystalloids by the use of intravenous colloids. The maintenance of a normal or slightly increased osmotic pressure seems to be effective in preventing the development of significant pulmonary compromise. After the initial 24 to 48 hours of monitoring in the intensive care unit, the central venous pressure line, arterial line, and Foley catheter are removed and the patient returned to a routine patient care ward. Management of the remainder of the postoperative course does not differ significantly from that of patients undergoing a primary RPLND. The average hospital stay after a postchemotherapy RPLND is approximately 6 to 7 days.

Results of Surgery

Earlier reports of 123 patients who underwent postchemotherapy RPLND only, postchemotherapy thoracotomy only, or simultaneous RPLND and thoracotomy showed that the overall distribution of histologic findings in these patients was approximately one-third scar tissue, one-third teratoma, and one-third residual carcinoma (35,40,115,116). A more recent review at Indiana University of the histologic findings in RPLND after partial response to chemotherapy showed that the distribution of scar, including cystic necrosis, teratoma, and carcinoma, was 44%, 44%, and 12%, respectively, after primary chemotherapy, and 10%, 40%, and 50%, respectively, after salvage chemotherapy (162).

Again, it should be pointed out that the previously described patients all had partial remissions after chemotherapy. In the patients who have achieved a complete remission with chemotherapy, surgery was not performed unless the patient had a subsequent relapse. The 10% relapse rate in those patients who underwent a complete clinical remission after primary chemotherapy corresponds very well to the findings of Richie, who noted a 10% incidence of residual carcinoma in those patients undergoing an RPLND after apparent complete clinical remission with primary chemotherapy (159a). At this time, the authors believe that the appropriate recommendation for treatment after complete remission with primary chemotherapy is observation only. Operating on the 90% of patients who would have negative findings does not seem justifiable. The 10% relapse rate that has been observed by the authors after patients are given four courses of primary BEP chemotherapy corresponds well with the 12% relapse rate reported by Vugrin and associates (199) after treatment with VAB-6.

Complications of Postchemotherapy Retroperitoneal Lymph Node Dissection

Two earlier reports in the literature have discussed the complications of postchemotherapy RPLND in sizable groups of patients (37,179). The rate of complications seems to be related proportionately to the bulk of disease present. This is evidenced by an overall combined complication rate of 12% in patients undergoing primary RPLND for stage I, IIA, or IIB disease versus an overall complication rate of 25% in those patients initially presenting with stage II or III disease who have undergone postchemotherapy RPLND. The death rate in the low-stage disease patients was 0.3%, while the death rate in the high-stage postchemotherapy node dissection patients was 3.0%. Of the complications, approximately half were minor. Only a small percentage of the major complications required reoperation. Virtually all of the deaths in the postchemotherapy node dissection group were related to complications of the previous chemotherapy, notably compromise in pulmonary function. This finding of compromised pulmonary function with a decrease in diffusion capacity and a restrictive defect as well has been noted by others (163).

A review of complications in postchemotherapy RPLND in 603 patients operated on at Indiana University from 1982 to 1992 was reported by Baniel and associates (3). The overall complication rate was 20.7% and the mortality rate was 0.8%. The most frequent severe complications were pulmonary, with six patients having adult respiratory distress syndrome, five of whom required prolonged ventilatory

support. Additional procedures such as nephrectomy and bowel resections did not add to morbidity.

Although there is a significant complication rate and a mortality rate now of less than 1%, the benefit gained from reassessment of patients with partial remissions after chemotherapy far outweighs the risks. Reassessment of the patient's pathologic status at that point allows appropriate follow-up or additional treatment.

Follow-up of Postsurgical Patients

Usually, all patients who have had an RPLND are seen again at the medical center by the urologist and medical oncologist approximately 3 to 4 weeks after surgery. Beginning with this first checkup, chest roentgenograms and serum markers are obtained monthly for the first year. A physical examination, with particular emphasis on recurrent abdominal masses, and inguinal, axillary, or cervical adenopathy, is performed every other month. After the first year has passed, the testing and physical examination can be decreased in frequency. During the second year, the chest roentgenograms and serum markers are performed every other month and physical examinations every 3 to 4 months. At the end of 2 years, the patient can be followed on a semiannual or annual basis. The one exception to this is patients who have had teratoma in a specimen obtained at surgery after chemotherapy. In this group, there seems to be a subset of patients who are prone to late relapses for as long as 5 to 20 years after surgery. In this particular set of patients, prolonged follow-up is recommended. Because the teratoma often recurs at the margins of resection in the retroperitoneum, a CT scan on an annual basis is recommended for the first 2 to 3 years.

Interstitial Cell Tumors

Interstitial cell tumors of the testicle are uncommon and are usually a benign growth developing within the body of the testis; they consist of recognizable interstitial (Leydig) cells. In Pugh's series (154), interstitial cell tumors accounted for 1.6% of all testis tumors. Other series in the literature have quoted the incidence of interstitial cell tumors to be as high as 3% of all testis tumors (124). These tumors may or may not have endocrine activity.

Most of these tumors occur in persons aged 20 to 60 years. Dalgaard and Hesselberg (30) reported that 23 (24%) of their 94 cases of interstitial cell tumors occurred in patients who had not yet reached puberty. All patients in the prepubertal range had tumors that showed endocrine activity. Most of these patients had precocious virilization; feminization was present occasionally. Although interstitial cell hyperplasia has been noted frequently in the atrophic undescended testis, interstitial cell tumors in a cryptorchid testis have been reported only rarely (184). In some cases, testicular atrophy has been present. In cases of larger tumors, spermatogenesis often has been arrested or totally absent. Symington and Cameron noted that all but one of their patients had a palpable mass in the testis at the time of detection. These masses generally were described as being firm or hard and circumscribed, although some were irregular. Gynecomastia was the next most common finding. This occurred in approximately half of the patients. Regression of gynecomastia has been reported in some patients after orchiectomy (30,184). Other complaints include testicular pain, diminished libido, and morning vomiting before the development of gynecomastia.

In the series of Symington and Cameron (184), most of the interstitial cell tumors were located within the body of the testis, with an occasional tumor extending into the spermatic cord. Tumors usually were well circumscribed, rounded, and solid, with a striking yellow-brown color. The size in this series ranges from 0.7 to 10.0 cm, with most tumors being less than 6 cm. The same authors reported that 9% of the tumors were malignant. It is interesting to note that all of these tumors were large (6 to 10 cm) and that most displayed areas of necrosis within the tumor. The sites of metastasis were retroperitoneal and mediastinal lymph nodes, bone, and lung. As with other testicular tumors, occasionally the tumor is associated with a hydrocele.

Sertoli Cell Tumors

Sertoli cell nodules or tumors are associated most often with undescended testes. In these cases, the nodules are tightly packed, immature seminiferous tubules with little or no lumen. Interstitial cells are characteristically absent from these nodules. The aggregations of tubules, although usually microscopic in size, may be large enough to be seen by the naked eye when examining a cryptorchid testis. Similar findings may occur in the testes of patients with testicular feminization. In contrast to patients with cryptorchid testes, the nodules found in patients with testicular feminization not only have the aggregates of Sertoli cell–packed tubules, but also prominent areas of interstitial cells. The Sertoli cell nodules or tumors are present in approximately 25% of those patients with testicular feminization. Although the tumors are most frequently small and multiple, some masses as large as 24 cm have been noted. These most commonly occur in older patients with an intraabdominal gonad (133). No cases of metastasis have been reported in instances of Sertoli cell tumors. It is interesting to note, however, that this patient population has an increased incidence of other testicular tumors, particularly seminoma. Morris and Mahesh (123) noted a 22% incidence of seminoma in 50 cases of testicular feminization with Sertoli cell nodules or tumors. This may represent a falsely elevated incidence because in many of the patients, the presence of the seminoma led to the diagnosis of Sertoli cell nodules or tumors in reverse order.

Sertoli Cell Stromal Tumors

According to Pugh (154), Sertoli cell stromal tumors account for approximately 1.2% of all testicular tumors. The age range of patients at presentation varied from 2 months to 80 years. Most of the tumors occurred in patients under the age of 40 years. In 25 of 32 patients, the tumor was manifested by painless testicular swelling. Four additional patients had painful testicular swelling. Three patients had gynecomastia at the time of presentation.

All patients were treated with orchiectomy. Only two patients underwent an RPLND. Other therapy included radiotherapy and chemotherapy. Of tumors in these 32 patients, 7 (22%) were malignant. Of the malignant tumors, 4 of the 7 had local spread involving the rete testis, epididymis, or lower spermatic cord. All of the malignant lesions showed local invasion of lymphatics or blood vessels or both. Metastasis involved the retroperitoneal and mediastinal lymph nodes. Liver, lung, brain, and bone also were involved in some cases. Mostofi (124) noted a 10% incidence of malignancy of Sertoli cell stromal tumors in his series of testis tumors.

TUMORS OF THE TESTICULAR ADNEXA

Part of "41 - TUMORS AND INFECTIOUS DISEASES OF THE TESTIS, EPIDIDYMIS, AND SCROTUM "

Tumors of the Rete Testis

Carcinoma of the rete testis is rare. Approximately 25 cases in the literature are thought to meet the criteria for carcinoma of the rete testis. The first cases of presumed carcinoma of the rete testis were reported by Curling in 1853. Feek and Hunter (53) set forth criteria for the diagnosis of carcinoma of the rete testis. Shillitoe (175) emphasized that the parameters set out by Feek and Hunter were not absolute but formed a basis for making the diagnosis. In 1981, Jacobellis and associates (89a) reiterated the criteria. According to these authors, the accepted criteria are (a) the tumor is located in the mediastinum of the testis rather than in the body of the testis proper; (b) a transition from normal epithelial structures to neoplastic structures is present in the rete testis; (c) no evidence of teratoma is present; (d) no primary tumor is present in another site; and (e) the parietal tunic is intact. Adenocarcinoma of the rete testis has been reported to occur in men ranging from 20 years (169) through 89 years of age (66).

Nochomovitz and Orenstein (139) noted that of the 21 cases they reviewed, 80% of the patients were older than 40 years and 70% were older than 60 years. Only two cases in this group were reported to occur in patients younger than 40 years of age. In both of these cases, the tumors developed in maldescended testes. Schoen and Rush (169) emphasize that tumors located in the posterior portion of the testis (rete testis) were likely to be missed unless the testis and surrounding structures were carefully palpated. They also noted that a hydrocele may easily conceal an underlying tumor of the rete testis. A scrotal mass is the most common initial finding. Other manifestations include scrotal pain, skin nodules, edema, and a draining sinus (139).

Once a tumor is suspected, the diagnosis is made by inguinal orchiectomy. Assuming that the aforementioned pathologic criteria are met, a metastatic workup must be performed to stage the disease. The workup is carried out similar to that in germ cell testis tumors. Survival from adenocarcinoma of the rete testis is inversely related to the amount of disease at presentation. Seven of 22 cases summarized by Nochomovitz and Orenstein (139) that had low-stage disease experienced survival from 4 to 42 months. Two of the seven patients underwent removal of localized metastasis, 1 and 42 months after orchiectomy. In general, patients who presented with advanced disease did poorly, with a mean survival of 8 months after the diagnosis.

Whitehead and associates (207) felt that radiation therapy had some benefit in patients with low- to moderate-volume disease. Occasional long-term survivals in patients who have had orchiectomy followed by radiation therapy have been reported. Skin recurrence in the incision, the scrotum, the perineum, or the shaft of the penis has been common. Management of the skin recurrences has been difficult.

According to Nochomovitz and Orenstein (139), four factors are important in dealing with adenocarcinoma of the rete testis: (a) early diagnosis of the neoplasm is important; (b) patients with tumor extending beyond the testis have a poor prognosis; (c) local skin recurrence is common; and (d) mechanical and inflammatory problems, such as epididymitis, hernias, and hydroceles, often mask the underlying tumor. The index of suspicion, particularly in older patients, should be high. An update on a total of 31 patients with this disease revealed similar findings as those reported before (139).

A review of 38 patients with adenocarcinoma of the rete testes by Sanchez-Chapado and colleagues shows that those with tumors 5 cm or smaller had a longer survival than patients with larger tumors. The overall 3- and 5-year disease-free survival rates were 49% and 13%, respectively (167).

Benign tumors of the rete testis are exceedingly rare and, to our knowledge, only four cases have been reported in the literature (71a,210,213). The pathologic findings of these lesions have been reported as papillary adenoma. Both of the patients described by Willis (210) were over the age of 50 years. The case reported by Yadav and associates (213) was in a patient aged 18 years. The fourth case, reported by Gupta (71a), was in a patient aged 12 years. In all of these cases, hydrocele was present at the time of initial examination, making the diagnosis of a mass of the rete testis more difficult. Despite the benign histologic appearance of these tumors, long-term clinical follow-up has not been reported.

Nistal and co-workers described another benign entity, cystic transformation of the rete testis in 38 patients. This

was diagnosed by ultrasound in autopsy and surgical specimens and was associated with adjacent tumors in some patients. Other patients were noted to have evidence of chronic compression due to chronic epididymitis, traumatic hydrocele, ischemia, or cirrhosis (138).

Tumors of the Epididymis

Tumors of the epididymis are very rare. They consist of benign and malignant primary tumors, as well as metastatic tumors. Each of these is considered in the following sections.

Primary Tumors of the Epididymis

In 1951, Longo and associates published the first substantial review of primary neoplasm of the epididymis (113). In this study, the authors reviewed the world literature covering 134 cases of primary epididymal tumors, as well as 19 cases seen at Mayo Clinic. The authors pointed out that the average age at diagnosis of an epididymal tumor was 41.5 years. A scrotal mass was the chief complaint in 76% of the cases, while the finding was incidental on physical examination in 18% of the cases. Some patients had noted scrotal enlargement for as long as 30 years before seeking medical attention. Of the 134 cases reported in the world literature, 74% of the tumors were benign and 26% were malignant. Overall, 53% of the tumors were described as adenomatoid, terminology originally applied by Golden and Ash in 1945 (65a). This tumor apparently is a truly benign neoplasm. More than 200 cases have been reported in the world literature and no metastases have ever been observed (70). Although adenomatoid tumors can occur in females as well as in males, approximately 70% of all cases have occurred in males. The tumors are usually symptomless, small, and well circumscribed. Microscopically, the tumor has mixed epithelial and stromal elements. The cell that is the main component of the epithelial element is eosinophilic and has a vacuolated cytoplasm. Irregular, somewhat branched-appearing tubular structures appear within the tumor. These tubular structures are believed to represent coalescence of the vacuoles from the cells, forming a false lumen (32). Nistal and colleagues (137) supported the concept that these cells were of mesothelial origin by showing the presence of microvilli in the free surface of the cells and by demonstrating by histochemical techniques the presence of acid mucopolysaccharides in the lumen in the tubular structure.

Patients with adenomatoid tumors most frequently have a painless intrascrotal solid mass, which on examination is well circumscribed within the epididymis and is usually less than 2.5 cm in diameter. The globus minor is involved approximately four times more often than the globus major (70,113). Because truly malignant lesions of the epididymis are rare, when a well-circumscribed solitary mass is encountered during surgical exploration through an inguinal incision, excision of the mass or epididymectomy is the normal treatment. Rarely is an orchiectomy required. In more than 200 cases reported in the literature, no metastatic tumors have been noted; however, local infiltration has been observed (72).

According to Broth and associates (13), who reviewed 278 primary tumors of the epididymis, leiomyoma was the next most frequent benign lesion after adenomatoid tumors. The leiomyomas accounted for 6% of the overall tumors. The third most frequent benign tumor was the papillary cystadenoma, which accounted for 4% of benign tumors. Other benign tumors included vascular lesions, cystic embryomas, fibromas, cholesteatomas, teratomas, lipomas, hamartomas, dermoid cysts, and adrenal cortical adenomas.

In a summary of epididymal tumors, Elsasser (51) reported 40 cases of papillary cystadenoma in the literature. Kallie and associates (94) reported that the consensus is that the papillary cystadenoma arises from the efferent ductules of the epididymis. These ductules are mesonephric in origin. Cystadenoma resembles a spermatocele with respect to its location and lining epithelium (94). Most of the papillary cystadenomas occur in the globus major of the epididymis. The tumor may be bilateral and appears to be associated with von Hippel–Lindau disease. In an Armed Forces Institute of Pathology study, four of ten patients with known von Hippel–Lindau disease who underwent epididymal examination had papillary cyst adenomas (152). Local excision of the mass through an inguinal incision is usually satisfactory treatment. There are no reports in the literature of recurrence from metastasis. However because this is often a part of the von Hippel–Lindau syndrome, other manifestations of this disease must be kept in mind. Areas of particular interest in urology are the development of pheochromocytomas and manifestation of renal cysts or malignant renal lesions. Between 13% and 25% of patients with von Hippel–Lindau disease develop renal cell carcinoma (84).

Primary Malignant Tumors of the Epididymis

In addition to reporting the distribution of benign epididymal and cord tumors by tissue type, Broth and associates also reported the distribution of primary malignant epididymal and cord tumors (13). Of the 278 tumors reported, 56 (20%) were primary malignant tumors. Sarcomas were more common than carcinomas. In a more recent review by Elsasser, 50% of the paratesticular tumors were malignant (51). Virtually all of the tumors in this report were sarcomas. Rhabdomyosarcomas were the most common, accounting for half of the tumors. Following this were leiomyosarcomas, fibrosarcomas, and liposarcomas. With the exception of rhabdomyosarcomas in a young child, the majority of sarcomas occurred in middle-aged or older patients.

Often, hydroceles hamper the palpation and diagnosis of a paratesticular mass. Approximately 10% of benign tumors are masked by hydroceles, while a greater percentage of patients with malignant tumors of the epididymis have hydroceles. Painless swelling of the scrotum also should make the examiner suspect a tumor (51). If a tumor is suspected, the patient should undergo an inguinal approach for exploration of the testis and paratesticular structures. If a mass is found, a high ligation of the cord structures should be performed as in the case of a primary testis tumor. In general, the higher the tumor is located along the cord structures, the more likely it is that the external inguinal lymphatics and the retroperitoneal lymphatics are involved.

In general, the prognosis of patients with primary malignant tumors of the epididymis is poor. In the series of extratesticular sarcomas reported by the Testicular Tumor Panel and Registry in Great Britain, many of which were primary lesions of the epididymis, over half of the patients died of disease within 2 years (69). Banowsky and Schultz (4) reported follow-up in 73 patients with extratesticular sarcomas. Two-thirds of these patients died of disease or developed metastases. Metastases were believed to have spread by lymphatics alone in 53% of these cases, by lymphatics and blood vessels in 37%, and primarily by hematologic means in 10%.

One exception to this poor outlook has been a multimodal therapy for treatment of rhabdomyosarcoma in children, reported by Ghavimi and colleagues (64). In this series, surgery, radiation therapy, and combination systemic chemotherapy were used in 11 children. Of the 11 children, 7 are free of disease 2 to 10 years after the initiation of treatment. Other more recent reports in the literature have shown mixed results using various forms of treatment for epididymal sarcomas. One review of fibrosarcomas of the epididymis by McCormack (117) noted that all patients who had recurrence other than local skin lesions overlying the original lesion were dead in less than 1 year.

At present, the optimal treatment for each type of primary malignant tumor of the epididymis is not clear. A radical orchiectomy through an inguinal approach is recommended. After the cell type of the lesion is documented, a careful review of the recent literature to seek advice on further therapy is recommended.

Metastatic Malignancies of the Epididymis

Solid tumor metastases to the epididymis are uncommon. Burger and Guthrie reported a case of metastatic colon carcinoma to the epididymis and summarized 15 cases in the literature (16). Of these 15, 9 of the lesions were from the gastrointestinal tract (7 stomach and 2 colon), 4 from the kidney, and 3 from the prostate (16). Most recently, Powell and associates reported 38 cases of secondary malignancies to the epididymis (150). In this series, urologic malignancies were the most common origin of the metastases. Of 38 total cases reported, 20 were from the urologic tract, with 14 originating from the prostate and 6 from the kidney. Of the remaining cases, 16 were from the gastrointestinal tract, with the stomach being the most common primary site, followed by colon and malignant carcinoid tumors of the ileum. Two cases of metastases from pancreatic tumors were reported. The prognosis of patients with metastatic tumors to the epididymis is most closely related to the prognosis of the primary disease. Often, the prognosis is poor because the metastases that are present represent an advanced stage of the primary disease. Some metastatic tumors of the epididymis have been discovered incidentally at the time of orchiectomy for carcinoma of the prostate. Others have been discovered because of pain or swelling of the scrotal contents. Four mechanisms that have been proposed to explain metastasis to the epididymis have been summarized by Powell and colleagues (150). These mechanisms include direct extension, retrograde venous extension, retrograde lymphatic extension, and arterial embolism. Eadie demonstrated retrograde lymphatic spread of a carcinoma of the stomach to the left testicle (42). This is the most likely mechanism of extension of metastasis from gastrointestinal tumors to the epididymis as well.

Tumors of the Cord Structures

Tabulations discussed in the previous section regarding tumors of the epididymis by Broth and associates (13) and Elsasser (51) included tumors of the cord structures as well as those of the epididymis. Approximately half of the tumors involving the cord structures are sarcomas. The majority of these are rhabdomyosarcomas and, particularly, embryonic sarcomas arising in children. Of the remaining sarcomas, the most common is leiomyosarcoma followed by fibrosarcoma, liposarcoma, and undifferentiated sarcomas. The incidence of tumor is highest distally in the cord structure near the testis. In this case, it is sometimes difficult to differentiate between a tumor of the cord structures and a tumor of the epididymis. The presence of a hydrocele often masks the presence of a tumor of the cord structures. The more proximally the tumor is located along the cord structures, the more likely it is that the external inguinal lymphatics will be involved. The retroperitoneal lymphatics are also commonly involved with these tumors. Finally, the treatment and prognosis of these tumors is essentially the same as previously outlined with epididymal tumors.

Tumors of the Scrotal Wall

Siegal and Goffey from the Mayo Clinic cited 182 cases that were identified as having lesions arising exclusively from the layers of the scrotal wall. Of these, 127 were available for histologic review. Nevi were the most common benign neoplasms, and squamous cell carcinomas (epithelioma)

were the most common malignant lesions. Tumors have been reported that arise out of virtually any of the components of the scrotal wall, from the epithelium to the mesenchymal elements. In the case of benign scrotal lesions, such as leiomyomas, simple excision is curative (177).

Squamous cell carcinoma of the scrotum is now exceedingly rare. The incidence has been reported to be fewer than ten cases per year in the United States (33). However, squamous cell carcinoma of the scrotum is important from a historical perspective. In 1775, squamous cell carcinoma of the scrotum was the first cancer recognized as an occupational neoplasm. Pott reported on the disproportionate incidence in chimney sweeps in newly industrial England (149). Subsequently, other occupations with significant exposure to oils, such as cotton mule spinning (a primarily left-sided disease) (77); machine operators in engineering (27); petroleum wax pressman (110); screw-making industry (196); and automatic lathe operators (2) have been reported.

The prognosis for patients with malignant tumors arising from the scrotal wall seems to be linked most closely with the ability to completely excise a localized tumor. Tumors such as leiomyosarcoma arising from the scrotal wall appear in all respects to be similar to those tumors arising from smooth muscle in the skin and all other areas. A summary by Dahl and Angervall (29) noted no correlation between the spread of sarcomas and the size of the tumor or the mitotic rate of the tumor. The one important prognostic factor that they described was the ability to completely excise the lesion at the time of initial surgery. All of the patients who had a complete resection of the lesion remained free of metastases. At present, recommendation for treatment of lesions arising from the scrotal wall includes wide local incision with frozen section, when possible, to distinguish benign from malignant neoplasms. Lymphatic drainage of the scrotal wall is to the inguinal lymph nodes with considerable crossover (140). Ileoinguinal lymphadenectomy for scrotal cancer is controversial and generally reserved for patients with palpable disease, similar to penile carcinoma (17,156). Unfortunately, adjunctive therapy, such as radiation or chemotherapy or both, has not proved useful in these lesions.

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42

THE PENIS: SEXUAL FUNCTION AND DYSFUNCTION

George S. Benson

Michel A. Boileau

G.S. Benson: Medical Officer, Food and Drug Administration, Rockville, MD 20857.

M.A. Boileau: Bend Urology Associates, Bend, OK 97701.

Contents

The diagnosis and treatment of male sexual dysfunction were largely ignored by urologists until approximately 20 years ago. Successful therapy—primarily acceptable penile prostheses—preceded a surge in investigative efforts to better understand the physiology of penile erection. Several new therapies based on experimental advances in the neurophysiology and neuropharmacology of penile erection have evolved. The acquisition of new knowledge in this area has occurred so rapidly and so many new diagnostic and treatment methods, including oral therapy, have emerged that much of the clinical diagnosis and therapy of erectile dysfunction remains controversial.

THE PENIS

Part of "42 - THE PENIS: SEXUAL FUNCTION AND DYSFUNCTION "

Anatomy

Penile erectile tissue is contained within three corporal bodies: two dorsally positioned corpora cavernosa and a ventrally positioned corpus spongiosum, which also contains the urethra (Fig. 42.1). Each of the three corpora is surrounded by tunica albuginea, a thick layer of fibrous tissue that separates the corpora from each other. Buck's fascia, a single fascial sheath that lies superficial to the tunica albuginea, envelops all three corporal bodies.

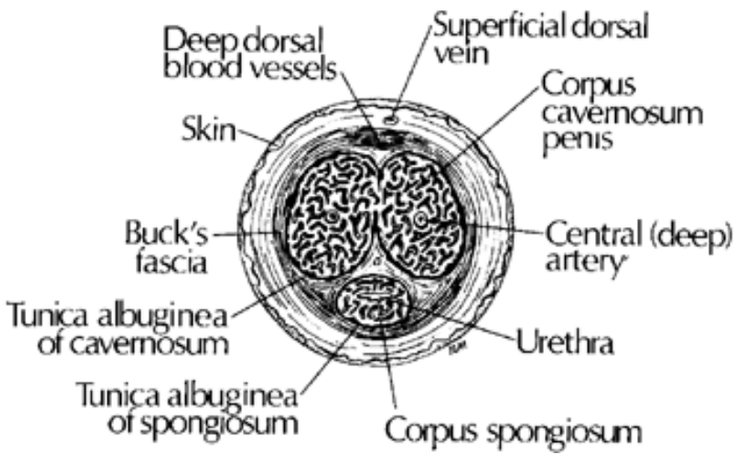

FIGURE 42.1. Cross-sectional anatomy of human penis.

The corpora cavernosa and the corpus spongiosum contain numerous cavernous spaces separated by trabeculae composed not only of smooth muscle but also of fibroblasts, collagen, and elastic fibers. The corpus spongiosum is composed of larger cavernous spaces and smaller trabeculae with fewer smooth muscle cells than found in the corpora cavernosa. When viewed with the electron microscope, the orientation and components of the trabeculae in the corpora cavernosa vary considerably. The surfaces of the trabeculae, the walls of the cavernous spaces, are covered by endothelial cells that resemble those found in blood vessels (26).

Arterial Supply

The penile arterial blood supply is derived from the paired internal pudendal arteries, which are terminal branches of the hypogastric arteries (Fig. 42.2). In the perineum, each pudendal artery gives off a perineal branch and then two arteries to the corpus spongiosum. The bulbar artery supplies the proximal corpus spongiosum; the urethral artery pierces the corpus spongiosum and then continues distally to the glans penis. Just outside the crus of the penis, each pudendal artery divides into the dorsal penile artery and the deep penile artery. The dorsal artery courses distally between the tunica albuginea of the corpora cavernosa and Buck's fascia. The deep penile artery penetrates the crus of the penis

and then courses distally within the corpus cavernosum as the deep (central) artery. Arteriographic studies have demonstrated considerable variation in penile arterial supply (40).

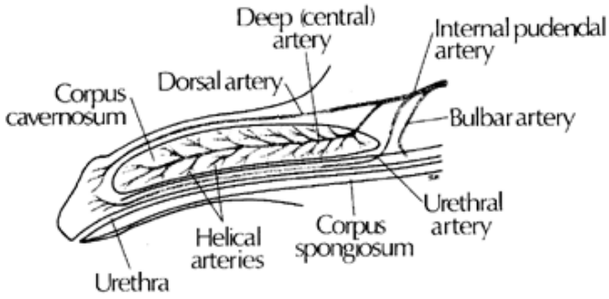

FIGURE 42.2. Arterial blood supply to human penis.

The deep (central) arteries supply nutrient vessels to the trabeculae, anastomoses that cross the septum to the opposite corpus cavernosum, and helical arteries. The helical arteries, which are more numerous in the proximal than in the distal corpora cavernosa, arborize into short end-arteries that then open directly into the cavernous spaces (259). In addition, numerous anastomotic channels interconnect all of the arteries of the penis (80,284). “Shunt arteries,” which connect the deep penile arteries with the arteries in the corpus spongiosum, also have been described (354).

Venous Drainage

The anatomy of penile venous drainage is complex and controversial, and the nomenclature is not standardized (345). Venous drainage is accomplished by at least three major pathways (259). The superficial dorsal vein lies superficial to Buck's fascia and is formed from multiple subcutaneous veins. The deep dorsal vein courses between Buck's fascia and the tunica albuginea of the corpora. Veins from the glans penis and emissary and circumflex veins from the corpora cavernosa drain into the deep dorsal system. The third major venous drainage system is composed of deep veins (venae profundae) of the corpora cavernosa. These relatively large vessels exit from the hilum of the penis (cavernosal veins) and from the penile crura (crural veins) and drain into the pudendal system. In addition to the aforementioned major drainage systems, bulbar and urethral veins drain the proximal corpus spongiosum.

An understanding of the venous drainage of various parts of the penis is further complicated by the recognition that numerous anastomotic connections exist between the major venous drainage systems just discussed (80,345). Furthermore, conflicting data make the resolution of significant questions difficult. For example, anatomically, the corpora cavernosa appear to drain into both the deep veins of the corpora cavernosa and through emissary veins, which penetrate the tunica albuginea and join the circumflex veins, which in turn empty into the deep dorsal vein. Deysach (80), however, found that the retrograde injection of India ink or cinnabar into the deep dorsal vein filled vessels of the glans penis and corpus spongiosum but did not penetrate into the corpora cavernosa. In addition, some clinical data also implicate the superficial dorsal vein as being important in the drainage of the glans penis and corpus spongiosum. In a clinical study of patients with priapism, cavernosograms demonstrated obstruction of the deep dorsal vein, and spongiosograms revealed that the superficial vein (lying above Buck's fascia) was patent (105). Furthermore, numerous small and large anastomotic connections have been described between the superficial dorsal vein and the deep dorsal vein (80).

A clearer understanding of the venous drainage of the penis in both normal and disease states is necessary for a more rational approach to clinical problems. Although the venous drainage of the corpora cavernosa probably is accomplished by both the deep dorsal and the venae profundae systems, the importance of each of these drainage systems in normal penile erection, priapism, and impotence secondary to “venous leaks” requires further anatomic definition.

Innervation

The innervation of the penis is derived from both divisions of the autonomic nervous system (sympathetic and parasympathetic) and from the somatic nervous system. Although cavernosal nerves have been recognized for years, recent investigation has significantly clarified our understanding of the gross and microscopic neuroanatomy of the penis and its vasculature.

Sympathetic nerves that originate in the low thoracic and upper lumbar regions of the spinal cord course retroperitoneally to condense into the superior hypogastric plexus (presacral nerve) located inferior to the aortic bifurcation. Sympathetic fibers then leave the superior hypogastric plexus as the right and left hypogastric nerves that fuse distally and contribute to the formation of the inferior hypogastric (pelvic) plexus (194) (Fig. 42.3).

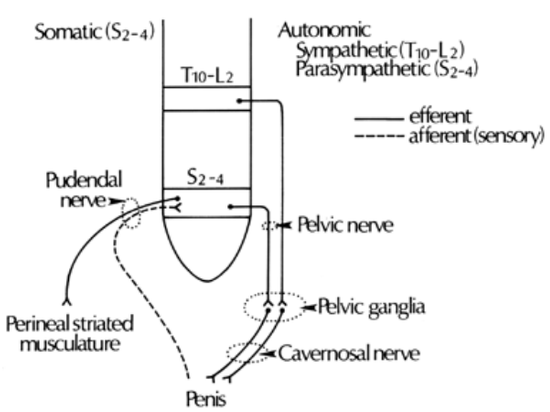

FIGURE 42.3. Innervation of penis.

The pelvic plexus also receives input from the parasympathetic nervous system, whose cell bodies are located in the

sacral (S-2 to S-4) portion of the spinal cord (Fig. 42.3). Parasympathetic nerves enter the pelvic plexus by means of the pelvic nerve, which courses in the endopelvic fascia. In humans, the pelvic plexus is located retroperitoneally beside the rectum. Nerve fibers from the pelvic plexus innervate not only the penis but also the lower urinary tract and rectum. Anatomically, it is difficult (if not impossible) to ascertain the origin of nerves (parasympathetic or sympathetic, preganglionic or postganglionic) leaving the pelvic plexus. Walsh and Donker (357) demonstrated that the branches of the pelvic plexus that innervate the corpora cavernosa are situated between the rectum and urethra and penetrate the urogenital diaphragm near or in the muscular wall of the urethra. They then enter the dorsal medial side of the corpora cavernosa.

The somatic innervation to the penis is carried in the pudendal nerve, whose cell bodies, like those of the parasympathetic pelvic nerve, are located in the sacral (S-2 to S-4) spinal cord. The pudendal nerve does not course through the pelvic plexus; it travels with the internal pudendal vessels along the lateral wall of the ischiorectal fossa (357). The dorsal nerve of the penis is a terminal branch of the pudendal nerve, and penile sensation is carried by means of sensory fibers in the pudendal nerve.

The peripheral innervation of the penis has been studied extensively. Adrenergic nerves, whose neurotransmitter by definition is a catecholamine, have been identified by histofluorescent techniques at the light microscopic level. Although the distribution of catecholamine-positive nerve fibers was initially reported to be sparse (319), subsequent studies have demonstrated that the human corpus cavernosum contains numerous adrenergic nerves that course through the trabeculae and approach the walls of the cavernous spaces (26) (Fig. 42.4). Very few adrenergic fibers are demonstrable in the corpus spongiosum. Blood vessels within the corpora cavernosa also contain many adrenergic nerve varicosities in the outer tunic (Fig. 42.5). Nerves that contain small, highly electron-dense vesicles that are chrome positive by an electron microscopic glutaraldehyde dichromate technique and therefore thought to contain norepinephrine also have been identified (230).

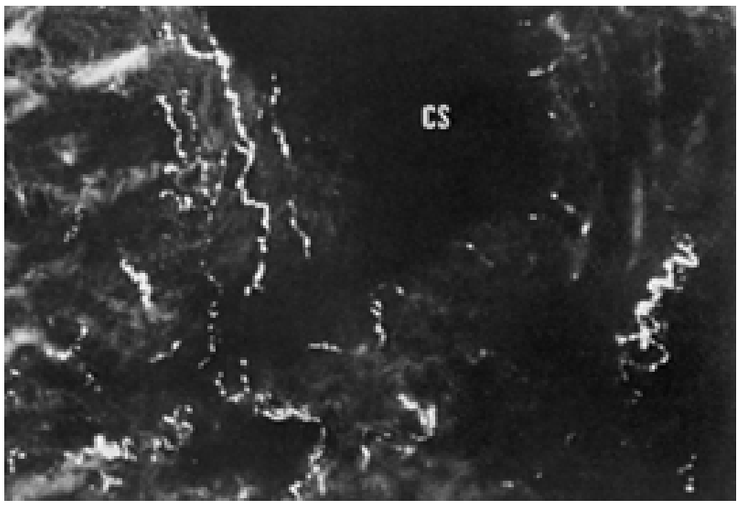

FIGURE 42.4. Micrograph of histofluorescent nerve fibers in the human corpus cavernosum. The brilliant fluorescence of the varicose catecholaminergic fibers near the cavernous space *(CS)* is easily differentiated from the dull glow of autofluorescent connective tissue located more peripherally (×80). (From Benson GS, McConnell JA. Erection, emission, and ejaculation: physiological mechanisms. In: Lipshultz LI, Howards SS, eds. *Infertility in the male,* 2nd ed. St. Louis: Mosby, 1991, with permission.)

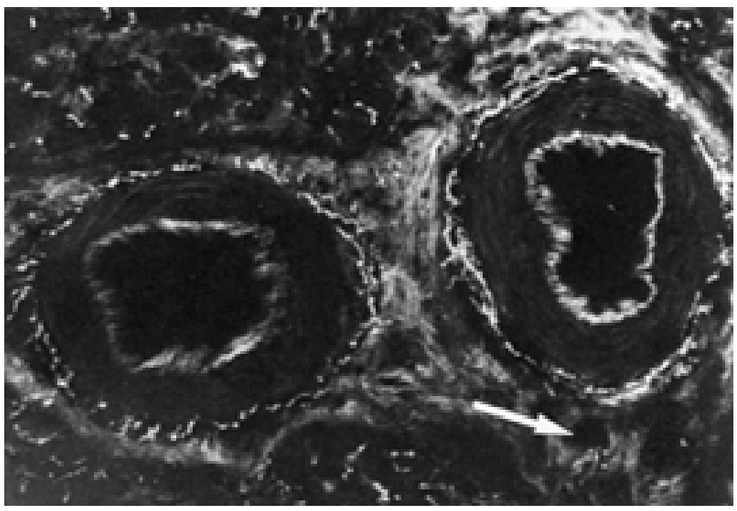

FIGURE 42.5. Fluorescent photomicrograph of paired central arteries in human corpus cavernosum (27-year-old man). Note the numerous adrenergic fibers at the periphery of these arterioles but the few fluorescent fibers near the small venule *(arrow)* (×200). (From McConnell JA, Benson GS. Innervation of human penile blood vessels. *Neurourol Urodynamics* 1982;1:199, with permission.)

Cholinergic nerves also are present within the corpora cavernosa. These nerves, whose neurotransmitter by definition is acetylcholine, have been identified classically at the light microscopic level by acetylcholinesterase staining. Controversy also exists as to the density of cholinergic innervation in the corpora. Some investigations have reported an abundant number of acetylcholinesterase-positive

nerve fibers within the trabeculae of the corpora cavernosa (319). Other studies, however, have described a scant distribution of cholinergic nerves within the corpora cavernosa and even fewer of these fibers within the corpus spongiosum (26). Acetylcholinesterase-positive nerve fibers are contained within the outer tunic of most penile arterioles (Fig. 42.6).

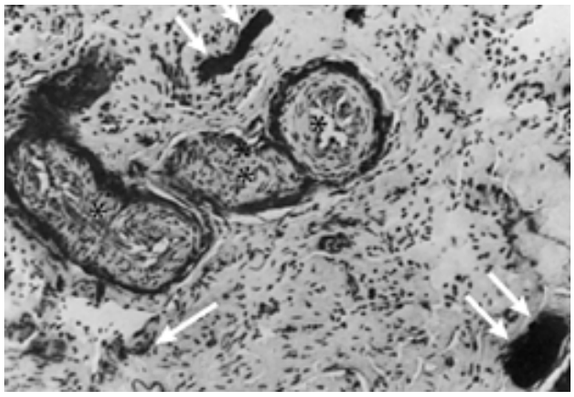

FIGURE 42.6. Photomicrograph of human corpus cavernosum (27-year-old man). Acetylcholinesterase-positive fibers are visible near each of the sections through the tortuous arteriole *(asterisks).* Nerve bundles containing acetylcholinesterase also are present *(arrows)* (×180). (From McConnell JA, Benson GS. Innervation of human penile blood vessels. *Neurourol Urodynamics* 1982;1:199, with permission.)

Nerves containing other putative neurotransmitters also have been identified anatomically within the penis of animals and humans. Using immunohistochemical techniques at the light microscopic level, vasoactive intestinal polypeptide (VIP) has been localized in nerve fibers near the trabecular smooth muscle of the corpora cavernosa, as well as around blood vessels (275) (Fig. 42.7). In addition, large VIP-immunopositive vesicles have been demonstrated in nerve terminals in penile tissues by electron microscopy (132). Various large vesicles that are not VIP immunoreactive also have been identified and are postulated to contain other peptides that may act as neurotransmitters (332).

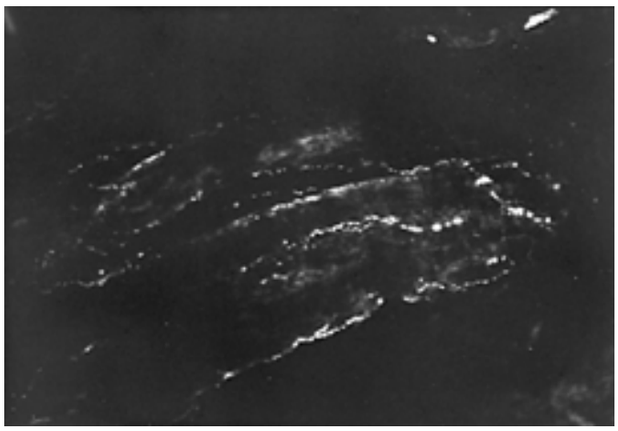

FIGURE 42.7. Monkey penile tissue demonstrating VIP fluorescent nerve fibers in trabeculae of corpus cavernosum (×100). (From Steers WD, McConnell JA, Benson GS. Anatomical localization and some pharmacologic effects of VIP in human and monkey corpus cavernosum. *J Urol* 1984;132:1048, with permission.)

Recently, much physiologic and pharmacologic evidence has been presented that implicates nitric oxide in the physiology of erection. Nitric oxide synthase, the enzyme that catalyzes nitric oxide production, has been identified in the pelvic plexus, cavernous nerves and their terminal endings within the corporal erectile tissue, branches of the dorsal penile nerves, and nerve plexuses in the adventitia of the deep cavernosal arteries in humans. In addition, these same nerves stain for reduced nicotinamide adenosine dinucleotide phosphate (NADPH) diaphorase. Because NADPH derives from nitric oxide synthase activity in neurons, this finding also supports the concept that nitric oxide is present in penile nerves (50). The significance of this finding is discussed in the following section.

PENILE ERECTION

Part of "42 - THE PENIS: SEXUAL FUNCTION AND DYSFUNCTION "

Hemodynamic Aspects

Penile erection and detumescence are primarily controlled by hemodynamic events. Increased arterial inflow appears to be of primary importance; the contribution of increased venous resistance to the production of penile erection remains controversial. Furthermore, our understanding of precise anatomic details (including “shunts”) and the neural control of vascular events is not complete.

More than half a century ago, Semans and Langworthy (315) demonstrated the importance of arterial inflow in the production and maintenance of a penile erection. They found in cats that aortic occlusion prevented the development of penile erection produced by sacral nerve root stimulation. After an erection had been produced by nerve stimulation, aortic occlusion resulted in detumescence. Similar animal studies were refined and again demonstrated the importance of increased arterial inflow in the production of erection. With pelvic nerve stimulation in the dog, Dorr and Brody (83) demonstrated that the dorsal artery perfusion pressure fell while venous pressure rose. Blood flow through both the dorsal artery and vein greatly increased. In addition, no venous pressure gradient with erection could be demonstrated when venous pressure was recorded at multiple sites from the erectile tissue distally to the internal pudendal vein proximally. These data are consistent with the hypothesis that the primary hemodynamic event leading to erection is increased arterial inflow and that increased venous resistance plays a minor, or insignificant, role.

Contradictory results have been reported in the canine model (209). With electrical stimulation of the cavernosal nerves, internal pudendal arterial flow was found to increase

by 250% during the early phases of erection (Fig. 42.8). This was accompanied by a 20-mm Hg decrease in internal pudendal artery pressure. With erection, the flow rate gradually decreased to slightly above basal levels. A new equilibrium was established at full erection, with corporal pressure approximately 10 mm Hg below the systolic arterial pressure. At full erection, flow into and out of the corpus cavernosum, although present, was greatly reduced. Furthermore, with the aorta occluded and with saline solution infusing directly into the corpus cavernosum, an initial drop in intracorporal pressure and decreased venous flow during erection were demonstrated with cavernosal nerve stimulation. Thus these investigators have concluded that tumescence is the result not only of active arterial dilation and increased arterial flow but also of active relaxation of the corporal trabeculae and restriction of venous outflow. The decreased venous outflow is thought to be secondary to compression of venules located in the corpora cavernosa just beneath the tunica albuginea.

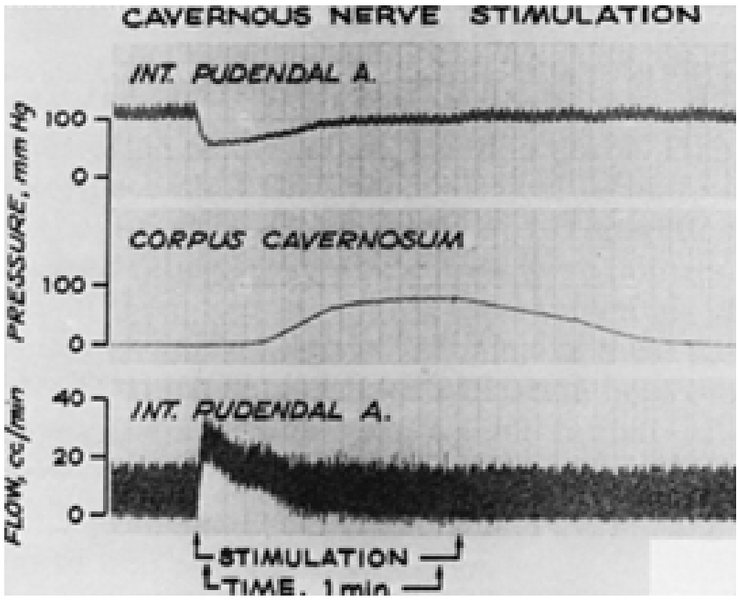

FIGURE 42.8. Changes in blood flow and pressure after cavernous nerve stimulation in the dog. (From Lue TF, Takamura T, Umraiya O, et al. Hemodynamics of canine corpora cavernosa during erection. *Urology* 1984;24:347, with permission.)

In animals, other data exist that implicate obstruction of venous return as an important mechanism in the production of penile erection (138). Anesthesia of the ischiocavernosus muscles produced by lidocaine injection often prevents goats, bulls, and stallions from copulating because of the inability to attain an erection (21,277). The highest pressures in the corpus cavernosum in the dog penis occur during intromission and coincide with contractile activity of the ischiocavernosus muscles measured electromyographically (277). Presumably, blockade of venous return secondary to skeletal muscle contraction may promote the development of penile erection. To the contrary, in the human, erection can occur without electromyographically measurable increases in bulbocavernosus, urethral sphincter, or deep transverse perineal muscle activity (178).

Although "venous valve mechanisms" and sphincteric-like smooth muscle structures surrounding penile veins have been described anatomically and hypothesized to contribute to the development of penile erection (60), physiologic investigation in humans is necessary to resolve the controversy concerning the possible role of increased venous resistance. Xenon washout techniques would appear to be an ideal method to resolve this question. In the flaccid state, there is minimum blood flow through the corpora cavernosa. If ^{133}Xe were placed into the corpora cavernosa and erection produced by visual stimulation, the rate of ^{133}Xe "washout" during erection should give valuable information concerning the importance of venous resistance to flow. This study has been done in humans by two groups of investigators with markedly conflicting results. Shirai and Ishii (318) reported an increase of disappearance of ^{133}Xe with erection and failed to show any significant increase in venous resistance. Wagner (355), however, described a decreased washout with erection, evidence that increased venous resistance and decreased venous flow occur with the development of an erection in humans. Primarily because of observations made by Lue and colleagues (209) and Aboseif and Lue (2), most investigators believe that penile erection is dependent not only on increased arterial inflow but also on relaxation of the corporal smooth muscle. Corporal smooth muscle relaxation and increased intracorporal pressure result in passive occlusion of corporal venous outflow.

Although active arterial dilation, corporal smooth muscle relaxation, and passive venous occlusion are generally considered the mechanisms of penile erection, other theories have been proposed. Venous "sluices" were hypothesized by Deysach (80) to open and close and thereby produce erection by altering venous outflow. For years, the most widely accepted hypothesis to explain penile blood flow was the "polster" theory advocated by Conti (68). In an anatomic study performed on cadavers, Conti described "polsters," that is, columns of smooth muscle cells within the intima of penile arteries and veins. Although such structures had been described anatomically by earlier investigators, Conti proposed that contraction and relaxation of these polsters could divert blood into and away from the cavernous spaces and thus induce erection and detumescence. Calcification and fibrosis of polsters have been cited as causes for impotence in elderly diabetic patients (298). No data supporting a physiologic role for polsters, however, have been published, and the functional importance of these structures has been questioned. In addition, anatomic studies have demonstrated no innervation to polsters. Finally, evidence has been presented that suggests that polsters are actually atherosclerotic changes in penile blood vessels (27) (Fig. 42.9). Wagner and colleagues (354) proposed a mechanism of erection based on "shunt arteries." According to their hypothesis,

the helicine arteries that supply the corpora cavernosa are constricted during detumescence, resulting in blood being diverted to the corpus spongiosum by means of shunt arteries. Erection results when the helicine arteries dilate and the shunt arteries constrict. To date, all of the theories of various “shunt” mechanisms resulting in penile erection remain physiologically unproved.

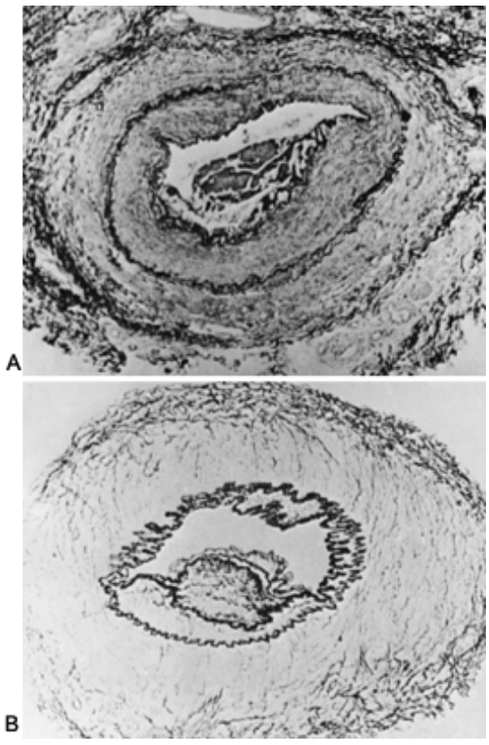

FIGURE 42.9. A: Atherosclerotic lesions from penile artery of 49-year-old man. **B:** Conti's drawing of penile polsters. (From Benson GS, McConnell JA, Schmidt WA. Penile “polsters”: functional structures or atherosclerotic changes? *J Urol* 1981;125: 800 and Conti G. L'erection du penis humain et ses bases morphologico-vasculaires. *Acta Anat Basel* 1952;14:217, with permission.)

Neurophysiology

The hemodynamic changes leading to penile erection and detumescence are clearly under neurologic control. One of the earliest investigations into the mechanisms controlling penile erection was Eckhard's demonstration that penile erection in the dog was produced by stimulation of the pelvic parasympathetic nerves, which he called the *nervi erigentes* (86). Eckhard was unable to produce an erection in the dog with stimulation of the hypogastric nerve, a sympathetic nerve. During the past century, investigators have attempted to understand and clarify Eckhard's findings.

In animals, the relative importance of the parasympathetic and sympathetic nervous systems in the control of erection was investigated by the classic studies of Muller (254) in the dog and Root and Bard (290) in the cat. In 1902, Muller observed that excision of the entire sacral and most of the lumbar spinal cord abolished reflex penile responses in the dog. Erection still developed, however, when the dog was placed with a bitch in heat. In addition, male dogs whose cords had been transected at a low thoracic level never exhibited erections in the presence of an estrous female; these animals, however, retained their ability to achieve full penile erection with penile stimulation. Forty-five years after Muller's study, Root and Bard performed similar, albeit refined, experiments in the cat. Excision of the sacral and lower lumbar spinal cord abolished erections normally produced by manipulation of the penis but did not alter the ability of the male cat to achieve an erection in the presence of an estrous female. The addition of spinal cord transection between T-13 and L-1 or T-11 and T-12 in cats that had previously undergone ablation of the lower spinal cord resulted in the cessation of erectile response to both tactile and psychic stimuli. Resection of the inferior mesenteric ganglion and hypogastric nerves also abolished erectile responses in animals whose lower spinal cord had been resected. Finally, resection of the sympathetic nerves (inferior mesenteric ganglion and hypogastric nerves) had no effect on erection when the lumbosacral spinal cord was left intact. The results of the work of Muller and Root and Bard indicate that at least in the dog and cat, two peripheral neural pathways exist that control erection: (a) a sacral (parasympathetic) mechanism that responds to both tactile and psychic stimuli and (b) a lumbar (sympathetic) mechanism that responds to psychic stimuli.

Although these studies describe the contributions of the parasympathetic and sympathetic nervous systems in a straightforward manner, other animal data cast doubt on this relatively simplistic scheme. Sacral parasympathetic nerve or nerve root stimulation does produce erection in the dog, cat, and rabbit. Stimulation of sympathetic nerves, however, has achieved conflicting results, which may be explained at least in part by species variability. With hypogastric nerve stimulation, Eckhard observed erection in rabbits, but not in dogs. However, other reports have indicated that in the dog, hypogastric nerve stimulation results in a slight increase in penile volume (9). In cats, hypogastric nerve stimulation does not result in erection and, in addition, actually results in contraction

of penile arteries and causes an erect penis to become flaccid (315).

Human data relating to the neurophysiology of erection are limited. Most of the information is retrospective and has been obtained by interview or questionnaire technique. In addition, the completeness of the neurologic lesion produced by spinal cord injury or neurosurgical ablative procedures is difficult to ascertain. A survey of sexual function in a large number of spinal cord–injured patients has been presented by Bors and Comarr (41). Patients with complete lower motor neuron lesions failed to achieve erection with genital stimulation. Of these patients, however, 24% reported erectile activity secondary to psychic stimuli. Most patients with upper motor neuron lesions (spinal cord lesions above the level of the sacral spinal cord) reported erections secondary to genital stimulation. The percentage of patients achieving erection with psychogenic stimulation depended on the level of the lesion: cervical (4%), thoracic T-1 to T-6 (0%), thoracic T-7 to T-12 (8%), and lumbar (57%). These human data are generally consistent with the feline data of Root and Bard and the canine data of Muller. Specifically, the development of penile erection secondary to genital stimulation appears to require an intact sacral reflex, whereas the sympathetic system appears capable of producing psychogenic erections through pathways that connect the cerebral cortex to the penis and its vasculature. Although patients who have undergone lumbar sympathectomy or extensive retroperitoneal lymph node dissection commonly develop symptoms consistent with sympathetic denervation (lack of seminal fluid emission or retrograde ejaculation), they do not report a disturbance in erectile function (166,179,291). Therefore, in humans, it would appear that the parasympathetic nervous system is of primary importance in penile erection and is probably capable of responding to both tactile and psychic stimulation. The sympathetic nervous system may be capable of producing erection secondary to psychic stimuli, but its role in sexual function is less clear and needs further definition.

Penile erection clearly is modified by supraspinal neurologic mechanisms. A better understanding of these mechanisms is necessary before we can rationally approach such problems as psychogenic impotence and the deleterious effects of drugs on erectile function. Animals have been studied to some extent with central nervous system (CNS) stimulation and ablation experiments. Human data consist primarily of case reports dealing with patients with CNS diseases or after ablative surgical procedures.

Hypersexual behavior in monkeys that had undergone removal of both temporal lobes, including the uncus and part of the hippocampus, was reported by Kluver and Bucy in 1939 (177). These animals exhibited frequent penile erections even under nonstimulated conditions. Stereotaxic electrical stimulation of specific parts of the brain, particularly the limbic system, is known to result in penile erection (84,218,219,288). In humans, impotence has been associated with temporal lobe lesions and after bilateral pallidofugal section for myoclonus (148,241).

Neuropharmacology

The neuropharmacology of penile erection has gained increasing attention in recent years, primarily because the introduction of intracorporal injection therapy, intraurethral therapy, and effective oral therapy has caused a resurgence of interest in the medical management of impotence. Numerous *in vitro* and *in vivo* animal and human experiments have been performed to study the responses of the penile vasculature and cavernosal tissue to pharmacologic stimulation. Because stimulation of the pelvic nerve produces erection and because the pelvic nerve has been classically thought to be made up primarily of a cholinergic nerve population, acetylcholine was previously thought to be the neurotransmitter responsible for penile erection.

However, several experimental observations cast doubt on a purely cholinergic mechanism. Although the erection produced by pelvic nerve stimulation can be abolished by pretreating animals with hexamethonium (a ganglionic blocking agent), atropine does not completely block the response (83,144). Studies in humans also are consistent with the concept that erection is an atropine-resistant phenomenon (353). In addition, the infusion of acetylcholine into animals does not produce an erection (82,83). Finally, strips of corporal smooth muscle in an *in vitro* muscle bath respond minimally, if at all, to stimulation with acetylcholine (26). Although it has been argued that, in these experimental situations, acetylcholine and atropine do not reach the vascular and corporal receptors, an equally plausible explanation is that penile erection is not a cholinergically (or exclusively cholinergically) mediated event. Evidence has been presented that corporal smooth muscle relaxation caused by acetylcholine is mediated by nitric oxide (300,301).

Efforts have been directed toward ascertaining whether a catecholamine could be responsible for initiating and maintaining penile erection. The penile vasculature and smooth muscle of the corpora cavernosa are generously supplied with adrenergic nerves, and high norepinephrine levels have been detected in the corpora cavernosa (237). In humans, the corpora cavernosa possess a high α-adrenergic receptor density determined by radioligand-binding studies (197). In the cat and rat, a portion of the sacral parasympathetic outflow is adrenergic (7,339), and these neurons conceivably could be responsible for the erection produced by pelvic nerve stimulation.

Strips of human corpora cavernosa relax when exposed to isoproterenol and salbutamol (β-adrenergic agonists) (4), and in the cat, erection has been produced by the intravenous infusion of salbutamol and phenoxybenzamine (an

α-adrenergic antagonist) (82). Other data, however, do not support the concept that an adrenergic mechanism is responsible for penile erection. The infusion of norepinephrine does not cause erection in the dog (83) or cat (82), and in fact, epinephrine causes constriction of canine penile arteries (92). Stimulation of human corporal strips *in vitro* with norepinephrine results in a marked contraction, which can be blocked by pretreating the strips with phenoxybenzamine (26). In humans, the oral administration of large doses of α- and ß-adrenergic blocking agents (phenoxybenzamine and propranolol) does not affect erections that result from mechanical or visual stimulation (353). The net effect of adrenergic stimulation therefore appears to promote penile detumescence (vascular constriction and corporal contraction) rather than erection.

It appears that the neuropharmacology of erection cannot be totally explained by classic cholinergic and adrenergic mechanisms (29). Numerous putative nonadrenergic, noncholinergic neurotransmitters have been investigated. Histamine, 5-hydroxytryptamine (serotonin), bradykinin, prostaglandins (PGE_1, PGE_2, and PGF_{2a}), and amino acids do not appear to be responsible for the production of penile erection (175,176). Likewise, no convincing evidence has implicated adenosine triphosphate (a putative purinergic neurotransmitter) to be important in the production of penile erection.

The search for a nonadrenergic, noncholinergic mechanism to explain the neuropharmacology of penile erection has included the evaluation of possible peptidergic mechanisms. The polypeptide most investigated to date is VIP. The anatomic localization of VIP in the penis at both light and electron microscopic levels has been previously described. VIP is known to have a vasodilatory effect (302,344) and has been demonstrated to cause relaxation of strips of rabbit, cat, monkey, and human corpora cavernosa (132,190,332,372). In other work using nonhuman primates, however, VIP had little or no effect on the corpora cavernosa urethra of the rabbit, guinea pig, dog, and cat and no effect on penile vessels in the bull (322). In human corporal strips, VIP causes a weak relaxant effect in tissue that previously has been contracted with norepinephrine stimulation and also has been reported to cause detumescence of the erect penis obtained by cavernous nerve stimulation in the monkey (332).

In the feline submandibular gland, VIP has been shown to be responsible for the atropine-resistant vasodilation seen with nerve stimulation (215). In this tissue, VIP and acetylcholine are present in the same neuron, and both are released with nerve stimulation. It is possible that a similar situation occurs in the penis and that VIP is responsible for some of the pharmacologic findings, such as atropine resistance, which at present are not well understood. It is equally possible that VIP and other polypeptides may act as neuromodulators to control the rate of release of acetylcholine at nerve terminals.

The recognition of the importance of nitric oxide in the physiology of vascular smooth muscle relaxation has led to new insights into the mechanisms responsible for penile erection. Nitric oxide is synthesized in many types of mammalian cells and is a modulator of several biologic activities, including endothelium-dependent dilation of blood vessels, inhibition of platelet aggregation, and macrophage cytotoxic activity (170,249). Nitric oxide synthase, located in nerves and endothelium, synthesizes nitric oxide and the amino acid citrulline from arginine and molecular oxygen (248). Nitric oxide does not interact with a receptor on the cell membrane, but it crosses the cell membrane and interacts with the enzyme guanylate cyclase. Activated guanylate cyclase catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The accumulation of cGMP induces a series of intracellular events that leads to smooth muscle relaxation. Phosphodiesterase type 5 inactivates cGMP. In strips of corporal smooth muscle from rabbits and humans, nitric oxide causes relaxation, which mimics electrical field stimulation. This relaxation occurs in the presence of guanethidine and atropine in the bathing media and is therefore thought to be mediated by nonadrenergic, noncholinergic neurons (52). Acetylcholine also is capable of causing endothelium-dependent relaxation by mechanisms that involve nitric oxide (301). Relaxant responses to nitric oxide are enhanced by pretreating the smooth muscle strips with a cGMP phosphodiesterase inhibitor. These observations support the hypothesis that stimulation of nonadrenergic, noncholinergic neurons in the corpus cavernosum cause corporal smooth muscle relaxation mediated by nitric oxide. In addition to cGMP, cyclic adenosine monophosphate (cAMP) may also be important in causing corporal smooth muscle relaxation. Both VIP and PGE_1 induce the formation of cAMP and cause corporal smooth muscle relaxation. In addition, VIP and neuronal nitric oxide synthase have been reported to be colocalized in the same nerves within the corpus cavernosum (88).

Valuable information concerning the neuropharmacology of erection has been obtained from the technique of intracorporal injection. Brindley's observation that the intracorporal injection of phenoxybenzamine (an α-adrenergic blocking agent) resulted in penile erection clarified to a large extent our understanding of the physiology of human corporal smooth muscle (42). Norepinephrine causes contraction of corporal smooth muscle, and this drug effect is blocked by phenoxybenzamine. Therefore relaxation of the corporal smooth muscle appears to be an important component in the development of penile erection. The intracorporal injection of the smooth muscle relaxant papaverine, an agent that does not act through neuroreceptors but rather directly on the smooth muscle cell, as well as the injection of multiple other agents also cause penile tumescence (43,350). The use of these drugs not only has created a new research approach to the understanding

of erection but also has been a valuable addition to the clinical diagnosis and therapy of impotence (320,385).

The neuropharmacology of the CNS as it relates to penile erection is less well understood than our understanding of peripheral mechanisms. In the rat, serotonin inhibits and dopamine activates male sexual behavior (123). Some of these animal data may be applicable to humans. Levodopa, for example, is known to cause heightened sexual activity (15,154). In addition, trazodone, a widely used antidepressant, affects the actions of serotonin, and priapism is a known side effect of this agent (235).

Hormonal Factors

Although most physicians agree that a relationship between male hormones and penile erectile activity exists, the nature of this relationship and the mechanisms responsible for hormonal control of sexual activity remain unclear. The difficulties encountered in separating libido from erectile ability in clinical studies are well known. In addition, neither the mechanism of action nor the primary site of action (penis, spinal cord, or brain) of androgens in promoting penile erection is understood.

Clinical studies on the effects of castration and studies using testosterone replacement in hypogonadal men have been conducted. In a study of patients with carcinoma of the prostate undergoing either orchiectomy, estrogen therapy, or both, Ellis and Grayhack (93) found that a number of patients retained their potency after castration. Castration plus estrogen therapy appeared to more adversely affect sexual function in this small group of patients than did castration alone. Although an argument can be made that these patients did not undergo objective posttreatment evaluation, retained sexual potency after bilateral orchiectomy has been reported by others (141,231,289).

Androgen replacement in hypogonadal men has been analyzed in placebo-controlled clinical evaluations (74,214,323). In this group of patients, androgen increases sexual activity and interest. The relationship between androgen and penile erection, however, is less clear. Hypogonadal men demonstrate decreased erectile activity during nocturnal penile tumescence testing and report fewer spontaneous daytime erections. These abnormalities are corrected with testosterone replacement (72,189). Laboratory-tested erectile responses to erotic films and fantasy are not abnormal, however, in hypogonadal men. These observations are consistent with the hypothesis that the major effect of androgens on male sexual function is to enhance libido and not to directly control penile erection in a sexual setting. Nocturnal erection appears to be testosterone dependent (189). Therefore certain types of stimuli that promote erection appear to be androgen sensitive, and others do not (14).

There are no current data to suggest that serum testosterone levels in the normal laboratory range are correlated with sexual behavior in humans (74). Although a “threshold” serum level of testosterone for sexual activity probably exists, changes in circulating testosterone concentration do not correlate with sexual activity or interest. Furthermore, testosterone is no more effective than placebo in restoring sexual potency to impotent men without androgen deficiency. In a controlled study involving these patients, more than half of the men reported marked improvement in sexual potency, regardless of whether they received androgen or placebo (23).

Animal models have been used to study the effects of androgens on sexual function. In the rat, castration results in a rapid disappearance of circulating testosterone. Castrated animals exhibit diminished ejaculatory behavior, decreased number of intromissions, and finally, loss of mounting behavior. The administration of testosterone restores normal sexual activity (74). Although testosterone is known to affect spinal reflex activity (139), the primary site of testosterone action in controlling sexual function is probably the brain. The implantation of small amounts of testosterone into the hypothalamic preoptic area, but not into other parts of the brain, restores normal sexual behavior in castrated rats (74).

Hormones other than androgens also are proposed to be important in controlling sexual function. In addition to a loss of libido, most men with hyperprolactinemia are impotent (271). Although a small number of patients with hyperprolactinemia and a normal serum testosterone level have been reported, most patients, and in some series, all of the patients, with hyperprolactinemia have markedly depressed serum testosterone levels (58). The mechanism responsible for depressed testosterone levels in hyperprolactinemic states is unknown. Increased prolactin may inhibit the action of luteinizing hormone (LH) on Leydig cell function or decrease the secretion of LH either by inhibiting the response of the pituitary to LH-releasing hormone or decreasing the secretion of the latter from the hypothalamus (58). However, impotence associated with this syndrome is not solely related to low testosterone levels. Testosterone replacement does not correct the erectile dysfunction. The fact that sexual function improves when prolactin levels are lowered by bromocriptine therapy has led to speculation that hyperprolactinemia per se may be related to impotence (58). Evidence also exists that supports the concept that the primary effect of hyperprolactinemia is one of diminished libido and that the impotence is secondary or psychogenic (13,311).

Summary

The realization of the importance of the smooth muscle of the corpora cavernosum in the physiology of penile erection has led not only to a better understanding of the erectile process but also to innovative approaches, including oral therapy, to the patient with erectile dysfunction. Penile erection is produced by three interrelated

processes: (a) relaxation of the smooth muscle of the corpora cavernosa, (b) arteriolar dilation, and (c) decreased venous outflow (probably from passive compression of venules just beneath the tunica albuginea). The sympathetic nervous system (acting through α-adrenergic receptors) causes contraction of corporal smooth muscles and arterioles and therefore promotes detumescence. Stimulation of parasympathetic nerves produces erection. The neurotransmitters that cause corporal smooth muscle relaxation appear not to be related to classic adrenergic, cholinergic mechanisms, and nitric oxide is an important mediator of this process. Major unanswered questions include the specific events leading to corporal smooth muscle relaxation, the influence of hormones on penile erection, and CNS control of the erectile process.

IMPOTENCE

Part of "42 - THE PENIS: SEXUAL FUNCTION AND DYSFUNCTION "

Etiology

Various diseases have been associated with impotence. In many instances, a cause-and-effect relationship has not been demonstrated; in other instances, clinical observations have significantly contributed to our understanding of both erectile physiology and impotence. Causative processes are categorized as follows: (a) neurologic disorders, (b) vascular disorders, (c) endocrine disorders, (d) surgical and traumatic disorders, (e) drug-associated erectile dysfunction, and (f) psychogenic erectile dysfunction (346).

Neurologic Disorders

Neurologic causes of impotence can be viewed most conveniently as peripheral neuropathy, spinal cord lesions, or lesions of the cerebral hemispheres.

Peripheral Neuropathy

Diabetic Neuropathy.

Diabetes mellitus is a common cause of impotence. This was first suggested as long ago as 1798 by Rollo (100). Diabetes has a profound effect on the vascular system, causing accelerated atherosclerosis and microangiopathy. This microangiopathy particularly affects the eyes, kidneys, and central and peripheral nervous systems. The incidence of impotence in diabetic men increases with age. In a study involving 198 diabetic men, impotence occurred in 7.5% of patients younger than 45 years of age, 23.2% at 50 years of age, 40.2% at 60 years of age, 58.4% at 70 years of age, and 80% at 80 years of age (295). These figures are two to five times higher than those found in healthy control subjects (39). The clinical course of impotence in diabetic men is most often gradual, beginning with decreased firmness or rigidity and progressively worsening.

The erectile abnormality associated with diabetes is thought by some to be primarily a neurologic rather than a vascular or endocrinologic problem. Ellenberg (90) identified peripheral neuropathy in 38 of 45 impotent diabetic patients, but others (226) have found a much lower incidence of neuropathy associated with impotence. Impotent diabetic men often have a peripheral neuropathy with diminished or painful sensation, muscle wasting and weakness, and trophic changes of skin and joints (39). However, impotence may be the first and only symptom of diabetes. Deutsch and Sherman (78) reported that up to 12% of impotent men have unrecognized diabetes mellitus. Masters and Johnson (227) suggest that there is a 200% to 300% higher incidence of abnormal glucose tolerance tests in men with impotence than in a representative cross section of the population. They also emphasize that careful maintenance of medical control often does not reverse the impotence once developed. Recent evidence suggests that the prevalence of impotence is lower in diabetic men who maintain good control of blood sugar, as measured by hemoglobin $A1_c$ (285). Libido is often preserved but may lessen as a result of frustration and other psychologic factors that occur because of lifestyle changes secondary to chronic disease. Impotence associated with diabetes cannot be assumed to be purely organic; psychologic factors also deserve attention.

The neuropathic changes associated with diabetes have long been considered one of the main causative factors in diabetic impotence. Somatic and autonomic neuropathy are more common in impotent than in nonimpotent diabetic men (54). A proportion of these patients complain of orthostatic hypotension and difficulty with micturition (91). Studies using instantaneous heart recordings have demonstrated that the onset of autonomic dysfunction may occur without evidence of peripheral neuropathy and may precede symptoms of autonomic dysfunction by a number of years (217). The association of autonomic neuropathy with diabetes mellitus is still not clear. Fairburn and colleagues (98) found no difference in cardiovascular autonomic neuropathy in impotent versus potent diabetic men. Ewing and associates (95) studied the vascular reflexes in 31 males with autonomic neuropathy. Of this group, 28 complained of impotence, and it was an isolated problem in 15. Vascular reflexes were studied by recording heart rate changes during the Valsalva maneuver and by measuring blood pressure response to sustained hand grip. Patients with abnormal vascular reflexes had greater evidence of peripheral neuropathy as measured by nerve conduction studies. There was a notable difference in responses of patients with impotence alone and the patients with other features of autonomic neuropathy with or without impotence. The vascular reflexes were less abnormal in those patients whose only manifestation of autonomic neuropathy was impotence. These investigators concluded that only when impotence is associated with other features of the disorder can it be attributed to autonomic neuropathy. Thus, if impotence is the only suggestion of autonomic neuropathy in the diabetic patient, other possible causes of sexual dysfunction should be sought.

Abnormalities of the sacral reflex in diabetic patients have been demonstrated by cystometric findings (90) and lengthened bulbocavernosus reflex latency times (156). Neuromorphologic changes can be seen by microscopic examination of the autonomic nerve fibers of the corpora cavernosa in impotent men (97). Ellenberg (91) reported the cystometric findings in 45 diabetic men who complained of impotence; only 8 had normal findings. The other 37 patients had increased bladder capacity (greater than 500 mL); 6 had residual urine with no cystoscopic evidence of bladder neck obstruction. Five of the diabetic patients had neither cystometric abnormalities nor involvement of the peripheral nervous system. Ellenberg concluded that impotence was psychogenic in 4 of these 5 patients as “indicated by the presence of morning erections and competence in extramarital situations in two and intermittent impotence in two.” Of note, only 3 of 30 diabetic patients without the complaint of impotence had abnormal cystometrograms (91).

Despite the fact that many accept autonomic neuropathy as the underlying disorder in impotent diabetic men, vascular factors may play an important role. Vascular changes in diabetic patients resulting in retinopathy and neuropathy are well known. These vascular lesions have been associated with impotence in the diabetic male (145). Ruzbarsky and Michal (298) reported on the morphologic changes in the arterial bed of the penis associated with aging. Microangiopathy occurred 10 to 15 years earlier in the diabetic man than in the nondiabetic man.

With Doppler studies, cystometrograms, and bulbocavernosus latency tests, Jevitch and associates (156) compared the vascular and neuropathic changes in a group of impotent diabetic men. Vascular obstructive changes occurred in 95% of the patients; 72% were severe and 23% mild. Abnormal neurologic studies were noted in only 34%. All of the patients with neurologic changes also had vascular abnormalities. In addition, 98% of the impotent diabetic men had normal antegrade ejaculation.

Hormonal abnormalities do not appear to play a prominent role in the sexual dysfunction of diabetic patients. In the prospective study by Ficher and colleagues (100), serum levels of testosterone, prolactin, LH, and follicle-stimulating hormone (FSH) were not significantly different in impotent diabetic patients when compared with impotent nondiabetic patients.

Uremic Neuropathy.

Patients with chronic renal failure, particularly those undergoing dialysis, are frequently impotent, with complete impotence noted in 20% to 60% of patients (67). Even though uremic neuropathy may contribute to impotence, the hormonal abnormalities associated with uremia may play the predominant role (67). Holdsworth and colleagues (150) found significant elevations of LH and FSH in uremic patients. Serum testosterone levels were subnormal. Histologic examination of testes biopsy samples revealed severe spermatogenic damage. Bailey (11) concluded that testicular suppression was a result of the cellular toxic effects of retained uremic toxins. A more detailed discussion follows in the section describing endocrine causes of impotence. In addition to the neuropathy and endocrinopathy associated with uremia, the vascular effects of uremia have been studied objectively (165). Cavernous artery occlusive disease was found in 78% of patients with chronic renal failure. In addition, corporovenous leakage was found in 90% of these patients.

Amyloidosis.

Amyloidosis with involvement of the autonomic nervous system can cause impotence. Neurogenic impotence appears to be particularly prominent in heredofamilial amyloidosis. Thus amyloidosis should be included in the causes of male sexual dysfunction. The clinical course of amyloidosis is slowly progressive, and patients usually die in renal failure. No specific therapy exists for amyloidosis (65).

Spinal Cord Lesions

Spinal Cord Injury.

In 1960, Bors and Comarr (41) published their now classic study on sexual function in a large group of patients with spinal cord injuries. The degree and type of sexual dysfunction depend on the level and completeness of the cord lesion. Bors and Comarr found that 94% to 100% of men with upper motor neuron lesions that were incomplete maintained some erectile activity. These lesions may interfere with psychogenic erections, but spontaneous erections and reflex-stimulated erections are common (39). Lower motor neuron or lumbar spinal cord lesions produce a different clinical picture. Reflex-stimulated erections are absent, but psychogenic erections occur in up to 90% of patients (39,41) with incomplete lesions and in 27% with complete lesions. In a more recent study, Comarr (66) reported 20 patients with complete lower motor neuron cord lesions. Eight patients could obtain psychogenic erection, but none had reflex-stimulated erections. Seven had successful intercourse, and five achieved ejaculation with orgasm. It has been suggested that these phenomena are mediated by means of the sympathetic nervous system because those preganglionic fibers leave the spinal cord at the lower thoracic and upper lumbar level (39). Complete lesions of the sacral spinal cord have the worst prognosis with reference to sexual function. In Piera's study (273) of 100 patients with spinal cord injuries, the 15 patients with complete lesions of the sacral cord had no erections and no ejaculation.

Sexual function is a major concern of patients with acute spinal cord injuries, and physicians should be cautious about predicting the clinical outcome early in the patient's course. Spinal shock with complete or almost complete absence of reflex activity below the level of the lesion commonly occurs (6). Genital reflexes and rectal sphincter activity are profoundly depressed. This may last for many weeks. Thus, before prognosticating, the physician should wait until spinal shock is reversed so that the level and

completeness of the spinal cord lesion can be assessed, thereby allowing for a more accurate prediction of the patient's future course.

Multiple Sclerosis.

Multiple sclerosis is characterized by loss of myelin in the white matter of the brain, brainstem, and spinal cord. Its effect on potency is variable. Vas (349) reported 37 patients between 18 and 50 years of age. Forty-three percent were either totally or partially impotent. Cartlidge (59) reported that 7 of 20 patients with multiple sclerosis were impotent. The severity of the impotence was directly related to the duration of the disease, but in several patients, sexual potency tended to remit and relapse. Sacral-evoked response measurement has been recommended in the evaluation of impotence associated with multiple sclerosis (128). In a comprehensive study of 41 men with multiple sclerosis, sexual dysfunction was present in 29. Of these 29, 8 patients had prolonged sacral latency times. The authors concluded that abnormal sacral-evoked responses may imply neurogenic impotence. In this study, the authors also observed patients with a combination of abnormal perineal electromyography, abnormal sacral latency, and bladder detrusor hyperreflexia, which suggests spinal cord dysfunction at multiple levels.

Other Spinal Cord Diseases.

Other spinal cord lesions that can affect potency include syphilis (tabes dorsalis), spina bifida, syringomyelia, amyotrophic lateral sclerosis, and compression from a herniated disc or tumor (346). Lateral cordotomies used to treat intractable pain also may result in impotence.

Idiopathic orthostatic hypotension (i.e., idiopathic autonomic insufficiency) is often referred to as *Shy-Drager syndrome.* This rare degenerative disorder of unknown cause is progressive, resulting in severe debility and death within 5 to 10 years of onset. It affects primarily middle-aged men, causing symptoms of autonomic dysfunction, such as loss of sweating, sphincter disturbances, orthostatic hypotension, and impotence (38).

Lesions of the Cerebral Hemispheres

Little information is available concerning the association of cerebral lesions and sexual potency. Frontal lobotomy, Parkinson's disease, Huntington's chorea, and electroshock therapy all may affect libido, but the effect on erectile function is unknown (39). Likewise, there is limited knowledge as to potency in men who have had strokes; presumably, the effect would be dependent on the site and severity of the lesion.

Vascular Disorders

Erection is essentially a hemodynamic phenomenon. Probably the most well-known cause of impotence is Leriche's syndrome, or thrombotic obliteration of the aortic bifurcation with resultant pain and claudication of the hips and thighs and impotence in males (196). Arteriosclerosis also affects the iliac, hypogastric, and pudendal vessels, as well as the small arteries of the corpora cavernosa. Fibrosis, calcification, and obliteration of the small cavernosal vessels occur with aging (298), and early changes can be identified in young men (27).

The role of vasculopathy in diabetic erectile dysfunction is not clear, and some investigators consider this dysfunction primarily neuropathic (90). This assumption may have developed from two suggestions: First, peripheral neuropathy most often occurs in the legs, it is common in diabetic patients, and it was believed that this peripheral neuropathy also would involve the pelvic and genital areas. Second, diabetic patients often have an enlarged bladder capacity, suggesting a relationship between neuropathy and impotence. However, peripheral neuropathy of the legs is rarely associated with disturbances of erection, bowel, or bladder function (287), and up to 30% of bladders with a capacity greater than 800 mL are urodynamically normal (365).

Vascular disease may be an important cause of erectile dysfunction in diabetic patients. As previously discussed, Jevtich and associates (156) found that vascular changes were more common than neurologic changes. More than 95% of the patients had evidence of penile arterial obstruction; 62% of the patients had penile arterial obstruction without any indication of peripheral neuropathy (156). The progressive nature of diabetic vascular changes should be expected to produce a gradual impairment of erectile function. Diabetes also may have an adverse effect on the smooth muscle of the corpora cavernosa. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence has been demonstrated (301).

The “iliac artery steal syndrome” is an unusual manifestation of large-vessel arteriosclerosis (243). Initiation of penile erection occurs normally, but active pelvic movement quickly results in detumescence. It appears that there is collateral circulation in the pelvis to compensate for arteriosclerotic occlusion. During sexual activity, the blood flow is drawn away from the penis to supply the muscles of the hips and buttocks.

Abnormal venous drainage of the corpora also may contribute to the erectile insufficiency. It is well known that creating an artificial venous runoff to treat priapism results in detumescence, and Ebbehøj and Wagner (85) described spontaneously occurring “venous leaks.” Surgical correction led to erectile improvement. Tudoriu and Bourmer (343) subsequently studied 300 cadaver penises and found evidence that corpora cavernosal leakage is common and that the incidence increases with age. In a study of 49 impotent patients, cavernosography and papaverine-induced erection revealed abnormal venous drainage in 38 patients (206). The term *abnormal venous leakage* is, in the vast majority of

cases, a misnomer. Although some cases of congenitally abnormal venous drainage undoubtedly exist, in most cases, venous leakage is not secondary to venous pathology but is caused by an abnormality of the smooth muscle of the corpora cavernosa. If the corporal smooth muscle does not efficiently relax and allow the cavernous spaces to fill with blood, the subtunical venules are not compressed and blood escapes from the corpora. A more correct term to describe this situation is *corporovenous leakage.*

Endocrine Disorders

In addition to diabetes mellitus, most other major endocrine abnormalities have been associated with impotence. However, the incidence of endocrine disorders in a population of impotent men is not clear. In a prospective study of 256 impotent men, an organic cause was found in 35.9%, a psychogenic cause in 38.3%, and a mixed or uncertain cause in 25.8%. The incidence of hypothalamic-pituitary-gonadal axis abnormalities in the entire group was 17.5%. However, in only 13 of those 45 patients could the impotence be directly related to the axis abnormality (262).

Testosterone is the primary androgen in humans and is secreted by the Leydig cells of the testis in response to LH. The secretion of LH is modulated by LH-releasing factor. These hormones interact in a negative feedback system. Lowering serum testosterone levels causes an increase in LH-releasing hormone, which leads to an elevation of LH. This increase stimulates the Leydig cells to restore the testosterone level to normal. FSH plays an integral role in inducing maximum Leydig cell sensitivity to LH during puberty. After puberty, however, the primary importance of FSH is its action on spermatogenesis.

Low levels of testosterone may result from abnormalities that exist at any point in the hypothalamic-pituitary-gonadal axis. Thus hypogonadism can be characterized as that caused by primary testicular disease or by hypogonadotropic hypogonadism. Testosterone is necessary to maintain male secondary sex characteristics, libido, and probably potency. Thus patients with endocrine abnormalities may present with a variety of symptoms. They may notice a change in body habitus or presence of gynecomastia. Commonly, they note a decrease in the size of the testicles. Physical examination may reveal a diminished size of the prostate and testes. It has been suggested that in adults, testicular size less than 4 cm in length is abnormal (265). A decreased serum total testosterone level confirms the diagnosis of hypogonadism. In cases of alcoholism, massive obesity, or thyroid dysfunction, a serum free testosterone level should be measured because decreased testosterone levels may be the result of low levels of testosterone-binding protein rather than endocrine abnormalities.

If testosterone is low, gonadotropin levels should be measured. Decreased or normal levels of LH and FSH indicate hypogonadotropic hypogonadism, whereas elevated levels of the gonadotropins in the presence of decreased testosterone levels indicate primary testicular dysfunction.

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism is caused by disorders of the pituitary and hypothalamus and may be part of a clinically recognized syndrome such as Kallmann's syndrome, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, or cerebellar ataxia (265). Hypogonadotropism may be secondary to a mass lesion or other endocrine disease, such as Cushing's syndrome, acromegaly, panhypopituitarism, hyperthyroidism, or hypothyroidism. Evaluation of hypogonadotropic hypogonadism should include anatomic studies to rule out a mass lesion or brain tumor and a complete endocrine evaluation.

Hypergonadotropic Hypogonadism

Nickel and associates (262) found that 7% of impotent patients had hypergonadotropic hypogonadism or primary testicular failure. Hypergonadotropism can be associated with chromosomal abnormalities, or it can be secondary to infection, surgery, or trauma. In the 18 patients with hypergonadotropic hypogonadism described, 2 had previously undiagnosed Klinefelter's syndrome and 13 had a history of an acquired testicular disorder, small atrophic testicles, and/or a low serum testosterone level. The remaining three patients had psychogenic impotence.

Hyperprolactinemia

Prolactin is secreted by the anterior pituitary under hypothalamic control. Inappropriate elevation of serum prolactin in some patients with pituitary tumors has been associated with galactorrhea and hypogonadism. Hyperprolactinemia also may be secondary to drugs or renal disease. Franks and Nabarro (109) reported impotence as the presenting symptom in 8 of 21 patients with prolactin-secreting pituitary tumors. In male patients with pituitary tumors and normal prolactin levels, only 2 of 19 were impotent. They recommended that “serum prolactin estimations should be made in the course of investigation of all patients with impotence.” Other investigators have challenged this recommendation, and in a careful study of 30 impotent males and 11 potent control subjects, Miller and associates (244) found no significant differences in serum prolactin levels among control, organically impotent, or psychogenically impotent patients. They concluded that impotence is not related to hyperprolactinemia per se and that the routine use of serum prolactin measurements in unscreened patients with impotence should be questioned.

Thyroid Dysfunction

The direct effect of thyroid disease on sexual function is unknown; however, occult hyperthyroidism has been implicated

as a cause of impotence (329). Thyrotoxicosis is associated with increased testosterone levels but normal levels of unbound free testosterone. This is caused by the increased levels of testosterone estrogen–binding globulin associated with hyperthyroidism. Elevated levels of total free estradiol, as well as LH, have been noted (64) and may be associated with gynecomastia, impaired spermatogenesis, decreased libido, or erectile dysfunction (169). Whether the erectile dysfunction is caused by hormonal abnormalities or what the overall impact of the thyrotoxicosis is are both unknown.

Renal Insufficiency

Chronic renal failure and hemodialysis result in a dramatic decrease in male sexual function (304,341). Even though most impotent uremic men have evidence of peripheral neuropathy, endocrine changes also have been noted and associated with impotence in these patients. Sherman (317) evaluated 14 patients with chronic renal failure receiving hemodialysis with neurologic, psychiatric, and endocrine studies. Seven of the patients were impotent, and all seven had prolonged nerve conduction velocities and absent bulbocavernosus reflexes. However, these patients also had abnormally low serum testosterone levels. Uremia appears to affect Leydig cell function. Guevara and associates (133) noted decreased testosterone levels with increased LH and normal FSH levels in their study of 26 men receiving hemodialysis. Thurm (341) noted that patients with chronic renal failure who were receiving home dialysis maintained a higher level of sexual activity than those receiving hospital-based dialysis. Of 10 patients dialyzed at home, 8 maintained adequate sexual relations. Of 12 patients dialyzed at the hospital, 10 were completely impotent and 2 had little desire for intercourse.

The psychologic and physiologic milieu of patients with chronic renal insufficiency is complex. For instance, the treatment of chronic renal failure associated anemia with recombinant human erythropoietin improves not only the quality of life but also sexual function (263). In addition, many of the drugs used in their treatment, particularly antihypertensives and antidepressants, have been implicated as a cause of erectile dysfunction. After renal transplantation, most patients report a return to preillness levels of sexual activity (304). Successful renal transplantation results in restoration of low serum testosterone levels to normal and improved erectile function in 70% to 80% of patients (304). If impotence persists after transplantation, it is likely related to abnormalities of the blood supply to the penis. Often, the internal iliac artery is used in an end-to-end anastomosis to the transplant renal artery. If a second transplant is performed with the opposite internal iliac artery in a similar fashion, the problem of impotence is markedly increased (127). It is now recommended that second renal transplants be performed with an end-to-side technique on the external iliac or common iliac artery (127).

Traumatic and Surgical Disorders

Trauma to the lower urinary tract reportedly causes impotence in a high percentage of patients. Most patients with a fractured pelvis have multisystem injuries, and there is a high incidence of injury to the bladder and posterior urethra. Up to 50% of these patients may be impotent (125). The initial management of posterior urethral injuries appears to influence potency rates. Patients managed by initial suprapubic cystotomy and later reconstruction have a lower incidence of impotence than those managed by primary repair (70,228).

Many urologic surgical procedures can cause impotence. It is common knowledge that radical prostatectomy for carcinoma of the prostate frequently results in erectile dysfunction, and it has been presumed that damage to pelvic nerves and blood vessels is the cause. However, some patients retain erectile function after radical prostatectomy. Finkel and Taylor found that of 14 patients who claimed preoperative potency and normal sexual performance, 6 (43%) reported postoperative normal erections and sexual intercourse (101a). Walsh and Donker (357) concluded that impotence results from injury to the autonomic innervation of the corpora cavernosa most commonly during dissection of the prostatic apex and transection of the urethra or during division of the lateral pelvic fascia and lateral pedicle. Modifying the procedure to preserve the cavernosal nerves has reduced the occurrence of impotence, and 1 year after surgery, 86% of patients are potent (358). Others have reported lower rates of preservation of potency following radical prostatectomy. Catalona and Bigg (61) found that 63% of men who underwent bilateral nerve-sparing prostatectomy and 39% who underwent a unilateral nerve-sparing prostatectomy were potent postoperatively, with a minimum of 6 months of follow-up. Patient age, preoperative sexual function, and type of surgery (bilateral versus unilateral nerve sparing) are currently recognized as being important factors in determining postoperative sexual function (279). A modification of total perineal prostatectomy that preserves the periprostatic autonomic nerves has been described (366).

The assumption that radical prostatectomy causes impotence has led many urologists to recommend external beam radiation therapy as an alternative. However, this too has been reported to cause impotence in 40% to 60% of patients (10). Interstitial radiation therapy may be less deleterious. Herr (146) reported that 90% of patients treated with iodine-125 implantation retained potency.

The various types of prostatectomy for benign disease also may result in impotence: simple perineal prostatectomy, 29%; suprapubic prostatectomy, 13%; and transurethral

resection, 5% (101). The mechanisms responsible for impotence after a simple prostatectomy, particularly a transurethral resection, are not clear. Although an organic cause cannot be totally excluded, a psychogenic cause is more likely. The myth that impotence is inevitable after prostatectomy is widely believed by patients and their spouses.

External sphincterotomy has been reported to cause impotence, but it appears that choice of technique may be an important factor. Kiviat (172) noted that 73% of his patients had some degree of erectile dysfunction after undergoing sphincterotomy at the 3 and 9 o'clock positions. Whitmore and associates (370) reported that of 28 patients who underwent lateral incisions of the external sphincter, 7% had a complete loss of erectile function and 14% had partial loss. They recommended that sphincterotomy be done at the 12 o'clock position and reported that, of 62 patients so treated, none had subsequent erectile dysfunction.

Leriche and Morel (196) first described impotence caused by infrarenal occlusion, and it is now known that approximately 80% of men who present with aortoiliac occlusive disease have significant erectile dysfunction (167). In men with reportedly normal preoperative potency, 21% to 88% have iatrogenic sexual dysfunction after aortoiliac revascularization (76). Ischemia secondary to diversion of pelvic blood flow and/or injury to the autonomic nerves during aortoiliac dissection have been proposed as the causes for postoperative impotence (106). A careful nerve-sparing aortic dissection and attention to preservation of improvement of pelvic blood flow have been reported to yield much improved results (76,299). Flanigan and colleagues (106) reported 110 men who underwent aortoiliac revascularization and whose sexual function was evaluated preoperatively and postoperatively; 30 patients (27%) were impotent both preoperatively and postoperatively, 67 patients (61%) had normal sexual function preoperatively and postoperatively, and 13 patients (12%) who were impotent preoperatively regained erectile function after surgery. No patient who was potent preoperatively was impotent postoperatively. The actual mechanism by which preservation of preaortic autonomic nerves preserves potency is unclear because it is known that complete preaortic retroperitoneal lymph node dissection with dissection of those nerves may result in ejaculatory incompetence because of absent seminal fluid emission or lack of bladder neck closure but does not cause erectile dysfunction (166,179). Also, the restoration of potency to preoperatively impotent men is most logically caused by reestablishment of pelvic blood flow because autonomic nerve function is unlikely to be enhanced.

The occurrence of erectile dysfunction after surgery for lower bowel disease seems to be dependent on the patient's age and the extent of the surgical resection (364,381). Watts and colleagues (361) noted that of 41 men who underwent rectal excision for ulcerative colitis, 8 were older than 50 years of age and 6 of these were impotent after surgery; of 33 patients younger than 50 years of age, only 1 was impotent postoperatively. Weinstein and Roberts (364) reported 24 men who had undergone colorectal resection (13 abdominoperineal resections and 11 anterior resections). None of the patients who underwent abdominoperineal resection were sexually active after surgery, whereas 8 of the 11 patients having an anterior resection remained sexually active. Two of the three who were not sexually active also had undergone a prostatectomy. The average age of these 24 patients was 64 years. In another review of 45 men undergoing rectal excision, all were younger than 50 years of age. Of 25 undergoing proctocolectomy, 1 (4%) was impotent postoperatively, and of 20 undergoing abdominoperineal resection, 3 (15%) were impotent (381).

Drug-induced Impotence

Medication may be the single most common cause of sexual dysfunction in our society. In a study of 1,180 men screened at one outpatient clinic, 401 were impotent. Of 188 who were more thoroughly evaluated, the most common cause of impotence was medication (324). The adverse effects of medication may be manifest as changes in libido, diminished erectile ability, or decreased ejaculatory capacity. Theoretic mechanisms for these drug effects include production of CNS sedation or depression, drug-related hyperprolactinemia, direct antiandrogen effects, or anticholinergic and antiadrenergic effects (151).

Even though many classes of drugs may affect erectile function, the two most often implicated are antihypertensive and psychiatric or antidepressant compounds. Antihypertensives are categorized as diuretics, vasodilators, or sympatholytics. Most antihypertensives have been associated with some erectile impairment, but diuretics seem to cause relatively few side effects. Thiazides and spironolactone may depress libido, and spironolactone causes enough hormonal alteration to result in gynecomastia (151,269).

Spironolactone's sexual side effects have been attributed to endocrine dysfunction (202). Despite its innocuous reputation, hydrochlorothiazide may have significant effects on sexual function. It alone was implicated as the cause of impotence in 9% of 861 patients at the Naval Medical Center in Oakland, California (149). The Medical Research Council of Great Britain (236) reported that 36% of patients taking bendrofluazide were impotent. Bulpitt and Dollery (48) questioned 477 patients in a hypertension clinic and found that 31% of men taking diuretics alone complained of impotence.

Sympatholoytic antihypertensives often are associated with impotence. Guanethidine, an agent that blocks peripheral adrenergic nerve activity of postganglionic neurons, is reported to cause impotence. In addition, retrograde ejaculation occurs in nearly two-thirds of patients treated with guanethidine (282). Phenoxybenzamine, an α-adrenergic

blocking agent, may inhibit emission and ejaculation, but erection is apparently unaffected (246). Prazosin, a selective α-adrenergic receptor blocking agent, is believed at present to cause few sexual side effects (379). At high dosages, the ß-adrenergic blocking agent propranolol may impair libido and erectile function (269,282). Several studies have reported impotence associated with propranolol, with an incidence as high as 15% (269).

Centrally acting sympatholytic agents include methyldopa, clonidine, and reserpine. With these agents, impotence may be more common and ejaculatory dysfunction less so (234). Because these drugs have a central action, this pattern of dysfunction is not surprising (282). Methyldopa may cause erectile failure in 25% to 33% of patients (346). It causes increased serum levels of prolactin, and it also may cause sedation and depression (151). Twenty-six percent of patients receiving methyldopa have been reported to complain of sexual dysfunction, but these undesirable side effects disappeared within 2 weeks of discontinuing the drug and instituting propranolol and hydralazine (269). The sexual dysfunction associated with clonidine is dose dependent and appears to be caused by the central effects of the drug. Impotence occurs in up to 25% of patients taking clonidine (282), and decreased libido is common (266,269). Reserpine, an agent that may cause significant depression, has been associated with both impotence and failure of ejaculation (282). It remains unclear as to whether erectile dysfunction reported to be secondary to antihypertensive medications is caused by the medication per se or is simply the result of decreasing the systemic blood pressure.

Antidepressant agents, including tricyclic antidepressants and the monoamine oxidase inhibitors, have central and peripheral actions. The tricyclic antidepressants possess sedative and anticholinergic effects and have been associated with decreased libido and impotence. Monoamine oxidase inhibitors interfere with the metabolism of sympathomimetic amines and are reported to cause diminished libido, erectile dysfunction, and impaired ejaculation (233).

Various commonly used drugs have been implicated as being causative factors in erectile dysfunction. Many of the tranquilizers, including the benzodiazepines and meprobamate, have been reported to reduce libido and consequently cause impotence (346). Decreased libido and impotence have been reported to be the most common side effects in patients taking clofibrate, an agent used to treat hyperlipidemia. These symptoms were noted in 14.1% of 1,065 patients taking this drug (269). Cimetidine, a histamine (H_2) receptor agonist used in the treatment of duodenal ulcer disease, has been associated with diminished libido and impotence in up to 50% of male patients (155). The mechanism by which cimetidine adversely affects male sexual function is unclear. Cimetidine therapy has been associated with gynecomastia and elevated prolactin levels (55,135). Peripheral H_2-receptor blockade in penile corporal smooth muscle also has been suggested as a mechanism (5). Although numerous pharmacologic agents have been implicated in sexual dysfunction (313), few well-controlled studies using objective parameters of sexual function have been performed to evaluate the effects of drugs on libido and penile erection.

Masters and Johnson (227) reported that alcohol was the second most common cause of impotence in their patients. Alcohol has been reported to cause depression of serum testosterone levels in intoxicated male alcoholics and in nonalcoholic men who are given large amounts of alcohol for several days. No similar depression was seen in nonalcoholic males after an episode of acute intoxication (297). Even though increased sexual activity has been attributed to alcohol because of decreased inhibitions, high levels can depress sexual arousal (296) and result in transient impotence. Cannabis, cocaine, and opiates also have been implicated in sexual dysfunction (313).

Psychogenic

All types of male sexual dysfunction, including impotence, premature ejaculation, and ejaculatory incompetence, may have a psychologic origin. Kaplan (159) described the normal sexual response cycle as having two phases: the excitement phase and the orgasmic phase. The excitement phase is characterized by both the subjective (being “turned on”) and objective (erection) changes commonly associated with sexual arousal. The objective manifestations of the excitement phase are dependent primarily on parasympathetic stimulation. The orgasmic phase is postulated to be under both sympathetic and voluntary control.

Men with primary psychogenic impotence often come from sexually repressed or religiously orthodox family backgrounds where sex was not discussed or was treated as sinful and immoral (225). The pathogenesis of secondary psychogenic impotence is poorly understood, possibly because the causes are so varied, and it may be the endproduct of an admixture of temperamental, emotional, familial, affective, cognitive, cultural, maturational, and biologic factors (199). Secondary psychogenic impotence is characteristically rapid in onset and selective in nature, occurring in one set of circumstances but not in others. Performance anxiety is regarded by many as the final common pathway to psychogenic impotence. In the classic example, the initial episode of erectile dysfunction may have a specific and explainable cause, such as intoxication or depression or the fear of discovery in a clandestine encounter. If the man were to approach the next encounter with fear and apprehension, he is likely to fail again, thus entering a vicious cycle of performance anxiety and erectile failure.

Psychogenic impotence can be more narrowly defined as either deficiency of desire (desire inhibition) or inability to maintain excitement even though it is present initially (excitement inhibition) (199). This distinction is important because excitement inhibition, including performance anxiety,

is treated more successfully than desire inhibition. Men with excitement inhibition often assume the “spectator role” (227) and remain vigilantly preoccupied with their erections and performance. These individuals often can be helped by sex therapy techniques. Most psychologically impotent men suffer from desire inhibition. Desire deficiency has many and varied causes, such as systemic illness, drugs, biologic disorders (e.g., Klinefelter's syndrome), and depression. Psychogenic desire deficiency tends to be situation specific or partner specific. This characteristic helps distinguish it from desire deficiency resulting from other causes.

Evaluation

Much of the interest in male sexual function and dysfunction can be traced to the work of Kinsey and associates (171). Public awareness of scientific advances in this field, particularly the introduction of acceptable and reliable therapy in the 1980s and 1990s, has resulted in increasing numbers of patients being evaluated and treated for impotence. Patients usually desire a quick remedy. The physician must remember that penile erection is a complex phenomenon and that the causes of erectile dysfunction are many, varied, and often interrelated. Education of the patient of this fact at the initial visit is often helpful; the patient needs to understand that organic impotence results in significant psychogenic overlay, just as primary psychogenic problems can result in impotence.

History and Physical Examination

At the initial visit, a careful history and physical examination are mandatory and are the most important part of the overall patient evaluation. The history should focus not only on medical problems that may relate to the patient's impotence but also on the specifics of the sexual dysfunction. Although almost any erectile dysfunction perceived or experienced by a given patient can be loosely defined as impotence, unrealistic patient expectations can be ascertained relatively easily. The duration and nature of onset of impotence often aid in differentiating a psychogenic from an organic cause. Patients with psychogenic impotence usually experience a rather abrupt onset of symptoms. Not uncommonly, this is associated with a traumatic event, such as a family death, job loss, or birth of a child with a congenital deformity. To the contrary, most causes of organic impotence result in a slow but progressive deterioration in erectile capacity. Changes in libido should be ascertained and, if present, may signify hormonal abnormality. The presence of morning erections and the occurrence of erections in situations apart from the usual sexual partner are important historical clues. A history relating to risk factors previously discussed should be obtained. Symptoms compatible with intermittent claudication should be sought. Specific questions related to systemic disease (e.g., atherosclerosis, diabetes), previous pelvic surgery, radiation therapy, bowel or bladder symptoms (indicative of neurologic disease), and cryptorchidism should be asked. The medications the patient is taking should be noted. As previously discussed, various drugs, but particularly those that act on the nervous or vascular systems, have been associated with erectile dysfunction. All unnecessary medications should be discontinued. Although it is reasonable to attempt to change dosages or medication in patients who require pharmacologic therapy for hypertension or psychiatric disease, such efforts in our experience generally have not proved to be beneficial.

A physical examination should be performed with particular attention to identifying vascular, neurologic, hormonal, and genital abnormalities. The femoral and peripheral pulses should be palpated and the abdomen and femoral areas auscultated for bruits. A limited neurologic examination should be performed. Perineal sensation in the area of the sacral dermatomes to pinprick, as well as the quality of rectal tone, should be ascertained. The presence or absence of a bulbocavernosus reflex, elicited by simultaneously squeezing the glans penis and noting anal sphincter activity, should be noted. A rectal examination to evaluate the prostate gland and palpation of the penis to identify plaques suggesting Peyronie's disease should be performed. The size, position, and consistency of the testes should be noted. The physical examination also should include an assessment of the character and distribution of body and facial hair, as well as gynecomastia, which may indicate a hormonal abnormality.

Additional Evaluation

There is little agreement concerning the optimal evaluation of the impotent patient after the initial history and physical examination. We initially obtain a serum testosterone measurement and serum multiple analyses in addition to urinalysis. Serum prolactin is not routinely measured, but the level is determined when an abnormally low serum testosterone level is found or when a history of decreased libido is obtained. The need for any “routine” endocrine testing has been questioned. Performing hormonal screening on only those patients with clinical signs of hypogonadism, that is either decreased libido or bilateral testicular atrophy, has been advocated (157). Thyroid function tests are performed only if there is suspicion of thyroid disease from history or physical examination. We do not perform routine psychometric testing. In patients with low morning levels of testosterone, serum levels of prolactin, LH, and FSH are determined.

The evaluation of most patients can reasonably stop after the history, physical examination, and blood studies just discussed are complete. We do not routinely perform vascular studies. Therefore patients older than 50 years of age with significant vascular risk factors, such as previous myocardial

infarcts, cerebrovascular accidents, hypertension, diabetes, or a strong family history of vascular disease, generally are not studied (129). Since the advent of successful medical therapy for erectile dysfunction, one can argue that initial vascular studies are rarely indicated. Neurologic testing, including measurement of sacral reflex latency time, is performed only in patients with suspected neurologic lesions and is rarely indicated or clinically useful. Urodynamic evaluation also may substantiate a suspected neurogenic component. Urodynamic evaluation also helps identify a patient requiring cystoscopy or transurethral resection of the prostate before the placement of a penile prosthesis. Finally, we do not routinely perform nocturnal penile tumescence testing.

The evaluation of patients presenting with impotence is not standardized and is controversial. Many of the methods currently used have been criticized because of the lack of standardization and normal control data.

Vascular Studies

For years, the most commonly used method for evaluating penile arterial blood flow was calculation of the penile-brachial index (PBI). These measurements are obtained with a 10-mHz Doppler probe positioned over the penile arteries. A pneumatic cuff is placed around the base of the penis and inflated until arterial flow ceases. The cuff is slowly deflated, and the point at which arterial flow is reestablished is the penile systolic blood pressure. The penile systolic blood pressure divided by the brachial systolic blood pressure yields the PBI. In general, a PBI of less than 0.60 is thought to be indicative of vasculogenic impotence (124). Most clinicians and investigators have abandoned the evaluation of the penile arterial supply with Doppler measured blood pressure indexes for several reasons. The Doppler signal is not specific, and the exact vessel being studied is difficult to ascertain. In addition, determinations are made with the penis in the flaccid state, and the findings may not be applicable to the erect penis. Finally, the study is operator dependent. Because of these shortcomings, measurement of the PBI has been largely abandoned.

Penile angiography should be reserved for patients who are potential candidates for a revascularization procedure. Suitable surgical patients are those with a demonstrable and surgically correctable arterial occlusion and patent distal flow. Even though a high proportion of organic impotence is vasculogenic, a relatively small proportion of patients are good candidates for angiography and revascularization (126,232).

Arteriography usually involves selective bilateral internal iliac visualization or selective pudendal arteriography. Some investigators recommend that the procedure be formed with the patient under general anesthesia. McDougal and Jeffrey (232) have found that these highly motivated patients often can be studied when liberal doses of intravenous diazepam and morphine are administered. Other investigators have stated that in unanesthetized patients, approximately 50% of apparent obstructions of the penile artery or its branches are functional in origin (40). In addition, visualization of penile arteries can be enhanced by the use of vasodilators injected either intraarterially or intracorporally.

Nocturnal Penile Tumescence

Erections during sleep were reported as early as 1940, but it was not until 1953 that Serinsky discovered rapid eye movement (REM) sleep and noted that the cycles of nocturnal penile tumescence (NPT) closely resembled the cycles of REM sleep (163). Subsequently, Fisher and associates (104) reported that in young males, nocturnal erections were definitely related to REM sleep and occurred five or more times nightly. Karacan and associates (163) found that NPT associated with REM sleep was most common in pubertal males and showed a steady decline in frequency and duration with aging. They also noted that the proportion of NPT associated with non-REM sleep increases with age. These early discoveries led to the development of transducers and recorders used to detect and measure engorgement of the penis, thus providing a reproducible and convenient means to measure NPT.

Karacan and associates (161) soon suggested that in impotent men, the presence of full, sustained erections during sleep was indicative of psychogenic impotence, and the absence of turgid nocturnal erections indicated organic impotence. NPT monitoring quickly became accepted as the only objective means to differentiate psychogenic and organic impotence and was routinely incorporated into the evaluation of erectile dysfunction at many centers. Some centers use elaborate sleep laboratories and monitor electroencephalographic activity and NPT activity and use video monitoring of erections. Other centers use simpler electronic measuring strain-gauge devices for in-hospital or at-home evaluation. The patient's time and financial considerations in performing NPT testing in a sleep laboratory are obvious.

Some limitations of NPT monitoring became apparent and included both technical problems with the strain gauges and monitors, as well as questions about the basic assumptions of NPT testing. The premise of NPT testing rested on the belief that normal penile tumescence detected by an average increase in circumference of 30 mm (15 to 45 mm) indicated that a rigid erection had occurred. Wein and associates (363) noted that 23 of 134 patients tested for nocturnal erections had significant penile expansion but did not achieve rigidity adequate for vaginal penetration. It became clear therefore that rigidity as well as expansion was an important parameter of penile erection.

To assess rigidity, the penile buckling pressure has been measured. When an erection is present, a pressure device is pressed against the glans penis and the pressure required to make the penis buckle is measured in millimeters of mercury. If the penis buckles at a pressure of less than 60 mm

Hg, it is too soft for vaginal penetration. If the penis does not buckle at pressures of 100 mm Hg or more, it is rigid enough for intromission. Buckling pressures between 60 and 100 mm Hg are equivocal (162).

Part of the controversy surrounding NPT stems from uncertainty as to the validity of NPT testing. The basic presumption is that the absence of nocturnal erections indicates organic dysfunction. This premise is not universally accepted. A number of investigators have noted that dreams with high anxiety content may not be associated with NPT at all (160) or may cause rapid detumescence (104). Conversely, there are numerous cases of patients with abnormal NPT patterns suggestive of impotence who report normal coital activity (314). On the basis of NPT testing, certain organic conditions may be misdiagnosed as psychogenic. Patients with hyperprolactinemia or "pelvic steal syndrome" are in this category (314). NPT testing alone is not adequate to differentiate psychogenic from organic erectile dysfunction. The presence of rigid nocturnal erections strongly supports a diagnosis of psychogenic impotence. The significance of impaired or absent nocturnal erections is not known, and in some instances, men with psychogenic impotence may not have nocturnal penile tumescence. Because of these shortcomings, NPT testing is not indicated for routine use (257).

Intracorporal Injection, Cavernosography, and Cavernosometry

The hemodynamic changes associated with penile erection involve increased arterial inflow, sinusoidal relaxation, and decreased venous outflow. Histologic studies show that smooth muscle is present in the walls of the sinusoids, as well as the walls of the penile arteries (205,208). In 1982, Virag (352) reported the discovery that intracorporal injection of the vasodilating drug papaverine resulted in penile erection. Subsequently, other drugs, such as phenoxybenzamine, and drug combinations, such as papaverine and phentolamine, have shown similar effects (42,385). Multiple other agents injected intracorporally, such as imipramine and verapamil, also have been reported to produce erection (43). PGE_1 alone or in combination with other agents (papaverine and phentolamine) is currently the most widely used drug for intracorporal injection (24,331). Maximum erection is usually evident within 10 to 20 minutes. Having the patient stand or kneel has been reported to enhance penile engorgement, and some patients require sexual stimulation to achieve maximum rigidity (385). Erection, or at least engorgement, lasts from a few minutes to several hours but in some cases may last much longer. Priapism is a significant complication associated with intracorporal injection and is discussed later.

The production of an erection with the intracavernosal injection of vasoactive drugs allows the penis to be evaluated in the erect state. In fact, the production of a rigid erection following intracavernosal injection has been interpreted to indicate that the penile vasculature (both arterial inflow and corporovenous occlusion) was intact. However, some evidence indicates that the production of an erection by this technique does imply normal corporovenous occlusive function but not necessarily normal arterial inflow. In 19% of cases with a rigid erection following intracavernosal injection, evidence of arterial occlusive disease existed (272).

Like low arterial inflow, abnormal or excessive corporovenous "leakage" from the penis causes impotence. Venous deterioration with increased leakage has been implicated as a cause of impotence in older men (343). The use of cavernosography and saline infusion techniques to determine venous outflow has been reported by a number of investigators (260,351,368). In these studies, however, there was no vasodilation or sinusoidal relaxation such as that pharmacologically induced by papaverine injection. Lue and associates (206) reported their findings with cavernosography during papaverine-induced erection. Because patients with arterial insufficiency would not benefit from cavernosography, they eventually selected patients who were unable to achieve or maintain a good erection but who had an excellent arterial response to papaverine as shown by pulsed Doppler analysis and sonography. In their study of 49 patients, 38 had evidence of abnormal venous drainage. They noted that an intracorporal pressure of 80 mm Hg almost completely stops venous outflow. If intracorporal pressure does not reach 80 mm Hg after papaverine injection, saline solution should be infused to produce further venous occlusion. Normal emissary veins should be occluded at this pressure, and only abnormally large veins remain open. If further infusion of 100 mL of saline at 80 mL per minute cannot increase the intracorporal pressure to 80 mm Hg, a large venous leak is diagnosed and can be localized with contrast cavernosography (206). The patients with excellent arterial dilation and blood flow after papaverine injection are the ones who are reported to benefit most from erection cavernosometry and cavernosography and are thought to be the most suitable candidates for venous ligation procedures.

The method used to diagnose venous leakage by cavernosometry and cavernosography is not standardized. It appears that cavernosometry after the intracavernous injection of vasoactive drugs provides more valuable information than cavernosometry performed with saline infusion alone (337). The best drug to use, optimal dosage, and best criteria to use to diagnose venous "leakage" are still unclear. The Society for the Study of Impotence has determined that a significant corporovenous leak should be diagnosed by either maintenance flow rate or by dynamic infusion cavernosometry and cavernosography (129). If the maintenance flow rate 10 minutes after 45 to 60 mg of papaverine or 10 μmg of PGE_1 injected intracorporally is greater than 30 mL per minute to maintain intracavernous pressure greater than 90 mm Hg or to produce a fully rigid erection, abnormal venous leakage is diagnosed (31). The clinical effectiveness of cavernosometry

and cavernosography is limited by several factors, including lack of normative data, operator dependence, variable interpretation of results, and poor predictability of the therapeutic outcome of venous surgery.

Neurologic Testing

When the history or physical examination indicates a potential neurologic cause for impotence, neurologic testing can be performed, although it is rarely clinically useful. Two important points need to be remembered. First, the presence of a demonstrable neurologic lesion does not mean that the lesion is responsible for the erectile dysfunction. Second, the neurologic studies used do not directly measure the integrity of the autonomic nerves that control penile erection.

The integrity of neural pathways can be ascertained by measuring evoked potentials. Both sacral-evoked potentials and genitocerebral-evoked potentials can be used (134,184). These studies require sophisticated instrumentation and have significant limitations in the evaluation of impotence. The sacral-evoked potential (sacral latency) is essentially an electrophysiologic procedure that measures the bulbocavernosus reflex (184). When this test is performed, the penile skin is stimulated and recordings are made from a needle electrode placed in the bulbocavernosus muscle. The time from stimulation to the first response in the bulbocavernosus muscle (latency) is measured.

Penile erection is normally governed by a reflex arc consisting of pudendal afferent (sensory) fibers and parasympathetic efferent (motor) fibers. The sensory portion of the reflex that governs erection and the sensory portion of the reflex, which is measured by sacral-evoked potential studies, are therefore identical. This portion of the reflex arc also can be evaluated by performing dorsal penile nerve conduction velocity (122). At present, however, the efferent (parasympathetic) portion of the reflex controlling erection cannot be accurately evaluated. The sacral-evoked response measures reflex activity over pudendal sensory nerves and pudendal (somatic) motor nerves. This study provides information concerning some reflex activity through the sacral spinal cord, but it does not directly test penile innervation.

Similar problems are faced by urologists in attempting to ascertain whether the motor fibers to the urinary bladder are intact. A cystometrogram that demonstrates detrusor contractions indicates that the parasympathetic motor fibers to the bladder are intact. When no detrusor activity is elicited, however, one cannot conclude that the bladder is denervated. Cystometry has been used as a study of the parasympathetic motor fibers in impotent patients, but its usefulness is limited. Impotent patients with obvious neurologic disease and voiding symptoms often have abnormal cystometrograms, but this study adds little useful information to the overall evaluation. Cystometry is rarely helpful in patients with no significant neurologic or urologic disease and a normal neurologic examination.

The objective measurement of the status of the CNS as it relates to erectile dysfunction is even more limited. Genitocerebral-evoked responses can be measured. The penis is stimulated as in the sacral-evoked response study and recordings made from electroencephalographic leads on the scalp (134). As with other neurologic studies, an abnormal genitocerebral-evoked response must be interpreted with caution. Although a neurologic abnormality may be demonstrated, it may bear no relationship to the patient's complaint of impotence. Neurologic tests are rarely indicated in the evaluation of the patient with erectile dysfunction. No available neurologic study can determine whether penile innervation is intact, and neurologic testing adds little to information gained from the history and physical examination.

Management

Drug Therapy

Oral Drug Therapy

Yohimbine, an indolic alkaloid obtained from the yohimbine tree, currently is used in the treatment of erectile dysfunction. For many years, this drug has been considered an aphrodisiac. This agent, in combination with testosterone and nux vomica extract, was in widespread use for the treatment of impotence in the 1960s (224,245,328). Morales and colleagues (251) reported that 6 of 23 patients given this drug “reported the reappearance of full and sustained erections and resumption of satisfactory sexual performance.” A subsequent report (250) showed no statistical difference between yohimbine and placebo in treating patients with organic impotence. A well-known side effect of the antidepressant drug trazodone is priapism. For this reason, this antiserotoninergic drug has been advocated for the treatment of erectile dysfunction, particularly psychogenic impotence. Little data on this drug's efficacy exist, but preliminary data suggest that response to trazodone is significantly better than that to placebo (188).

A significant advance in the medical therapy of erectile dysfunction occurred with the U.S. Food and Drug Administration approval of sildenafil (Viagra) in 1998. This selective type-5 phosphodiesterase (PDE) inhibitor is approximately 4,000 times more selective for type-5 PDE than for type-3 PDE and 10 times more selective for type-5 PDE than for type-6 PDE (12). Nitric oxide released from nerves or endothelium causes an increase in cGMP, which results in smooth muscle relaxation. Type-5 PDE causes the breakdown of cGMP in corporal smooth muscle. The inhibition of type-5 PDE results in accumulation of cGMP and promotes cavernosal smooth muscle relaxation (335). *In vivo,* sildenafil increases intracavernosal pressure in response to cavernous nerve stimulation (57). The direct injection of sildenafil into the penis, however, does not produce a rise in intracavernous pressure (8). In addition, administration of

sildenafil to animals that have undergone bilateral cavernous nerve transection and have been exposed to erectogenic central stimuli fails to increase intracavernous pressure (8). These data support the concept that an intact neural input is necessary for sildenafil to be effective.

Sildenafil has been reported to improve erections in patients with psychogenic, organic, and mixed factors. Many trials have shown that the success rate of sildenafil use is in the range of 65% to 80% (335). In a meta-analysis of data from 3,361 patients with predominately organic erectile dysfunction, sildenafil improved erections to a degree sufficient for intercourse always or almost always in 48% of patients with severe erectile dysfunction, defined as the inability to ever obtain or maintain an erection (334). Men with destruction of both cavernosal nerves would be unlikely to respond to sildenafil. Following radical prostatectomy, the efficacy of sildenafil appears to be greatest in men who have undergone bilateral nerve-sparing surgery, less with unilateral nerve-sparing surgery, and least with ablation of both cavernosal nerves (384). Because many patients with erectile dysfunction, regardless of etiology or prior therapy, can potentially respond to sildenafil, this drug can be recommended as first-line therapy in the absence of a contraindication to its use.

An absolute contraindication to the use of sildenafil is the concomitant use of nitrates. The use of these two drugs in combination can lead to a precipitous drop in blood pressure. The use of sildenafil in patients with cardiovascular disease is controversial (62). Side effects with sildenafil use include nasal congestion, dyspepsia, and diarrhea. In addition, approximately 3% of men taking sildenafil experience blurred vision or a visual color tinge. These visual disturbances have been attributed to the fact that sildenafil is only ten times more selective for type-5 than for type-6 PDE, which is present in the retina.

Testosterone Therapy

The alkylated testosterone drugs methyltestosterone and fluoxymesterone have been widely used primarily because they can be given orally. Both agents have the significant disadvantage of poor gastrointestinal absorption and liver toxicity (375). For these reasons, their use has been replaced by the parenteral use of intramuscular esterified testosterone. The National Institutes of Health (NIH) Consensus Development Conference Statement on impotence (257) recommended that “oral androgens, as currently available, are not indicated.” Significant side effects can occur with testosterone therapy. Despite the fact that hepatotoxicity has been markedly reduced when esterified rather than alkylated testosterone is used, evaluation of liver function studies before and periodically during therapy is prudent. No evidence exists implicating testosterone therapy as a cause of prostate cancer, but testosterone is contraindicated in the presence of prostate cancer. Patients receiving testosterone should be monitored with digital rectal examination and serum prostate-specific antigen determination. Androgen therapy also has been demonstrated to increase hematocrit and red blood cell volume by stimulating erythropoietin production. Patients with hematocrit values greater than 48% appear to be at risk from cardiovascular complications (187).

Intracorporal Injection Therapy

The use of intracorporal injection of vasoactive agents has been described previously. Initial clinical trials using intracorporal papaverine and combinations of papaverine and phentolamine in the treatment of impotence reported excellent results, particularly in the therapy of impotence secondary to neurologic causes (320,385). PGE_1 has been advocated as being superior to either papaverine or combinations of papaverine and phentolamine. PGE_1, like papaverine and phentolamine, causes relaxation of corporal tissue *in vitro* (140). In addition, enzymes that locally metabolize PGE_1 are present in penile tissue, and therefore the risk of priapism is at least theoretically reduced (294). Large clinical series have been reported, which attest to not only the efficacy but also the low complication rate (including priapism) with the use of this agent (153,331). The use of a drug combination of PGE_1, papaverine, and phentolamine also has been advocated (24).

Significant complications of the use of intracorporal papaverine alone, combinations of papaverine and phentolamine, and PGE_1 have occurred. The development of fibrotic penile lesions has been reported (69), and penile nodules have been reported to occur in up to 57% of patients who administer their own injections for 1 year (198). The acidic pH of papaverine may be related to the development of these fibrotic lesions. In animal studies, long-term use of intracorporal papaverine causes not only fibrosis in the area of the injection sites but also smooth muscle hypertrophy in other areas of the corpora (3). Hepatotoxicity is a known side effect of papaverine, but this has been an uncommon adverse effect of intracorporal papaverine use (198).

The most significant complication of intracorporal injection therapy for impotence is the development of priapism (136). The true incidence is unknown, but the number of patients who experience priapism is undoubtedly related to the patient population being treated and the type and dose of drug or drug combination being used. In large series, priapism has been reported to occur in less than 1% to 4% of patients (198,321).

The mainstay of therapy of drug-induced priapism has been the intracorporal injection of α-adrenergic agonists. Because erection has been induced artificially by drugs that relax corporal smooth muscle, the injection of agents (α-adrenergic agonists) that contract corporal smooth muscle is both theoretically sound and clinically efficacious (210). Several agents have been recommended, including epinephrine, norepinephrine, metaraminol, and phenylephrine (207,359).

Phenylephrine appears to be particularly efficacious and results in fewer cardiovascular side effects than the other agents and has become the drug of choice to treat priapism (81). When treating priapism, the recommended dose of phenylephrine is 0.05 mg injected intracavernosally on each side (total dose of 0.1 mg) (359). The use of α-adrenergic agonists has been advocated for initial therapy of priapism of a variety of causes (207). Complications from the treatment of priapism with α-adrenergic agonists have occurred (207,211). Because of the potential for significant cardiovascular morbidity, these agents should be used with care.

Although intracorporal injection therapy is efficacious in a large number of impotent patients, both the patients best suited for this form of therapy and the best drug (and dosage) remain in doubt. For example, patients with neurogenic impotence tend to respond to lower dosages of vasoactive drug than patients with impotence secondary to other causes (321). Only approximately 40% to 50% of patients enrolled in at-home drug injection programs are still administering their own injections after 1 year (198).

Intraurethral Drug Therapy

The intraurethral administration of alprostadil through a novel delivery system designed to administer a pellet of PGE_1 was introduced in 1997. The drug is transferred through the urethral mucosa and corpus spongiosum to the corpora cavernosa. Alprostadil causes activation of adenylate cyclase, which leads to increased levels of cAMP and smooth muscle relaxation. After one pass through the pulmonary vasculature, between 60% and 90% of systemic PGE_1 is inactivated (292). The drug is available in 125-, 250-, 500-, and 1,000-μmg strengths to allow dosage titration. In the initial trials, symptomatic hypotension occurred in 3% of patients, dizziness occurred in 4% of patients, and syncope occurred in 0.4% of patients during in-clinic dosing. For this reason, titration should be carried out under medical supervision. The most common side effect is penile pain, which occurs in 36% of patients. Initial studies indicated that intercourse and erections sufficient for intercourse rates to be approximately 50% to 65% (142,268). Subsequent reports have indicated lower success rates (367).

Vacuum-constriction Devices

Vacuum-constriction devices provide effective and acceptable therapy for erectile dysfunction for some patients. The devices consist of a plastic cylinder, tubing connected to a handheld vacuum pump, and elastic constriction bands (Fig. 42.10). High patient acceptance and low morbidity have been reported (255,377). A survey of 1,517 users of the device revealed that 92% achieved erection with the device, and 77% had intercourse at least every 2 weeks (377). The successful use of this device in difficult clinical settings, such as with patients who have had penile prostheses removed, also has been reported (253).

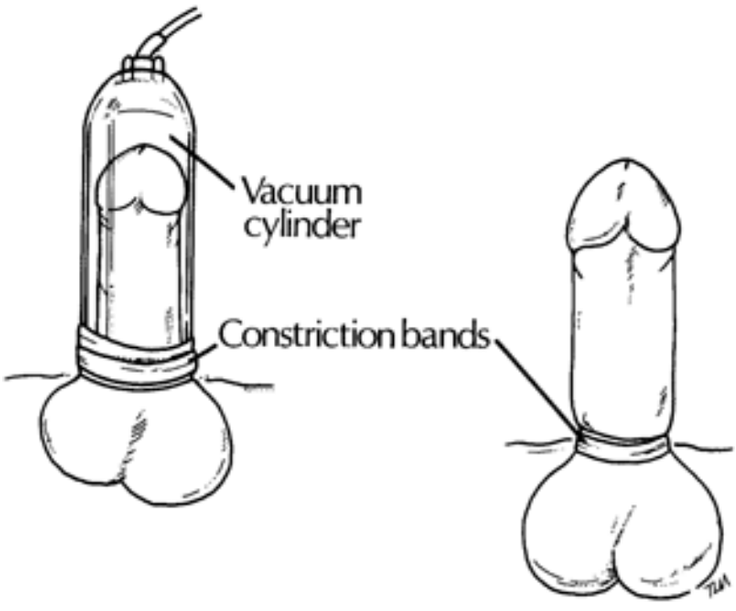

FIGURE 42.10. Vacuum-constriction device.

Penile Revascularization and Venous Ligation Procedures

Penile revascularization to treat vasculogenic impotence was introduced by Michal. The Michal I operation involved the direct anastomosis of the inferior epigastric artery to the corpus cavernosum. The procedure was abandoned because of many failures within the first months, and the initial success rates of 60% to 70% were modified to 40% when patients were followed for 1 year (316). The Michal II modification involved the anastomosis of the inferior epigastric artery to the dorsal artery of the penis. In their initial series, 13 of 18 patients improved (242). Others have reported similar encouraging results. Of eight patients revascularized by McDougal and Jeffrey (232), four reported normal sexual function, and two reported markedly improved sexual function at least 1 year after the operation. The Michal II operation presumes that blood from the inferior epigastric artery flows into the dorsal artery of the penis and then retrograde to the pudendal artery where it bifurcates into the dorsal and profunda penile arteries. The ideal candidate for this operation is the patient in whom the arterial occlusion is located proximal to the bifurcation of the pudendal artery into the dorsal and deep penile arteries with patent vessels distally. A modification of the Michal II procedure has resulted in the restoration of coitus with improved erection in 80% of patients (129). Direct revascularization of the profunda penile arteries with the inferior epigastric artery also has been reported (216,261). Venous

arterialization procedures as described by Virag also have been reported to be successful in a significant number of cases (25). These procedures consist of anastomosing the inferior epigastric artery to the deep dorsal vein of the penis with or without the creation of a fistula between the vein and the cavernous body.

Only a limited number of men with vasculogenic impotence are candidates for revascularization procedures. McDougal and Jeffrey (232) have outlined a careful evaluation to properly select patients. Of 44 patients thought to have organic impotence, 28 were found, by venous occlusion plethysmography, to have a penile blood flow measurement of less than 2 ml^3/100 cm^3 of tissue per minute. These 28 patients underwent pudendal angiography, which demonstrated significant arterial occlusive disease in 13, and 11 of those 13 underwent revascularization. In those patients in whom the penile arteries were demonstrated angiographically, the results of revascularization were successful. Angiographic visualization of the penile arteries indicates patency, and the use of tolazoline hydrochloride or another vasodilator may be necessary to avoid false-negative results. The key to successful penile revascularization appears to be careful patient selection.

After the demonstration that increased venous resistance is important in the physiology of normal erection, many investigators have sought the optimal surgical approach for patients with erectile dysfunction secondary to “venous leakage.” Venous ligation surgery was described in the early 1900s by Wooten (380). More recently, Ebbehøj and Wagner (85) reported successful restoration of potency after closure of a venous leak between the corpora cavernosa and the glans. Wespes and Schulman (369) reported an 80% success rate in patients with venous leakage by ligating the deep dorsal vein and its tributaries. Lue (213) has advocated including ligation of the cavernous and crural veins. The rationale for venous ligation surgery in most patients is questionable. Demonstrated “venous leaks” are almost always the result of inadequate relaxation of the corporal smooth muscle and are not primarily a “venous disease.” As reported success rates have fallen, enthusiasm for venous ligation surgery has waned (293). According to the 1993 NIH Consensus Statement on Impotence, “this has tempered enthusiasm for these procedures, which are probably therefore best done in an investigational setting in medical centers by surgeons experienced in these procedures and their evaluation.”

Penile Prostheses

Semirigid Prostheses

The concept of inserting a rigid rod inside the penis to facilitate coitus was a logical extension of the fact that various mammals (e.g., dogs, bears, raccoons, walruses) have a bone-os penis-in the penis. Loeffler and Sayegh (201) reported the first use of an artificial synthetic implant for the correction of organic impotence. They noted that reconstructive surgeons previously had favored autogenous grafts, but bone usually undergoes absorption when used as a free graft unless placed in contact with living bone. Autogenous cartilage often curled. These two characteristics made the use of autogenous grafts unsuitable in the penis. These investigators constructed a perforated penile implant from acrylic and surgically placed it in the groove between the corpora cavernosa. Absorbable sutures placed through the perforations held it in place until fibrous tissue formation fixed it in position permanently. They later modified these prostheses with silicone for construction (191,192,200,201).

In 1967, Pearman (270) described a silicone prosthesis developed from a mold formed by injecting hot paraffin in the space between Buck's fascia and the tunica albuginea of a cadaver's penis. The resulting prosthesis was a three-fifths circle on cross section and could extend from the corona to the suspensory ligament. Interestingly, one modification of the prosthesis included a metal spring, suggestive of the silicone–silver wire prosthesis introduced by Jonas and Jacobi (158) some years later.

Because of their placement between Buck's fascia and the tunica albuginea, these early implants were prone to instability, displacement, and even extrusion (256). Beheri (22) first suggested placement of prostheses within the corpora cavernosa in 1966. In 700 patients, he implanted paired polyethylene prostheses within the corpora and reported good stability and cosmesis (22). Lash (192) also eventually advocated intracorporal placement, with the prosthesis extending from midglans to pubis. Morales and associates (252) also used intracorporal placement, but the rigidity and narrow contour of the prosthesis caused problems with pain and perforation. Eventually, Small and associates (325) developed paired penile implants with an exterior of medical-grade silicone and a core of silicone sponge (called the *Small-Carrion prothesis*). The prosthesis provided adequate length and, more important, normal width to the penis. Even though firm, it had enough flexibility to keep the phallus inconspicuous while in the normal position or against the abdominal wall. The Small-Carrion prosthesis was introduced in 1975 and was widely used (164,239,240,258,326).

In 1977, Finney (102) introduced a hinged silicone penile implant. He noted that with the Small-Carrion prosthesis, it was not possible to preoperatively determine the appropriate sizing, thus requiring that several sizes be kept available. Also, the implant maintained the penis in an upright, erect state, sometimes requiring constrictive clothing to conceal it. Finney recognized that even though the earlier Lash prosthesis extended only to the pubis and allowed the penis to hang normally, it imparted adequate rigidity to the penile shaft. With these considerations in

mind, he developed a prosthesis with a tail that could be trimmed to facilitate intraoperative sizing, a hinge section at the level of the penis to allow dependent positioning, a rigid shaft, and an anatomically correct conical tip to improve positioning under the glans.

Operative Techniques.

The intracorporal prostheses introduced by Beheri (22) and Morales and associates (252) were inserted through a dorsal midline penile incision. To minimize trauma and scarring to the phallus, Small and associates (325) advocated a perineal surgical approach (Fig. 42.11). The patient was placed in a semilithotomy position and a Foley urethral catheter inserted to help identify the urethra during the procedure. A midline perineal incision was developed from the base of the scrotum toward the anus. Sharp dissection allowed identification of the bulbocavernosus muscle. The bulbocavernosus muscle and urethra were retracted to one side and the ischiocavernosus muscle and penile crus identified. Once identified, the crus was opened longitudinally with a 2- to 3-cm incision. The intracorporal space was developed with Hegar dilators proximal to the ischial tuberosity and distal to the end of the corpus cavernosum. Dilation was performed initially with a no. 5 Hegar dilator and advanced to a no. 10 or 11. The prosthesis of appropriate size was then inserted. The procedure was repeated on the opposite crus. Small and colleagues (325) noted that the 13.3-cm (medium) or the 14.5-cm (long) prosthesis was usually required, and they attempted to use the widest possible prosthesis. The wounds were closed with 3-0 chromic catgut; no drains were left. The Foley catheter was removed immediately after surgery, and broad-spectrum antibiotics were given postoperatively. For patients who were impotent after pelvic fracture or who had a perineal urethroplasty, Small and associates (325) suggested either making the skin incisions laterally directly over each crus or in the midline at the penoscrotal junction, thus avoiding scarred tissue.

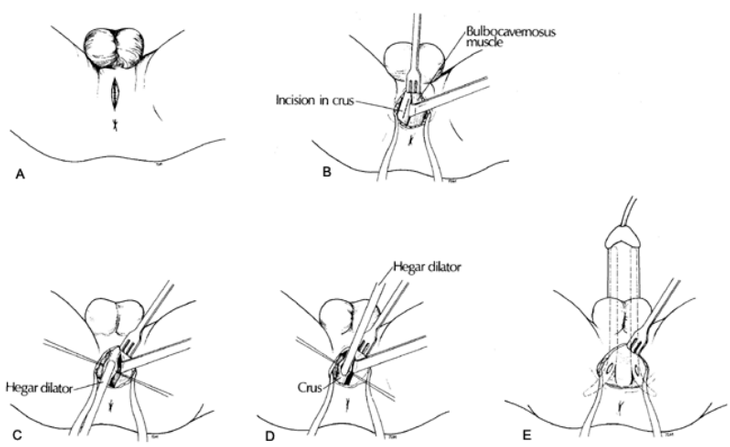

FIGURE 42.11. Perineal approach for placement of semirigid penile prostheses: through a midline perineal incision **(A);** the corpus spongiosum and penile crura are exposed and the crus incised **(B).** The corpus cavernosum is dilated distally **(C)** and proximally **(D).** A prosthesis is placed in each corpus cavernosum **(E).** (Redrawn from Small MD, Carrion HM, Gordon JA. Small-Carrion penile prosthesis: new implant for management of importance. *Urology* 1975;5:479.)

The penoscrotal approach was later popularized by Barry and Seifert (18) (Fig. 42.12). They emphasized that even in patients without trauma or previous surgery, there were inconveniences with the perineal approach, such as perineal fat incision and incision of the ischiocavernosus muscles. Damage to the dorsal neurovascular bundle was a possible complication of the dorsal penile approach.

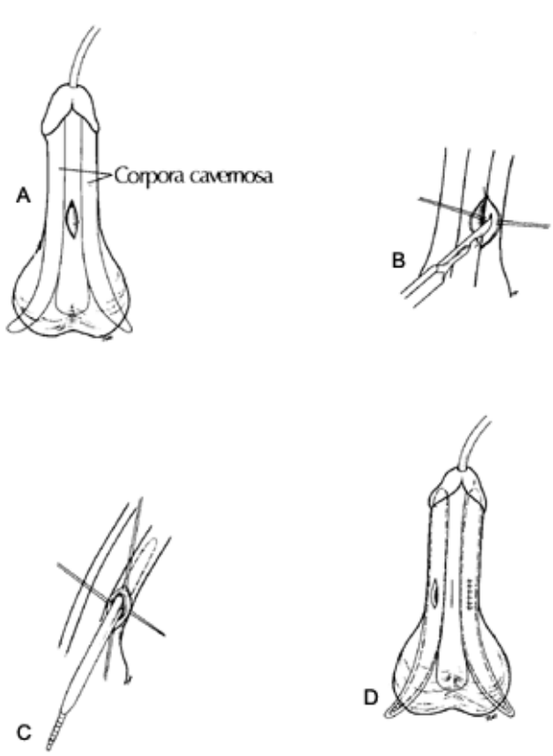

FIGURE 42.12. Penoscrotal approach for the insertion of paired semirigid penile prostheses: through a midline incision the corpus spongiosum (urethra) and corpus cavernosa are exposed **(A);** with traction sutures in the tunica albuginea the corpus cavernosum is incised longitudinally **(B);** the cavernosal space is dilated with the prosthesis or with dilators **(C);** and a prosthesis is placed in each corpus cavernosum **(D).** (Redrawn from Barry JM, Seifert A. Penoscrotal approach for placement of paired penile implants for impotence. *J Urol* 1979;122:325.)

The surgery was performed with the patient in the supine position. A Foley catheter was inserted. A 5-cm midline incision was made over the urethra at the penoscrotal junction. The tissues overlying the urethra were incised to

the level of the corpus spongiosum, then dissected laterally to identify the tunica albuginea. The skin, subcutaneous tissue, and Buck's fascia were retracted laterally and stay sutures fixed in the tunica albuginea. A 5-cm longitudinal incision was made between the stay sutures. The corpus cavernosum was dilated with Hegar dilators. The procedure was repeated on the opposite side. The prosthesis was inserted, and the incisions in the tunica albuginea were closed with a running 3-0 polyglycolic acid suture. The subcutaneous tissues and skin were closed with 4-0 chromic catgut. During the procedure, a 1-g/dL neomycin sulfate solution was used as wound irrigant. An aminoglycoside or cephalosporin was used preoperatively, and the Foley catheter was removed 24 hours after the procedure (18).

In their introduction of the silicone–silver wire prosthesis, Jonas and Jacobi (158) described a dorsal subcoronal approach. This approach also has been used satisfactorily by others (29). A semicircular dorsal incision is made in the coronal sulcus. Buck's fascia is incised, and a 1- to 5-cm linear incision is made bilaterally in the tunica albuginea. The corpora cavernosa are then dilated with Hegar dilators, and the appropriate length of the prosthesis is determined with the sizer. The prostheses are then inserted, and placement in the distal corpora may be facilitated by the use of an eyelid retractor. The incisions in the tunica albuginea may be closed with absorbable or nonabsorbable suture. Most surgeons recommend the use of preoperative antibiotics, and some advocate use of a mild-pressure dressing (29,158,183). With all of the semirigid prostheses, an implant is placed in each corpus cavernosum. Gaur (117) has advocated in the placement of only one implant, claiming that results were satisfactory and significant cost savings could be realized.

Complications.

Complications associated with the semirigid penile implants are usually related to pain, inappropriate size, or infection. Other serious problems include urethral or skin erosion, urinary retention, or skin necrosis secondary to pressure dressings.

Kaufman and associates (164) reviewed their experience with 1,207 cases, finding that major complications occurred in 7.8%. Before the introduction of antibiotics, the reported incidence of infection was 15%; however, this was reduced to less than 5% with the use of antibiotic protocols (306). Predictably, diabetic patients seem to be at highest risk for developing infection (164,182,306). Before surgery, care must be taken to find any possible source of infection, such as pustules, infected wounds, or infected urine. If such a source is found, surgery must be postponed until the infection has healed adequately. The patient should be shaved at the time of surgery, not the evening before, and should undergo careful preoperative skin preparation with an antiseptic soap. Systemic antibiotics are used routinely. Once an intracorporal infection is established, both prostheses should be removed; the two corpora cavernosa communicate freely, and it is unlikely that an infection will be isolated to one side. Pain lasting longer than 4 weeks is another major problem. It appears that diabetic patients are more likely than nondiabetic patients to have protracted, even incapacitating pain. In fact, diabetic patients may constitute 70% of this group (164).

Other complications are related to inappropriate sizing. If the prosthesis is too short, the patient may have an “SST,” or flexion deformity. This can be corrected by dorsal tacking sutures anchoring the glans penis back over the head of the prosthesis (Fig. 42.13). If the prosthesis is exceedingly short, there may be inadequate rigidity in the distal portion of the penis for intromission or disconcerting mobility of the prosthesis. A more subtle problem with more serious consequences is placement of a prosthesis that is too long. This results in persistent pain, bowing of the penis, and increased risk of eventual erosion.

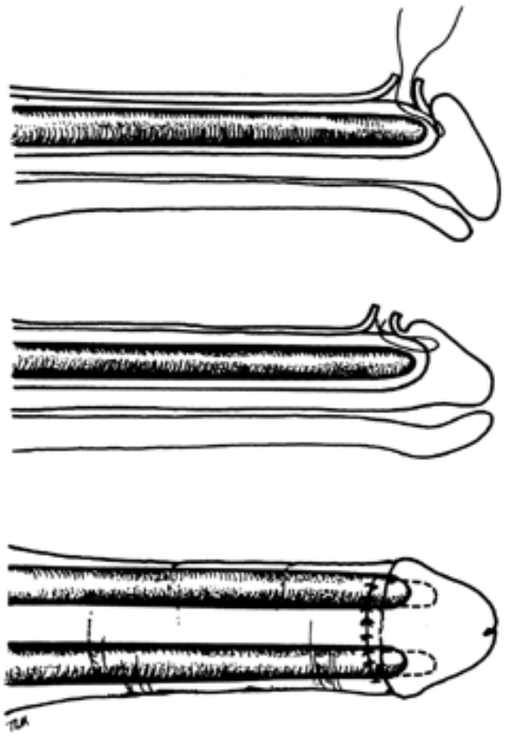

FIGURE 42.13. Correction of “SST” flexion deformity caused by inserting prostheses that are too short. Nonabsorbable horizontal mattress sutures are placed through the tunica albuginea and the substance of the glans. When tied, the sutures pull the glans back over the tips of the prostheses. (Redrawn from Kaufman JJ, Lindner A, Raz S. Complications of penile prosthesis surgery for impotence. *J Urol* 1982;128:1192.)

A tragic complication of implant surgery is penile gangrene. Two cases have been reported in patients who had pressure dressings applied after surgery, and four other cases

occurred in diabetic patients, even though no pressure dressings were used (186,229,306).

Inflatable Prostheses

In 1972, Kothari and associates (180) described an implantable fluid transfer system that might be useful in the treatment of impotence. The next year, Scott and associates (312) revolutionized the management of impotence with their report of the implantable inflatable penile prosthesis. Since then, there have been many modifications in the design of the prosthesis and the technique of implantation.

The device consists of two inflatable cylinders: one of which is placed in each corpus cavernosum; a pump that is placed in the scrotum; and a reservoir that is placed extraperitoneally beneath the rectus muscle (Fig. 42.14).

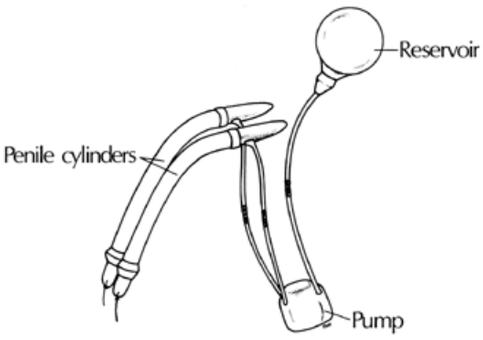

FIGURE 42.14. Scott multicomponent inflatable penile prosthesis. [Redrawn from Reimenschneider HS, Moon SG, Oliver WA, et al. Scrotal implantation of the inflatable penile prosthesis. *J Urol* 1981;126:747 (reference 283).]

Operative Techniques.

The components can be implanted through either a dorsal incision extending from the proximal penis over the pubis or through a penoscrotal incision (Fig. 42.15). The patient is placed in the supine position, and a urethral catheter is inserted. A single midline incision is made in the scrotum just below the penoscrotal junction. The urethra and corpora cavernosa are exposed. Traction sutures are placed in each corpora cavernosum, and a longitudinal 1.5- to 2.0-cm incision is made through the tunica albuginea, exposing the cavernosal tissue. The incision is kept more proximal than distal. A space is developed within the corpus cavernosum extending from the distal subglandular extent to the proximal attachment to the ischium. The space is dilated serially with Hegar dilators. The appropriate penile cylinder length is determined with the Furlow inserter (112). A cylinder is then positioned in each corpus with the inserter. The corporal incisions are closed, and care is taken to have the cylinder tubing exit through the incision at the point at which cylinder and tubing are attached. In cases in which the tubing was juxtaposed with the cylinder under the tunica albuginea, erosion and leakage occurred. A subdartos scrotal pouch is bluntly developed, on the right for right-handed individuals and on the left for left-handed patients, for placement of the pump. A finger is then placed in the inguinal canal to retract the spermatic cord laterally and to identify the inguinal ligament and the pubic tubercle. Just above the inguinal ligament and adjacent to the pubic tubercle, the transversalis fascia is punctured with dissecting scissors or a right-angle clamp. The puncture site is widened and a space bluntly developed in the perivesical space medial to the epigastric vessels. The empty reservoir is positioned in this space and then filled. In patients who have had previous inguinal or pelvic surgery, such as cystectomy, it is best to place thereservoir in the preperitoneal space under direct vision, usually through a separate inguinal or abdominal incision.

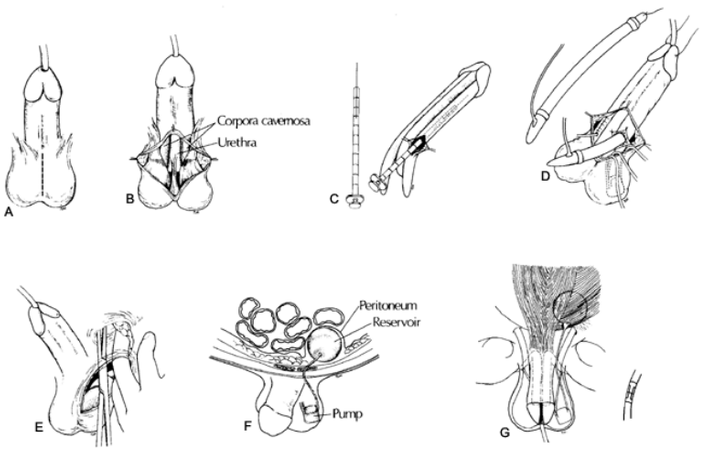

FIGURE 42.15. Placement of the Scott multicomponent inflatable implant. Through a midline scrotal incision **(A)**, the urethra and corpora cavernosa are exposed **(B).** Stay sutures are placed in the tunica albuginea. Through a longitudinal incision, the corporal tissue is dilated, and the corporal length is measured with the Furlow inserter **(C).** The inflatable cylinders are positioned within the corpora cavernosa with the Furlow inserter needle to pass the thread in the tip of the cylinder through the glans penis, providing a means to pull the cylinder into proper position. The corporal incisions are closed so that the cylinder tubing exits directly through the tunica and is not trapped against the cylinder **(D).** Through the inguinal canal, the spermatic cord is retracted laterally and the transversalis fascia is punctured just lateral to the pubic tubercle **(E).** The empty reservoir is pushed through the inguinal canal and through the opening in the transversalis fascia into the perivesical space. The reservoir is filled. The pump is positioned in the scrotum **(F).** The tubing connections are completed and the incisions closed **(G).** (Redrawn from Reimenschneider HW, Moon SG, Oliver WA, et al. Scrotal implantation of the inflatable penile prosthesis. *J Urol* 1981;126:747.)

The pump is situated low in the scrotal pouch so that the deflation valve is lateral, and it is held in place with an externally applied Babcock clamp. Tubing to the contralateral penile cylinder is passed through the scrotal septum to prevent torsion or retraction of the pump. The tubing to all components is then cut to the appropriate length and connected. The intrascrotal tissues just above the pump are closed with absorbable sutures to keep the pump position low in the scrotum. The scrotal incision is then closed with absorbable sutures. The cylinders are left partially inflated.

Antibiotic irrigation is used generously throughout the operative procedure, and systemic preoperative antibiotics are used routinely. The urethral catheter is removed within

1 day. The patients are taught how to operate the pump beginning 3 to 4 weeks after surgery, by which time most pain has disappeared.

Intracorporal Inflatable Prostheses

Intracorporal inflatable prostheses incorporate the advantages of both the semirigid and multicomponent inflatable prostheses. These inflatable implants are completely contained within the corpora cavernosa. These devices function on the principle of transferring a small amount of fluid from a distensible reservoir to a nondistensible chamber. When the fluid is transferred under pressure to the nondistensible chamber, it gives the implant rigidity. Flaccidity is regained by bending the prosthesis to override the pressure threshold of the release valve. The surgical technique for implantation of these devices is the same as that used for placement of the semirigid implants.

Two-piece Inflatable Prostheses

Two-piece inflatable prostheses consist of cylinders and a combination reservoir and pump. The reservoir–pump is placed in the scrotum (Fig. 42.16). These devices can be placed through either an infrapubic or a penoscrotal incision.

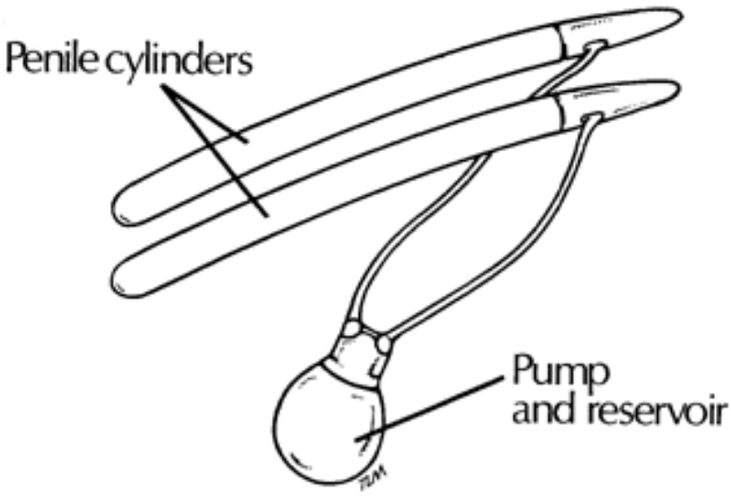

FIGURE 42.16. Two-piece inflatable prosthesis.

Complications.

The inflatable penile implant offers a more physiologic result than the semirigid rod prostheses. Surgical revision rates of up to 43% have been reported (99). The mechanical malfunction rate increases as the length of follow-up is extended, but with continued modification of

the devices, the mechanical failure rates have significantly lessened. There have been relatively few complications with the pumps and reservoirs. However, cases of reservoir erosion into the large bowel and bladder have been reported (193). Most problems have been related to cylinder leaks, aneurysms, or tubing kinks (99,164,168,222). Since the introduction of rear-tip extenders and careful attention to the exit site of cylinder tubing, the incidence of cylinder leaks has decreased (99,223). The incidence of nonmechanical complications, such as infection, is low, and problems with persistent postoperative pain are uncommon (17,168).

Patient and Partner Satisfaction.

The first report on women's reactions to penile implants was published in 1978 by Kramarsky-Binkhorst (181), who interviewed 31 female partners of patients who had previously received a Small-Carrion semirigid penile implant. Less than half (42%) of the women reported that the couple was totally satisfied with the results of the operation; however, a most important observation was made. There seemed to be a direct relationship between perceived success and the level of preoperative consultation and education by the surgeon. In addition, Kramarsky-Binkhorst (181) recognized that the couple's interpersonal relationship was a critical factor in the outcome.

Priapism

Priapism has been clinically defined as a prolonged, painful, penile erection. The disease process is named for Priapus, a Greek god and symbol of good agriculture and hunting who is portrayed as having an enormous phallus. Historically, priapism has been considered to be a low-flow state. A prolonged, painful erection occurs because venous outflow is compromised. Dark blood (with an acidic pH and low Po_2) is typically found on corporal aspiration and therapy has consisted primarily of surgical shunting procedures designed to improve penile venous drainage. Although high-flow priapism was described more than 40 years ago (51), this second type of priapism has only recently been widely recognized. High-flow priapism is clinically recognizable because the erection is painless and corporal aspiration yields bright red blood. Priapism may be a spectrum disease (204), and the separation of priapism into purely low-flow and high-flow states may be artificial.

Etiology

Low-flow Priapism

Hematologic Causes. One or more priapistic episodes have been reported in 38% to 42% of patients with *sickle cell disease* (87,108). Theories to explain the pathophysiology of priapism in these patients include the relatively acidic state of the corpora during erection, mild acidosis accompanying hypoventilation during sleep, and abnormal endothelial adherence. Paradoxically, four cases of patients with sickle cell disease have been reported with high-flow rather than low-flow priapism (280,333).

The incidence of priapism in *leukemic* patients is less than 1%. Chronic granulocytic leukemia is responsible for 50% of leukemic priapisms (309,336). The cause of priapism in these patients is thought to be hyperviscosity and sludging secondary to high white blood cell counts.

Several reports have convincingly linked *total parenteral nutrition* (TPN) and priapism (89,173). This syndrome has been associated with infusions of 20%, but not 10%, fat emulsions.

Oral Medications. A variety of oral medications, particularly antidepressants and antipsychotic drugs, have been associated with priapism. The highest incidence of priapism is seen with the nontricyclic antidepressant trazodone. Phenothiazines, particularly chlorpromazine, have also been linked to priapism. Priapism has also been associated with several antihypertensive agents, including guanethidine, hydralazine, and prazosin (35). Heparin has also been implicated (174).

Intracavernosal Injection Therapy. Currently, the most common cause of priapism is probably the intracavernosal injection of vasoactive drugs. The incidence of priapism is less with the use of PGE_1 than with papaverine or combinations of papaverine and phentolamine, but priapism has been reported to occur after the injection of only 5 μmg of PGE_1 (308).

Malignant Penile Infiltration. Metastases to the penis may cause priapism. The most common primary tumors responsible for priapism are bladder (30%), prostate (30%), colon (16%), and kidney (11%) (276). The life expectancy of patients with priapism secondary to malignant disease is short.

Neurogenic Causes. Priapism may be seen immediately after high spinal cord injury. Priapism secondary to spinal cord injury usually resolves spontaneously and does not require therapy. Cerebrovascular accidents and other neurologic diseases have been mentioned as causes of priapism, but such cases are rare.

Idiopathic Priapism. Depending on the patient population, no cause of priapism can be identified in 30% to 50% of cases (274).

High-flow Priapism.

The primary event leading to high-flow priapism is not venous occlusion, but rather high sustained arterial flow (378). The venoocclusive mechanism associated with normal erection is not activated, and the penis remains erect because of unregulated high arterial inflow. Because of high inflow and outflow, hypoxia and acidosis do not develop. The etiology of almost all cases of high-flow priapism is penile or perineal trauma. Injury to the cavernosal artery results in a cavernous artery to corporal tissue fistula (286). Arterial inflow bypasses the helicine arteries and is unregulated. Because the venoocclusive mechanism is not activated, high inflow and high outflow coexist. The number of reported cases of high-flow priapism is limited. In 1994, Bastuba and co-workers (20) added seven case reports to the twelve prior reports of arteriographically confirmed high-flow priapism. Although most reported cases are secondary to external penile or perineal trauma, laceration of the cavernosal artery during the intracorporal injection of vasoactive drugs is a recognized cause of high-flow priapism (20). Cases of high-flow priapism not associated with trauma have occurred. Three patients with sickle cell disease and no history of trauma who presented with high-flow priapism have been reported (280,333).

Evaluation.

A history and physical examination should be performed. Historical findings consistent with a diagnosis of low-flow and high-flow priapism should be sought. Current medications, a history of sickle cell disease, and a history of penile or perineal are particularly important. With high-flow priapism secondary to trauma, there is often a delay from the time of injury to onset of priapism (20). Unlike patients with low-flow priapism, patients with high-flow priapism do not have significant penile pain. Physical examination should include a search for evidence of trauma. In patients with low-flow priapism, the corpora cavernosa are rigid while the glans penis remains soft. The penis in cases of high-flow priapism has been described as being 60% to 100% rigid (44). The patient should be examined for lymphadenopathy and abdominal masses. Initial laboratory studies should include a complete blood count and sickle preparation to rule out leukemia and sickle cell disease as possible etiologies.

Because therapy and the timing of therapy are dictated by whether the priapism is low flow or high flow, aspiration of the corpora should be performed after the initial evaluation. The finding of dark blood indicates low-flow priapism, whereas the finding of bright red blood indicates high-flow priapism. It has suggested that blood gas values of pH less than 7.25, Po_2 less than 30 mm Hg, and Pco_2 greater than 60 mm Hg define ischemic priapism (45). Color duplex scanning has also been advocated (44). This noninvasive study can determine the presence of high-flow priapism and provide information concerning the location of any injury. Angiography is not essential to make the diagnosis of high-flow priapism (20). In most cases, angiography is performed in conjunction with embolization to treat cases of high-flow priapism.

Therapy.

The differentiation of low-flow from high-flow priapism is important because the treatment of the two conditions is markedly different. In low-flow priapism, therapy is directed at improving venous drainage, whereas in high-flow priapism, the goal is to decrease arterial inflow. Because histologic changes in the penis occur early in low-flow priapism (330), early therapy is indicated. The therapy of high-flow priapism is not an emergency; potency is usually restored after therapeutic intervention, even when the priapism has been present for weeks or months (20).

The therapy of three etiologies of priapism requires special mention. Patients with priapism secondary to metastatic infiltration should generally be managed expectantly. Patients with priapism secondary to leukemia should be treated with chemotherapy and/or penile radiotherapy. Priapism in patients with sickle cell disease is treated initially with hydration, alkalinization, analgesia, and hypertransfusion to increase the hemoglobin to greater than 10 mg/dL and reduce hemoglobin S to less than 30%. If these measures fail, corporal aspiration and instillation of an α-adrenergic agonist can be performed (108,137). Shunt procedures are performed as a last resort in priapism secondary to sickle cell disease.

A diagnosis of low-flow priapism is made when corporal aspiration reveals dark blood. The corpora are then irrigated with saline and an α-adrenergic agonist instilled. The drug of choice is phenylephrine (359). From 100 to 200 μmg is injected (half into each corpora). This dose can be repeated several times with careful patient monitoring and particular caution exercised in patients with preexisting cardiovascular disease. If aspiration, irrigation, and intracorporal α-adrenergic agonist does not result in detumescence, a surgical shunt procedure should be performed. These shunts can be classified as (a) cavernoglanular, (b) cavernospongiosal, (c) cavernosaphenous vein, and (d) cavernopenile dorsal vein. Cavernoglanular shunts are the easiest and fastest to perform. The Winter shunt is performed by excising cores of tunica albuginea between the distal corpora and the glans penis using a Tru-Cut biopsy needle (376). If persistent detumescence is not achieved, an open surgical shunt is indicated. The Ebbehøj and Al-Ghorab procedures

are also cavernoglans shunts. The Ebbehøj procedure consists of a stab wound incision with rotation of the knife blade to create a communication between the corpora cavernosa and the glans. In performing the Al-Ghorab operation, a 2-cm transverse incision is made in the glans penis 1 cm distal to the coronal sulcus (Fig. 42.17) (94). The ends of the corpora cavernosa are identified. and circular incisions are made and a portion of tunica albuginea removed from each corporum. The incision in the glans is then closed with running absorbable suture. Patients who do not achieve detumescence with a corporoglanular shunt require creation of another type of shunt. Grayhack described the use of the saphenous vein to shunt blood from the corpora (Fig. 42.18) (131). The saphenous vein is identified, transected distally, tunneled under the skin, and anastomosed end-to-side to a window created in the tunica albuginea. This procedure, as well as the cavernopenile dorsal vein shunt (19), is technically demanding, and the risk of pulmonary embolus exists. The Quackels cavernospongiosum shunt is performed through a perineal incision (Fig. 42.19) (278,360). The corpus spongiosum and corpus caverosum are exposed and incised. The shunt is created by suturing the two corpora together, first the inner edge and then the outer edge. This shunt can be performed either unilaterally or bilaterally. This shunt should be performed as far proximally as possible to lessen the chance of urethral injury. Despite early surgical intervention for low-flow priapism, postoperative erectile dysfunction is approximately 50% (33).

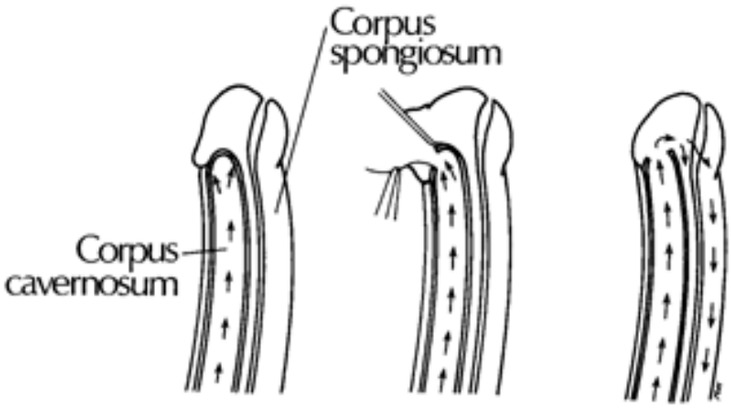

FIGURE 42.17. Technique for establishing an Al-Ghorab shunt. (Redrawn from Ercole CJJ, Pontes JE, Pierce JM Jr. Changing surgical concepts in the treatment of priapism. *J Urol* 1981; 125:210.)

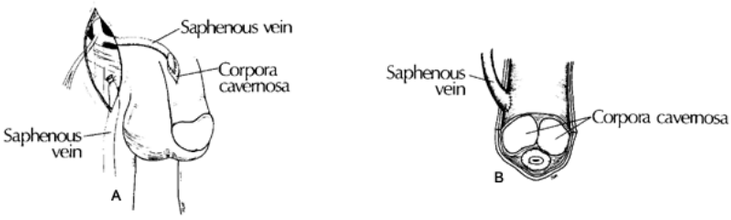

FIGURE 42.18. A cavernosaphenous shunt is created by tunneling the transected saphenous vein under the inguinal skin **(A)** and making an end-to-side anastomosis with the corpus cavernosum **(B).** (Redrawn from Grayhack JT, McCullough W, O'Conor VJ Jr, et al. Venous bypass to control priapism. *Invest Urol* 1964;1:509.)

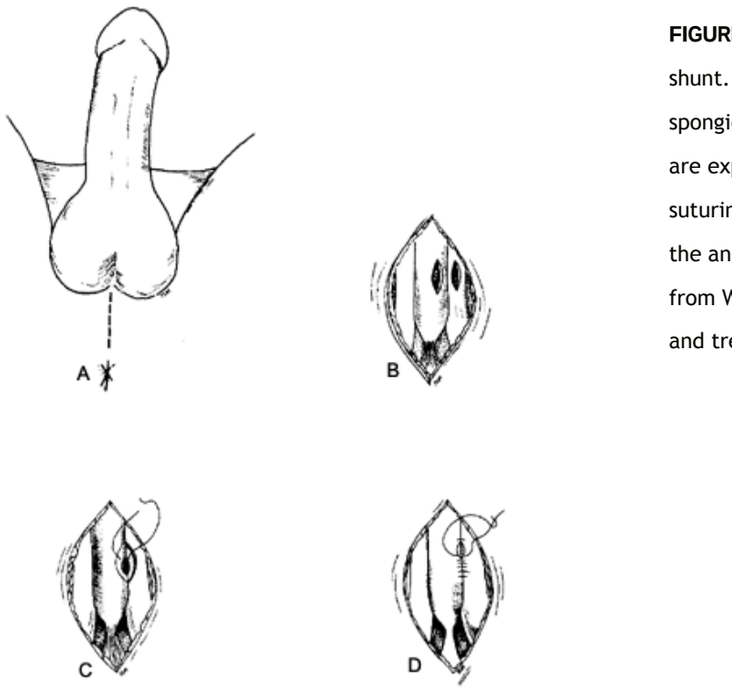

FIGURE 42.19. Creation of a spongiosum-cavernosum shunt. Through a perineal incision **(A)** the corpus spongiosum (midline) and the corpus cavernosum (lateral) are exposed and incised **(B).** The shunt is created by suturing the two corpora together, first the inner edge of the anastomosis **(C)** and then the outer edge **(D).** (Redrawn from Wasmer JM, Carrion HM, Mekras G, et al. Evaluation and treatment of priapism. *J Urol* 1981;125:204.)

In high-flow priapism, the fact that the penis is well perfused argues against immediate intervention. In addition,

spontaneous resolution has been reported to occur (44). Pharmacologic therapy has been attempted. α-Adrenergic agonists have been used in high-flow priapism in an attempt to decrease arterial flow. Typically, the penis becomes less rigid initially after the injection but then quickly resumes its priapistic state. Both cavernosal artery ligation and embolization have been used in the treatment of high-flow priapism. Ricciardi and co-workers (286) reported two cases of high-flow priapism secondary to trauma; one resolved spontaneously and the other was treated by surgical ligation of the involved cavernosal artery. Two of the four patients treated by Brock and associates (44) underwent an open surgical procedure. Most patients with high-flow priapism have been treated with arterial embolization. This therapy was initially described by Wear (362). The high-flow priapism in all seven cases reported by Bastuba and co-workers responded to this therapy. In two of the three cases reported by Brock, however, angiographic embolization was not successful and open surgical ligation was performed. The use of autologous clot for embolization has been advocated because it permits rapid restoration of blood flow after clot lysis, minimizes complications, and potentially allows for recovery of normal sexual function (356). Absorbable gelatin sponge also produces transient interruption of arterial flow through the lacerated vessels. Because of the small number of reported patients, the possibility of permanent erectile dysfunction should be explained to the patient prior to therapy.

Peyronie's Disease

Peyronie's disease is a sexually crippling condition of the penis that may result in penile pain, penile curvature prohibiting intromission, and impotence. The mean age of afflicted patients is 53 years, and the clinical course of the disease is variable. The penile curvature is caused by plaque formation secondary to fibrosis of the loose areolar tissue between the tunica albuginea and the corpus cavernosum (327). Light microscopic studies suggest that the plaque originates as a lymphocytic and plasmacytic infiltrate developing in the perivascular spaces of the areolar tissue. Electron microscopic studies corroborate these findings and support the suggestion that there is a process originating as a vasculitis in the tunica albuginea (348). Demyelination of nerve axons has been noted in specimens of plaque, suggesting the potential of neuropathology even before surgery (348). Bacteria have been identified in vascular areas of the tunica albuginea, the vicinity of the urethra, and the periurethral glands, but this is an uncommon finding (36,327), and infection is not considered a primary cause of Peyronie's disease. The vasculitis and inflammatory infiltrates lead to gradual fibrosis that with longer duration eventually compresses the erectile tissue of the corpora cavernosa as the plaque develops. These findings have been confirmed by others who found that in patients with symptoms of less than 6 months' duration, the primary pathologic finding was vascular changes with perivascular infiltration by lymphocytes. In patients with long-term symptoms, biopsy specimens showed no acute vascular changes, but the tissue was rich in fibroblasts (53). Other findings include calcium deposits, bone, cartilage, and even bone marrow formation (327,347). In summary, Peyronie's disease begins as an inflammatory process and progresses to a fibrotic stage, eventually forming a plaque that may mature to bone or cartilage. The plaque is most often located on the dorsum of the penis and may involve the septum between the corpora cavernosa (340). Chesney (63) found multiple plaques in 22% of 250 patients. The plaques most commonly are 1 to 2 cm in width and 2 to 4 cm in length, and penile curvature occurs in 80% to 100% of cases (247).

Even though Peyronie's disease was first described in 1743, its cause is still unknown (75). Numerous factors have been implicated but none proved. Suspected causative factors have included arteriosclerosis, diabetes mellitus, trauma, phlebitis, medications, infections, heredity, or an immune reaction (71,264,267,347,373,382). Bivens and associates (37) reported that 2 of 6 patients with carcinoid syndrome had Peyronie's disease and suggested that elevated levels of serotonin were responsible for the fibrosis found in the retroperitoneum, endocardium, and penises of these men.

Approximately 10% of patients with Peyronie's disease have other types of fibromatoses, such as Dupuytren's contracture, plantar fibromatosis, and fibrosis of the auricular cartilage (36,63), suggesting that an immunologic factor may be involved. Vande Berg and colleagues (347) used scanning and transmission electron microscopy and demonstrated osteoblast-like cells and osteoid formation originating from vascular lumina in areas adjacent to calcified Peyronie's plaques. They suggested that this may result from an autoimmune stimulus associated with some form of vascular trauma. The association between Peyronie's disease and the histocompatibility antigens of the B7 cross-reacting group suggests that Peyronie's disease may be a pathologic response to an infective agent similar to the B7 antigen. The histocompatibility antigen HLA-B27 has been linked to a variety of fibrosing disorders, particularly ankylosing spondylitis. HLA-B27 also may be related to idiopathic retroperitoneal fibrosis and to the fibrotic changes associated with rotator cuff syndrome (47,374). Noting these relationships, Willscher and colleagues (373) tissue-typed eight patients with idiopathic Peyronie's disease; seven were found to possess an antigen of the B7 cross-reacting group. Citing the suspected immunologic cross-tolerance between HLA-B27 antigen and bacteria of *Klebsiella–Enterobacter* species in patients with ankylosing spondylitis, they suggest that Peyronie's disease may be a characteristic response to a yet unidentified agent that is similar to the B7 cross-reacting group antigens. Nyberg and associates (264) subsequently identified three families with an inherited form of Peyronie's

disease associated with Dupuytren's contracture and the presence of HLA-B27 cross-reacting antigens. Leffell and associates (195) could not substantiate these findings. They phenotyped 28 men with Peyronie's disease for their HLA-A, HLA-B, and HLA-C locus determinants. There was no significant association of any individual B7 cross-reactive antigen or of the B7 antigens considered as a group.

The only reports documenting a specific antecedent agent noted that cessation of ß-adrenergic blocking agents (propranolol and metoprolol) resolved the symptoms of Peyronie's disease in several patients (267,382). There is also much uncertainty as to the natural history of Peyronie's disease. The mean age of afflicted patients is 53 years, and the clinical course of the disease is variable. It is self-limited in up to 50% of cases (111) and may resolve spontaneously in 12 to 18 months (56). A retrospective study indicates that the spontaneous resolution rate may not be as high as that previously reported. In a retrospective review of 97 patients followed for 3 months to 8 years, 13% of the patients believed the disease to be one of gradual resolution, 47% believed there had been little or no change, and 40% believed that the disease pattern was one of gradual progression (120).

In 1949, Scardino and Scott (305) suggested vitamin E for the treatment of Peyronie's disease, noting that vitamin E deficiency interfered with the normal repair of connective tissue, resulting in contracture of scar tissue. Even though it has been widely used, the beneficial effects of vitamin E in the management of Peyronie's disease have not been proved. Potassium *para*-aminobenzoate has been a mainstay of therapy for many years, but it is difficult to ascertain any beneficial effect of this agent, and problems with hypoglycemia, nausea, and vomiting have occurred (247,383). In addition, patients find it inconvenient to take 24 tablets daily. Radiation therapy has been reported to be effective in providing pain relief (49,111,143,203,247). With orthovoltage, external radiation therapy complications are essentially nonexistent (111,247). Carson and Coughlin (56) administered doses between 600 and 1,600 rad over a 10- to 90-day period. The average radiation dose was 900 rad. Relief of pain was seen in 78.5%, improvement in the plaque was noted in 13.3%, and penile curvature improved in 6.2%. The average interval to improvement was 5.8 months.

Various other treatments have been used: ultrasound (147), steroid injection (77), topical ß-aminopropionitrile (118), and collagenase injections (119). The plethora of treatments tried in this disease suggests that there is not one that is standard, widely accepted, or predictably efficacious. Also, the natural history is variable; some patients may improve with no therapy, and most authors believe that the results with nonsurgical treatment differ little from those with no treatment (46).

The role of surgery in the management of Peyronie's disease is determined by the severity of curvature or the degree of the patient's disability. A waiting period of from 18 to 24 months after the onset of symptoms until the disease has stabilized is advised (30). The reason why some patients with Peyronie's disease experience erectile dysfunction and others do not is unclear. Venoocclusive dysfunction occurring in the area of the plaque has been suggested (116). In the report of 106 patients by Bystrom and colleagues (53), only 18 were actually impotent but 55 found intromission difficult or impossible because of penile curvature. Early attempts at surgical correction focused on incision of the fibrous plaque (152), but this often resulted in an unstable erection. Subsequent efforts were directed to grafting of the surgical defect with various materials, such as fat, saphenous vein, dermis, or patches of synthetic graft (238).

In 1974, Devine and Horton (79) introduced the use of the dermal graft. After complete excision of the Peyronie's plaque, a dermal patch of exact size was removed from the abdominal wall and sutured into the penile defect with the fat on the inside. They reported good results, and their subsequent experience was also favorable (371). However, Melman and Holland (238) were less enthusiastic. All seven of their patients were completely impotent 1 year or longer after surgery. The cosmetic results of the dermal graft inlay technique were excellent, but they recommended placement of a penile prosthesis to restore a straight phallus and sexual function. Gangai and associates (115) reported that only 30% of their patients were sexually functional after plaque excision and grafting. They also recommended excision of the plaque and stenting with a penile implant. Raz and colleagues (281) advocated simple incision of the fibrotic plaques and placement of a stenting penile prosthesis. No attempt was made to graft the defect in the tunica albuginea. In their series of 12 patients, satisfactory function and cosmetic results were obtained. Use of the inflatable prosthesis also has provided good results (114,221,338).

In patients with Peyronie's disease and impotence, most authors advocate a penile-straightening procedure and placement of a penile prosthesis. There is still disagreement, however, as to the procedure of choice in patients with Peyronie's disease and adequate erectile function. If only a straightening procedure is performed, the patient must be made aware of the fact that he may develop impotence postoperatively. If the patient is willing to undergo further surgery for the placement of a prosthesis should he become impotent, the performance of only a penile straightening procedure is reasonable. The Nesbit procedure, which consists of excising a wedge of tunica albuginea on the side opposite to the plaque, provides a simple surgical correction in these men that obviates the need for a stenting implant and does not affect erectile function (71,130). This procedure, however, often results in penile shortening. The relationship between Peyronie's disease and impotence is not clear, so the primary treatment with penile prostheses is controversial. Several other surgical procedures have yielded excellent results in small series. Laser destruction of the

plaque and placement of a deep dorsal vein patch graft resulted in retained potency in 8 of 8 patients (107). Incision of the plaque and placement of a polypropylene patch graft was successful in maintaining potency in 9 of 9 patients (96).

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The views expressed are those of the author and not of the U.S. Food and Drug Administration.

43

BENIGN AND MALIGNANT LESIONS OF THE PENIS

Gerald Sufrin

Robert Huben

G. Sufrin: Department of Urology, University at Buffalo, Kaleida Health, Buffalo, NY 14203.

R. Huben: Department of Urology, State University of New York at Buffalo, Roswell Park Cancer Institute, Buffalo, NY 14203.

Contents

In addition to infectious, inflammatory, and vascular lesions of the penis, a wide spectrum of benign, premalignant, and malignant neoplasms of the penis has been described. Although the majority of such lesions originate from the epithelium of the penis, other tumors also occur. A useful classification of penile neoplasms has been proposed and is modified in Table 43.1 .

TABLE 43.1. CLASSIFICATION OF PENILE NEOPLASMS

Primary Tumors	Nonepithelial
Epithelial	Lymphoma
Benign	Sarcoma
Condylomata acuminata	Mesenchymal
Molluscum contagiosum	Benign
Papilloma	Malignant
Hemangioma	Angiosarcoma
Nevi	Kaposi's sarcoma
Sebaceous cyst	Rhabdomyosarcoma
Premalignant	Leiomyosarcoma
Balantitis xerotica obliterans	Malignant schwannoma
Leukoplakia	Fibrosarcoma
Malignant	Histocytoma
Epithelial	Lymphohematogenous
Carcinoma *in situ*/penile intraepithelial neoplasia	Lymphoma
Erythroplasia of Queyrat	**Metastatic Tumors**
Bowen's disease	Solid
Bowenoid papulosis	Prostatic carcoma
Verruciform tumors	Transitional call cancer
Squamous cell carcinoma	Rectosigmoid cancer
Basal cell carcinoma	Renal cancer
Melanoma	Testis cancer
	Lung cancer
	Lymphohematogenous
	Lymphoma
	Leukemia

Modified from Narayana AS. Penile neoplasms: clinical, diagnostic, and therapeutic features. In: Culp DA, Loening SA, eds. *Genitourinary oncology.* Philadelphia: Lea & Febiger, 1985:471, with permission.

BENIGN PENILE TUMORS

Part of "43 - BENIGN AND MALIGNANT LESIONS OF THE PENIS "

Condylomata Acuminata

Condylomata acuminata, or venereal warts, are most commonly located on the corona of the glans, on the frenulum, and on the inner foreskin, but perianal, perineal, scrotal, and intertriginous involvement is not unusual (21,135). The penile shaft may also be involved. Grossly, condylomata appear as friable, papillary, multifocal, and multicentric cauliflower-like lesions; occasionally, they reach a large size or extensive distribution (152). The microscopic appearance is that of an undulating outer layer of keratinized tissue covering papillary fronds that are supported by connective tissue stroma. Other features (Fig. 43.1) include orderly rows of squamous cells in the epithelial pegs and the presence of a dermal lymphocytic infiltrate.

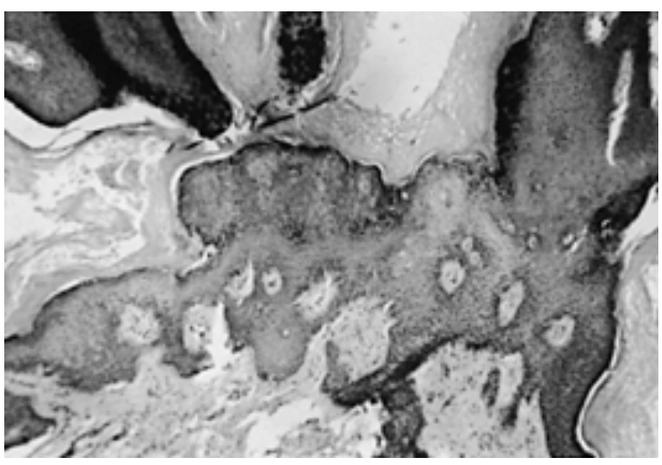

FIGURE 43.1. Condylomata acuminata. Note the papillary hyperplasia with multiple vacuolated superficial squamous epithelial cells. Focal parakeratosis is also present. (Hematoxylin-eosin, ×240.)

Condylomata acuminata are caused by infection with human papillomavirus (HPV), a double-stranded DNA virus containing approximately 8,000 base pairs. The use of DNA hybridization with specific HPV probes has identified more than 65 types of HPV that differ by more than 50% in the viral genome (266). In condyloma acuminata, HPV-6 and HPV-11 are most commonly detected and have been called *benign HPV types* (266). In malignant and premalignant lesions of the cervix and penis, however, HPV-16 and HPV-18, so-called oncogenic HPVs, are most commonly detected (253,266,291). Although there have been reports of penile cancers containing HPV-6 and HPV-11, these may coexist with the oncogenic viruses and the finding of different HPV types in condylomata and penile cancer

suggests that condylomata acuminata are not premalignant lesions.

Sexual transmission of condylomata acuminata is widespread, with an estimated increase in incidence of 459% from 1973 to 1988. Rosenberg and associates (245) examined 199 male partners of women with HPV-associated disease of the lower genital tract and found evidence of HPV infection in 77%. O'Brien and associates (200) reported the results of DNA analysis of the lesions of 26 men with genital condylomata and found that 13 had infection with HPV-6, 2 with HPV-11, 2 with HPV-31, and 9 with infection that could not be identified with the hybridization procedure. The sexual partners of men with genital condylomata should be examined for the presence of both condyloma and cervical neoplasia. Detection of subclinical lesions is facilitated with 5-power optical magnification before and after application of 3% acetic acid. When dilute (3%) acetic acid is applied to the genital area with soaked gauze and left on for 5 to 15 minutes, the appearance of whitened patches is suggestive of HPV infection. However, biopsy is necessary to confirm the histologic diagnosis of condyloma.

Podophyllin/podophyllotoxin is widely used to treat smaller condylomata, but because podophyllin application may cause bizarre histologic changes that may be confused with cancer, a thorough biopsy should be performed on suspicious lesions before podophyllin therapy. Podophyllin is applied weekly for at least 6 weeks and washed off 3 to 4 hours after each application. Larger condylomata may require either excision, fulguration, electrodesiccation, cryotherapy, or laser vaporization, although the propensity for recurrence indicates that adjunctive, in addition to ablative, therapy is often necessary (21). The possibility of urethral involvement should also be considered based on history and careful inspection and palpation; if the urethra is involved, it can be managed by neodymium:yttrium-aluminum-garnet (Nd:YAG) laser and adjunctive intraurethral fluorouracil cream (38,97) or bacille Calmette-Guérin (BCG) (21).

Molluscum Contagiosum

Molluscum contagiosum is a venereally transmitted lesion that is increasing in incidence (204). Molluscum contagiosum has also been seen with increasing frequency in patients with AIDS, although cutaneous cryptococcal infections in this patient population may mimic molluscum contagiosum (129,181).

Molluscum contagiosum is caused by a virus of the paravaccinia group. After an incubation period of 8 weeks or longer, lesions develop that are initially smooth and papular and occurrence in epidermal cysts has been reported. If the lesions persist, they become pitted, slightly transparent, globular, and protuberant. With pressure, bleeding and the discharge of a firm granular mass, the “molluscum bodies,” may result (134). Histologic examination of these lesions reveals a mass containing large inclusion bodies showing eosinophilic degeneration of epithelial cells (Fig. 43.2). This condition may be self-limited and may not require specific therapy, although topical trichloracetic acid, liquid nitrogen, or cantharidin has been used (134).

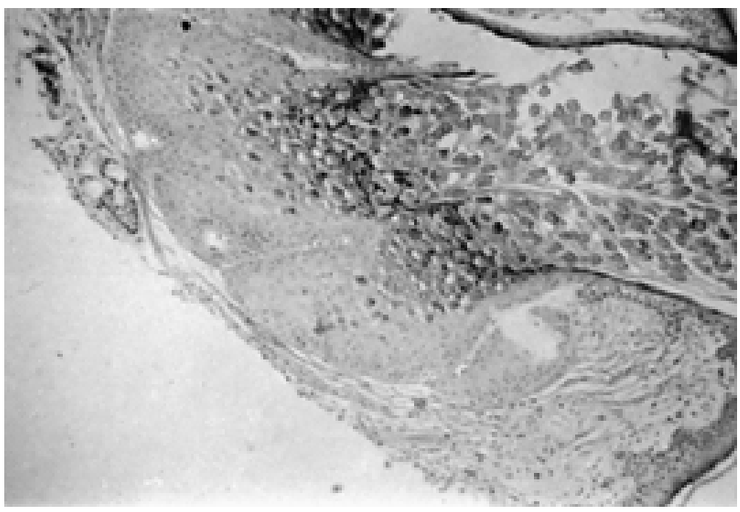

FIGURE 43.2. Molluscum contagiosum. This shows the typical inverted cuplike lesion of molluscum contagiosum. Also present are the classic intranuclei viral inclusion bodies (“molluscum bodies”) in the superficial and keratotic layers. (Hematoxylin-eosin, ×240.)

Hirsutoid Papilloma

Hirsutoid papillomas of the penis, also called *pearly penile papules,* have a reported incidence of 8% to 30% and occur

in a circumferential distribution on the corona and sulcus of the glans (175). The lesions consist of one or more rows of whitish-yellow papules from 1 to 2 mm in diameter; the papules occur without symptoms or pathologic significance. Histologically, these papules represent epithelial thickenings consisting of a core of connective tissue covered by an acanthotic epidermis over a vascular network and are considered to be acral angiofibromas (155,222). The characteristic distribution and appearance of these lesions simplifies diagnosis, and the absence of HPV in these lesions has been confirmed by polymerase chain reaction (68). Treatment, although not essential, is often requested by the patient, and in such cases, CO_2 laser in continuous-wave (CW) mode or cryotherapy is effective (175,222).

Other Benign Lesions

Other benign lesions of the penis include angiomas, nevi, and sebaceous cysts. Hemangiomas appear as well-defined red papules that are commonly found on the glans. Generally, these lesions are self-limited and have a tendency toward spontaneous regression. Larger lesions or those that bleed may require excision, ligation, or sclerotherapy.

A variety of benign pigmented tumors may involve the penis, and their major importance is in distinguishing these tumors from malignant melanoma. Nevus cell nevi, or pigmented nevi, are the most common of these lesions and may be differentiated histologically on the basis of their location within the skin: (a) junctional nevi, which are seen only in childhood; (b) compound nevi, which are rare after puberty; and (c) intradermal nevus cell nevi, which are usually seen only in adults (135). A particularly conspicuous representative of the last-named type is the papillary and hairy nevus, also called the *bathing suit nevus* when advanced (134).

Sebaceous or inclusion cysts may occur wherever sebaceous glands are present and are commonly seen in the scrotum. There are no sebaceous glands on the glans penis, but ectopic sebaceous glands are found on the inner surface of the foreskin and on the shaft of the penis. These heterotopic glands look like small aggregates of white-yellowish grains that are either somewhat raised or are level with the surface of the skin.

PREMALIGNANT LESIONS OF THE PENIS

Part of "43 - BENIGN AND MALIGNANT LESIONS OF THE PENIS "

Premalignant lesions of the penis include balanitis xerotica obliterans and leukoplakia (169,219,228).

Balanitis Xerotica Obliterans

Balanitis xerotica obliterans (BXO), by definition, is lichen sclerosus et atrophicus limited to the glans and prepuce (36,61,299). The etiology of BXO is unclear, although autoimmune factors, chronic balanoposthitis, HPV-16 infection, hormonal, and because an association with HLA-29 and HLA-B44 has been shown, genetic factors have been proposed as causally related to BXO (229). The lesion usually, but not exclusively, occurs in uncircumcised patients and originates on the glans or prepuce as small erythematous areas that ultimately coalesce to form whitish plaques (197). The prepuce becomes thickened by a sclerosing and atropic process of the glans and foreskin with the development of glanular fissures and erosions leading to phimosis and/or meatal stenosis (263). Histologically, the lesion is characterized by hyperkeratosis, flattening of the dermal-epidermal interface, fibrosis of the upper dermis, and a lymphocytic infiltrate in the middermis (Fig. 43.3). Approximately 6% of patients with BXO will progress to squamous carcinoma *in situ* or frank invasive penile cancer (195,228); thus close follow-up and biopsy when indicated is essential.

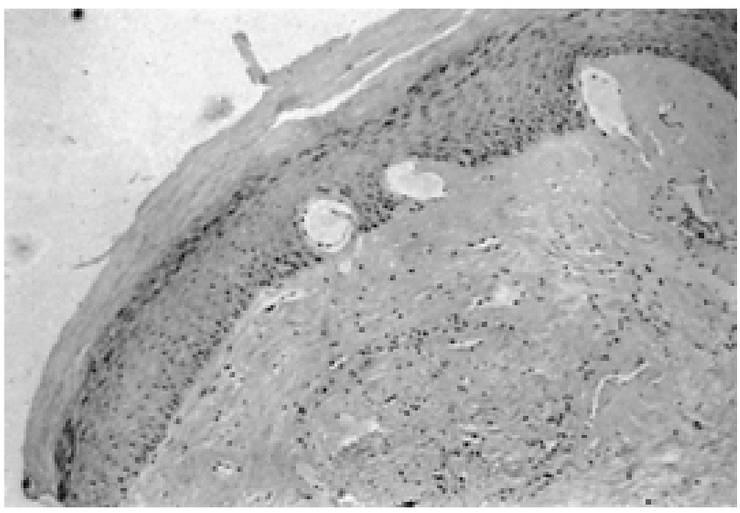

FIGURE 43.3. Balanitis xerotica obliterans. Marked hyperkeratosis and slight thinning of the epithelium, with sclerosis of the upper dermis and vascular dilation. (Hematoxylin-eosin, ×240.)

Therapeutic options in the treatment of BXO include high-potency topical corticosteroids (e.g., clobetasol 0.05%), 2% to 3% testosterone propionate ointment, antibiotics, and if unsuccessful, excision of the lesion or circumcision if the prepuce in involved (179,197). If meatal stenosis occurs, meatotomy or meatoplasty is indicated; if urethral stricture secondary to BXO develops, excision and staged free-graft urethroplasty using nongenital skin is recommended (293).

Leukoplakia

Leukoplakia of the glans penis is a rare lesion associated with either chronic irritation, inflammation, or diabetes (184). Clinically, the condition appears as one or more white plaques or scaly patches that tend to involve the meatus. The differential diagnosis includes BXO, lichen planus, and candidiasis (184). Histologically, the findings of leukoplakia include hyperkeratosis, parakeratosis, irregular acanthosis or atrophy of the malpighian layer, and disorderly arrangement of keratinocytes. Cellular atypia may or may not be marked.

The association of leukoplakia and squamous cell cancer is poorly understood, but leukoplakia is often found adjacent to or contiguous with squamous cell carcinoma. Initial management of suspected leukoplakia should include a thorough biopsy, particularly of any ulcerated areas, to rule out coexisting epidermoid cancer. Initially, less severe cases of leukoplakia may be managed by removing the source of irritation or inflammation (e.g., by circumcision). Persistent or progressive lesions require excision, with periodic follow-up, because recurrences have been reported after resection (184).

MALIGNANT LESIONS OF THE PENIS

Part of "43 - BENIGN AND MALIGNANT LESIONS OF THE PENIS "

Carcinoma In Situ of the Penis and Penile Intraepithelial Neoplasia

The term *carcinoma in situ* (CIS) *of the penis* is a descriptive histologic diagnosis encompassing the clinical entities of erythroplasia of Queyrat (Bowen's disease of the glans), Bowen's disease of the penile shaft, and bowenoid papulosis (81,89,179). In addition, because of the use of terminology in the literature, the term *penile intraepithelial neoplasia* (PIN) grade III has also been used for CIS (57,303,312). PIN is usually found on biopsy of suspicious penile lesions and has been classified into three grades (I to III) with the term *PIN* being restricted to grades I and II and the term *CIS* being reserved for grade III (37,312). Clarification of this ambiguity in terminology is provided by the recognition of oncogenic HPV-16 in 92% of patients with PIN III but in only 14% of patients with PIN I or II, while the nononcogenic HPV-6 or HPV-11 was found in 46% of PIN I and II but 0% of PIN III (57). Recent data support use of combinations of 5-flurouracil (5-FU) cream, interferon-α-2a, and CO_2 laser vaporization for PIN I and II and 5-FU plus CO_2 laser vaporization in PIN III (37).

Erythroplasia of Queyrat

Erythroplasia of Queyrat (EQ) is squamous cell CIS of the penile mucosa affecting the glans, inner surface of the prepuce, and/or the coronal sulcus of the penis. It is seen typically in elderly uncircumcised patients and presents with equal frequency as either solitary or multiple demarcated, nontender, shiny, bright red velvety plaques (86,230). HPV has been detected in EQ, and it has been suggested that coinfection of HPV-8 with oncogenic HPV (e.g., types 16, 39, or 51) lead to EQ (303). Progression of EQ to invasive squamous cell cancer of the penis occurs in 10% to 33% of cases, and if invasion occurs, regional node metastases are found in 20% (179). The differential diagnosis of EQ includes psoriasis, tinea, syphilis, BXO, circinate balanitis, candidiasis, and drug eruption. EQ demonstrates the same histologic changes as Bowen's disease, including acanthosis, loss of epidermal cell polarity, replacement of mature keratinocytes with basaloid cells showing nuclear atypia, and an infiltrate rich in plasma cells (Fig. 43.4).

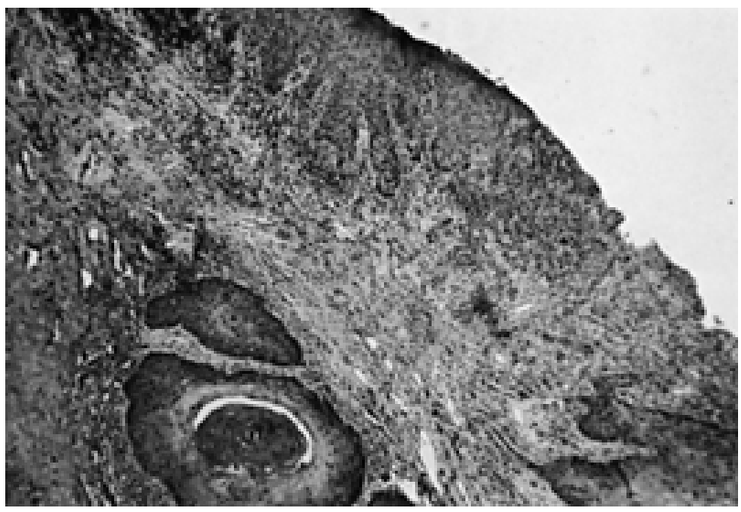

FIGURE 43.4. Erythroplasia of Queyrat. Note the full thickness of squamous epithelium composed of atypical cells with hyperchromatic irregular nuclei and loss of polarity. Marked vascularization and a dense chronic inflammatory infiltrate in the submucosa are apparent. (Hematoxylin-eosin, ×240.)

Topical therapy with twice daily 5% 5-FU cream for 3 to 4 weeks has been reported to be effective, although ulceration or nodularity suggesting invasion is a contraindication to this therapy and posttreatment biopsy is essential. When the lesion is limited to the prepuce, circumcision is recommended. Lesions that fail to respond to topical therapy should undergo either surgical excision or Mohs micrographic surgery (184). Interestingly, whereas Bowen's disease has a complete response rate of 89% to topical 5-aminolevlunic acid and photodynamic therapy, results in

EQ are inconsistent and EQ does not at this time appear to be a legitimate target for photodynamic therapy (277).

Bowen's Disease

Squamous cell CIS of the mucocutaneous epithelium of the glans or prepuce is referred to as *EQ,* whereas CIS of the follicle-bearing skin (i.e., the penile shaft) is referred to as *Bowen's disease of the penis* (Fig. 43.5). Clinically, penile Bowen's disease appears as a solitary plaque, dull-red in color with crusting and oozing. Histologically, Bowen's disease strongly resembles EQ with parakeratosis, acanthosis, lack of maturation of surface epithelium, and replacement of keratinocytes with atypical basaloid cells (145,179). Both Bowen's disease of the penis and EQ are associated with HPV-16, although progression to invasive squamous cell cancer is more common in EQ (10% to 33%) than in Bowen's disease (5%) (179). Several therapies for Bowen's disease have been described, including topical 5-FU, Mohs micrographic surgery, laser treatment, cryotherapy, and aminolevulinic acid with photodynamic therapy. Recurrence is such that excision of the lesion with a 5-mm margin is the most effective means to control the local lesion (284).

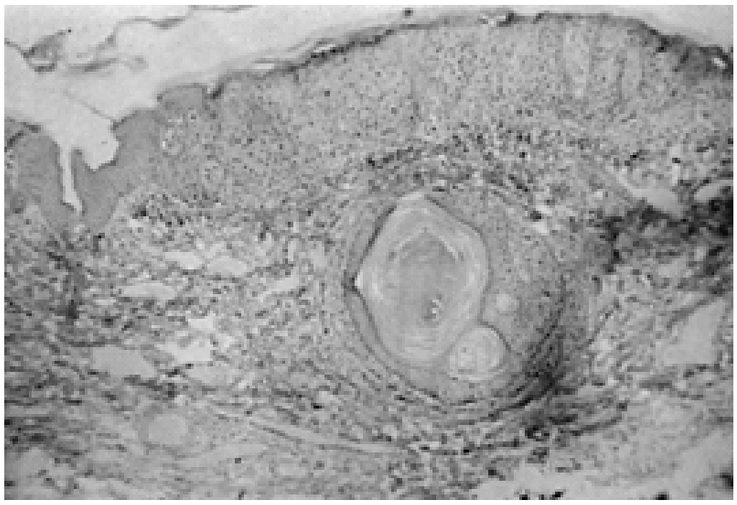

FIGURE 43.5. Bowen's disease. Abnormal epithelium composed of atypical squamous cells, with scattered, bizarre multinucleated cells. Note similar involvement in the wall of the ectopic hair follicle. (Hematoxylin-eosin, ×240.)

Bowenoid Papulosis

Bowenoid papulosis of the penis is a lesion of multiple red-brown or violaceous papules that may coalesce into plaques or into verrucous lesions ranging in diameter from 0.2 to 3.3 cm. These lesions occur primarily on the penile shaft but can also occur on the glans, prepuce, frenulum, or coronal sulcus of young, sexually promiscuous, circumcised males (133,258). Bowenoid papulosis is associated with multiple HPV subtypes, including benign subtypes and the oncogenic HPV subtypes 16, 18, and 33 (118). Histologically, dissociation between benign-appearing architecture and the cytologic features of malignancy, such as keratinocytes with crowded, large, pleomorphic hyperchromatic nuclei with atypical mitoses, is the most characteristic histologic feature of Bowenoid papulosis (214). Although Bowenoid papulosis may persist for years, regress spontaneously, or in immunocompromised or elderly patients progress to become invasive squamous cell carcinoma, recurrence after treatment is common (258). Treatment by surgical excision, CO_2 laser, cryotherapy, electrodesiccation, topical retinoic acid, or 5-FU is appropriate therapy, although periodic reevaluation is necessary because of the tendency to recur and/or progress (179).

Verruciform Tumors of the Penis

The classification of penile lesions has been somewhat controversial, and there exists a subtype of low-grade squamous cell carcinoma appearing grossly as an exophytic papillary lesion that has been classified as a “verruciform tumor of the penis” (44,242,264). The verruciform group of penile tumors includes the benign condyloma acuminatum described previously as well as the malignant verrucous carcinoma or Buschke-Lowenstein tumor, warty condylomatous squamous cell carcinoma of the penis, and papillary squamous cell carcinoma of the penis not otherwise specified (44). The latter two penile lesions are rare and have only recently been described; the reader is referred to Cubilla and associates for further discussion (44).

Although terminologic, pathologic, and clinical ambiguity has existed between the terms *verrucous carcinoma of the penis, Buschke-Lowenstein tumor,* and *giant condylomatosis of the penis,* it is now generally accepted that these are synonymous terms for an exophytic, well-differentiated, locally invasive variant of squamous cell carcinoma of the penis (3,117,257). The lesion typically originates from the glans, prepuce, or uncommonly, the shaft and has a propensity to infiltrate deeply and cause local destruction; however, it rarely exhibits nodal or visceral metastases.

Penile amputation, either total or partial, is currently the recommended treatment for this lesion, although CO_2 laser ablation has been shown effective in some cases (26). Treatment of verrucous carcinoma with chemotherapy (i.e., bleomycin and cisplatin) is generally ineffective, as is radiotherapy, which also may result in transformation of the lesion into a poorly differentiated metastasizing squamous cell cancer (159,300). Recently, the use of subcutaneous interferon-α 2×10^6 IU for varying schedules has shown promising results in patients unwilling to undergo amputation or who experience local recurrence (159).

Squamous Cell Carcinoma of the Penis

In the United States and in industrialized countries, squamous cell cancer of the penis is uncommon, with an

incidence of 1 per 100,000 or less than 1% of all cancers and cancer deaths in men. On a global level, however, this lesion occurs more frequently and is associated with significant morbidity and mortality such that insight into its etiology, diagnosis, treatment, and possible prevention is important.

Incidence and Epidemiology

There is a marked social, economic, and geographic variance in the incidence of penile cancer, and in certain areas of the Indian subcontinent, Africa, and Latin America, this lesion accounts for at least 10% of all male cancers, in contrast to an incidence of 0.4% in the United States (Table 43.2).

	1972[a]	1977[b]	1987[c]
Africa			
Nigeria	0.2	NR	NR
Rhodesia	6.6	NR	NR
Mali	NR	NR	0.6
Gambia	NR	NR	0.9
America			
Brazil			
Recife	6.8	NR	2.2
San Paulo	2.9	2.1	3.4
British Columbia, Canada	0.8	1.1	0.6
Cali, Columbia	2.0	2.0	1.7
Kingston, Jamaica	6.4	5.7	NR
United States	0–1.6	0–2.1	0.1–0.8
Puerto Rico	4.6	4.1	3.0
Mideast			
Israel			
Jews	0.0	0.0	0.1
Non-Jews	0.1	0.4	0.2
Asia			
Bombay, India	1.7	2.0	1.8
Osaka, Japan	0.5	0.3	0.3
Singapore			
Chinese	1.2	1.1	0.6
Malay	0.1	0.7	0.0
Europe			
United Kingdom	0.7–1.9	0.4–1.0	0.3–1.0
Denmark	1.0	1.1	1.0
Finland	0.6	0.5	0.5
Hungary	0.5–1.0	0.4–1.2	0.5
Poland	0.5–1.1	0.7–1.2	0.8–1.0
Spain	1.0	1.1	0.6–1.0
Switzerland	0.5	0.3–0.7	0.4–1.2
Oceania			
Hawaiian	0.0	0.6	0.0
White	0.2	0.7	0.6
Chinese	0.8	0.0	0.0
New Zealand	0.0–0.6	0.5–0.7	0.1–0.5

[a]From Muir CS, Nectoux J. Epidemiology of cancer of the testis and penis. *Monogr Natl Cancer Inst* 1979;53:157.
[b]From Waterhouse J, Shanmugaratnam K, Muir C, et al, eds. Cancer incidence in five continents. *IARC Sci Publ* 1982;4:750.
[c]From Parkin DM, Muir CS, Whelan SL, et al, eds. Cancer incidence in five continents. *IARC Sci Publ* 1992;6:892.
NR, not reported.

TABLE 43.2. AGE-ADJUSTED INCIDENCE RATES (CASES PER 100,000 MEN) OF PENILE CANCER OCCURRING BY CONTINENT FOR REPORTING PERIODS ENDING 1972, 1977, AND 1987

In Europe, the rates are low, but unlike in the United States or Japan, there is an urban preponderance in some areas. The relatively high incidence in India likely relates to the large Hindu population, who do not practice circumcision, and contrasts to the low frequency of this lesion among Muslims, who do so (124). Differences in incidence between various regions in Africa as well as between neighboring tribes has been noted. Among uncircumcised males in Uganda, the incidence of penile carcinoma is such that different tribes living in the same region have a similar incidence of this malignancy, whereas members of the same tribe living in different regions exhibit rates reflecting the area in which they live (254). Similarly, the incidence of penile carcinoma among migrants varies with their site of residence, rather than with their area of origin. The incidence of penile carcinoma among the Chinese of Singapore is lower than that of Chinese in general, but it remains elevated compared with the Japanese (Table 43.2). Interestingly, the incidence of penile carcinoma among Chinese living in the continental United States or Hawaii is lower than that for Chinese living in the Orient, further suggesting the relevance of geographic and environmental factors. The rarity of penile carcinoma in Israel reflects the rarity of this lesion among Jews in general and with the practice of neonatal circumcision. Finally, although penile carcinoma is uncommon in the United States, age-adjusted incidence figures suggest an increased frequency of this lesion in African Americans and Hispanics living in the United States as compared with Caucasians (188,212).

Time Trends and Relative Frequency

In the United States and Western Europe, the incidence of penile cancer has remained stable over the last 25 years, with an annual incidence of about 10 per 1 million (59,83,212). Using the surveillance, epidemiology, and end results (SEER) data, trends could not be detected within individual age groups and the age-adjusted rate for Caucasian males from 1984 to 1986 was 5.89 per million (83). Similarly, the incidence of basal cell carcinoma and of melanoma of the penis was unchanged over the same period (83).

In some regions where a high incidence of penile cancer had previously been noted, a decline is now apparent. In Hong Kong, the incidence fell from 3% during the period of 1930 to 1958 to 1.1% during 1961 to 1964 (22). In the Philippines, the relative frequency of penile cancer fell from 12% to 0.6% between 1925 and 1961, and in Puerto Rico, a 50% decline in the age-adjusted penile cancer incidence occurred between 1950 and 1977 (167,288). This trend

toward a decrease in frequency in previously high-incidence areas may reflect improvement in environmental conditions, hygiene, and possibly an increase in the practice of neonatal circumcision.

Factors Associated with the Risk of Developing Penile Carcinoma

Various factors have been associated with the risk of developing penile carcinoma, including age, circumcision, racial factors, phimosis, smegma, venereal disease, trauma, socioeconomic status, occupation, tobacco use, ultraviolet radiation exposure, multiple sexual partners, and the presence of untreated premalignant lesions (153,188).

Age

Although penile carcinoma is rare in males younger than 25, the age-specific rate of this lesion increases with each decade thereafter (93,192); Table 43.3 shows the increasing incidence of penile cancer in the United States as a function of patient age. In addition, in those areas with a high incidence of penile carcinoma (e.g., Brazil), the age at onset of this lesion is lower and a higher proportion of cases occur in younger patients compared with those areas where the incidence of this lesion is low (e.g., New York State) (Table 43.2).

Age Interval (yr)	Whites	African Americans	Total
15–24	0.02	0.00	0.01
25–34	0.08	0.00	0.07
35–44	0.31	1.77	0.43
45–54	0.72	1.16	0.74
55–64	2.17	3.39	2.24
65–74	4.51	7.33	4.66
≥75	6.23	3.66	6.46

Data from Hall NEL, Schottenfeld D: Penis. In: Schottenfeld D, Fraumens JF Jr, eds. *Cancer epidemiology and prevention.* Philadelphia: WB Saunders, 1982:964, with permission.

TABLE 43.3. AGE-RELATED INCIDENCE RATES (CASES PER 100,000 MEN) OF PENILE CANCER AMONG WHITES AND AFRICAN AMERICANS IN THE UNITED STATES

Circumcision

Squamous cell carcinoma of the penis is rare among populations that circumcise males in infancy, as illustrated by the virtual absence of this lesion in Jews and only a slightly higher incidence in Muslims, who undergo circumcision between the ages of 4 and 9 years (20,153). Further evidence for the preventive role of neonatal circumcision is seen in Uganda, where among tribes practicing circumcision, the rate of penile carcinoma is 0.5 per 100,000 males, compared with tribes not practicing circumcision, in whom the rate is 2.9 per 100,000 males (234). Other factors, however, must also be important among uncircumcised individuals because the incidence of penile cancer in uncircumcised males has been found to vary from 0.8 per 100,000 males in the Kigezi district of Uganda to 8.9 per 100,000 males in the Joru district (254). Similarly, when uncircumcised individuals migrate from an area of low incidence to an area of high incidence of penile cancer, and vice versa, the frequency of penile carcinoma reflects the area of residence rather than the region of origin.

Inadequate or incomplete circumcision or circumcision performed late in childhood, adolescence, or adulthood is much less effective in preventing the development of penile carcinoma than neonatal circumcision. Witness, for example, the equal frequency of this lesion among Mohammedans, who undergo delayed circumcision, with Chinese, who do not undergo circumcision (283). Delayed circumcision offers only slight protection against the development of penile carcinoma, as shown by South African Bantus, who undergo circumcision during or after puberty (101). Similarly, circumcision performed in adults is not protective, and in two large studies, 11% of cases of penile carcinoma occurred among patients circumcised in adulthood (121,164).

The medical consequences of circumcision have been debated, and a mortality of one death in more than 500,000 circumcisions described (29). Even though reports of severe disfigurement as a result of circumcision are extant, neonatal circumcision has a lower mortality and morbidity rate compared with the use of general anesthesia in adult circumcision; reports questioning the advisability of routine neonatal circumcision ignore its proven effectiveness in preventing penile carcinoma.

Racial Factors

Early studies suggesting that penile carcinoma was uncommon in African Americans compared with whites (140) may have reflected bias in reporting as well as in the accessibility to medical services. In contrast, recent comparisons of the incidence between African Americans and whites in various regions of the United States have indicated that the lesion is more common in African Americans (Table 43.3). It is unlikely, however, that racial or genetic factors alone account for differences in incidence, but rather that epigenetic, socioeconomic, or environmental factors determine the increased incidence of penile cancer in African Americans (93,256). In addition, and in contrast to whites, a 17% incidence of subsequent development of a second primary neoplasm (e.g., lung or prostate) was noted in African Americans an average of 7 years after diagnosis of the primary penile lesion, and of these patients, 70% died as a result of their second malignancy (113).

Phimosis

Phimosis is the most common coexisting anatomic abnormality found in patients with penile carcinoma and has been

noted in 52% of patients with this lesion (10,65,250). Phimosis acquired during the growth of penile cancer has been reported in 15% of cases. Although control data are difficult to obtain, congenital phimosis was reported in 2.4% of Belgian army conscripts and in 2.3% of males in a report from the former USSR (261). Thus, although a far greater number of males have phimosis than develop penile carcinoma, phimosis is a risk factor in the development of this lesion. In histologic studies of the phimotic prepuce epithelial atypia, it was noted in 35% compared with 0% of patients without phimosis (240). Moreover, the phimotic preputial cavity provides optimal conditions for the action of carcinogens and for the early and undetected growth of this lesion (261). Smegma and phimosis are each independent risk factors for the development of penile cancer (103,153).

Hygiene and Venereal Disease

A correlation between venereal disease and subsequent development of penile carcinoma has been recognized, and a history of venereal disease has been reported in up to 22% of patients with penile cancer (94). Although a history of gonorrhea or syphilis may be obtained in patients with penile carcinoma, causation is unproven and may reflect the influence of coexisting HPV infection, sexual promiscuity, as well as multiple sexual partners, which correlates with risk of penile cancer (153,217).

Poor hygiene may be associated with, rather than a cause of, penile carcinoma, although Frish and colleagues (76) have concluded that improved personal hygiene accounts for the reduction in penile cancer in uncircumcised males. Among Ugandan tribes whose members do not undergo circumcision, the rate of penile carcinoma is lower among tribes with high, as compared with tribes with low, standards of personal cleanliness (254). Similarly, in Sweden, where circumcision is not routine but where standards of hygiene are high, penile carcinoma is uncommon (65). The importance of personal hygiene is further emphasized by the paradoxically high incidence of penile carcinoma in residents of northern Thailand, a population that bathes frequently (178). This bathing, however, is done in public, with the individual partially clothed and the genitalia therefore inadequately cleansed in the process.

Penile Trauma

Chronic trauma may be a risk factor for cancer of the penis, as evidenced by the high incidence of penile carcinoma among the Zulus, who practice routine circumcision but sustain chronic trauma by wearing protective devices over the glans (153). Interestingly, a history of recurrent small tears and abrasions of the penis has also been reported to be a risk factor in penile cancer (103,153).

Socioeconomic Factors

A direct correlation between the incidence of penile cancer and the patient's socioeconomic level has been noted (7,188). However, in a study from Denmark in which all patients with penile carcinoma from 1942 to 1962 were studied and selection bias was thereby minimized, a relatively even distribution among social class was reported (121). It was concluded that the incidence of penile cancer was relatively uniform among various social classes, and no definitive conclusions regarding socioeconomic class and penile carcinoma is possible at this time (93).

Occupation

Agricultural workers, as compared with men in mercantile or manufacturing occupations, are at increased risk of developing penile carcinoma (121). In a study in which less than 7% of the population was employed in agriculture, 12% of all deaths from penile carcinoma occurred among agricultural workers (93). In industrialized, as contrasted to agrarian, economies, however, farming may be associated with poverty and with a paucity of medical services, so farming itself may not be a risk factor (93).

Other potential occupational factors include asbestos exposure with subsequent development of squamous cell carcinoma of the glans or prepuce, as well as that of a house painter who developed squamous cell cancer of the base of the penis (231).

Other Factors

In a population-based case-control study, it was found that the risk of penile cancer among cigarette smokers was three times that of nonsmokers, and it was speculated that this may relate to the inhibitory effect of cigarette smoking on antigen-presenting dendritic or Langerhans cells (95,153). In patients with psoriasis who were treated with oral methoxsalen and then ultraviolet radiation, an increase in the risk of penile and scrotal cancer was observed (280). Additional investigations suggested that this increase was due to the combination of psoralen and ultraviolet radiation because increased exposure to ultraviolet radiation alone was not associated with an increased incidence of squamous cell cancer of the penis (83).

Squamous Cell Carcinoma of the Uterine Cervix in Sexual Partners of Men with Penile Cancer

There is no convincing evidence that the husbands of women with carcinoma of the uterine cervix are at increased risk of developing penile cancer, but there is evidence that wives of husbands with penile carcinoma are at increased risk of developing cervical carcinoma (215). Wives of men with penile cancer have at least a threefold higher incidence of cervical cancer compared with wives of men without

penile cancer, and circumcision reduces the risk of both cervical cancer and penile cancer (78,158,283). The role of sexually transmissible agents in the etiology of tumors of the male and female genital tract is suggested by finding HPV in a variety of genital tumors, including squamous cell cancer of the penis, cervix, and vulva (12,171). Moreover, with the use of 5% acetic acid to screen for HPV infection in males, it was found that of male sexual partners of women with cervical carcinoma, 33% demonstrated intraepithelial neoplasia and 60% of these lesions contained HPV DNA sequences (12). Finally, epidemiologic studies of carcinoma of the cervix, vagina, and penis are consistent with the hypothesis that tumors at these sites have common or similar etiologies (i.e., sexually transmitted infections) (313).

Etiology

Various factors have been causally associated with the development of penile carcinoma, although only two—smegma and viruses—have received attention as specific etiologic agents (239,261,285).

Smegma

Smegma is thought to represent the debris of desquamated epithelial cells originating from epithelium of the glans or inner surface of the foreskin (261). It has been proposed that *Mycobacterium smegmatis,* present in the preputial sac of 50% of men, causes degradation of smegma into proximate carcinogens, such as hydrocarbons and sterols (211,226). Whether smegma derives solely from desquamating epithelial cells or from the secretions of Tyson's and other preputial glands at the coronal sulcus is unsettled. Some workers find no evidence of coronal glands opening into the preputial sac, whereas others note the presence of such structures (9,240).

Evidence for the carcinogenicity of smegma or its degradation products is persuasive and smegma placed in a buried skin tunnel of mice resulted in a 3% incidence of carcinoma (226). Topical application of carcinogens such as 7,12-dimethyl-benz(a)anthracene to the rabbit penis produced carcinoma only if phimosis (experimentally induced) was present (261). It is proposed that phimosis permits retention of smegma or its derivatives, both of which are carcinogenic, and that prolonged contact results in malignant epithelial transformation.

Viruses

A convincing association between HPV infection and penile carcinoma has been demonstrated (23,56,100,161,168,304). It is suggested that viral or virally induced factors either inactivate tumor-suppressor genes (p53 or Rb) or their products or activate cellular oncogenes such as c-rasHa (291). HPV DNA has been detected in malignant penile tissue in up to 70% of lesions studied and in patients with HPV-positive lesions, 84% to 100% show HPV-16, and 8% to 15% HPV-18 (45,100,292,314).

Approximately 50% of invasive penile cancers show HPV DNA, and 80% of early or *in situ* lesions do so (56,168). Interestingly, the foreskin of 0% to 4% neonates and 6% to 10% of otherwise healthy males also demonstrate HPV DNA (45,243). It has also been found that the lesions of 92% of patients with PIN, EQ, or Bowen's disease were positive for oncogenic HPV DNA and that none of the patients with verrucous carcinoma were positive for oncogenic HPV DNA (45). Finally, when the metastatic lymph nodes from patients whose penile carcinoma contained HPV-16 DNA were studied, it was found that more than 50% also showed HPV-16–positive nodes (259,304). Because the penile cancer tissue of a number of patients did not show HPV DNA, it has been suggested that penile cancer may develop in two distinct settings—HPV positive and HPV negative—and that separate mechanisms of carcinogenesis may be operative (100).

Pathology

Gross Pathology

Squamous cell carcinoma of the penis usually begins as a small nodular, papillary, or ulcerative lesion on the glans or prepuce, and origin from the shaft is rare. Typically, the prepuce is present and often phimotic, either primarily or secondary to tumor growth, thus obscuring the primary lesion until locally advanced. Ulceration eventually occurs in 85% of cases and secondary infection in 90%. This results in a discharge and an inflammatory infiltrate in the deep tissue that may simulate tumor extension. The clinically palpable inguinal lymph nodes often present at the time of initial diagnosis of penile cancer are, in about 50% of cases, due to an inflammatory rather than a metastatic etiology, this inflammation being secondary to coexisting infection of the penile lesion. Although the size of the lesion bears no consistent relationship to prognosis, larger lesions are more often associated with a less favorable outcome and a higher incidence of nodal and visceral metastases than smaller ones (14); however, this is disputed (65).

In gross clinical appearance and pattern of growth, penile cancer has been classified as either exophytic (papillary, polypoid, or fungating) or endophytic (flat, infiltrating, or indurated), both occurring with approximately equal frequency (15,121,164). The rate of tumor growth, the tumor size at diagnosis, and its duration before diagnosis are the same for both patterns, although 5-year survival for patients with papillary lesions is somewhat higher than patients with endophytic lesions (14,165).

Exophytic lesions appear as wartlike excrescences that ulcerate and metastasize relatively late in the course of their growth, whereas endophytic lesions tend to ulcerate and metastasize earlier and to grow laterally and infiltrate deeply.

Histopathology and Grading

Carcinoma of the penis typically arises from the squamous epithelium of the glans or mucosa of the foreskin and only rarely from the penile shaft. Squamous cell or epithelioid cancer is the most common histologic type of penile cancer, although other histologic variants of penile cancer, including basaloid squamous cell carcinoma, adenoid squamous cell carcinoma, spindle cell or sarcomatoid carcinoma, and squamous cell carcinoma with glandular component (either mucoepidermoid or adenosquamous carcinoma), have been described (298). Because of the rarity of these latter lesions and the paucity of clinical information concerning them, they are not discussed here (44,85,120,140).

Squamous cell cancer of the penis is typically composed of well- to moderately well-differentiated hyperchromatic cells that vary in cellular and nuclear size and shape with a loss of normal basal to superficial maturation and polarity (187). Figure 43.6 and Figure 43.7 show neoplastic cells invading the basement membrane and adjacent stroma with formation of keratinizing whorls and pearl formation. Lateral to the malignancy, the nonneoplastic epithelium becomes thickened, and deep to the lesion, the stroma shows capillary engorgement and an infiltrate of lymphocytes, mast cells, and polymorphonuclear leukocytes. Surface ulceration and secondary infection of the lesion increase the local inflammatory response, and despite the vascular nature of the penis, penile cancer is primarily a locoregional disease that metastasizes first to regional lymph nodes, with early hematogenous dissemination being distinctly uncommon.

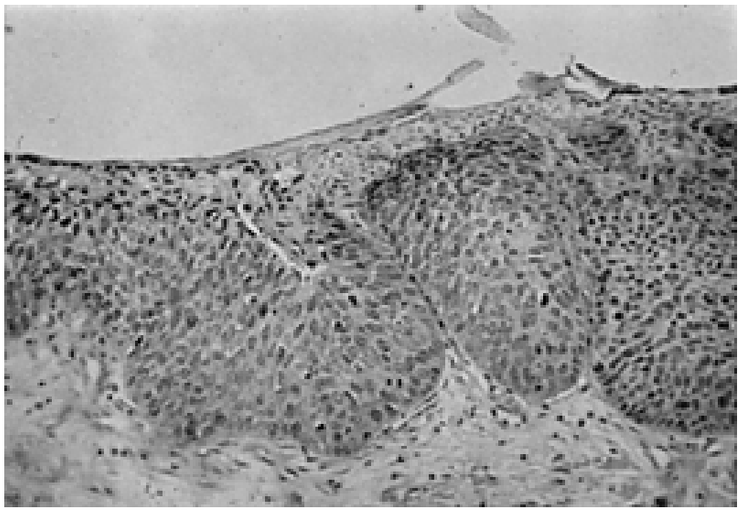

FIGURE 43.6. Penile carcinoma. Panoramic view of moderately differentiated squamous cell cancer of the penis involving the surface, with adjacent infiltration. (Hematoxylin-eosin, ×80.)

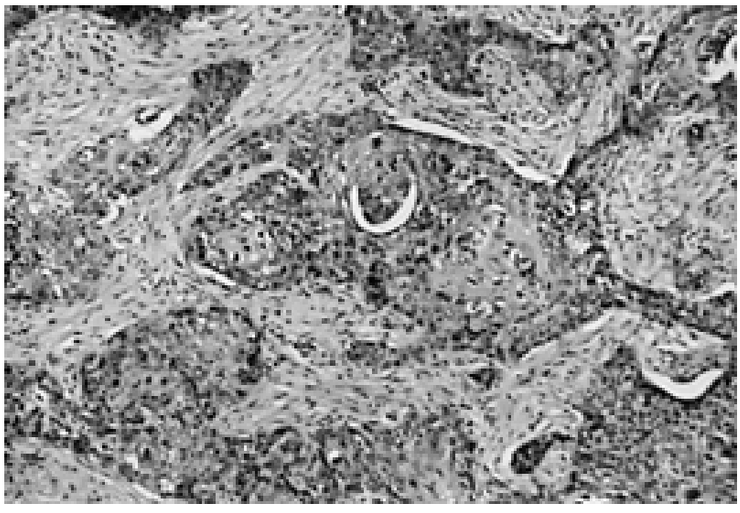

FIGURE 43.7. Penile carcinoma. General view of infiltrating component of penile squamous cell carcinoma involving the corpora cavernosa. (Hematoxylin-eosin, ×80.)

In addition to a classification of penile cancer based on gross clinical appearance as described earlier, classifications of penile cancer, based on various histologic criteria, are far more valuable (43,75,165). Frew and associates (75), as well as other investigators (66,250), have described a solid and a cord pattern with the 5-year survival rate of patients with the solid pattern (96%) being superior to that of patients whose tumor exhibits the cord pattern (76%). The solid pattern, which is believed to be less aggressive than the cord pattern, consists of large, rounded clumps and sheets of cells with cellular masses that tend to be smooth and rounded, each of which may show invasion. The cord pattern consists of a smaller cell mass irregular in outline, with small clumps and cords of cells invading underlying tissue in advance of the bulk of the tumor.

Marcial and co-workers (165), on the other hand, have identified five histologic patterns of growth, including intraepithelial, leukoplakia, verrucous, compact, and plexiform, with the plexiform type showing the highest degree of cellular anaplasia and the intraepithelial and leukoplakic varieties showing the least degree of anaplasia. The intraepithelial and leukoplakia patterns have the most favorable 5-year survival (67% and 72%, respectively), whereas the compact and plexiform patterns have the poorest (36% and 17%, respectively) (43,65).

Cubilla and associates (43) defined four distinct microscopic patterns of growth: superficially spreading epidermoid carcinoma (SS); vertical growth carcinoma (VG); verruciform (V), which includes Buschke-Lowenstein tumors and papillary carcinoma; and multicentric carcinoma (MC). The SS pattern was most commonly seen (42%) and, compared with VG, the second most common pattern (32%), had a lower histologic grade, incidence of perineural invasion, and frequency of inguinal node metastases. However, if patients with the SS pattern were treated by circumcision for preputial lesions or by limited resection for

glanular lesions, there was a marked tendency for recurrence. The V pattern occurred only in 18% of cases, was of low histologic grade, and rarely showed vascular invasion; in addition, although corporal invasion occurred in two-thirds of cases, nodal metastases were not reported. Only 8% of the lesions were of the MC type, and because this pattern appeared similar in clinical behavior to the SS type, it was suggested that similar therapeutic recommendations for the two types were appropriate (43).

In contrast to classifications of penile cancer based on histopathologic patterns, the microscopic grading of penile cancer offers another important variable for tumor characterization (15). The classic grading criteria of Broders are based on cell and nuclear morphology, which differs from that of Maiche and associates (160), who proposed a new grading system based on four microscopic parameters, including the degree of keratinization, the number of mitotic cells, the extent of cellular and nuclear atypia, and the presence or absence of lymphocytes. Maiche and associates (160) concluded that this system correlated well with stage at diagnosis and with 5- and 10-year survival rates. Using various grading criteria, studies have shown a correlation between tumor grade and nodal status, with up to 15% of patients with low-grade tumors having nodal metastases and 40% of those with moderate- to high-grade lesions exhibiting nodal dissemination (14,65,131,250,294).

Survival correlates with tumor grade are summarized in Table 43.4 . Low-grade tumors have better 5- and 10-year prognoses than moderate- to high-grade lesions (10,94,250,294), and two or three times as many patients with moderately to poorly differentiated or high-grade lesions die of their tumors, compared with patients with well-differentiated or low-grade lesions (75,121). Using Maiche and associates' grading system (160), the 5- and 10-year survival for patients with grade I tumors is 85%, whereas for grade III lesions, it is 55% and for grade IV lesions, 30%.

TABLE 43.4. RELATION BETWEEN TUMOR GRADE AND SURVIVAL IN PATIENTS WITH PENILE CARCINOMA

	Grade			
	Low		Moderate-high	
	No. of Cases	%	No. of Cases	%
5-yr survival	185/285	65	74/180	41
10-yr survival	43/91	47	27/76	35

Data from Baker BH, Spratt JS Jr, Perez-Mesa C, et al. Carcinoma of the penis. *J Urol* 1976;116:458; Gursel EO, Georgountzos C, Uson AC, et al. Penile cancer: clinicopathologic study of 64 cases. *Urology* 1973;1:569; Hardner GJ, Bhanalaph T, Murphy GP, et al. Carcinoma of the penis: analysis of therapy in 100 consecutive cases. *J Urol* 1972;108:428; Marcial VA, Figueroa-Colon J, Marcial-Rojos RA, et al. Carcinoma of the penis. *Radiology* 1962;79:209; Salavierra JC, Hope-Stone HF, Paris AMI, et al. Conservative treatment of carcinoma of the penis. *Br J Urol* 1979;51:32.

Biochemical, serologic, chromosomal, and molecular studies of penile cancer are limited. However, elevation of the squamous cell carcinoma tumor-associated antigen TA-4 was found in the serum of 45% of patients with metastatic penile cancer, and TA-4 levels correlated with disease progression (307). The loss of chromosomes 13, 17 (site of the p53 gene), and 22, as well as structural chromosomal abnormalities, have also been reported in penile cancer (207,308). The p53 and p21 genes and/or their gene products are important factors in malignant transformation and in tumor progression, and deletion or mutation of these genes is found in many human tumors, including penile cancer (66,140). In 35 patients with squamous cell carcinoma of the penis, p53 was expressed in 89% of cancers and p21 in 39%; p21 expression was found to be either dependent or independent of p53 expression (140). However, all HPV-positive cases showed p53 expression, and expressions of p21, the proximate effector of p53, was found only in cases positive for HPV. Finally, and congruent with Higgins and co-workers (100), it has been proposed that penile carcinomas may result either from progression of lesions caused by oncogenic types of HPV (i.e., HPV-16) or through alterations of p53 unrelated to HPV infection.

Local Tumor Growth and Dissemination

As the tumor grows locally, progressive destruction of the prepuce, glans, and penile shaft occurs. Buck's fascia serves initially as a barrier to invasion, and the cancer is relatively slow to penetrate the corporal fascia (33). With invasion of the erectile tissue, the incidence of tumor dissemination increases, although despite the extensive venous sinusoids of the corpora, early dissemination is primarily lymphatic (121) and knowledge of the penile lymphatics is therefore relevant (Fig. 43.8).

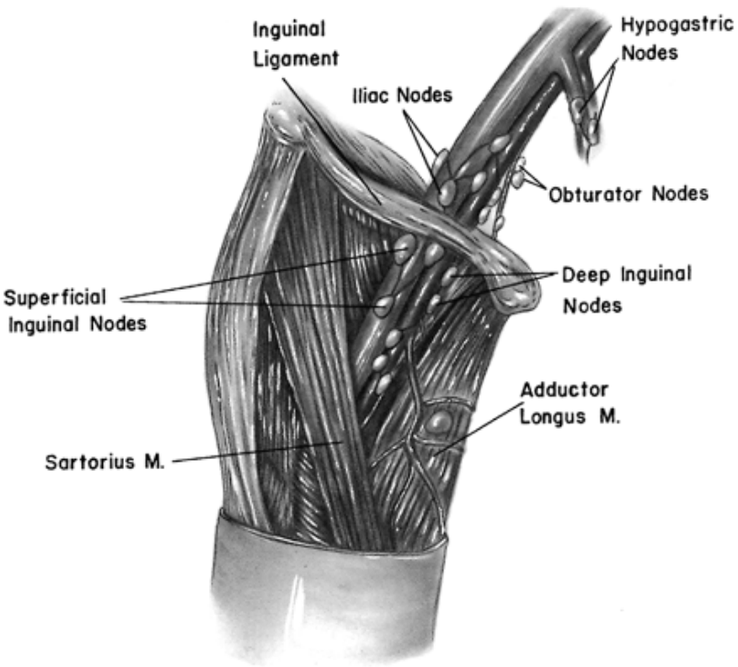

FIGURE 43.8. Unilateral view of relevant pelvic and inguinal lymph nodes. The regional lymph nodes of the penis are the superficial and deep inguinal nodes, the external iliac, hypogastric, and obturator lymph nodes. Although a unilateral view is shown for clarity, the lymphatic drainage of the penis is bilateral.

Lymphatic Anatomy

The regional lymph nodes of the penis, as defined by the American Joint Committee on Cancer (AJCC), are the superficial inguinal, the deep inguinal, the external and internal iliac, and the pelvic (including the obturator) lymph nodes (69,272). The efferent lymphatics of the superficial inguinal lymph nodes drain into the deep inguinal nodes located below the fascia lata, which then drain into the external iliac hypogastric or obturator nodes. For purposes of summarizing penile lymphatic drainage, three regions of the penis can be defined: (a) the prepuce, skin of the penile shaft, and subcutaneous tissue; (b) the glans, urethra, and corpus spongiosum; and (c) the corpora cavernosa.

The lymphatics of the prepuce drain toward the dorsum of the penis, merging with those of the skin of the penile shaft and with those of the subcutaneous tissue, forming lymph channels that drain into the superficial inguinal nodes (13,27,58).

The lymphatics of the glans converge toward the frenulum and join with the lymphatics of the urethra and corpus spongiosum. This combined system forms a collar of interconnecting channels at the base of the penis, which drain either into the deep inguinal nodes or through lymphatics traversing the inguinal canal directly into the external and internal iliac nodes. Indeed, this potential direct drainage into the deep pelvic lymph nodes explains why tumors of the glans or those invading the urethra or corpus spongiosum may exhibit pelvic metastases in the absence of inguinal lymph node involvement (237). The lymphatics of the corpora cavernosa drain into the superficial and deep inguinal lymph nodes, which drain into the iliac and pelvic nodes. Because the penile lymphatics anastomose freely and cross the midline along the shaft and at the base of the penis and because of the free communication between the right and left inguinal nodes via subcutaneous lymphatics, bilateral, and not unilateral, metastases may be expected. Therefore, when lymphadenectomy is indicated, bilateral, and not unilateral, resection should be performed (27).

Hematogenous dissemination with osseous, hepatic, or pulmonary metastases is uncommon, having been noted at initial diagnosis in only 1.2% of cases (121). Even in locally advanced lesions, lymphatics remain the principal mode of metastasis (13,27). Hematogenous spread occurs when tumor emboli reach (a) the pelvic veins and the inferior vena cava or (b) the dorsal vein of the penis, the prostatic plexus of veins, and then pass through the vessels of the lateral pelvic wall into the inferior vena cava (27,187). However, hematogenesis metastases also occur through extracaval routes, that is, through the lateral sacral veins, Batson's paravertebral plexus, and then into the systemic venous system (187). Finally, in locally advanced cases, direct extension of the tumor into the pubic bone, abdominal wall, or scrotum may occur and necessitate extensive resection to achieve at least local control.

Distribution and Significance of Nodal Metastases

At initial presentation, approximately 60% of patients will have palpable inguinal adenopathy, although in only 45% of cases of palpable adenopathy will metastases be found (33,53,66,75,94,250,311). In contrast, of those patients

whose inguinal lymph nodes are clinically impalpable at diagnosis, 18% (reported range of 8% to 39%) will have unsuspected, usually unilateral, occult metastatic disease (11,14,33,206,235). Moreover, this incidence of occult disease correlates with the observation that approximately 14% of patients who have impalpable inguinal nodes at initial presentation subsequently manifest nodal metastases, and 95% of these patients do so within 18 months. Although a clinically negative lymph node examination has a negative predictive value of 82%, 83% to 94% of patients whose nodes are clinically negative on the initial examination and who subsequently develop palpable adenopathy will be found to have nodal metastases (14,66,123,206,236). Therefore, at the time of initial presentation, about 44% of all patients with penile cancer have nodal metastases, which in 26% of all cases are macroscopic and in 18% of all cases are microscopic (33,66,75,94,108,119,123,237).

Among patients with inguinal node metastases, lymphadenectomy may be curative, although the presence of pelvic lymph node metastases is associated with a 5-year survival rate of less than 5% (236,275). Importantly, the incidence of pelvic node metastases correlates with inguinal node status, because pelvic node metastases in the absence of inguinal node metastases are rare. However, pelvic node metastases occur in 23% of patients with up to three positive inguinal nodes and in 56% of patients with more than three positive inguinal nodes (205,206,236,275).

Factors predictive of regional lymph node metastases in patients with penile cancer include invasion of the corpora, tumor grade, and the response of initially palpable inguinal nodes to definitive treatment of the primary lesion and to a 6- to 8-week course of antibiotics (106,206). The degree to which the primary penile lesion invades the corpora correlates with nodal status and is reflected by the fact that inguinal node metastases have been reported in only 13% of Jackson stage I lesions but in 48% to 66% of stage II lesions (94,173). Using tumor, node, metastasis (TNM) staging, inguinal node metastases were observed in 4% to 18% of stage T_1 lesions, in 47% to 64% of T_2 lesions, and in 71% of T_3 lesions (108,206,273). In contrast, the studies of Lopes and associates (147) and of Ravi (237) have failed to demonstrate that the extent of corporal and/or adjacent structure invasion (stages T_2 to T_4) is predictive of nodal metastases.

Tumor grade has also been correlated with nodal metastases, with 19% to 29% of grade I, 46% to 65% of grade II, and 82% to 86% of grade III lesions being associated with positive lymph nodes (62,106,273). In contrast, Lopes and co-workers (148) have reported that on multivariate analysis, only the presence of lymphatic or venous tumor emboli correlated with nodal metastases.

It has also been observed that if inguinal nodes remain palpable 6 to 8 weeks after definitive treatment of the primary lesion and a course of antibiotics, about 90% of such nodes will harbor malignancy. It has also been noted that if initially impalpable inguinal lymph nodes subsequently become palpable, there is a 94% likelihood that such nodes will contain metastases (207,237,275,294).

Paradoxically, the duration of symptoms before diagnosis (i.e., the delay in diagnosis) does not correlate with the incidence of nodal metastases (14,65,148). Moreover, with the exception of lesions confined to the prepuce, which show nodal metastases in less than 10% of cases, the site of origin of the primary lesion, its clinical T stage, size at diagnosis, and the presence or absence of corporal invasion, bear no consistent relationship to the presence or absence of nodal metastases (65,66).

Cause of Death

In patients diagnosed with penile carcinoma, approximately 50% to 60% will die of unrelated malignant or nonmalignant causes, emphasizing the competing mortalities that coexist in patients with this lesion (14,131,194,274). Overall, the 5- and 10-year disease-specific survival rates are 72% and 66%, respectively, and corresponding disease-free survival rates of 56% and 42%, respectively, have been reported (105,274). Of those patients in whom penile carcinoma is the proximate cause of death, mortality results from either regional recurrence with hemorrhage secondary to erosion of large vessels, sepsis secondary to infection of necrotic and/or malignant lymph nodes, the cachexia and inanition of malignancy, or local recurrence with invasion of the pubis, scrotum, and abdominal wall (148,274). Distant metastases may ultimately occur in up to 10% of patients and, when present, may be the immediate cause of death. Metastases are usually pulmonary, although osseous and hepatic lesions also occur.

Signs and Symptoms

The average age at diagnosis is 60.1 years (range of 15 to 92 years). Presenting symptoms consist of a penile mass, lump, or nodule in 47% of patients; a penile ulcer or sore in 35%; and an inflammatory lesion or bleeding from the external surface of the penis in 17%. It is of interest that in 0.7% of cases, carcinoma has been found incidentally during the course of an adult circumcision. Squamous cell carcinoma of the penis originates on the glans in 48% of cases, on the prepuce in 21%, in both loci in 9%, and in the coronal sulcus in 6% of cases. Although the penile shaft is a distinctly uncommon site of origin of squamous cell carcinoma of the penis and occurs in less than 2% of cases, involvement of the shaft by direct extension of tumors originating on the glans or prepuce occurs in 14% and tumors restricted to the prepuce or coronal sulcus only rarely are associated with nodal metastases. At diagnosis, approximately 60% of lesions are larger than 2.0 cm in maximum diameter, and penile carcinoma is noteworthy for the delay by patients in seeing a physician. The average interval between the initial perception of a penile lesion by the patient and his presentation to a physician is 10 months,

with a range of 3 to 26 months. The biologic significance of this delay, however, is uncertain (147), and a large series reported a 46% rate of nodal metastases among patients with symptoms of less than 6 months' duration at the time of diagnosis and a 50% rate of nodal metastases among patients with symptoms of more than 6 months' duration at the time of diagnosis.

Diagnosis of the Primary Lesion

There are no unique physical characteristics diagnostic of penile cancer. Biopsies should be performed on suspicious lesions, and the use of salves, creams, ointments, or fulguration should be deferred until a definitive diagnosis has been established. Reports have noted physician delay in diagnosing this lesion, and a critical factor in its early diagnosis is an early index of suspicion “not only in patients with nodules, papillomas, or ulcerations but also in those with lesions which might be described as unusual or inflammatory” (27). Other penile lesions may resemble penile carcinoma, and the differential diagnosis includes EQ, BXO, tuberculosis, herpes progenitalis, gummatous ulceration, granuloma inguinale, and condyloma. Adequate biopsy and histologic study remain the diagnostic standard, although fine-needle aspiration cytology, if positive, is also effective (13,27,30,270).

If the prepuce can be retracted, a sore, pimple, or wart may be noted early in the disease, but in men with a new onset of phimosis, penile cancer should be excluded as a cause. With progression of the untreated lesion, ulceration, erosion, infection, fistula formation, hemorrhage, and urethral obstruction may occur. Because penile carcinoma may appear as or coexist with benign penile lesions, the need for a high level of suspicion in seemingly benign lesions is warranted and generous indications for prompt biopsy must be emphasized.

If phimosis precludes adequate visualization and biopsy, one or more longitudinal preputial slits can be made, with care taken to avoid the suspected lesion, thereby exposing the growth without risking dissemination. Biopsy is the definitive technique for diagnosing the type and extent of penile lesions, even though other techniques have been described (54). Corpus cavernosography is useful in detecting extension into the corpora, but noninvasive techniques, including computed tomography (CT) scan, ultrasound, or magnetic resonance imaging (MRI) of the penis, provide accurate assessment of local tumor extent (54,109,125,289). Moreover, in low-grade, clinically low-stage lesions for which nonsurgical therapy is contemplated, these techniques allow further precision in initial staging and posttreatment follow-up.

Staging of Penile Cancer

As summarized in Table 43.5, various systems for staging penile cancer have been used. At present, the TNM system of the International Union Against Cancer (UICC) and the identical classification of the AJCC, both in their most recent 1997 iterations, are in widest use (69,96,272). Each system recognizes clinical as well as histopathologic assessment, and the inaccuracies inherent in clinical staging attests to the importance of histologic confirmation. When clinical T stage (cT) is compared with pathologic T stage (pT), 74% of patients were staged correctly and 26% incorrectly (106,294). Of those staged incorrectly, 60% were overstaged and 40% understaged. Of all patients staged clinically, 16% were overstaged and 10% understaged (106). Among patients who clinically were believed to be free of inguinal node metastases (cN0), 30% to 40% were found to have metastases (pN+) and 20% to 30% of patients thought to harbor nodal metastases (cN+) were on pathologic study found to be free of metastases (pN_0) (98,106,294).

	AJCC/UICC 1997	Jackson 1966
Primary Tumor (T)		
Primary tumor cannot be assessed	T_X	
No evidence of primary tumor	T_0	
Carcinoma *in situ*	T_{is}	
Noninvasive verrucous carcinoma	T_a	
Tumor invades subepithelial connective tissue	T_1	I[a]
Tumor invades corpus spongiosum or cavernosum	T_2	II
Tumor invades urethra or prostate	T_3	
Tumor invades other adjacent structures	T_4	IV
Regional Lymph Nodes (N)		
Regional lymph nodes cannot be assessed	N_X	
No regional lymph node metastasis	N_0	
Metastasis in a single superficial, inguinal lymph node	N_1	III
Metastasis in multiple or bilateral superficial inguinal lymph nodes	N_2	
Metastasis in deep inguinal or pelvic lymph node(s) unilateral or bilateral	N_3	
Distant Metastasis (M)		
Distant metastasis cannot be assessed	M_X	
No distant metastasis	M_0	
Distant metastasis	M_1	IV

[a]Limited to glans or prepuce.

TABLE 43.5. COMMONLY USED SYSTEMS FOR STAGING PENILE CANCER

Historically, at the time of clinical diagnosis and using the staging system of Jackson (119), 56% of patients present with stage I disease, 14% with stage II disease, 27% with stage III disease, and 3% with stage IV disease (14,53,66,94,194). The pathologically confirmed stage at diagnosis in patients with penile cancer using Jackson's staging is as follows: stage I, 58%; stage II, 13%; stage III,

25%; and stage IV, 4% (53,66,119,131,250). The congruence between clinical and pathologic staging at diagnosis in the aggregate, despite the discordance between clinical and pathologic staging that occurs in individual patients, may relate to a 22% rate of clinical overstaging and a 14.6% rate of clinical understaging, with errors balancing in some of these studies. In addition, not all reports provide simultaneous clinical and pathologic staging; hence, reports from which clinical data were derived are not necessarily the same as those from which pathologic reports were obtained.

Based on the TNM system, 19% of all patients at diagnosis present with clinical stage T_1, that is, cT_1 disease (range of 15% to 53%), 49% with cT_2 (range of 32% to 56%), 29% with cT_3 (range of 13% to 43%), and 3% with cT_4 disease (range of 2% to 4%) (106,157,206,237). Comparison between clinical T stage (cT) and clinical node stage (cN) demonstrates that between 18% and 25% of cT_1 lesions are cN+, 47% to 56% of cT_2 lesions are cN+, and 69% to 71% of cT_3 lesions are cN+ (157,206). Finally, when the TNM system is applied to histopathologic findings, pT_{is} is found in 1%, pT_1 in 34%, pT_2 in 54%, and pT_3 in 11% (106).

Evaluation of Regional Lymph Nodes

Regional lymph node status is an important prognostic marker in penile cancer (236), and inguinal lymphadenectomy in patients with nodal metastases is of proven therapeutic value (174). However, diagnostic and/or prophylactic lymphadenectomy for patients with clinically negative lymph nodes remains controversial because this would expose a substantial number of patients who do not harbor metastases to the morbidity of inguinal lymphadenectomy. In addition, the reliability of the modified inguinal lymphadenectomy has been questioned (40,110,147,260). To limit morbidity, a variety of noninvasive or minimally invasive techniques have been used to evaluate the inguinal nodes, including lymphangiography, CT, MRI, percutaneous aspiration, fine-needle biopsy, modified superficial inguinal lymphadenectomy, and sentinel-node biopsy with or without lymphoscintigraphy and immunohistochemistry (34,40,110,151,289). In contrast to the inguinal nodes, pelvic node evaluation has, in addition to several of the aforementioned techniques, included laparoscopic node dissection and “open” pelvic lymphadenectomy (8). Attempts to identify noninvasive, yet accurate, predictors of regional node metastases have been unsuccessful, although patients with palpable inguinal nodes at diagnosis that persist after treatment of the primary lesion and a 6- to 8-week course of antibiotics are likely to harbor nodal metastases. In addition, inguinal nodes greater than 2 cm in diameter or inguinal node fixation is predictive of pelvic node metastases. Assessment of nodal status by CT or MRI is based primarily on nodal size, and neither technique is capable of defining internal nodal architecture (289). Because inflammatory and other nonmalignant processes may produce nodal enlargement, these techniques are insufficiently reliable for diagnosis. Despite this, CT and MRI are useful in the staging and follow-up of patients with penile cancer, particularly if observation, rather than lymphadenectomy, is elected.

In an effort to minimize the morbidity of inguinal lymphadenectomy while maximizing information on nodal status, the sentinel-node biopsy technique of Cabanas (34), and more recently, combined lymphoscintigraphic and immunohistochemical techniques (110), have been introduced. Based on penile lymphangiographic studies, a nodal basin including the so-called sentinel lymph node of the penis was identified (33). According to Cabanas, the sentinel lymph node of the penis is located at the anteromedial aspect of the superficial epigastric vein, medial and superior to the epigastric vein, medial and superior to the epigastric–saphenous junction (33). The sentinel node is believed to be the initial nodal site for metastases, and this concept has subsequently been extended to breast, vulvar, and colorectal cancer and to melanoma (186). In penile cancer, Cabanas (34) reported the absence of subsequent inguinal node metastases and a 5-year disease-free survival of 90% among sentinel node–negative patients. Others (71,72) concluded that despite a false-negative rate of up to 20%, sentinel-node biopsy identifies patients who will benefit from regional lymphadenectomy. Patients who still have palpable inguinal nodes (cN_{1-2}) after ablation of the primary lesion and a course of antibiotics and who then undergo sentinel-node biopsy have a twofold increase in the yield of positive nodes as compared with patients with clinically negative nodes (cN_0) (15.7% versus 7.5%) (71).

Subsequent studies demonstrated the development of deep inguinal and iliac node metastases following a negative inguinal node biopsy, with a false-negative rate of up to 22% illustrating the limitations of Cabanas' technique (301). Furthermore, among patients in whom bilateral inguinal node biopsy was carried out using a somewhat more extensive technique than that of Cabanas (average number of nodes removed, 6.8), it was found that in 20% of those patients in whom the sentinel node was negative for cancer, metastases to other inguinal nodes occurred (39,41,237). The limits of a negative inguinal node biopsy are that 12% of patients died of inguinal metastases despite a negative biopsy and that the 5-year disease-free survival for inguinal-node biopsy–negative patients was only 83% (218,236).

To improve the reliability of sentinel-node biopsy, a new technique that combines technetium-99m lymphoscintigraphy, and patent blue V dye for more precise node localization with immunohistochemistry for enhanced pathologic evaluation has been introduced (132). Although reports using this technique in penile cancer are limited, extensive studies in other cancers, including melanoma, breast, colorectal, and vulvar carcinoma, indicate that this

is a very valuable technique that may eliminate unnecessary lymphadenectomy (51,110,186).

Similar results regarding the accuracy of even more extensive dissection of the sentinel node have been reported (218). Gallium-67 citrate scanning for detection of nodal metastases has been reported, but in view of the propensity of gallium to localize in neoplastic as well as in inflammatory nodes, gallium's specificity (and thus usefulness) is limited.

To enhance the accuracy of sentinel-node biopsy, preoperative lymphoscintigraphy using technetium-99m–labeled nanocolloid is injected 24 hours before biopsy and patent blue V dye is injected immediately before biopsy and followed by immunohistochemical staining of the resected node(s) (132). Use of a gamma probe facilitates localization of the sentinel node, the patent blue V dye facilitates dissection of the sentinel node (132), and immunohistochemistry enhances the accuracy of pathologic evaluation (110). Although studies of lymphoscintigraphic localization of sentinel nodes in penile cancer are limited (110,279), studies of other cancers suggest that this is a valuable technique that may preclude unnecessary lymphadenectomy with its attendant morbidity (51,186).

Treatment and Survival

The therapy of penile carcinoma involves several considerations, including treatment of the primary penile lesion, evaluation and treatment (if indicated) of the regional lymph nodes, and treatment of systemic metastases (if present).

Treatment of the Primary Lesion

The 3- and 5-year survival rates of patients in whom penile cancer remains untreated are 6.3%and 2.6%, respectively (14,15,94). Although many of these patients had clinically advanced disease when initially diagnosed, these figures provide some insight into the natural history of penile cancer. In contrast, the overall 5-year survival of patients treated for penile carcinoma irrespective of tumor stage, grade, or type of therapy used is summarized in Table 43.6 . When the overall 5-year survival and the survival of patients either with or without nodal metastases in studies reported before 1984 are compared with survival rates in recent studies, improved results are noted. These statistics may reflect earlier diagnosis; improved staging; refinements in surgical technique; the availability of broad-spectrum antibiotics; and better preoperative, perioperative, and postoperative care. Moreover, the wide range of survival figures reflects factors associated with studies performed at disparate locations and time periods, inconsistent reporting practices and patient selection, and competing therapies.

	No. of Patients	Crude 5-year Survival: All Patients		Inguinal Lymph Node Status			
				Metastases Absent		Metastases Present	
		Mean (%)	Range (%)	Mean (%)	Range (%)	Mean (%)	Range (%)
Pre-1984[a]	4,240	52	21–80	66	50–90	27	10–65
Post-1984[b]	1,128	71	62–85	85	74–100	50	15–77

[a]Data from references 6, 10, 15, 33, 66, 67, 94, 114, 119, 121–123, 131, 136, 138, 142, 165, 190, 194, 198, 267, 297, and 311.
[b]Data from references 24, 55, 71, 74, 108, 130, 157, 173, 176, 183, 196, 206, 224, 237, and 275.

TABLE 43.6. FIVE-YEAR SURVIVAL OF PATIENTS WITH CARCINOMA OF THE PENIS: COMPARISON OF RESULTS OF STUDIES PUBLISHED BEFORE 1984 WITH RESULTS OF STUDIES PUBLISHED AFTER 1984

When patients are stratified according to the status of their regional lymph nodes, the negative impact of nodal metastases on survival is apparent. Indeed, regional nodal metastases result in a survival rate approximately half that observed among patients free of such metastases (Table 43.6). The survival of patients with penile carcinoma in relation to tumor stage and to the results of surgical therapy (e.g., partial or total penile amputation) versus radiotherapy in the treatment of the primary lesion is presented in Table 43.7 .

	Tumor Stage							
	I		II		III		IV	
	Mean (%)	Range (%)	Mean (%)	Range (%)	Mean (%)	Range (%)	Mean (%)	Range (%)
Surgical amputation (partial or total)	65	54–77	42	39–57	27	13–50	0	0
Radiotherapy (brachytherapy or teletherapy)	68	46–88	51	45–62	21	15–41	5	0–7

Data from references 49, 53, 66, 67, 108, 119, 121, 131, 170, 176, 190, 196, 198, 238, and 250.

TABLE 43.7. FIVE-YEAR SURVIVAL RATES BY TUMOR STAGE IN PATIENTS WITH CARCINOMA OF THE PENIS TREATED BY EITHER RADIOTHERAPY OR SURGICAL AMPUTATION OF THE PRIMARY PENILE LESION

Surgery

The goal of treatment of the penile lesion is to eradicate the tumor, prevent local recurrence, and insofar as possible, preserve urinary and sexual function. A variety of therapies to achieve these goals have been used and are listed in Table 43.8 . Surgical options include circumcision, local excision of the lesion, and partial or total amputation. The location and extent of the penile lesion determines which option is most appropriate, and for small, well-localized tumors restricted to the prepuce, circumcision is a legitimate option, although failure (i.e., penile recurrence) has been noted in up to 30% of cases (14,15,65,194,232,305). Of patients with preputial lesions, 70% are cured of their primary tumor, although 20% eventually develop regional lymph node metastases

(Table 43.9) (14,53,194,232,267). Local excision of glanular lesions should be restricted to selected patients, and in these individuals, a 5-year survival rate of 82% has been noted, although 31% of patients treated by local excision experience recurrence requiring subsequent partial amputation (65,121).

Surgery	Chemotherapy
Circumcision	Topical
Excision	Systemic
Partial penectomy	Chemosurgery
Total penectomy	Cryosurgery
Radiotherapy	Laser
External beam	Neodymium:yttrium-aluminum-garnet
Interstitial	
Mold	

TABLE 43.8. THERAPEUTIC OPTIONS IN TREATMENT OF PRIMARY PENILE LESION IN PATIENTS WITH CARCINOMA OF THE PENIS

Therapy	Number of Patients	Crude 5-Year Survival (%)		Initial Complete Response of Lesion (%)		Synchronous (Partial Response) (%)		Metachronous (%)		Total (%)		Subsequent Development of Inguinal Node Metastases (%)	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Surgery													
Circumcision	58	60	29–99	69	50–100	ND		30		30		20	
Excision	106	82	60–85	56	23–72	ND		31	26–40	31		40	
Amputation (partial or total)	2,021	52	41–64	90	50–99	3		8	4–12	11		14	8–42
Radiotherapy													
Teletherapy	622	58	40–80	56	32–85	39	19–51	21	18–24	44	31–62	16	6–20
Brachytherapy (interstitial or mold)	262	71	58–92	70	50–86	20	15–25	18	4–30	26	17–45	6	0–16

ND, no data.
Data from references 6, 14, 15, 27, 32, 47, 49, 53, 55, 65–67, 71, 75, 94, 99, 107, 114, 119, 121, 131, 136, 170, 176, 194, 196, 198, 208, 221, 232, 238, 248, 250, 267, 297, and 311.

TABLE 43.9. RESULTS OF VARIOUS THERAPIES FOR THE PRIMARY PENILE LESION IN PATIENTS WITH PENILE CARCINOMA

Partial or total amputation of the penis remains the most widely used surgical treatment of primary penile carcinoma (99,121,131,137,143). Traditionally, partial amputation is recommended to patients whose lesion involves the glans or distal shaft and when resection of tumor with a 2-cm tumor-free margin proximal to the malignancy can be achieved (172). Recently, however, a histologically tumor-free margin of 1.0 to 1.5 cm has been reported as being sufficient for local cure (102). If the tumor invades the proximal shaft or base of the penis or if the extent of the disease prevents performance of a partial amputation, then total penectomy with creation of a perineal urethrostomy is indicated (172). Innovative procedures for penile and urethral reconstruction that maintain function have been reported (18,60,87,149,251). Irrespective of nodal status, the 5-year survival rate of patients undergoing either partial or total amputation of the penis is 50%, with local control being achieved in about 90% of cases (Table 43.9) (131,137,138,194).

Local recurrence of tumor following partial or total amputation occurs in 10% of patients, with metachronous failure three times more common than immediate or synchronous failure (14,53,121,136,250). Among patients in whom regional lymph nodes are thought clinically to be free of metastases and who undergo either total or partial amputation, 14% subsequently develop nodal metastases, usually between 4 and 24 months after treatment of the primary lesion (53,131,137,311). Finally, of patients who are thought to be free of visceral metastases at diagnosis and who undergo penectomy, 11% subsequently develop visceral metastases, usually within 18 to 36 months after treatment of the primary lesion (136). Stricture of the newly created urethral meatus requiring dilation occurs in about 20% of patients, and in half of those with meatal stenosis, reoperation and revision of the stenotic meatus is needed (136,138,310).

Radiotherapy

To minimize the cosmetic, functional, and psychologic consequences of penile amputation, radiotherapy in the form of either teletherapy (external beam) or brachytherapy has been used (66,99,119,176,202,252). Brachytherapy may be either contact or pleisobrachytherapy using surface molds with iridium or radium sources or interstitial insertion of radioactive wires, usually iridium, directly into the lesion (5,80). External beam radiotherapy produces a complete response rate of up to 56%, and brachytherapy achieves complete response in up to 70% of patients (Table 43.9). Local failure (i.e., either persistence or local recurrence of disease) has been reported in 16% of patients treated with brachytherapy and in 40% treated with external beam therapy (55,235,247,252).

There is a modest increase in the 5-year survival rate among patients whose primary penile lesions are treated with external beam radiotherapy compared with those treated with brachytherapy; this is not due to differences in tumor stage or grade (Table 43.9). In patients receiving

either brachytherapy or teletherapy and in whom the regional lymph nodes are clinically negative, a 5-year survival rate of up to 80% has been reported (32,55,176). Up to 20% of patients who are thought to have inguinal lymph nodes free of metastases on initial clinical examination and who undergo radiotherapy to the penile lesion subsequently develop inguinal metastases. This statistic correlates with the previously noted 14% incidence of subsequent inguinal node metastases in patients initially thought to be free of nodal metastases but who on prophylactic node dissection are found to harbor micrometastases (49,55,170).

The importance of tumor volume in patients being considered for brachytherapy as contrasted to external beam therapy or teletherapy is paramount because patients with tumor volumes greater than 8 cm^3 are poor candidates for brachytherapy (241). If either form of radiation therapy is ineffective, partial or total amputation is effective in 90% to 100% of cases, provided the recurrence is promptly diagnosed. Complications from therapy are more common with interstitial than external beam therapy and include meatal stenosis in 15% to 30% of cases, urethral stricture in 20% to 35%, penectomy for complications of radiation in the absence of recurrent malignancy in 5% to 15% of cases, and telangiectasia and catarrhal reaction in almost all cases (55,66,247,256).

Comparison of the survival of patients whose primary lesions were initially treated by radiotherapy (either teletherapy of brachytherapy) with those treated surgically shows little overall survival advantage between radiotherapy and surgery as long as local recurrence is diagnosed and treated promptly. Even though this conclusion is based on nonrandomized studies and the decision whereby a given patient received either radiotherapy or surgical amputation is unstated, there is, for a given tumor stage, little difference in ultimate survival between radiotherapy and surgery of the primary lesion (Table 43.9). Partial or total penile amputation represents the most common initial form of therapy, although among patients with limited penile lesions, radiotherapy is a legitimate therapeutic consideration. Survival depends less on the type of therapy of the primary penile lesion than on the stage of the lesion at diagnosis. If radiation of the primary lesion fails to sterilize the cancer or if subsequent recurrence develops, amputation can be performed without compromising prognosis. Clearly, patients treated with radiotherapy merit a posttreatment biopsy to ensure disease sterilization.

Chemotherapy

Because bleomycin tends to accumulate in the skin, patients with penile cancer have been treated with it (116). In a study of patients treated with bleomycin, there was a 50% survival rate for up to 5 years; when bleomycin was combined with either surgical extirpation, radiotherapy, or both, 80%, 73%, and 72% of patients, respectively, survived for up to 5 years (116). In another study of 15 patients treated with bleomycin, a complete response rate of 20%, a partial response rate of 73%, and no response rate of 7% was noted, but 64% of patients required subsequent penile amputation for local control (139). The optimal response to bleomycin occurred in tumors confined to the glans or prepuce, in tumors that were well differentiated, in older patients, and in patients who received a total bleomycin dose smaller than 750 mg (139).

Selection of bleomycin as the primary treatment of penile cancer remains a challenge, and bleomycin's definitive role in managing this lesion is unclear. When combined with surgery, bleomycin may enhance local control while potentially minimizing the extent of surgery necessary (116). Combination therapy using bleomycin and radiation achieved complete remission of the local penile lesion in 93% of cases (62). Indeed, this combination provided a local cure rate that compared favorably with surgery, did not compromise survival, preserved function, and resulted in a 5-year survival rate for stage T_1 to T_2, N_0 lesions of 95% (62,183).

Mohs or Micrographic Surgery

Other approaches permitting retention of penile function include microscopically controlled (i.e., Mohs) micrographic surgery (180,271,295) and cryotherapy (154). Micrographic surgery using either the fixed or fresh tissue technique involves local excision of the primary tumor in layers, with histologic tracking of residual neoplastic elements ultimately separating malignant from adjacent nonmalignant tissue (180,185). The overall 5-year cure rate was 74%, and using Jackson's staging system, the rate was 86% in patients with stage I disease, 62% in patients with stage II disease, and 0% in patients with stage III disease (185). A local failure rate of 6% has been reported for Mohs technique, and tumor stage and grade, size of the primary lesion, and the failure of prior surgical or radiation therapy were important factors in predicting the effectiveness of Mohs surgery. The ultimate assessment of the effectiveness of chemosurgery in treating penile cancer awaits evidence of its reproducibility by others, but in appropriately selected cases, this therapy provides excellent local control while retaining penile function.

Laser Therapy

The Nd:YAG laser is effective in treating penile cancer while maintaining penile integrity, although laser therapy is reserved for small *in situ* or only microscopically invasive carcinomas (107,244,248,287,306). Cure rates of up to 100% were achieved in patients with CIS, but only 66% of patients with T_1 lesions achieved cure and a local failure rate of 6% to 22% has been reported (107,162). It therefore appears that for low-stage lesions, the Nd:YAG laser, and

perhaps cryosurgery, can provide high cure rates while avoiding the deleterious effects of amputation or radiotherapy (182,255). However, additional studies are necessary before the therapeutic indications for the use of these therapies can be assessed. In addition, obtaining adequate representative tissue for a definitive histologic diagnosis before destruction of the primary lesion is essential, as is posttreatment biopsy to ascertain cure.

Quality of Life After Therapy of the Primary Lesion

Of the various therapies for the primary penile lesion, partial or total penectomy is generally associated with the lowest incidence of local recurrence. However, the impact of this procedure on the patients' emotional, interpersonal, and sexual quality of life is of concern, and studies addressing this matter are of interest (48,201,202 and 203). Studies by Opjordsmoen and Fossa (201) concluded that patients undergoing amputation (partial or total) had a poorer outcome with regard to sexual function than patients undergoing organ-sparing procedures, while in other parameters of quality of life measured (e.g., well-being or social and mental symptoms), no differences were apparent. Moreover, mental symptoms, primarily anxiety and depressive disorders, have been well documented in patients with penile cancer, but it appears that this is due to the disease itself and not the type of therapy selected (201). In contrast, the study of D'Ancona and associates (48) found that sexual function in patients undergoing partial amputation was normal or slightly diminished in 64%, male self-image and relationships with their partners unchanged, sexual interest and satisfaction normal, and in 64%, frequency of intercourse unchanged. However, reasons for the difference in findings regarding sexual functioning between the studies of Opjordsmoen and Fossa and those of D'Ancona and associates are unclear.

Definitive Therapy of Regional Lymph Nodes

Therapeutic approaches to the regional lymph nodes in patients with penile cancer have included lymphadenectomy, external beam radiotherapy, and a combination of lymphadenectomy with either preoperative or postoperative radiotherapy (6,11,66,108,206,236).

Lymphadenectomy

Following definitive treatment of the primary lesion, lymphadenectomy should be deferred for 6 to 12 weeks, during which time a course of antibiotics is administered to permit coexisting inflammatory and/or infectious lymphadenitis to resolve. This approach has not led to any reports of clinically resectable lesions becoming unresectable and has the advantage of reducing the incidence of wound infection while providing opportunity for expectant management should the inguinal adenopathy resolve (75).

Patients in whom palpable nodes fail to resolve, in whom nodes enlarge while under observation, or in whom lymph nodes previously impalpable become palpable should undergo therapeutic lymphadenectomy.

The survival of patients with nodal metastases is about half that of patients free of such metastases, and when patients with node-positive disease are stratified as to the extent of nodal metastases, tumor burden correlates with survival (Table 43.10); early removal of microscopic nodal disease can improve survival (150,309). It has been shown

that among patients with initially clinically negative nodes and in whom nodal metastases subsequently develop, a high cure rate is achieved by prompt lymphadenectomy, in contrast to patients in whom the treatment of nodal metastases is delayed (70,71). In comparison to therapeutic lymphadenectomy, the indications for prophylactic lymphadenectomy are less certain and the lymph nodes of up to 75% of patients undergoing prophylactic lymphadenectomy have been found to be free of metastases. The size of the primary lesion; its grade; and the presence or absence of venous, lymphatic, or corporal invasion are predictive of nodal status and identify potential candidates for prophylactic lymphadenectomy (1,2,42,108,147,174). Because the morbidity of even modified lymphadenectomy is not inconsequential, close surveillance of patients with clinically negative lymph nodes has been recommended (1,247,276).

	Ravi (237)	Horenblas, et al. (108)	Srinivas, et al. (275)	Fossa, et al. (71)
Total number of patients	201	110	119	79
5-year survival (%)				
Status of lymph nodes				
Inguinal				
pN_0	95	100	74	89
pN+	53	63	28	
Iliac				
pN+	0			
Volume of nodal metastases				
pN_1	81	79	82	80
pN_2	50	17	54	80
pN_3	—	—	40	18
Unilateral pN+	86	79		
Bilateral pN+	60	17	12	

TABLE 43.10. EFFECT OF THE PATHOLOGIC STATE OF REGIONAL LYMPH NODES AND THEIR STRATIFICATION ON THE 5-YEAR SURVIVAL RATE OF PATIENTS WITH CARCINOMA OF THE PENIS

Paradoxically, the absence of nodal metastases in patients undergoing prophylactic lymphadenectomy does not ensure cancer-free survival, and the 5-year survival of such patients ranges from 71% to 95% (6,11,123,137,144,146). The reasons for failure in such cases include inguinal recurrence, perineal recurrence, or distant metastases (206,224,236,309). The interval during which lymph nodes initially thought to be benign subsequently manifest metastases is such that 50% occur within 16 months of treatment of the primary lesion and 75% within 34 months, with nodal metastases only rarely appearing beyond 5 years of initial diagnosis of the primary lesion (1,107,205,206,274). Of patients who die after treatment of penile cancer, 92% to 97% do so within 5 years (65).

The advantage of prophylactic inguinal lymphadenectomy in patients with clinically negative (cN_0) lymph nodes is that if nodes are found to be involved pathologically (pN+), survival is somewhat superior to that for patients in whom nodes initially are clinically negative but then become positive and in whom lymphadenectomy is then performed (206,237). In addition, prophylactic lymphadenectomy may identify a cohort of pN+ patients with a tumor burden lower than that of patients undergoing therapeutic lymphadenectomy. Patients who are found to have limited nodal disease appear to have a prognosis superior to that for patients with larger tumor burdens (Table 43.11). Patients who are poorly compliant with the close follow-up needed in expectant management regimens and patients whose inguinal areas are difficult to evaluate are better served by prophylactic lymphadenectomy.

	Immediate-early			Delayed
		Prophylactic LAD (cN_0)	Therapeutic LAD (cN+ and pN+) (%)	$cN_0 \rightarrow cN+$ (%)
Study	Overall Crude 5-year Survival (%)	pN_0 (%)	pN+ (%)	pN+ (%)	pN+ (%)
McDougal, et al. (173)	89	100	84	66	0[a]
Fossa, et al. (71)	72	89	NR	79	83
Fraley, et al. (74)	60	100	NR	75	8
Pow-Sang, et al. (224)	74	80	63	NR	NR
Ravi, (237)	96	94	100	NR	76
Ornellas, et al. (206)	62	87	29	NR	3

[a]One patient.
NR, not reported.

TABLE 43.11. FIVE-YEAR SURVIVAL OF PATIENTS WITH CARCINOMA OF THE PENIS STRATIFIED ACCORDING TO TIMING OF PERFORMANCE OF LYMPHADENECTOMY (LAD) AND NODAL STATUS

Radiotherapy

A 5-year survival rate of 30% among patients with penile cancer who were believed to have inguinal node metastases on clinical examination and who received radiotherapy has been reported. However, in patients treated by radiotherapy, the true histologic nodal status is unknown and nodes clinically suspicious for metastases may not in fact contain metastases. This results in a spuriously high cure rate for patients receiving nodal radiotherapy because an unknown number of individuals clinically thought to have nodal metastases (cN+) in fact do not (pN_0). Based on other studies, if we assume that only 50% to 60% of patients with clinically suspicious lymph nodes actually contain metastases, the ability of radiotherapy to control nodal metastases might actually approach only 15%. In addition, prophylactic radiation of the regional nodes in patients with clinically negative nodes (cN_0) did not prevent 25% of individuals with stage I disease from developing nodal metastases (65,190). This convincingly indicated that radiotherapy is of minimal therapeutic value in treating even low-volume nodal disease because 14% of patients with clinically negative nodes are known to develop nodal metastases and 18% of patients with clinically negative nodes who undergo

prophylactic lymphadenectomy are found to have occult metastatic disease (15,53,94,237,297).

Systemic Chemotherapy for Metastatic Disease

Reports of systemic chemotherapy in treating metastatic penile carcinoma (Table 43.12) are generally based on relatively few patients; often involve a combination of therapies; lack controls, randomization, and statistical analysis; and have inconsistent follow-up (4,64,77,128,156,220,269). Despite these limitations, results of single-agent and combination chemotherapy have been reported using agents such as bleomycin, methotrexate, cisplatinum, vincristine, and 5-FU. Moreover, these agents have been used either in a therapeutic setting for established metastases, as neoadjuvant therapy in an attempt to increase resectability of nodal metastases, or as an adjunct following lymphadenectomy for pathologically proven metastases (Table 43.12).

TABLE 43.12. CHEMOTHERAPY IN THE TREATMENT OF METASTATIC PENILE CANCER

Agent(s)	No. of Patients	Site of Metastases	Response (%)			Range of Response Duration (mo)	References
			Complete	Partial	None		
Single-agent Therapy							
Methotrexate	22	Nodes, bone, lung, skin	10	45	45	2–11	Ahmed et al., 1984; Garnick et al., 1979; Sklaroff and Yagoda, 1979
Cisplatinum	47	Bone, soft tissue, lung	5	21	74	1–8	Ahmed et al., 1984; Gagliano et al., 1989; Merrin, 1979; Sklaroff and Yagoda, 1980
Bleomycin	27	Nodes, bone, lung, testis	4	24	72	3–5	Ahmed et al., 1984; Kyalwazi et al., 1974; Maiche, 1983
Multiple-agent Therapy							
Vincristine + bleomycin	3	Nodes, bone, perineum	0	0	100	1	Williams and Blackard, 1974
Cisplatinum + 5-fluorouracil	17	Nodes, bone, lung, pleura	0	47	53	2–57	Hussein et al., 1990; Kattan et al., 1993; Shammes et al., 1992
Cisplatinum + methotrexate	3	Nodes, bone	0	100	0	1–84	Kattan et al., 1993
Bleomycin + methotrexate	4	Nodes, pleura	25	0	75	5–9	Kattan et al., 1993
Neoadjuvant Therapy							
Vincristine + bleomycin + methotrexate	5	Nodes	0	60	40	20–72	Pizzocaro and Piva, 1988
Methotrexate + bleomycin + cisplatinum	1	Nodes	0	100	0	+18	Germiyanogly et al., 1993
Adjunctive Chemotherapy							
Vincristine + methotrexate	12	Nodes	91	9	0	18–102	Pizzocaro and Piva, 1988

Table 43.12 indicates objective response rates for the single agents bleomycin, methotrexate, and cisplatinum and for a variety of combinations, including these agents and vincristine, although the reported duration of such responses varies. Paradoxically, bleomycin, shown to be effective in treating the primary penile lesion of squamous cell carcinoma of the penis, appears to be relatively ineffective when used alone in the treatment of metastatic disease, and development and use of other agents and of combinations of existing agents is warranted (91,116). Of note is the combination bleomycin, methotrexate, and either vincristine or cisplatinum in the neoadjuvant setting, rendering resectable 66% of patients with unresectable inguinal nodes (82). Also of note is the response of nodal metastases to the combination of methotrexate and bleomycin followed by radiotherapy (3). The combination of cisplatin, methotrexate, and bleomycin in a phase II study showed a response rate (complete or partial) of 32.5% (91). The intensity of this regimen, however, was such that 12.5% of patients died related to their treatment and 17% of patients had one or more life-threatening toxic episodes (91). Recently, a phase I study of several types of squamous cell carcinoma, including penile cancer, has been reported using etretinate and interferon-α based on the concepts of promoting differentiation of malignant cells as well as inhibiting proliferation (246).

When used as an adjuvant to ilioinguinal lymphadenectomy, the combination of vincristine, bleomycin, and methotrexate has produced a complete response rate of 92%, although duration of follow-up has varied. Even though cure has not been documented and a comparative group of patients undergoing only lymphadenectomy not studied, it is noteworthy that approximately 40% of the patients studied had positive pelvic nodes, a uniformly poor prognostic finding (220). Aggressive combination chemotherapy for metastatic disease appearing subsequent to lymphadenectomy, or in association with lymphadenectomy in patients at risk for dissemination (e.g., those with positive pelvic lymph nodes or with high-volume inguinal nodal disease), or in the neoadjuvant setting may be a legitimate therapeutic approach (64).

Technique of Ilioinguinal Lymphadenectomy

The term *inguinal lymphadenectomy* refers to removal of the superficial and deep inguinal and subinguinal lymph nodes, with the superior limit of dissection being approximately 2 cm above the inguinal ligament; the lateral margin of dissection being the sartorius muscle; the medial margin, the adductor longus; and the distal margin, the apex of the femoral triangle. Pelvic (iliac) lymphadenectomy includes extirpation of the common, external, and internal iliac lymph nodes and obturator nodes (111).

Preoperative Preparation

Ilioinguinal lymphadenectomy requires that the patient be in optimal metabolic condition, and the frequently coexisting regional lymphadenitis should have been treated with appropriate antibiotics before surgery. We suggest delaying regional lymphadenectomy for 6 to 12 weeks after excision of the primary lesion, during which time antibiotics are administered to sterilize any nodal infection because such infections at the time of lymphadenectomy will compromise wound healing.

Optimal preoperative hydration and nutritional status should be established before surgery and an infusion of Ringer's lactate solution and preoperative prophylactic antibiotics begun 12 hours before the procedure. In addition, the use of mini-dose heparin should be considered as a possible strategy to reduce embolic events and small-vessel thrombosis with consequent necrosis of skin flap margins.

Inguinal lymphadenectomy is initially performed, and because of crossed lymphatic drainage, bilateral dissection is preferred. Pelvic lymphadenectomy is not done prophylactically but is performed only if inguinal lymph nodes are positive for cancer.

Position

The patient is placed in the supine position with the legs abducted at the thigh, flexed at the knee, and externally rotated, with appropriate padding used. The scrotum and the penis are draped out of the operative field. To facilitate the pelvic dissection, a sacral roll may be placed.

Incision

A variety of incisions for ilioinguinal lymphadenectomy have been described, and these are outlined in Fig. 43.9 . We

currently favor a suprapubic midline incision for bilateral pelvic lymphadenectomy combined with bilateral curvilinear, somewhat oblique groin incisions 1 cm inferior to the inguinal ligament extending from below and medial to the anterior superior iliac spine and sufficiently medial to allow ample exposure of the femoral triangle (Fig. 43.10).

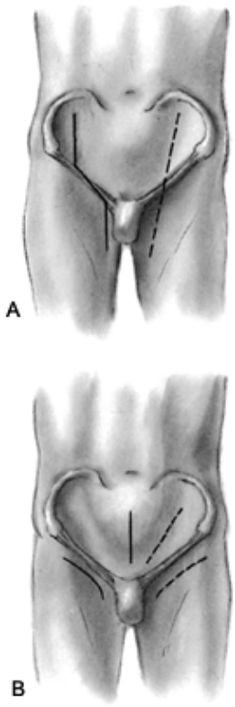

FIGURE 43.9. Incisions employed for ilioinguinal lymphadenectomy. **A:** Combined incisions for pelvic and inguinal lymphadenectomy. **B:** Skin bridge techniques. Lymphadenectomy should be deferred until all evidence of lymphadenitis has resolved. Irrespective of the incision selected, excessive thinning of the skin margins, and dessication of flaps should be avoided.

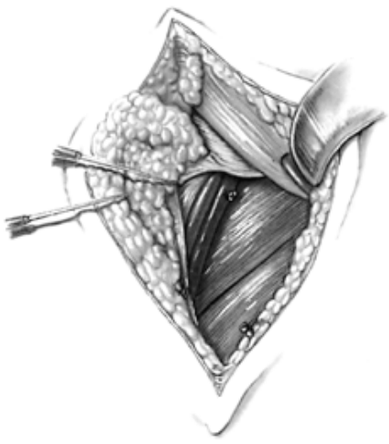

FIGURE 43.10. The skin flaps for the inguinal dissection have been developed and the medial margin of resection defined. The great saphenous vein has been ligated at its junction with the femoral vein, and the lymphatics emerging from beneath the inguinal ligament through the femoral canal are illustrated.

Inguinal Lymphadenectomy

After the incision has been made, skin flaps are raised and elevated laterally toward the sartorius, medially to the adductor longus, cephalad 2 cm above and parallel to the inguinal ligament, and caudally to beneath the apex of the femoral triangle. The skin flaps are made approximately 3 to 4 mm in thickness at their edges but can be thicker at their base in an effort to prevent flap necrosis. During dissection, the skin edges should be protected and kept moist, and the flaps should be handled atraumatically (Fig. 43.10).

The fascia lata is incised and reflected from the adductor longus and pectineus and sartorius muscles. Excision of the node-bearing tissue may be initiated superiorly and the fibrofatty node-bearing tissue dissected from under and above the inguinal ligament.

Superiorly, the adipose tissue is dissected off the surface of the external oblique aponeurosis down to the inguinal ligament and from the spermatic cord just distal to the superficial inguinal ring. As the dissection continues, the sheath of the femoral vessels is incised, the vessels exposed, and the surrounding node-bearing tissue resected. Approximately 2.5 cm below the inguinal ligament, at its junction with the femoral vein, the great saphenous vein is ligated and divided (Fig. 43.10). If possible, the great saphenous vein should also have been identified distally at the inferior aspect of the dissection and previously ligated and divided (Fig. 43.11).

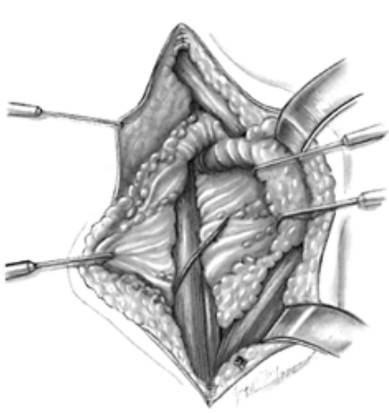

FIGURE 43.11. The lateral aspect of the inguinal dissection, the sartorius muscle, is shown. The fascia lata has been incised and reflected medially with the specimen, and the distal extent of dissection, the apex of the femoral triangle, is also shown. The lateral femoral cutaneous nerve should be preserved if possible. Dissection posterior to the femoral vessels is unnecessary and risks damage to the deep femoral vessels.

As the dissection of the femoral artery proceeds, the deep femoral artery should be identified and preserved, and particular care taken to prevent injury to the femoral nerve, which is lateral to the femoral artery. At the lateral aspect of the dissection, the lateral margin of the sartorius is exposed and the lateral femoral cutaneous nerve preserved as it emerges from under the inguinal ligament and courses anterior to the sartorius under the fascia lata (Fig. 43.11). The inguinal dissection should extend distally to the apex of

the femoral triangle. Dissection posterior to the vessels is unnecessary and risks injury to the deep femoral artery.

Pelvic Lymphadenectomy

When, pelvic (iliac) lymphadenectomy is performed, en bloc nodal resection has been recommended; however, we believe this is not essential because such dissection is unnecessarily tedious and the pelvic and inguinal dissections can be completed separately, provided that all nodal tissue posterior to the inguinal ligament is excised (52).

Following retroperitoneal exposure of the iliac vessels and identification of the ureter, dissection is initiated at the origin of the common iliac vessels and extended distally to encompass the perivascular fibrofatty node-bearing tissue surrounding the common, external, and internal iliac vessels and the obturator vessels and nerve (Fig. 43.12). The pelvic lymphadenectomy performed in connection with penile cancer should extend somewhat more distally than that performed for prostatic or vesical carcinomas because of the importance of clearing the femoral canal of lymphatic tissue (Fig. 43.13). Indeed, relevant nodal tissue is located adjacent to the terminal portion of the external iliac vessels under the inguinal ligament, and in some cases, division of this ligament with subsequent repair lateral to the femoral artery is essential for adequate excision of nodal tissue. For closure, the sartorius muscle is separated from its origin, and the entire thickness of the muscle is reflected medially, with care taken to preserve its blood supply. The sartorius is then transposed to cover the femoral vessels by suturing it to the inguinal ligament over the femoral artery and vein (Fig. 43.14). In contrast, if extensive excision of a fixed mass results in a defect too large to close, primarily myocutaneous flaps, revascularized free flaps, or as recently described, use of a skin-stretching device is effective (177,286). The inguinal ligament and falx inguinalis are then sutured to Cooper's ligament laterally to close the potential hernia space in the femoral canal.

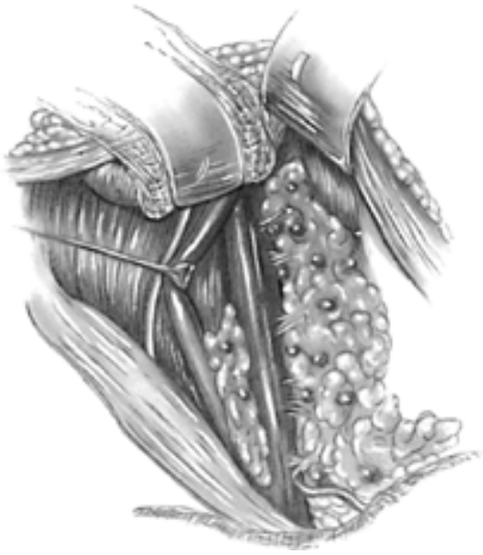

FIGURE 43.12. The area of the iliac vessels has been exposed retroperitoneally, the peritoneal contents retracted cephalad and medially, and the ureter identified and protected. Shown here is the fibrofatty node-bearing tissue being removed from the external and common iliac arteries, with the iliac vessels and obturator fossa yet to be exposed. Metal clips may be used to secure small vessels and lymphatics.

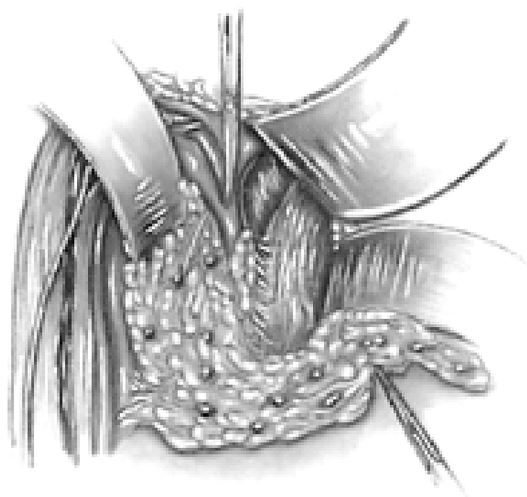

FIGURE 43.13. The node-bearing tissue is being dissected from the hypogastric vessels and the obturator artery thereby exposed. The dissection is continued and the obturator nerve isolated. At the conclusion of the pelvic dissection, the iliac vessels and obturator nerve are skeletonized.

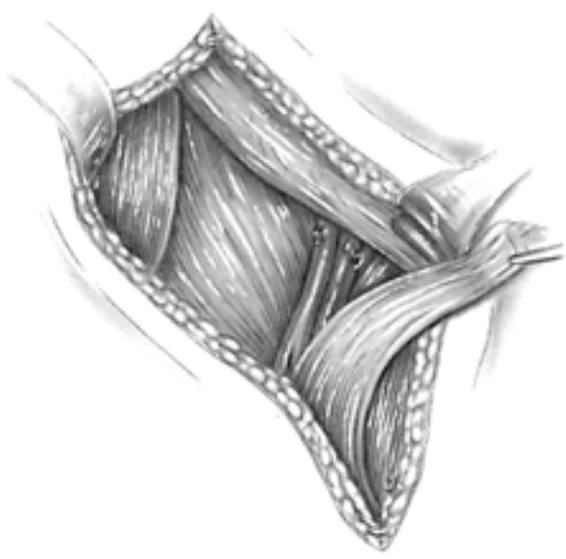

FIGURE 43.14. The sartorius muscle has been sharply detached from its origin, with care taken to preserve its vascular supply, which enters the muscle posteriorly and approximately 10 cm below its origin. The sartorius is mobilized only enough to allow it to be placed over the femoral vessels. The free end of the sartorius is sutured to the inguinal ligament over the femoral artery and vein with interrupted nonabsorbable sutures. Similarly, the lateral edges are secured to adjacent muscle.

The edges of the skin flaps are resected for approximately 3 to 4 mm because redundancy of the skin flaps often occurs as a result of dissection; the flaps are then anchored to the underlying muscle to close potential dead spaces. Hemostasis must be meticulous. Suction catheters are placed under the flaps to include both proximal and distal flaps, and the skin edges are approximated after excising any tissue of questionable viability.

Postoperative Care

Suction catheters are maintained until all drainage ceases, and the patient is kept at bed rest to facilitate this. Support stockings are valuable, and the recommendations of Karakousis and co-workers (126) should be followed to reduce the incidence of postoperative complications. The complications following inguinal or ilioinguinal lymphadenectomy and, in some cases, the debilitating long-term consequences of this procedure, coupled with less-than-unequivocal evidence for the therapeutic value of prophylactic lymphadenectomy, accounts for the hesitancy of some investigators to recommend “prophylactic” lymphadenectomy in patients with clinically negative nodes. Ilioinguinal lymphadenectomy has been associated with a mortality rate of 1% to 3% and a morbidity rate of 30% to 50%. Table 43.13 summarizes the types and incidence of complications following ilioinguinal lymphadenectomy based on several studies (15,27,122,138,142,302).

Complication	Frequency		References
	No.	%	
Skin flap necrosis			
Mild	51/175	29	Beggs and Spratt, 1964; Fraley et al., 1985; Jackson, 1966; Johnson and Lo, 1984b; Skinner et al., 1972; Whitmore and Vagaiwala, 1985
Severe, requiring grafting	48/246	20	Buddington et al., 1963; Fraley et al., 1985; Johnson and Lo, 1984b; Ravi, 1993a; Whitmore and Vagaiwala, 1985; Yu et al., 1978
Scrotal edema	17/78	22	Ayyappan et al., 1994
Seroma	15/84	18	Johnson and Lo, 1984b; Whitmore and Vagaiwala, 1985
Edema			
Incapacitating	41/361	11	Beggs and Spraft, 1964; Johnson and Lo, 1984b; Kuruvilla et al., 1971; Lesser and Schwarz, 1955; Ravi, 1993a; Whitmore and Vagaiwala, 1985
Mild to moderate	53/331	16	Johnson and Lo, 1984b; Kuruvilla et al., 1971; Lesser and Schwarz, 1955; Ravi, 1993a; Whitmore and Vagaiwala, 1985
Wound infection	10/81	12	Fraley et al., 1985; Johnson and Lo, 1984a
Lymphocele	6/67	9	Johnson and Lo, 1984b
Thrombophlebitis	6/124	5	Beggs and Spratt, 1964; Johnson and Lo, 1984b; Skinner et al., 1972; Whitmore and Vagaiwala, 1985
Lymphorrhea	1/30	3	Beggs and Spratt, 1964

TABLE 43.13. INCIDENCE OF POSTOPERATIVE COMPLICATIONS FOLLOWING THERAPEUTIC LYMPHADENECTOMY IN PATIENTS WITH PENILE CARCINOMA

Use of the sartorius muscle to cover the femoral vessels has sharply reduced femoral vessel hemorrhage as a source of postoperative mortality (302). Of concern, however, is skin flap necrosis, which occurs in approximately 20% of cases, and incapacitating edema, which occurs in 11% (Table 43.13). Modifications in the surgical technique of inguinal lymphadenectomy, including use of selected incisions, careful flap development, trimming of flaps, prophylactic antibiotics, suction drainage, postoperative elastic support, and leg elevation, have produced a 50% reduction in the incidence

of flap necrosis severe enough to require grafting and the elimination of severe incapacitating edema (40,126).

Prognostic Factors

Several factors have been evaluated as potential prognostic markers, including the presence or absence of inguinal or pelvic node metastases, vascular (i.e., lymphatic or venous) invasion, volume of nodal metastases, tumor size, depth of invasion, tumor grade, tumor ploidy, tumor growth pattern, S-phase fraction, location of lesion on penis, and patient age and symptoms (1,90,92,98,105,148,206,225,256,10). On univariate analysis, the prognosis for survival has been correlated with the size of the primary lesion, nodal status, tumor grade, and presence or absence of corporal invasion (104,274). Interestingly, on multivariate analysis, the size of the primary lesion was excluded but nodal status, tumor grade, and presence or absence of corporal invasion were found to be independent prognostic factors (105,274). Factors that show no consistent relationship to prognosis include duration of symptoms before diagnosis, patient age at diagnosis, and race (147,184).

Other Epithelial Malignancies of the Penis

Basal Cell Carcinoma of the Penis

Basal cell carcinoma is among the most common malignancies of humans, and because it typically occurs in areas exposed to ultraviolet radiation, it is not surprising that this lesion only rarely occurs on the penis and that only 0.25% of all basal cell cancers occur on the penis. The average age at diagnosis is 58 years, and circumcision has no influence on reducing the risk of developing this lesion. Of these lesions, 60% occur on the shaft, 23% on the prepuce, and 17% on the glans (84). The lesion usually presents as a nodule or scaly plaque, has a limited risk of metastases, and is usually only locally invasive. Indeed, in two-thirds of cases reported, local excision is curative, and in another 20%, radiotherapy appears to have been effective. However, in cases unresponsive to or unsuitable for organ-sparing therapy, partial or total penectomy may be necessary (84).

Primary Melanoma of the Penis

Primary melanoma of the penis is rare and can arise on the glans, foreskin, or shaft. The average age at diagnosis is the sixth or seventh decade of life, which is older than the age at diagnosis of melanomas in other sites. Moreover, in contrast to squamous cell cancer, melanoma is rare in African Americans (163). The lesions vary in gross appearance from blue, black, or red to brown; they may ulcerate and most commonly arise *de novo,* although transformation of preexisting lesions has been noted (234,281). Because of the limited number of cases reported, a simplified staging system has been proposed: stage I, localized to the penis; stage II, metastatic to the regional lymph nodes; and stage III, distant dissemination (25). However, this staging system ignores two other critical prognostic factors in penile melanoma: (a) the thickness of the primary lesion, because lesions less than 1.0 mm in thickness have a more favorable prognosis than thicker lesions; and (b) the level of invasion of the primary lesion, although the thinness of the penile skin may facilitate early dissemination (191).

As in squamous cell cancer of the penis, diagnosis is often delayed and 40% to 60% of patients first present with nodal metastases (stage II or III disease) (16).

The rarity of this lesion is such that meaningful survival figures cannot be derived; indeed, therapy for the potentially most curable (stage I) lesion is subject to debate. Some investigators conclude that for clinical stage I lesions, particularly those less than 1.5 mm in thickness, partial amputation with a 3- to 5-cm tumor-free margin is appropriate and that prophylactic regional lymphadenectomy is of no value. If the primary lesion is greater than 1.5 mm in thickness, bilateral superficial inguinal lymphadenectomy is appropriate, even in the absence of palpable adenopathy (281). Others, however, have advocated performance of a total penectomy with perineal urethrostomy and radical ilioinguinal lymphadenectomy for all stage I lesions, although even with this approach inguinal recurrences have been reported (25,28). For clinical stage II disease, partial penectomy, if possible, and regional lymphadenectomy are appropriate; however, because of the high incidence of coexisting occult distant metastases and the fact that in melanoma, compared with squamous cell cancer, the regional nodes are less effective as barriers to dissemination, the prognosis is worse than that for similarly staged squamous cell cancer (281). Finally, in stage III disease, because of the absence of truly effective systemic therapy for melanoma, regional lymphadenectomy is recommended for palliation (281). The prognosis of primary penile melanoma is poor because of the occurrence metastatic disease.

Primary Lymphoma

Primary extranodal lymphoma of the penis, where the penis appears to be the sole site of lymphoma, is also rare. Because later nodal disease may develop and because the lesion is responsive to chemotherapy or radiotherapy, partial or complete amputation is rarely, if ever, indicated (166).

Primary Sarcomas of the Penis

Primary soft tissue or mesenchymal malignancies (i.e., sarcomas) of the penis are rare, with putative origin from one of several cell types: endothelial neural, muscular, or fibrous (50). Malignant neoplasms of endothelial origin consist of angiosarcomas (hemangiosarcoma, endothelioblastoma,

and malignant hemangioendothelioma), which arise *de novo* or are radiation induced and which tend to occur on the penile shaft, and Kaposi's sarcomas, which occur most commonly on the glans (141,227,282,290). Sarcomas arising from neural elements of the shaft or glans consist of malignant schwannomas (neurofibrosarcomas) and clear cell cancers of neuroectodermal origin. Those of myogenic origin demonstrate features of either smooth muscle (leiomyosarcomas) (Fig. 43.15) or striated muscle (rhabdomyosarcomas), with the latter occurring in children (46,50). Finally, malignancies of fibrous tissue origin include fibrosarcomas, osteogenic sarcomas, fibrous histiocytomas, and epithelioid sarcomas (63,112,213,223). Although the rarity of the various sarcomas of the penis—with the possible exception of Kaposi's sarcoma, particularly in patients with AIDS—makes generalizations difficult, it seems that such lesions tend to occur at an earlier age and to present as a mass as either nontender (70%) or tender (30%) (50). Because many of these lesions may be only locally invasive and indolent in growth, assessment of their extent with ultrasound or MRI is reasonable because organ-sparing therapy may include excision, radiation therapy, or chemotherapy, although in some cases partial or total amputation is necessary (50,79,233).

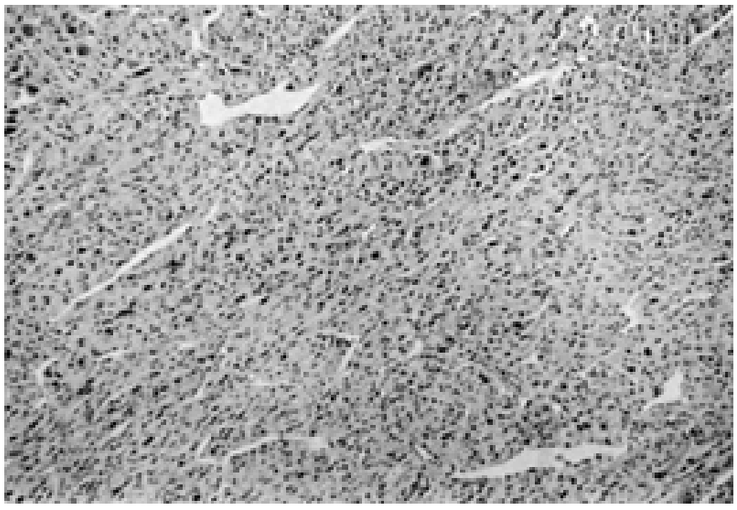

FIGURE 43.15. Leiomyosarcoma. Note the interlacing bundles of smooth muscle cells with cigar-shaped nuclei and elongated, wavy cytoplasmic processes (×240).

Metastases to the Penis from Other Primary Lesions

Although the penis is an unusual site for metastatic disease, metastases to the penis are well documented and those from other organs occur 50 times more commonly than those of lymphohematologic origin (19,216,223). Of metastatic neoplasms to the penis, approximately 30% arise from the prostate, 30% from the bladder, 16% from the rectosigmoid, 11% from the kidney (usually the left kidney), 4% from the testis, and the remainder from a diversity of other sites (30,117,249). Among patients with metastatic carcinoma to the penis, the diagnosis of penile metastases occurs simultaneously with that of the primary lesion in one-third of cases, within 2 years of diagnosis of the primary lesion in another one-third, and after 2 years in the remainder. In prostate and bladder cancer patients, the average interval between diagnosis of the primary prostatic or vesical lesion and that of the penile metastases is 33 to 36 months (17). In 80% of patients with metastases to the penis, evidence of additional metastatic sites is found, and in 20%, the penis appears at least initially to be the only site of metastases. Metastases to the penis have been reported to occur by either direct extension, by retrograde venous or lymphatic flow, or by embolization. Metastases are reported to occur, in order of diminishing frequency, in the corpora cavernosa (30%), the glans (20%), the corpora cavernosum and spongiosum together (10%), or in some combination of these sites (40%) (17,223). So-called malignant priapism, produced by neoplastic infiltration of the corpora cavernosa or by compression of the dorsal vein, may be complete, partial, or tumefactive (17,223). In addition, urinary retention secondary to invasion of the urethra occurs in one-third of patients, and swelling, multiple nodules, or a mass that might mimic Peyronie's disease occurs in another one-third (17). Diagnosis of metastases to the penis is based on history and physical examination and is confirmed by biopsy (core biopsy or fine-needle aspiration biopsy) (270). Although the extent of penile metastases may be determined by cavernosography, CT, ultrasound, or MRI is more effective.

The therapy for metastatic disease to the penis depends primarily on the nature and prognosis of the primary lesion and is generally palliative. Local resection or excision or, if this is not possible, partial or total amputation, is particularly effective in relieving symptoms, especially those of urinary obstruction or pain. However, radiotherapy, chemotherapy, and hyperthermia in combination with radiotherapy have been beneficial (19,189). In most cases, development of disease metastatic to the penis is a poor prognostic sign, with more than 50% of such patients dying within 6 months. However, 40% may live longer than 6 months and 20% longer than 12 months, with most of these patients having the primary lesion in the genitourinary tract (17,189,223).

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44

DERMATOLOGIC LESIONS OF THE PENIS

Kenneth E. Greer

B. Dale Wilson

K.E. Greer: Department of Dermatology, University of Virginia, Charlottesville, VA 22908.

B.D. Wilson: Department of Dermatology, Roswell Park Cancer Institute, Buffalo, NY 14263.

Contents

A spectrum of benign premalignant and malignant lesions of the external genitalia, particularly the penis, has been reported. In the following section, the common cutaneous lesions of the penis are described. Benign, premalignant, and malignant lesions of the penis are presented in the succeeding section. Important, unusual dermatologic lesions also are presented.

CUTANEOUS LESIONS OF THE PENIS

Part of "44 - DERMATOLOGIC LESIONS OF THE PENIS "

Pearly Penile Papules

Pearly penile papules are asymptomatic dome-shaped papules on the coronal margin and sulcus (Fig. 44.1 and Fig. 44.2). Histologically, vascular networks are surrounded by dense connective tissue (2,67). No therapy is required.

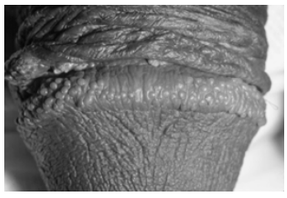

FIGURE 44.1. Pearly penile papules are dome-shaped on the coronal margin and sulcus. See also Color Figure 44.1.

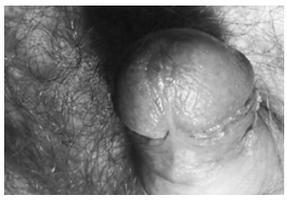

FIGURE 44.2. Dome-shaped pearly penile papules on the coronal margin.

Angiokeratomas

Traub and Tolmach (128) presented a comprehensive study of the literature in reporting a case of angiokeratoma of Mibelli, noting that “angioma plus keratosis does not constitute angiokeratoma of Mibelli, for an angiokeratoma of Mibelli is not an angioma; the condition is merely an alteration in the blood vessels associated with hyperkeratosis of the epidermis.” Although Mibelli's cases had a predilection for the hands, feet, and elbows and had a previous history of pernio, Fordyce reported cases of the scrotum; cases of angiokeratomas in atypical locations are reviewed by Traub and Tomach (128) (Fig. 44.3 and Fig. 44.4).

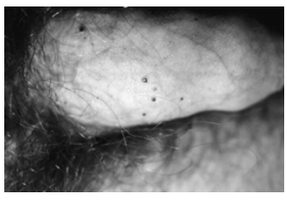

FIGURE 44.3. Violaceous and erythematous papules with variable scaling located on the scrotum. See also Color Figure 44.3.

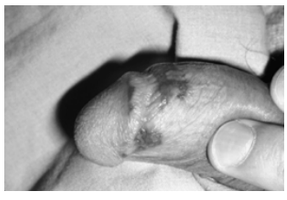

FIGURE 44.4. *Candida albicans* as a secondary infection on moist papules on the glans penis. See also Color Figure 44.4.

Imperial and Helwig (61) reported the clinicopathologic findings in a review of 35 cases of angiokeratoma of Fordyce. The combined features of angiokeratomas are (a) marked vascular dilation of the papillary vessels, forming a large lacuna in the papillary region of the dermis; (b) acanthosis and elongation of the rete ridges encircling vascular lacunae, suggesting the formation of a blood cyst; (c) an intimate vascular and epidermal relationship; (d) moderate to marked hyperkeratosis; and (e) a direct communication between the vascular cystic paces in the dermal papilla and the dilated veins in the deeper dermis. The cause of angiokeratomas is unknown, but two-thirds of the patients reported had a history of venous obstruction (4,108).

Venous Lakes

Venous lakes have been reported on the glans penis (72). Clinically, these lesions are dark blue, but pressure removes most of the blood, leaving a reddish color. Histologically,

the lakes have thin walls, little muscle tissue, and mostly, a single cell layer of endothelium. They lack elements that make them spontaneously contractile. Therapy can include local excision or destruction by desiccation (72). Sclerotherapy has been reported for other vascular blemishes but not specifically for venous lakes, and argon or tunable dye laser surgery has been used with success in the treatment of venous lakes (16). The differential diagnosis may include lymphangiomas (Fig. 44.5).

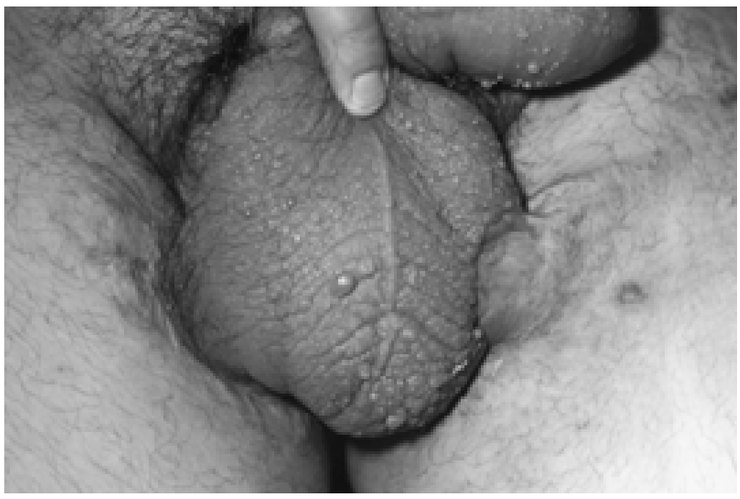

FIGURE 44.5. Lymphangioma resembling papules of Fox-Fordyce. Erythematous papules on the shaft and scrotum. See also Color Figure 44.5.

Angiolymphoid Hyperplasia with Eosinophilia

Wells and Whimster (134) first suggested angiolymphoid hyperplasia with eosinophilia as a distinct pathologic entity in a study of nine patients, and Rao and associates (105) first reported a case occurring on the penis. This is a benign condition that may persist for years. The nodules are predominantly in the subcutaneous tissue; however, some may enter into the dermis or underlying muscle fascia or muscle. They are unencapsulated masses of angiolymphoid hyperplasia with four components: (a) exuberant proliferation of capillary vessels, frequently canalized masses of endothelium; (b) massive infiltration of eosinophils and increased numbers of mast cells; (c) reticulin formation but little fibrosis; and (d) lymphoreticular hyperplasia, increasing with duration, and often lymphoid follicle formations in lesions of 1 year's duration or more.

Epithelioid hemangioma is probably a variant of angiolymphoid hyperplasia with eosinophilia (122). Ultrastructural studies and immunohistochemical analysis for factor VIII–related antigen and ulex europaeus agglutinin I demonstrated that the lesions were of endothelial origin.

The differential diagnosis may include eosinophilic granuloma, lymphocytoma and follicular lymphoma, atypical pyogenic granuloma, angiomatous lymphoid hamartoma, persistent reactions to insect bites, and eosinophilic lymphofolliculosis of the skin, or Kimura's disease (134).

Verruciform Xanthoma

Verruciform xanthoma was described initially as an oral lesion either normal or reddish in color or sometimes pale or "hyperkeratotic," having a rough, pebbly surface with either a sessile or pedunculated base (114); however, this lesion also occurs on the penis (41,73,81). Verruciform xanthoma is a rare benign tumor. The differential may include verrucous carcinoma, wart, squamous cell carcinoma, and seborrheic keratosis. Serum triglycerides, cholesterol, and glucose determinations usually are normal. (33,91,92,129).

Histologically, the squamous epithelium reveals hyperkeratosis, acanthosis, and parakeratosis (73,110). The upper dermis contains a diffuse collection of round cells with abundant cytoplasm and a centrally located, small vesicular nucleus. Electron microscopic studies (110) reveal histiocytes distended with lipid vacuoles of various sizes and electron density (110). Treatment is usually by conservative excision.

Lichen Sclerosus Et Atrophicus

The characteristic lesion of lichen sclerosus et atrophicus (LSA) is an irregular, often polygonal, flat, ivory-colored lesion (Fig. 44.6). The lesion may be topped by whitish papules that can be slightly elevated, with a rosy or moderately pigmented zone around the lesion. These papules may coalesce to form a plaque, but in general the outline of the indurated papules can be determined. Each papule has on its shiny, smooth surface one to several black or dark, horny, comedo-like plugs, or minute, beadlike depressions, which show the former sites of horny plugs. As atrophy occurs, the keratotic plugs or central delling becomes more prominent. At times, keratotic plugging is formed only histologically, not clinically. At end stage, a white parchmentlike wrinkling may occur (Fig. 44.7).

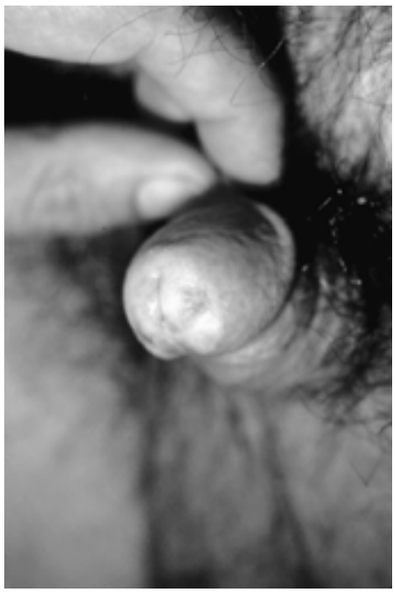

FIGURE 44.6. Progressive circumferential sclerosis at the meatus in lichen sclerosus et atrophicus (can lead to stenosis). See also Color Figure 44.6.

FIGURE 44.7. End-stage stenosis is present on glans with parchmentlike atrophy.

LSA occurs at any age, with the average age being 50 years, although it is reported to be associated frequently with phimosis in boys and in the elderly (9,24,27,36,55,107). All races appear to be affected (62). The cancer risk in childhood is low but is suggested to be 5% in women (79). LSA is less common in circumcised males (131) and is the most common indication for circumcision in children (107). Anal stenosis has been reported in association with LSA (118).

Histologically, the earliest lesions demonstrate papillary dermal edema, with flattening of the rete ridges and papillary bodies and separation of elastic tissue from the papillary bodies of the epidermis. There is a superficial perivascular

infiltrate predominantly composed of lymphocytes, which may be sparse or dense. With progression, lesions may demonstrate a variable degree of inflammation in the middermis, at times bandlike in formation. The epidermis shows hyperkeratosis with atrophy and keratotic plugging of dermal appendages. There is increased papillary edema with vacuolar formation at the dermal–epidermal junction and, on occasion, liquefaction necrosis suggestive of lichen planus. There may be subepidermal bullae with edema of the papillary dermis.

Ultrastructure studies of lichen planus–like lesions show normal dermal collagen fibers in contrast to idiopathic lichen planus, in which fibers were referred to as *thin* or *beaded* (84).

LSA has been reported to occur following radiation therapy and also may occur as an isomorphic response (135). Organ-specific antibodies found in patients with LSA suggest an autoimmune process (47).

LSA of the penis may not induce malignancy but has been reported in association with penile malignancies (13,32,132). Early circumcision has been suggested to possibly prevent the development of LSA (39,77).

Therapy for LSA has included surgical excision (when feasible) with the involvement of the glans penis (138). Intralesional and sublesional injection of corticosteroids also may be effective (20).

Psoriasis

Psoriasis is a familial papulosquamous disease that frequently involves the glans penis, similar to lichen planus and lichen nitidus. Individual papules or coalescent plaques can be present (29,48) (Fig. 44.8). Most often, therapy is the use of less potent topical corticosteroids (29).

FIGURE 44.8. Typical erythematous psoriatic papules on the glans penis and sulcus. See also Color Figure 44.8.

Histologically, there is acanthosis of the epidermis with elongation of the dermal papillae, increased mitosis in the basal zone, an absent or diminished stratum granulosum, and microabscesses of polymorphonuclear leukocytes in the epidermis. The dermal infiltrate is composed primarily of lymphocytes and histiocytes.

Patients undergoing phototherapy for psoriasis with oral 8-methoxpsoralens and ultraviolet A radiation (UVA, PUVA) have been reported to have an increased risk of developing penile and scrotal tumors (119,123). There is a divergence of opinions comparing the European, Japanese, and American experience relating to the development of cutaneous carcinomas (123).

A modified Goeckerman regiment using tar preparations before ultraviolet B radiation (UVB) has been suggested as a promoter of carcinogenesis initiated by coal tar (86,120). Other possible factors as cocarcinogens with PUVA are ionizing radiation, arsenic, history of skin cancer, methotrexate, and other immunosuppressives.

Appropriate shielding of the genitalia is recommended before PUVA therapy. UVB appears to have a lower carcinogenic potential in the series of psoriatics treated (123), but genitalia also should be shielded.

Lichen Planus and Lichen Nitidus

Lichen planus and lichen nitidus are papulosquamous diseases; their exact etiologies are unknown. They are worldwide in distribution, rare in childhood, and usually seen in the 30- to 60-year-old age group. Clinically, penile lesions can demonstrate individual papules and plaques (Fig. 44.9 and Fig. 44.10), which may be hypertrophic or atrophic.

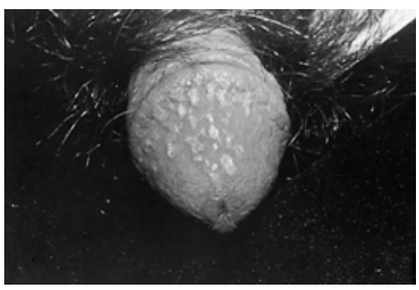

FIGURE 44.9. Polygonal violaceous papules with Wickham's striae on the glans penis.

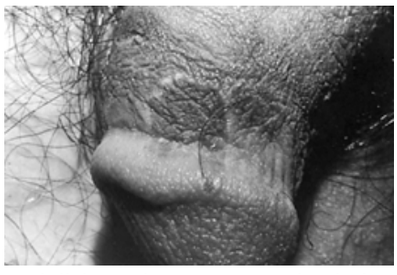

FIGURE 44.10. Papules have coalesced to annular plaques at the sulcus.

In oral lichen planus, severe dysplasia associated with the concomitant lichen planus is associated with the development of precancerous lesions (95). Twenty-five percent of patients with lichen planus have genital lesions, yet the association with malignancy is rare (8,76). In addition, the loss of epidermal antigens associated with malignant changes occurs in lichen planus without that sequela (1). Phimosis has been induced by lichen planus (64). Therapy for lichen planus depends on the extent of disease and primarily includes topical or systemic corticosteroids.

Lichen nitidus is thought by some to be a variant of lichen planus, although histologically it is distinguished by the “clawlike” focal lichenoid infiltrate at the basement membrane zone (111). Clinically, tiny, flat-topped papules are seen on the glans penis; these are usually asymptomatic but are sometimes pruritic (Fig. 44.11). Generally, no therapy is necessary; corticosteroids are usually ineffective, although they may provide symptomatic relief.

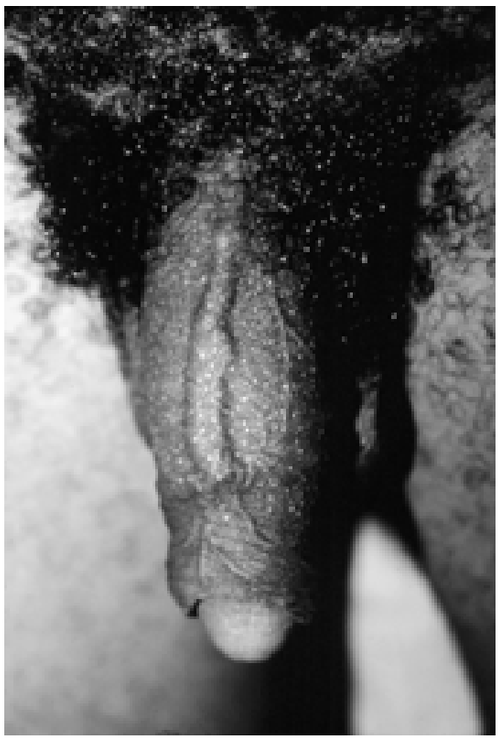

FIGURE 44.11. Numerous flat-topped papules typical of lichen nitidus on the glans penis. See also Color Figure 44.11.

Dermatitis Venenata

Penile lesions can be induced by agents that may cause a contact dermatitis (e.g., poison ivy). Neomycin-induced contact allergies are common and can produce a contact dermatitis of the glans and shaft of the penis (Fig. 44.12). Condoms, contraceptive jellies, clothing, and industrial exposures can produce a contact dermatitis as well (Fig. 44.13). Therapy includes elimination of the allergen, local compresses, and topical corticosteroids.

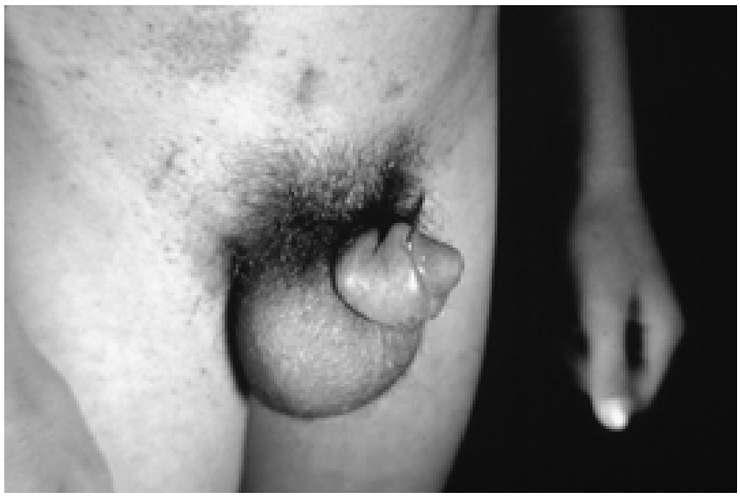

FIGURE 44.12. Contact dermatitis of the glans and shaft of the penis and the scrotum. See also Color Figure 44.12.

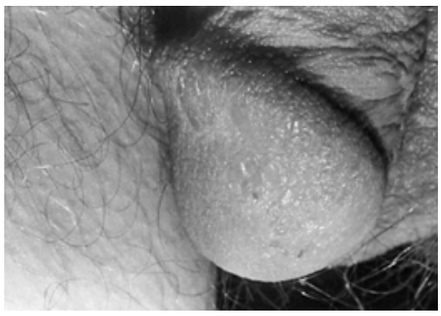

FIGURE 44.13. Early contact dermatitis caused by a condom. Demonstrates erythema on the glans and shaft of the penis.

Balanitis

Balanitis refers to inflammation of the glans and may be caused by fungal infections, such as *Candida albicans* (Fig. 44.14) or tinea (Fig. 44.15). Candidiasis may be primary or a complication of another dermatitis (94). Some sexual partners may be allergic to the *Candida* organism. Circumcision may be necessary in resistant cases. Some cases are idiopathic (Fig. 44.16). Autodigestion of the glans penis and urethra by activated transplant pancreatic exocrine enzymes has been reported (127). Squamous cell carcinoma has been reported in association with chronic herpes simplex balanitis (37).

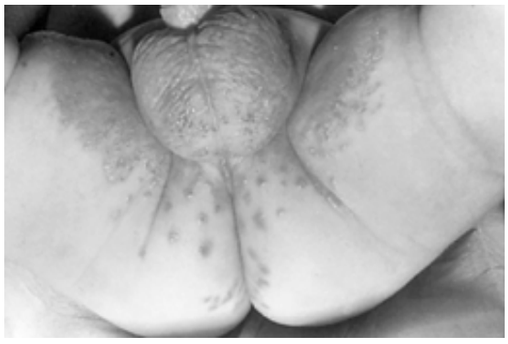

FIGURE 44.14. Satellite pustules typical of Candida extend throughout the groin, including the scrotum and penis.

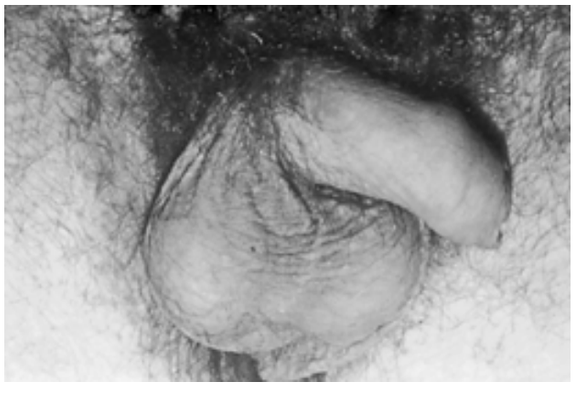

FIGURE 44.15. Tinea involving the groin, scrotum, and penis.

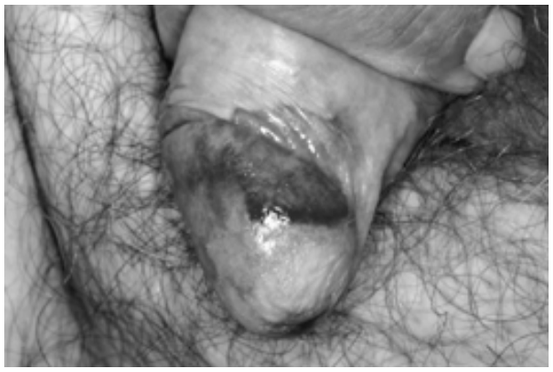

FIGURE 44.16. A moist plaque found in nonspecific balanitis on the glans penis. See also Color Figure 44.16.

Zoon's balanitis (137) affects the glans and prepuce in middle-aged and elderly men. The surface is shiny and moist (Fig. 44.17). Histologically, there is an intense plasma cell infiltrate.

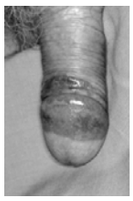

FIGURE 44.17. Zoon's balanitis occurs more typically on the glans and prepuce of the penis. See also Color Figure 44.17.

Fixed Drug Eruptions

Fixed drug eruptions are circumscribed lesions that recur persistently at the same site with ingestion of the inciting drug. Initially, an erythematous, elevated patch that may become bullous is present (Fig. 44.18). Fixed drug eruptions have been reported from tetracyclines (30), sulfamethoxazole-trimethoprim (Septra), and cotrimoxazole (6,125). Other drugs exacerbate fixed drug eruptions less frequently (26). Fixed drug eruptions can present with a hemorrhagic-appearing bulla on the glans penis (Fig. 44.19).

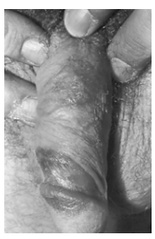

FIGURE 44.18. Fixed drug reaction to tetracycline with two nummular patches on the glans and shaft of the penis.

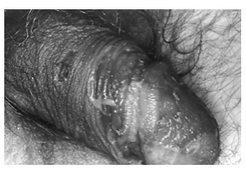

FIGURE 44.19. A bullous fixed drug reaction with subsequent denudation of the epidermis.

Cysts of the Penis

Median raphe cysts of the penis occur primarily on the ventral aspect of the penis in young men (46) (Fig. 44.20). The postcoital development of median raphe cysts has been reported (115).

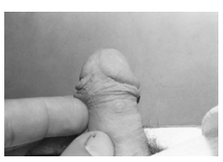

FIGURE 44.20. This nodule on the ventral shaft is a median raphe cyst.

Cysts of the median raphe represent defects in the embryonal development of the genitalia (7,46,112,126). Asarch and co-workers (7) noted two theories regarding their origin: (a) they arise from epithelial nests incidental to incomplete closure of the urethral or genital fold, or (b) they develop from split-off outgrowth of epithelium after primary closure of the folds. Locally, irregularly shaped, empty cystic spaces are present in the cutis without connection to the overlying epithelium (7,46). They are lined by pseudostratified columnar epithelium. Surgical excision is the treatment of choice.

Serotonin-storing cells were detected in several varieties of median raphe cysts, suggesting that these cysts arise from the endodermal part of the urethra (38). The differential diagnosis includes apocrine cystadenoma (54), mucoid cyst (28), epidermal cyst, steatocystoma, glomus tumor, dermoid cyst, and urethral diverticula.

Mucoid Cysts

Mucoid cysts of the penis are rare lesions that usually present as small, superficial masses on the prepuce or glans penis (28). Although apparently cystic clinically, histologically the cystic nature is not always evident. The characteristic histologic findings of the cysts include a lining of stratified columnar epithelium often associated with mucous cells or mucous glands or both. These cysts probably arise from ectopic, urethral mucosa-entrapped remnants remaining in penile skin during embryologic development.

Amyloidosis

Primary amyloidosis of the penis is rare (17,75,133). The penile lesions are painless, tan or yellow, rubbery nodules. Amyloidosis is characterized by an extracellular deposition of fibrillar proteins that demonstrate beta-pleated sheets on x-ray diffraction, a positive Congo red stain, and a green birefringence in polarized light. Secondary amyloidosis is associated with chronic granulomas, lymphomas, rheumatoid arthritis, and other chronic diseases (Fig. 44.21).

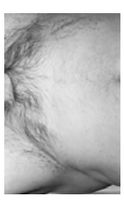

FIGURE 44.21. Secondary amyloidosis with papules in the groin.

Therapy for amyloidosis is contingent on the symptoms. Radical surgery with reconstruction of the urethra or glans penis may be necessary if symptoms of urinary obstruction are present (22,96). Other cases may not require therapy.

Epidermal Cysts

Epidermal cysts are common, although not frequently described. Most small epidermal cysts occur on the shaft

(Fig. 44.22). They vary in size from 1 mm to several millimeters. Therapy is simple excision or marsupialization of the cyst wall.

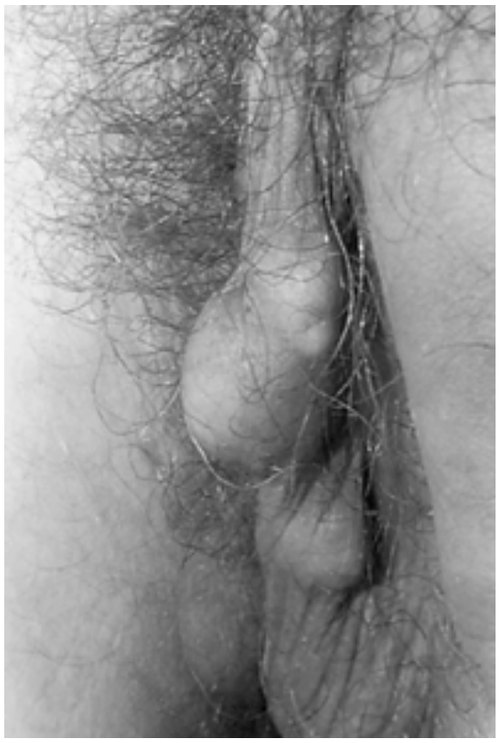

FIGURE 44.22. Epidermal cysts at the base of the shaft of the penis.

Tuberculosis of the Penis

Tuberculosis of the penis is rare, and in a review of 110 cases, 72 were the result of ritual circumcision (78). Three modes of presentation occur: (a) a primary, usually ulcerative lesion of the glans; (b) secondary to a tubercle elsewhere in the urogenital tract, usually by extension from the urethra; and rarely, (c) by hematogenous spread. A number of authors have subsequently reported cases of tuberculosis of the penis (3,25,66,74,90,116).

Histologically, the epidermis may show an ulceration;however, the dermis contains tuberculoid granulomas with many giant cells and foci of caseation. Therapy is by antituberculosis drugs, with or without adjunctive surgery.

Elephantiasis of the Penis

Elephantiasis is characterized by a persistent and morbid enlargement of the affected parts (35). The cause of elephantiasis is an obstruction classified as (a) infectious, (b) noninfectious, or (c) idiopathic.

Infectious causes may include filariasis, erysipelas, lymphogranuloma inguinale, chancroid, syphilis, leprosy, and nonspecific skin infections (35,69,85). Noninfectious causes are all mechanical and include scars, constricting bands, and ablation of lymphatics, for example, surgical treatment of cancers. Idiopathic etiologies include Milroy's disease and a number of unclassified disorders.

Therapy is contingent on the cause and resultant deformity (31,35,69).

Scabies

Epidemics of scabies, occurring in 30-year cycles with a 15-year hiatus between the end of one epidemic and the beginning of the next, have been noted (98). The cyclic nature has been attributed in part to “prompting factors,” such as poverty, poor hygiene, sexual promiscuity, and other socioeconomic factors. There appear to be important immunologic factors in the pathogenesis of scabies. A functional, delayed hypersensitivity reaction is associated with partial immunity if cured after sensitization to the etiologic agent (23). Interdermal skin tests are positive after 6 months of disease. Further studies of Norwegian scabies demonstrates a predilection for the mentally retarded and physically debilitated (89). These patients may have a specific anergy to interdermal tests. Norwegian scabies occurs in recipients of renal transplants and in other immunosuppressed patients (100).

Orkin (98) describes several forms of scabies: (a) Scabies in clean persons shows minimal findings; burrows are difficult to find. This form often is misdiagnosed. (b) Scabies incognito follows the use of topical corticosteroids; the distribution and morphologic features may be

atypical. When other concurrent skin diseases are present (e.g., psoriasis, mycosis fungoides), scabies can be overlooked. (c) Nodular scabies is manifested by pruritic nodules that occur predominantly on covered body areas, including the male genitalia, the groin, and axillary regions. Histologically, these nodules may stimulate lymphoma, cytosis, or arthropod bites. (d) Animal-transmitted scabies, of which the major source is dogs, has a greater ease of transmission but is usually self-limited unless the patient is reexposed to the canine source. (e) Scabies in children may appear as eczematous or papulovesicular with an atypical distribution including the head, neck, palms, and soles. (f) Scabies with syphilis coexists with other venereal diseases. (g) Norwegian scabies is highly contagious owing to the increased number of organisms; it usually is seen in institutional patients (the elderly and mentally retarded).

Scabetic papules localized to the penis may be erythematous, nodular, or excoriated (Fig. 44.23). Therapy may include the use of 1% lindane cream or lotion or 10% crotonotoluide in males (98). Permethrin 5% cream now is considered the treatment of choice in infants and small children because of its high efficacy and low risk of side effects (99).

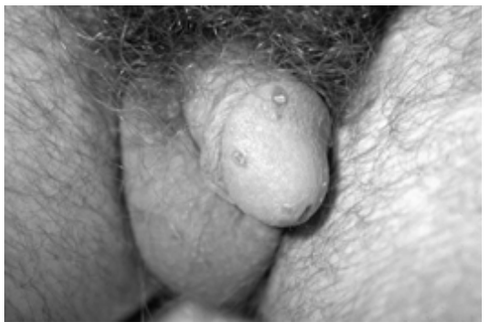

FIGURE 44.23. Scabies with papules on the glans and shaft of the penis.

See also Color Figure 44.23.

Patients who are immunosuppressed may develop Norwegian scabies resistant to lindane (5,21). Multiple drug therapies have been intensively required. Oral ivermectin has shown promise as a systemic therapy for endemic scabies (58).

PENILE TUMORS

Part of "44 - DERMATOLOGIC LESIONS OF THE PENIS "

Penile tumors often create anxiety in the patient and may be seen early in their development, especially in the young or middle-aged man. Proper management is contingent on the recognition of benign, premalignant, and malignant neoplasms on both clinical and histologic criteria. However, there are entities whose clinical and histologic appearance defy easy characterization. This section presents and summarizes some of the more common skin tumors of the penis. Carcinoma of the penis is discussed in Chapter 43 .

Pseudoepitheliomatous, Keratotic, and Micaceous Balanitis

Pseudoepitheliomatous, keratotic, and micaceous balanitis (PKMB) is a rare tumor characterized by thickened, scaly, and micaceous patches on the glans penis, and although considered benign, it is capable of becoming locally invasive and should be treated like other tumors of low-grade malignant potential (11). This condition occurs exclusively in older men and follows a prolonged course. Although some reports (11,82) note a history of phimosis, others do not (106).

Histologically, there is massive hyperkeratosis, acanthosis, and mild rete ridge hypertrophy. There may be mild dysplasia but no cytologic changes to suggest malignancy (50). However, with dermal invasion, some authors have suggested the appearance of early carcinomatous changes (12). An inflammatory infiltrate may be present in the dermis, but its severity is variable.

The histologic features and tendency toward recurrence are suggestive of verrucous carcinoma (14,65). The term *micaceous and verrucous malignant balanitis* has been suggested (14). PKMB has demonstrated chronicity and a benign pattern over years (63); however, there was an associated fatal fibrosarcoma occurring in the same patient.

The differential diagnosis of PKMB includes squamous cell carcinoma, keratoacanthoma, erythroplasia of Queyrat (Bowen's disease), penile horn, and giant condyloma (Fig. 44.24).

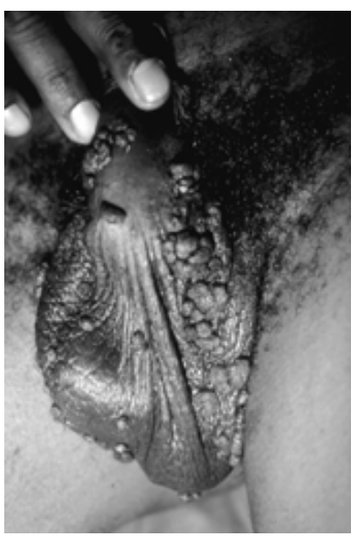

FIGURE 44.24. Condyloma acuminatum with hyperkeratotic papules on the glans penis and sulcus. See also Color Figure 44.24.

Conservative surgical management has been attempted, but local recurrences have been noted. Mohs' surgical excision appears to be the treatment of choice for PKMB, because the margins are well-controlled, ensuring tumor extirpation. Radiation therapy can be considered when surgical excision would be mutilating.

Penile horns have been associated with and are seen more frequently in circumcised men and have been associated with chronic irritation, verrucae, surgical trauma, keratoacanthoma, and squamous cell carcinoma (102,104).

Bowenoid Papulosis

Bowenoid papulosis probably has been recognized on occasion as a histologically malignant-appearing disease, usually with a benign course (40,71). The term *bowenoid papulosis* was coined to delineate this disease complex, which is characterized histologically by the features of Bowen's disease (squamous cell carcinoma in situ) but associated clinically with a benign course, because clinical impressions are those of benign diseases in prebiopsy diagnosis (42,52,55,68,71,113).

Clinically, the papules occur predominantly on the shaft rather than on the glans of the penis (Fig. 44.25), which may clinically suggest a diagnosis of papulosquamous diseases (psoriasis, lichen planus), a linear nevus, or more frequently, verrucae (124,130). Some present symptomatically as pruritus ani (121).

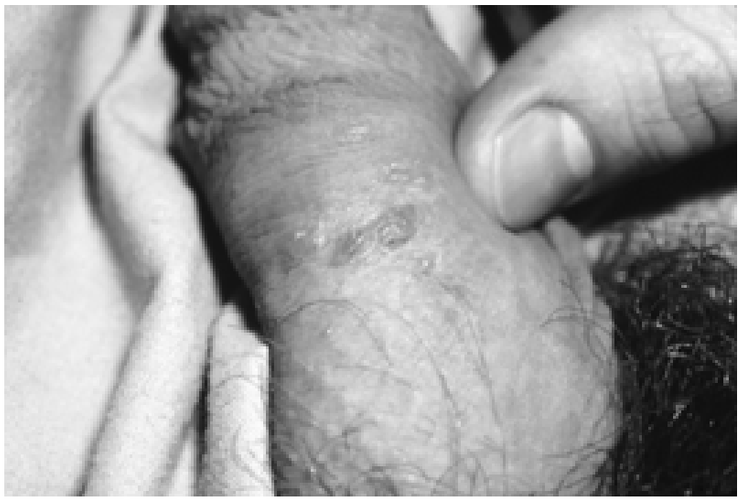

FIGURE 44.25. Papular Bowes's disease on the shaft of the penis. See also Color Figure 44.25.

Clinical features that distinguish bowenoid papulosis from Bowen's disease include early onset, occurrence in uncircumcised men, and multiplicity of lesions. The duration of the disease varies from less than 2 months to more than 10 years. It has been reported in women as well, with a frequency equal to that of males (130,136).

Histologically, there is hyperkeratosis with prominent parakeratosis; psoriasiform epidermal hyperplasia; a focally prominent granular zone, with crowding of epidermal nuclei; an increased number of mitotic figures at all levels of the epidermis; atypical keratinocytes with large hyperchromatic and pleomorphic nuclei; multinucleated keratinocytes; and atypical mitotic figures. The papillary dermis contains dilated vessels suggestive of verrucae with a superficial infiltrate of lymphocytes and histiocytes. Although initial electron microscopy failed to demonstrate viral particles, viruslike particles in bowenoid papulosis have been described.

The human papillomavirus (HPV) has been demonstrated with nick-translated, biotinylated DNA probes for HPV types 6, 22, 16, and 18 in giant condylomata, Bowen's disease, verrucae, and highly differentiated verrucous carcinoma (56,57,80,101), and HPV types 6 and 11 have a tendency to reflect a benign course compared with HPV types 16 and 18, which reflect a malignant trend. However, there are exceptions to the rule (43,44,80).

Bowenoid papulosis was suspected to be sexually transmitted (10,60) to a male sexual partner of a woman with squamous cell carcinoma and an HPV infection. Similarly, sexual partners of those with bowenoid papulosis are at increased risk of cervical cancer (93,109).

There have been reports of spontaneous regression of lesions, although bowenoid papulosis has progressed to Bowen's disease (34). No known cases have progressed to include squamous cell carcinoma or metastasis; however, some lesions may be locally aggressive, specifically with meatal involvement.

Therapy may include surgical excision, electrodesiccation with or without curettage, cryosurgery, CO_2, or neodymium:yttrium-aluminum-garnet (Nd:YAG) laser surgery (70), topical fluorouracil, salicylic acid, topical steroids (130), and interferon (53).

Erythroplasia of Queyrat

Queyrat described erythroplasia of the glans penis, suggesting that this disease represented a precancerous process, although the histologic features were of Bowen's disease (103).

Paget is said to have written the first report describing a similar case, which was also considered premalignant (87), and Brown (19) followed a case histologically for 5 years, reporting on its eventual outcome. Clinically, these lesions may appear as an erythematous patch, as papules similar to bowenoid papulosis, or as warts (Fig. 44.26,Fig. 44.27 and Fig. 44.28) (49).

FIGURE 44.26. Bowen's disease with an erythematous localized patch on the shaft of the penis. See also Color Figure 44.26.

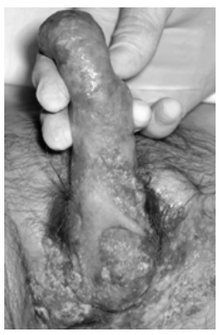

FIGURE 44.27. Bowen's disease extends from the scrotum to the shaft of the penis. See also Color Figure 44.27.

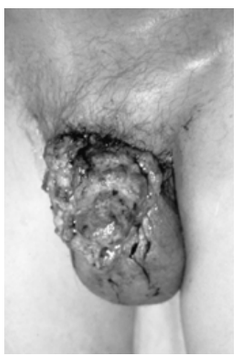

FIGURE 44.28. Papular Bowen's disease suggestive of condyloma is on the shaft near the sulcus. See also >Color Figure 44.28.

Therapy includes 5-fluorouracil (45), Mohs' micrographic surgery (15,88), and laser surgery (18,51).

Giant Condylomata Acuminata

Condylomata acuminata may extend to the glans, prepuce, and shaft of the penis or may be localized (97) (Fig. 44.29 and Fig. 44.30). Giant condylomata can have the gross clinical appearance of cancer (83,117).

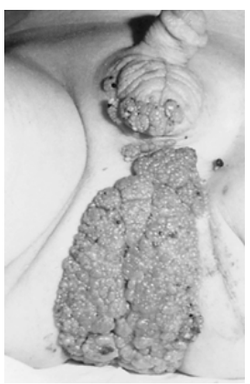

FIGURE 44.29. Condyloma acuminatum verrucous nodules extending from the rectum to the scrotum.

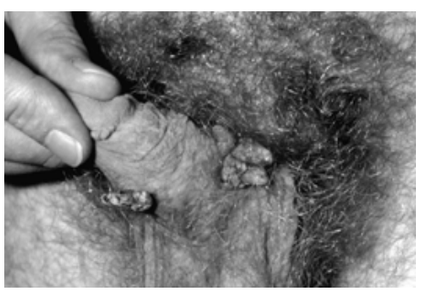

FIGURE 44.30. Early papules of condyloma acuminatum. See also Color Figure 44.30.

Histologically, giant condylomata may be benign or malignant; malignant condylomata can be distinguished microscopically from benign giant condylomata. In malignant lesions, the prickle cell layer is reduced and replaced by large, pale cells without cellular bridges; these cells may be

vacuolated and multinucleated with occasional mitotic figures. The basal layer may contain pleomorphic nuclei. The central areas often contain keratohyaline material in addition to inflammatory cells. These features classify malignant condylomata as intermediate between squamous cell carcinoma and giant condylomata acuminata.

Treatment of giant condyloma includes conventional or Mohs' micrographic excisional surgery (59,88).

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SECTION II
PEDIATRIC UROLOGY

45

EARLY DEVELOPMENT OF THE GENITOURINARY TRACT

Douglas E. Coplen

Joseph Ortenberg

D.E. Coplen: Department of Surgery, Division of Urology, Washington University–St. Louis; Division of Pediatric Urology, St. Louis Children's Hospital, St. Louis, MO 63110.

J. Ortenberg: Division of Pediatric Urology, Children's Hospital; Departments of Urology, Louisiana State University & Ochsner Clinic, New Orleans, LA 70118.

Contents

An understanding of the development of the genitourinary tract is essential in the diagnosis and management of congenital anomalies of the urinary tract. Embryologically, the genital and urinary tracts are intimately related. Although much is known regarding the morphologic development of the genitourinary tract (26,80,92,109), it is only during the last few years that some of the molecular mechanisms involved in these processes have been identified. This is largely a result of the identification of genes expressed during development and the use of techniques for single-gene disruption (62,65).

An error in any of a multitude of molecular steps can result in abnormal genitourinary development. Teratogens in early embryonic life can also affect the developing embryo. A maternal viral infection can increase the incidence of urologic anomalies (53), as can exposure to progestational (masculinizing) agents. Physical forces can also result in physical changes in the fetus even late in gestation (112).

The urogenital system is derived predominantly from the intermediate mesoderm of the early embryo. This mesoderm undergoes epithelial transformation to form the ducts and tubules that make up the urogenital tracts and kidneys (99) (Table 45.1). The mesonephric duct forms in the cervical region and progresses caudally toward the cloaca. This duct is important in the formation of the upper urinary tract, seminal transport system, and female reproductive tract.

TABLE 45.1. ADULT DERIVATIVES AND VESTIGIAL REMNANTS OF EMBRYONIC UROGENITAL STRUCTURES

Male	Embryonic Structure	Female
Testis	Indifferent gonad	*Ovary*
Seminiferous tubules	Cortex	*Ovarian follicles*
Rete testis	Medulla	*Medulla*
Ductuli efferentes	Mesonephric tubules	Epoophoron
Paradidymis		Paroophoron
Appendix of epididymis	Mesonephric duct	
Ductus epididymis		Duct of epoophoron
Ductus deferens		Gartner's duct
Ureter, pelvis, calyces, and collecting tubules		*Ureter, pelvis, calyces, and collecting tubules*
Ejaculatory duct and seminal vesicle		
Appendix of testis	Paramesonephric duct	*Uterine tube* *Uterus* *Vagina*
Urinary bladder	Urogenital sinus	*Urinary bladder*
Urethra		*Urethra*
Prostatic utricle		*Vagina*
Prostate gland and bulbourethral glands		*Urethral and paraurethral glands*
Penis	Phallus	*Clitoris*
Ventral aspect of penis	Urogenital folds	*Labia minora*
Scrotum	Labioscrotal swellings	*Labia majora*

*Functional derivatives are in italics.

RENAL AND URETERAL DEVELOPMENT

Part of "45 - EARLY DEVELOPMENT OF THE GENITOURINARY TRACT "

The development of the kidney and ureter are intimately related. An abnormality of one structure is often associated with an abnormality in the other. Normal development of the kidney and ureter has been described using data derived from microdissection of fetal specimens (26,92). Renal development depends on the presence of the urogenital ridge that contains the nephric, gonadal, and genital duct primordia (Fig. 45.1B). The three distinct stages of renal development—the pronephros, mesonephros, and metanephros—develop sequentially and are found in the ridge (26,80,92,109).

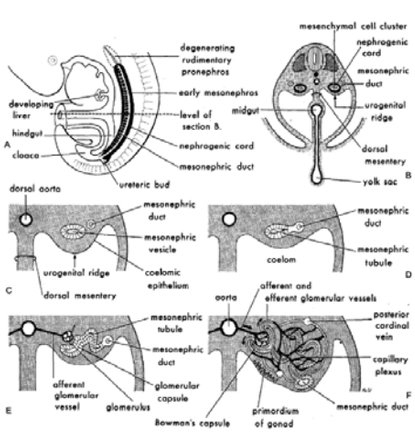

FIGURE 45.1. A: Sketch of a lateral view of a 5-week embryo shows the degenerating pronephros and the extent of the mesonephros. **B:** Transverse section through the embryo showing the urogenital ridge that contains the nephric, gonadal, and genital primordia. **C** to **F:** Transverse sections showing development of mesonephric tubule. The vesicle coalesces with the mesonephric duct and develops a cuplike outgrowth with a capillary ingrowth (a primitive glomerulus). The branching increases the surface area, enhancing the capacity for interchanging material with the blood. (From reference 80, with permission.)

The pronephros is the earliest stage in nephric development in humans. The pronephros is the mature excretory structure in primitive vertebrates but does not have function in humans. The nephrogenic cord undergoes epithelial transformation to form tubules that connect with paired pronephric ducts that extend caudally and empty into the

cloaca. The pronephros completely disappears by the fourth embryonic week. If the pronephros or its duct do not develop, the mesonephros will not appear.

The mesonephros is present between the fourth and eighth weeks of gestation. The mesonephros is the permanent kidney in amphibians and may function transiently in mammals until the metanephros develops. The mesonephros consists of glomeruli and tubules that drain into the mesonephric duct (Fig. 45.1D to Fig. 45.1F). As tubules are forming in the lumbar region, the thoracic tubules degenerate. By the ninth week, most of the mesonephros has disappeared, except for the duct and a few tubules that persist as genital ducts in males or vestigial remnants in females (see Table 45.1 and subsequent section on urogenital development).

The kidneys (metanephros) begin development in the fifth week, when the ureteral bud appears on the lower end of the mesonephric duct near its entry into the cloaca (Fig. 45.1A). The metanephros forms as result of a reciprocal epithelial-mesenchymal interaction between the ureteral bud and the metanephric blastema (38,62,65,99). Signals from the ureter induce metanephric mesenchyme in the caudal part of the nephrogenic cord to condense and proliferate. Reciprocal signals from the mesenchyme induce the ureteral bud to grow and branch (38). An abnormality in either the ureteral bud or the metanephric mesenchyme adversely affects renal development.

As the ureteral bud grows cephalad, the metanephros enlarges and rapidly differentiates. The cephalad end of the ureteral bud expands within the metanephros to form the renal pelvis. Outgrowths from the renal pelvis push radially into the metanephros and form primary collecting ducts. As the kidney grows, the tubules continue to branch into the peripheral zone of the kidney. The major calyces subdivide, and the tubules that drain into a minor calyx constitute a renal pyramid.

The nephron, which consists of the glomerulus, proximal convoluted tubule, loop of Henle, and the distal convoluted tubule, is derived from the metanephros. Vesicular masses that arise from the mesoderm adjacent to the ends of the collecting ducts develop a central cavity and become S-shaped. One end of the S develops into the distal convoluted tubule that connects with the terminal end of the collecting tubules. The other end becomes the glomerulus and Bowman's capsule.

Nephron development occurs at an exponential rate. More than 80% of nephrons have developed by the middle of the second trimester, and nephron formation is complete by 36 weeks (92). Urine formation begins at 8 weeks and continues throughout gestation. Fetal kidneys contribute urine to the amniotic cavity and maintain the appropriate volume of fluid that is essential for normal lung development. They play only a small role in salt and water balance, which is managed by the placenta. Oligohydramnios is associated with pulmonary hypoplasia and compression deformities of the head, thorax, and extremities.

The rate of urine production is substantial in the fetus and approaches 50 mL per hour (96). This urine is hypotonic compared with fetal and maternal serum, having a sodium concentration of less than 100 mEq/mL, chloride less than 90 mEq/mL, and osmolality less than 210 mOsm/mL (34,35).

Molecular Basis of Ureteral Budding and Metanephros Differentiation

The importance of a gene in development is shown if three conditions are met (62,65). First, the gene must be expressed where organ development is occurring. Second, the

gene must be expressed during organ development. Third, if the gene is disrupted, normal organ development must not occur. There are now more than 250 candidate genes/proteins that are listed in the Kidney Development Database (19). This database was started in 1993 and is rapidly enlarging. There were 27 new entries between January 1999 and June 2000. Figure 45.2 shows genes that are clearly required for nephrogenesis, although clearly not completely defining the process. Excellent reviews cover renal and ureteral development (62,65). A flowchart of many mechanistic controls of nephrogenesis is shown in Fig. 45.2 .

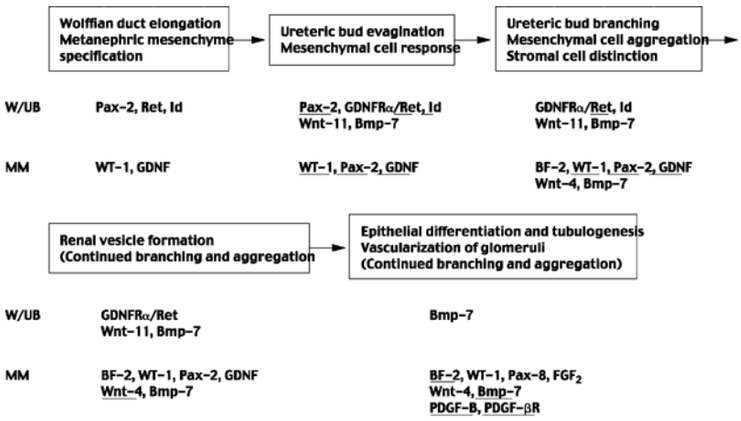

FIGURE 45.2. Flowchart indicating some of the critical genes involved in metanephric kidney development. Boxes summarize the steps in organogenesis. Listed genes are expressed during these periods and are grouped according to expression in the wolffian duct and ureteric bud *(W/UB)* or the metanephric mesenchyme *(MM).* Genes that are required primarily for certain steps in development are in boldface and underlined. The genes are listed in order of appearance. The expression pattern is recapitulated as renal development continues. Genes are discussed in the text. (From reference 62, with permission.)

Examination of ureteral bud development reveals the complexity of the multiple transcription factors, growth factors, receptors, and matrix proteins involved. Mice with targeted inactivation of RET have renal agenesis and hypodysplasia (100). The primary defect is a failure of the ureteric bud to emerge and respond to signals from the metanephric blastema. The receptor ligand is produced by the metanephric blastema and has been identified as glial cell line–derived neurotrophic factor (GDNF) (126). WT-1, the transcription factor that is the product of the Wilms' tumor suppressor gene, is essential for ureteric budding (60). In the absence of this factor, the metanephros condenses, but without the ureteral bud, it undergoes programmed cell death (apoptosis). The Wnt-11 gene is expressed only in that segment of the mesonephric duct adjacent to the metanephric blastema (58). As development continues, this is expressed only at the tip of the branching bud and not at the stalk.

Wnt-4 and BMP-7 are regulators of nephron maturation. Wnt-4 transcripts are found in aggregating mesenchymal cells adjacent to the growing ureter and its branches. Mice with disrupted Wnt-4 die at birth with renal agenesis. The mesenchyme is undifferentiated, and there is little evidence of epithelial formation. Bmp-7 is a member of the transforming growth factor-ß (TGF-ß) family of signaling molecules and is initially found in the mesonephric duct and later in the metanephros (71). Deficient animals show condensation and development of the mesenchyme but few glomeruli form, and there is increased interstitial and stromal tissue in the mutant kidneys. Thus nephron development requires both ureteric bud and mesenchymal signals for conversion of mesenchyme to epithelium.

Transcription factors coordinate the expression of differentiation programs. BF-2 is localized in stromal cells surrounding the ureteric bud and differentiating metanephros. This localization relates to the proposed function in regulating ureteral growth and differentiation of mesenchymal cells (44). WT-1 (see previous discussion) and Pax-2 (see following discussion) are two additional transcription factors important in renal development.

Renal Developmental Abnormalities

A number of puzzling features are associated with developmental renal abnormalities. Most are unilateral or asymmetric and have predominance in one gender, depending on the abnormality. Genetic analyses of syndromes of multiple organ anomalies that include the kidney show both autosomal (13) and X-linked inheritance (95). Multifactorial inheritance of vesicoureteral reflux (40% to 50% of siblings) has been reported (87). It is likely that most anomalies are the result of complex hereditary traits resulting from minor mutations in multiple specific genes involved in embryogenesis (Fig. 45.3) (91).

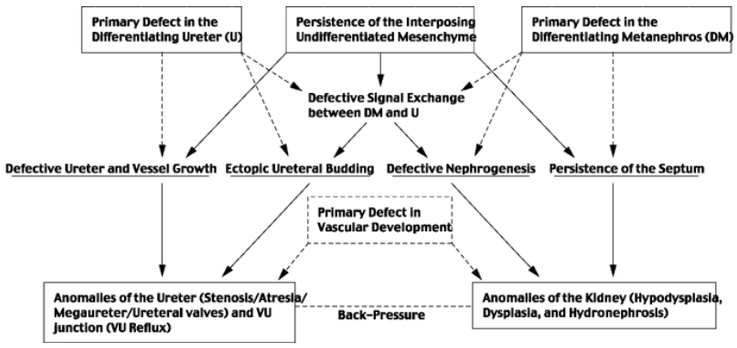

FIGURE 45.3. Potential mechanisms involved in formation of urinary tract malformations. A primary defect in the ureter or the metanephric mesenchyme can result in abnormalities of the ureter, kidney, or both structures. Persistence of undifferentiated mesenchyme disturbs normal development. Obstruction and elevated pressures imposed on the parenchyma may promote development of hydronephrosis or dysplasia. (From reference 91, with permission.)

The Pax-2 gene has been identified as a specific gene associated with renal anomalies (98). This gene is a transcriptional regulator that is widely expressed during development of both ductal and mesenchymal components of the urogenital system. In a homozygous mouse model, newborn mice lack kidneys, ureters, and genital tracts (123). Heterozygotes have kidneys that are reduced in size and hypoplastic. This is an interesting feature of this family of genes. This semidominant character of loss of function mutations is termed *haploinsufficiency.* The effect on development depends on the amount of product protein in the cell.

The renin-angiotensin system is important in renal development. The effects of angiotensin at the type 1 (AGTR1) and type 2 (AGTR2) receptors have been studied. AGTR1 is a proliferative receptor that influences hypertrophy, matrix deposition, cellular proliferation, and stimulation of growth factors. AGTR2 decreases cell growth, influences apoptosis, and stimulates antiproliferative substances (10). AGTR1 is localized to epithelial precursors in nephrogenic areas, and AGTR2 is expressed antenatally in the undifferentiated mesenchyme surrounding the ureteric bud and in the renal interstitium. Once nephrogenesis is complete, AGTR2 is no longer expressed in the upper urinary tract.

If AGTR1 is deleted, mice have progressive damage to the kidney shortly after birth. These kidneys are morphologically normal but develop progressive collecting system dilation consistent with obstruction. Histologically, the ureteral musculature and renal pelvis are poorly developed. AGTR1 allows normal development of the renal pelvis and ureter along with normal pacemaker and peristaltic activity (79).

The angiotensin type 2 receptor is important in programmed cell death. Studies show that the congenital anomalies are preceded by delayed apoptosis of undifferentiated mesenchymal cells surrounding the urinary tract during ureteral budding and expansive growth of the kidney and ureter.

AGTR2 null mutant mice display congenital anomalies of the kidney and urinary tract (86). The spectrum of renal pelvic dilation, ureteropelvic junction obstruction, multicystic dysplasia, megaureters, and nondilating reflux has been identified. As in humans, these renal abnormalities are not associated with other somatic anomalies and the inheritance

does not follow a typical Mendelian pattern. Male pups are more commonly affected than females. AGTR2 is localized on the X chromosome, which may be important in the male predominance in these anomalies.

Dysplasia

Renal hypoplasia and oligonephronia mean a deficiency in the total nephron population. Fibrosis, cartilage, and immature renal tubules characterize renal dysplasia (6). This may involve the entire kidney (multicystic dysplastic kidney) or can be segmental in nature. Dysplasia is most commonly associated with obstruction (34,35) or reflux (72).

Controversy exists concerning the role of obstruction and reflux in the development of hypoplasia and dysplasia. Mackie and Stephens (72) proposed that the abnormalities resulted from defective induction by ectopic ureteral buds and deficiencies in the ectopic sections of the metanephros as opposed to being pressure related. Certainly, obstruction can have an additive effect on the abnormal induction. When dysplasia is an isolated finding, it is almost certainly the result of abnormal metanephric induction (see previous discussion).

Renal Ascent/Vasculature

While the kidney differentiates between the ninth and twelfth week, the metanephros ascends, rotates, and revascularizes (74). Ascent occurs from the fourth lumbar vertebra to the first lumbar or twelfth thoracic vertebra as a result of both cephalad migration and caudal growth of the fetus. While the kidney ascends, the renal pelvis rotates 90 degrees from an anterior position to a medial position. Arteries that are located higher on the urogenital ridge progressively supply the kidney. Failure of any of these steps to occur results in anomalies of number, volume, position, and form.

Lateral branches off the dorsal aorta progressively supply the mesonephros. As the mesonephros involutes, most of the lateral branches disappear; however, some persist as the inferior phrenic, adrenal, renal, and gonadal arteries. There are many variations of renal arterial supply that are largely dependent on the renal position. If the kidney is ectopic, the arterial supply arises from the branches of the aorta that would have atrophied if the kidney had ascended to a normal location.

The inferior vena cava forms between the sixth and eight weeks of gestation. Ventral subcardinal veins communicate with postcardinal veins that are sequentially replaced by the dorsally located supracardinal veins. Connections between subcardinal veins result in the common drainage of the left renal, adrenal, and gonadal veins. The right adrenal and gonadal veins drain directly into the vena cava because the right subcardinal vein forms the vena cava above the renal vein. Normally, the right supracardinal vein persists as the cava below the kidneys. If the subcardinal vein persists, a retrocaval ureter occurs.

EMBRYOLOGY OF THE URETER

Part of "45 - EARLY DEVELOPMENT OF THE GENITOURINARY TRACT "

The distal end of the mesonephric duct that is incorporated into the urinary system is called the *common mesonephric duct.* This expands in trumpet fashion into the urogenital sinus (future bladder and urethra) to form half of the trigone (114).

This duct can be divided into caudal, middle, and cranial regions (Fig. 45.4). The attachment of the ureter to the mesonephric duct switches from a posterior to an anterolateral location. With expansion and absorption into the urinary tract, the orifices of the ureteral bud and mesonephric duct (wolffian) become independent and move away and settle in the bladder and urethra, respectively.

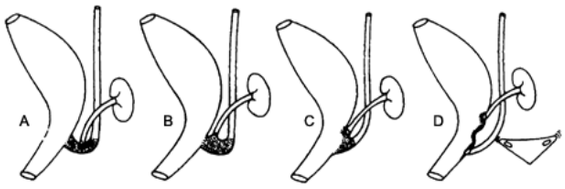

FIGURE 45.4. Embryologic rearrangement and migration of the orifices of the ureteric bud and ureters from the wolffian duct to the urinary tract and formation of the trigone. A single ureter arises from a normal position on the duct **(A)** *(middle black dot)* and migrates to the lateral cornu of the trigone **(D). B** and **C** show the expansion of the common excretory duct and wolffian duct into the urethra and bladder. (From reference 115, with permission.)

The more caudal section of the mesonephric duct ends up laterally positioned on the trigone, and the cranial position ends up in the urethra. For example, in ureteral duplication, the most caudal bud (lower pole of kidney) ends up in a more cephalad position on the trigone, and the cranial bud (upper pole of kidney) ends up at the bladder neck or urethra (ectopic) as defined by the Weigert-Meyer law (78). The location of the ureteral orifice can be related to renal development. Stephens (72) proposes that these abnormalities are programmed at the time of budding off the mesonephric duct. If the bud arises remote from the normal site, it projects into the caudal or cranial portion of the metanephric blastema and results in dysplasia. Based on this theory, abnormal ureteral budding results in the coexistence of high-grade reflux and renal dysplasia. Certainly, the previously mentioned bidirectional signaling between the bud and blastema also plays a role in these clinical findings.

Ureteroceles

A single embryologic theory does not explain all ureteroceles. Chwalla (12) suggested that incomplete breakdown of the ureteral membrane that exists between the ureteral bud and mesonephric duct is an obstruction leading to the formation of a ureterocele. It is unclear in some anatomic studies whether this membrane truly exists. This theory would explain the majority of ureteroceles but does not explain the development of ureteroceles with patulous ureteral orifices in the urethra.

Stephens (113) and Tanagho (119) suggested that the distal ureteral segment is acted upon by the same stimuli that lead to expansion of the urogenital sinus to form the bladder. In ureteroceles with patulous orifices, obstruction of the orifice by the vesical neck might result in intravesical dilation. However, if this were always true, genitourinary ectopic ureters would have ureteroceles. To reconcile this, Tanagho (119) postulated that ureterocele formation results from delayed arrival of the bud into the bladder, with expansion occurring as part of the flaring of the common excretory duct.

Mitchell has suggested that a ureterocele is the result of an abnormal induction of the trigone by many of the genes and growth factors that are important in renal growth and development. Stephens' histologic studies (113) support this concept. Histologic analysis of the intravesical portion of ureteroceles shows deficiencies in the trigonal musculature of patients with ureteroceles that were not present in ectopic ureters without ureterocele formation (113). This field defect results in pseudodiverticulum (ureterocele eversion) and reflux into laterally displaced poorly supported ureters.

GONADAL DEVELOPMENT

Part of "45 - EARLY DEVELOPMENT OF THE GENITOURINARY TRACT "

The gender of the embryo is established at fertilization when the X chromosome of the ovum is united with a paternal Y or X chromosome. The genetic sex determines the gonadal sex, which in turn causes appropriate transformation of the internal ductal system and external genitalia. Although the genetic sex is determined at conception, the gonad is initially bipotential. Differentiation of the testis precedes that of the ovary and follows a critical sequence, or the female gonad will develop by default. In the past decade, considerable knowledge has been gleaned about the role of the Y chromosome and the molecular genetics of testicular determination.

The primitive (indifferent) gonads arise from the intermediate mesoderm medial to the mesonephros. Both testis and ovary arise from three different sources: (a) the mesodermal (coelomic) epithelium (or mesothelium) situated on the posterior wall of the abdomen, (b) the mesenchyme in this region, and (c) the primordial germ cells. During the fifth week after ovulation, the mesoderm on the ventromedial side of the mesonephros thickens. The underlying mesenchyme proliferates, producing a bulge—the genital ridge (Fig. 45.1B).

During the fifth week, primordial germ cells leave the posterior wall of the yolk sac and travel along the wall of the hindgut, through the dorsal mesentery into the genital ridge (Fig. 45.1B). Migration of the germ cells into the genital ridge is promoted by various chemotactic factors from the developing gonad that may exert long-range effects (36). Long cytoplasmic processes link many germ cells together as they actively move in an amoeboid fashion. Germ cell survival, proliferation, and migration are promoted by mast cell growth factor, encoded by the Steel locus gene (22). Mast cell growth factor is the ligand that binds to the tyrosine kinase receptor for protooncogene protein encoded by the c-kit protooncogene. The c-kit ligand exists as a soluble protein as well as in a membrane-bound form (49).

Simultaneously, fingerlike projections of the coelomic epithelium extend into the genital ridge to give rise to the primary sex cords. In the 46,XY mouse embryo, the basement membrane of the coelomic epithelium is temporarily discontinuous, allowing migration of epithelial cells into the gonad, which eventually give rise to Sertoli cells or potentially the granulosa cells of the ovary in the female (54). For the gonadal ridge to form, two genes are necessary: WT-1 and SF-1. WT-1 plays a key role in gonadogenesis: Mice of both sexes missing WT-1 fail to develop both kidneys and gonads (60). In the 6-week-old human male, SF-1 has been detected in the nucleus of cells in the coelomic epithelium and in the somatic component of the gonadal primordia,

coinciding with WT-1 protein immunolocalization in the undifferentiated gonad (20).

At this point, the bipotential gonad is composed of a cortical region containing somatic and germ cells as well as a medullary region consisting of primary sex cords. At the cranial end of the gonad, cords of epithelial cells extend into the core of the gonad, forming the rete, which also joins the mesonephric duct (105). Formation of the müllerian or paramesonephric duct begins at this stage.

Extensive research has allowed a better understanding of the molecular biology of sexual differentiation. The SRY (sex-determining region of the Y chromosome) gene, situated on the short arm of the Y chromosome is pivotal in this process, but multiple other X-linked and autosomal genes are also involved. SRY encodes a protein with a high mobility group (HMG) DNA-binding domain. SRY is believed to regulate downstream gene expression either in a positive or negative fashion and functions by changing chromatin structure (77). Changes in DNA configuration may alter transcription with SRY activating the process of sexual differentiation or inhibiting a repressor of male expression (23,59). In XX males and XX true hermaphrodites, SRY is often detected (82,120). The origin of this anomalous SRY gene may be translocation of the paternal SRY from the Y chromosome onto the paternal X chromosome (28,90). Mutations in SRY cause sex reversal in 46,XY individuals (11). Mutations in the SRY gene may alter the configuration of the HMG DNA-binding domain, and these distortions in the SRY protein affect DNA-binding characteristics (43).

Sertoli cells under the influence of SRY mediate differentiation of the male gonad (68,93). Human SRY in contrast to mouse SRY does not have a transcriptional activation domain, and intermediate cofactors are likely required to activate the Sertoli cells (43). Sertoli cells migrate into the bipotential primary sex cords and induce testicular formation. Once the Sertoli cells are committed, other key genes are activated and transcribed, such as SOX-9 (SRY HMG BOX–related gene 9), DAX-1 [dosage-sensitive sex reversal (DSS)], adrenal hypoplasia gene on XP_{21}, and müllerian-inhibiting substance (MIS) or anti–müllerian hormone (AMH) gene. SRY expression begins at 41 days after ovulation, and peak expression is detected at 44 days after ovulation, when the sex cords are first visible. As demonstrated by immunohistochemistry, SRY transcripts are demonstrable within human Sertoli cells of the sex cords at this stage (42).

SOX-9 situated on chromosome 17 plays a key role in gonadal and cartilage formation. Fourteen mutations with loss of SOX-9 function have been identified (11), and the majority of patients with 46,XY have sex reversal. SOX-9 acts as a transcription factor by its DNA-binding domain (11) and acts in conjunction with SRY to promote testis formation. Duplication of SOX-9, in the absence of SRY, can cause XX sex reversal (48). Sertoli cell differentiation is influenced by SOX-9, but minimal expression of SOX-9 is noted in the ovary (15). SOX-9 protein is demonstrable in the cytoplasmic compartment of somatic cells of male and female human gonads (20,57). During Sertoli cell differentiation and sex cord formation at 6.5 weeks, SOX-9 expression is found in the nuclei of Sertoli cells (20).

MIS or AMH causes regression of the female ductal system. The gene for MIS is located on chromosome 19 (16). In the human embryo, MIS has been demonstrated by immunohistochemistry in the cytosol of the Sertoli cell but is not found in the fetal ovary (20). SF-1 and WT-1 promote expression of MIS (81). MIS is a nonsteroidal glycoprotein that is split to enhance its activity on the müllerian duct. MIS may also be involved in testicular development and inhibits germ cell proliferation (73).

Absence of the DAX-1 gene situated on the short arm of chromosome 21 (Xp 21) results in adrenal hypoplasia and hypogonadotropic hypogonadism and cryptorchidism in males (128). In contrast, duplication of the DAX-1 gene with the 46,XY karyotype produces male-to-female sex reversal as well as testicular dysgenesis (DSS) (2). In the mouse, DAX-1 expression in the genital ridge occurs at the same time as SRY, and DAX-1 may antagonize SRY action (116). In the testis, as SRY expression declines, so does DAX-1; however, DAX-1 persists in the ovary. It has been postulated that SRY initiates differentiation of the testis, following which SF-1 and WT-1 act downstream (77). SRY may repress DAX-1, allowing normal testicular development in the mouse (37,77). In contrast, more recent research in the human embryo demonstrated a lower level of DAX-1 expression in the indifferent 46,XY gonadal ridge as early as 33 days after ovulation, coinciding with SF-1 expression, and before detection of SRY protein. This low level of DAX-1 expression persisted during and after testicular determination, raising questions about the true role of DAX-1 in testicular differentiation of the human compared with the mouse (42).

Sex differences are demonstrable in human gonads around 6 to 7 weeks of gestation as Sertoli cells in the primary sex cords induce formation of seminiferous tubules. In the outer portion of the testicular sex cords, germ cells migrate into the sex cords, become enclosed in tubules, and undergo mitotic arrest in the form of prespermatogonia (105). The seminiferous tubules remain solid until puberty. The inner portion of the sex cords gives rise to the rete testis, which ultimately connects to the efferent ductules, derived from mesonephric tubules. During the eighth week, Leydig cells develop from the mesenchyme of the mesonephros. The Leydig cells are partitioned outside of the tubules. MIS (4) may inhibit proliferation of the Leydig cells. The stromal cells and future vascular and peritubular myoid cells migrate from the mesonephros into the testis. Mesonephric cells migrate into XY but not XX gonads in response to a chemoattractant. These mesonephric cells give rise to the endothelial cell population, the myoepithelial cells surrounding the vasculature, and the peritubular myoid cells that separate the Sertoli cells from the Leydig cells (75).

The rapidly developing testis requires a more extensive blood supply compared with the ovary to import nutrients and to export testosterone and MIS. Synthesis of testosterone begins at 9 weeks, inducing differentiation of the wolffian duct. Testosterone production is stimulated by human chorionic gonadotropin (hCG), which reaches peak levels at 8 to 12 weeks. The testis becomes rounded and covered by a dense capsule—the tunica albuginea.

In the absence of SRY, the bipotential gonad differentiates into an ovary. The primordial germ cells remain in the cortical region of the ovary. SOX-9 is expressed later in the ovary compared with the testis (42) and the SOX-9 protein is demonstrable only in the cytosol of the future granulosa cells, but not in the nucleus (20), indicating a lack of DNA binding. The primary sex cords in the medulla regress, and the germ cells, oogonia, are concentrated in the outer cortical region. Viable germ cells are required for ovarian differentiation; otherwise, a streak ovary will ensue (68). The secondary sex cords of the ovary are derived from the mesothelium of the genital ridge. These extend into the underlying mesenchyme to envelop the primordial germ cells and ultimately form the follicular cells of the ovary. The oogonia replicate by mitosis to reach 7 million in number by the fifth month of gestation; they then enter meiosis to become primary oocytes arrested at the diplotene stage of meiotic prophase. At 16 weeks, primordial follicles begin to develop, containing primary oocytes surrounded by a monolayer of follicular or granulosa cells. Mesenchymal cells become flattened around the granulosa cells to form the theca (104). The cortex of the ovary contains the majority of the follicles, whereas the medulla is formed of connective tissue and blood vessels, predominantly from the mesonephros.

LOWER URINARY TRACT/ BLADDER FORMATION

Part of "45 - EARLY DEVELOPMENT OF THE GENITOURINARY TRACT "

The development of the lower urinary tract is closely related to that of the genital tract. The differential development of the urogenital sinus into male and female structures is discussed in a later section of this chapter.

The cloaca is the caudal extension of the hindgut. The cloacal membrane is the ectoderm that extends from the tail bud to the body stalk. The urorectal septum is a mass of mesodermal tissue at the notch between the allantois and hindgut that extends caudally. By the seventh week, the cloaca has been divided into the rectum and urogenital sinus (Fig. 45.5). At this point, the external genitalia are not distinguishable as male or female with labioscrotal swellings and urogenital folds on either side of the cloacal membrane.

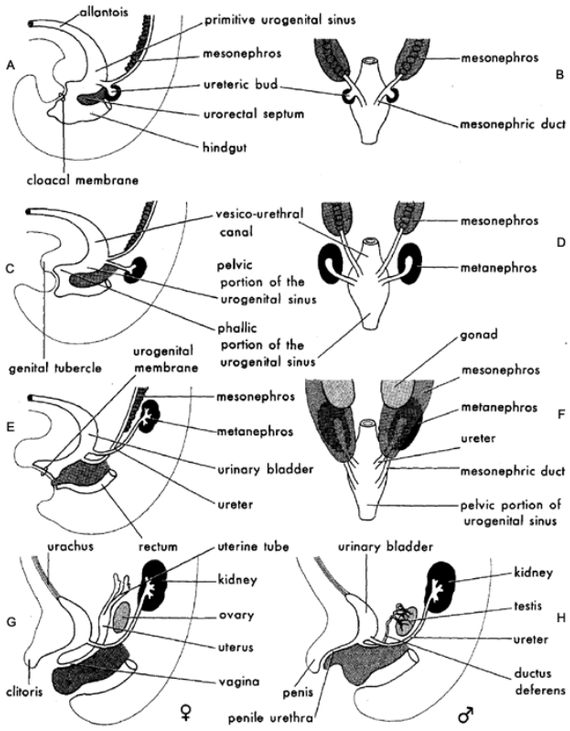

FIGURE 45.5. Division of the cloaca in the urogenital sinus and the rectum; absorption of the mesonephric ducts; and development of the urinary bladder, urethra, and urachus. **A:** Lateral view of the caudal half of a 5-week embryo. **B, D, F:** Dorsal views. **C, E, G, H:** Lateral views. Stages **G** and **H** are reached by about 12 weeks. (From reference 80, with permission.)

By the seventh week, the mesonephric ducts are absorbed into the dorsal aspect of the urogenital sinus (18). As described earlier, the ureters move cephalad and lateral while the mesonephric duct moves caudally. The trigone is initially mesodermal in origin. The epithelium is initially replaced by the endoderm of the urogenital sinus. The lamina propria, muscular layers, and serosa arise from the surrounding mesenchyme. The development of the bladder is the result of complex interactions between the epithelium and mesenchyme (21).

The bladder elongates as the abdominal wall forms below the umbilicus. The urachus (apex) is contiguous with the

allantoic stalk. By birth, the urachus becomes a thick fibrous cord (the median umbilical ligament). Initially, the bladder is a cylindrical tube. The tubular bladder acts as a conduit and becomes a more spherical storage vesical later in gestation.

Bladder muscle appears by 7 weeks of gestation and shows significant orientation into layers by 21 weeks gestation (85). Animal studies show that bladder compliance is poor in early gestation and increases as gestation progresses (3,16). Both active smooth muscle tension and connective tissue matrix influence compliance and capacity. The ratio of type III to I collagen and the absolute amount of type III collagen correlate with bladder compliance with improved compliance associated with decreased quantities of type III collagen. The development of the detrusor layer is key because it seems to have the largest impact on bladder storage and emptying.

Mechanical distention of the bladder is made possible with development of a continence mechanism. The urethral sphincter encircles the urethra by 16 weeks (8,76,85). Because this occurs before the trigone is fully developed, the cyclic bladder expansion may aid in normal bladder development (14). Obstruction secondary to posterior urethral valves or absence of urine storage secondary to bilateral ectopia or exstrophy may lead to abnormal development of the trigone.

DESCENT OF THE GONADS

Part of "45 - EARLY DEVELOPMENT OF THE GENITOURINARY TRACT "

The testes and the ovaries are initially situated at the tenth thoracic level (31). From the gonad, a cordlike structure called the *gubernaculum* forms during the seventh week. This cylinder of embryonic mesenchyme extends from the gonad to the site of the inguinal canal. At the beginning of the third month, each processus vaginalis herniates from the lower portion of the peritoneal cavity obliquely through the abdominal wall, forming the inguinal canal (125). The gubernaculum extends through the inguinal canal, linking each labioscrotal swelling to the gonad. In the female, the processus vaginalis extends through the canal of Nuck into each labia and becomes obliterated by the eighth month. The gubernaculum connects the ovary to the developing ureterovaginal canal at its union with the future fallopian tube. The ovary descends due to elongation of the lumbar region and, by 12 weeks, is situated at the pelvic brim. The superior portion of the gubernaculum ultimately becomes the ovarian ligament, and the inferior portion forms the round ligament, between the uterus and the labia majora.

In the male fetus, the proximal end of the gubernaculum connects to the testis itself (25) or to the mesonephric duct/epididymis (40,70). The testis descends to the upper pelvis by 12 to 16 weeks but then ascends, potentially due to elongation of the gubernaculum (9). Testicular descent has been divided into two phases: (a) intraabdominal migration characterized by gubernacular outgrowth and (b) later transinguinal passage (67), due to gubernacular regression (64). Between 16 and 24 weeks, significant gubernacular growth occurs. The gubernaculum enlarges by producing extracellular matrix material that absorbs water (46). By 24 weeks, the gubernaculum is as wide as the testis, creating a potential passageway for the testis.

In the clinical arena, disorders of androgen metabolism such as 5α-reductase deficiency or androgen activity such as complete androgen insensitivity are typically associated with undescended testes, but the testes may be extraabdominal (124). Research into factors controlling gubernacular development and regression has involved rodents and various mammals as well as humans, with considerable variability in gubernacular morphology, timing of testicular descent, and the role of the cremasteric muscle. Testicular descent occurs before birth in the calf, pig, and human. Recent theories concerning testicular descent have included (a) activation of the hypothalamic-pituitary-gonadal axis with direct androgenic effect on the gubernaculum (24,108); (b) direct neural control of the gubernaculum and cremasteric muscle via the genitofemoral nerve with androgens acting indirectly at the spinal nucleus of this nerve (122); (c) stimulation of fetal androgen secretion by placental gonadotropins with additional modulation by maternal epidermal growth factor (EGF) (64), MIS (103), or placental estradiol (41); and (d) alternate control of descent by protein substances such as insulin-like hormone produced by the Leydig cells (83).

Different hormones may control the two phases of testicular descent, and controversy exists about whether gubernacular proliferation is independent of androgens or MIS. In the rat, which exhibits postnatal testicular descent, androgen receptors and peak 5α-reductase activity have been identified in the gubernaculum during the outgrowth phase, when this structure is composed of dense mesenchymal tissue (32,50). Inhibition of 5α-reductase or androgen receptor blockage will result in cryptorchidism in the rat only if exposure occurs during gubernacular outgrowth phase (106,107).

In contrast, porcine 5α-reductase activity and androgen receptor binding were at a low level in the gubernaculum during testicular descent (45,47). Factors stimulating gubernacular growth include polypeptides such as EGF, insulin fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). A low-molecular-weight extract of the fetal porcine testis produced the strongest effect on the gubernaculum, and this factor was named *Descendin* (27). Subsequently, the proliferation of fetal porcine gubernacular cells was demonstrated in response to a low-molecular-weight protein derived from the testis (127), but not from the ovary.

Leydig insulin-like hormone, also known as *insulin-3* (Insl3), is produced by the Leydig cells in response to SF-1 and regulates gubernacular outgrowth (129). Male mice with a knockout of the Insl3 gene demonstrated cryptorchidism with a female-type gubernaculum and testes situated below the kidneys. Development of the genitalia was otherwise normal, as was serum testosterone. At birth, heterozygous Insl3-deficient males had unilateral or bilateral testicular maldescent that corrected spontaneously, whereas males with homozygous deficiency of Insl3 remained cryptorchid and developed abnormal spermatogenesis and infertility (83). This model suggested that Insl3 acts in a dosage-sensitive fashion on the mouse gubernaculum and controls transabdominal migration of the testis.

The final phase of testicular descent—gubernacular regression and transinguinal migration—takes place between 24 and 32 weeks in the human fetus. This process occurs postnatally in the rat, rabbit, and dog and is associated with a rise in testosterone and dihydrotestosterone levels (24,55,97). Although 5α-reductase activity and androgen binding in the gubernaculum are low during testicular descent (27,45), androgen may act on the epididymis. In the human, the epididymis precedes the testis through the inguinal region (40). Higher testosterone concentration in the epididymis of the infant compared with that of the adult (7) may signify that the epididymis is the target organ for androgens and mediates testicular descent.

Alternatively, androgens may act indirectly via the genitofemoral nerve that innervates the gubernaculum and cremasteric muscle (122). Transection of the genitofemoral nerve results in cryptorchidism, and the spinal nucleus of this nerve is androgen sensitive. Boys with cryptorchidism show abnormalities of the cremasteric muscle suggestive of denervation.

Estrogens are known to impair testicular descent, and exposure to exogenous estrogens, such as DES, causes cryptorchidism (97). In newborn boys with cryptorchidism, the syncytiotrophoblastic region of the placenta demonstrated increased expression of estradiol compared with the placenta of normal boys (41). Research about intrauterine exposure to exogenous estrogens revealed that DES downregulated Insl3 expression in embryonic mouse Leydig cells, resulting in cryptorchidism and retention of müllerian ductal structures (84).

GENITAL DUCTS

Part of "45 - EARLY DEVELOPMENT OF THE GENITOURINARY TRACT "

Two pairs of genital ducts develop in both sexes: mesonephric (wolffian) and paramesonephric (müllerian) (Fig. 45.6). The mesonephric ducts drain the primitive kidneys but persist as the male genital ducts. The tubules of the rete testis become connected with 5 to 12 residual mesonephric tubules that give rise to the efferent ductules. The paramesonephric ducts develop as an invagination of the coelomic epithelium lateral and adjacent to the mesonephros (1). The funnel-shaped proximal end empties into the coelomic (peritoneal) cavity. They run parallel to the mesonephric ducts until they reach the region of the urogenital sinus. The lower segment of the müllerian duct crosses anterior to the mesonephric ducts and fuses into a Y-shaped ureterovaginal primordium. This projects into the urogenital sinus (Müller's tubercle). A mesonephric duct enters the urogenital sinus on each side of the tubercle.

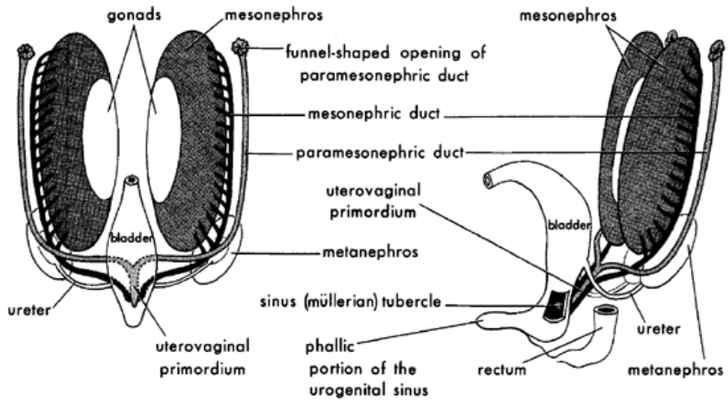

FIGURE 45.6. A: A frontal view of a 7-week embryo showing the paired genital ducts at the indifferent stage. **B:** Lateral view of a 9-week fetus shows the sinus (müllerian) tubercle on the posterior wall of the urogenital sinus. (From reference 80, with permission.)

Masculinization of the Ductal System

As noted, during the sixth to seventh weeks, the Sertoli cells produce MIS that causes regression of the müllerian structures by 8 to 10 weeks (52). SF-1 and WT-1 genes together promote MIS expression, and it has been proposed that the DAX-1 gene inhibits this synergistic effect (81). EGF enhances proliferation of the cells of the reproductive tract, and MIS blocks EGF activity (7). Remnants of the müllerian duct at the cranial end include the appendix testis, a small appendage of tissue on the superior aspect of the testicle. The sinus tubercle remains, forming the verumontanum (colliculus seminalis) on the dorsal wall of the future prostatic urethra. The caudal end of the müllerian duct may persist as the prostatic utricle, a diverticulum of the proximal urethra. At 8 weeks, the Leydig or interstitial cells produce testosterone with stimulation by hCG, causing

proliferation of the mesonephric ducts, even as the mesonephros is involuting. EGF acts in a synergistic fashion with testosterone by enhancing the action of androgens due to an increase in receptor binding sites (39). Direct diffusion of testosterone down the lumen of the wolffian ducts is responsible for the stabilization of the epididymis, vas deferens, seminal vesicles, ampullae of the vas deferens, and ejaculatory ducts. The proximal end of each mesonephric duct becomes convoluted and transforms into the epididymis. The androgen receptor in the fetal epididymis is similar to the androgen receptors in the external genitalia and other locations (33). Distal to the epididymis, smooth muscle envelops the mesonephric duct, giving rise to the vas. The cephalic end of each mesonephric duct involutes, but a remnant may persist as the appendix epididymis. As noted, during the ninth week, mesonephric tubules connect the rete testis with the epididymis, forming the ductuli efferentes. At the inferior aspect of the testis, mesonephric tubules may persist as a small remnant—the paradidymis.

During the tenth week, a bud sprouts from the caudal end of each mesonephric duct near the urogenital sinus to form the seminal vesicle (61). The segment of each mesonephric duct between the seminal vesicle and the urogenital sinus is termed the *ejaculatory duct.* Development of the prostate begins in the tenth week under the influence of androgens, as endodermal buds from the urogenital sinus grow into the surrounding mesenchyme to form the glands of the peripheral zone. Acid phosphatase, which was detectable in the urogenital sinus as early as 7 weeks, could also be identified in the primitive prostatic glands at 11 to 14 weeks of gestation (56). The prostatic outgrowths form five or more groups of solid prostatic cords, which develop a lumen by 11 weeks (69). The mesenchyme surrounding these cords differentiates into smooth muscle and connective tissue. The glands of the median lobe develop later from the complex epithelium covering the verumontanum and may possibly be of mesonephric or paramesonephric origin (88). The median lobe demonstrates minimal acid phosphatase activity, confirming the different origin of this segment of the prostate (56). Urethral and paraurethral glands (of Skene) in the female correspond to the prostate.

Testosterone and dihydrotestosterone mediate these changes through binding to androgen receptors (5,63). Inferior to the developing prostate, the bulbourethral glands form during the same time frame. Paired epithelial buds grow from the urogenital sinus at the junction of the pelvic and perineal urethra. The ducts elongate and canalize, with lobular acini at the superior aspect (111).

Feminization of the Ductal System

In the absence of androgen effect, the mesonephric ducts regress (39). In the female, remnants of the mesonephric duct include the epoophoron and paroophoron in the ovarian mesentry (Gartner's cysts). The müllerian ducts are retained because MIS is not secreted in the female fetus. Even in the absence of ovaries, the female ductal system persists. The fallopian tubes differentiate from the cephalic segments of the müllerian ducts. Inferiorly, fusion of the müllerian ducts forms the uterovaginal primordium, from which the uterus and superior portion of the vagina are derived. After the ducts unite at 8 weeks, a central lumen is formed, extending caudally to the sinus tubercle where a solid tip is present initially (101). During this process, as the müllerian ducts are drawn toward the midline, peritoneal folds are created on each side—the broad ligaments. The myometrium and endometrial stroma, as well as the parametrium, develop from the splanchnic mesoderm alongside the uterovaginal primordium.

Various theories have been proposed about the embryologic origin of the lower portion of the vagina. Paired endodermal outgrowths of the urogenital sinus, called the *sinovaginal bulbs,* develop in the region of the sinus tubercle. Evagination of the dorsal wall of the urogenital sinus in the region of the sinovaginal bulbs occurs at 9 weeks of gestation, to later form the lower vagina. Confirmation that the origin of this evagination is from the urogenital sinus has been documented by immunohistochemistry. Uroplakin, a membrane protein of the urothelium, has been demonstrated in the epithelium of the urogenital sinus as well as in the evagination of the 9-week-gestation human fetus. According to one theory, this region ultimately becomes the lower vagina (101). The lower end of the uterovaginal canal is temporarily occluded by a mass of tissue, termed the *cellular plate.* According to other views, the vaginal plate arises from the müllerian ducts, or a combination of the müllerian and mesonephric ducts (61). Subsequently, the vaginal plate elongates during the third to the fifth month, and a lumen develops by desquamation, so patency of the distal vagina is established. During remodeling of the vaginal plate, its junction with the urogenital sinus slides downward to the lowermost aspect of the sinus, with a partition remaining between the two structures. Ultimately, the distal most vagina becomes exteriorized from the urogenital sinus and differentiates into the vestibule of the vagina. Controversy exists about the origin of the vaginal epithelium—from the urogenital sinus, mesonephric duct, or müllerian duct. The origin of the hymen, which separates the vagina from the urogenital sinus, is also in question, and origins from the vagina, mesenchyma, or urogenital sinus have been proposed (89).

Buds arise from the urethra and extend into the mesenchyme to form urethral glands and paraurethral glands (of Skene). The vestibular glands of Bartholin are formed as outgrowths of the urogenital sinus itself.

GENITAL DEVELOPMENT

Part of "45 - EARLY DEVELOPMENT OF THE GENITOURINARY TRACT "

The external genitalia of the developing fetus are capable of developing either the male or female phenotype. Endodermal

cells from the cloaca extend along the ventral midline surface of the tubercle to form the embryologic urethral plate beginning in the sixth week of gestation. The primordia of the external genitalia inherently feminize unless virilized by activity of dihydrotestosterone between the ninth and twelfth weeks of gestation. This hormone stimulation causes the tubercle to elongate, prompts fusion of the urethral folds, and tubularizes the urethral groove beginning proximally and continuing to the level of the glans. The anatomic development of the penis and hormonal control of this development are extensively covered in Chapter 52 and Chapter 53 .

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46

PERINATAL UROLOGY

Marc Cendron

Jack S. Elder

M. Cendron: Departments of Surgery (Urology) and Pediatrics, Dartmouth Hitchcock Medical Center, Children's Hospital at Dartmouth, Lebanon, NH 03756.

J.S. Elder: Departments of Urology and Pediatrics, Case Western Reserve University; Department of Pediatric Urology, Rainbow Babies & Children's Hospital, Cleveland, OH 44106.

Contents

The last 25 years have brought about dramatic changes in the evaluation and management of urologic problems encountered in the neonatal period. Prenatal ultrasound has revolutionized the approach to congenital anomalies, in particular, those involving the genitourinary tract. Current technology allows the detection of urinary tract and renal lesions as early as 10 to 12 weeks of gestation and has provided insight regarding the natural history of these lesions before birth (468). A majority of pregnant women undergo sonographic screening, allowing the fetus to be evaluated before it becomes sick. The development and use of experimental animal models have further expanded our understanding of the pathophysiology of certain disorders, such as obstructive uropathy. Combined with refinements in surgical and anesthetic techniques, early prenatal diagnosis has provided the pediatric urologist with the opportunity to counsel parents and subsequently to offer specialized high-quality care for the newborn diagnosed prenatally with a congenital abnormality of the urinary tract (116).

This chapter presents an overview of the embryology and ontogeny of renal function, an understanding of which is paramount in the evaluation of the fetal urinary tract. Prenatal ultrasound screening is discussed as it pertains to the urologist. The urologic evaluation of the newborn with prenatally diagnosed genitourinary lesions is reviewed with special consideration to dilation of the upper urinary tract, the most common entity diagnosed on prenatal ultrasound screening (310). Finally, common urologic problems encountered in the neonatal period are discussed, including conditions that are being seen with increasing frequency in children who have been in the pediatric intensive care for prolonged periods.

DEVELOPMENTAL ASPECTS OF RENAL PHYSIOLOGY IN THE FETUS AND NEWBORN

Part of "46 - PERINATAL UROLOGY "

Embryology of the Kidney

Until recently, little information was available regarding developmental renal physiology. With the survival of extremely premature infants and the study of fetal animal models, a better understanding of the functional development of the fetal kidney has emerged (64). Although the placenta functions as the main hemodialyzer for the fetus, the fetal kidneys play a significant role in blood pressure regulation, fluid and electrolytes homeostasis, acid–base balance, and the synthesis of certain hormones.

Before attaining its functional status at about 14 weeks of gestation, the kidney has undergone three stages of morphogenic and physiologic development (73). The first stage of formation of the kidney is the pronephros, a nonfunctional organ, which involutes by 5 weeks of gestation. The mesonephros is the second stage of kidney formation, consisting of about 20 pairs of glomeruli and thick-walled tubules, which secrete urine. The mesonephros degenerates but contributes to the formation of the ureteral bud, which arises from the dorsal aspect of the mesonephric duct. During the fifth week of gestation, the ureteral bud elongates and penetrates the mesonephric blastema, an area of undifferentiated mesenchyme located at the caudal end of the nephrogenic ridge, causing differentiation into the excretory system of the kidney during the seventh week.

The molecular mechanisms regulating renal organogenesis currently are being studied in animal models and in cell–culture line systems (317). Metanephric organ culture systems have aided in elucidating the regulation of growth and branching of the ureteral bud, the changes in extracellular matrix composition, and the cell adhesion events that occur during nephrogenesis (409). Some of the growth factors controlling cellular proliferation and differentiation following induction also have been characterized (46,183). Branching of the ureteral bud, for instance, is regulated by the mesenchyme and by growth factors provided by other surrounding tissues. The specific mechanisms have not been clearly identified, but recent experimental data suggest that chondroitin sulfate proteoglycans may be important factors in branching morphogenesis (292). To date, few peptide growth factors have been identified as responsible for metanephric development (282). However, recent studies suggest that postinductive nephrogenesis is the result of a series of meticulously genetically programmed set of events that may be regulated by a finely tuned balance of local growth factors, transcriptional factors, and distal effector molecules such as epithelial growth factors (EGF) and tissue inhibitor of metalloproteinase-2 (TIMP-2) (222,586). In addition to cell differentiation and proliferation, it has become increasingly clear that renal organogenesis may also involve other important events, such as programmed cell death or apoptosis (528). Specifically, experimental data suggest that metanephric cells may undergo apoptosis if they are not induced by the ureteral bud (30,300). Abnormalities in renal development may also be the result of anomalous regulation of the apoptotic process as demonstrated genetically altered animals (414).

As the kidney develops under the influence of both the inductive process and under the influence of various gene products and growth factors, dividing branches of the ureteral bud penetrate the mesenchyme, compressing it and fragmenting it into separate aggregate islands of cells (409). These oval masses elongate to form tubular structures that become sinuous and establish connections with the ampullae of the ureteral bud. Subsequently, the ureteral bud undergoes a series of approximately 15 generations of divisions, always in two branches. As described, this branching process and its interaction with the developing mesenchyme is regulated by numerous factors, including specific genes such a Pax2 (539). Also involved are adhesion molecules that mediate the attachment of cells to one another and to the surrounding matrix (149). Early in nephrogenesis, the

polar aspect of the ureteral bud divides more rapidly than its midportion. The first four or five polar and two or three interpolar branches coalesce to form the renal pelvis (Fig. 46.1A). The next three to five branches organize to form the major calyces (392). Further divisions of the ureteral bud result in the formation of the minor calyces. First-generation collecting tubules develop at the papillary ducts and represent branching distal to the minor calyces. The collecting tubules represent five to seven additional generations of tubules. By 20 weeks of gestation, approximately 30 million tubules have developed and differentiation of the renal collecting system is complete (416).

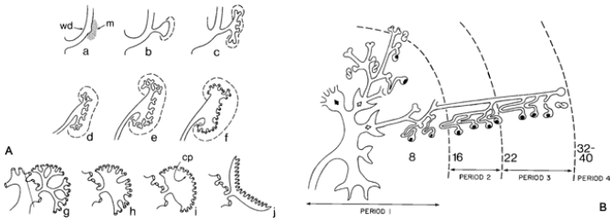

FIGURE 46.1. A: Embryology of the upper urinary tract: the ureteral bud. *a,* Bud arises from the wolffian duct *(wd)* and penetrates the metanephric mesenchyme *(m). b,* The mesenchyme caps the expanded end of the bud. *c,* The bud develops polar, hilar, and ampullary projections, which dichotomize. *d, e,* More dichotomous divisions. *f,* Confluence of the lumens of the divisions forming the pelvis and major calyces. *g,* Second series of ampullary divisions to form the minor calyx (shown in one only). *h,* Confluence of lumens except first division which forms the infundibulum. *i,* Expansion of the lumen to form rounded minor calyx with orifices of the papillary ducts in the convex cribriform plate *(cp). j,* Inversion of the plate to form the papilla. **B:** Embryology of the upper urinary tract: the nephronic components. The minor calyces are shown in the early spherical shape with cribriform plate *(solid arrow)* and later indented forming papilla *(open arrow).* Nephrons develop in periods according to the nature of ampullary activity. Period 1, 8 to 15 weeks, temporary nephrons induced by dichotomizing ampullae of branching collecting ducts; period 2, 16 to 21 weeks, the ampulla induces nephrons that are linked by a common duct to a collecting duct—the so-called arcades in the inner cortex. Period 3, 22 to 32 weeks, the ampulla advances toward the capsule, inducing nephrons that connect independently to its newly formed collecting duct in the outer cortex. Period 4, 32 to 40 weeks, the ampullae rarely divide, and the already established nephrons mature. (Courtesy of F. Douglas Stephens, M.D.)

The nephron arises from differentiated cells of the metanephric blastema, which becomes the glomerulus, Bowman's capsule, proximal and distal convoluted tubules, and loop of Henle (Fig. 46.1B). Simultaneously, the nephron becomes vascularized by an ingrowth of capillaries that arise from the middle sacral and common iliac arteries. Experimental evidence suggests that differentiation imparts angiogenesis-stimulating activity to the metanephric blastema. Recently, a specific heparin-binding angiogenesis factor has been isolated and characterized from the embryonic mouse metanephros (439). In addition, fibronectin has been found to have an important role in the guided migration of capillary endothelial cells into the primitive S-shaped tubules (469). Therefore formation of the renal unit (or nephron) is the result of close interaction between three distinct cell types brought together by organized migration and differentiation. These cell types are the epithelium of the wolffian duct–derived ureter, the mesenchyme of the metanephric blastema, and the endothelial cells (472). Further nephron development occurs at nearly an exponential rate as the ureteral bud continues to divide.

In summary, the ureteral bud forms the collecting system, namely the ureter, renal pelvis, calyces, papillary ducts, and collecting system, whereas the metanephric blastema forms the entire excretory system (i.e., the nephrons). By 20 weeks of gestation, the ureteral bud has completed its series of divisions and the ductal system is complete. At this point, approximately one-third of the ultimate number of nephrons are present; these nephrons form the juxtamedullary zone of the future renal cortex (387). Elaboration of the nephrons progresses along vertical extensions in the ends of the collecting ducts. Nephron formation is actually completed by 36 weeks of gestation (Fig. 46.2 and Table 46.1). From then, until the child is 2 to 3 years of age, the nephrons undergo maturation, and hypertrophy occurs through 12 years of age.

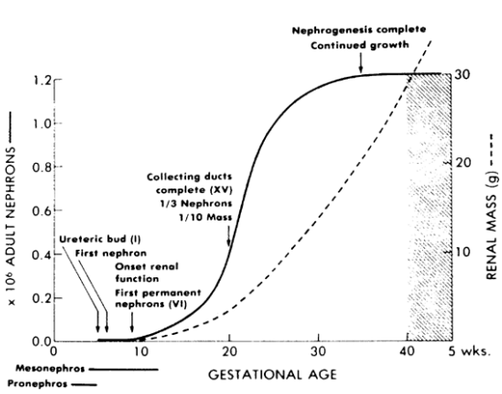

FIGURE 46.2. Fetal renal development. The branching of the collecting system is complete by 20 weeks, but the majority of nephrons and most of the functional mass form in the cortex after 20 weeks. (From Harrison MR, Golbus MS, Filly RA, et al. Management of the fetus with congenital hydronephrosis. *J Pediatr Surg* 1982;17:728, with permission.)

TABLE 46.1. NEPHROGENESIS IN THE HUMAN

Week of Gestation	Number of Nephrons	%
8	20,200	0.01
20	350,500	43
24	680,000	83
28	767,000	93
36[a]	822,000	100

[a]Completion of nephrogenesis.
From Potter EL. *Normal and abnormal development of the kidney.* Chicago: Year Book Medical, 1972, with permission.

Morphology of the Kidney

The human kidney has multiple lobes, whereas the kidney in the rat, rabbit, and cat is unipapillary with a single calyx (416). At 10 weeks of gestation, three to four lobes have developed. As branching of the ureteral bud continues, the number of lobes gradually increases, and by the end of the fourth month, approximately 15 lobes are present. Each papilla forms a renal lobe, with one or two papillae opening into one calyx. The lobes are hemispheric, with the calyx in the center and the tubules radiating outward with their attached nephrons, capped by the residual undifferentiated blastema. As vascular development proceeds, large blood vessels in the papillae become fixed in position; in these areas, further peripheral growth is impaired. As a result, tubules lateral to the blood vessels may protrude from the surface of the kidney, forming secondary lobulation. At 36 weeks of gestation, when nephron formation is complete, approximately 30 lobes and lobulations may be seen (416) (Fig. 46.3). As renal maturation occurs and the nephrons increase in length and tortuosity, the demarcation of the surface of the kidney becomes less distinct. However, the lobar structure is permanent.

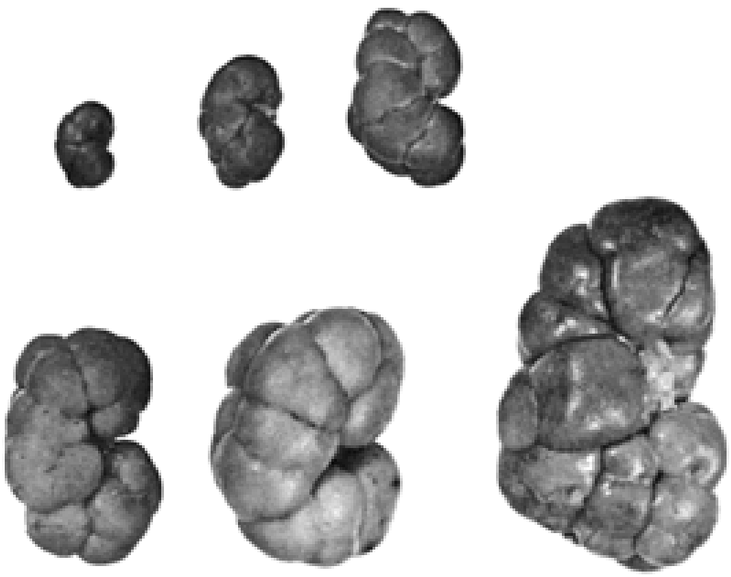

FIGURE 46.3. The lobes of the kidney gradually increase in number and size during fetal development. Weight of kidneys and fetuses from which they were removed: 0.4 g and 93 g, 0.9 g and 254 g, 1.6 g and 508 g, 3.7 g and 1,065 g, 7.5 g and 2,080 g, 11.2 g and 3,070 g. (From Potter EL: *Normal and abnormal development of the kidney*. Chicago: Year Book Publishers, 1972, with permission.)

Initial renal morphogenesis occurs at the level of the upper sacral segments. The vertebral column of the embryo straightens as it grows, and the kidneys undergo growth in a cranial direction. During the eighth week, the kidney comes into contact with the large fetal adrenal gland, and by the end of the eighth week, renal ascent is nearly complete. The renal pelvis initially forms on the ventral surface of the kidney. As the kidney ascends, the kidneys rotate medially 90 degrees.

In summary, several events appear to be crucial to the development of two normal kidneys: (a) development of a single ureteral bud from each mesonephric duct during the fifth week of gestation; (b) induction of the metanephric blastema by precise directional growth of the ureteral bud into the blastema; (c) branching of the ureteral bud; (d) formation of the nephrons in conjunction with vascular ingrowth in the renal mesenchyme; and (e) ascent of the kidneys during the sixth, seventh, and eighth weeks.

Renal Function in the Fetus

The developing fetal kidney is very different functionally from the newborn kidney (501). Throughout normal gestation, the placenta is the major regulatory organ of the fetal environment. Urine formation by the fetal kidney begins between 9 and 12 weeks of gestation. Evidence for early urine production is documented by distention of the renal pelvis (416). Hydrostatic pressure generated by the accumulation of urine in the collecting system in the early stages appears to be influenced by the development of Chwalla's membrane at the caudal end of the ureteral bud (352). This phenomenon may be responsible for the early canalization and dilation of the collecting system. Subsequent rupture of Chwalla's membrane at 9 weeks of gestation allows the urine to flow into the bladder. Others have demonstrated kinks and folds in the early ureteral development resulting from recanalization of the ureteral bud that may be precursors of obstructions at the ureteropelvic junction (UPJ) and ureterovesical junction (UVJ) (8,393).

Renal Blood Flow in the Fetus

Despite the fact that the kidneys constitute a larger percentage of body weight in the fetus than later in life, the fetal kidneys receive only 2% to 4% of the total cardiac output (10,197,461). Approximately 40% to 60% of the fetal cardiac output travels through the placenta.

Autoregulation, a phenomenon by which the kidney is able to preserve its blood flow at a constant level during major changes in perfusion pressure, may exist in the fetus (501). At birth, following clamping of the umbilical cord, the cardiac output increases, accompanied by a substantial rise in the renal vascular resistance, which maintains the intrarenal blood flow at rates similar to those late in gestation. As renal vascular resistance gradually decreases, an increasing proportion of the cardiac output is directed to the kidney for glomerular filtration, such that 15% to 18% of total output is received by the newborn kidneys. Renal blood flow, as estimated by *p*-aminohippuric (PAH) clearance, doubles by 2 weeks of age and reaches adult levels by 2 years of age (corrected for body surface area) (460).

Several factors are known to influence fetal renal hemodynamics. These include the renin-angiotensin system (RAS), arginine vasopressin, atrial natriuretic factor, certain prostaglandins, kallikrein-kinin, and the sympathetic nervous system (9,446). In the human fetus, renin has been localized in the mesonephros and in the metanephros by 8 weeks of gestation (79). A role for the RAS has been postulated in the process of angiogenesis because renin also has been identified in the mesonephric and renal arteries (273). In addition, the high serum renin level found in the human newborn may account for the high renal vascular resistance (21,205,301,526). The intrarenal distribution of blood flow in the fetus differs quantitatively from that of the newborn (447). In the latter stages of gestation, glomerular blood flow appears to shift toward the superficial cortex, whereas no change in the medullary nephron perfusion occurs. This trend continues after birth and reflects diminishing vascular resistance in the outer cortex (386). This centrifugal pattern of changing distribution of intrarenal blood flow appears to parallel the changes in glomerular maturation (Table 46.2). In the newborn, the volume of outer cortical glomeruli is proportionately less than that of the middle and inner cortical glomeruli, but in adulthood, the size of the glomeruli from these three regions is similar (174,509).

Age (Days)	Cortical[a] (nl/min)	Juxtamedullary[b] (nl/min)
1	0.9	17.2
15	4.1	43.2
30	19.3	42.1

[a]Eighty percent of all glomeruli.
[b]Twenty percent of all glomeruli.
From Spitzer A, Brandis M. Functional and morphological maturation of the superficial nephrons. Relationship to total kidney function. *J Clin Invest* 1974;53:279, with permission.

TABLE 46.2. NEPHRON GLOMERULAR FILTRATION RATE IN THE GUINEA PIG

Throughout gestation, renal blood flow appears to be regulated by both humoral and neural factors. Changes in vascular resistance, after birth, allow greater perfusion of the kidney, which results in an increasing glomerular filtration rate (GFR). The decrease in renal vascular resistance might be due to decreases in circulating levels of vasoconstrictor catecholamines, vasopressin, and angiotensin or to concomitant

increases in levels of vasodilator prostaglandins (103,200,373). Most of the increase in renal blood flow occurs in the outer zone of the cortex and is critical in urine production and glomerular filtration.

Glomerular Function in the Fetal Kidney

Urine is excreted by the fetal kidney as early as the fifth week of gestation, when the mesonephros is capable of making urine. Renal tubular function begins in the metanephric kidney between 9 and 12 weeks of gestation. By 14 weeks, the loop of Henle is functional and tubular reabsorption occurs. At term, urine flow rate average is more than 1 L per day (Fig. 46.4). Urine production in the fetus has been estimated by ultrasound measurements of bladder dimensions and frequency of fetal micturition (60).

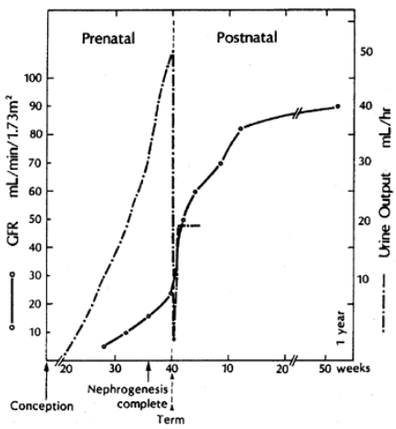

FIGURE 46.4. Changes in glomerular filtration rate *(GFR)* and urine output during fetal development and infancy. A report (Rabinowitz, et al. Measurement of fetal urine production in normal pregnancy by real time ultrasonography. *Am J Obstet Gynecol* 1989;161:1264) suggests that urine output at term may be 50 mL per hour.

GFR, which reflects the kidney's ability to filter blood, increases progressively with gestational age (500) (Fig. 46.4). Fetal GFR is dependent on several factors, including the permeability of the glomerular wall, the surface area available for filtration, and the ultrafiltration pressure, which depends on efferent arteriolar resistance, capillary blood flow, and the protein concentration in arterial plasma (221). However, relatively little information is actually available on fetal GFR (501).

Estimation of glomerular filtration in the perinatal period is based on determination of inulin clearance, which has been studied in neonate and premature, low-birth-weight infants (106,569). These methods are not entirely accurate and may vary, but they have been improved by the use of constant infusion techniques and by factoring in body weight as opposed to body surface area (105,569). GFR is dependent on the following factors:

1. Ultrafiltration pressure

   Hydrostatic pressure within the glomerular capillary (P_{GC})

   Oncotic pressure within the capillary (Onc_{gc})

   Hydrostatic pressure within the proximal tubule (P_{pt})

   Ultrafiltration pressure = $P_{gc} - (Onc_{gc} + P_{pt})$

2. Permeability of the glomerular wall
3. Surface area of the filtration membrane

Wilkins (569) confirmed that from gestational age 26 weeks to 40 weeks, GFR quadruples. After birth, GFR continues to mature slowly and progressively for about 4 months after birth. During the first 2 years of life, the rate of increase in GFR is much greater than that of somatic growth. It remains constant thereafter in the range of 90 to 100 mL/min/1.73 m^2. Studies in very-low-birth-weight infants have shown that as early as 26 weeks of gestation, the fetal kidney has the capacity to assume excretory function and that this capacity can be achieved 2 days after birth (569). The mechanisms responsible for the rapid increases in GFR are not well understood. Because 80% to 90% of nephrons are formed by 26 weeks of gestation, their functional potential may be stimulated by the redistribution of blood flow through the kidneys, which occurs after removal of the fetus from the intrauterine environment.

The ontogeny of the three primary parameters affecting GFR has been studied carefully in animal models. In the newborn guinea pig, it appears that a relatively small increase in the ultrafiltration pressure occurs, which can account for 10% of the increase in overall GFR (510). The permeability of the glomerular capillaries also increases causing a slight increase in GFR. Finally, there is a progressive increase in the filtering surface area (511). In the newborn kidney, the glomeruli are larger relative to the tubules when compared with their relative sizes in infants and children (174). With renal growth and maturation, there is a modest increase in glomerular size, but the capillary network within the glomerulus continues to develop, with a resultant increase in the total surface area for filtration. A twentyfold- to twenty-fivefold increase in capillary surface area has been demonstrated in various species (269,471), and it accounts for 85% of the rise in total GFR.

Renal development and maturation occur in a centrifugal pattern. Thus, at any stage, the most mature nephrons are located in the deep (juxtamedullary) cortex, and the most immature nephrons are in the outer cortex. Although the majority of nephrons are located in the outer cortex, at birth the blood flow is directed primarily to the deeper cortical nephrons, whereas in the adult kidney, blood flow to the

inner and outer cortex is equal. Thus there is a similar changing pattern of distribution of glomerular filtration with an increasing ratio of outer cortical GFR to inner cortical GFR with age (386,531). Table 46.2 reflects the early centrifugal changes in glomerular filtration in the deep cortical and outer cortical nephrons.

Tubular Function

The proximal convoluted tubule, loop of Henle, distal convoluted tubule, and collecting ducts are responsible for handling the filtrate from the glomerulus. Tubular functions include regulation of fluid volume, electrolyte balance, acid–base balance, and excretion of nitrogenous waste products. In the fetus, tubular function is reduced compared with that in postnatal life. Maturation of tubular function does occur in parallel to the increase in prenatal GFR (Table 46.3).

	Premature Infant	Term Infant	Adult	Age of Maturation (mo)
Glomerular filtration rate (mL/min/1.73 m^2)	8–10	20–30	120	12–24
Renal plasma flow (mL/min/1.73 m^2)		120–150	630	3–6
Filtration fraction (%)		30–40	20	6–36
T_m glucose (mg/min/1.73 m^2)		35–100	300	12–24
Urinary dilution (mOsm/L)	50	50	50	—
Maximum urinary concentration (mOsm/L)	400–600	400–600	1,200–1,400	3
Maximum urine-to-plasma osmolar ratio	2.5		4	3
Ammoniogenesis	Lowered	Normal		
Urinary acidification	Normal[a]	Normal[a]		2
Hydrogen ion excretion	Normal or lowered	Lowered		

[a]Except in metabolic acidosis.
Modified from Royer P. The kidney in the newborn. In: Royer P, Habib R, Mathieu H, et al, eds. *Pediatric nephrology.* Philadelphia: WB Saunders, 1974:116 (reference 458), with permission.

TABLE 46.3. FUNCTIONAL DEVELOPMENT OF THE KIDNEY

Transport of filtrate from the tubular lumen to interstitial fluid or peritubular capillaries is called *reabsorption,* and transport from the capillary to the tubular lumen is termed *secretion.* Transport may be active (against an electrochemical gradient and requiring metabolic energy) or passive (along an electrochemical gradient). Substances that are passively transported include water, certain organic acids, and urea. Substances that are actively reabsorbed include sodium, glucose, and amino acids. Other substances, such as organic bases and PAH, are secreted actively.

There are two types of active transport mechanisms in the kidney: systems that cannot be saturated and systems that are limited by a transport maximum (T_m). An example of a transport system that cannot be saturated is sodium transport. Characteristically, a relatively constant fraction of these substances is transported and excreted. In contrast, transport of glucose, bicarbonate, and PAH is limited. In systems limited by a T_m, all of the substance is reabsorbed or secreted until the maximum amount that can be transported, the T_m, is reached. The T_m for a substance must be distinguished from the plasma threshold for that substance. For example, the plasma threshold for glucose is the plasma concentration at which glucose first appears in the urine. In contrast, the T_m for glucose is the maximum amount that the tubules can reabsorb and is measured in milligrams per minute.

Although the plasma osmolality in humans is relatively constant at approximately 300 mOsm/L, the osmolality of the urine varies from 50 to 1,500 mOsm/L, depending on hydration, age of the patient, and state of maturation of the tubular system. Urine is concentrated as a result of a solute concentration gradient in the renal medulla. The solute concentration in the cortex and at the corticomedullary junction is isosmotic with arterial plasma, whereas at the tip of the papilla, solute concentration is extremely hypertonic compared with arterial plasma.

The concentration gradient is created by active transport of sodium out of the ascending limb of the loop of Henle. The extent of the gradient is directly proportional to the length of the loop of Henle. Blood flow through the medullary region of the kidney permits maintenance of the concentration gradient. The vasa recta loop up and down through the medulla, preventing dissipation of the concentration gradient created by active sodium transport out of the loop of Henle. As plasma travels down the descending limbs of the vasa recta, water leaves and solutes enter plasma because the plasma is going from a lesser to a more concentrated environment. As the plasma enters the

ascending limb of the vasa recta, water enters and solutes leave the plasma passively because the plasma is going from a concentrated to a more dilute environment. The ultimate effect is that plasma leaving the vasa recta is slightly hypertonic compared with plasma entering the vasa recta, resulting in some dissipation of the concentration gradient. If blood flow through the medulla is slowed, the dissipation is lessened; if blood flow increases, dissipation is increased.

Approximately half of the concentration gradient is provided by active reabsorption of sodium. The additional solute that allows the mature kidney to concentrate urine to 1,500 mOsm/L is urea.

The concentration of solutes in the tip of the papilla of the mature kidney is approximately 1,500 mOsm/L. As urine traverses the collecting tubules and collecting ducts that run through the medulla, it becomes more concentrated. If the walls of the collecting tubule are permeable to water, the fluid in the collecting tubules has the same solute concentration as that in the deepest portion of the medulla; that is, it is quite concentrated. On the other hand, if the collecting duct and distal convoluted tubules are impermeable to water, the urine remains dilute. Antidiuretic hormone (ADH), produced by the posterior pituitary gland, regulates the permeability of the collecting duct and distal convoluted tubule.

In summary, urinary concentration depends on the ability of the ascending limb of the loop of Henle to transport sodium actively out of the tubular lumen into the interstitium, the length of the loop of Henle, permeability of the distal convoluted tubule and collecting duct to water, availability of ADH, ability of the kidney to respond to ADH, excretion of urea, solute load, and blood flow through the vasa recta.

All mammalian fetuses normally excrete urine hypotonic to plasma. Although the mechanisms for hypotonic urine in the fetus are not entirely understood, one reason is that fetal urea is cleared through the maternal circulation, preventing the development of a high concentration gradient. Thus urinary sodium and chloride concentrations are substantially lower than plasma levels.

At birth, the neonate is able to concentrate urine to a maximum osmolality of 400 to 600 mOsm/L. The neonatal kidney gradually increases its concentrating ability and achieves an adult level at approximately 3 to 6 months. The inability of the newborn to concentrate urine is related to an inefficient countercurrent multiplier system with diminished accumulation of urea in the medulla, increased medullary blood flow, decreased tubular responsiveness to circulating ADH, and a relatively short loop of Henle (587).

The major limitation in concentrating ability is the low rate of urea excretion, which results because the infant is in a substantially anabolic state and uses most of its dietary nitrogen intake for growth. Infants fed a high-protein diet demonstrated a rapid increase in urinary concentrating ability, with the increase being entirely attributable to increased urinary urea (146). In the normal infant, with increasing length of the loop of Henle and increasing blood flow to the outer cortex, higher concentrations of urea in the renal papilla result, allowing improvement in concentrating ability.

Another reason for the limited urine-concentrating ability of the newborn kidney is the low ADH activity. Bioassayable ADH is low or absent in infants younger than 2.5 months of age (264), and there is also evidence of a relative insensitivity of the distal tubule to ADH (473).

The newborn infant is able to dilute the urine as well as an adult, lowering urinary osmolality to 50 mOsm/L. Premature infants can decrease the osmolality to levels as low as 25 to 35 mOsm/L (18). Furthermore, infants from 3 weeks to 13 months have a better urine-diluting capacity than adults, but it diminishes with age (449).

However, the newborn is unable to excrete a water load as well as an adult. For example, infants given a water load of 3% of their body weight excrete only 10% of the load in the first 3 hours, whereas an adult excretes all of it during this time (17). Furthermore, the infant has a maximum urinary flow of 6 to 8 mL/min/1.73 m^2 compared with 12 mL/min/1.73 m^2 in the adult (31). Thus, although an infant's kidney is able to dilute urine as well as an adult's, its diuretic capacity is limited. Nevertheless, the immature kidney can double its urine output after administration of furosemide (303). In the rat, there is experimental evidence that there is an unelucidated factor in adult blood not present in infant rats that allows the kidney to generate a full diuretic response (507).

The ability of the infant to reabsorb and excrete sodium depends in large part on gestational age. The healthy term infant usually is in positive sodium balance regardless of the amount of salt in the diet (512). The fractional sodium excretion (Fe_{Na}) is determined by the following formula:

$$Fe_{Na} = (U_{Na}/P_{Na})/(U_{Cr}/P_{Cr})$$

where U_{Na} = urinary sodium concentration

P_{Na} = plasma sodium concentration

U_{Cr} = urinary creatinine concentration

P_{Cr} = plasma creatinine concentration

In very premature infants, serum sodium levels may be very low due to excessive urinary excretion (levels of sodium excretion up to 16% of filtered sodium load) and may result in significant hyponatremia. The exact cause of this is still being studied, but indications are that it may be due to failure of proximal tubular reabsorption (569). In the term infant, on the other hand, fractional sodium excretion is low, approximately 0.1% to 0.2% (495). This low sodium excretion is probably secondary to the high plasma renin and aldosterone concentrations that are five to ten times higher in the neonate than in the adult (21). It has been speculated that constant sodium removal is used for the

development of new bone in the neonate and that the removal of sodium serves as a constant stimulus for renin release (353).

Although term infants retain sodium easily, they have a limited ability to excrete a salt load compared with adults (204). Because experimental aldosterone blockade does not alter the fractional sodium excretion in rats (159), it has been hypothesized that this limited ability to excrete a salt load may be secondary to an inability to elaborate natriuretic factors, such as oxytocin and kallikrein (522).

In contrast, premature infants less than 35 weeks of gestation have a natriuresis resulting in a negative sodium balance (527), with fractional sodium excretion varying between 0.8% and 6.0% (495). During this period, the premature infant reduces the high total body water content (approximately 80%) and extracellular fluid compartment (approximately 50%) (571). The negative sodium balance is probably secondary to multiple factors, including inefficient absorption in the gastrointestinal tract, short length of the proximal convoluted tubule in preterm infants, and a decreased sensitivity of the distal convoluted tubule to aldosterone (495). Appropriate recognition of this physiologic loss of sodium is important because aggressive replacement of the sodium loss can result in sodium and fluid retention, which could increase the risk of a symptomatic patent ductus arteriosus or necrotizing enterocolitis (40,41).

An important buffering mechanism in the maintenance of acid–base balance is the excretion of hydrogen ions by the kidney. The normal newborn has a relative metabolic acidosis. The urine in the neonate, and especially in the preterm infant, is alkaline during the first week of life and becomes acidic during the second week (147). Furthermore, premature newborns are unable to acidify their urine as well as term infants. Urinary pH often is more than 6 in premature infants (527). The early production of alkaline urine is normal, and evaluation for renal tubular acidosis need not be undertaken (22).

Although term newborns ultimately excrete an acidic urine, they have a diminished capacity for excreting hydrogen ions compared with adults (525). One explanation for this limited capacity may be that the renal excretion of ammonia is less, particularly in the premature infant (495).

In addition, the renal threshold for bicarbonate reabsorption in the fetus and neonate is lower than in the adult and is altered by changes in the extracellular fluid volume (ECFV) (445). The expanded ECFV in the normal fetus and neonate depresses proximal tubular bicarbonate reabsorption. However, as the ECFV falls during the first few weeks of life, increasing bicarbonate reabsorption occurs, resulting in a rise in plasma bicarbonate and serum pH and a decrease in urine pH. Thus, although the infant is able to excrete usual acid loads, in the presence of a metabolic acidosis, the newborn may require supplemental bicarbonate.

Another example of tubular immaturity is glucose excretion. Urinary glucose concentrations in premature infants less than 34 weeks of gestation are significantly higher than in older infants. Similarly, fractional excretion of glucose is high before 34 weeks of gestation (19). Thus sick premature infants less than 34 weeks of gestation receiving hyperalimentation for maintenance of sufficient caloric intake may be at risk for significant glycosuria. If unrecognized, this situation could result in an osmotic diuresis and dehydration. Consequently, infants receiving solutions of 10% dextrose should have their urine monitored frequently for the presence of glucose, particularly if they are less than 34 weeks of gestation.

Determination of Renal Function in the Fetus

Evaluation of GFR is important in infants with structural or functional abnormalities of the urinary tract or if nephrotoxic medications are being used. Traditionally, GFR has been based on a determination of creatinine clearance by the following formula:

$$C_{Cr} = [(U_{Cr} \times V)/P_{Cr}] \times (1.73/SA)$$

where C_{Cr} = creatinine clearance (mL/min/1.73 m^2)

U_{Cr} = urine creatinine concentration (mg/dL)

V = urine volume (mL/min)

P_{Cr} = plasma creatinine concentration (mg/dL)

SA = surface area (m^2)

The GFR in infants and children is compared with adult levels by using a correction factor; that is, the GFR is expressed as milliliters per minute per 1.73 m^2.

Creatinine is filtered, as well as reabsorbed and secreted. Using creatine may overestimate the GFR compared with measurements using inulin, which is neither reabsorbed nor secreted. However, although inulin clearance is a more precise method of determining GFR, it is impractical. In children between 1 and 12 years of age, a simple formula has been derived that estimates GFR from the plasma creatinine and a child's length (480):

$$GFR = (0.55 \times L)/P_{Cr}$$

where L = length (cm). This formula is similar to the one derived earlier by Barratt (32) and also applies to females between 13 and 21 years of age. However, in males between 13 and 21 years of age, the formula results in a significant underestimation of GFR, and in this group, a more accurate formula (479) is as follows:

$$GFR = 1.5 \text{ (age in years)} + 0.5\ (L/P_{Cr})$$

A third formula is used for determination of GFR in term infants between 1 week and 1 year of age is as follows (478):

$$GFR = (0.45 \times L)/P_{Cr}$$

The third formula is not applicable to infants younger than 1 week of age because serum creatinine during this period is

a reflection of the maternal renal status and it takes approximately 1 week for the term newborn with normal renal function to reach a baseline creatinine level. In addition, the formula has not been verified in premature infants.

Another technique of measuring renal function in infants uses a radionuclide, such as technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc DTPA), which is cleared by glomerular filtration:

$$GFR = Vd \times (0.693/T_{½})$$

where Vd = volume of distribution

$T_{½}$ = half-time of disappearance of the radionuclide

When this system is used, it is possible to determine the GFR by drawing a single specimen of blood at a specified time after injection of the radionuclide.

Although formulas using serum creatinine and body weight or height are relatively accurate in children with normal renal function, they are not very accurate in children with renal insufficiency.

In a preliminary report, Chandhoke and colleagues (83) presented a newer and presumably more accurate method of assessing GFR using iothalamate that is infused subcutaneously with an insulin pump. After 24 to 48 hours of infusion, the distribution of the iothalamate reaches an equilibrium and serum and urine samples are obtained, making it possible to derive the GFR. The technique has been compared with inulin clearance in adults with normal and abnormal renal function and has been extremely accurate. Extensive trials in children are under way.

Periodic determination of GFR in the sick neonate, particularly the premature infant, is important when the dosages of drugs that are excreted primarily by the kidney are calculated. When nephrotoxic drugs such as aminoglycosides are used, serial measurements of serum creatinine and trough drug levels should provide sufficient information to be certain that dosage is appropriate. Furthermore, in infants born earlier than 34 weeks of gestation, serum creatinine concentration often remains unchanged from maternal levels until 34 to 35 weeks of conceptional age is reached because the GFR is too low to clear creatinine from the plasma. The contribution to serum creatinine by maternal creatinine, ongoing creatinine production, rate of creatinine excretion, conceptional age, hemoconcentration or hemodilution associated with postnatal weight loss or fluid therapy, and the influence of nonrenal factors on GFR vary independently in any given infant (20). However, regardless of renal or conceptional age, if the serum creatinine rises, the clinician should be alerted to renal dysfunction secondary to a structural or functional renal abnormality or to nonrenal factors, such as mechanical ventilation, that may alter the GFR in the neonate (544).

With the ability to image the fetal urinary tract came the opportunity of assessing renal function before birth. At present, direct measurement of renal function *in utero* is not technically feasible. However, fetal renal function can be inferred from (a) measurements of fetal urine outputs, (b) sonographic appearance of the kidneys, and (c) analysis of fetal urine composition after percutaneous aspiration. Newer modalities, such as magnetic resonance imaging (MRI), may also be on the horizon (565).

Fetal urine output has been studied in a variety of animal models. In 1964, Chez and associates (88) studied urinary flow *in utero* in rhesus monkeys using indwelling catheters placed in the urethra or bladder. They demonstrated that average urine flow was 5 mL/kg per hour.

In 1973, Campbell and co-workers (74) studied human fetal urine output by measuring the size of the bladder in three dimensions by ultrasound (bladder size = 4/3 × π × length × width × breadth ÷ 2) and determining the number of times the fetus voids per hour. In a series of patients between 32 weeks of gestation and term, the fetal bladder cycle varied from 50 to 155 minutes, with a mean of 110 minutes. The bladder volumes were noted to increase from 11 mL at 32 weeks to 40 mL at term. Rabinowitz and colleagues (422) have shown that fetal urine output increases from 5 mL per hour at 20 weeks to 51 mL per hour at term. Data from other studies have shown that (a) in the small fetus, urine output is lower, corresponding to fetal size rather than gestational age; (b) the fetus of a diabetic mother has an increased urine output; and (c) the fetus with anencephaly and polyhydramnios has a normal urine output (303,580,581). In addition, administration of intravenous (IV) furosemide to the mother during the last trimester doubles fetal urine output (303,582). Therefore it appears that the volume of amniotic fluid is not a reliable indicator of fetal renal function except at the extremes of oligohydramnios.

The sonographic detection of cortical cysts and increased cortical echogenicity has been associated with irreversible renal damage in the fetus (329). Normal fetal kidneys beyond 30 weeks of gestation exhibit an echotexture similar to that of liver, with an internal architecture showing a differentiation between cortex and medulla. The medulla containing tubules and fluid appears darker. In contrast, a dysplastic kidney exhibits no internal architecture and may have increased echogenicity caused by a disruption in normal histology. The dysplastic fetal kidney is characterized by the presence of disorganized metanephric structures surrounded by fibrous tissue, which may be associated with cortical cysts (246). More than 90% of dysplastic kidneys with cortical cysts are associated with an obstructive process occurring during nephrogenesis. Mahoney and associates (329) studied the kidneys of 49 fetuses with obstructive uropathy and found that the presence of cortical cysts had 100% specificity and a positive predictive value of 100% for the presence of renal dysplasia. However, the absence of cortical cysts cannot ensure the absence of renal dysplasia. Of the dysplastic kidneys, only 44% had cortical cysts. Increased echogenicity of the kidney's alone also was shown

to be less specific and to have a lower positive predictive value than the presence of cortical cysts. The evaluation of renal function solely on the basis of renal echogenicity is further limited by the subjective nature of this feature. Ultrasonographic examination of the fetal kidneys may provide prognostic information if cortical cysts and increased echogenicity are detected, but it is less specific in their absence (113). Furthermore, when seen in conjunction with oligohydramnios and fetal bladder distention, increased renal echogenicity is highly predictive (87%) of bladder outlet obstruction (279).

Fetal urine is an ultrafiltrate of fetal serum. Glick and co-workers (201) observed that fetuses with congenital hydronephrosis and normal renal function produce hypotonic urine, whereas those with poor function made isotonic urine. In this initial study from the fetal treatment program in San Francisco, 20 fetuses with bilateral hydronephrosis were evaluated, 18 of which had percutaneous drainage of fetal urine before birth. In an attempt to determine prognostic criteria of renal function, urine electrolytes were studied. Prognostic features for “good” renal function included urinary sodium less than 100 mEq/L, chloride less than 90 mEq/L, osmolality less than 210 mOsm/L, and urine output greater than 2 mL per hour. Other reported prognostic criteria for good renal function were normal to moderately decreased amniotic fluid and a normal echogenic appearance of the kidneys. These criteria were established as a possible means to select those fetuses with sufficient renal function to have a favorable postnatal outcome if *in utero* decompression of an obstructive process was carried out early enough to prevent the sequelae of obstructive uropathy. These criteria have been challenged by several groups because normal controls in normal fetuses were not provided. In addition, these criteria failed to take into account variation in urine electrolytes during gestation (153,376,570). More recently, Johnson and associates (271) have recommended sequentially sampling fetal urine to establish patterns of progressive improvement or worsening of values so as to provide a better assessment of renal damage.

Subsequent to the 1985 study, Crombleholme and associates (113) evaluated a subsequent series of 40 fetuses with bilateral hydronephrosis and found that the prognostic criteria accurately predicted a good outcome after intervention, showing a statistically significant difference in survival in the good versus poor prognosis group (81% versus 12.5%). In addition to measuring the levels of fetal urine sodium, chloride, and osmolarity, other groups have evaluated urine Ca^{2+}, PO_4, and $ß_2$-microglobulin to assess fetal renal function (369,376). Nicolini and colleagues (375) found that fetal urinary calcium and sodium were significantly elevated in fetuses with renal dysplasia compared with those fetuses noted to have lower urinary tract obstruction but normal renal histology and normal clinical outcome. Urinary calcium levels were reported to be the most sensitive indicators of renal dysplasia (100%), but they lacked specificity (60%). Urinary sodium was slightly less sensitive (87%) but was found to be the most specific (87%). Urinary PO_4, creatinine, and urea were not helpful in confirming renal dysplasia. Muller and co-workers (369) found that $ß_2$-microglobulin levels were significantly elevated in patients with an elevated creatinine (greater than 0.56 mg/dL at 1 year of age) and recommended its use as a predictor of renal function at 1 year of age. The same group of French researchers have further published reference values for fetal urine markers (369).

FETAL MEMBRANES

Part of "46 - PERINATAL UROLOGY "

The extraembryonic or fetal membranes include the chorion, amnion, yolk sac, and allantois (213,365,542). These membranes are intimately related to the placenta, which develops from (a) the chorion (fetal portion) and (b) the endometrium (maternal portion). The fetal membranes and placenta are essential to fetal growth and development by providing several important functions, such as protection by cushioning, nutrition, respiration, and excretion.

Implantation of the blastocyst on the uterine wall begins on the sixth or seventh day after fertilization. The trophoblast rapidly proliferates and differentiates into the cytotrophoblastic and syncytiotrophoblastic layers of the placenta. In addition, lacunar networks develop, creating a primitive uteroplacental circulation. Finally, primary villi form on the outer surface of the chorionic sac. By the end of the second week, the conceptus is completely embedded within the endometrium. Concurrently, the yolk sac and the amniotic cavity develop (Fig. 46.5). The allantois appears during the third week.

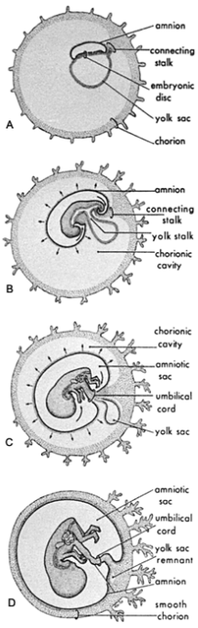

FIGURE 46.5. Drawings illustrating how the amnion becomes the outer covering of the umbilical cord and how the yolk sac is partially incorporated into the embryo as the primitive gut. At 3 weeks **(A),** 4 weeks **(B),** 10 weeks **(C),** and 20 weeks **(D).** (From Moore KL. *The developing human. Clinically oriented embryology,* 3rd ed. Philadelphia: WB Saunders, 1982, with permission.)

The yolk sac serves several important functions during embryogenesis. First, it appears to provide nutrients to the embryo during the second and third weeks while the uteroplacental circulation is being established. Second, angiogenesis begins in the yolk sac during the third week and persists until hematopoietic activity in the liver begins in the sixth week. Furthermore, germ cells form in the yolk sac and subsequently migrate to the gonadal ridge. Finally, the dorsal aspect of the yolk sac is incorporated into the embryo during the fourth week as an endodermal tube—the primitive gut. This structure gives rise to the epithelium of the gastrointestinal tract, trachea, bronchi, and lungs. By 12 weeks, the yolk sac is quite small but may still be identified. The stalk of the yolk sac usually is detached from the gut during the fifth week; persistence of the yolk stalk results in a diverticulum from the ileum, known as *Meckel's diverticulum,* with an incidence approximating 2% (365).

The allantois appears during the third week as a small fingerlike diverticulum from the caudal wall of the yolk sac. Although this structure functions as a reservoir for excretory products or as a respiratory chamber in some vertebrates, in humans it does not function. However, hematopoiesis

occurs on its walls during the first 2 months, and its blood vessels become the umbilical vein and arteries. The allantois itself connects the urinary bladder to the umbilicus. As the bladder increases in size, the allantois becomes much smaller and forms the urachus. After birth, the urachus becomes the median umbilical ligament and extends from the dome of the bladder to the umbilicus.

The amnion, the innermost of the fetal membranes, is derived from the cytotrophoblast adjacent to the dorsal aspect of the germ disc. As the amnion grows, it gradually obliterates the chorionic cavity, concurrent with ventral longitudinal folding of the embryo. The primary junction of the amniotic cavity with the embryo is on its ventral surface. The amnion provides the epithelial covering for the umbilical cord. The amnion therefore lines the expanding amniotic cavity, which holds increasing volumes of fluid. Early in pregnancy, the amniotic fluid appears to be a transudate of maternal plasma. During the first trimester, amniotic fluid production results from the active transport of electrolytes and other solutes across the amnion, which is composed of a single layer of cells. There is passive diffusion of water along the osmotic gradient thus generated (556). As the fetal kidneys start to produce urine and as flow through the urinary tract occurs, fetal urine is the major source of amniotic fluid. It is also likely that before keratinization of fetal skin at about 17 weeks, some of the amniotic fluid may be derived from water transport across the highly permeable fetal skin (5,400).

The volume of amniotic fluid increases at a relatively constant rate during pregnancy until the end of the second trimester. Regulation of amniotic fluid volume depends not only on urine production by the fetus but also on fetal swallowing, which starts between 8 and 11 weeks of gestation (538). By the end of the second trimester (24 weeks), the volume of amniotic fluid has increased steadily to approximately 800 mL, with this volume remaining relatively constant throughout the remainder of gestation. A mild decrease in volume is seen just before term (Table 46.4). Normally, amniotic fluid volume ranges from 500 to 2,000 nil (237,418). During the first half of gestation, the amniotic fluid has an electrolyte composition and osmolality similar to that of fetal and maternal blood (326). Later, amniotic fluid osmolality progressively decreases with advancing age, reaching values of 250 to 260 mOsm/kg H_2O near term. The amniotic fluid composition of various electrolytes parallels the variations in osmolality. Later in gestation,

sodium and chloride concentrations decrease, and urea and creatinine concentration increase (556). Regulatory mechanisms of amniotic fluid volumes have not been completely studied, but there are three possible mechanisms involved: (a) water and solute transport across fetal membranes, (b) regulation of excretion and absorption by the fetus, and (c) maternal influences via the placenta over the fetus' fluid status.

TABLE 46.4. AMNIOTIC FLUID VOLUME DURING PREGNANCY

Gestation (wk)	Volume (mL) Fetal	Urine Output (mL/24 hr)
14	100	—
16	185	—
18	360	—
20	380	—
24	450	—
28	800	230
32	850	293
36	850	439
40	800	655

Data from Haswell GL, Morris JA. Amniotic fluid volume studies. *Obstet Gynecol* 1973;42:725; and Queenan JT, Thompson W, Whitfield CR, et al. Amniotic fluid volume in normal pregnancies. *Am J Obstet Gynecol* 1972;114:34, with permission.

The amniotic fluid provides several functions; it (a) allows symmetric growth and development of the fetus, (b) allows the fetus to move freely, (c) cushions the embryo and fetus against external forces, (d) aids in maintaining body temperature of the embryo and fetus, and finally (e) may have a role in lung development (59).

An excessive amount of amniotic fluid (more than 1.5 to 2 L) is termed *polyhydramnios* (or hydramnios) and a significantly diminished fluid volume is termed *oligohydramnios* (less than 0.5 L). Throughout gestation, the circulation of amniotic fluid is a very dynamic event. The fetus swallows up to 500 mL per day as the urine output increases (470). The placenta also may play an important role in the turnover of amniotic fluid, and the biologic half-life of water in amniotic fluid has been reported to be as low as 90 minutes (258,484).

Obstetric evaluation of the fetus by ultrasound includes an assessment of amniotic fluid volume, particularly in the second and third trimesters. Several methods have been proposed. These include subjective assessment, measurement of the single, deepest pocket of fluid seen, amniotic fluid index, planning metric measurement of total intrauterine volume, and several mathematical formulas. In clinical practice, variability for all of these methods is low and is too similar to provide a basis for choosing one over the other (140,366). Currently, the amniotic fluid index seems to be the most widely used criterion to evaluate amniotic fluid volume.

Polyhydramnios

As previously noted, *polyhydramnios* refers to the presence of an excessive amount of amniotic fluid. It occurs in 0.25% to 0.67% of pregnancies. Greater than 2,000 mL of amniotic fluid during the third trimester constitutes polyhydramnios. The diagnosis may be suggested by maternal symptoms including excessive abdominal pressure, a protuberant or rapidly increasing size of the abdomen, excessive uterine contractions, or dyspnea. Physical signs include evidence of a disproportionate increase in uterine fundal height, abdominal girth, weight gain, and abdominal striae. Although the fetal head may be balloted, the extremities often are difficult to identify with certainty. In addition, it may be difficult to hear the fetal heart tones.

In 2% of patients with polyhydramnios, the excessive amniotic fluid accumulates acutely, usually by 23 to 25 weeks of gestation, resulting in a very tense and tender uterus (419). Chronic polyhydramnios is much more common and is diagnosed during the third trimester by abdominal examination or abdominal ultrasound.

Other conditions and fetal malformations associated with polyhydramnios are shown in Table 46.5 (39,417). Approximately one-third are idiopathic. In women with diabetes mellitus, polyhydramnios is more common when the diabetes is severe. The most common associated congenital anomaly is anencephaly; approximately half of pregnancies associated with anencephaly have polyhydramnios. In addition, abnormalities of formation of the upper gastrointestinal tract, such as tracheoesophageal fistula or esophageal or duodenal atresia, also have a high incidence of hydramnios.

TABLE 46.5. ASSOCIATED CONDITIONS AND FETAL MALFORMATIONS ASSOCIATED WITH DISORDERS OF AMNIOTIC FLUID VOLUME

Polyhydramnios (% of Total)	Oligohydramnios
Diabetes mellitus (25)	Bilateral renal agenesis
Anencephaly (20)	Posterior urethral valves
Erythroblastosis fetalis (11)	Prune-belly syndrome
usually associated with	Urethral atresia
hydrops fetalis)	Bilateral renal dysplasia
Multiple gestation (8)	Pulmonary hypoplasia
Meningocele or encephalocele	Growth retardation
Tracheoesophageal fistula	Amnion nodosum
Esophageal or duodenal atresia	Amniotic fluid leak
Pyloric stenosis	Limb defect
Klippel-Feil syndrome	Fetal demise
Cleft palate, cleft lip, or both	Abdominal pregnancy
Achondroplasia	
Diaphragmatic hernia	
Multiple anomalies[a]	
Trisomy 18	
Idiopathic (34)	

[a]Not central nervous system.

The prognosis in a pregnancy complicated by polyhydramnios is poor. Perinatal mortality is 35% to 40%, and the incidence of stillborn infants is 10% to 20%. Perinatal mortality associated with twin gestations, erythroblastosis fetalis, and diaphragmatic hernia is quite high.

Recently, a small number of mothers with polyhydramnios have been treated with indomethacin, which reduces fetal urine output and consequently diminishes amniotic fluid volume considerably. This treatment has been reported to result in significant neonatal renal dysfunction in a few cases (498).

Oligohydramnios

Oligohydramnios occurs in approximately 0.4% to 5.0% of pregnancies, depending on the sonographic criteria and source of patients, and carries an increased risk of fetal abnormality and morbidity (357,404). Because the daily turnover of amniotic fluid depends in large part on adequate

fetal urinary output, oligohydramnios often is associated with obstructive lesions of the urinary tract. Usually, the diagnosis is made during prenatal ultrasound examination. In some cases, the diagnosis is subjective and may require serial ultrasound examinations to assess more accurately the true amniotic fluid volume.

If oligohydramnios is found or suspected and an associated urinary tract abnormality is suspected, one of two patterns generally is seen. In bilateral renal agenesis, neither the kidneys nor bladder are identified. The sonographic diagnosis of this condition is highly accurate (450). Bilateral renal agenesis usually results in oligohydramnios, but cases of normal amniotic fluid volume associated with this condition have been reported (534). On the other hand, if oligohydramnios results from bladder outlet obstruction secondary to posterior urethral valves (PUV) or prune-belly syndrome, characteristically a distended bladder is seen associated with bilateral hydronephrosis. Small cysts in the kidneys may be detected by ultrasound and indicate renal dysplasia. The fetal mortality rate for pregnancies complicated by oligohydramnios is high, particularly when it is detected before 27 to 30 weeks of gestation (357,499). Further discussion of the diagnosis and management of these conditions is presented elsewhere in this chapter.

When the urinary tract is normal in the presence of oligohydramnios, fetal growth often is retarded. Other associated conditions include amnion nodosum and a chronic amniotic fluid leak (377) (Table 46.5).

Because amniotic fluid normally cushions the fetus, oligohydramnios often results in compression abnormalities. When oligohydramnios is secondary to bilateral renal agenesis, the phenotypic condition is referred to as *Potter's syndrome* (Fig. 46.6). Characteristically, such a fetus has external features suggestive of intrauterine compression,

including a flattened nose, a recessed chin, low-set aberrantly folded ears, spadelike hands, talipes equinovarus, and hypoplastic lungs. Currently, it is thought that amniotic fluid is important in allowing normal lung development, largely by its cushioning effect. Support for this hypothesis is provided by reports of monozygotic twins, one of whom had renal agenesis (345,534). Both fetuses were cushioned by the normal amniotic fluid and were born with normally developed lungs and without the secondary features of Potter's syndrome. The possible role of amniotic fluid in directly stimulating pulmonary development is unclear at this time.

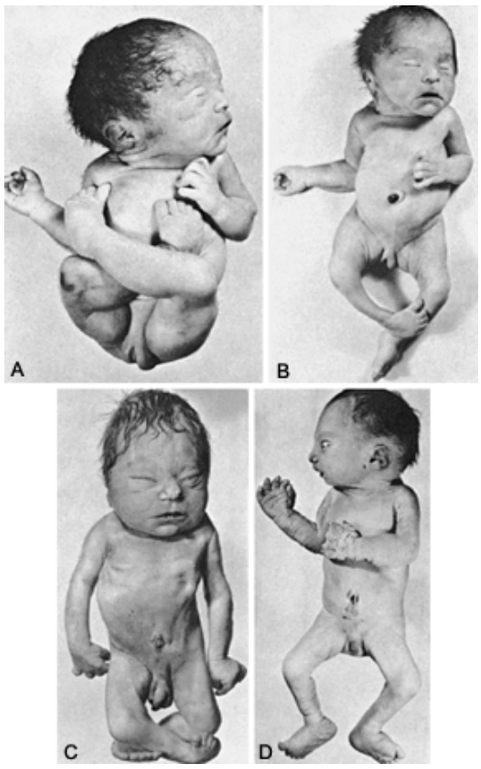

FIGURE 46.6. Infants with Potter's syndrome. **A, B:** Infant with renal agenesis in intrauterine position and with legs extended showing how intrauterine fixation causes bowing of legs. Note low-set ears. **C:** Bowing of legs and deformity of chest from intrauterine fixation resulting from oligohydramnios. **D:** Excessive amount of skin causing enlargement of the hands often associated with renal agenesis. All infants appear remarkably senile. (From Potter EL. *Normal and abnormal development of the kidney.* Chicago: Year Book Medical, 1972, with permission.)

Umbilical Cord

The site of attachment of the umbilical cord to the placenta is determined at implantation and is usually near the center of the placenta. If the blastocyst does not attach to the placenta at the embryonic pole, the connecting stalk (i.e., the umbilical cord) attaches to the placental margin or to the chorion. The cord is usually 55 cm in length and 1 to 2 cm in diameter. Excessively long or short cords are uncommon (360,371). Usually, there are two arteries and one vein encased in a mucoid substance called *Wharton's jelly,* which is rich in mucopolysaccharides. The umbilical vein is longer than the arteries, and the vessels are longer than the cord, resulting in significant tortuosity of the cord vessels and looping of the cord itself.

Approximately 1% of newborns have only one umbilical artery, which is associated with a variety of fetal anomalies, including the urinary tract (58). In the past, it was believed that such neonates deserved routine radiographic imaging of the genitourinary tract. A recent study of screening renal ultrasound in 27 infants with a single umbilical artery showed that 5 (19%) had a renal anomaly (318). Consequently, imaging of the urinary tract by ultrasonography is advisable if there is a single umbilical artery.

Fetal circulation differs from postnatal circulation. In the fetus, well-oxygenated blood is provided by the placenta through the umbilical vein. Approximately half of this blood travels through the portal sinus and hepatic sinusoids, and the other half bypasses the liver, passing through the ductus venosus into the inferior vena cava. After passing through the heart, which has its own unique fetal circulatory pattern, blood of medium oxygen saturation travels down the aorta. Blood that is to return to the placenta travels through the umbilical arteries, which are large branches of the hypogastric arteries. The umbilical arteries have a branch, the superior vesical artery, at the level of the bladder, and then continue on to the umbilicus adjacent to the urachus. At birth, following the development of the neonatal circulatory pattern, the umbilical vein fibroses and becomes the ligamentum teres. The umbilical arteries distal to the branch of the superior vesical artery become the lateral umbilical ligaments. Near the base of the bladder, the obliterated umbilical artery is an important landmark in the identification and dissection of the distal ureter.

ENDOCRINE FUNCTION OF THE PLACENTA

Part of "46 - PERINATAL UROLOGY "

The placenta represents the site of exchange between maternal and fetal circulation. In addition to its filtering role, the placenta appears to have an active metabolic role and an important endocrine function, which contributes to the maintenance of the pregnancy and growth of the fetus (Fig. 46.7) (76,274,385). Furthermore, it serves as an immunologic barrier, allowing the fetus to grow and develop with the maternal autogenically different environment. The trophoblast that forms the epithelium through which the exchanges occur possesses the important property of allowing the passage of certain macromolecules. Active transports, as well as exchanges, over concentration gradients also are known to occur. Interestingly, it appears that the intimate relationship between trophoblast and fetal capillaries is due to the influence of the trophoblast itself on fetal capillary growth. The exact controls that the placenta exerts on fetal growth are unknown, however. Certain influences, such as that of human chorionic gonadotropins (hCG), are recognized with regard to sexual differentiation and adrenal gland development. Fetal hCG plasma levels influence fetal testosterone secretion from the testis. Peak secretion of fetal testosterone occurs at about 12 weeks of gestation concomitantly with wolffian duct development and differentiation

of the external genitalia (96). In addition, hCG may have a role in maintaining the fetal zone of the adrenal gland early in gestation.

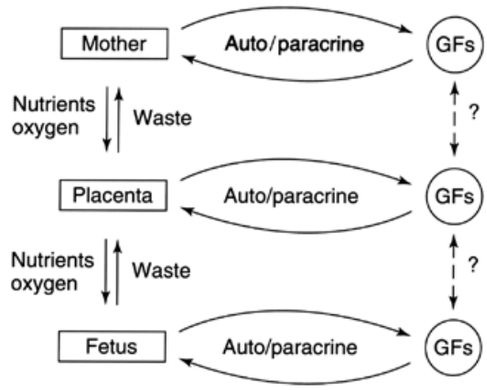

FIGURE 46.7. The transfer of substrates and waste between mother and fetus is, for the most part, unidirectional. Adequate transfer of substrates (nutrients and oxygen) from the mother to the fetus via the placenta, and efficient removal of waste from the fetus to the mother are essential for normal fetal growth. Growth factors *(GFs)* are synthesized in the maternal reproductive tissues, placenta, and fetus and act locally in an autocrine/paracrine manner. Endocrine transfer of growth factors between the mother, placenta, and fetus has not been shown to occur. (From Growth factors in fetal growth. In: Thorburn GD, Harding R, eds. *Textbook of fetal physiology.* Oxford: Oxford University Press, 1994, with permission.)

The placenta has a very important endocrine role and throughout pregnancy secretes certain hormones, such as placental l-lactogens, progesterone, and estrogen, the regulation of which is poorly understood. Later in pregnancy, glucocorticoids produced by the fetus induce placental estrogen production, which in turn induces parturition. The placenta may influence fetal growth early, but later the fetus appears to become more autonomous and have a role in regulating placental function. Fetal growth factors originate from the fetus, but fetal growth itself depends on the normal development and function of the uterus and placenta. Placental growth factors also have been identified, but their role on the fetus is unclear (385). The placenta is known to contain a high concentration of EGF receptors. EGF is a direct stimulator of DNA synthesis and may regulate fetal growth mainly by its influence on placental development. For fetal growth to occur, different cellular processes, specifically proliferation and differentiation, are regulated by intercellular communications. There appears to be no central regulatory process but rather an integrated system where cell-to-cell and cell-to-matrix interactions are mediated by effector molecules within the extracellular matrix, by peptide growth factors, and by intercellular recognition molecules. The exact role of the placenta with regard to fetal growth remains to be determined precisely. The weight of the placenta has been demonstrated to increase with gestational age, and fetal weight is directly correlated to placental weight (364).

PRENATAL ULTRASOUND OF THE URINARY TRACT

Part of "46 - PERINATAL UROLOGY "

Since its introduction in the 1950s, ultrasonographic evaluation of the fetus has undergone significant improvement. Technological advances have allowed for earlier and more precise identification of congenital anomalies. The safety of ultrasound has been studied extensively, leading to the American Institute for Ultrasound in Medicine (AIUM) Bioeffects Committee to conclude that, with judicious use of ultrasound screening in pregnancy, the benefits outweigh any potential risks (16).

The first report of the use of ultrasonography in pregnancy was published in 1958, and the first reported ultrasound diagnosis of a fetal urologic anomaly was published in 1970 (138,190). The introduction of this diagnostic modality heralded in a new era in medicine, an era in which a noninvasive diagnostic technique could reveal congenital anomalies in the fetus, thus allowing for prenatal counseling, early management, and possible intervention should the lesion be amenable to treatment. Availability of sonographic screening in the fetus has increased dramatically, such that several European countries have instituted programs for routine prenatal screening. Controversies do exist with regard to the indications and extent of use of ultrasound in pregnancy, as well as to when it should be administered (189). Prenatal ultrasonography has become an important component of the fetal evaluation. Suspected anomalies can be precisely delineated, and a team of specialists can offer expert advice and counseling. Options in the management and treatment can be discussed in order to plan for delivery and care of the newborn under optimal conditions (325).

With the increasing availability and use of ultrasonography, indications for screening of the fetus have been better defined: determination of gestational age by biparietal head diameter, suspicion of a gestational abnormality, and strong family or maternal histories of prior congenital anomalies. Practice guidelines have been formulated and proposed by the American College of Obstetrics and Gynecologists (15).

Although routine prenatal ultrasound has been advocated (160), a recent multicenter, randomized study of screening ultrasound in more than 15,000 low-risk pregnant women failed to conclusively demonstrate a significant difference in adverse outcome as defined by fetal death, preterm labor and delivery, significant neonatal morbidity, and neonatal death (168). Unfortunately, studies such as this one, designed to evaluate the efficacy of ultrasound as a diagnostic tool that is possibly helpful in improving clinical outcomes, fail to take into account the fact that the natural history of certain congenital anomalies has not been investigated fully and that, in turn, standardized management protocols do not exist for these prenatally diagnosed conditions. At present, current recommendations are to offer the options of a routine ultrasound to any pregnant patient following in a discussion of the potential risks and benefits (189).

The overall incidence of detectable fetal anomalies is approximately 1%. The diagnostic accuracy depends on the expertise of the ultrasonographer, the quality of the equipment, the extent of the malformation, and timing of the study. The type of institution reporting rates of congenital anomaly diagnosed prenatally influences the reported incidence of fetal anomalies: Tertiary centers may include anomalies that have been referred from obstetricians and radiologists, significantly increasing the frequency of various anomalies.

The incidence of urologic anomalies detected *in utero* is approximately 1 in 500. In addition, a wide spectrum of dilation of the urinary tract can be seen, making hydronephrosis the most commonly detected congenital condition that is observed by prenatal ultrasound. It may represent up to 50% of all abnormalities detected by prenatal ultrasound. By pooling a number of reports, it has been calculated that the incidence of detectable urinary tract dilation *in utero* is 1 per 100 pregnancies, but of these, only 1 in 500 is believed to represent a significant urologic problem (533). Thus the

urologist must be familiar with prenatal ultrasound diagnoses and with the information one should expect to obtain at different times in gestation, as well as the accuracy of ultrasound in detecting urogenital abnormalities.

Table 46.6 lists the primary structural anomalies and conditions of urologic significance that may be revealed during a prenatal ultrasound examination. In all of these conditions, with the exception of primary vesicoureteral reflux (VUR) and cloacal exstrophy, prenatal ultrasound usually demonstrates an abnormality, although a specific diagnosis can be made only on postnatal evaluation. Most of the obstructive anomalies occur primarily in males.

TABLE 46.6. GENITOURINARY ANOMALIES DETECTABLE BY PRENATAL ULTRASONOGRAPHY

Condition	Sex (Ratio)	Frequency	Kidney(s)	Ureter(s)	Bladder	Amniotic Fluid	Prognosis
Ureteropelvic junction obstruction (unilateral)	M/F (3–4:1)	1:2,000	Hydronephrosis	Not seen	Normal	Normal	Good after surgical correction
Multicystic kidney (unilateral)	M/F (1:1)	1:3,000	Large with cysts of variable size	Not seen	Normal	Normal	Normal
Primary obstructive megaureter	M/F (3:1)	1:10,000	Hydronephrosis	Dilated	Normal	Normal	Good after surgical correction
Ectopic ureterocele or ureter	M/F (1:6)	1:10,000	Large cyst; possible duplex kidney	Dilated	Normal or enlarged	Normal	Good after surgical correction
Posterior urethral valves	Male	1:8,000	Bilateral hydronephrosis possible cortical cysts	Dilated	Enlarged	Variable; diminished or absent in severe obstruction	Usually good after surgical correction or drainage; poor if oligohydramnios is present
Prune-belly syndrome	Nearly always male	1:40,000	Bilateral hydronephrosis; possible cortical cysts	Dilated	Enlarged	Variable; diminished or absent if severely affected	Usually fair to good; may need surgical drainage; poor if oligohydramnios is present
Vesicoureteral reflux	M/F (1:5)	1:100	Hydronephrosis if reflux high grade	Variable	Normal; dilated if reflux high grade	Normal	Good; may need surgical correction
Infantile polycystic kidney disease	M/F	1:6,000–1:14,000	Large, echogenic	Not seen	Small or not seen	Usually absent or severely diminished	Poor
Renal agenesis	M/F (2.0–2.5:1)	1:4,000 (bilateral) 1:1,500 (unilateral)	Not seen Not seen	Not seen Not seen	Not seen Normal	Severely diminished or absent Normal	Stillbirth Normal
Hydrocolpos	Female		May have hydronephrosis	Not seen	Normal	Normal	Good after surgical correction
Ovarian cyst	Female		Normal (cyst may be confused with kidney or bladder)	Not seen	Normal	Normal	Good after surgical correction

Normal Ultrasound Findings

In the normal fetus, current diagnostic capabilities allow for the detection of urinary tract anomalies as early as 12 to 14 weeks of gestation (66,401). The role of ultrasound in the evaluation of the fetal urinary tract is twofold: (a) to identify the fetuses with any anomalies involving the urinary tract and (b) to monitor these lesions and characterize their effect on the overall health of the fetus. Variables that must be considered in the evaluation of the fetal urinary tract are gestational age at diagnosis, area of the urinary tract where lesions are identified, degree of dilations of the urinary collecting system, evidence of obstruction, and associated anomalies elsewhere in the fetus.

Normal fetal anatomy can be identified very early in gestation. The bladder is visible at 10 weeks and appears as an echolucent area at the base of the fetal trunk (160,161). The size of the bladder may vary as it fills and empties in a cyclical manner. The maximum bladder capacity typically is 10 mL at 30 weeks and 50 mL at term. The presence of a filled bladder and normal kidneys gives presumptive evidence of adequate renal function. Conversely, nonvisualization of the urinary bladder, particularly in association with oligohydramnios, suggests poor renal function and poor prognosis (65).

Although the kidneys may be visualized by 12 to 13 weeks, they should be identified in 90% of cases by 17 weeks (312). The fetal kidneys are seen in transverse section just below the level of the umbilical vein early in gestation. Fetal renal growth can accurately monitored throughout pregnancy (203). The kidneys may be recognized by their typical shape and by the presence of a central echo from the intrarenal portion of the collecting system (Fig. 46.8). The renal collecting system (calyces and pelvis) should not be seen. The renal pelvis, when visible, is indicative of hydronephrosis. According to Hoddick, distention of the renal pelvis may range in anteroposterior (AP) diameter from 3 to 11 mm in up to 18% of normal fetuses studied after 24 weeks of gestation (23,247). It was suggested that a pelvic diameter larger than 10 mm or a ratio of the AP pelvic diameter to the AP renal diameter of greater than 0.5 indicated significant fetal hydronephrosis. These criteria were subsequently modified by Kleiner and associates (293) with the addition of caliectasis as an additional indicator of significant hydronephrosis. The renal parenchyma appears to have a similar echo texture to that of the liver, and later in development, the corticomedullary junction may be visible. Standards for normal renal size have been established in the fetus (212,266,312,466,482). The kidney circumference can be estimated to be equal to one-third of the abdominal circumference throughout gestation. A formula to determine normal fetal kidney length has been proposed: kidney length (mm) = 16 + 0.06 × gestational age in weeks (266). Normally, the fetal ureter should not be seen.

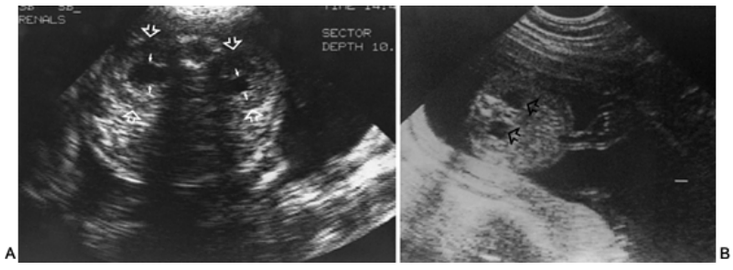

FIGURE 46.8. A: Normal kidneys. Transverse section through both fetal kidneys shows bilateral prominence of renal pelvis (right, 8 mm; left, 6 mm) *(tiny arrows).* Transverse anteroposterior renal width (right, 21 mm; left, 20 mm) *(open arrows).* RP/RD ratio: right, 38%; left, 30%. Both kidneys were normal with extrarenal pelvis on postdelivery follow-up. **B:** Normal kidneys. Renal pelvis prominence bilaterally (right, 9 mm; left, 8 mm) *(open arrows)* in fetus at 22 weeks of gestation. Four subsequent examinations showed less prominence of the renal pelvis. At 32 weeks of gestation and 3 days after delivery, no renal pelvic dilation was present. (From Arger PH, Coleman BG, Mintz MC, et al. Routine fetal genitourinary tract screening. *Radiology* 1985;156:486, with permission.)

The fetal adrenals may be recognized after the thirtieth week and appear as relatively hypoechoic ovoids or triangular structures superior to the upper poles of the kidneys. They are approximately half as large as the normal kidney. Later in gestation, the kidneys are surrounded by retroperitoneal fat, which assists greatly in their visualization.

Fetal sex also can be determined early in gestation. Determination of sex requires unequivocal visualization of the penis, scrotum or both, or of the labia majora. Birnholz (50) demonstrated the sexual identity of 40% of fetuses less than 24 weeks of gestation. Misdiagnosis occurred in 3%. Accuracy of 100% was reported in another study of second-trimester examinations (519). Nonvisualization of the genitalia during the second trimester generally is due to a prone or complete breech fetal position or may be related to impaired imaging secondary to maternal obesity or oligohydramnios (50).

Determination of fetal sex is important primarily in patients whose fetuses are at risk for X-linked genetic disorders, such as hemophilia, chromic granulomatous disease, and Lesch-Nyhan syndrome. In addition, sonographic imaging of the fetal external genitalia may help in assessing the result of maternal steroid therapy in the female fetus with congenital adrenal hyperplasia (CAH).

Prenatal Detection of Genitourinary Anomalies

Genitourinary anomalies detectable by prenatal ultrasonography are summarized in Table 46.6 .

Bilateral renal agenesis occurs in approximately 1 of 4,000 pregnancies (415). Unilateral renal agenesis is two to three times more common. Renal agenesis is thought to occur from an abnormality of the mesonephric duct or ureteral bud, resulting in failure of the metanephric blastema to differentiate. In such cases, the kidney and ureter are absent. Approximately 40% of infants with bilateral renal agenesis are stillborn, and those born alive die rapidly from pulmonary hypoplasia. Morphologic features in bilateral renal agenesis include low-set ears, prominent epicanthic folds, hypertelorism, and pulmonary hypoplasia (416). If the diagnosis of renal agenesis is made early in gestation, therapeutic abortion should be considered. If the diagnosis

is made later in gestation, management of the associated complications, including breech presentation and intrapartum fetal distress, may be facilitated and neonatal resuscitation avoided.

Diagnosis of bilateral renal agenesis is made by the findings of oligohydramnios, absent kidneys, and nonvisualization of the urinary bladder. The most reliable indicator is the inability to visualize the urinary bladder because the adrenal glands in these fetuses tend to be ovoid and may resemble fetal kidneys (65,415). The diagnosis of renal agenesis can be confirmed by imaging the bladder intermittently over a period of at least 2 hours. If the bladder continues to remain nonvisualized, 10 mL of furosemide should be infused intravenously into the mother to confirm fetal anuria (232,304).

The prenatal diagnosis of bilateral renal agenesis has been quite accurate at experienced centers. Romero and co-workers (450) reported on 49 patients who were being evaluated for possible bilateral renal agenesis. The diagnosis was made and confirmed in 18 patients. There was only one false-negative ultrasound and no false-positive studies in their original report. However, in an addendum, the authors reported that three false-positive diagnoses were made. In these three newborns, kidneys reportedly were present and morphologically normal in two and abnormal in one. Apparently, these infants experienced severe intrauterine growth retardation, and the authors were less certain about their ability to establish the diagnosis of renal agenesis prenatally with 100% accuracy.

Bilateral renal agenesis has a polygenic inheritance pattern, with a recurrence rate of 2% to 5%. In the series by Romero and associates (450), 3 of 16 (19%) fetuses in whom there was a family history of bilateral renal agenesis were found to have this diagnosis. In a study of parents and siblings of index patients with bilateral renal agenesis, severe dysgenesis, or both, 9% had an asymptomatic renal malformation, most frequently unilateral renal agenesis (453).

Very early in gestation, amniotic fluid may be present in association with bilateral renal agenesis, but it diminishes rapidly during the second trimester. Bilateral renal agenesis may be associated with normal amniotic fluid if there is another defect that impairs the normal flow of amniotic fluid, such as esophageal atresia, or if the fetus is part of a monoamniotic twin pregnancy with a normal twin (534).

Hydronephrosis, or dilation of the upper urinary tract, is the most common urologic abnormality found by prenatal ultrasound. Dilation of the renal collecting system and/or ureter may be caused by either an obstructive process, such as UPJ obstruction, UVJ obstruction, or bladder outlet obstruction, or it may be secondary to VUR (55). Physiologic or nonobstructive dilation of the upper urinary tract refers to mild hydronephrosis for which no cause can be determined. Other anomalies, such as multicystic dysplastic kidney or a distended loop of bowel, may be misinterpreted as hydronephrosis.

The causes of fetal hydronephrosis are many but can be divided broadly into obstructive and nonobstructive dilation. This distinction usually cannot be made unequivocally on prenatal ultrasonography but is very important with regard to the ultimate effect on renal function. A distended renal pelvis alone does not imply that high intrapelvic pressures exist that might impair renal development and

thus cause a reduction in function. The fetal and neonatal renal pelvis is extremely compliant and therefore may accommodate greater volumes at lower pressures. However, as renal pelvic distention increases, so do the chances of having a functionally deleterious lesion. Furthermore, unilateral distention will not, in general, affect significantly on overall kidney function, whereas bilateral hydronephrosis may be associated with abnormal renal development.

The development of sonographic criteria that help in distinguishing physiologic from pathologic hydronephrosis has greatly contributed to the ability to assess the information provided by prenatal ultrasound (23,173,217,247,280,293,339). Appropriate clinical management requires an accurate delineation of the abnormality or abnormalities, as well as an appreciation of the natural history of untreated lesions and their impact on the developing fetus. Over the last 15 years, much progress has been made in defining the natural history of various forms of obstructive uropathy by careful follow-up of untreated cases and by the establishment of certain animal models that recreate fetal hydronephrosis (52,66,67,229,373,433,575).

A complete understanding of the natural history of fetal hydronephrosis is still evolving, especially in cases of upper urinary tract dilation detected before 20 weeks of gestation. A recent report by Bronshtein and co-workers (66) that describes the use of transvaginal ultrasound screening in the early stages of pregnancy found that fetal hydronephrosis may vary greatly over the course of gestation. In fact, of 27 cases of fetal hydronephrosis (renal pelvis greater than 3 mm) diagnosed between 13 and 17 weeks of gestation, only 6 displayed any evidence of urinary tract dilation postnatally; 10 cases of unilateral hydronephrosis disappeared between 15 weeks of gestation and term. Parameters of abnormal renal pelvic dilation in fetuses less than 20 weeks of gestation need to be further defined.

To better define fetal hydronephrosis and its effect on the developing urinary tract, ultrasonographic features, including a measurement of overall growth and development of the fetus, amniotic fluid index, gender, renal parenchymal appearance, extent of dilation of the collecting system, unilateral or bilateral involvement, bladder size and emptying, bladder wall thickness, and external genitalic anomalies, must be evaluated systematically. Because of the increased incidence of associated malformations, the fetus should be evaluated for extrarenal anomalies. The fetus with hydronephrosis should be scanned several times during gestation to monitor the evolution of the process.

Several series have reviewed the accuracy of diagnosing fetal hydronephrosis by ultrasound (26,55,494,560). False-positive scans have been noted in 9% to 22% of prenatally suspected uropathies (379,433). The incidence of physiologic or minimal hydronephrosis has not been well ascertained. However, progression of mild or physiologic hydronephrosis occasionally can be seen later in gestation or postnatally. In a recent study, Morin and associates (368) showed that 6.5% of patients initially thought to have mild fetal hydronephrosis required postnatal surgical treatment for a significant urologic lesion. Progression to pathologic levels of hydronephrosis is most often associated with UPJ obstruction or VUR (336,379,560,593).

Fetal renal dimensions measured by ultrasound are important in diagnosing lesions that may affect renal functional development. Later in gestation, a fetal renal pelvis AP diameter greater than 10 mm after 24 to 26 weeks of gestation usually is associated with an obstructive process (23,271,336). In many series, no abnormalities were found postnatally if the renal pelvis was less than 10 mm in diameter (217). More recently, however, anecdotal reports of progression of fetal hydronephrosis and subsequent documented pathologic dilation of the upper urinary tract have been described in fetuses with pelvic diameters less than 10 mm (81,178).

With ultrasound screening being performed earlier in gestation and with improvements in sonographic resolution, dilation of the upper urinary tract is being diagnosed more frequently. Certain sonographic criteria, including caliectasis, worsening hydronephrosis, and increased cortical echogenicity, appear to have some prognostic significance (80). Other specific sonographic criteria, such as AP renal pelvis diameter, AP renal pelvis-to-kidney ratio, transverse diameter of renal pelvis-to-kidney ratio, renal parenchymal thickness, and caliectasis, have been analyzed by Corteville and colleagues (104). Of the criteria, caliectasis correlated best with functionally significant renal lesions. Current recommendations are that fetuses found to have an AP diameter of the renal pelvis greater than 10 mm, an AP pelvic-to-renal cortex ratio greater than 0.5, or evidence of caliectasis after 24 weeks of gestation be evaluated postnatally. The frequency of prenatal monitoring by ultrasound should be limited to having an initial study at 16 to 21 weeks and a single follow-up after 28 weeks. More frequent scanning can be the cause of significant parental anxiety and will, in general, add little to the diagnosis or management (226).

Mild fetal hydronephrosis and transient dilation of the urinary tract are issues that have clouded postnatal management. The etiology and significance of mild fetal hydronephrosis (AP diameter of the renal pelvis less than 10 mm after 24 weeks of gestation) have not been fully elucidated. Hoddick and co-workers (247) demonstrated that the degree of maternal hydration had no significant influence on the fetal urinary tract. These findings were later confirmed by Allen and associates (11). Potential causes for mild dilation of the fetal urinary tract include transient obstruction, VUR, and natural kinks and folds that may occur early in development (56,251,372,593). The hormonal milieu of the fetus, as well as the degree of fetal bladder distention, also may influence renal pelvic diameter. Maternal hydronephrosis

is seen commonly in pregnancy, and progesterone, a smooth muscle relaxant, also may play a role in mild fetal hydronephrosis.

Obstructive uropathy refers to urologic lesions that significantly affect the development of renal function and are caused by a fixed obstruction within the urinary tract. Careful sonographic evaluation of the dilated fetal urinary tract may accurately localize the level of obstruction. The three most common causes of obstructive uropathy in the fetus are UPJ obstruction, ectopic ureterocele, and PUV.

UPJ obstruction is the most common cause of neonatal hydronephrosis (316). This lesion may vary in its severity, can cause very large distention of the renal pelvis, and may be bilateral. Although the pathogenesis is not well understood, partial ureteral obstruction early in pregnancy (first or second trimester) may result in pelvocaliectasis and renal dysplasia, whereas late partial obstruction may only cause pelvocaliectasis. Complete ureteral obstruction occurring before 10 weeks of gestation may be the cause of multicystic dysplastic kidney and contralateral hydronephrosis in the newborn (207,474). UPJ obstruction is believed to be an abnormality in the development of the UPJ or proximal ureters with disorganization in the smooth muscle and connective tissue elements resulting in a narrowed ureteral lumen (223).

In general, UPJ obstruction is secondary to an intrinsic obstruction caused by an aperistaltic segment at the UPJ, but a second renal artery supplying the lower pole is often an associated finding and has been implicated in the pathogenesis of hydronephrosis. UPJ obstruction usually occurs unilaterally, although in 21% of patients diagnosed in infancy, the condition is bilateral (Fig. 46.9). In the presence of unilateral UPJ obstruction, the amniotic fluid and bladder are normal, and the ipsilateral ureter is not visualized by ultrasound. The degree of renal pelvic and calyceal dilation and thickness of renal cortex are variable. A distended renal pelvis alone does not imply that kidney function is reduced because the fetal and neonatal renal pelvis are extremely compliant.

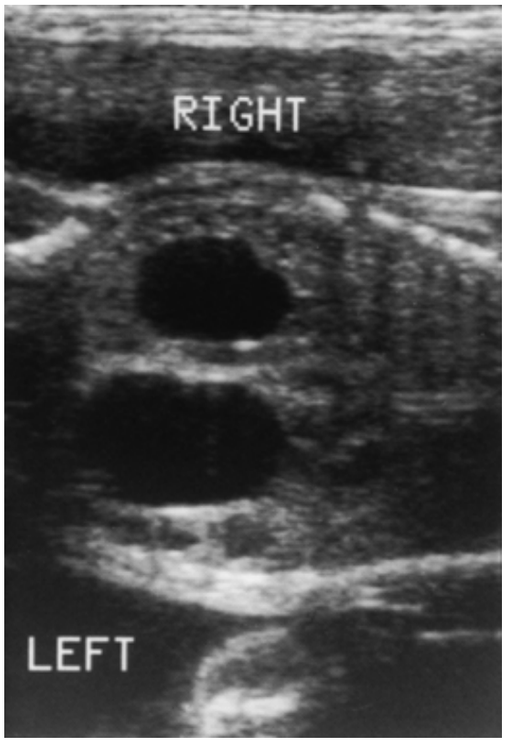

FIGURE 46.9. Bilateral ureteropelvic junction obstruction in fetus at 26 weeks of gestation.

The diagnosis of UPJ obstruction prenatally depends on fulfilling the echographic criteria for significant pelviectasis, in the absence of a dilated ureter, distended bladder, ectopic ureterocele, and posterior urethra. The prenatal sonographic diagnosis of UPJ obstruction is thus a diagnosis of exclusion that can be achieved with a good degree of reliability (293). In general, the prognosis of unilateral UPJ obstruction is good because of the normal contralateral kidney. Cases of bilateral UPJ obstruction are at risk for poor outcome because of compromise in both kidneys (177).

In complete ureteral duplication, the ureter draining the upper pole opens into the bladder caudal and medial to the lower-pole ureter. The upper-pole ureter commonly ends in an expansion between mucosa and muscle of the bladder known as a *ureterocele.* Hydronephrosis is common in the upper pole, as is obstruction-induced dysplasia (72). Every fetus exhibiting hydronephrosis should undergo careful inspection of the bladder to exclude a ureterocele as a cause. Ectopic ureterocele obstructing the bladder outlet may result in bilateral hydronephrosis (432). Obstructing ectopic ureterocele is the third leading cause of neonatal hydronephrosis (316). More than 80% of affected neonates are female, and the condition is bilateral in 10% to 15% of patients. In male patients, 40% have a single system drained by the ureterocele.

Megaureter may be detected by prenatal ultrasound and is characterized by a dilated kidney and ureter and usually a normal bladder. *The condition may be bilateral and may or may not be obstructive.* In nonobstructed cases, the megaureter may be secondary to VUR, may be physiologic (secondary to high urinary flow in the fetus), or may result from a mild functional obstruction at the UVJ. Complete evaluation of the condition is deferred until after birth, and early delivery is not usually warranted. When bilateral hydroureteronephrosis is detected, a distended bladder suggests

bladder outlet obstruction secondary to PUV, prune-belly syndrome, urethral atresia, or high-grade reflux.

PUV is the second most common cause of neonatal hydronephrosis (Fig. 46.10). This condition is of particular concern because bladder outlet obstruction often has a very deleterious effect on both bladder and kidney development (399). Infants born with this condition exhibit a spectrum of disease; in the most severe cases, prenatal sonographic findings include oligohydramnios, a dilated urinary bladder and posterior urethra, bilateral hydronephrosis, and subcortical renal cyst formation indicative of renal dysplasia. In addition, ascites and abdominal wall distention may be present. The sonographic features of PUV may vary considerably in the fetus, depending on the gestational age and severity of obstruction. Thickening of the bladder wall with trabeculation and a dilated posterior urethra may be detected later in pregnancy (80).

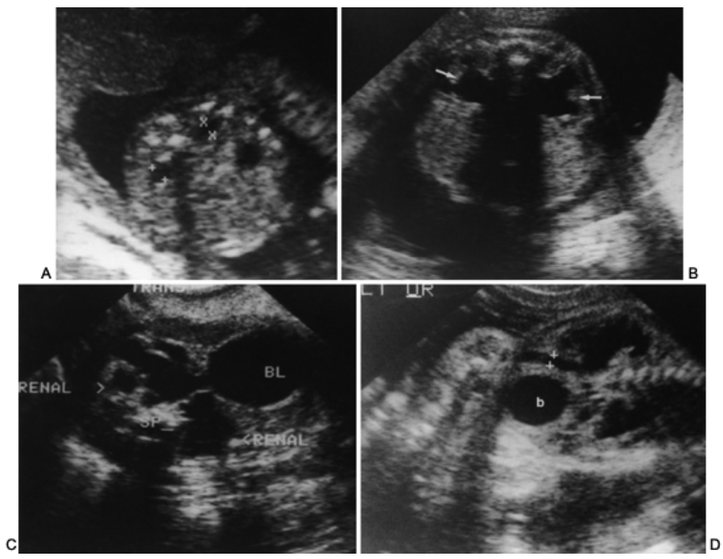

FIGURE 46.10. Posterior urethral valves. **A:** Transverse section at 21 weeks of gestation shows minimal bilateral pelvic prominence *(+, x).* Right and left pelves measure 5 mm. **B:** Transverse section shows bilateral hydronephrosis (right, 14 mm; left, 21 mm) at 33 weeks of gestation *(arrows).* **C:** Oblique sagittal section shows prominent bladder *(BL).* SP, spine. **D:** Longitudinal section through left kidney shows hydronephrosis plus dilated ureter *(+).* b, bladder. (From Arger PH, Coleman BG, Mintz MC, et al. Routine fetal genitourinary tract screening. *Radiology* 1985;156:487, with permission.)

The most important prognostic feature in the fetus with bladder outlet obstruction is the presence or absence of sufficient amniotic fluid. Oligohydramnios or anhydramnios detected during the second trimester, associated with bilateral hydronephrosis, is indicative of severe bladder outlet obstruction and nearly always is fatal (339). The primary cause of neonatal mortality is an inability to ventilate the lungs because of severe pulmonary hypoplasia. Many of these infants also have such severe renal dysplasia

that even if they were to survive from a respiratory standpoint, renal function would be extremely poor or nonexistent (101). Infants with bladder outlet obstruction associated with oligohydramnios have external morphologic features characteristic of Potter's syndrome. In the fetus with bladder outlet obstruction, the degree of hydronephrosis may be less than with primary UPJ obstruction, but the bladder is dilated in the former condition.

The fetus with *prune-belly syndrome* also has a sonographic appearance similar to that described for PUV, and the two conditions cannot be distinguished prenatally. However, prune-belly syndrome is less common, and the chances of a viable newborn with either condition depend primarily on the presence or absence of amniotic fluid. An occasional female with this condition and impaired gastrointestinal motility have been reported (201); it may be a forme fruste of the megacystis-microcolon-hypoperistalsis syndrome.

Although *multicystic dysplastic kidney* is the most common cause of an abdominal mass in the neonate, it is less common than UPJ obstruction. Grossly, the reniform contour of the kidney is lost. A grapelike cluster of cysts of varying size replaces the renal cortex, and these kidneys do not function. The prenatal diagnosis is based on these macroscopic findings (Fig. 46.11). Characteristically, multiple cysts of varying size are seen unilaterally without identifiable parenchyma. However, the presence of one central dominant cyst with peripheral cysts of similar size can cause confusion in trying to distinguish this from UPJ obstruction. Indeed, a number of reports evaluating prenatal ultrasonography have not indicated an ability to distinguish UPJ obstruction from multicystic kidney. Multicystic kidney occurs bilaterally in 20% of patients and is fatal. Hydronephrosis of the contralateral kidney occurs in 10% of patients and is usually due to UPJ obstruction (125).

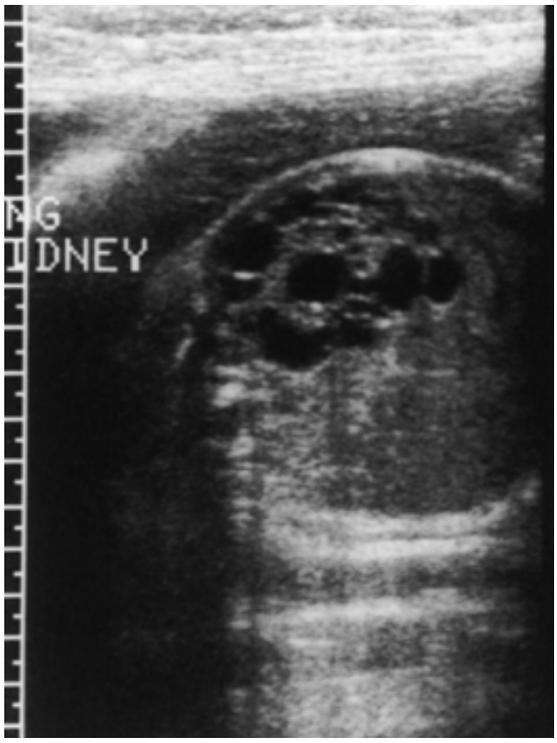

FIGURE 46.11. Multicystic kidney at 31 weeks of gestation. Note multiple cysts of varying size without identifiable parenchyma.

Infantile polycystic kidney disease is an autosomal-recessive disorder that affects the kidneys and liver. In this condition, the kidneys undergo cystic dilation of the collecting tubules. In contrast to the adult form of the disorder (autosomal dominant with large cysts), the cysts generally are 1 to 2 mm wide. The liver demonstrates periportal fibrosis and bile duct proliferation. One of the earliest reports of successful *in utero* diagnosis of polycystic kidney disease was by Garrett and colleagues (190). Romero and associates (451) reported a series of ten fetuses with infantile polycystic kidney disease, and the diagnosis was made correctly prenatally in nine. Characteristically seen was oligohydramnios, nonvisualization of the urinary bladder, bilateral renal enlargement (kidney circumference–abdominal circumference greater than 2 standard deviations above the mean), and a typical highly echogenic appearance secondary to sound refection off the wall of the numerous dilated tubules. Nephromegaly may not be demonstrated until 24 weeks of gestation. Thus an ultrasound performed before 24 weeks in patients at risk should be repeated at 24 weeks to be more certain of the correct diagnosis. Although most infants with this disorder are stillborn or die within the first few weeks as a result of renal failure, pulmonary hypoplasia, or both, an occasional patient survives only to succumb to the complications of periportal fibrosis later in childhood.

Adult polycystic kidney disease is an autosomal-dominant disorder that occasionally presents in infants and has been detected prenatally (355). Typically, the kidneys are enlarged, and abnormally reflective, macroscopic cysts are often present. In addition, there is accentuation of the corticomedullary junction. In contrast, in autosomal-recessive (infantile) polycystic kidney disease, the corticomedullary junction typically is not seen and the kidneys are highly echogenic without macroscopic cysts.

At present, prenatal detection of hydronephrosis should positively affect the postnatal outcome by allowing prenatal consultation by the pediatric urologist and the formulation of a management plan geared toward the prevention of further renal deterioration. The site of delivery may be changed to a tertiary care setting for early postnatal intervention. In general, however, postnatal management can be

organized in a nonemergent basis. Only in rare cases is prenatal intervention indicated to prevent fatal consequences of obstructive uropathy.

FETAL INTERVENTION

Part of "46 - PERINATAL UROLOGY "

The ability to identify congenital lesions in the fetus has increased our understanding of the natural history of the lesions prenatally and also has introduced new therapeutic options. In the fetus diagnosed with bilateral dilation of the upper urinary tract and suspected of having obstructive uropathy, intervention has been proposed. However, fetal intervention is an area that has generated tremendous controversy not only because of medical concerns but also because of the ethical and legal issues at hand (131,150,220,346,520). The goal of management of a fetus with congenital hydronephrosis is to prevent the sequelae of the obstructive process. These sequelae include renal maldevelopment as seen in renal dysplasia causing renal failure and oligohydramnios caused by urinary retention and pulmonary hypoplasia (233,234). However, at the root of medical concerns regarding treatment of fetal hydronephrosis are the questions regarding accuracy of diagnosis, timing of intervention, safety of the procedure for both the fetus and mother, and most important, the beneficial effects of interventions with regard to clinical outcomes, an issue that has yet to be properly evaluated. Furthermore, reliable echographic criteria of obstructive uropathy have not been well defined, especially early in pregnancy. Therefore a major dilemma in the management of the fetus with bilateral hydronephrosis is selecting those fetuses who may benefit from early intervention (i.e., those fetuses with obstruction severe enough to compromise renal and pulmonary development, but not so severe that the renal damage is irreversible, even if relief of the obstructive process is accomplished). Several methods have been proposed to assess the functional capacity of the kidneys in a fetus suspected of having obstructive uropathy: evaluation of the sonographic appearance of the fetal kidneys, volume of amniotic fluid, and measurements of fetal urine electrolytes and proteins (81).

Renal dysplasia has been studied in various animal models (38,45,202,517). Its pathogenesis may be multifactorial, and several theories have been proposed: (a) early high-grade obstruction, (b) lateral ectopia of the ureteral bud causing induction of the metanephric blastema in an abnormal area, (c) an abnormal metanephric blastema, or (d) abnormal induction of the metanephric blastema by the ureteral bud (328,481). The dysplastic fetal kidney is characterized by the presence of disorganized metanephric structures surrounded by fibrous tissue, which may harbor cortical cysts (47,441). The sonographic detection of cortical cysts implies the presence of severe renal dysplasia and indicates irreversible renal damage (442). More than 90% of dysplastic kidneys with cortical cysts are associated with an obstructive process occurring early in nephrogenesis. Dysplastic kidneys display abundant fibrous tissue within the parenchyma, which on ultrasound, may appear more echogenic. As discussed earlier, increased renal echogenicity as seen on ultrasound in the fetus is less specific and of lower positive predictive value than the presence of cortical cysts (329). Furthermore, renal dysplasia may be associated with large cystic formations within the parenchyma. Multicystic renal dysplasia (MCDK) typically has cysts of varying size, interfaces between the cysts, nonmedial location of the largest cyst, and an absence of organized parenchyma (182). MCDK is usually unilateral and may be associated with contralateral urologic anomalies that warrant postnatal evaluation (176,294).

The amount of amniotic fluid is not a very useful prognostic indicator except at the extreme of oligohydramnios or anhydramnios (42,113,231). Unfortunately, by the time the amniotic fluid volume has been reduced to pathologic levels, fetuses with obstructive uropathy already show features of renal dysplasia and pulmonary hypoplasia that may be incompatible with life (42,112). In addition, genitourinary anomalies often are found in association with other congenital anomalies, especially chromosomal abnormalities (201,367).

Two additional screening tools that have shown some promise in helping to determine fetal renal function and that may provide some prognostic indicators are fetal urine production as measured by the amniotic fluid index (140) and fetal urine electrolyte sampling (369). As the fetal kidneys begin making urine at 13 weeks of gestation, an ultrafiltrate of fetal serum is produced, which is hypertonic because of selective tubular reabsorption of sodium and chloride in excess of free water (246,351). Between 16 and 21 weeks of gestation, the fetal urine becomes progressively more hypotonic (350,375). Fetuses that display dilation of the upper urinary tract and are found postnatally to have normal renal function produce hypotonic urine, whereas those with poor renal function have been shown to produce isotonic urine (201,228,354,563). The reasons why the fetal kidney subjected to longstanding obstruction produces isotonic urine have not been clearly elucidated, but it has been suggested that intrinsic and parenchymal changes, such as dysplasia, may alter the reabsorption of sodium and chloride and thus cause varying degrees of salt wasting (201).

In an attempt to better ascertain fetal renal function, Glick and colleagues (201) studied 20 fetuses with suspected obstructive uropathy using percutaneous aspiration of fetal urine via a 4-Fr balloon-tip catheter inserted into the fetal bladder during gestation. In evaluating urine electrolytes, prognostic features for good renal function were proposed. These urine electrolyte features of adequate renal function in a fetus with sonographic evidence of obstructive uropathy

include a urinary sodium of less than 100 mg, a chloride of less than 90 mg, an osmolality of less than 210 mOsm/L, and a urine output of more than 2 mL per hour. These criteria were considered in the context of normal renal echogenicity and in the face of normal to moderately decreased amniotic fluid. Despite use by some investigators (384), urinary creatinine excretion has not been shown to be helpful in prognosticating the renal function in fetuses with obstructive uropathy. Since Glick and colleagues' initial report (201), the prognostic criteria for renal function have been disputed. Wilkins and associates (570) reviewed nine cases of fetal obstructive uropathy; the prognostic criteria were helpful in predicting poor outcome, whereas in the good prognostic criteria group of five fetuses, only one had a good outcome, but it happened to be the one who underwent *in utero* decompression using a vesicoamniotic shunt. Furthermore, Elder and co-workers (153) reported several cases in which fetal urine electrolytes were believed to be misleading with regard to the ultimate renal function in fetuses with obstructive uropathy. Recently, in addition to fetal sodium, chloride, and osmolality, Nicolini and associates (376) evaluated fetal urine creatinine, urea, electrolytes, calcium, and phosphate. Urinary calcium and sodium were found to be significantly higher in fetuses with renal dysplasia compared with those with lower urinary tract obstruction and normal clinical outcomes. Fetal urine calcium levels were believed to be the most sensitive indicator of renal dysplasia (100%) but had a specificity of only 60%. The sensitivity to urinary sodium was less sensitive (87) but was more specific (80%) than urinary calcium. $ß_2$-Microglobulin, a urinary protein that can be measured in fetal urine, was reported by Muller and colleagues (369) to be elevated in fetuses who had an elevated serum creatinine 1 year postnatally. More recently, this group reported their experience with other urinary parameters using nuclear magnetic resonance spectroscopy and found that fetuses with renal insufficiency excreted higher levels of certain amino acids, such as alanine, valine, and threonine (370). However, to date, no reliable marker of renal damage that would allow early diagnosis of obstructive uropathy, thus enabling early intervention before the onset of irrevocable renal dysfunction, has been identified.

In utero intervention to relieve an obstructive process affecting the lower urinary tract is thought to improve neonatal outcome by restoring normal levels of amniotic fluid and thus avoiding pulmonary maldevelopment. When oligohydramnios occurs during the early stages of lung development (16 to 24 weeks of gestation), the fetus displays pulmonary hypoplasia, characterized by a delay in the structural development of the lungs (373,568). Pulmonary hypoplasia may occur in the fetus with oligohydramnios from (a) mechanical restriction of lung growth and thoracic development secondary to external compression or (b) insufficient amniotic fluid bathing developing airways, thus preventing stretching of the developing bronchi and bronchiole.

Several factors suggest that mechanical factors may prevent normal lung development. First, infants with bilateral renal agenesis and oligohydramnios have typical facial features and limb defects (flattened nose, recession of the chin, aberrant folding of the ears, spadelike hands, and talipes equinovarus) and hypoplastic lungs. However, in monoamniotic twin pregnancies in which one identical twin has bilateral renal agenesis, pulmonary hypoplasia is not present (534). Similarly, newborn infants with bilateral renal agenesis and an alternative source of amniotic fluid such as esophageal atresia (534) or myelomeningocele (28) have more normal-appearing lungs histologically. Second, pulmonary hypoplasia results in the fetus with congenital diaphragmatic hernia. In this instance, the hypoplasia represents developmental arrest of both lungs secondary to direct compression by the herniated viscera (263).

If amniotic fluid levels are restored by relieving the obstruction early in gestation, survival rates are markedly improved, whereas untreated oligohydramnios has been associated with a near 100% neonatal mortality rate (113). Therefore *in utero* decompression would appear to prevent neonatal demise from pulmonary hypoplasia, but its effect on ultimate renal function is less clear. The severity of renal dysfunction in a fetus with obstructive uropathy depends on the timing and the severity of the obstruction. It has become clear that the pathophysiology of obstructive uropathy is quite variable with regard to its effect on the kidneys.

Fetal intervention for urologic anomalies detected prenatally by ultrasound has consisted primarily of methods that would allow improved drainage of the obstructed urinary tract. Indications for possible *in utero* intervention are listed in Table 46.7 . As previously noted, although the primary objective of intervention is to restore normal fetal development, the primary cause of morbidity and mortality in the newborn is pulmonary hyperplasia (309). Despite the introduction of new techniques, such as extracorporeal membrane oxygenation (ECMO), which has helped in the management of neonatal respiratory distress, in the long run, the natural history of obstructive uropathy has been shown to be variable and in some cases extremely debilitating (91,196,399).

Indications
Presumed obstructive hydronephrosis, persistent or progressive, bilateral or in a solitary unit
Oligohydramnios
Otherwise healthy fetus without severe structural or karyotypic abnormalities
Adequate fetal renal functional indices (urine output >2 mL/hr, Na^+ <100 mmol/L, Cl^- <90, osmolality <210 mOsm/kg H_2O)
Without overt renal dysplasia (minimal echogenicity, hydronephrosis proportional to lower tracts)
Adequate informed consent
Contradictions
Presence of associated severe anomalies
Chromosomal abnormalities
Unilateral hydronephrosis with an adequately functioning contralateral kidney
Bilateral hydronephrosis without oligohydramnios
Severely dysplastic kidneys
Evidence of urethral atresia
Presence of a normal twin

From Blyth B, Duckett JW. Neonatal obstructive uropathy. In: Reed GB, Claireaux AE, Cockburn F, eds. *Diseases of the fetus and newborn*. London: Chapman and Hall, 1995, with permission.

TABLE 46.7. PRENATAL INTERVENTION FOR HYDRONEPHROSIS

A fetal surgery registry was established to determine the risk of fetal intervention and to evaluate the clinical outcomes with regard to survival and quality of life (343). To date, 90 patients have been entered from 20 centers (115). In the initial report from the International Fetal Surgery Registry, 72 patients with suspected fetal obstructive uropathy were treated with a vesicoamniotic shunt. The most common diagnosis was PUV (29%, 21 of 73 patients), whereas in 45% (33 of 73), the diagnosis was unknown or unreported. The overall survival rate was 41% (30 of 73). Of the 43 deaths, 11 (26%) were from voluntary termination

of pregnancy. Three deaths (7%) were thought to be related to intervention. Of the 29 patients who died in the perinatal period, 27 (93%) died from pulmonary hypoplasia, whereas only 1 (2%) died from renal failure. The clinical experience for fetal intervention clearly suffers from the lack of consistency and from the wide range of underlying diagnoses. The data have been collected from 20 centers with no apparent coherent approach to diagnoses and with no defined patient selection criteria. Some patients had oligohydramnios, whereas others were treated despite presence of normal amniotic fluid volumes. Several other studies have been carried out to retrospectively assess the results of prenatal intervention. (184,334). A significant number of patients had poor outcomes, and the postnatal evaluation and ultimate diagnoses underscore the heterogeneity of conditions treated *in utero.* At present, fetal intervention for bladder outlet obstruction *in utero* remains experimental and should be carried out only in a small number of centers where an experienced team is available to counsel, assess, and treat the complex cases. Parents should be cautioned of the risks and potential poor outcomes.

Thus far, the efficacy of prenatal decompression of the urinary tract has not been evaluated clearly because of the lack of a prospective, randomized trial. There are so few patients who may intact benefit from *in utero* intervention that such a trial may be difficult to accomplish. Furthermore, the indications for fetal intervention have not been clearly defined. The most critical factor in evaluating fetuses with obstructive uropathy is the amniotic fluid volume. If this volume is normal or slightly diminished, it is likely that the fetal renal function is satisfactory and that sufficient pulmonary development may take place, obviating the need for intervention. Gestational age is important is determining whether drainage of the fetal urinary tract may result in a successful outcome or whether it may be more worthwhile delivering the child for early, immediate, definitive treatment of the urinary tract. Certainly, early delivery of the child may provide the opportunity to decompress the urinary tract in a child who may already have some degree of pulmonary development.

The time of intervention procedures in the fetus is critical. If an obstruction is diagnosed before 20 weeks of gestation and there is associated anhydramnios, the probability of severe irreversible renal dysplasia is very high and it is unlikely that fetal intervention will be effective in restoring any degree of renal function (42). Thus, in such cases, either voluntary termination of pregnancy is recommended or the pregnancy is allowed to continue until term without fetal therapy. If oligohydramnios and hydronephrosis are detected at 32 weeks of gestation or later, early delivery of the fetus should be considered. In these cases, fetal lung maturity should be confirmed with a lecithin-to-sphingomyelin amniotic fluid ratio. Term delivery is usually recommended if the amniotic fluid volume is normal. Therefore there is a critical window between 20 and 32 weeks of gestation during which fetal intervention might be considered in a small number of cases.

The simplest and safest method of intervention for fetal hydronephrosis is needle aspiration of the fetal bladder or kidney to assess renal function (201). The bladder can be drained and urine obtained for analysis (272). The fetal bladder may then be reimaged after a few days (342) or, alternatively, may be allowed to drain continuously for a few hours to determine urine output (201). The most common procedure for relief of an obstructed process in the fetus is vesicoamniotic or peritoneoamniotic shunt. The latter procedure has been reported in a few infants noted to have urinary ascites. Several interventional techniques have been reported and are listed in Table 46.8 .

Procedure	No. of Cases
Vesicoamniotic or peritoneoamniotic shunt	21
Aspiration of bladder	
Single	11
Multiple	7
Aspiration of kidney	
Single	4
Multiple	3
Renoamniotic shunt	4
Attempted shunt	10
Radiographic study	6
External drainage, kidney or bladder	2
Ureterostomies	1
Vesicostomy	1

*Some fetuses underwent more than one procedure.

TABLE 46.8. FETAL INTERVENTION IN 57 PATIENTS[a]

The complication rate for fetal intervention is high and is usually 50% (Table 46.9). The most common problem is failure of the shunt to drain for an extended period, requiring shunt replacement. In most cases, the shunt drains for only 3 to 4 weeks. Although some of the shunts have migrated, in most patients, the shunt appears to become inspissated with particulate matter from the amniotic fluid. In addition, there have been anecdotal reports of shunt-induced abdominal wall defects with herniation of the bowel through the trocar insertion site or maternal ascites from an amniotic fluid leak into the maternal peritoneal cavity (337,343,444,452). In the initial report from the fetal surgery registry in seven patients (12%), labor ensued within 2 days of the fetal intervention. Finally, cases of chorioamnionitis were noted to occur after routine use of prophylactic antibiotics and during a period of long-term

(4 to 16 hours) bladder catheterization (113). Therefore it is clear that the use of vesicoamniotic shunts is limited by the relatively brief duration of decompression, risk of infection both for the mother and fetus, catheter obstruction or dislodgment, fetal injury during placement, and potential inadequate decompression of the fetal urinary tract.

Complication	No. of Cases
Shunt migration or poor drainage	11
Onset of labor within 48 hr	7
Urinary ascites	4
Chorioamnionitis	3
Extrusion of shunt (laparotomy)	2
Amniotic fluid leak	2
Perforated jejunum	1
Periureteral scarring	1
Placental hemorrhage	1
No complications	32

*Some fetuses had more than one complication.

TABLE 46.9. COMPLICATIONS OF FETAL INTERVENTION IN 57 PATIENTS[a]

Recently, open fetal surgical procedures and fetoscopic techniques have been devised to obviate the difficulties experienced with vesicoamniotic shunting, although these techniques are still in the experimental stages of development (112,165,166). Anecdotal reports of endoscopic treatment also have appeared (421).

In summary, fetal surgery for obstructive uropathy remains limited to a very small number of cases and is currently being investigated in various animal models. The procedure should be carried out only at a tertiary care center, and the interventional team should be experienced in the diagnosis, management, and follow-up of fetuses with congenital anomalies. The current trend is to support the fetus *in utero* without surgery and to let the pregnancy come to term (346).

Other Forms of Prenatal Intervention with Urologic Application

Hydronephrosis is not the only urologic condition in which attempts have been made to modify postnatal outcome by prenatal methods. Meningomyelocele and CAH also have been detected prenatally and represent areas in which prenatal efforts may be beneficial.

Myelodysplasia occurs in approximately 1 per 1,000 births in the United States, but over the last 50 years, a steady decrease in the number of neural tube defects, including myelodysplasia, has been observed. Contributing to this decline is the prenatal recognition of defects by ultrasound or by elevations in α-fetoprotein (AFP) in the mother's serum (515). Maternal serum AFP concentrations greater than 3 standard deviations above mean are associated with a 70% rate of open neural tube defects (482). Ultrasonography can help in ascertaining the cause of an elevated serum AFP concentration by accurately determining the presence in the fetus of spina bifida. Prenatal counseling allows for management options to be reviewed with parents. Recent information suggests that cesarean delivery without labor resulted in a substantially better lower-extremity motor function when compared prospectively with vaginal delivery. However, the impact of the form of delivery on the function of the lower urinary tract is unclear. Prenatal recognition of fetal hydrocephalus, which occurs in 80% to 90% of children with myelodysplasia, can allow earlier shunting and improved outcomes. Recent reports on *in utero* closure of the neural tube defect has not yielded significant improvement in bladder function as evaluated by urodynamic testing (249).

Congenital Adrenal Hyperplasia

CAH is an autosomal-recessive disorder and the most common cause of ambiguous genitalia in the newborn. In girls, significantly elevated fetal adrenal androgen levels cause masculinization of the external genitalia. Masculinization is thought to occur between 10 and 16 weeks of gestation, when the testes normally masculinize the genital tubercle. Prenatal diagnosis of CAH is based on the detection of elevated 17-hydroxyprogesterone and adrenal androgen concentrations in amniotic fluid and HLA typing of cultured amniotic fluid cells (412,558). However, these tests cannot be completed before 16 to 17 weeks of gestation, and if one waited until the diagnoses were made to institute therapy, it would be too late to prevent significant masculinization. Accordingly, suppression of the fetal pituitary-adrenal axis with a glucocorticoid during gestational weeks 10 to 16 has been performed in an attempt to prevent masculinization of the female fetus (120,167). This therapy

has been used in pregnant women who have already delivered one child with CAH. If the testing determines that she has another girl with CAH, steroid therapy is continued. The purpose of the treatment is to prevent masculinization of the female external genitalia; it has no effect on the long-term need for steroid therapy after delivery.

David and Forest (120) treated six mothers at risk with either hydrocortisone or dexamethasone in early pregnancy. In two mothers, it was determined that there was a female fetus with CAH. Steroid therapy was continued until term, and both were found to have a severe salt-wasting 21-hydroxylase deficiency. In one, the genitalia were essentially normal, and the other had mildly virilized genitalia, which probably would not need reconstructive surgery. Evans and co-workers (167) reported one case of treatment of a fetus at risk for CAH. Fetal adrenal gland suppression was maintained by administering dexamethasone to the mother, but the infant was heterozygous for CAH.

In the future, prenatal diagnosis of CAH and other hereditary diseases may be facilitated using DNA probes (348,395).

Important ethical and legal consideration also have evolved from the improvements in the prenatal diagnosis of congenital anomalies and, in particular, from attempts in treating these disorders (95). The first and foremost ethical consideration is that invasive therapy for fetal hydronephrosis must be considered experimental. Much has yet to be learned with regard to the development of the lungs and urinary tract, as well as the pathophysiology of obstructive uropathy. Few of the reported efforts of therapeutic intervention have met with success or have been proved to alter the natural history of existing congenital anomaly, so as to provide objective improvements in clinical outcome.

Intimately related to the recognition that therapy for fetal hydronephrosis is experimental is the necessity of providing informed consent. Policies regarding informed consent for *in utero* surgery and fetal research were established by the District Council and Council on Scientific Affairs, the American Medical Association (107). They state that (a) voluntary informed consent in writing should be given by the pregnant woman, acting in the best interest of the fetus; and (b) alternative treatments or methods of care, if any, should be reviewed carefully and explained fully. If safer and simpler treatment is known, it should be pursued. In addition, it has been recommended that an impartial physician, the mother's own physician, anesthetist, and other family members, particularly the father, be consulted to participate in the decision making (180).

In conclusion, the management options for a fetus diagnosed early in gestation with bilateral hydronephrosis include the following:

1. Observation, which would involve monitoring of the amniotic fluid and its volume, evaluation of renal pelvic dilation, evaluation of the renal parenchyma, size of the bladder, and emptying of the bladder. The ideal frequency of follow-up studies remains to be determined (335). Serial ultrasounds are certainly recommended if the diagnosis is made before 30 weeks (187).
2. Termination of the pregnancy if the urinary tract anomaly appears to be incompatible with postnatal life. These lesions include severe early obstructive uropathy with evidence of severe renal dysplasia and pulmonary hypoplasia with oligohydramnios or anhydramnios. In these cases, termination can be carried out before 24 weeks. Genetic counseling is certainly recommended in these conditions (262).
3. Early delivery can be carried out at gestational age 30 to 32 weeks or later. Evaluation of lung maturity is helpful to ascertain the risk for the fetus (128). Delivery at a tertiary care facility is recommended in these cases.
4. Percutaneous shunting. Indications for fetal intervention are listed in Table 46.7 . Several catheter systems are available for use, but a versatile, reliable catheter has not yet been developed. Two experimental procedures, open fetal surgery and fetoscopic or endoscopic procedures, are on the horizon.

RADIOGRAPHIC EVALUATION OF THE URINARY TRACT IN THE NEWBORN

Part of "46 - PERINATAL UROLOGY "

Prenatal Evaluation

Dilation of the upper urinary tract of the fetus may be due to the following:

- Anomalous UPJ
- UPJ obstruction
- Retrocaval ureter
- Primary obstructive megaureter (UVJ obstruction)
- Primary nonobstructed, nonrefluxing megaureter
- VUR
- Midureteral stricture
- Ureterocele (ectopic or orthotopic)
- Ectopic ureter
- PUV
- Prune-belly syndrome
- Urethral atresia
- Hydrocolpos
- Pelvic tumor
- Cloacal abnormality

The long-term renal function in the affected renal unit is variable. In cases in which the degree of hydronephrosis is significant (greater than 15 mm) with caliectasis and renal parenchymal thinning from longstanding obstruction, renal function in the involved kidney may be severely compromised. If the obstruction has occurred before 24 weeks of gestation, dysplastic changes may be identifiable by an increase in the echogenicity of the kidney or the presence of cortical cysts (329).

The prenatal diagnosis of unilateral hydronephrosis may be suggestive of obstruction, but VUR also can be identified, especially during the cycles of filling and emptying of the fetal bladder. VUR is associated with changes in the degree of ureteral and pelvic dilation (238,372,593). Prenatal ultrasonographic identification of VUR requires follow-up in the postnatal period in the form of a postnatal ultrasound and voiding cystourethrogram (VCUG). Recent studies suggest that the natural history of prenatally diagnosed VUR differs from postnatally diagnosed VUR because it affects a higher percentage of males; it is more severe and is associated with a higher incidence of coexistent anomalies (593).

UVJ obstruction most commonly is found unilaterally. Dilation of the ureter may be identified also with varying degrees, but massive renal pelvic dilation is not usually seen. The dilated ureter can be confused with the bladder, pelvic cysts, or a dilated loop of bowel. Duplication of the upper urinary tract should be suspected when hydronephrosis is seen in conjunction with cystic dilation of the upper pole of the kidney or the presence of a ureterocele in the bladder (185).

If the amniotic fluid volume is normal and the fetus has no other anomalies before 30 weeks of gestation, one ultrasonographic evaluation will be necessary before birth to determine progression or regression of the hydronephrosis (194) (Fig. 46.12).

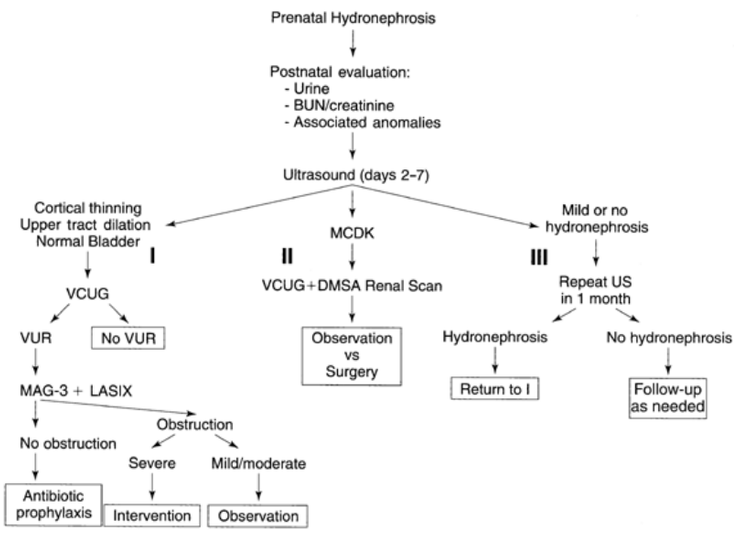

FIGURE 46.12. Algorithm for the postnatal evaluation of fetal hydronephrosis. BUN, blood urea nitrogen; MCDK, multicystic dysplastic kidney; US, ultrasound; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux. (Modified from Cendron M, D'Alton ME, Crombleholme M. Prenatal diagnosis and management of the fetus with hydronephrosis. *Semin Perinatol* 1994;18:163, with permission.)

When bilateral hydronephrosis is identified early in gestation, of greatest concern is the possibility of a urinary tract obstruction. Bilateral hydronephrosis attributable to obstruction is most often infravesical but also may occur at the level of the UVJ or UPJ. The most common cause of infravesical obstruction is PUV, which occurs in approximately 1 in 5,000 to 1 in 8,000 boys, with a wide spectrum of severity (240).

It is thought that high intravesical pressure is transmitted to the upper urinary tracts, which contributes to the maldevelopment of the kidneys. The fetus may respond to bladder

outlet obstruction by several popoff mechanisms, including bladder diverticula, massive VUR, or urinary ascites (91,575).

The fetus that presents with bilateral hydronephrosis should be evaluated for degree of dilation and whether or not the criteria for minimal pyelectasis versus pathologic hydronephrosis are met. The fetus with significant bilateral hydronephrosis and dilated bladder should undergo a complete diagnostic evaluation (Fig. 46.13 and Fig. 46.14). This evaluation should include a complete ultrasound survey to identify any associated anomalies and a genetic amniocentesis because the incidence of associated chromosomal anomalies is approximately 10% (343,575). The fetus with high-grade bladder outlet obstruction and decreasing amniotic fluid or oligohydramnios should undergo bladder tap for fetal urine sodium, chloride, osmolality, Ca^{2+}, PO_4, and $ß_2$-microglobulin (201,369). The fetal kidneys should be examined carefully to exclude cortical cysts or increased echogenicity (329). If renal function is preserved as indicated by a favorable prognostic profile, fetal treatment

should be considered. The treatment selected depends on the gestational age. Those at 32 weeks of gestation or later can be considered for early delivery and immediate postnatal decompression. Those fetuses at 28 to 32 weeks may be considered for short-term decompression *in utero* with vesicoamniotic shunts. The fetus diagnosed before 28 weeks of gestation should be considered for open vesicostomy or fetoscopic vesicocutaneous fistula to provide long-term decompression (112,114,165,230).

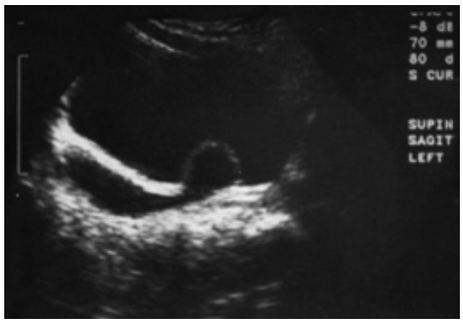

FIGURE 46.13. Baby boy with bilateral hydroureteronephrosis and distended bladder requires prompt evaluation to diagnose ureteral valves.

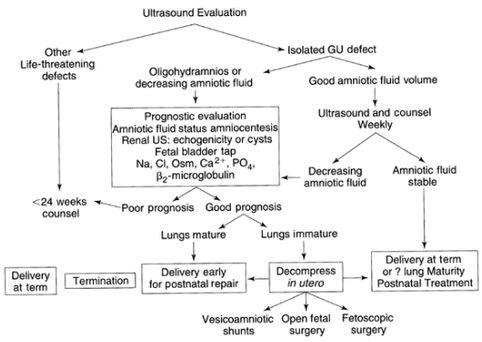

FIGURE 46.14. Algorithm for the prenatal management of the fetus with bilateral hydronephrosis. GU, genitourinary; US, ultrasound. (Modified from Cendron M, D'Alton ME, Crombleholme M. Prenatal diagnosis and management of the fetus with hydronephrosis. *Semin Perinatol* 1994;18:163, with permission.)

Postnatal Evaluation by Ultrasound

Newborn ultrasonography is the initial step in the evaluation of the newborn urinary tract. It has even been proposed as a screening test that would complement prenatal ultrasound evaluation. Indeed, in a recent prospective study of 437 healthy infants between 2 and 10 months of age who underwent a screening ultrasound, 6 (1.4%) had a significant urologic anomaly (517). At present, its use is confined to the follow-up of fetuses diagnosed *in utero* with hydronephrosis and in the initial evaluation of newborns suspected of harboring congenital anomalies. These include babies with multiple congenital anomalies such as the CHARGE association, chromosomal abnormalities, congenital heart disease, malformations of the ears, severe hypospadias, intersex conditions, myelodysplasia, single umbilical artery, family history of duplex systems or VUR, and exposure to various teratogens or cocaine (216,318,425,485).

A renal ultrasound examination in babies usually begins with the bladder because the cold gel often stimulates a bladder contraction. Supine longitudinal views of the pelvis are performed to determine bladder volume and thickness and extravesical or intravesical masses, as well as to follow the course of a dilated ureter. A transverse scan is then performed to aid in determination of bladder volume. In females or in a newborn with ambiguous genitalia, the uterus may be visualized. In a neonate with suspected PUV, posterior urethral dilation occasionally may be appreciated both in transvesical and perineal images (94).

Next, the kidneys are imaged. The kidneys are studied with longitudinal scans, with particular attention to the upper poles (to detect the presence of duplication) and kidney size. Neonatal kidneys normally range from 4 to 6 cm in length, 2 to 3 cm in width, and 1.5 to 2.5 cm in diameter (356). The best view of the right kidney is obtained through a supine longitudinal scan through the liver, whereas the left kidney is more likely to be visualized optimally by a prone longitudinal scan through the spleen. In infants with VUR or infection, renal scarring may be detected but calyceal morphology may not be distinct.

Attention also should be directed to identification of the adrenal glands. These structures are imaged optimally in the positions used to identify the upper poles of the kidneys. In the newborn, significant adrenal enlargement is suggestive of CAH. In such patients, the size of the adrenal glands may be compared with reported normal values (388).

The echogenicity of the kidneys should also be assessed. Organs with a uniform parenchymal composition, such as the liver and spleen, produce a homogeneous echo pattern that provides an excellent acoustic window for examining the adjacent kidney. In infants up to 6 months of age, cortical echogenicity may be equal to that of the liver. Another important feature is the prominent hypoechoic pyramids, which may be mistaken for dilated calyces or cysts.

Timing of the neonatal ultrasound is important to the interpretation of its clinical relevance. The renal pelvis may be moderately dilated on antenatal sonography, yet appear normal in the first few days of life despite significant obstruction because oliguria during the first 24 to 48 hours of life may cause a distended renal pelvis to shrink transiently (306). If the neonatal ultrasound is normal, a VCUG should be obtained to determine whether reflux is present and a renal ultrasound should be repeated in 3 weeks. Dejter and Gibbons (124) reported on 49 dilated renal units detected antenatally, 9 of which were normal on the postnatal evaluation done in the first few days of life. In follow-up, one had a UPJ obstruction, one had a UVJ obstruction, two had VUR, and three had nonobstructive dilation of the collecting system necessitating continuing radiologic evaluation. Thus 50% of neonates with antenatal hydronephrosis and a normal postnatal sonogram within 48 hours of birth required reconstructive surgery or had VUR.

The severity of hydronephrosis has been standardized by the Society for Fetal Urology (SFU) (332) (Table 46.10). The hydronephrotic grade is based on the severity of renal pelvic and calyceal enlargement, as well as the presence of

renal cortical atrophy. In general, only those kidneys with grade 3 or 4 (out of 4) hydronephrosis secondary to suspected obstruction require surgery (331).

TABLE 46.10. SOCIETY FOR FETAL UROLOGY GRADING OF HYDRONEPHROSIS

Grade of Hydronephrosis	Central Renal Complex	Renal Parenchymal Thickness
0	Intact	Normal
1	Slight splitting	Normal
2[a]	Evident splitting, complex confined within renal border	
3	Wide-splitting pelvis dilated outside renal border and calices uniformly dilated	Normal
4	Further dilation of renal pelvis and calices (calices may appear convex)	Thin

[a]An extrarenal pelvis extends outside the renal border, yet because the calices are not dilated hydronephrosis is grade 2. When the major calices are imaged but are not dilated, hydronephrosis is also grade 2.
From Maizels M, et al. Grading nephroureteral dilatation detected in the first year of life: correlation with obstruction. *J Urol* 1992;148: 1809, with permission.

Voiding Cystourethrography

Any newborn with a prenatal diagnosis of hydronephrosis should undergo a VCUG, even if the postnatal ultrasonogram is normal. Usually, the study is obtained before the baby leaves the hospital because if VUR is present, antimicrobial prophylaxis should be started. Furthermore, in newborn male infants, infravesical obstruction must be excluded, even if sonography or isotope renography indicates probable upper tract obstruction.

In a boy with hydronephrosis, a radiographic VCUG should always be obtained to evaluate the lower urinary tract to exclude urethral and bladder disease. However, in girls, in whom these abnormalities are less common, it may not be so important to obtain a radiographic cystogram. A nuclear cystogram confers approximately 1% to 2% of the radiation exposure of a standard radiographic study, but the anatomic detail from the nuclear cystogram is considerably less than with the standard radiographic VCUG. Furthermore, the grading system for the nuclear cystogram has not been established, and the two studies are not always comparable. In addition, reflux associated with a duplication anomaly demonstrated on the radiographic VCUG might not be apparent on a nuclear study. Most children's hospitals have digital fluoroscopy units, which result in significantly less radiation exposure during a VCUG. Consequently, the clinician must decide which of the tests should be done.

Indications for VCUG in the newborn include the following conditions: prenatally diagnosed hydronephrosis, unilateral multicystic dysplastic kidney to rule out contralateral reflux (485), suspected bladder outlet obstruction (e.g., PUV, urethral anomalies), and suspected duplicated upper collecting system with or without ureterocele (267). If the neonate has ambiguous genitalia, contrast material should be injected into all genitourinary cavities, allowing the anatomic definition of the bladder and other genital cavities; this procedure is termed a *genitogram.*

What If the Initial Sonogram Is Normal?

A common dilemma is whether a full evaluation is necessary if the initial renal sonogram is normal. Assuming a significant degree of fetal renal pelvic dilation (i.e., 4 mm AP pelvic diameter at less than 33 weeks at gestation, 7 mm after 33 weeks) (104) was present, the child may have VUR. For example, Bouachrine and colleagues (57) reported that 17 of 42 (40%) infants with prenatally diagnosed reflux had mild antenatal renal pelvic dilation as the only sign of a urinary tract abnormality. Tibballs and de Bruyn (535) reported that of 982 children referred for treatment of antenatal hydronephrosis, among 255 renal units with reflux, the postnatal sonogram was normal in 177 (70%). Furthermore, in children with dilating grades of reflux, renal sonography often is normal. For example, Blane and colleagues (54) reported that 12% of children with grade V, 31% with grade IV, and 80% with grade III reflux had a normal renal sonogram. Because reflux may cause intermittent renal pelvic dilation, theoretically these babies may have reflux, and early diagnosis and medical treatment of reflux may reduce the likelihood of developing reflux nephropathy (156). On the other hand, others have advocated performing a VCUG only if the postnatal sonogram was normal (145,557); however, in their reports, neonates with a normal postnatal renal sonogram were not systematically evaluated to determine the real incidence of reflux in this group. Consequently, we generally recommend performing a VCUG even if the postnatal renal sonogram is normal.

Nuclear Medicine Studies

In the newborn with a suspected structural urologic anomaly, nuclear medicine studies play an important role in diagnosis and in helping to direct treatment or assess results of therapy. Radionuclide studies of the kidneys (renograms) may be used to assess renal perfusion, glomerular function of each kidney, structural anomalies, and the presence or absence of obstruction (244). The advantages of radiopharmaceuticals include the absence of systemic pharmacologic effects or allergic reactions, lower radiation exposure than conventional urography, and no need for fasting or special preparation of the bowel. If there is renal failure or significant renal insufficiency, the images with radiopharmaceuticals are inferior.

Two radiopharmaceuticals are used primarily for assessing functional of the kidney and whether obstruction is present (diuretic renogram): technetium (Tc)-99m MAG-3 (mercaptoacetyltriglycerine) and Tc-99m diethylenetriaminepentaacetic acid (DTPA). When the clinician is interested primarily in assessing whether a particular moiety of a duplicated collecting system is functioning (e.g., with an ectopic ureter or ureterocele) or whether reflux nephropathy is present in a neonate with VUR, Tc-99m dimercaptosuccinic acid (DMSA) is preferred. At times, DMSA is unavailable; in these instances, Tc-99m glucoheptonate (GHA) is used, although the images are inferior to those obtained by DMSA. DTPA is cleared almost entirely by glomerular filtration (95%), without significant retention by the renal parenchyma. The remainder of the radionuclide is protein bound.

MAG-3 is secreted by the renal tubules and has a rate of excretion more than three times that of DTPA, with 73% normally excreted by 30 minutes (164,465). The images obtained are similar to those obtained with DTPA in older children, but in the neonate, there is less background

activity with MAG-3, making it a superior radiopharmaceutical. The disadvantages of MAG-3 is that its shelf life is short and it is more expensive than DTPA. Differential renal function is computed in an identical manner to DTPA (406). DTPA is excreted primarily by glomerular filtration.

The renal handling of MAG-3 and DTPA can be divided into three phases: (a) radionuclide uptake by the kidney, (b) transit through the renal parenchyma, and (c) washout into the collecting system. Estimation of glomerular filtration is determined by the activity recorded in the kidney between 1 and 3 minutes after injection of the radionuclide corresponding to parenchymal transit time. Differential renal function is computed by comparing differential uptake from 1 to 3 minutes. Accumulation of radionuclide within the kidney is proportional to GFR. In the later phase of the study, the high urinary concentration of MAG-3 or DTPA with normal or near-normal renal function can provide excellent visualization of the upper urinary tract and bladder. Renal anomalies, such as pelvic kidney, crossed fused ectopia, horseshoe kidney, or urinary extravasation, can be delineated easily.

^{99m}DMSA is retained by the renal tubules and the most sensitive radiopharmaceutical for imaging the renal parenchyma in the absence of obstruction. It is often used to assess renal scarring or to compare the relative function of the upper- and lower-pole moieties of a duplicated collecting system. The study will not demonstrate whether upper urinary tract obstruction is present. In the neonate or premature infant, however, uptake of DMSA may be low due to renal functional immaturity, low plasma flow, and reduced bulk of tubular tissue. DMSA scanning provides functional information about the kidneys and demonstrates areas of decreased function, such as focal dysplasia, scarring, or acute infection (51,440,462). After the injection of DMSA, renal images are obtained 2 to 3 hours later. GHA is secreted, and some of the radiopharmaceutical is retained by the renal tubules, providing similar but lower-quality images compared with those obtained by DMSA.

Renal scanning usually is performed in the following situations (532):

1. Assessing whether upper tract obstruction is present in a neonate or infant with hydronephrosis (diuretic renogram-MAG-3 or DTPA)
2. Confirming that a multicystic kidney has no function (MAG-3, DMSA, or DTPA)
3. Determining whether the upper pole of an obstructed duplex system (ureterocele or ectopic ureter) functions (MAG-3, DTPA, DMSA, or GHA)
4. Confirming that a kidney is absent in a neonate in whom the ultrasound demonstrates renal agenesis (MAG-3, DMSA, or DTPA)
5. Demonstrating a fusion anomaly of the kidney (horseshoe kidney or crossed renal ectopia; MAG-3, DMSA, or DTPA)
6. Determining whether a child has acute pyelonephritis (DMSA) or evidence of renal scarring from previous infection (DMSA or GHA)

Diuretic Renogram

Diuretic renography is a provocative method of evaluating patients found to have dilation of the upper urinary tract in whom an obstructive process is suspected. The theoretical basis of this test is twofold: If an obstructive lesion is present, then (a) renal function, more specifically glomerular filtration, may be impaired, and (b) a dilated upper urinary tract will retain a larger amount of radionuclide that will not wash out if increased urine flow is generated by the administration of a diuretic (97). Two radionuclides tracers are used for diuretic renography: DTPA and MAG-3. Imaging is superior with MAG-3 compared with DTPA because of a smaller volume of distribution and faster clearance.

The technique for the diuretic renal scan is critical to its correct interpretation and requires attention to detail to ensure reliability and reproducibility. In general, neonates and young infants are placed supine for the study; mechanical restraint usually is necessary. At some institutions, infants are placed prone, however, because this may affect better upper tract drainage. Ideally, the child should be well hydrated because relative dehydration prolongs parenchymal transit and delays urinary excretion. MAG-3 or DTPA is injected intravenously as a bolus. Subsequently, 4-second posterior images are recorded with a high-resolution collimator. One minute after injection, images of the kidneys are obtained each minute. Normally, the renal parenchyma is well visualized during the first minute; by 2 to 3 minutes, activity is seen in the collecting system, and by 6 to 9 minutes the bladder is visualized.

The differential renal function of each kidney is calculated between 60 and 180 seconds after injection of the radiopharmaceutical, which represents parenchymal transit and reflects glomerular function. On computer images, regions of interest are selected from each kidney and background activity is subtracted. The activity within each kidney is expressed as a percentage of the total renal counts, and this differential activity is used to compute differential renal function. In a kidney with a duplex system in which there is upper-pole obstruction, the regions of interest of the affected kidney may be broken down further and used to determine relative function of the upper and lower segments.

To determine whether significant obstruction is present, furosemide is administered intravenously, with a recommended dose of 1 mg/kg when the hydronephrotic system shows maximal accumulation of radionuclide, but not later than 30 to 60 minutes. It is important to distinguish hydronephrosis secondary to suspected UPJ obstruction from UVJ obstruction, in which the ureter should

contain a large amount of radionuclide before furosemide is given. The activity over each kidney is measured and the half-time clearance determined. The half-time ($T_{½}$) represents the number of minutes required for half of the radiopharmaceutical to drain from the collecting system after administration of furosemide. O'Reilly and colleagues (389) have defined several types of responses to furosemide (Fig. 46.15). Compared with drainage in the older child, in the newborn, drainage typically is delayed, primarily because the GFR is low. A nonobstructed system should have a $T_{½}$ of less than 10 to 15 minutes, whereas a $T_{½}$ of greater than 20 minutes is consistent with but not necessarily diagnostic of obstruction. If the $T_{½}$ is between 15 and 20 minutes, the results are indeterminate. The $T_{½}$ is computed from the peak of renal activity, not the actual time of diuretic administration, because if the hydronephrotic system is not completely filled when furosemide is administered, the radionuclide may continue to accumulate for several minutes in the collecting system before it begins to drain. If a normal drainage pattern begins, then levels off, the slope of the drainage curve should be used to extrapolate $T_{½}$. If the collecting system does not fill completely within 1 hour after injection of MAG-3 or DTPA or if the kidney has less than 20% of total renal function, the diuretic washout curve may be prolonged, even if the system is not obstructed.

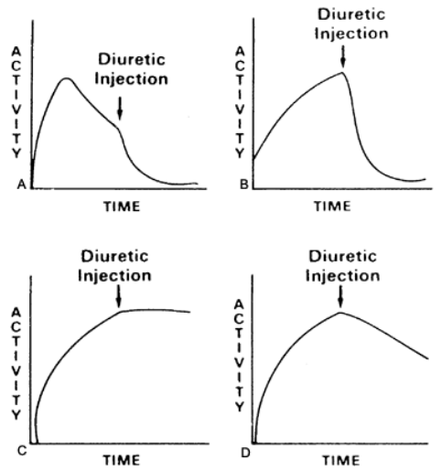

FIGURE 46.15. Patterns of response to furosemide in DTPA renal scan. Normal response **(A),** dilated nonobstructed system **(B),** dilated obstructed collecting system **(C),** and equivocal response **(D).** (From Kelalis PP, King LR, Belman AB, eds. *Clinical pediatric urology,* 2nd ed. Philadelphia: WB Saunders, 1985, with permission.)

Technical Considerations Affecting Interpretation of Diuretic Renogram

Numerous variables may affect the interpretation of the diuretic renal scan, particularly in the newborn (Table 46.11) (156).

Renal maturity	Volume of urine in bladder
Renal function	Outlined regions of interest
Hydration status	Patient position
Type and dose of radiopharmaceutical	Patient movement
Dose of diuretic	Capacity of upper tract
Timing of diuretic administration	Severity of obstruction
Vesicoureteral reflux	Site of obstruction
	Method of data interpretation

TABLE 46.11. FACTORS AFFECTING DIURETIC RENOGRAPHY IN THE NEONATE

Renal Maturity

In the newborn, there is temporary but significant renal functional impairment that may confuse the diagnosis of obstruction by renography, because there is no readily available measurement to determine when renal function is too immature for diuretic renogram accuracy. Koff and associates (296) studied the diuretic response of the normal kidney in 33 infants with unilateral hydronephrosis caused by either multicystic kidney or UPJ obstruction. These infants were not formally hydrated, nor was a bladder catheter used. In neonates younger than 1 month of age, 68% of the normal kidneys had a $T_{½}$ of greater than 9 minutes; of the infants studied between 1 and 4 months of age, 33% had a prolonged $T_{½}$; and all infants older than 4 months had a normal $T_{½}$ in the normal kidney. Prematurity was a significant factor as well. Of 9 term infants younger than 1 month of age, 5 (55%) had a $T_{½}$ of less than 9 minutes in the normal kidney, whereas none of the 8 premature infants had a $T_{½}$ of less than 9 minutes. Consequently, when the neonate is studied with a diuretic renal scan, drainage of the normal kidney must be assessed carefully. If the normal contralateral kidney shows impaired drainage, the study is invalid and cannot be used to provide a satisfactory indication of whether obstruction is present. In these cases, other clinical information must be used to assess the kidney with suspected obstruction. If the hydronephrotic kidney is functioning as well as the nonhydronephrotic kidney, the renal scan should be repeated 6 to 12 weeks later.

Renal Function

In a kidney with significantly reduced renal function secondary to a UPJ obstruction or PUV, or with a primary renal functional abnormality, the diuretic renogram may be difficult or impossible to interpret. In general, if the

differential renal function is less than 20% or if the kidney has not reached its peak intensity by 60 minutes after administration of MAG-3 or DTPA, the diuretic phase cannot be used to provide an indication of definite obstruction.

Hydration Effect

State of hydration has an important effect on the diuretic response. Dehydration prolongs parenchymal transit and the diuretic response. In a study by Howmann-Giles and co-workers (254), of 12 patients with a prolonged $T_{½}$, in 10 the $T_{½}$ decreased to the normal range with infusion of 360 mL/m^2 normal saline solution over 30 minutes before the study. Although forced hydration is not physiologic, it reduces the likelihood that prolonged $T_{½}$ is secondary to prolonged parenchymal transit. In many centers, the family is asked to feed the infant immediately before the study.

Dose and Timing of Diuretic Administration

Although O'Reilly and colleagues (390) recommended an administered dose of 0.5 mg/kg furosemide, in children, and in particular the newborn, 1 mg/kg provides a stronger and more reliable effect. If the infant is well hydrated, significant dehydration is unlikely to result. Children with renal insufficiency may require as much as 4 mg/kg furosemide to stimulate satisfactory diuresis. If a catheter is used to drain the bladder during the diuretic study, urine output can be measured to determine whether diuretic response is adequate.

The timing of diuretic administration is controversial. O'Reilly (391) recommends administration at 20 minutes in all patients. However, in a nonobstructed hydronephrotic or poorly functioning kidney, the radionuclide might not accumulate maximally in the collecting systems by 20 minutes. If furosemide is administered too soon, the radionuclide will continue to accumulate in the kidney for a variable period before drainage occurs, potentially simulating an obstructed kidney.

Bladder Effect

Approximately 15% of children with a UPJ obstruction have VUR (248). Consequently, if the VCUG demonstrates reflux, bladder catheterization during the diuretic renogram is mandatory. Whether bladder catheterization should be done in all cases, however, is controversial. A full bladder impairs drainage of the upper tracts. Thus a nonobstructed kidney may begin to drain after furosemide is given, but the drainage response may be blunted as the bladder fills, spuriously prolonging the $T_{½}$. It can be argued that bladder catheterization is not a normal physiologic situation. Furthermore, infants often void during furosemide diuresis, and there may be some risk of causing iatrogenic urinary infection in the hydronephrotic kidney with placement of a urethral catheter. On the other hand, if the bladder is not catheterized, it may be difficult to determine whether impaired upper tract drainage is secondary to a distended bladder or obstruction. The ideal diuretic renal scan should include a continuously drained bladder, although this is not routinely done by most pediatric nuclear medicine departments at present.

Outlined Regions of Interest

Differential renal function is computed by comparing the differential uptake for 1 minute, between 1 and 3 minutes after injection of the radiopharmaceutical. The renal images that are analyzed, or “regions of interest,” are extremely important to this analysis. Background activity from the liver or spleen may affect the number of counts, and this activity must be subtracted. In reality, the computed uptake of a kidney may be altered significantly by changing the region of interest. In some institutions, the regions are drawn outside the area of perceived renal activity; at other institutions, the region of interest is drawn tightly to the edge of the kidney. Recognition of this variable is important because often the decision of whether to operate on a hydronephrotic kidney is based largely on whether the differential glomerular function is affected significantly.

Position of the Infant

In some cases, drainage of urine from the kidney may be improved by placing the child in the prone or upright position rather than supine during the study because the bladder becomes more dependent.

Site of Obstruction

If the neonate has a megaureter, ideally the renal pelvis and ureter should be filled with the radionuclide before furosemide is administered. If the diuretic is administered prematurely and renal pelvic drainage is impaired, the study probably should be repeated before deciding on a diagnosis of obstruction. If the diuretic is administered at the appropriate time, currently it is unresolved whether to assess drainage from the renal pelvis and ureter separately or as one entire system.

Interpretation of Diuretic Renogram

The diuretic renogram does not actually measure obstruction; rather, it monitors the ability of the kidney to respond to a volume challenge. Thus accuracy of the study depends on a number of biologic factors that influence this response. The clinician should never rely on the written report to determine whether an obstructive lesion is present. The study should always be reviewed by the urologist to assess specifically which of these variables might have adversely affected the outcome of the test and whether it should be repeated under modified conditions or when renal function is better.

Another important aspect in evaluation of the study deals with the interpretation and comparison of follow-up examinations. For example, how does one assess stability or deterioration of renal function or obstruction? If the differential renal function remains stable but the $T_{½}$ becomes prolonged, is there deterioration of function, is there worsening obstruction, or is this simply a difference in technique between the two studies?

Recommended Protocol for Diuretic Renogram in the Neonate

Because the method of diuretic renography varies among nuclear medicine practitioners, and recognizing the limitations of the diuretic renogram in the neonate with hydronephrosis, the SFU and the Pediatric Nuclear Medicine Club developed a standardized method for the diuretic renogram in the neonate (97). Ideally, infants should be older than 1 month at renography to reduce the likelihood that renal function is immature, and premature infants should be even older before the initial renogram. Oral hydration is offered as desired, beginning 2 hours before the study. The bladder is catheterized to ensure that it is empty, and the catheter is left to continuous open drainage or intermittent syringe evacuation of the bladder via the catheter. Urine output of 4 to 5 mL per minute is expected during the active diuresis in a well-hydrated infant. Prophylactic antiseptic therapy is adinistered during the study and for 3 days afterward. Before the study, a dilute normal saline solution is administered at a rate of 10 mL/kg over 15 minutes, before injection of MAG-3 or DTPA, and is continued for 15 minutes after injection. The renogram should be recorded in the supine position. After injection of MAG-3 or DTPA, the regions of interest encompass the entire kidney, including the dilated renal pelvis, with a region of interest for background subtraction defined as 2 pixels wide around the entire outer perimeter of the kidney. The percent differential renal function is determined by measuring the total counts of the renogram curve for each kidney minus background between the intervals of 90 and 150 seconds after the appearance of the abdominal aorta. Furosemide is administered at a dose of 1 mg/ kg after 20 to 30 minutes or when the dilated pelvis or ureter is thought to be filled on the scintigram images. It may be necessary to place the patient in the prone position to allow the radioactive agent to be distributed evenly throughout the entire dilated pelvis and ureter. Methods used to monitor $T_{½}$ clearance include (a) $T_{½}$ from the time of furosemide injection, (b) $T_{½}$ from the peak of the curve, and (c) $T_{½}$ of the extrapolated slope of the primary response to furosemide. Most likely, one of the latter two will prove most accurate.

Other Imaging Studies of the Upper Urinary Tract

In select situations, such as with severe hydronephrosis and a renal fusion anomaly or an ectopic kidney, imaging studies other than ultrasonography, VCUG, and renal scintigraphy are necessary for diagnosis and to plan management.

A computed tomography (CT) scan of the urinary tract often provides useful information. It outlines the urinary tract and is extremely sensitive in assessing whether a kidney is functioning. The test generally is done with sedation. In recent years, MRI also has been studied, although it has not come into widespread use (380,435). The advantage is that there is no exposure to ionizing radiation and it provides anatomic detail, but the study does not provide sufficient functional information and it requires general anesthesia.

The indications and use of intravenous urography (IVU) to assess the newborn urinary tract have decreased steadily over the last 20 years because of the increased availability of sonography and isotope imaging. The anatomic resolution of the IVU can be excellent, but at birth, renal function may be too immature to allow for adequate concentration of the contrast material within the collecting system, thus preventing satisfactory visualization, which may be further obscured by copious bowel gas. However, 2 to 3 weeks after birth, visualization of the kidneys and collecting system can be obtained following administration of 2 to 3 mL/kg of contrast medium.

The IVU provides excellent anatomic delineation of the upper urinary tract and can be used to identify specifically an area of obstruction, as well as to determine whether the patient has a duplex collecting system (163). In addition, renal scarring from VUR may be identified. However, its use for follow-up has diminished because radionuclide imaging can provide reliable quantitative estimation of relative renal function.

Retrograde Pyelography

With the radiologic studies currently available, retrograde pyelography rarely adds important diagnostic information in the evaluation of hydronephrosis in the newborn, even with a UPJ obstruction (464). In a neonate, urethral or ureteral injury may occur from the study. If ultrasound, IVP, and the renal scan do not provide sufficient visualization of the upper tract, antegrade pyelography usually is preferable to retrograde pyelography.

ANTEGRADE PERFUSION STUDIES OF UPPER URINARY TRACT

Part of "46 - PERINATAL UROLOGY "

Another method to evaluate the hydronephrotic kidney is the Whitaker test, in which fluid is infused into the kidney

at a constant rate and the differential increase in pressure in the kidney, compared with the pressure in the bladder, is measured. A variant of this is the constant-pressure perfusion test, in which fluid is infused at a constant pressure to assess the change in output.

Constant Volume Perfusion (Whitaker Test)

The Whitaker test generally is performed when other diagnostic tests, such as sonography, excretory urography, and diuresis renography, either do not agree or are inconclusive in establishing a diagnosis (567). The test is much more invasive than the other procedures because it requires insertion of a needle or small nephrostomy tube into the kidney, with the patient under general anesthesia.

After administration of general anesthesia, the child is placed in the prone position. Access to the hydronephrotic collecting system is obtained percutaneously, either using sonography or after injecting a bolus of contrast medium intravenously and imaging the kidney fluoroscopically. Spinal needles of 22 or 20 gauge are commonly used, although we have selectively used a pigtail nephrostomy tube. The needle resistance is subtracted from the renal pressure to determine intrapelvic pressure. If the kidney is extremely hydronephrotic, a second needle may be inserted into the kidney to measure the pressure continuously. A urethral catheter is inserted as well. A Harvard pump or similar apparatus is used to deliver a constant flow through the kidney at a set rate. Usually, the bladder catheter is left open and allowed to drain during the procedure, except in situations of suspected secondary UVJ obstruction. Each institution has its own protocol for performing the study. In some centers, the study is initiated by infusing 5 mL per minute for 5 to 10 minutes and checking the renal pressure with a manometer or pressure transducer every 5 minutes. If the pressure remains within a physiologic range, the inflow is increased to 10 mL per minute for another 5 to 10 minutes. In some cases (generally in older children), the fluid infusion is increased to 15 mL per minute. This study also allows infusion of contrast medium to examine the upper urinary tract fluoroscopically, which often is as helpful as the pressure readings.

A maximum renal relative pressure (renal pelvic pressure minus needle resistance minus bladder pressure) less than 15 cm H_2O indicates absence of obstruction, pressure greater than 22 cm H_2O is indicative of resistance to urinary flow, and maximum pressure between 15 and 22 cm H_2O is considered indeterminate.

The Whitaker test measures only drainage, not function. The implication is that the kidney that has impaired drainage by the Whitaker test is likely to develop renal functional impairment.

Numerous technical variables may influence the Whitaker test, including the concentration of contrast medium (if used), the gauge and length of the perfusion needle, temperature of the solution, and flow rate (537). For example, as the temperature of contrast increases, its viscosity decreases. Diminished viscosity of the infusate results in diminished resistance by viscous drag. Not surprisingly, viscous drag was greater using a 9-cm-long needle, compared with a shorter needle. In these studies, the greatest intrinsic resistance resulted with high rates of infusate flow using 25% contrast, with the maximum pressure difference 5.0 cm H_2O at 11.5 mL per minute.

Although the Whitaker test was developed in children, there are no reports of its use in large series in neonates and infants. Because the kidneys and ureters are smaller, we can speculate that the desired maximum rate of flow should be lower in an infant than in an older child or adult. However, no one is certain what the appropriate infusion rate should be. Is a dramatic rise in renal pressure at 10 mL per minute significant? Assuming a two-kidney system, this infusion rate would be equivalent to 1,200 mL per hour, which is a greater volume than the urinary output in most infants over 24 hours. Consequently, an infusate rate of 10 mL per hour is not physiologic. Furthermore, standards for abnormal renal pressure in neonates have not been established, although these should be similar to those in older children. In an unpublished report, Ransley noted that in neonates and infants with a UPJ obstruction, using a second needle to measure renal pressure, intrarenal pressures between 100 and 300 cm H_2O have been obtained in some patients, even at infusate rates of only 5 mL per minute (427). More data are required to clarify this issue.

Constant Pressure Perfusion

The Whitaker, or constant volume perfusion test, assesses the compliance of the renal pelvis (and ureter in hydroureteronephrosis) with suspected upper tract obstruction. Upper tract obstruction is characterized by the necessity for increased renal pelvic pressure to cause urinary flow to the bladder. As a result of dissatisfaction with the Whitaker test, the study has been modified to use constant pressure perfusion rather than constant flow (585). Constant-pressure perfusion is independent of upper tract compliance, uses low fixed pressures in the renal pelvis, and measures the rate of flow out of the upper tract into the bladder at various pressures. In a pig model, one kidney was isolated and a nephrostomy tube was inserted into the renal pelvis. A bag of saline solution served as the constant pressure reservoir, and the height of the bag was adjusted to achieve the desired intrarenal pelvic pressure. The contralateral ureter was clamped, and fluid outflow through the ureter was measured with a urethral catheter. The authors found that in the normal pig, flow should always occur with

renal pelvic pressures less than 5 cm H_2O, with a flow rate of approximately 5 mL per minute. At 10 cm H_2O renal pelvic pressure, drainage was 12 mL per minute. When partial obstruction was created, the flow rate from the kidney was more than 3 standard deviations below the normal curve. When the Whitaker model of continuous flow is used in the same animals, an inflow of 5 mL per minute yielded an equivocal pressure rise and at a flow rate of 10 mL per minute the system demonstrated obstruction.

In theory, the constant-pressure perfusion technique is advantageous over constant flow in that it measures flow out of the upper tract at various renal pelvic pressures. Furthermore, the results were more reproducible and had less overlap with normal or equivocal values. In the human, however, an obvious limitation in a patient with two kidneys is the difficulty in determining the outflow from the single obstructed kidney. The authors speculated that this might be accomplished by using radionuclide perfusion and assessing outflow by scintigraphy. Further work on this important model is under way.

MANAGEMENT OF THE NEWBORN WITH GENITOURINARY ANOMALIES

Part of "46 - PERINATAL UROLOGY "

Parental Issues

Prenatal diagnosis of congenital anomalies not only has permitted counseling and early management but also has introduced significant stress during pregnancy, especially if invasive procedures are recommended (236,548). This stress can be managed adequately by providing the parent(s) with adequate information and nondirective counseling (262). Difficult management decisions should be handled with a multidisciplinary approach coordinated by a genetic counselor who acts as the liaison between the parent(s), referring physician, and the perinatal team. The counseling should ensure comprehensive and compassionate care in cases in which termination is considered or in which the outcome of the pregnancy is poor.

Postnatally, the mother–child interactions are especially important in establishing bonding.

Bonding

Bonding refers to the strong emotional and affectional relationship that occurs between a mother and father and their newborn infant. Although bonding has been demonstrated to occur at the time of prenatal ultrasound (179), most important are the first few days or weeks of an infant's life (344). The classic references on this subject are by Klaus and Kennell (289,290). The long-term significance of bonding is controversial, and there is extensive discussion in the literature regarding the importance of the extensive early mother–newborn contact and its effect on the subsequent parent–child relationship and behavior (291,299,307,308). Early mother–infant contact has been associated with improved speech between mother and child at 2 years (438), and at age 5, such offspring have been reported to have higher intelligence quotients and better scores on language comprehension tests than those with limited mother–infant contact in the neonatal period (437). Furthermore, following neonatal illness and hospitalization, there is a significantly increased incidence of child abuse and neglect (327,381) and failure to thrive in the absence of organic causes (487).

Anesthesia

In general, neonatal surgery is quite safe from an anesthetic standpoint when the patient is healthy and a staff with extensive experience in pediatric anesthesia is available (250). However, in the transition from fetus to neonate, there are important circulatory and hematologic considerations. In addition, newborn infants may be at risk for retrolental fibroplasia or postoperative apnea under certain circumstances.

Retrolental fibroplasia (RLF; retinopathy of prematurity) is a major cause of blindness or impaired vision in low-birth-weight infants on ventilators. When the retinal vasculature is immature, elevated inspired oxygen concentrations result in a PaO_2 higher than normal, with the potential for significant arterial narrowing and the destruction of newly formed capillary endothelium. A vasoproliferative process results, leading to RLF. There have been cases of RLF developing in infants in whom the only supplementary oxygen received was during anesthesia (48,358). At a conceptional age of 40 weeks (i.e., term), approximately 40% of newborns have an immature retina. However, this incidence decreases to 0% at 45 weeks (420). The risk of RLF developing in a child with an immature retina during anesthesia may be minimized by maintaining the Pao_2 at less than 90 mm Hg (14).

There is a subgroup of newborn infants that may develop an apneic episode following general anesthesia (564). The primary group at risk consists of prematurely born infants who have had a previous episode of apnea, whether idiopathic or otherwise (323). Such infants less than 55 to 60 weeks of conceptional age (15 weeks after term) appear to be at particular risk (305). Reasons for this higher risk are unclear. However, apneic episodes in prematurely born infants have been attributed to immaturity of the respiratory system (489,490). In infants with a history of neonatal apnea, alveolar hypoventilation during sleep and an abnormal response to hypercapnia and hypoxia have been demonstrated (257,488). It is postulated that inhalational anesthetics as well as narcotics affect the ventilatory control mechanism and predispose to postoperative apnea for 48 hours (323). Infants born at term who have not experienced apnea do not appear to have an elevated risk for ventilatory complications following general anesthesia.

At birth, the ductus arteriosus constricts but has the potential to reopen during the first week of life under certain conditions. For example if Pao_2 falls to fetal levels within the first few days of life, the ductus arteriosus may reopen with right-to-left shunting of blood away from the lung, referred to as *persistent fetal circulation syndrome* (118). This phenomenon could be caused by a very brief episode of hypoxia, as potentially could occur during induction of anesthesia.

Finally, the red blood cells (RBCs) in the neonate are undergoing qualitative and quantitative changes. In the first few months of life, fetal hemoglobin predominates in RBCs and differs from adult hemoglobin in its inability to bind 2,3-diphosphoglycerate. This inability results in oxygen binding more efficiently to hemoglobin, making it more difficult to release oxygen to the tissues. Furthermore, during the first 3 to 4 months of life, the total hemoglobin concentration decreases to its lowest level. Thus, at 3 months of age, the infant's oxygen-carrying capacity may be compromised quantitatively and qualitatively (118). This effect is compensated for by an increase in cardiac output. However, the effects of many anesthetic agents include reduction of the cardiac output, increase of the intrapulmonary shunt (decreasing Pao_2), and decrease in peripheral oxygen consumption. The margin for error is reduced, and the risk of anesthesia may be increased in the first few weeks of life, particularly if hypovolemia, hypoxemia, or anemia is present and undetected.

The preceding discussion is not meant to exaggerate the anesthetic risks of neonatal surgery. With the skills of a pediatric anesthesiologist, general anesthesia may be administered safely to practically any infant, but the potential risks must be understood by the surgeon.

Abdominal Masses

An abdominal mass in the neonate demands urgent evaluation (424,562). Table 46.12 shows the distribution of abdominal masses based on a collation of five large series. Excluded are babies with distended bladders without hydronephrosis, isolated splenomegaly, pyloric stenosis, pelvic tumors palpable only by rectal examination, and babies with hydrocolpos in whom the diagnosis was obvious because of a bulging imperforate hymen. Nearly two-thirds of abdominal masses detected within the first month of life arise from the urinary tract, and 10% occur in the female genital system. Half are secondary to either hydronephrosis or multicystic kidney. It has been reported that during the first 2 days of life, an abdominal mass is more likely to be a multicystic kidney, whereas beyond 2 days of age, hydronephrosis is more common (219).

	Number
Kidney (65%)	
Hydronephrosis (e.g., UPJ obstruction, UVJ obstruction, ureterocele)	80 (28%)
Multicystic kidney	63 (22%)
Polycystic kidney disease	18
Renal vein thrombosis	5
Solid tumor	13
Ectopy	4
Total	183
Retroperitoneum (9%)	
Neuroblastoma	17
Teratoma	3
Hemangioma	1
Abscess	4
Total	25
Bladder (1%)	
Posterior urethral valves	2
Female genital system (10%)	
Hydrocolpos	16
Ovarian cyst	13
Total	31
Gastrointestinal (12%)	
Duplication	17
Giant cystic meconium ileus	4
Mesenteric cyst	3
Ileal atresia	2
Volvulus (ileum)	2
Teratoma (stomach)	1
Leiomyosarcoma (colon)	1
Meconium peritonitis with ascites	1
Ascites	1
Total	32
Hepatic or biliary (3%)	
Hemangioma (liver)	3
Solitary cyst (liver)	2
Hepatoma	1
Distended gallbladder	1
Choledochal cyst	1
Adenomatoid malformation of the lung	1
Total	9

*Distended bladder, hepatomegaly, and splenomegaly excluded in most series.
UPJ, ureteropelvic junction; UVJ, ureterovesical junction.
Modified from Griscom NT. *AJR Am J Roentgenol* 1965;93:447; Raffensperger J, Abousleiman A. *Surgery* 1968; 63:514; Wedge JJ, Grosfeld JL, Smith JP. *J Urol* 1971;106:770; Wilson DA. *Am J Dis Child* 1982;136:147; and Emanuel B, White H. *Clin Pediatr* 1968;7:529.

TABLE 46.12. DISTRIBUTION OF ABDOMINAL MASSES OF 280 PATIENTS IN THE NEONATAL PERIOD[a]

Nearly all neonatal masses arising from the genitourinary tract may be diagnosed accurately based on history, physical examination, ultrasound, and nuclear renal scan (574).

The history may provide important clues to the source of the abdominal mass. One should inquire whether prenatal ultrasonography was performed and, if so, at which week of gestation. Ideally, these films should be obtained and reviewed. As has already been detailed, prenatal ultrasonography is extremely sensitive in identifying a variety of obstructive urologic lesions (Fig. 46.16). Normal prenatal

ultrasound late in gestation in which the fetal urinary tract was visualized would tend to exclude hydronephrosis and multicystic kidney as etiologic factors (187).

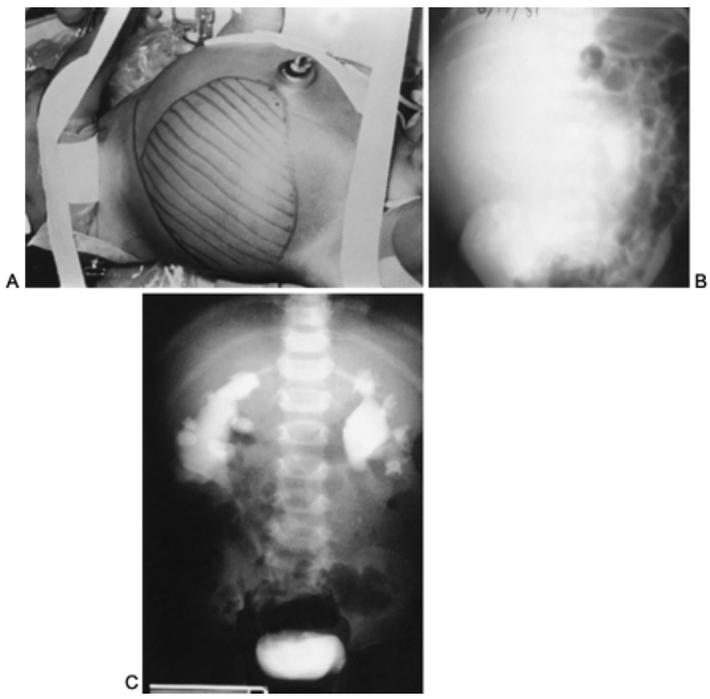

FIGURE 46.16. Neonate with large abdominal mass discovered on prenatal ultrasonography and found to have bilateral hydronephrosis. **A:** Extent of palpable right abdominal mass is marked out. **B:** Preoperative intravenous pyelogram (IVP) showing large right abdominal mass and left hydronephrosis. The right kidney was found to be severely hydronephrotic secondary to a ureteropelvic junction obstruction, and a right pyeloplasty was performed. A left pyeloplasty was performed subsequently. **C:** Postoperative IVP demonstrating excellent function bilaterally.

A history of fever developing in the neonatal period suggests an obstructive lesion because febrile illnesses in the neonate are rare. Persistent vomiting in the first few days of life may be indicative of a gastrointestinal disorder. In a boy, the stream should be visualized because most boys with urethral valves have a weak urinary stream. Infants with severe dehydration and those with diabetic mothers have an increased incidence of renal vein thrombosis (RVT).

Family history is important as well. Infantile polycystic kidney disease is an autosomal-recessive disorder, and infant deaths are often noted in the family history. Duplication of the urinary tract often is hereditary and has a polygenic mode of inheritance. Consequently, if there is a family history of duplication of the urinary tract, one might suspect an ectopic ureterocele or ureter as the diagnosis. Similarly, multicystic kidney has been observed to recur in family members.

Physical examination is important. In the first few days of life, the newborn is particularly easy to examine. The kidneys are nearly always palpable in the newborn. If the lower poles of the kidneys are positioned close to the midline, one should suspect a horseshoe kidney. In such circumstances, palpation along the anterior aspect of the spine may detect the isthmus. The lower quadrants are examined in the customary manner. By compressing the abdomen from both sides, one may detect a mobile abdominal mass, such as an intestinal duplication or ovarian cyst.

Another important aspect of examination is transillumination (139). This technique helps distinguish between masses that are solid and those that are filled with fluid or air. In addition, in the neonate, it may aid in identifying the liver edge, stomach, bladder, and gallbladder. Bladder massage may be a helpful diagnostic aid. Rather than forcefully

expressing the bladder (Credé method), one gently massages the bladder between the index finger and thumb. Within 1 to 2 minutes, if the bladder is moderately full, voiding will commence. One may judge the stream, assess residual urine, note bladder thickness, and obtain a clean urine specimen in this manner.

A complete examination also includes blood pressure measurement, respiratory tract and genitalia assessment, and a rectal and bimanual examination. Hypertension may occur with neuroblastoma or infrequently with hydronephrosis. Respiratory distress in the newborn often is associated with bladder outlet obstruction and may be indicative of hypoplastic lungs. In a female infant, a bulging interlabial mass is suggestive of hydrometrocolpos. Rectal examination may help disclose the origin of a solid lower abdominal tumor, such as a sacrococcygeal teratoma.

After the physical examination, ultrasonography is the next diagnostic step. In most cases, an experienced ultrasonographer is able to demonstrate the location of the mass and whether it is cystic or solid. A multicystic kidney has characteristic sonographic features that usually distinguish it from hydronephrosis. If it appears that the mass is either a hydronephrotic or multicystic kidney, a VCUG should be performed to assess whether there is VUR and, in males, whether bladder outlet obstruction (i.e., PUV) is present. If a tentative diagnosis of unilateral UPJ obstruction, UVJ obstruction, or multicystic kidney is made, the newborn may be discharged with its mother and allowed to return after 3 or 4 weeks for a renal scan. A scan should be performed urgently, because if the renal mass is a hydronephrotic kidney secondary to a UPJ obstruction, early pyeloplasty probably will be necessary.

If a solid tumor is suspected, a sonogram or CT scan should be performed. It is likely that the mass represents a mesoblastic nephroma, and a nephrectomy should be performed before discharge from the hospital. Wilms' tumors rarely occur in the newborn period. The management of RVT is discussed later in this chapter. Other urologic problems that may require immediate treatment include PUV, hydrocolpos, and an ovarian cyst.

The list in Table 46.12 should not be construed as a complete list of all neonatal abdominal masses. Other masses that have been encountered include focal renal dysplasia manifested as a unilateral solid renal mass (152) and oxalosis and neonatal leukemia (210), both of which were diagnosed after the detection of bilateral renomegaly.

Multicystic Kidney

The multicystic kidney is the second most common cause of an abdominal mass in the neonate (Table 46.12) and is the most common cause of an abdominal mass in the first 2 days of life (219). It represents a severe form of renal dysplasia and is associated with ureteral atresia. The etiology is uncertain, although Stephens (518) suggests that during migration of the developing kidney from the sacral to the lumbar level, the normal arterial cascade providing vascularity to the kidney may not occur, resulting in an ischemic insult, producing the multicystic kidney and associated ureteral atresia. Before the era of antenatal ultrasound, nearly all multicystic kidneys were detected in the newborn after detection of an abdominal mass. However, the widespread use of antenatal ultrasound has resulted in the majority of multicystic kidneys being detected before birth. However, at times, a multicystic kidney cannot be distinguished from an obstructed hydronephrotic kidney prenatally (98). Therefore prompt postnatal evaluation is necessary. The multicystic kidney is almost always unilateral, with the left side being more commonly involved. Bilateral multicystic kidney is incompatible with life. A few cases of autosomal-dominant inheritance of multicystic kidney have been reported (513).

Diagnosis

Most multicystic kidneys detected by antenatal ultrasound are not palpable unless the cysts are quite large. In one series, only 13% were palpable. When the kidney is palpable and enlarged, examination usually reveals a unilateral firm mass that has an irregular surface caused by the cysts and which may feel like a bunch of grapes. Transillumination demonstrates the mass to be lucent. Although the kidney usually is in a lumbar location, it may occur in a pelvic kidney, crossed fused ectopia (454), or a horseshoe kidney (Fig. 46.17). Ultrasound is usually diagnostic, but occasionally strikingly resembles a kidney with a UPJ obstruction, termed the *hydronephrotic variant* (467). Thus the diagnosis must be confirmed by renal scan, which should demonstrate a photopenic area with less than 1% differential function. A few multicystic kidneys, have been reported to demonstrate significant function or renal scan in the neonate, leading to uncertainty about the diagnosis (75). Because the contralateral kidney has a 20% chance of being abnormal (551), careful imaging of this kidney with an ultrasound is mandatory. In addition, a VCUG should be performed because there is a significant incidence of lower urinary tract anomalies and 15% have reflux (486).

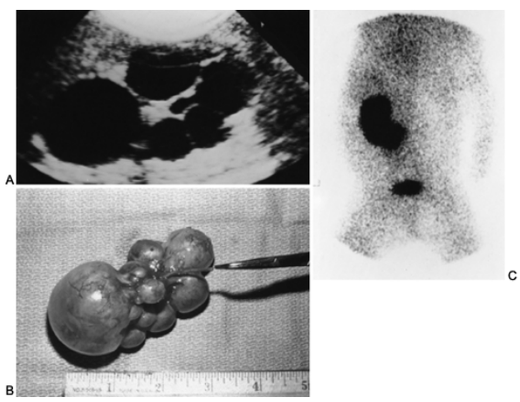

FIGURE 46.17. Infant born with palpable right abdominal mass. **A:** Sonogram of right kidney demonstrating multiple echolucent cysts of varying sizes with no discernible cortex. **B:** DTPA renal scan demonstrating absence of flow and function on the right side. The infant also has a horseshoe kidney with a ureteropelvic junction obstruction of the left kidney on the left side of the image. **C:** Multicystic kidney, gross specimen.

Management

Left untreated, most multicystic kidneys become smaller relative to total body size, and some regress completely (551). In a registry of children with a multicystic kidney, 23% of those managed nonoperatively until 3 years of age showed complete regression (553). With a mean observation period of 4.9 years, John and co-workers (270) reported that 48% showed complete regression, 33% were reduced in size, 15% showed no change, and 4% increased in size.

Complications associated with multicystic kidneys include gastric outlet obstruction and respiratory depression (540); hypertension (504); malignancy (33,49,121,134,235,362,382,423); nodular renal blastema, which is a precursor to Wilms' tumor (134); and focal nephroblastomatosis (551).

Because of the occult nature of these potential problems, annual follow-up with ultrasonography and blood pressure measurement is recommended. If the kidney causes symptoms because of its large size or if any cysts enlarge, the stromal core increases in size, or hypertension develops, nephrectomy is recommended (561). It should be noted, however, that cyst regression does not mean that the multicystic kidney poses no risk because the tumor elements are thought to arise from the stromal component, not the cystic component. Alternatively, in lieu of follow-up screening, nephrectomy may be performed as an outpatient through a 3-cm incision when the child is 3 to 12 months old (151). The Section on Urology of the American Academy of Pediatrics has ongoing registry to determine the long-term “risks” of nonoperative management of multicystic kidneys.

Ureteropelvic Junction Obstruction

Congenital hydronephrosis secondary to UPJ obstruction is a common disorder of childhood, with an incidence approximating 1 in 1,000. In the past, approximately 75% of children with this anomaly were diagnosed beyond 1 year of age (505). However, with increasing use and improved sophistication of prenatal ultrasound, 30% to 50% of children with UPJ obstruction are diagnosed prenatally, before they become symptomatic. Currently, less than 15% of neonates with a UPJ obstruction present with an abdominal mass. Other typical presentations include urinary tract infection (UTI), VATER (*v*ertebral defects, *a*nal atresia, *t*racheoesophageal fistula with *e*sophageal atresia, and *r*adial and *r*enal anomalies) screening, urinary ascites, and as an incidental finding during cardiac catheterization for congenital heart disease.

In most series, the sex incidence and left-sided preponderance are similar to those described in older children (Table 46.13). Approximately two-thirds of newborns with UPJ obstruction are boys, and in 60%, the obstruction is on the left side. Approximately 5% to 10% have bilateral involvement (Fig. 46.16). Approximately 15% have VUR (248). In children with unilateral UPJ obstruction, contralateral renal anomalies are common, including agenesis, duplication of the collecting system, malrotation, ectopia, and multicystic kidney. The etiology of UPJ obstruction is uncertain. The most attractive proposed theory is failure of recanalization of the metanephric cord between the fifth and sixth week of fetal development (459).

Series	No. of Patients (Time Period)	Bilateral	M/F	L/R	Prenatal Diagnosis	Nephrostomy	Reoperation Rate
Williams and Karlaftis, 1966	26 (1951–1964)	10	17:9	?	0	All	Not reported
Robson, et al., 1976	33	10	23:10	18:5	0	All, with stent	
Snyder, et al., 1980	49 (1969–1978)	6	34:15	?	0	Almost all, with stent	9/49
Bejjani and Belman, 1872	11 (11/76–4/81)	2	5:6	6:3	?	3 (2 with stent)	1/11
Perlmutter, et al., 1980	24 (1971–1978)	8	19:5	?	0	20/27 with stent	2/27
Thomas, et al., 1982	16 (1964–1979)	4	?	?	0	"Advantageous"	7% of all patients had reoperation
Valayer and Adda, 1982	31 (1968–1980)	3	24:7	17:11	?	6	1/31
Roth and Gonzales, 1983	16 (1976–1982)	4	12:4	7:5	6	4 with stent	0/16
Murphy, et al, 1984	21 (1973–1983)	4	10:11	9:8	6	All	1/21
King, et al., 1984	11 (1982–1983)	0	?	?	?	Generally, no nephrostomy	
Mandell, et al., 1984	6	0	?	2:4	6	?	0/6
Children's Hospital of Philadelphia (Sheldon, et al, 1992)	28 (1973–1982)	5	21:7	13:10	5	17 nephrostomy and stent	2/31
Koyle and Ehrlich, 1988	17	3	.?	?	17	6 (with stent)	0/20
Bernstein, et al., 1988	67 (1981–1987)	6	?	?	52	45	1/67
Totals	356	65 (18.3%)	165:34 (2.2:1)	72:46 (1.6:1)			17/27 (6.1%)

TABLE 46.13. INFANT PYELOPLASTIES

Without ultrasound, the most common sign leading to diagnosis of UPJ obstruction in the newborn is the presence of an abdominal mass. Other associated symptoms and signs include fever (secondary to UTI, more common in girls), hematuria, vomiting, and failure to thrive. In contrast, in older children, abdominal or flank pain and UTI are the most common presentations (151,505).

A spectrum of abnormalities is seen pathologically in UPJ obstruction (223,224). The UPJ may show reduced muscle bulk, muscular malorientation, thickened adventitia, and infiltration by inflammatory cells. Approximately 20% are normal by light microscopy (223). By electron microscopy, abundant collagen fiber is in the obstructed UPJ and between the muscle cells just proximal to the UPJ. In the renal pelvis, there is variable muscle cell damage with increased collagen and ground substance deposition and disrupted nexuses. An accessory lower pole renal artery is present in 10% to 20% of patients and usually is anterior to the obstructed UPJ (464,505). However, in most patients, the obstruction produced is due to a stenotic or dysfunctional UPJ that does not allow normal propulsion of urine from the renal pelvis to the ureter (396). When an accessory lower-pole artery is present, a distended pelvis may pull the ureter up such that it drapes over the vessel and kinks the ureter, further obstructing the system. The vessel usually is an associated finding and not the primary cause of obstruction. There is a group of patients who appear to develop

intermittent obstruction at the UPJ. In such patients, there appears to be a borderline functional obstruction, and during high rates of urine flow, the renal pelvis decompensates, resulting in severe abdominal pain and vomiting (Dietl's crisis). When the pelvis finally drains sufficiently, the pain resolves. This situation exists more commonly in older children and adults and is rare in neonates; often, there is a crossing accessory lower-pole vessel.

Evaluation

In a newborn with hydronephrosis detected by prenatal sonography, a UPJ obstruction often is suspected if the ureter is nondilated and the bladder is normal. In some cases, there is an abdominal mass, but in most cases, the examination is normal and the perinatal finding is incidental (Fig. 46.18, Fig. 46.19, and Fig. 46.20). If there is an abdominal mass, a solitary kidney, or bilateral hydronephrosis, prompt evaluation is suggested. Otherwise, the workup does not need to be as urgent. Renal function should be assessed with serial serum creatinine levels, recognizing that it may not become normal (0.4 mg/dL) until 1 week of age. The radiologic evaluation consists of a renal ultrasound, VCUG, and diuretic renogram.

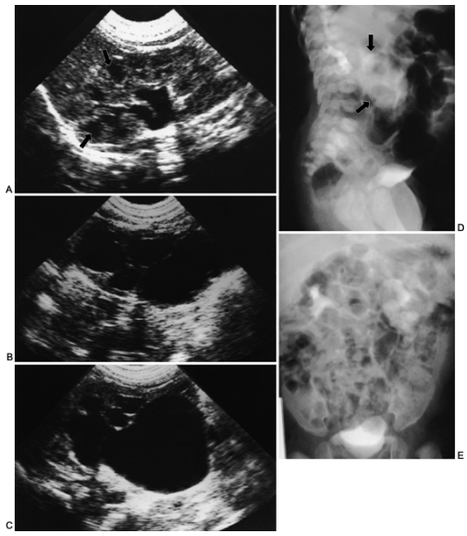

FIGURE 46.18. A: Normal neonatal renal ultrasound. Note prominent intrarenal pelvis and corticomedullary junctions *(arrows).* **B, C:** Renal ultrasounds in newborn with left ureteropelvic junction obstruction. Note large renal pelvis communicating with clubbed calyces. Cortex is quite thin. **D:** Intravenous pyelogram (IVP) performed at 1 week of age. Film was taken 1 hour and 45 minutes after injection. Note large left renal pelvis *(arrows)* of the left kidney. Patient underwent pyeloplasty in the neonatal period. **E:** IVP 2.5 months postpyeloplasty, a 15-minute film. Visualization of the left kidney was prompt. Note persistently clubbed calyces.

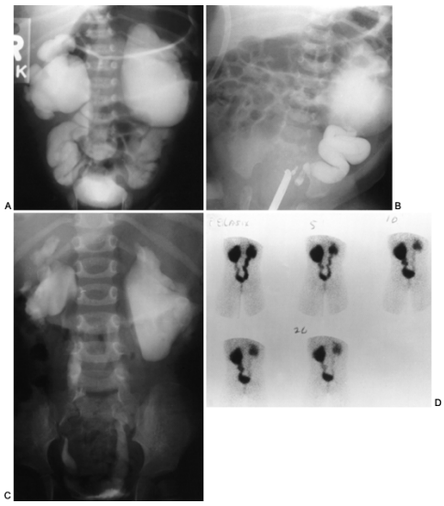

FIGURE 46.19. Example of bilateral hydronephrosis that is apparently nonobstructive. As newborn, a large abdominal mass was palpable. Serum creatinine was 0.3 mg/dL. **A:** Intravenous pyelogram (IVP) performed at 3 days of age 5.5 hours after injection demonstrating marked bilateral hydroureteronephrosis with multiple transverse folds in the ureters. **B:** Left retrograde pyelogram performed at 2 months of age. Child was followed nonoperatively and maintained on antimicrobial prophylaxis. Serial IVPs and renal scans were obtained. **C:** IVP at 2.5 years of age demonstrating nearly complete resolution of hydronephrosis. Renal units are dysmorphic. **D:** DTPA diuretic renogram at 3.5 years of age. Left kidney is on left side of image. Percent uptake: left, 3.2%. Differential function: left, 46%; right, 54%. Cortical transit time: left, 3.5 minutes; right, 2.5 minutes. After administration of furosemide, $T_{½}$; left kidney on left side of image, 9 minutes; right, less than 5 minutes.

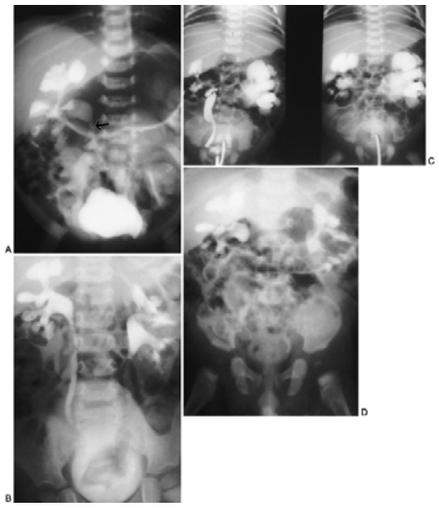

FIGURE 46.20. Example of Ostling's valves or ureteral folds. **A:** Intravenous pyelogram (IVP) showing bilateral hydronephrosis. Note tortuous upper ureter on right side *(arrow).* **B:** Right retrograde pyelogram again demonstrating tortuosity of upper ureter. **C:** IVP 1 year later. The child has undergone left pyeloplasty. Note diminished calycectasis on the right side. **D:** IVP 2 years after initial study. Ureteral folds persist but are straightening out.

If the initial ultrasound is normal, the finding may be secondary to oliguria, which occurs immediately postnatally (306), and a repeat study should be performed in 3 weeks. Hydronephrosis should be graded according to the SFU grading scale, from 0 to 4 (332). If there is severe hydronephrosis with marked parenchymal thinning, generally seen in neonates with an abdominal mass secondary to a UPJ obstruction, or if there is bilateral hydronephrosis, a prompt VCUG and diuretic renogram should be done. In most cases, the evaluation may be delayed until the infant is 4 to 6 weeks of age to allow renal maturation with an increased GFR, which will enhance the accuracy of the diuretic renogram (97). In such cases, the infant should be discharged on oral amoxicillin 50 mg daily. In addition, in boys with hydronephrosis, circumcision is recommended to diminish the risk of UTI. An IVP generally is not performed because the diuretic renogram provides much more information regarding function of the hydronephrotic kidney and severity of obstruction. Furthermore, visualization of the kidney is likely to be suboptimal because of insufficient concentration of the contrast media and overlying bowel gas.

A VCUG is necessary to ascertain that the male urethra is normal and to determine whether there is VUR, which is present in as many as 15% of children with a UPJ obstruction (248). At times, the reflux may be high grade (315,333) (Fig. 46.21). Performing a pyeloplasty in a child with reflux may subject the repair to high pressures and result in an anastomotic leak.

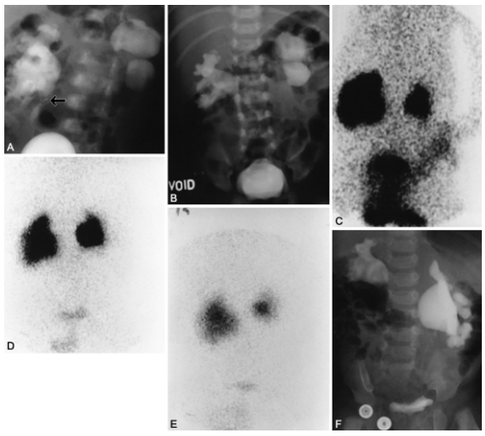

FIGURE 46.21. Example of left ureteropelvic junction obstruction and bilateral vesicoureteral reflux. **A, B:** Voiding cystourethrogram demonstrating bilateral grade III-IV reflux. Note Ostling's valve or ureteral fold *(arrow). B:* Postvoid film. **C:** Delayed image after DTPA renal scan performed at 3 weeks of age showing stasis in left kidney. $T_{½}$ normal on right, prolonged on left side. Percent uptake: left side, 1.2%; right side, 1.5%. Differential function, left, 45%; right, 55%. Because of excellent function in the left kidney on the left side of the image, it was decided not to perform a pyeloplasty at this time. **D, E:** DTPA diuretic renogram at 4 months of age. Left kidney is on the left side of the image. **D:** Prefurosemide image. **E:** Image 15 minutes after administration of furosemide. $T_{½}$ on right side, 7 minutes; 40% washout of radionuclide at 20 minutes on the left side. Percent uptake: left, 2.7%; right, 2.1%. Differential function: left, 56%; right, 44%. **F:** Intravenous pyelogram performed at 5 months of age. Pyeloplasty has not yet been performed. Case demonstrates continued growth of left kidney despite obstruction on furosemide washout curve.

The most important diagnostic study is the “well-tempered” MAG-3 diuretic renogram. This study is covered in detail previously in this chapter in the section on nuclear medicine studies. In general, extrapolating the drainage slope from the point of maximal activity, a $T_{½}$ greater than 20 minutes is consistent with obstruction. However, if the first study shows significant drainage after diuretic administration and the differential renal function in the hydronephrotic kidney is at least 35% to 40%, the infant generally may be followed nonoperatively and the “well-tempered” diuretic renogram repeated 3 months later because the obstruction often reduces in severity or disappears with time. Exceptions to this approach include an infant with a solitary kidney, bilateral hydronephrosis, reduced renal function, an abdominal mass, or the rare infant with nearly constant abdominal pain which has been attributed to colic.

With current methods of diagnosis, percutaneous nephrostomy and antegrade pyelography rarely are necessary. Antegrade pyelography may aid in distinguishing a UPJ obstruction from a multicystic kidney. However, the renal scan is likely to be as accurate, if not more accurate, because a congenital UPJ obstruction almost always demonstrates at least 5% function in the newborn, whereas a multicystic kidney demonstrates minimal or no flow or function. If the diagnosis is in doubt, an antegrade study of a multicystic kidney generally demonstrates that the cysts do not communicate.

It may be worthwhile to place a percutaneous nephrostomy temporarily if the salvageability of an obstructed kidney is in doubt or in the presence of respiratory distress compounded by abdominal distention secondary to a tremendously dilated obstructed renal pelvis. Although percutaneous nephrostomy in the newborn is safe and generally successful, it may result in edema, inflammation, infection, or hemorrhage in the pelvis that can result in a very difficult pyeloplasty.

Immediate Versus Delayed Surgical Arrangement

In the human, nephrogenesis is completed by 36 weeks of gestation. At birth, blood flow is redistributed, with an increasing proportion directed to the peripheral nephrons. During the first 6 months of life, the GFR increases rapidly and the ability of the kidney to concentrate and acidify urine improves. Chronic urinary tract obstruction can result in decreasing GFR and renal blood flow, and impaired concentrating ability (186). Unfortunately, there is no reliable method to predict recovery of renal function following relief of obstruction (555).

In the newborn rat (corresponding to the human fetus in the last trimester), when partial ureteral obstruction is created, the GFR on the hydronephrotic side is variably affected, being 10% to 43% less than the contralateral side, with compensatory hypertrophy of the normal side (276,277,278 and 279). Furthermore, the single-nephron GFR may be elevated on the hydronephrotic side, with minimal

redistribution of glomerular filtration (276). The alterations in GFR appear to stabilize over time, as do the changes in renal morphology (92,279). Similar studies have been performed in the newborn guinea pig, which correspond to the human in that nephron formation is complete at birth. In this model, neonatal ureteral obstruction results in variable hydroureteronephrosis, with the intraureteral pressure inversely proportional to a reduction in GFR (86). These studies suggest that although partial ureteral obstruction may cause diminished kidney function, the changes may not progress over time. In UPJ obstruction, there is partial obstruction that is variable in severity. Accordingly, one might infer from these studies that with a mild UPJ obstruction a mild diminution of renal function is likely to remain stable, whereas with high-grade obstruction, progressive deterioration of renal function is likely.

To better understand the natural history of apparent UPJ obstruction in infants, Ransley and associates (428) performed a study in which selected newborns with hydronephrosis and a suspected UPJ obstruction and satisfactory differential renal function were followed nonoperatively. Their management plan separated patients into three groups based on the “function” of the “obstructed” kidney on DTPA diuretic renogram.

Group I:Normal function: normal uptake curve (parenchymal transit time) with greater that 40% of overall function

Group II:Moderately reduced function: delayed uptake curve with 10% to 40% of overall function

Group III:Severely reduced function: flat uptake curve with less than 10% of overall function

Group I was managed expectantly. The concept was that if the kidney had good function despite a long period of antenatal obstruction, surgical intervention might not be necessary in an asymptomatic child. In those with moderately reduced function (group II), it was assumed that the partial obstruction was severe enough to warrant early surgical therapy. If the renal function was severely affected, it was distinguished from a multicystic kidney either by antegrade pyelogram or temporary percutaneous nephrostomy.

Of a total of 142 kidneys, 106 were group I, 27 were group II, and 9 were group III (428). Of the 9 group III patients, 3 (33%) underwent pyeloplasty and 6 (67%) had a nephrectomy because of poor function. Of the 27 group II patients, 23 underwent early pyeloplasty. Of these, 9 (39%) had marked improvement in differential function, 5 (22%) had moderate improvement, and 9 (39%) had no change. Of the group I patients, 6 underwent early pyeloplasty. Of the 100 patients who were followed nonoperatively, 23 (23%) eventually required a pyeloplasty, 19 (83%) requiring it by 3 years of age. Reasons given for pyeloplasty included deteriorating differential renal function in 14 (61%), UTI in 3 (13%), pain in 1 (4%), concentrating defect in 1(4%), and “other” in 4 (18%). Of the 14 patients with deteriorating renal function, only 5 (36%) returned to the original level of differential function. Mean follow-up was less than 3 years. Of the 66 kidneys with a renal pelvic diameter of more than 12 mm, 23 (35%) eventually underwent pyeloplasty, whereas none of 34 with a pelvic diameter of less than 12 mm required surgical intervention.

This report was the first study of a large group of patients with suspected UPJ obstruction followed nonoperatively. In retrospect, there were significant problems with the methodology of the diuretic renograms used to diagnose obstruction. For example, only 0.2 mg/kg of furosemide was administered 20 minutes into the study, rather than 1 mg/kg at peak activity in the renal pelvis, as is currently recommended. Consequently, the diuretic stimulus was minimal. In addition, hydration before the diuretic renogram was not monitored. Furthermore, a catheter was not used to drain the bladder (209). Finally, using a liberal definition of obstruction (decrease in activity to 75% within 10 minutes or to 50% of activity within 20 minutes), 27% of the group I patients never showed an obstructive pattern. Therefore this study is not ideal for documenting the natural history of suspected UPJ obstruction.

Cartwright and associates (77) studied 97 newborns with suspected UPJ obstruction. Of 39 with at least 35% differential renal function followed nonoperatively, only 6 (15%) underwent pyeloplasty, with average follow-up of 18 months (range of 6 to 48 months). All three of the patients with differential renal function of less than 40% who underwent pyeloplasty because of decreasing renal function returned to their initial levels. One might question whether early pyeloplasty in these three patients would have allowed renal function to improve to 50%, which would have been ideal. In those followed nonoperatively, all maintained differential functions greater than 40% with follow-up as late as 48 months.

Takla and associates (530) studied 51 patients with SFU grades 2, 3, and 4 hydronephrosis initially managed nonoperatively and found that 4% of those with grade 2, 56% with grade 3, and 71% with grade 4 hydronephrosis ultimately underwent pyeloplasty. In the remaining patients, the hydronephrosis resolved, usually by 18 months of age.

In contrast, Ulman and co-workers (545) reported 104 infants with SFU grade 3 or 4 hydronephrosis initially managed nonoperatively a mean of 6.5 years. Of the patients followed nonoperatively, hydronephrosis resolved in 69% and improved in 31%. However, 33% still had a $T_{½}$ of greater than 20 minutes on their most recent diuretic renogram. Of the infants, 23% underwent pyeloplasty. All were younger than 18 months of age and showed progressive hydronephrosis and/or reduction in differential renal function. In these kidneys, postoperative differential renal function exceeded the predeterioration level in all kidneys.

Palmer and colleagues (394) reported the initial results of a prospective randomized trial comparing observation to

pyeloplasty in infants with SFU grade 3 or 4 hydronephrosis. All had differential renal function greater than 40% on their initial renal scan and a prolonged $T_{½}$. Of the 32 infants studied, in the observation group, 25% had significant deterioration in renal function and underwent pyeloplasty. The remaining observation patients were stable. Those undergoing pyeloplasty had less hydronephrosis and a shorter $T_{½}$ drainage curve at follow-up compared with the observed group.

These observations may be interpreted in several ways. First, it may be that some partially obstructed kidneys have significant functional impairment at birth but that the capacity for renal maturation, with increasing GFR secondary to redistribution of blood flow to cortical nephrons, during the first year of life is maintained. Another explanation is that the early diuretic renogram is erroneous and that during the period of transitional nephrology the differential renal function and capacity for washout in these kidneys is different than in older children. This position was vigorously disputed by Chung and co-workers (90), who performed well-tempered diuretic renograms and found no significant differences in renal function or washout in neonatal and follow-up studies in patients managed nonoperatively. Finally, it must be remembered that all of these studies base “renal function” on the results of the differential renal function, which has significant potential for variability.

Elder and colleagues (154) reported the results of renal biopsies performed in 55 children undergoing pyeloplasty. Overall, 63% showed minimal or no obstructive histologic changes. However, of those with differential renal function greater than 40%, 21% showed significant histopathology (reduced glomerular number, glomerular hyalinization, interstitial inflammation). In contrast, of those with a differential function less than 40%, 33% showed minimal or no obstructive changes. Consequently, in 25% of the patients, the findings on renal biopsy did not correspond to the computed differential renal function and suggest the need for more sensitive markers of obstruction.

The critical question in patients with suspected UPJ obstruction is what is obstruction? Koff and Campbell (295) define obstruction as identifying “evidence of obstructive injury, such as a failure of expected improvement in renal function, compensatory hypertrophy in the contralateral kidney or progressive hydronephrosis.” By this definition, no neonate with unilateral hydronephrosis would undergo pyeloplasty until follow-up studies confirmed evidence of obstructive injury. Allen (12), on the other hand, has stated “it makes no more sense to wait for evidence of progressive renal damage before making diagnosis of obstruction than it does to wait for a tumor to metastasize before calling it a cancer.” Peters defines obstruction as “a condition of impaired urinary drainage that if uncorrected will limit the ultimate functional potential of a developing kidney.” Woodard (584) stated “to delay surgery…until measurable deterioration in renal function has occurred seems to deny the patient the benefit of state-of-the-art management.” Unfortunately, no one knows how many of these children later will become symptomatic with abdominal or flank pain. Although there are many viewpoints on the indications for pyeloplasty and appropriate timing (136,297,340), the physician managing these infants nonoperatively must be able to provide assurance that no permanent injury will occur.

Our approach to neonates with a perinatal diagnosis of suspected UPJ obstruction is as follows. In children with unilateral hydronephrosis, no abdominal mass, and a normal contralateral kidney, the hydronephrosis is graded (1 to 4). Those with grade 3 and 4 hydronephrosis are most likely to require pyeloplasty. A VCUG is obtained during the first few weeks of life, the child is placed on prophylactic amoxicillin or cephalexin, and circumcision is recommended for boys. At 6 weeks, a well-tempered renogram is performed. If differential renal function is greater than 35% to 40% and any significant drainage is noted after administration of furosemide, even if the $T_{½}$ is greater than 20 minutes, the child is managed nonoperatively and kept on prophylaxis with trimethoprim-sulfamethoxazole, which is safe to administer after 2 months of age. A follow-up renal sonogram and diuretic renogram are performed 3 months later. If there is deterioration in differential function, worsening of the diuretic washout curve, or worsening hydronephrosis, pyeloplasty is recommended. If these parameters remain stable or improved, however, follow-up 3 to 6 months later with another diuretic renogram is performed and management is individualized. If there is an abdominal mass, a solitary kidney, bilateral hydronephrosis, or impaired renal function, pyeloplasty is performed any signs of obstruction are present.

On occasion, urography of the fetal or neonatal urinary tract may disclose mild to moderate hydronephrosis and a dilated ureter a few centimeters distal to the UPJ. In many of these patients, the apparent dilation is secondary to *Ostling's valves,* which represent transverse folds of the upper ureter (393). They are usually nonobstructive and resolve over time (Fig. 46.20).

Pyeloplasty: Technical Points

The infant is admitted to the hospital on the day of surgery, and rooming in by one of the parents is encouraged. Preoperatively, the anterior or posterior location of the extrarenal pelvis is determined because it may help in determining the surgical approach. Lateral or oblique views on the urogram or ultrasound are helpful in this regard. The anterior muscle-splitting approach clearly is indicated if the pelvis is anterior (142), but because the pelvis is posterior in most infants, a lumbotomy incision may be preferred.

If a flank incision is used, the infant is placed with the appropriate flank elevated 30 degrees, with the opposite side

flexed over a rolled towel. The peritoneum should be mobilized widely and retracted medially. In general, the kidney does not need to be mobilized.

We have found the posterior lumbotomy to provide an excellent surgical approach to the kidney in the neonate (206). The infant is placed in the supine position, and a towel is placed under the abdomen to push the kidney further posteriorly. A 45-degree incision is made in the costovertebral angle. This approach is minimally traumatic because no muscles are cut. The exposure is optimal (except when the renal pelvis is anterior), and opening and closing the incision is rapid.

In general, a dismembered Anderson-Hynes pyeloplasty is performed. The pelvis is exposed completely by dissecting bluntly in the plane just superficial to its intrinsic blood supply. The dissection of the upper ureter should be minimal, just enough to permit resection of the narrow segment and spatulation. The ureter is not elevated or placed on traction with umbilical tape or vessel loop. Following these precautions results in the preservation of maximal blood supply to the anastomosis. When a large redundant pelvis is present, the pelvis is resected to 1 cm from the edge of the renal parenchyma. If a decompensated large-capacity floppy pelvis is left unresected, the likelihood of an unanticipated kink at the ureteropelvic anastomosis when filling occurs is increased.

Holding sutures are placed to help position the tissues for precise approximation and to avoid the need for handling the tissue with forceps. Optical magnification (×2.0 to 3.5) is beneficial in ensuring precise suture placement and a watertight anastomosis. The pelvis is closed with a running 6-0 polyglycolic acid (PGA) suture. The ureteropelvic anastomosis is performed with 6-0 or 7-0 PGA sutures. Between three and five interrupted sutures are placed at the apex, allowing more precise alignment of this critical portion of the anastomosis. The remainder of the anastomosis is performed with a running stitch, allowing a watertight closure. The anastomosis is performed over a small feeding tube passed a few centimeters down the ureter. Passage of a catheter into the bladder is avoided because it may cause edema of the UVJ, resulting in mild obstruction, increased intrapelvic pressure, and possible breakdown of the anastomosis. The renal pelvis should be irrigated before closure to remove any blood clots.

There is no consensus as to whether a nephrostomy or a ureteral stent should be used. Numerous series have demonstrated that a pyeloplasty in a neonate may be performed safely without proximal drainage (457). However, several points must be considered. It may be more difficult to produce a perfect anastomosis in a small ureter. Edema may make coaptation of the walls of the anastomosis more likely, leading to the postoperative synechiae, obstruction, or both. These considerations would encourage the use of a nephrostomy and possibly a stent (25). When a nephrostomy is not used, leakage of urine is common during the first few postoperative days. Although extravasation of urine without drainage induces an inflammatory tissue reaction, a minor amount of leakage is not problematic if the area is drained adequately. Therefore proper management of the drain is essential. One other option is to use an internal double-J stent for several weeks postoperatively. The disadvantage of the indwelling stent is that is must be removed 4 to 6 weeks later under anesthesia. Another alternative is the Salle stent (Cook), which is a double-J stent with a proximal end that is brought out through the renal parenchyma and flank; this stent drains into a bag.

Ipsilateral VUR or a full bladder may subject the anastomosis to high intraluminal pressure and may result in excessive leakage from the fragile anastomosis. Cystoscopy or intraoperative urethral catheterization may cause sufficient irritation in a newborn to allow unwanted bladder distention and probably should be avoided, as should retrograde ureteral catheterization. If a nephrostomy is not used, the infant should be checked carefully during the first 24 hours and catheterized every 4 to 6 hours if the child does not void to prevent a significant increase in the intrapelvic pressure.

Proximal drainage (e.g., nephrostomy) generally is recommended with a solitary kidney, a bilateral pyeloplasty, or an unusually small or thin-walled ureter. In general, a 12-Fr Malecot catheter is used as a nephrostomy, with two of the wings excised. In a patient whose kidney has been demonstrated postoperatively to have little or no function, a nephrostomy provides a way of demonstrating postoperatively that no obstruction is present. The catheter is placed in a lower-pole calyx. Because there is a theoretical advantage in urine transversing the anastomosis immediately postoperatively, when a nephrostomy is used, an option is to clamp it immediately and use it as a backup only if there is significant drainage from the anastomosis, obstruction, or urinary infection. When the nephrostomy is left open, it may be allowed to drain into a double diaper. Such drainage eliminates twisting, kinking, and inadvertent removal of tubes that may occur when the infant moves about the crib with the nephrostomy tube attached to a drainage bag. The infant may be discharged with an indwelling nephrostomy as soon as feeding is progressing satisfactorily and the clinical situation is stable.

Delayed opening of the anastomosis protected by a nephrostomy is common in the infant pyeloplasty. The drainage tubing may be elevated (hump the tube) 30 cm to increase the intrapelvic pressure and encourage the anastomosis to open. Gravity drainage may be reinstituted if the baby is fussy and to check for residual urine.

A reoperation rate of 8% to 10% in infant pyeloplasties has been reported, similar to series of older patients, although with greater experience there have been lower complication rates. The technical failures may be secondary to traumatic dissection, devascularization of the ureter, excessive traction on the ureter resulting in ischemia or creation

of an anastomosis that is too tight, or extravasation from an undrained anastomotic leak with subsequent fibrosis.

Follow-up studies include an ultrasound and diuretic renogram.

Megaureter—Nonrefluxing

In a child with a megaureter, the condition may be obstructive or nonobstructive and refluxing or nonrefluxing (158). In most cases, there is no reflux.

Nonrefluxing megaureter results from an aperistaltic segment of the distal ureter that does not allow normal propulsion of urine. In this condition, sonography shows a dilated ureter and renal pelvis with variable renal parenchymal atrophy. VCUG shows no reflux in most cases. Before the era of antenatal ultrasound, most patients with this condition presented with flank pain, a flank mass, pyelonephritis, hematuria, or stone disease. Approximately 70% of individuals with this condition are male and two-thirds are on the left side.

Although severe hydronephrosis may be present, the natural history of this condition is that there is a tendency to gradual reduction in hydronephrosis over a period of several years. For example, in one series of 35 neonates with a primary nonrefluxing megaureter, 10 underwent early repair, whereas 25 were followed nonoperatively (37). With a mean follow-up of 7.3 years, none of the 25 exhibited deterioration in differential function or demonstrated signs of obstruction. In another series of 21 patients with nonrefluxing megaureters with obstruction on the initial scan, 6 underwent early reconstruction, whereas 15 were observed (436). Of the patients who were managed nonoperatively, two showed functional deterioration and three, who were not receiving antimicrobial prophylaxis, developed UTIs. Finally, Liu and colleagues (322) found that 11 of 67 (17%) neonatal megaureters managed nonoperatively ultimately needed repair because of deteriorating renal function in 8 and breakthrough UTIs in 3. Consequently, it appears that most of these patients may be followed nonoperatively on antibiotic prophylaxis and serial monitoring of renal function and drainage.

In these neonates, a VCUG and renal sonogram should be obtained before discharge. Early management is identical to that of neonates with a suspected UPJ obstruction. If an abdominal mass, solitary kidney, or bilateral hydroureteronephrosis is present, a well-tempered diuretic renogram should be obtained promptly. Otherwise, the study is deferred until 6 to 8 weeks of age. If the differential renal function is at least 35% to 40%, the child is managed nonoperatively and follow-up diuretic renograms and/or renal sonograms are obtained every 3 to 6 months. Circumcision is recommended for boys, and all are administered antimicrobial prophylaxis. As long as the child remains asymptomatic and the severity of hydronephrosis remains stable or decreases, nonoperative management may continue. On the other hand, if the differential renal function is low or is diminishing, the $T_{½}$ is prolonged, the child is symptomatic, or the hydronephrosis worsens, repair is indicated.

When repairing a megaureter, one must be certain to remove the narrowed distal ureteral segment and part of the redundant ureter. Although Hendren's (239) technique of extensive ureteral excisional tapering has stood the test of time, ureteral plication has been demonstrated to be a reliable method of repair if the ureter is not too wide, with a low incidence of postoperative obstruction. Two techniques have been used: ureteral plication (514) and ureteral folding (148,281). The tailoring needs to be performed only up to a few centimeters proximal to the intramural segment. In general, we have stented these tailored ureters for 3 weeks with a small double-J stent that is connected to a small suture that is brought out through the urethra and taped to the lower abdomen.

Early repair of megaureter has a higher complication rate than in older children. For example, Peters and associates (403) reported on megaureter repair in 42 infants operated on at a mean age of 11.8 months. In that series, early complications occurred only in those younger than 6 weeks of age and included transient apnea in three, UTI in one, hyponatremia in one, and meningitis in one. Six had postoperative reflux, and none had obstruction. Greenfield and others (214) reported on repair of 11 megaureters in infants younger than 6 months old. Of these children, two had transient ureteral obstruction immediately after stent removal and persistent grades I and II reflux in two children.

Posterior Urethral Valves

The most common cause of bladder outlet obstruction in the newborn is PUV. The embryology, clinical features, and long-term management are described in Chapter 50 . Although Young (590) described three types of valves in 1919, presently only type I and type III valves are thought to be clinically significant. Type I valves are represented by leaflets or sails that extend distally from either side of the verumontanum to the anterior urethral wall at the level of the urogenital diaphragm. More than 90% of valves are type I. A type III valve is a diaphragm just distal to the verumontanum that has a small central perforation. Patients with type III valves tend to have more severe bladder and upper urinary tract obstruction.

A recent study suggests that most congenital posterior urethral obstructions are similar. Dewan and co-workers (129) performed antegrade voiding cystourethrography in boys with suspected valves. Subsequently, cystoscopy demonstrated that all had a “type III” urethral membrane. After passing the cystoscope into the bladder and then withdrawing the cystoscope back into the urethra, all had the appearance of a type I valve. This report suggests that the catheter

used for VCUG disrupts the valve membrane, giving it a type I appearance.
The incidence of PUV is approximately 1 in 5,000 to 1 in 8,000 boys. There is a wide spectrum in the presenting symptoms and long-term prognosis following treatment. Because of the high-grade bladder outlet obstruction throughout gestation, many children with valves have severely compromised renal function secondary to renal dysplasia.

Diagnosis

The newborn with urethral valves may have an abdominal mass (48%), failure to thrive (10%), urosepsis (8%), or urinary ascites (7%). When the bladder is empty, most will have a walnut-size firm mass in the pelvis, which corresponds to the trabeculated bladder muscle. In as many as half, the diagnosis of valves is suggested by prenatal ultrasonography (Fig. 46.10). Prognosis is significantly better if ultrasound studies performed before 24 weeks of gestation were normal; more than half detected by 24 weeks died or were in chronic renal failure (135,260,261). In addition, dyspnea at birth associated with pneumothorax or pneumomediastinum may be the initial sign of severe urethral obstruction. A normal urinary stream is an uncommon finding.

When the diagnosis of urethral valves is suspected, a VCUG should be performed. A thick trabeculated bladder with a very distended posterior urethra and valve leaflets is seen. Other finds include detrusor hypertrophy, often with cellules or diverticula; bladder neck hypertrophy; and a thin stream distal to the valve leaflets. Half of these patients have VUR, with 25% having bilateral and 25% having unilateral reflux (Fig. 46.22). The radiographic appearance of urethral valves is not confused with prune-belly syndrome, although both of these conditions can cause significant bladder and upper urinary tract dilation.

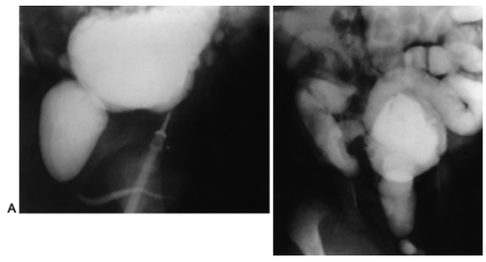

FIGURE 46.22. A–B: Examples of voiding cystourethrogram demonstrating typical posterior urethral valves. Note dilated posterior urethra, hypertrophy of bladder neck, and trabeculated bladder. Bilateral vesicoureteral reflux demonstrated in **B.**

The other important radiographic study is a renal and bladder sonogram. It is critical to obtain baseline views of the renal collecting systems to assess pelvic and calyceal dilation, as well as cortical echogenicity, which may be indicative of the presence of dysplasia. Sonographic presence of the corticomedullary junction in newborns with urethral valves is an important prognostic indicator of good renal function following drainage of the urinary tract (Fig. 46.23). Conversely, if the corticomedullary junction is not visualized and does not appear on subsequent ultrasound examinations, most develop renal insufficiency (256). Suprapubic or perineal ultrasound may demonstrate the dilated posterior urethra, and thus one might establish the diagnosis of valves on the basis of an ultrasound before the VCUG is performed (94) (Fig. 46.24).

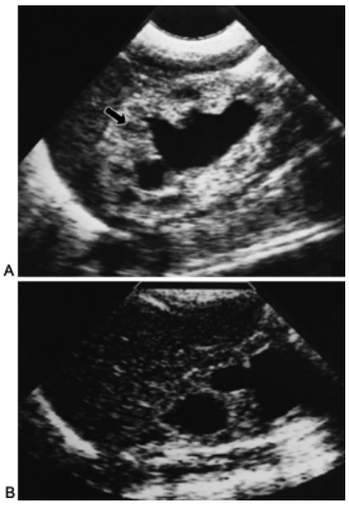

FIGURE 46.23. Sonograms of kidneys from infants with posterior urethral valves. **A:** Corticomedullary junction is present *(arrow).* At birth, creatinine rose to 2.8 mg/dL but fell to 0.6 mg/dL following valve ablation. **B:** Corticomedullary junction absent. The infant progressed to chronic renal failure.

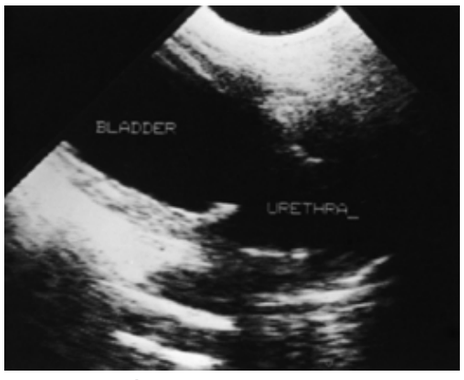

FIGURE 46.24. Suprapubic ultrasound demonstrating dilated bladder and posterior urethra strongly suggestive of posterior urethral valves.

Management

After the diagnosis of urethral valves is made, the bladder should be drained with a 5- or 8-Fr pediatric feeding tube. A Foley balloon catheter may not drain satisfactorily because the balloon has a tendency to occlude the ureteral orifices or it may cause severe bladder spasm and prevent normal drainage of the upper urinary tracts (275). When passing the ureteral catheter, there is a tendency for the tip of the

tube to bump on the bladder neck and coil in the dilated posterior urethra, compromising effective drainage. In this circumstance, most of the urine tends to drain around the feeding tube. If there is a question, the appropriate position should be confirmed either by sonography or when the VCUG is done. Repeatedly adjusting the tip of the catheter increases the likelihood of a secondary infection of the urinary tract.

Broad-spectrum antibiotics are given intravenously to minimize the chance of developing a nosocomial bacterial infection. The serum creatinine is monitored, and electrolyte abnormalities, including acidosis and hyperkalemia, need to be managed before surgical treatment of the lesion is undertaken. In addition, repeat sonography of the upper tracts may be performed to assess the response to bladder drainage.

Initial treatment of the valves depends on the age at presentation and the size and condition of the child. The goal of therapy is to provide optimal upper tract drainage and preserve bladder cycling to allow satisfactory bladder growth with maximal compliance (93,144,502). In the past, use of inappropriately large endoscopic instruments for valve ablation resulted in urethral strictures. With improvement in the optics of the 8-Fr pediatric cystoscope, fulguration can be performed in most small infants safely. In the newborn, the 8-Fr cystoscope is used to examine the bladder, with assessment of the degree of trabeculation, the presence of diverticula, and the position of the ureteral orifices, as well as examination of the valves. In most cases, the 3-Fr Bugbee electrode may be inserted through the operating channel of the 8-Fr cystoscope. The valve leaflets should be ablated at the 5 and 7 o'clock positions, and on occasion at the 12 o'clock position.

Complications with transurethral valve ablation are rare; the most common is incomplete valve ablation. Urethral stricture may occur if the cystoscope is too large for the urethra or if the diathermy current comes into contact with the metal of the cystoscope (491). If the water used for intraoperative irrigation is too high, the elevated pressure may be transmitted to the kidneys and result in forniceal rupture with urinary ascites (122).

Before the availability of miniature endoscopic equipment, a method of valve ablation was a modified crochet hook. Subsequently, Whitaker and Sherwood (566) redesigned the hook (Fig. 46.25) such that it engages only valves and not the bladder neck, verumontanum, or external sphincter. Except for the crotch of the hook, the entire instrument is insulated to prevent spread of diathermy current. It is important to use low-cutting current with the device. It may be used under fluoroscopic guidance in the radiology suite without the necessity for general anesthesia.

A cystogram in the operating room confirms adequate relief of obstruction. Experience with this technique has confirmed its effectiveness in relieving bladder outlet obstruction, although some patients have required secondary valve ablation (84). Unfortunately, the Whitaker hook is no longer made, although some centers still have it in available in their inventories. Its most appropriate use may be in countries where miniature endoscopic equipment is unavailable.

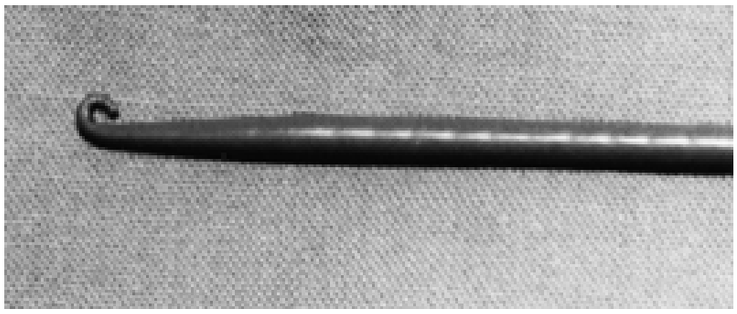

FIGURE 46.25. Tip of insulated crochet hook developed by Whitaker and Sherwood (566). Tip of hook engages only the valve leaflets. Crotch of hook is not insulated allowing diathermy ablation of valves.

Cromie and colleagues (117) reported using a venous valvulotome to incise the valve leaflets at the 12 o'clock position under local anesthesia. Of the ten patients, two underwent later resection of small nonobstructive valve leaflet remnants.
Other techniques for valve ablation also have been described. Zaontz and Gibbons (592) reported antegrade ablation of valves through an established vesicostomy. The technique also has been used percutaneously in neonates (591). The technique involves distending the bladder and performing a percutaneous cystotomy with a 12-Fr trocar midway between the symphysis and umbilicus in the midline. The obturator may be removed, leaving the 12-Fr sheath in the bladder. The 11.5-Fr resectoscope then may be passed through the sheath with visualization of the valves through a 0-degree lens. Visualization has been reported to be quite good. Following this procedure, neither a suprapubic tube nor a urethral catheter was necessary postoperatively.
If the urethra is too small to accommodate the pediatric cystoscope and miniature Bugbee electrode, cutaneous vesicostomy is an alternative form of management (143,259). The dome of the bladder should be brought to the skin at a level such that the posterior bladder wall will not prolapse into the stoma (Fig. 46.26). The vesicostomy should calibrate to 24 Fr.

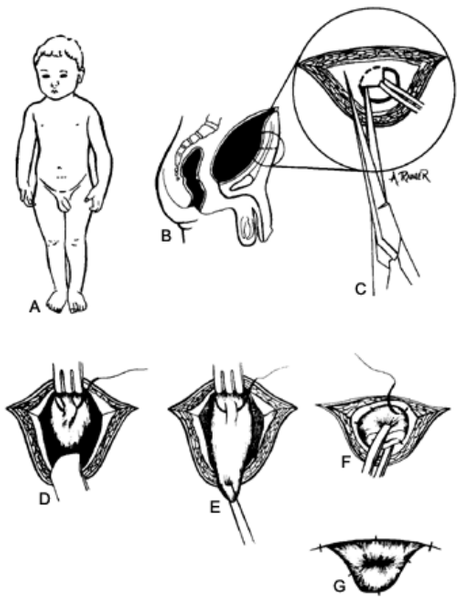

FIGURE 46.26. A–G: Diagram of cutaneous vesicostomy. Incision is made halfway between the pubic symphysis and umbilicus. Holding sutures are placed through the bladder wall for traction, and the bladder is mobilized superiorly until the dome is reached. The dome of the bladder is then exteriorized.

Following definitive therapy, the child should be monitored closely by ultrasound to be certain that the upper urinary tracts are decompressed satisfactorily. A high serum creatinine should decrease gradually. In a newborn who has undergone only valve ablation, however, if the serum creatinine remains unchanged or does not decrease at least to 1.0 to 1.2 mg/dL, proximal diversion by vesicostomy. In the past, cutaneous pyelostomy was thought by some to be a superior form of upper tract diversion compared with cutaneous vesicostomy. However, supravesical diversion does not seem to prevent progression to end-stage renal disease in many of these children because of underlying renal dysplasia (93,192,536). Furthermore, proximal diversion results in the absence of urine going to the bladder and thereby prevents bladder cycling, which may result in poor bladder compliance (i.e., the “valve bladder”) (144,408), although this theory is not universally accepted (265). An alternative is to insert a percutaneous nephrostomy tube for temporary diversion and identify those few patients who might benefit from cutaneous pyelostomy (192). An alternative is the Sober-en-T temporary high diversion for urethral valves, in which a cutaneous ureterostomy is performed, and the distal ureter is sutured to the upper ureter just distal to the renal pelvis (320,506). The advantage of this approach is that the upper urinary tract is diverted, but some of the urine drains to the bladder, which preserves long-term bladder cycling. In select cases, cutaneous pyelostomy may be necessary if a

child has urosepsis secondary to pyonephrosis. If upper urinary tract diversion is performed, concurrent renal biopsy should be done to assess renal morphology.

The long-term prognosis for infants with PUV depends on multiple factors (443) (Fig. 46.27). Among the most important are the serum creatinine level 1 month after urinary drainage and whether a pop-off valve, such as unilateral VUR associated with a nonfunctioning kidney (VURD syndrome), a large bladder diverticulum, or urinary ascites is present. If the serum creatinine level falls below 0.8 to 1.0 mg/dL 1 month after treatment, renal function usually remains sufficient to prevent the need for dialysis, particularly if the renal corticomedullary junction is intact on sonography (256). More recently, a serum creatinine less than 0.8 mg/dL 4 to 5 days after bladder drainage is predictive of satisfactory long-term renal function (127). Attempts to identify biochemical parameters, such as transforming growth factor-β1, that might be useful in predicting long-term response to therapy have been unsuccessful to date (126).

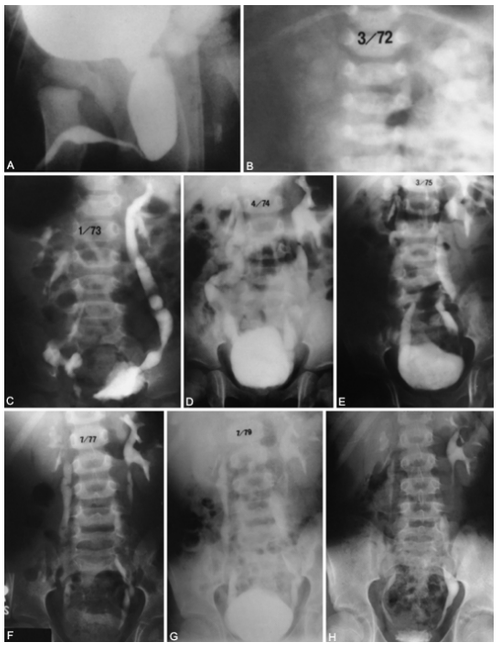

FIGURE 46.27. Example of long-term follow-up in a patient with posterior urethral valves. Infant was born with urinary ascites. Child underwent primary resection of urethral valves. **A:** Voiding cystourethrogram with typical posterior urethral valves. **B:** Initial intravenous pyelogram demonstrating bilateral hydronephrosis. **C–H:** Initial improvement was observed, and long-term follow-up shows good results. Vesicoureteral reflux of the right kidney ceased within 3 years. Note the straightening of the ureters with time. (**A–G** from Duckett JW, Snow BW. Disorders of the urethra and penis. In: Walsh PC, Gittes RF, Perlmutter AD, et al, eds. *Campbell's urology,* 5th ed. Philadelphia: WB Saunders, 1986, with permission.)

In patients with unilateral VUR associated with nonfunction, the prognosis has been quite good. It has been called the *VURD* (valves, unilateral reflux, and dysplasia) *syndrome* (252). The refluxing ureter acts as a pop-off valve, preventing the deleterious effects of high vesical pressure on the opposite kidney. A similar phenomenon occurs when a giant vesical diverticulum is present (Fig. 46.28). In five patients with this entity, all have good renal function and some have surprisingly normal upper urinary tracts (443). Finally, the presence of urinary ascites in newborns with PUV has been recognized as another protective factor, with an upper or lower urinary tract leak allowing the kidneys to develop without the deleterious effects of high pressure (Fig. 46.29).

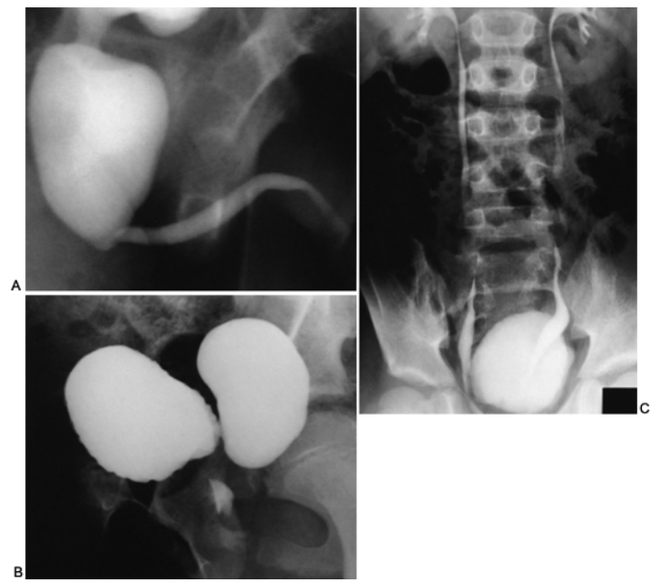

FIGURE 46.28. Example of bladder diverticulum as a protective feature in a child with posterior urethral valves. **A:** Voiding cystourethrogram showing typical posterior urethral valves. **B:** Lateral image on cystogram showing large vesical diverticulum. **C:** Intravenous urogram before valve ablation showing normal collecting systems and medial deviation of lower left ureter secondary to large diverticulum.

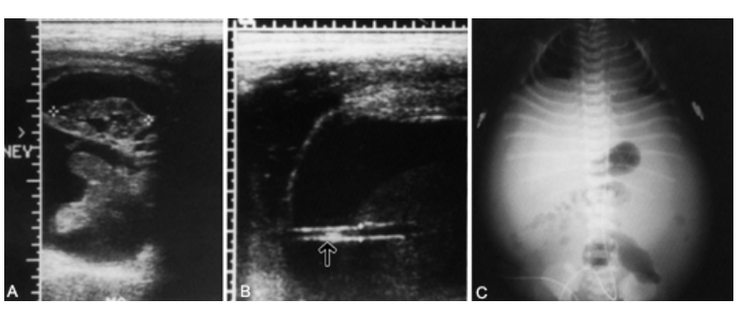

FIGURE 46.29. Urinary ascites secondary to posterior urethral valves. **A:** Prenatal ultrasound, 38 weeks of gestation, showing right kidney and ascites. **B:** Massive ascites, resulting in stretching of umbilical vein *(arrow).* L, liver. **C:** Abdominal film at birth, showing characteristic appearance of ascites. Note umbilical artery catheter.

In one series of 71 boys with valves and long-term follow-up, 20 (28%) had one of the protective mechanisms. Of these, only one (5%) had a serum creatinine greater than 1.0 mg/dL. In contrast, of the 51 boys without a pop-off mechanism, 20 (39%) had an elevated creatinine and 7 (14%) were on dialysis or had undergone renal transplantation (443). However, Cuckow and colleagues (119) reported that only 25% of boys with the VURD syndrome had a normal GFR at 5 to 8 years of age.

The risk of end-stage renal disease in boys with PUV is significant. In a series of 98 boys with follow-up between 11 and 22 years, Parkhouse and colleagues (398) reported that 31 (32%) had poor renal function; 10 (10%) had died of renal failure, 15 (15%) had endstage renal failure, and 6 (6%) had chronic renal failure but were not yet receiving dialysis. Adverse prognostic factors included presentation before 1 year of age, bilateral VUR, and diurnal incontinence after 5 years of age, the last being the most important factor. The association of diurnal incontinence and poor renal function in these patients most likely is related to detrusor instability and detrusor sphincter dyssynergia, which many of these boys develop, resulting in elevated upper urinary tract pressures and gradual deterioration in renal function.

When urethral valves are discovered in the newborn, it is likely that the infant will have high urine output resulting from a renal concentrating defect. Consequently, the parents of these infants should be advised that their child is much more likely than other infants to become severely dehydrated with viral gastroenteritis or other febrile infections that might increase the child's fluid requirements.

Anterior Urethral Valve

Another form of urethral obstruction that may be apparent in the newborn is the anterior urethral valve (Fig. 46.30). This anomaly is rare, and its embryologic origin is uncertain. Usually, the valve is a filamentous cusp on the ventral aspect of the urethra, resulting in the development of a diverticulum that by virtue of its size may obstruct the distal urethra. Nearly all occur in the bulbous or pendulous urethra. If the diverticulum is large, it may be visualized as a cystic mass on the ventral aspect of the penoscrotal junction, which increases in size when the infant voids. In addition, a prolonged dribbling stream is noted. If obstruction is severe, the neonate may develop renal insufficiency. Diagnosis is confirmed by VCUG. In addition, a renal ultrasound to assess the upper urinary tracts should be performed.

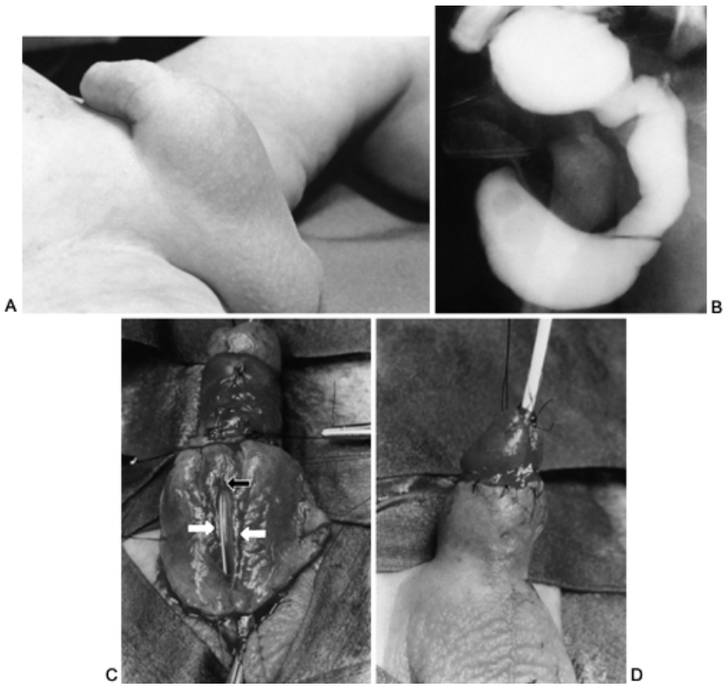

FIGURE 46.30. Example of anterior urethral valve. **A:** Infant born with cystic firm mass at penoscrotal junction. **B:** Voiding cystourethrogram showing huge ventral diverticulum secondary to anterior urethral valve. Note distal anterior urethra. Infant also had bilateral vesicoureteral reflux. **C:** Neonate underwent primary open resection of valve and diverticulum. Intraoperative view demonstrates large diverticulum *(solid white arrows)* and anterior urethral valve *(black arrow).* **D:** Postoperative photograph. A 6-Fr Silastic stent is used for bladder drainage.

Treatment is based on the size of the diverticulum and renal function. If the diverticulum is small, the cusp may be ablated by transurethral resection. Another technique is incision with a venous valvotome (117). However, if the diverticulum is massive or if there is significant VUR and poor bladder emptying, open surgical resection of the diverticulum and valve cusp is necessary. A 6-Fr silastic urethral stent may be left in place to drain continuously into the diaper for 10 to 14 days. If renal function is impaired, temporary catheter drainage of the bladder may be necessary to stabilize the infant and correct electrolyte abnormalities. If the serum creatinine fails to decrease to a satisfactory level, resection of the diverticulum and valve and perineal urethrostomy provide reliable drainage. Alternatively, cutaneous vesicostomy should be considered in these patients (463). In one recent series of 17 patients, 1 underwent supravesical diversion, 5 underwent temporary vesicostomy, 5 had open urethroplasty, and 6 underwent transurethral fulguration (549). All had continence and minimal or no hydronephrosis at follow-up.

Gross Hematuria

Gross hematuria in the neonate is an uncommon event but requires emergency diagnosis (63). The unusual nature of hematuria in this age group is exemplified by the report by Emanuel and Aronson (162) in which only 35 cases were encountered at a busy children's hospital over a 27-year

period. In that series, seven patients (20%) had RVT, seven (20%) had obstructive uropathy, and six (17%) had infantile polycystic kidney disease. In 11 (31%) of the patients, the cause of the hematuria was unknown.

Another cause of neonatal hematuria is stone disease, which occurs with some frequency in premature newborns receiving parenteral furosemide therapy and which is discussed later in this chapter.

Other potential causes of hematuria in the newborn include endocarditis (383) and peripheral venous air embolus (573); it can also occur secondary to indomethacin therapy for patent ductus arteriosus (102). Although renal disease is a common cause of hematuria in the older pediatric age groups, glomerulonephritis is rare in the newborn.

Renal Vein Thrombosis

RVT is a common cause of neonatal hematuria. The neonatal kidney seems to be particularly vulnerable to RVT because of low renal perfusion pressure. RVT occurs primarily in conditions associated with dehydration and polycythemic sludging. For example, infants of diabetic mothers experience osmotic diuresis and have a substantially increased incidence of RVT. In addition, it may occur following

diarrhea, perinatal stress, sepsis (fever with increased fluid requirements), cyanotic congenital heart disease (with resultant polycythemia), acute hypoxia, sickle cell disease, cytomegalovirus infection, hypotension, or seizures, and it is associated with polyhydramnios, toxemia, and maternal diuretic use (434). There is a moderate male predominance. Sludging in the renal venules results from low perfusion pressure, whereas contracture of the extracellular volume leads to increased blood viscosity and further diminishes renal blood flow, with predisposition to thrombosis. RVT is thought to originate in the arcuate and interlobar veins at the corticomedullary junction. The thrombotic process extends along the venous tributaries to the cortex, as well as centrally along the interlobar veins to the main renal vein (324). Following RVT, severe renal congestion occurs, leading to further impairment of arterial perfusion with thrombosis.

Among cases of RVT in childhood, almost 65% occur during the neonatal period, whereas 30% occur after the age of 1 year (324). In addition, RVT has been recognized prenatally and may even cause fetal distress (110,130). Evidence for the latter includes the finding of organized RVTs with calcification in the newborn period. An early postnatal renin-mediated hypertension may result.

Diagnosis

The classic features of neonatal RVT include palpable renal mass (60%), gross hematuria (70%), thrombocytopenia (90%) less than 75,000/μmL, consumptive coagulopathy (prolonged clotting time, elevated fibrin split products), leukocytosis, proteinuria, and anemia (32%). Other features in some cases include hypertension and renal failure.

If there is edema of the lower extremities, one should suspect thrombosis of the inferior vena cava. In RVT, the blood pressure is usually normal or low. With bilateral RVT (20% of cases), the blood urea nitrogen (BUN) and serum creatinine levels usually are elevated. The prognosis of bilateral RVT is ominous compared with unilateral RVT.

As in the evaluation of other renal masses, ultrasonography is the initial procedure of choice for the diagnosis of RVT (434). The findings depend on the stage at which the examination is performed and extent of the thrombus. Initially, the interlobular and interlobar thrombus appears as highly echogenic streaks. These streaks commence in a peripheral, focal segment of the involved kidney and persist for only a few days. In the first week, the affected kidney swells and becomes echogenic with prominent echo-poor medullary pyramids. Later, the swelling increases and the kidney becomes heterogenous with loss of corticomedullary differentiation. Thrombus within the renal vein or veins and possibly the inferior vena cava is seen also. In the early stages of RVT, color Doppler may demonstrate absent intrarenal and renal venous flow. Adrenal hemorrhage is a recognized association and may be identified also. Ultimately, the kidney may recover, show focal scarring, or become atrophic.

Management

Initial therapy is directed at correction of the fluid and electrolyte abnormalities and prevention of propagation of the venous thrombus. Careful attention must be paid to correcting dehydration and electrolyte abnormalities and to restoring acid–base balance. In addition, underlying conditions such as cardiac disease must be treated. In the presence of acute renal failure, peritoneal dialysis may be necessary. Operative management rarely is necessary on an emergency basis.

The extent of the venous thrombus must be assessed. If the ultrasound demonstrates unilateral involvement, no therapy may be necessary. A baseline renal scan should be obtained to assess function of the involved kidney, and CT may be used to provide a baseline for the extent of venous involvement. With bilateral RVT, the prognosis is more ominous, particularly if the thrombus involves the vena cava as well (208).

Definitive therapeutic options include prevention of propagation of the thrombus, thrombolysis, and formal thrombectomy. Systemic heparinization may be used to prevent thrombus propagation, although the risk of propagation occurring with restoration of fluid and electrolyte balance is low. There is no consensus regarding the efficacy of heparin therapy for unilateral RVT (324).

The development of thrombolytic agents such as urokinase (208) and streptokinase (71) has provided the physician with a more definitive way of stimulating resolution of the thrombus, but these drugs should be reserved for bilateral RVT. Whether to perform thrombectomy is controversial. With vena caval thrombosis, the vena cava may remain permanently occluded, but collateral venous channels generally develop and provide satisfactory drainage.

The overall survival rate is high (324). Most deaths are related to the underlying disease, not renal infarction. Long-term sequelae include (a) a nonfunctioning, completely fibrosed, shrunken kidney; (b) a partially fibrosed kidney with impaired function; (c) renovascular hypertension; (d) nephrotic syndrome; (e) chronic renal infection; and (f) chronic renal tubular dysfunction. Often, the prognosis may be inferred based on the DTPA scan performed during acute stages of the disease.

In unilateral RVT, the most serious complication is hypertension, which usually results from an atrophic kidney. In such cases, renin-mediated hypertension is present, and nephrectomy is curative (503). Jobin and co-workers (268) reported that 5 of 6 patients followed 21 months to 12 years after neonatal RVT were hypertensive. However, only three had an atrophic kidney. Furthermore, not all patients with small scarred kidneys following RVT developed hypertension. If significant return of renal function is going to

occur, visualization on the renal scan may be expected within 4 to 6 weeks. In some small kidneys labeled as “congenitally hypoplastic,” unrecognized RVT is the probable underlying cause.

Renal Failure

With the expertise of neonatal intensive care units for premature neonates, acute renal failure probably is occurring with increasing frequency. Acute renal failure should be suspected in any infant who has a sustained decrease in urine output to less than 1 mL/kg per hour, a persistent serum creatinine level greater than 1 mg/dL (in newborns beyond 34 weeks of gestation), or hematuria. Although renal failure may be associated with normal or even increased production of urine, most neonates with acute renal failure have oliguria or anuria.

Because 92% of term newborns pass urine within 24 hours of birth and 99.4% do so within 48 hours (493), renal failure should be suspected in any infant who fails to void within 48 hours after delivery.

In the neonate, as in the older child and adult, renal failure is characterized as prerenal, renal, or postrenal (Table 46.14). In prerenal and in many patients with intrinsic renal failure, the kidneys are basically normal, although the renal insult may result in permanent impairment of function. In contrast, many patients with postrenal failure have irreversible renal damage, often from congenital abnormalities.

Prerenal	Intrinsic	Postrenal
Hypotension secondary to:	Congenital anomalies	Posterior urethral valves
Sepsis	Cystic dysplasia	Anterior urethral valve
Maternal antepartum hemorrhage	Hypoplasia	Prune-belly syndrome
Twin-to-twin hemorrhage	Agenesis	Urethral atresia
Intrinsic neonatal hemorrhage	Polycystic kidney disease	Ectopic ureterocele
Cardiac surgery	Inflammatory	Ureteropelvic or ureterovesical obstruction
Congestive heart failure	Congenital syphilis or toxoplasmosis	Extrinsic tumor compressing bladder outlet
Asphyxia neonatorum	Pyelonephritis	
Dehydration	Metabolic	
? Intermittent positive pressure breathing	Oxalosis	
? Continuous positive airway pressure	Vascular Renal vein thrombosis Renal artery thrombosis Hemolytic uremic syndrome Disseminated intravascular coagulation Cortical necrosis Perinatal asphyxia Sepsis Shock Acute tubular necrosis Nephrotoxins Maternal use of nonsteroidal antiinflammatory medication Dehydration Transient renal dysfunction	

TABLE 46.14. MAJOR CAUSES OF RENAL FAILURE IN THE NEONATE

The most common cause of acute renal failure in the newborn is prerenal failure, whereas the most common cause of intrinsic renal failure is perinatal asphyxia (283,521). Prerenal failure may also result from perinatal asphyxia when blood is shunted away from the kidneys to improve circulation to the brain and heart.

Renal development in the fetus whose mother is azotemic progresses normally. Often, these infants are born prematurely. Interestingly, renal size at birth in these cases has been reported to be at the upper limits of normal (62), raising the possibility that compensatory growth might be occurring *in utero.*

Prerenal Failure

There are numerous causes of diminished renal perfusion that may result in renal failure in the neonate (Table 46.14). Hypotension may result from sepsis, fetal and perinatal hemorrhage (e.g., twin–twin transfusion, complications of amniocentesis, abruptio placenta, birth trauma), neonatal

hemorrhage (severe intraventricular hemorrhage, adrenal hemorrhage), necrotizing enterocolitis, perinatal asphyxia, and hyaline membrane disease. Furthermore, renal blood flow may be compromised in patients with congestive heart failure or in those with a patent ductus arteriosus. In these patients, total blood volume may be normal or increased. In addition, newborn infants have a higher ratio of body surface area to body mass than older children and adults, and this may result in increased insensible and sensible fluid loss through the skin, especially when the baby is under a radiant warmer. Hypovolemia and shock in the newborn may occur secondary to RVT. Finally, diarrhea in the neonate may result in prerenal azotemia and acute renal failure. When it is severe, prerenal failure may result in cortical necrosis.

Intrinsic Renal Failure

Intrinsic renal failure implies that inadequate kidney function is secondary to inherent kidney damage. All of the conditions that cause prerenal failure may result in intrinsic renal damage if the insult is severe. Some of these infants may have renal failure secondary to congenital renal anomalies. In most of these patients, the diagnosis can be made rapidly from a history of oligohydramnios, features of Potter's syndrome, or both.

Vascular complications are an important cause of neonatal renal failure. Sick neonates with umbilical artery catheters may develop aortic thrombosis or bilateral renal artery thrombosis. RVT and renal artery thrombosis are covered elsewhere in this chapter. Disseminated intravascular coagulation may result from sepsis or necrotizing enterocolitis.

Acute tubular necrosis (ATN) may result from the same insults as cortical necrosis but only if the insult is less severe. Often, it is secondary to nephrotoxic medication. For example, aminoglycosides are potent nephrotoxic agents that have been studied much more in adults than in newborns. Because the GFR in the newborn is low, it is important to measure peak and trough drug levels when these agents are used. Although the blood flow distribution in the newborn kidney, which favors the juxtamedullary nephrons, might make aminoglycoside nephrotoxicity less common in the neonate (109), toxicity has been demonstrated. Indomethacin, a prostaglandin synthesis inhibitor, is used in the pharmacologic closure of the ductus arteriosus in premature infants. Its major toxicity is renal, and Vert and associates (550) reported transient oliguria in 16 of 18 infants treated with indomethacin. The toxic effect of indomethacin appears to be diminished considerably by the administration of concomitant furosemide (588). Nonsteroidal antiinflammatory agents, such as indomethacin, also have been administered to diminish amniotic fluid volumes in women with polyhydramnios, presumably by diminishing fetal urine output. In a recent report, three premature infants with prenatal exposure to indomethacin developed renal failure, which was fatal in one case (498). Angiotensin-converting enzyme inhibitors taken by women for control of hypertension may have an adverse effect on renal development, particularly if taken during the second and third trimesters (225,589).

Another cause of intrinsic renal failure is transient oliguric renal failure with enlarged kidneys and echogenic medullary pyramids (245). In these patients, there was no apparent cause, and all eventually had a normal serum creatinine; none required dialysis.

Postrenal Failure

There is a discussion of these entities elsewhere in this chapter, as well as other chapters in the text. In general, oligohydramnios is present if the obstruction is severe enough to cause renal failure in the newborn. Whether relief of obstruction may allow satisfactory renal function to occur depends on a number of factors, including the severity and duration of obstruction.

Diagnosis

The most important sign of acute renal failure in the neonate is oliguria, with a urine output of less than 1 mL/kg per hour. Measurement of urine output in premature infants may be inaccurate while they are in an incubator or isolette because significant evaporation occurs within 15 minutes (98). In infants, the newer highly absorbent diapers that contain a gel-based absorbent also may absorb ambient moisture, spuriously elevating recorded urine output.

Often, the history and physical examination provide important clues to the diagnosis. For example, respiratory distress syndrome, hypoxia, shock, congestive heart failure, and sepsis, as well as dehydration, may cause renal failure. Enlarged kidneys may be secondary to RVT, hydronephrosis, infantile polycystic kidney disease, or multicystic kidneys. Urinary ascites may be secondary to PUV. The presence of edema usually indicates volume overload. In most of these conditions, treatment of the underlying condition will allow resolution of satisfactory renal function. However, until renal function does resolve, careful monitoring of electrolytes and volume status is necessary.

If the cause of renal failure is not readily apparent from the initial clinical evaluation, a battery of studies is in order, including complete blood cell count with RBC morphology and platelet count; prothrombin time; partial thromboplastin time; serum electrolyte, BUN, creatinine, uric acid, calcium, phosphorus, glucose, total protein, and albumin concentrations; blood pH, PO_2, and PCO_2); urinalysis; urine culture; urinary sodium concentration; creatinine clearance; osmolality; electrocardiogram (ECG); chest x-ray film; and renal ultrasound.

Postrenal causes of acute renal failure are apparent from the ultrasound examination. Using the studies shown in

Table 46.15, Mathew and co-workers (347) found that the fractional excretion of sodium and the renal failure index were of greatest value in distinguishing prerenal from intrinsic renal failure. Practically speaking, once volume overload and urinary obstructive causes are excluded, a fluid challenge may be given. In general, 20 mL/kg of normal saline or Ringer's lactate may be administered intravenously over 1 to 2 hours. If oliguria persists, furosemide in a dose of 1 mg/kg of body weight is administered. If there is still no response, the dose of furosemide should be increased to 2 mg/kg. If no further increase of urine output is observed during the following hour, intrinsic renal failure should be suspected and fluid administration reduced. Although furosemide may protect the kidney during recovery from renal ischemia, after intrinsic renal failure has developed, repeated doses of furosemide may cause ototoxicity.

	Prerenal	Intrinsic
Urine osmolality (mOsm/kg H_2O)	>400	<400
Urinalysis	Normal	>5 RBCs/HPF
Urine sodium (mEq/L)	31 ± 19	63 ± 35
Urinary (U)/plasma creatinine (P_{Cr})	29 ± 16	10 ± 4
Fe_{Na} %	<2.5 (x = 0.9)	>2.5 (x = 4.2)
RFI	<3.0 (x = 1.3)	>3.0 (x = 11.6)

Fe_{Na}%, fractional sodium excretion; HPF, high-power field; RFI, renal failure index [(U_{Na}/U_{Cr}) x PG].
Modified from Mathew OP, Jones AS, James E, et al. Neonatal renal failure: usefulness of diagnostic indices. *Pediatrics* 1980;85:57, with permission.

TABLE 46.15. DIAGNOSTIC INDICES IN NEONATAL ACUTE RENAL FAILURE

Management

After the cause of renal failure is determined, attention must be directed to the volume status and electrolytes of the infant while the underlying condition resolves.

Because acute renal failure is nearly always oliguric, fluid intake must be monitored carefully. A 5- or 8-Fr pediatric feeding tube should be inserted into the bladder to monitor urine output. Fluid intake should be restricted to insensible water loss plus other nonrenal losses, such as gastrointestinal. If the infant is normovolemic, urine losses should be measured and replaced with an equal volume each hour. In the presence of volume overload, the desired amount of weight loss should be subtracted from the total replacement fluids. In the newborn, daily insensible water loss is 40 mL/kg per 24 hours, although it may be higher in low-birth-weight infants (521). Insensible water loss is increased if the infant is under a radiant warmer or is febrile; it is decreased if the neonate is on a respirator. Insensible water loss should be replaced as electrolyte-free water in a 10% dextrose solution. Urinary losses should be replaced with a solution containing the same concentration of sodium as is present in the urine. The neonate should be weighed at least every 12 hours to monitor fluid balance. A daily loss of 0.5% to 1.0% of body weight is to be expected (521).

Hyponatremia may result from fluid overload with dilution of extracellular sodium. If the infant is asymptomatic, fluid and sodium restriction is adequate. If the infant is symptomatic or the sodium concentration is less than 120 mEq/L, 3% saline should be administered in a dose of 6 mL/kg over 1 to 2 hours, which should increase the serum sodium concentration by 5 mEq/L.

Hyperkalemia may be severe in the presence of acute renal failure and can be fatal if untreated. Accordingly, the potassium level should be monitored frequently and promptly treated if significantly elevated. However, before treatment, one must check to be certain that the specimen was not hemolyzed. If the potassium concentration is 7 mEq/L or less, it may be managed with cessation of potassium intake and administration of sodium polystyrene sulfonate (Kayexalate), which exchanges 1 mEq of potassium for 2 to 3 mEq of sodium. Sodium polystyrene sulfonate 1 g/kg body weight is mixed with 10% sorbitol or 10% dextrose in water (1 g/4 mL) and given rectally as a retention enema. It should be retained for 3 to 4 hours to have maximal effect. This dose of sodium polystyrene sulfonate should reduce serum potassium approximately by 1 mEq/L. Repeated doses of sodium polystyrene sulfonate may cause hypernatremia. If the serum potassium is greater than 7 mEq/L or ECG changes are present, more aggressive therapy is necessary. If only peaked T waves on the ECG are present, IV sodium bicarbonate 2 mEq/kg and sodium polystyrene sulfonate enemas may be used. If widening of the QRS complex is seen on ECG, 0.5 mL of 10% calcium gluconate should be given slowly intravenously, with constant ECG monitoring. It should be followed by sodium bicarbonate 2 to 3 mEq/kg. The duration of effect of these agents is short, and dialysis should be instituted. Another effective treatment is glucose 2 g/kg (administered as 25% dextrose) plus insulin 0.5 U/kg.

Metabolic acidosis usually is present in acute renal failure and may be managed with IV sodium bicarbonate 1 to 3 mEq to maintain the serum pH between 7.25 and 7.35.

Serum phosphorus and calcium may be abnormal in renal failure. The serum phosphorus concentration may be maintained within normal range by administering aluminum hydroxide 20 mg/kg per day three times daily orally to maintain a serum phosphorus level between 5 and 6 mg/dL. If hypocalcemia develops, 500 mg per day of calcium gluconate or carbonate should be started once the phosphorus concentration is normal and the gastrointestinal system allows normal intake. Intestinal absorption of calcium may be enhanced by using 0.1 to 0.4 mg per day of dihydrotachysterol.

The nutritional status of infants with renal failure is important because improved nutrition may diminish the

metabolic complications of renal failure. If the infant is able to tolerate feedings, breast milk is optimal, although PM 60/40 is satisfactory. If the infant is unable to tolerate enteral feedings, peripheral or central hyperalimentation should be used.

Indications for dialysis include severe fluid overload, hyperkalemia, electrolyte abnormalities that cannot be corrected medically, or severe central nervous system (CNS) depression secondary to uremia. Peritoneal dialysis generally is performed (82,298). The catheter may be placed at the bedside in the intensive care unit under sedation or general anesthesia.

Prognosis

The prognosis of infants with acute renal failure depends largely on the etiology. Chevalier and associates (86) reviewed 16 neonates with acute renal failure and determined significant prognostic factors. Nine had renal failure secondary to perinatal asphyxia, and three were secondary to congenital heart disease. Half were oliguric. All of the nonoliguric infants survived, whereas half of the oliguric patients died, usually from renal failure. Of the eight oliguric patients, the three that were anuric 3 days or less and had demonstrable renal perfusion by renal scan survived. In contrast, all four infants who had anuria 4 days or longer and had no perfusion on renal scan died. Thus anuria lasting 4 days or more and lack of visualization by renal scan are poor prognostic signs. Another adverse prognostic sign is significant prematurity. For example, Meeks and Sims reported 30 neonates with a mean gestational age of 31 weeks; mortality was 90%.

More recently, with improved neonatal intensive care unit (NICU) care, the prognosis for babies with acute renal failure seems improved, particularly if the baby is term (13,411).

Urinary Tract Infection

In the newborn, UTI often presents with symptoms and signs of sepsis, including fever (50%), weight loss (75%), and cyanosis (40%) (576). Other findings include a distended abdomen, jaundice, and symptoms referable to the CNS, such as irritability and seizures. Thus, if a newborn is not growing satisfactorily and seems ill, a UTI should be suspected. In a series of infants younger than 3 months of age with fever, 11% were secondary to UTI (302). In 75% of newborns, *Escherichia coli* is the etiologic agent, with *Klebsiella* accounting for approximately 10% (199).

In contrast to older age groups, between 70% and 80% of newborns with a UTI are boys (199). Beyond the neonatal period, the incidence of UTI in males drops considerably. The vast majority of newborn boys with symptomatic UTIs who do not have obstructive abnormalities are uncircumcised (199,577). Pathogenic bacterial organisms colonize the newborn prepuce (188), conferring a greater risk of UTI in uncircumcised boys until 3 to 6 months of age, when the foreskin usually begins to retract. In females, the highest incidence of UTI also is in the newborn period.

Diagnosis

The method of obtaining the urine specimen must be assessed before one decides that an infant has a UTI. For example, if a plastic bag is used to obtain the specimen, the genitalia must be washed thoroughly, the bag must be removed within a few minutes of voiding, and the urine either must be refrigerated or cultured immediately. Urine cultures obtained with a plastic bag are most informative if the culture is negative. If the culture from the plastic bag is a single organism with a colony count greater than 100,000/mL and the infant is symptomatic, a UTI may be presumed, as long as the specimen was obtained by the previous guidelines. The presence of significant pyuria also provides confirmation that the neonate has a UTI.

On the other hand, in asymptomatic infants or uncircumcised boys, if the culture grows a mixed group of organisms or the colony count is less than 100,000/mL, the urine specimen should be obtained in another manner. A catheterized specimen may be obtained by sterilely passing a 5- or 8-Fr pediatric feeding tube into the bladder. If a urethral abnormality or preputial contamination is suspected or if one has difficulty identifying the infant female urethra, a suprapubic aspirate (SPA) should be done (Fig. 46.31). Before an SPA is performed, the bladder should be palpable. In the newborn, the bladder is an abdominal organ, and it is relatively easy to obtain a suitable specimen to culture. An SPA should not be attempted if the bladder is not palpable because complications may result. The procedure is performed after cleaning the suprapubic area with an antiseptic solution. A 22-gauge needle then is inserted periappendicular to the lower abdominal wall in the midline one fingerbreadth above the pubic symphysis. A local anesthetic generally is not necessary.

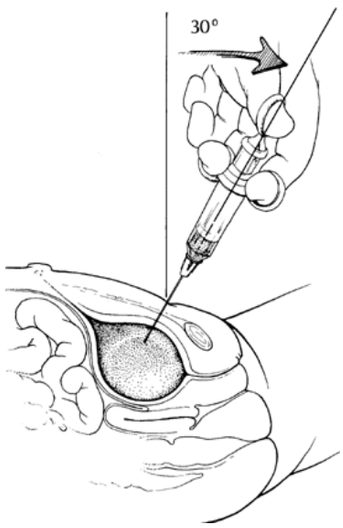

FIGURE 46.31. Suprapubic aspiration for collection of bladder urine with a full bladder. The needle is inserted 2 cm cephalad to the pubic symphysis perpendicular to the axis of the child.

Management

Because most neonates with a UTI have evidence of sepsis and broad-spectrum parenteral antibiotics are necessary, these children should be hospitalized. Generally, IV gentamicin and ampicillin are given until the culture and sensitivities are available. Fever and vomiting may increase the infant's fluid requirements substantially, and urine output must be monitored closely. IV antibiotics should be continued until the infant has been afebrile for 48 hours, at which time a suitable oral agent may be used. However, if the child has a positive blood culture as well, parenteral antibiotics may need to be given for a longer period. Because the newborn's renal function is

low, peak and trough aminoglycoside levels must be obtained regularly.

Two antimicrobial agents that are used commonly in older children and adults should not be used in the newborn. Trimethoprim-sulfamethoxazole is a combination medication that interferes with bacterial folic acid metabolism and in the newborn also may interfere with bilirubin excretion and cause jaundice. Nitrofurantoin interferes with the bacterial Krebs' cycle but is contraindicated in the newborn because of potential hepatotoxicity and a risk of hemolytic anemia.

If a newborn has a symptomatic UTI, he or she should continue to be given oral antibiotics until a radiographic evaluation has been obtained. This evaluation should include a VCUG to study the lower urinary tract and either a renal ultrasound, IVP, or renal scan, depending on the child's age and findings of the VCUG. The evaluation should be performed while the child is still in the hospital. An ultrasound does not provide sufficient visual evidence of the presence or absence of reflux (593).

A renal ultrasound should be used to study the upper urinary tracts and the bladder. If either the ultrasound or VCUG is abnormal, a renal scan should be obtained. The specific type of scan to order depends on whether reflux, hydronephrosis, a duplex collecting system, or PUV is identified (532).

In a study of 100 patients less than 8 months of age with a UTI, 45% of the girls and 7% of the boys had a urinary tract abnormality. The most common finding was VUR (199). In another study of newborns with UTIs, nearly half demonstrated varying degrees of reflux (44). Thus radiographic evaluation of these infants is important.

Even if reflux or an obstructive anomaly is not found, the child clearly is at risk for developing pyelonephritis. Because the kidneys are most likely to develop scarring secondary to reflux and infection during the first 2 years of life, a course of antimicrobial prophylaxis with nitrofurantoin or trimethoprim-sulfamethoxazole should be used until the child is at least 1 year old. In addition, a follow up IVP or DMSA scan should be performed at 1 year of age to detect renal scarring.

Adrenal Hemorrhage

Because of its large size and hypervascularity in the newborn, the adrenal gland is susceptible to spontaneous hemorrhage or to trauma with subsequent hemorrhage. Small unilateral or bilateral adrenal hemorrhage is a common finding at postmortem examination of infants and the incidence by ultrasonographic screening is 1.9 per 1,000 births (172), but clinically significant neonatal adrenal hemorrhage is much less common.

The relatively large size of the newborn adrenal glands, their hyperemia, and any condition that causes venous congestion or stasis within the adrenal tend to make the adrenal gland more susceptible to trauma (503). Traumatic delivery seems to be an important factor (503), but asphyxia, sepsis, hemorrhagic disorders, and hypoprothrombinemia also are predisposing conditions (286). Adrenal hemorrhage is reported to occur more commonly on the right side (53), probably because venous engorgement caused by temporary vena caval occlusion or compression is dampened by the renal vein on the left side, whereas the right adrenal vein drains directly into the vena cava. In approximately 10% of patients, the condition is bilateral.

Diagnosis

A triad of findings is usually present with adrenal hemorrhage: (a) flank mass (more than 85%), (b) jaundice (more than 80%), and (c) mild anemia (approximately 50%) (286). Jaundice is secondary to reabsorption of blood from the retroperitoneum and depends on the degree of hemorrhage and rapidity of reabsorption. Another presenting sign in boys may be scrotal hematoma, with blood from the adrenal bed dissecting along the fat tissue in the inguinal canal or through a patent processus vaginalis (255,359).

Most clinically significant cases become apparent by the time the patient is 1 week of age.

As in the diagnosis of many adrenal masses, ultrasound is extremely useful (Fig. 46.32). Usually, a well-defined echo-free area superior to an inferiorly displaced kidney is identified, but in other cases, the adrenal hemorrhage may have a solid appearance. If clots and necrotic tissue are present in the hemorrhagic area, a mixed pattern is encountered. The differential diagnosis includes congenital neuroblastoma, in which the adrenal gland has a solid appearance and demonstrates blood flow by power Doppler sonography, whereas blood flow will not be present in adrenal hemorrhage (123). Following complete liquefaction, the mass becomes completely echo free (402). Ultrasound is the best method to use to follow these infants because it demonstrates the progressive decrease in size and resolution of the hemorrhagic area, as well as subsequent calcification (402).

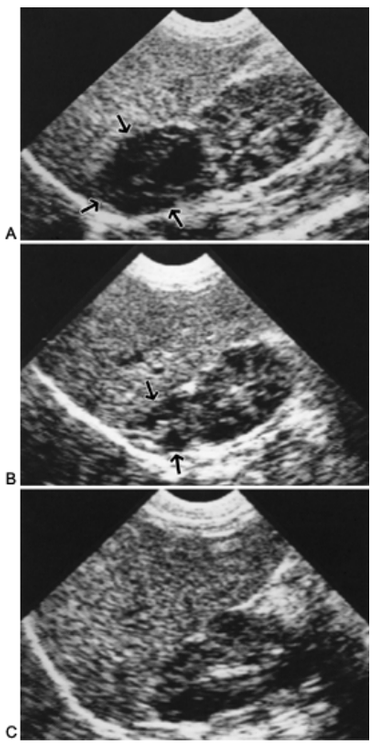

FIGURE 46.32. Patient at 17 days of age, ultrasound of adrenal hemorrhage. **A:** A 4.0-by-3.7-by-2.7-cm complex mass *(arrows)* in region of right adrenal gland. Echolucent areas suggest liquefaction. **B:** Patient at 1 month of age. The mass *(arrows)* has diminished in size, measuring 2.0 by 1.5 cm. **C:** Patient at 2 months of age. Adrenal gland is normal. Adrenal hemorrhage has resolved completely.

In addition to serial hematocrits, serum bilirubin, and abdominal ultrasound, other studies should be performed. Measurement of the 24-hour urinary excretion of vanillylmandelic acid, homovanillic acid, and catecholamines is important because an increase in these substances, particularly vanillylmandelic acid, is virtually diagnostic of neuroblastoma. In addition, a CT scan may demonstrate the lesion, confirm that it is not a neoplasm, and demonstrate that the ipsilateral kidney is functioning. Simultaneous RVT and idiopathic adrenal hemorrhage have a recognized association (314) and probably explain reports of nonvisualization of the kidney on IVP in a small proportion of infants with adrenal hemorrhage (286).

Management

In most patients, adrenal hemorrhage is self-limited, particularly when the hematoma remains intracapsular. Rarely, with extensive hemorrhage, capsular rupture with retroperitoneal bleeding may occur. Ultrasonography is useful in following resolution of the hematoma, and serial hematocrit and serum bilirubin levels should be obtained. The adrenal typically calcifies following adrenal hemorrhage. Calcification may occur as early as 7 days and usually may be visualized radiographically about 2 weeks after the hemorrhage. Initially, a thin rim of calcification is seen surrounding the mass. As reabsorption of the hematoma occurs, the calcified area condenses and takes the shape of the adrenal gland. In contrast, the calcification that frequently occurs in neuroblastoma typically is stippled throughout the mass.

Adrenal Abscess

An unusual complication of adrenal hemorrhage is adrenal abscess. Theories regarding the etiology of adrenal abscess have included (a) hematogenous bacterial seeding of a normal adrenal gland with subsequent abscess formation and (b) bacterial seeding of neonatal adrenal hemorrhage with formation of an abscess (195). In a review of reported cases of neonatal adrenal abscess, Atkinson and co-workers (24) found that maternal infection at the time of delivery and forceps or breech delivery were common. Clinical findings included palpable mass, fever, leukocytosis, and jaundice. Most cases have been diagnosed at 1 to 4 weeks of age.

Ultrasound has been extremely useful in demonstrating the character and extent of the abscess. The abscess is identified as a suprarenal fluid-filled mass, and layered debris is frequently noted with changes in position. The differential diagnosis includes an obstructed upper-pole duplication anomaly, adrenal hematoma or pseudocyst, upper-pole hydrocalyx, neuroblastoma with hemorrhage and necrosis, and cystic Wilms' tumor (24). Failure of a suspected adrenal hemorrhage to resolve or evidence of a gradual increase in the size of the mass with evidence of systemic disease should raise suspicion.

Ideally, the diagnosis can be made before the suppurative process extends to adjacent organs; in almost one-third of reported cases, the kidney has been removed (24). Treatment of a neonatal adrenal abscess consists of excision of the abscess, incision and drainage, or percutaneous aspiration and antibiotics (195,313).

Scrotal Mass

In most cases, a firm testicular mass in the newborn male represents testicular torsion. Anatomically, testicular torsion in the newborn is extravaginal with twisting of the entire spermatic cord (Fig. 46.33). In contrast, in pubertal boys, testicular torsion is intravaginal, that is, within the tunica vaginalis. In the perinatal period, extravaginal torsion is speculated to result from loose or absent connections between the gubernaculum and the scrotal wall.

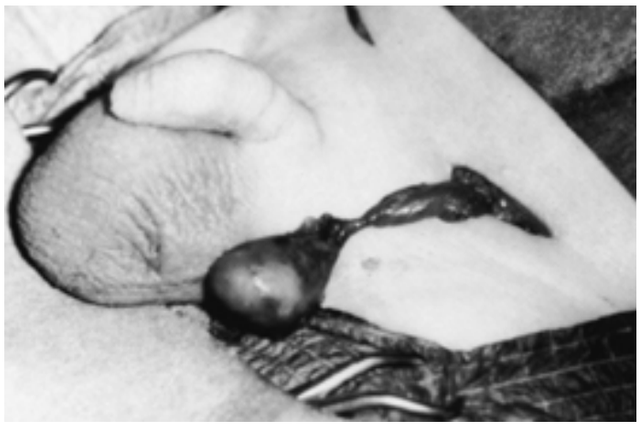

FIGURE 46.33. Neonatal extravaginal testicular torsion, left side. Inguinal approach is preferable.

In most neonates with testicular torsion, the event occurs *in utero.* Consequently, the mass is hard, is painless, and does not transilluminate. The scrotal skin may be discolored and edematous.

Other diagnoses to consider include scrotal hematoma (which could be secondary to adrenal hemorrhage), incarcerated inguinal hernia, testis tumor, idiopathic testicular infarction, meconium peritonitis, and testicular strangulation secondary to an inguinal hernia. If the scrotal swelling transilluminates, it usually represents either a hydrocele or, less commonly, an inguinal hernia. The other diagnosis of concern in the newborn is testicular tumor (319). However, testicular neoplasms are extremely rare in the neonate, and most are benign lesions. Given these considerations, the diagnosis of testicular torsion in the newborn usually is straightforward, but imaging is recommended. Color Doppler ultrasound demonstrates an inhomogeneously hypoechoic testis surrounded by a slightly echogenic rim with absent intratesticular blood flow (29,78,523).

Whether to perform immediate or even elective surgical exploration is controversial. The likelihood of salvaging a torsed testis that is detected at delivery is remote. Nevertheless, there is a significant risk that the contralateral testis may undergo extravaginal torsion, and this risk is present until at least 8 weeks beyond term (69). However, the long-term risk for contralateral intravaginal torsion seems low. In a survey of 67 pediatric surgeons and urologists in Great Britain, only 6 cases of torsion of a solitary testis were identified (363). Another possible long-term complication of leaving an atrophic neonatal testis in place is the risk of antisperm antibody formation, but there is no evidence that a newborn necrotic testis stimulates such antibody formation.

We are not aware of any cases of testicular torsion discovered at delivery that have been salvaged. Consequently, we do not advocate routine immediate surgical exploration in which unilateral testicular torsion is recognized at delivery.

Because the main risk of unilateral testicular torsion noted at birth is the chance of contralateral extravaginal torsion (99), one should perform prompt exploration of the involved side to establish the diagnosis and then pex the contralateral normal testis, or advise the parents of the issues and have them monitor the scrotal appearance closely for the first 2 to 3 months of life for signs of contralateral torsion. If the baby is healthy and pediatric anesthesia coverage is available, prompt elective exploration of the involved side is recommended, and assuming torsion is found, contralateral scrotal orchiopexy is advocated (141,407). This form of management was advocated in a survey of pediatric urologists.

Whether to perform testicular exploration through the inguinal canal or scrotum is controversial. The inguinal approach allows definitive treatment if a hernia or hydrocele needs correction or radical orchiectomy if a tumor is encountered. For most cases, a scrotal approach is satisfactory. For contralateral scrotal orchiopexy, suture fixation of the testis is not advised. Instead, placing the testis in a dartos pouch will provide optimal permanent fixation and avoid the risk of damage to the testis from a suture. A transverse scrotal incision should be made, a dartos pouch created, and then the tunica vaginalis opened and the testis placed in the dartos pouch.

Ascites

Ascites refers to an abnormal accumulation of fluid in the peritoneal cavity. In the neonate, ascites are uncommon

and typically are secondary to extravasation from the urinary tract, accounting for 25% of cases. Other causes of neonatal ascites include gastrointestinal disorders (e.g., bowel obstruction), cardiac disease, liver disease, toxoplasmosis, ovarian cyst, and chylous ascites. In addition, ascites has been observed in association with persistent cloaca in girls secondary to intraperitoneal reflux through the genital system (6). In 15% of patients, the diagnosis is unknown (218).

As many as 70% of newborns with urinary ascites have PUV (483) (Fig. 46.29). Other etiologies include urethral atresia, VUR, neurogenic bladder, ureterocele, ureteral stenosis, and bladder perforation (218,541). In most patients with urinary ascites, the site of extravasation is unknown. When extravasation from a fornix or the renal pelvis occurs, urine may accumulate within the retroperitoneum with subsequent rupture into the peritoneum. In other patients, there may be rupture of the distended pelvis directly into the peritoneal cavity. In cases of bladder perforation, the dome of the bladder ruptures into the peritoneal cavity.

Earlier reviews emphasized the significant mortality associated with urinary ascites, as high as 70% (218,483). More recently, with improved neonatal care, mortality has been considerably lower, now reported at approximately 12% (215).

In some neonates with ascites, the condition may not be evident until 1 or 2 weeks of age. In such patients, poor feeding, vomiting, and progressive abdominal distention are reported.

In most cases, neonates with ascites should be evaluated initially by abdominal ultrasound, which confirms the presence of ascitic fluid and may demonstrate dilation of the upper urinary tracts or a distended, thick-walled bladder in the presence of obstructive uropathy. However, if the kidneys are decompressed because of forniceal rupture, the dilation may be minimal. A VCUG should be performed to determine whether PUV are present, to aid in detecting whether the site of extravasation is the bladder, and to detect reflux. A peritoneal tap may be necessary, particularly if severe abdominal distention is present or if respiratory function is compromised. In other cases, it is performed for diagnostic purposes. In patients with urinary ascites, one would expect to find an elevated BUN concentration and creatinine in the ascitic fluid. However, because the ascites equilibrate with serum rapidly, it is not a valid study. Because of their ineffective excretion, serum BUN concentration and creatinine usually are elevated.

Management

Parenteral antibiotics should be instituted. Following stabilization of the infant, adequate urinary diversion should lead to resolution of the ascites, because the reduced pressure on the upper urinary tracts will allow the leak to close. An 8-Fr pediatric feeding tube placed into the bladder should achieve this. If it does not, cutaneous vesicostomy or possibly even cutaneous pyelostomy may be necessary. Once the child has been stabilized sufficiently, operative ablation of the valves may proceed.

Urinary ascites may be secondary to a problem other than urethral valves. For example, a ruptured bladder is present in 25% of newborns with urinary ascites. Although the most common cause is urethral valves, it also may be secondary to neurogenic bladder (341) or iatrogenic during umbilical artery cutdown (241,430). In nearly all patients, it has been discovered within the first day or two of life. Management has consisted of suprapubic cystostomy or cutaneous vesicostomy, with a survival rate of 94% (541).

Ultimately, many have surprisingly normal-appearing upper urinary tracts (215,397). The upper or lower leak from the urinary tract seems to act as a pop-off valve and allows renal development to proceed more normally (443).

Related to urinary ascites is the *isolated perirenal urinoma* (Fig. 46.34). In some patients, it is secondary to urethral valves, whereas in others, it is secondary to UPJ obstruction. Interestingly, when the urinoma is contained within Gerota's fascia, the kidney usually is severely dysplastic. Presumably, severe obstruction has occurred, and if the leaking urine is contained within Gerota's fascia, there is insufficient decompression of the urinary tract to allow satisfactory renal development. When this condition occurs bilaterally in the absence of ascites, the outcome is always fatal.

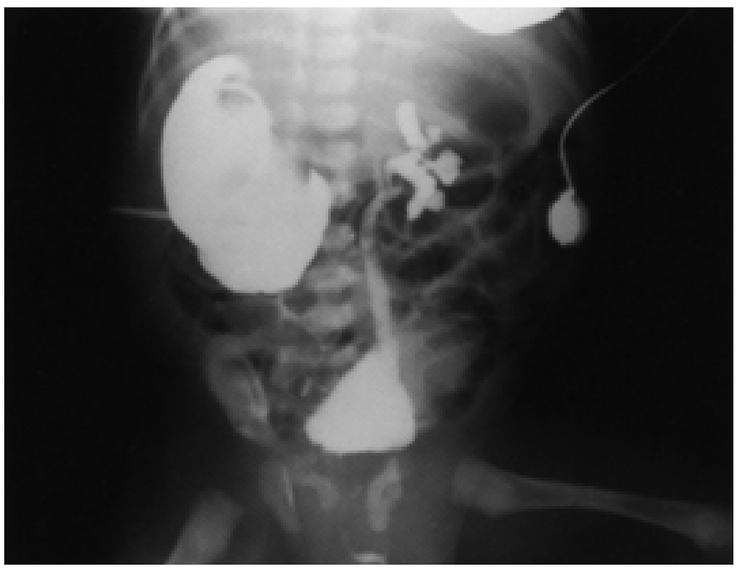

FIGURE 46.34. Neonate with right perirenal urinoma secondary to posterior urethral valves. Simultaneous cystogram shows left vesicoureteral reflux.

Vesicoureteral Reflux

Some neonates with medium- and high-grade vesicoureteral reflux are detected by the finding of hydronephrosis on prenatal sonography (156). Approximately 80% of such patients are boys (156,170). The male predominance is

thought to be secondary to transient urethral valvelike urethral obstruction *in utero* that resolves before birth (27). The high intravesical pressures generated seem to destabilize the UVJ. Infants with reflux have had abnormal urodynamic patterns including low bladder capacity in combination with extremely high detrusor pressure levels (hypercontractility) and high-capacity bladder with normal or low detrusor pressure levels (496,497).

A complication of bilateral high-grade reflux is the *megacystis-megaureter syndrome* (68,338) (Fig. 46.35). This syndrome primarily affects boys. Most of the voided urine refluxes into the upper urinary tracts, resulting in a weak urinary stream, a large bladder, and significant residual urine mimicking bladder outlet obstruction. However, the bladder is smooth walled, and no obstructive component is demonstrated on VCUG. This pattern of constant recycling of large volumes of refluxing urine has been termed *aberrant micturition.* Ureteral reimplantation with tapering is necessary to correct the condition, although cutaneous vesicostomy is a temporizing procedure that may allow the ureters to diminish in caliber, which may facilitate later ureteral reimplantation (Fig. 46.36). Reduction cystoplasty is not necessary or effective.

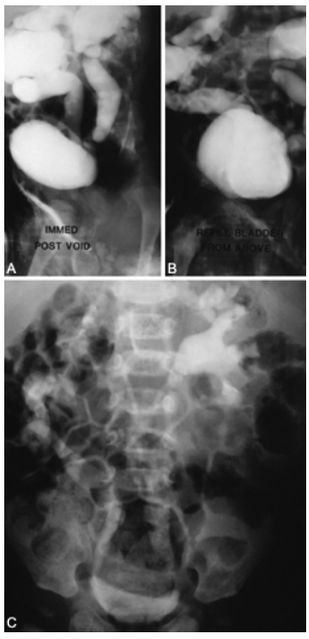

FIGURE 46.35. Newborn with bilateral grade V reflux and congenital heart disease. **A:** Voiding cystourethrogram demonstrating severe reflux. The infant was placed on a program of clean intermittent catheterization to decompress the upper urinary tracts during recovery from corrective heart surgery. **B:** Intravenous pyelogram 6 weeks after bilateral transtrigonal ureteral reimplantation. Tapering was not necessary.

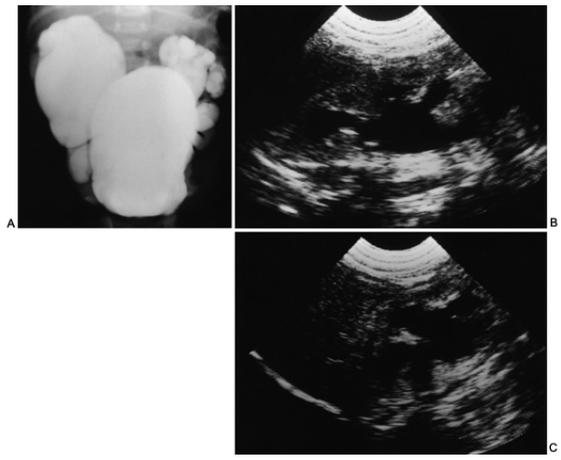

FIGURE 46.36. Newborn with distended abdomen and renal insufficiency. **A:** Voiding cystourethrogram shows huge smooth-walled bladder with bilateral grade V reflux, the typical picture of megacystis-megaureter syndrome. **B, C:** Following cutaneous vesicostomy, renal function improved, with serum creatinine clearance dropping to 0.7 mg/dL. Ultrasound at 9 months of age shows nicely decompressed upper urinary tracts. Cortex is quite thin. **B:** Left kidney. **C:** Right kidney.

If the neonate has grade III or higher reflux, consideration should be given to obtaining a DMSA renal scan to determine the baseline differential renal function. Often, the affected kidney shows significant reduction in differential renal function, even though no infection has occurred (410).

Initially, neonates with reflux are usually managed medically. They are placed on antimicrobial prophylaxis with amoxicillin or cephalexin for 2 months and then switched to trimethoprim-sulfamethoxazole or nitrofurantoin. Circumcision is recommended for male neonates to decrease the risk of UTIs (243). They undergo a follow-up sonogram every 6 to 12 months and follow-up cystography every 12 to 18 months.

Neonates with reflux are more likely to show spontaneous resolution than older children with similar reflux grades. For example, 20% to 35% of ureters with grade IV and V reflux have reflux resolution with 2 years (57,170,243). However, as many as 25% have a breakthrough UTI, and ureteroneocystostomy is recommended in these cases (214). The success rate for surgical correction of reflux in infants can be high (321,546). Although these patients have been reported to have abnormal urodynamic patterns, late follow-up of operated patients demonstrates that nearly all have a normal voiding pattern and bladder capacity (546).

Other Neonatal Urologic Conditions

Megacystis-microcolon-intestinal hypoperistalsis syndrome was described in 1976 (43). The condition is characterized by abdominal distention, lax abdominal musculature, a huge bladder, incomplete intestinal rotation, bilious vomiting, and diminished or absent intestinal peristalsis. Approximately 80% of patients are female (429). All patients have microcolon and small bowel dilation. The cause of this condition is unknown. Unfortunately, some infants die within the first few years of life because of an inability to obtain sufficient nutrition through their abnormal gastrointestinal tracts. VUR usually is present, but it generally is low

or moderate in grade. Bladder emptying may be ineffective, and clean intermittent catheterization may be necessary to ensure vesical drainage.

A nonlethal variant of this syndrome has been termed *chronic intestinal pseudoobstruction*, *hollow visceral myopathy*, and *pseudo-Hirschsprung's disease*, in which there is megacystis and colonic dilation without aganglionosis. In this disorder, there is a slight male predominance, usually there is poor bladder emptying and many have hydronephrosis (193,211). In a report of 24 patients, 9 patients died from extensive gastrointestinal involvement, and of the remaining 15, all but 1 were performing clean intermittent catheterization or had a cutaneous vesicostomy (193).

Prune-belly syndrome probably represents a transient congenital urethral membrane obstruction at 8 to 10 weeks of gestation, resulting in severe dilation of the upper urinary tract. The urethra recanalizes and decompresses the system, leaving the stigmata of prune-belly syndrome, with a severely dilated bladder and upper urinary tract, bilateral cryptorchism, and the characteristic wrinkled abdomen. Some of these neonates have severe renal dysplasia and associated pulmonary hypoplasia. The prognosis probably depends on how soon the urethra recanalizes.

The newborn with *classic bladder exstrophy* usually is otherwise healthy and has normal renal function. Associated anomalies of other organ systems are uncommon. We believe that primary closure within 48 hours of birth is ideal in nearly all cases because the bony pelvis usually can be brought together anteriorly without the need for iliac osteotomies because of residual circulating maternal relaxin. Early closure is recommended even if the bladder is small.

In contrast, *cloacal exstrophy* represents the most devastating urologic congenital anomaly. These infants are likely to

have anomalous upper urinary tracts and defects in the spine and gastrointestinal tract.

Hypertension in a premature infant affects as many as 0.8% of babies and is most common in babies with bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage, or an indwelling umbilical artery catheter. In term babies, hypertension is much less common and is most often secondary to a renovascular abnormality or renal parenchymal disease (181). The blood pressure varies with gestational age at birth and weight (594). In the normal term male newborn, blood pressure is 72 mm Hg systolic and 47 mm Hg diastolic and the ninety-fifth percentile is 92/72 mm Hg. The blood pressure tends to be lower in female neonates. The most common etiologies are coarctation of the aorta and *renal artery thrombosis* secondary to umbilical artery catheter complication. Causes of urologic significance that may be encountered in the newborn include renal artery stenosis, RVT, polycystic kidney disease, MCDK, UPJ obstruction, mesoblastic nephroma, and the 11-hydroxylase deficiency form of CAH (35,181,361). Initial evaluation includes serum electrolytes, BUN, creatinine, calcium, plasma renin, complete blood count and platelet count, urinalysis, chest radiograph, and renal sonogram with Doppler. In select cases with a urologic etiology, renal scintigraphy is necessary. In patients who are resistant to medical therapy, the cause is often surgically correctable (426).

Micropenis is a small penis that is structurally normal but more than 2.5 standard deviations below the mean in stretched penile length (4). In a term newborn, the critical length is 2.5 cm. Many of these patients have a cerebral abnormality involving the hypothalamic-pituitary axis. Early evaluation of the etiology followed by testosterone stimulation should be performed (155). In the past, if no demonstrable penile growth occurred with androgen stimulation, gender reassignment was often recommended. However, this philosophy is currently being reconsidered (431).

Circumcision

In pediatrics, few topics generate as much controversy as whether a newborn male should undergo circumcision, mostly because indications for neonatal circumcision have been obscured by factors such as cultural prejudices; parental preferences; presumption about medical necessity and health benefits; physicians' biases; and aesthetic choices of the family, physician, and society (456). Although it is the most common surgical procedure performed in the United States, circumcision is seldom performed in European countries, China, and South America.

It has been estimated that approximately one-sixth of the world's population practices circumcision for religious reasons (85,374). The practice goes back to as early as 2300 B.C. in Egypt, and it has been suggested that it may have derived from the practice of mutilating prisoners of war while retaining them capable of laboring as slaves (70).

Circumcision as a means of preventing disease was strengthened by the two World Wars and the increased belief in the United States, Canada, and Australia that circumcision provided an additional measure of hygiene (191). By the 1960s, the indications for neonatal circumcision came under increased scrutiny and three reports by the Task Force of Neonatal Circumcision from the American Academy of Pediatrics (AAP) have tried to define guidelines for the procedure. In 1975, the conclusion was that routine neonatal circumcision had no valid medical indications. However, in 1989, as several published reports had suggested that uncircumcised infants were at increased risk for UTI, the AAP concluded that “newborn circumcision has potential medical advantages, as well as disadvantages and risks. When circumcision is being considered, the benefits and risks should be explained to the parents and informed consent obtained” (2). In 1999, the AAP updated its policy statement (1). Its position was essentially unchanged, with the exception that it emphasized the importance of local anesthesia for the procedure.

There are several nonreligious justifications supporting neonatal circumcision to ensure good hygiene. These include the prevention of UTI, penile cancer, venereal diseases, cervical cancer, and phimosis, as well as lessening the risk of balanoposthitis.

Reports linking the presence of an intact foreskin and UTIs in the first 6 months of life have been responsible for the resurgence of the sentiment in favor of neonatal circumcision. Subsequently, epidemiologic studies have shown a tenfold increase in the incidence of UTIs among uncircumcised male infants, and a higher risk of serious sequelae, such as bacteriemia and meningitis (199,579). The increased risk of UTI is presumed to be secondary to the presence of uropathogens under the prepuce (578). There was also an increased risk for UTIs in prepubertal males (111) and young adult uncircumcised males (median age of 30) (508). Although uncircumcised boys are at increased risk for UTIs, routine neonatal circumcision may prevent UTIs in only 1% to 2% of all newborn males.

Squamous cell carcinoma of the penis is extremely rare in males circumcised at birth (476). Penile cancer occurs much more frequently in areas where circumcision is not practiced and poor hygiene is prevalent. For example, in Brazil, the rate of penile cancer is ten times higher in poor regions as compared with the more developed parts of the country. The incidence of penile cancer in the United States is reported to be between 0 and 2.1 per 100,000, representing less than 1% of all cancers in men (559). This incidence is similar to that of Denmark (1.1 per 100,000) and Japan (0.3 per 100,000), countries where neonatal circumcision is not practiced routinely.

Whether circumcision reduces the risk of sexually transmitted diseases (STDs) has been controversial. An increased

risk has been attributed to minor frenular injuries during intercourse and to the larger surface area of the penis in uncircumcised men. In some studies, however, an increased incidence of STDs in uncircumcised men has been attributed to demographic factors. Nevertheless, in a recent report, Lavreys and associates (311) studied 746 HIV-1–seronegative men and found that uncircumcised men were 4 times more likely to become HIV-1 positive and 2.5 times more likely to develop genital ulcers compared with circumcised men. However, there was not an increased incidence of genital warts in uncircumcised men. Other studies have achieved with similar findings (475).

Because circumcision is so prevalent in the United States, education regarding hygiene of the uncircumcised penis has lapsed, and benign neglect may have contributed to an increased rate of balanoposthitis and phimosis in boys who have not been properly instructed to retract their foreskin and wash their penis. A better understanding of the relationship between glans and prepuce can help illustrate the care of the uncircumcised penis. In the newborn, physiologic adhesions of the inner aspect of the prepuce to the glans prevent retraction and serve to protect the glans. Desquamated cells may accumulate and form smegma beads, which are benign.

If circumcision is carried out, a careful review of the potential complications should be given to the parents and informed consent obtained (230). Various instruments and procedures can be used, including a Gomco clamp, Bronstein or Mogen clamp, and Plastibell (456). None have a significant advantage over the others.

When neonatal circumcision is performed, local anesthesia is recommended. Available options include the topical application of a cream containing eutectic mixture of local anesthetic cream (lidocaine and prilocaine; EMLA), dorsal penile nerve block, and a penile ring block (227,288). Randomized controlled trials have demonstrated that a dorsal penile nerve block is more effective than EMLA cream (253,529). In addition, the prilocaine in EMLA cream poses a risk for methemoglobinemia (100), although the risk is quite low. Consequently, a dorsal penile nerve block or ring block at the base of the penis with 1% lidocaine is preferred.

Circumcision should not be performed in neonates with hypospadias, chordee without hypospadias, a dorsal hood deformity, a webbed penis, or a small penis. In addition, many neonates with a large hydrocele or hernia are more likely to develop secondary phimosis and a buried penis if circumcision is performed. In a report by Williams and others (572), 8% of boys referred for initial circumcision had an inconspicuous or hidden penis.

The complication rate after circumcision ranges between 0.2% and 3% (36,89). Immediate complications include pain, hemorrhage, removal of insufficient or excessive penile skin, trapped penis from scarring of the skin edges over the glans, infection, and urinary retention from a tight bandage. Late complications include meatal stenosis, which may require meatoplasty; formation of a synechia or skin bridge between the residual prepuce and glans; chordee; inclusion cyst at the circumcision line; urethrocutaneous fistula; removal of a portion of the glans; and slough of a portion or the entire penis from excessive use of cautery. Recently, the U.S. Food and Drug Administration (FDA) issued a warning regarding malfunction of some Gomco and Mogen clamps that had resulted in 105 circumcision injuries between 1996 and 2000 (171).

Bleeding usually results from oozing from the frenulum or occasionally from a large arterial or venous vessel on the penile shaft. Bleeding usually can be controlled with compression, but occasionally, cautery with a silver nitrate stick or ophthalmic cautery is necessary; in some cases, hemorrhage must be controlled with a suture. If cautery is used, ventrally one must be careful not to injure the urethra. Wound infection is rare and usually is prevented by applying antibiotic ointment to the circumcision wound. Another potential complication is severe penile vasoconstriction secondary to inadvertent injection of concentrated epinephrine instead of lidocaine. Treatment of this unusual problem is either local infiltration with 0.4 mg of phentolamine or insertion of a caudal catheter to induce a sympathetic block (7).

Many of the other problems with healing can be managed in the office if the baby is seen 2 or 3 weeks after the circumcision. Filmy penile adhesions are common and have been reported to be present in 71% of infants, 30% of 1- to 5-year-olds, and 2% of children older than 9 years of age (413,547). These adhesions usually cause no problems and will come apart on their own over time. Occasionally, epithelial debris will accumulate and helps separate the adhesion. In some cases, dense skin bridges form between the penile shaft and glans—these will never come apart and need to be excised. This procedure can be performed as an office procedure under local anesthesia, or if the adhesions are extensive, excision under general anesthesia is necessary. If too much penile shaft skin is removed, application of antibiotic ointment and adherent gauze to the open wound usually yield a satisfactory result. Typically, most of the skin will grow back and bridge the defect. Immediate skin grafting rarely is necessary and may result in a disfigured penis and graft site. In addition, suturing the skin edges together to bridge the gap is not recommended because the penile shaft may end up with insufficient skin. If too much skin is left, revision of circumcision may need to be considered. In some babies, the penis retracts into the suprapubic fat pad or scrotum. This situation is most common if the baby had a large hydrocele or hernia or in babies born with a webbed penis. A cicatricial scar may result, resulting in a trapped penis, which can cause urinary retention and/or UTI in the most severe cases. If this situation is recognized early, the cicatrix may be opened bluntly in the office. Alternatively, application of a topical corticosteroid cream

may loosen the scar tissue. If the problem is not corrected satisfactorily, correction of hidden penis under anesthesia will be necessary when the child is older.

The most serious circumcision complications include urethral injury and removal of part of the glans or part or all of the penile shaft. Partial glans removal has been reported to occur with a Mogen clamp; in these cases, the excised tissue should be preserved and immediately sutured back to the penis (492). A microscopic repair is unnecessary. When repair is performed within 8 hours of the injury, most penises heal nicely. In extremely rare cases, penile necrosis may result from thermal injury. One way a thermal injury can occur is if a metal clamp is applied to the foreskin and the cautery is used to excise the foreskin; if the cautery comes into contact with the metal clamp, an electrical/thermal injury to the shaft can result. Thermal injury to the penis also can result from inappropriate use of the YAG (yttrium-aluminum-garnet) contact laser in performing a circumcision. When an ablative penile injury occurs, the optimal therapy is unresolved at this time. One option is to reassign the baby to a female gender and perform bilateral orchiectomy (61). Unfortunately, these children may grow up with a male identity, presumably from androgen imprinting *in utero* and shortly after birth (132,133,431). On the other hand, current efforts for penile reconstruction in such cases have suboptimal cosmetic and functional results. These cases should be referred immediately to a tertiary center with a team approach including pediatric urology, endocrinology, plastic surgery, child psychiatry, and ethics for definitive management.

UROLOGIC PROBLEMS IN THE NEONATAL INTENSIVE CARE UNIT

Part of "46 - PERINATAL UROLOGY "

Candidiasis

With improvement in the respiratory, nutritional, and antimicrobial management of preterm infants, increasing numbers of extremely premature neonates are surviving. However, these neonates often are intubated for weeks and receive long-term IV hyperalimentation with the resultant risk of bacterial superinfection.

As many as 40% of nosocomial UTIs that develop in NICUs are secondary to *Candida* (405). Nearly all infants who develop renal candidiasis have a variety of predisposing features, including treatment with broad-spectrum antibiotics and prolonged fluid therapy with central or peripheral (or both) intravascular catheters or needles. Approximately half weigh less than 1,500 g at birth. The most common clinical manifestation is the development of oliguria or anuria, which occurs in 85% of patients. Physical findings also may include hypertension, a palpable flank mass or abdominal distention, and subcutaneous abscesses. The serum creatinine often is elevated.

The diagnosis is made by urine culture obtained by suprapubic bladder tap or percutaneous renal aspiration. Renal candidiasis is confirmed by the presence of more than 10,000 colonies of *Candida albicans* per milliliter of urine, isolating *Candida* in the sediment obtained from 10 mL of suprapubic urine centrifuged for 3 minutes at 3,000 rpm, or growth of *Candida* in urine obtained from the kidney.

Early in the disease course of systemic candidiasis, the urine culture may be positive, although the blood cultures may be negative. In such cases, primary renal candidiasis is excluded by the absence of pathologic changes on renal ultrasonography and by the presence of *Candida* from other sources, such as the endotracheal tube or IV catheter. A positive urine culture for *Candida* should prompt an arterial (not venous) blood culture, followed by antifungal therapy. Systemic candidiasis can be detected early and possibly avoided by routine urine cultures by suprapubic bladder aspiration in the neonatal intensive care unit (ICU). With current antifungal therapy, few infants die from either systemic candidiasis or its treatment, but rather from complications of its predisposing factors.

Radiographic evaluation may demonstrate unilateral or bilateral hydronephrosis associated with an intrapelvic filling defect that represents a fungal ball. Renal scan generally demonstrates that the involved kidney or kidneys exhibit poor function.

The treatment of renal candidiasis involves IV antifungal therapy in conjunction with local instillation of antifungal agents, surgical removal of the fungal balls, or both. At present, 5-flucytosine and amphotericin B are the drugs of choice for primary IV therapy. When used in combination, these drugs are synergistic and prevent the emergence of a resistant strain. An adverse effect of 5-flucytosine is bone marrow suppression, and amphotericin B may cause nephrotoxicity, hypotension, and thrombocytopenia; however, amphotericin B has been reported to have less toxicity in very-low-birth-weight infants (287). The latter drug has been well tolerated in infants by gradually increasing the dosage of 0.25 to 1.0 mg/kg per day. Furthermore, by combining these two agents, the therapeutic doses of the individual drugs are smaller, diminishing the risk of toxic effect (242). The imidazole derivatives miconazole and ketoconazole, which have been used to treat fungal infections in adults, have not been used widely in the treatment of infant renal candidiasis.

IV antifungal therapy may be necessary for 4 to 6 weeks. In general, the endpoint of therapy is the inability to isolate *C. albicans* from specimens of urine sediment obtained 1 week apart. Alternatively, the *Candida* antigen mannin may be found in the sera of patients with disseminated candidiasis (477). If mannin is detected, antifungal therapy should be continued until the antigen is no longer detected. For persistent candidemia, fluconazole has been reported to be effective (448).

When a large fungal ball is present, medical management

often is not sufficient. Most cases will require a percutaneous nephrostomy to be placed in the involved kidney so that irrigation with a solution of amphotericin B (1 mg in 100 mL of normal saline daily) may be performed. The irrigant provides a high concentration of antifungal agent, allows the bezoar to dissolve gradually, and provides a flushing effect. Percutaneous removal of the fungal ball may be achieved under anesthesia. Alternatively, open surgical removal of the bezoar or nephrectomy may be necessary.

Nephrolithiasis

One of the more common urologic problems encountered now with the improved care of the premature neonate is the development of renal calcifications secondary to furosemide administration (198,378). The overall incidence of nephrolithiasis in infants treated in the NICU is approximately 2.5% (198) and was 11% in those weighing 1,250 g or less (198). Furosemide is used extensively in the management of infants with patent ductus arteriosus and to mobilize interstitial water in respiratory distress syndrome secondary to bronchopulmonary dysplasia; it results in substantial hypercalciuria. Filtered calcium, in large part, is resorbed in the proximal tubule in the loop of Henle. Furosemide further increases the excretion of calcium, as well as sodium and potassium.

The development of urolithiasis in these preterm infants appears to be multifactorial: (a) high dosages of furosemide necessary to control the bronchopulmonary dysplasia, (b) prolonged half-life of furosemide in premature infants, and (c) development of secondary hyperparathyroidism. Other contributing factors include excessive calcium intake, phosphate depletion, chronic corticosteroid therapy, distal renal tubular acidosis, excessive glucose intake, and immobilization. Furthermore, nephrocalcinosis is more common in low-birth-weight neonates with a family history of stone disease and in white neonates (284).

Essentially all of the reported infants developing renal calcifications or calculi have received furosemide 2 mg/kg per day or more for at least 2 weeks, with a mean duration of therapy of approximately 4 weeks before calcification was noted. Many of the affected infants have received furosemide at dosages substantially higher than 2 mg/kg per day. Importantly, long-term use of furosemide in the premature infant is associated with ototoxicity and secondary hyperparathyroidism (198).

The half-life of furosemide in the premature infant is prolonged. In the normal adult, the plasma half-life of the drug is between 33 and 100 minutes, compared with values between 4 and 44 hours in neonates. In adults, slightly more than half of total plasma clearance of furosemide is accounted for by renal clearance, with the remainder excreted through the biliary and intestinal tracts. However, in the premature infant, the GFR is low, hepatic function is immature, and furosemide is excreted unchanged almost entirely in the urine (543). Thus the prolonged half-life of furosemide also contributes to the development of hypercalciuria.

All of the infants who developed nephrolithiasis had a gestational age of 34 weeks or less at birth. In these preterm infants with stone disease, the spot urine calcium-to-urine creatinine concentration ratio (mg/mg) has been significantly elevated, greater than 3.0 (normal is less than 1.24) (379). The total urinary excretion of calcium has varied from 15 to 30 mg/kg per day of calcium compared with a normal level of less than 4 mg/kg per day of calcium.

Most of the infants developing nephrolithiasis have been asymptomatic, although in one series, 6 of 10 had a UTI and 3 had associated sepsis. It is likely that the infections were related to colonization of the catheterized urinary tract.

Preterm infants in ICUs often have frequent radiographic evaluation, and the renal calculi may be detected by a careful radiologist. At times, the stones may continue to grow undetected, and a few staghorn calculi have been reported. In patients with suspected renal calculi, ultrasonography will provide confirmation of the suspected diagnosis and may demonstrate other areas of nephrocalcinosis.

The treatment of renal calculi in these infants generally is nonoperative. Administration of 20 mg/kg per day of chlorothiazide concurrently with furosemide has resulted in radiographic diminution or disappearance of most calculi. A few infants have undergone early surgical removal of the calculus. Extracorporeal shock wave lithotripsy has been used in only a few of these patients.

The mortality rate has been high because of the severity of the bronchopulmonary dysplasia. Postmortem examination of affected kidneys has demonstrated the calculi to be composed of calcium oxalate and calcium phosphate. In general, the microscopic renal involvement is bilateral, even if only one side is involved on x-ray film. Calcium deposits have been found in the collecting tubules and interstitial areas of the renal papillae. Ezzedeen and co-workers (169) reported on the follow-up between 9 and 56 months of nine neonates with renal calcification. Total resolution was noted in four patients and improvement in one with medical management. Renal length was normal in 17 of 18 kidneys, but GFR was reduced in four patients. The need for continued urologic management in such patients is apparent.

The differential diagnosis of intrarenal calcification in the premature infant is limited. In addition to renal calculi, renal calcification following renal cortical necrosis and RVT has been reported. In renal cortical necrosis, peripheral linear calcifications are found, whereas following RVT, lacelike and reticular calcifications are suggestive of an intravascular location (198). Nephrocalcinosis in association with metabolic disorders, such as primary hyperoxaluria, has not been reported in infants younger than 2 months of age.

In summary, the urologist should recognize that preterm infants are at risk for the development of renal calculi when they are receiving high dosages of furosemide and that, in

most cases, the problem may be managed by administration of concurrent chlorothiazide.

Umbilical Artery Catheter Complications

Another condition of urologic significance related to improved intensive care management of premature neonates is complications of umbilical artery catheterization. These catheters have been used for more than 20 years and have become standard in the treatment of sick newborn infants. Usual indications include the need to gain arterial access for reliable monitoring and blood pressure, frequent blood sampling for blood gas and pH values, exchange transfusion, cardiac catheterization, and infusion of fluid and nutrients. It is estimated that approximately 2% of all infants have an umbilical artery catheter. Until recently, polyvinyl chloride catheters impregnated with barium in sizes 3.5 and 5 Fr have been used. The overall incidence of major complications is approximately 3% (524).

Small infants appear to be at greater risk for thrombotic complications from an umbilical artery than larger infants, but the size of the catheter does not appear to play a role. The level of catheter placement is controversial. Although catheters placed at the level of the thoracic aorta have a significantly lower incidence of complications, when complications do occur, they tend to be much more devastating.

One of the most serious complications associated with the use of such catheters is occlusion of the distal aorta secondary to thrombosis. The diagnosis is suggested by the development of congestive heart failure, hypertension, and lower limb ischemia. Involvement of one or both renal arteries is suggested by the development of anuria. Often, patients have had demonstrable low-flow states, hypoxia, hypercoagulable states, and sepsis. Placement of the umbilical artery catheter below the thoracic aorta and frequent replacement or manipulation predispose to thrombosis. Persistent hypertension in infants with aortic thrombosis strongly suggests renal involvement and must be managed aggressively.

Other umbilical artery catheter complications of urologic significance include vesicoumbilical fistula (554) and urinary ascites (137,552).

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47

ANOMALIES OF THE KIDNEY

Stephen A. Koff

Khaled H. Mutabagani

S.A. Koff: Department of Surgery, The Ohio State University College of Medicine and Public Health, Columbus, OH 43210; Section of Pediatric Urology, Children's Hospital, Columbus, OH 43205.

K.H. Mutabagani: Department of Physiology, King Abdul Aziz University College; Department of Surgery, New Jeddah Clinic Hospital, Jeddah, Saudi Arabia 21472.

Contents

ANOMALIES OF NUMBER

Part of "47 - ANOMALIES OF THE KIDNEY "

Renal Agenesis

Embryologic Considerations

For the kidney to develop properly, a normal ureteral bud must penetrate a normal metanephric blastema at the proper time. These events typically occur between the fifth and the seventh week of gestation. Major factors that alter the morphology or sequence of these events, such as absence of the nephrogenic ridge or failure of ureteral bud formation, prevent the kidney from developing. Although the kidney obviously will not form in the absence of metanephric tissue, it is genuinely unclear in renal agenesis which is the primary developmental abnormality, the nephrogenic ridge or the ureteral bud. Studies by Potter (98) on the fetus and infant suggest that the primary abnormality rests in failure to develop a normal ureteral bud; she observed that if any portion of the ureter was present, some identifiable renal tissue usually existed. In contrast, an extensive review of autopsy material by Ashley and Mostofi (7) disclosed that in many cases of renal agenesis there was partial or complete formation of the ureter and wolffian duct structures. They also observed examples of renal dysgenesis occurring without a formed ureter. Although these findings are to some extent conflicting, they do support a theory that the ureteral bud directly stimulates the differentiation of the renal parenchyma, and they also indicate that the potential for renal differentiation rests in the nephrogenic ridge itself. This potential suggests that the stimulus for ureteral bud formation resides, at least partly, in the developing metanephros.

The embryologic basis for renal agenesis appears to be an early insult to the developing ureteral bud, which prevents normal renal organogenesis from progressing. The ultimate clinical expression of this teratogenic event depends on its severity and extent (unilateral or bilateral renal agenesis) and on the sex of the fetus because wolffian duct derivatives are much less commonly affected than müllerian duct structures. Also, even though there is close proximity between the renal and gonadal anlage on the nephrogenic ridge, injuries to the developing gonads are rare in this condition.

Bilateral Renal Agenesis

Bilateral renal agenesis is a rare anomaly, with an incidence of approximately 1 in 4,000 births. It occurs much more often in males than in females (72%), and most affected

infants are of low birth weight (less than 2.5 kg). Amniotic fluid is characteristically absent in all cases, although no other feature of pregnancy or maternal state is abnormal. Approximately one-third of births are stillborn; the survivors usually succumb to the effects of severe pulmonary hypoplasia within a short time.

The kidneys and renal arteries are usually completely absent, although dysgenetic vestiges may at times be noted. The ureters are completely absent in approximately half of the infants, as is the bladder, which often is absent or hypoplastic. The adrenal glands usually are present but typically ovoid because they are not compressed by the kidneys and fail to assume their characteristic shape (7). The infant with bilateral renal agenesis is characteristically deformed. The face is prematurely senile, with a flat nose, large flattened and lowered ears, and a depression below the lower lip. A prominent skinfold covers the inner canthus of each eye. In addition, the legs are often bowed and clubbed. This constellation of features, along with pulmonary hypoplasia, has been termed *Potter's syndrome* (Fig. 47.1 and Fig. 47.2). However, these features are not pathognomonic or specific for bilateral renal agenesis. Elegant experimental studies on the fetal rat subjected to repeated amniocentesis (27); observations by Bain and associates (8) on infants with leakage of amniotic fluid; and documentation of Potter's syndrome in babies with polycystic kidney disease, bilateral renal dysplasia, and urethral atresia or obstruction indicate that all of the features of Potter's syndrome are attributable to the mechanical effects of insufficient amniotic fluid volume.

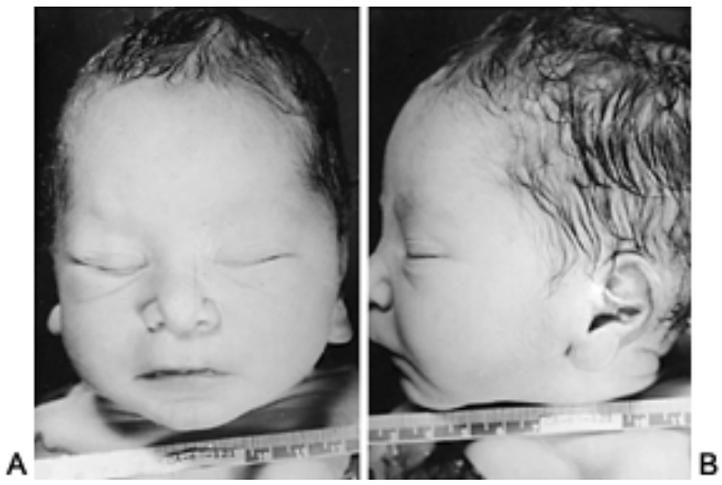

FIGURE 47.1. Characteristic Potter's facies in an anephric child who survived only hours. Note flat nose, large flattened and lowered ears, depression below lower lip, and inner canthal skinfolds.

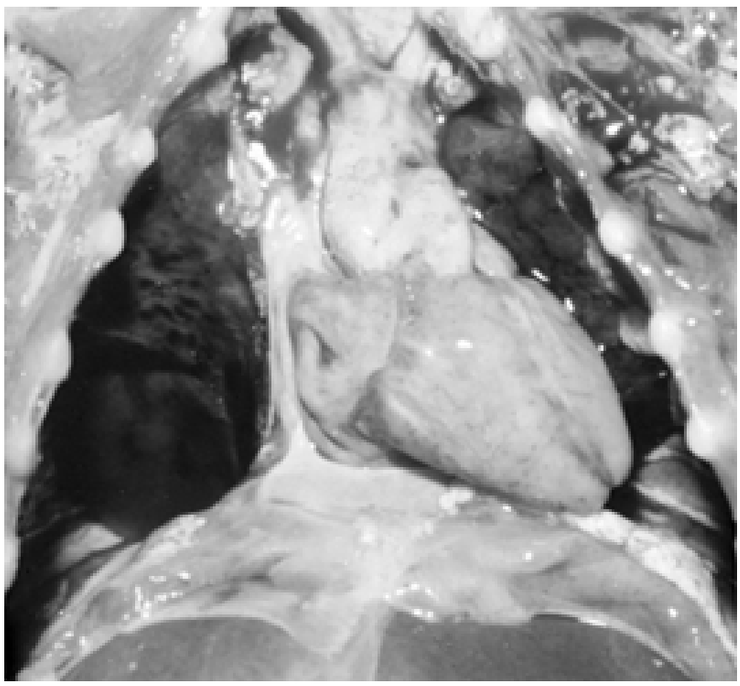

FIGURE 47.2. Bell-shaped chest and pulmonary hypoplasia in stillborn child with bilateral renal agenesis.

Bilateral renal agenesis is incompatible with life, and thus its clinical significance is limited. With characteristic body features and associated oligohydramnios, the diagnosis should be readily apparent and can be easily confirmed by ultrasonography, renal scintigraphy, and if necessary, umbilical artery catheterization with aortography. In addition, the diagnosis of Potter's syndrome can be made prenatally. This raises important controversies and implications in fetal therapeutics (48).

Unilateral Renal Agenesis

Because of the potentially asymptomatic nature of this anomaly, its reported incidence varies according to the population surveyed. Necropsy studies suggest an occurrence of approximately 1 in 1,000, whereas clinical presentation may be 1 in 1,500 (33,127). Males dominate in a ratio of 1.8:1 (30).

The clinical significance of solitary kidney relates to associated genitourinary tract abnormalities and to its potential for pathologic complications. Genital anomalies occur commonly and are three to four times more frequent in females than in males. In girls, partial or complete nonunion of the müllerian ducts is the most commonly occurring embryologic defect. This defect is usually expressed clinically as an obstructed hemivagina and uterus didelphis, which produces lower abdominal pain after menarche. These signs and symptoms are often diagnosed incorrectly because hematocolpometra is seldom considered as a likely diagnostic possibility in an otherwise healthy menstruating young woman (120,143) (Fig. 47.3). Magnetic resonance imaging (MRI) is particularly useful in defining müllerian duct anomalies and establishing a correct diagnosis in this setting (124). A spectrum of renal anomalies including unilateral agenesis may occur in certain patients with the Mayer-Rokitansky-Kuster-Hauser syndrome, which is defined by congenital absence of the vagina and uterus. Two

forms of this condition occur in otherwise normal genotypic and phenotypic females who have a shallow pouch replacing the vagina. In the typical form, complete absence of the vagina is associated with bilateral symmetric rudimentary uterine anlagen (noncanalized muscular buds) and normal ovaries and fallopian tubes. In the atypical form, the uterine remnants are asymmetric (aplastic or enlarged), the fallopian tubes are abnormal (aplastic or hypoplastic), and the ovaries may be cystic and anomalous. Interestingly, the ovarian and renal anomalies occur almost exclusively in the atypical form of this syndrome (96,122,125).

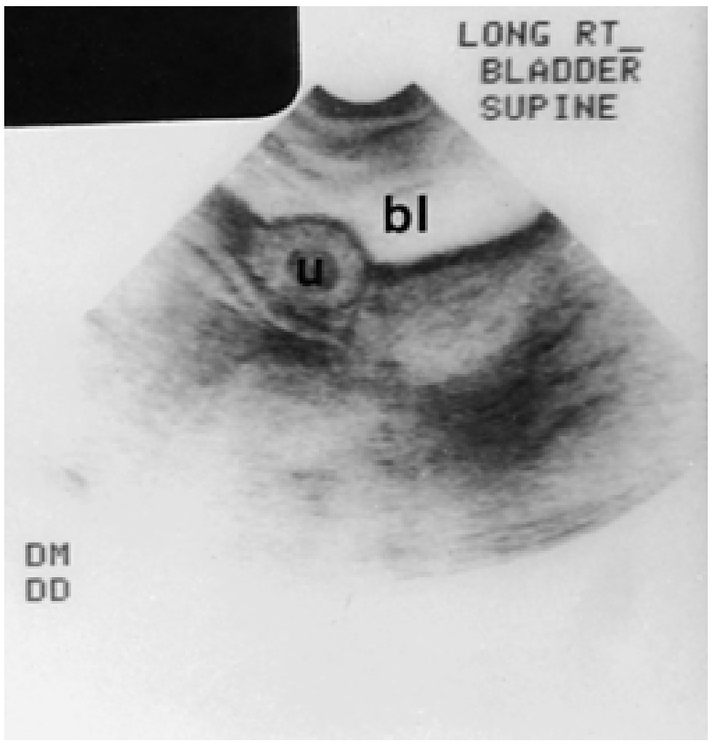

FIGURE 47.3. Pelvic ultrasonogram demonstrates right-sided partially fluid-filled pelvic mass in a 15-year-old girl with solitary left kidney and menstrual irregularity. The mass proved to be an obstructed duplication of the uterus and vagina with hematometrocolpos. u, uterus; bl, bladder.

Genital anomalies are much less common in males, although hypospadias, undescended testes, hypoplastic or absent vas deferens, and seminal vesicle and prostatic cysts have been reported (57,136). In both sexes, patients with ipsilateral renal agenesis (or severe dysplasia) may develop cystic dilations within the pelvis. In males, these typically represent seminal vesicle cysts, whereas in females, Gartner's cysts occur. Sheih and others (115) performed screening renal ultrasound studies on 280,000 children and found 235 with a congenital solitary kidney. Of these, 13 had seminal vesicle or Gartner's cysts, an incidence of 0.005%. The embryologic connection between renal agenesis and pelvic cystic disease was made more obvious in those cases in which dilated ureters were identified entering the cysts.

Except as previously noted, the gonads are usually normal, although urologic anomalies may be associated with and lead to the diagnosis of unilateral renal agenesis. These include vesicoureteral reflux and obstruction at the ureterovesical and ureteropelvic junctions (18). The ipsilateral adrenal gland would be expected to be normal because of its separate embryologic development. Interestingly, the adrenal has been reported to be absent in approximately 10% of cases of renal agenesis (85). Associated nongenitourinary tract anomalies occur in up to 25% of affected individuals and commonly involve the cardiovascular, gastrointestinal, and skeletal systems.

The diagnosis of unilateral renal agenesis is often made during an evaluation for urinary symptoms or as part of an investigation in patients with abnormalities of the external genitalia or other organ systems. Females are often identified at puberty during an evaluation for menstrual irregularities or a mass. In males, the external genitalia may give a clue to diagnosis, but finding an absent vas deferens or hypoplastic epididymis does not necessarily indicate that there will be an absence of the kidney (20,130). Likewise, absence of the kidney does not signify absence of the testis in those instances when the testis is undescended and impalpable. The clinical diagnosis of unilateral renal agenesis and its relationship to multicystic renal dysplasia becomes confusing and even more significant when fetal ultrasound studies are considered. Mesrobian and co-workers (81) reported on the occurrence of unequivocal unilateral multicystic renal dysplasia detected in three fetuses during maternal ultrasound examination, which completely disappeared during fetal development so that no trace of a kidney or cystic structure was seen on subsequent ultrasonograms performed after birth. It is thus apparent that some solitary kidneys may not result from a lack of induction of the metanephric blastema, but rather reflect an acquired insult to the developing kidney. The incidence and significance of this finding requires further clarification, but it does help explain certain embryologic findings such as cystic dilations of the seminal vesicle or Gartner's duct associated with renal agenesis. Some of these cases may represent ureteral ectopia with early and total obstructive renal injury.

Investigations used to make the diagnosis of unilateral renal agenesis can include excretory urography, ultrasonography, radionuclide imaging, computed tomography (CT), and MRI. Cystoscopy is usually not helpful, even though it may reveal an asymmetric or absent hemitrigone typically without visualization of a ureteral orifice. However, these cystoscopic findings are not pathognomonic of renal agenesis. They merely indicate that the ureter does not enter the bladder normally; it may be ectopic. Consequently, cystoscopy is not used to confirm the diagnosis of renal agenesis.

Although the susceptibility of a solitary kidney to pathologic complications is now recognized to be no greater than that of a normal kidney, early studies suggested that solitary kidneys were predisposed to disease and carried an increased mortality. In recent times, such a potential has not been

observed, and unilateral renal agenesis is compatible with normal longevity. Beginning *in utero,* the solitary kidney shows evidence of compensatory hypertrophy (80). By adulthood, the solitary kidney associated with renal agenesis develops a hemodynamic response to protein challenge that is no different from other types of acquired solitary kidney as occurs in renal donors and other uninephrectomized patients, which indicates normal renal reserve (28). However, in following the clinical course of 157 patients with unilateral renal agenesis, Argueso and associates (6) did observe that while survival data was the same as for age-matched controls, the risk of developing proteinuria, hypertension, and renal insufficiency was increased. Prolonged follow-up of these patients thus appears warranted.

Hereditary Renal Adysplasia

Most cases of renal agenesis and renal dysplasia generally have been considered as isolated findings, occurring sporadically and not part of any inherited syndromes. Recent reports suggest alternatively that because of a common pathogenesis, renal agenesis, small kidneys with solid dysplasia, and large kidneys with solid or cystic dysplasia should be viewed as a spectrum of disease that includes multicystic renal dysplasia. In addition, familial renal agenesis and dysplasia have been shown to occur together and to be inherited along autosomal-dominant lines with variable inheritance (10,84,103,118).

Hereditary renal adysplasia was first described by Buchta (13) in 1973 as the occurrence of renal agenesis and hypoplasia/dysplasia in two kindreds where a predominantly autosomal-dominant inheritance pattern with variable penetrance was suggested. Roodhooft (103) clarified the familial nature of bilateral renal adysplasia and found that 9% of parents and siblings of afflicted individuals had asymptomatic renal abnormalities. Recent evidence by Murugasu (84), who studied three kindreds with hereditary renal adysplasia where two or more children in each family were affected, indicated that (a) at least one family member had a clinically silent anomaly; (b) normal kidneys in parents did not protect offspring from developing anomalies; and (c) empiric risks for offspring and first-degree relatives were 50% and 25%, respectively. These findings suggest that the strong genetic predisposition is along the lines of a dominant gene with variable expression. Because of this higher-than-expected incidence of silent genitourinary tract abnormalities as well as the increased risk to parents of having another infant so affected, there is a strong need for careful and complete genetic screening of the proband's family, pregnancies, and subsequent children. Although the risks of recurrence of the different forms of hereditary renal adysplasia have generally applied only to the renal components, Battin (9) has identified a kindred in which müllerian duct abnormalities (vaginal atresia or anomaly) were inherited in an autosomal-dominant pattern.

Supernumerary Kidney

The supernumerary kidney is a rare condition in which a free accessory renal organ exists as a distinctly separate parenchymatous mass and blood supply associated with two usually normal kidneys. It is generally distinguishable from the normal ipsilateral kidney by its smaller size and abnormal position. Typically, the supernumerary kidney is located caudal to the normal kidney. When in this position, the supernumerary ureter is usually a bifid branch of the normal ureter. This contrasts with the cranially placed supernumerary kidney whose ureter is characteristically completely duplicated and separate from the normal ureter and may empty ectopically (86). Pathologic conditions such as calculus disease and hydronephrosis have been reported in more than 50% of patients. However, it may not indicate a true increased susceptibility, but rather may merely be an indication for their recognition (108). When it is diagnosed, therapy for supernumerary kidney should be directed toward and reserved for pathologic processes affecting the kidney rather than simply its abnormal position or apparent redundancy.

ANOMALIES OF POSITION

Part of "47 - ANOMALIES OF THE KIDNEY "

Embryologic Considerations

During normal embryologic development, the permanent kidneys are initially positioned in the pelvis opposite the sacral somites, with their pelves facing anteriorly. Through a combination of axial trunk lengthening, elongation of the ureter, intrinsic renal growth, and rotation, the metanephros ascends to a higher position (Fig. 47.4). By the eighth week of gestational life, migration has been completed, and the kidney resides in the upper retroperitoneum opposite the second lumbar vertebra with the hilum facing medially. During ascent, the vascular supply to the kidney is locally derived until it reaches its final position, where the main

renal arteries and veins develop. Because of the interdependence of renal ascent, rotation, and vascular supply, anomalies of renal position often are associated with bizarre and at times puzzling alterations in morphology and function that become interpretable and subject to classification only on the basis of these embryologic processes.

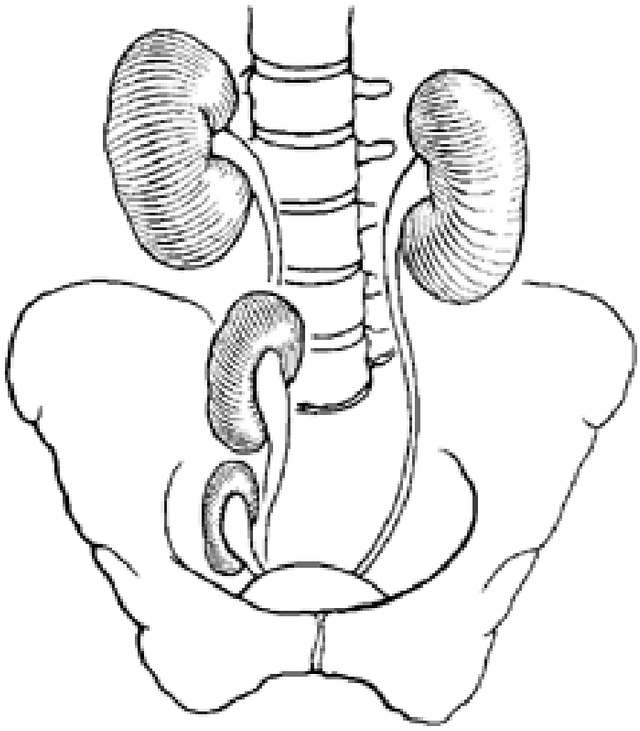

FIGURE 47.4. Ascent of kidney is associated with medial rotation.

Malrotation

Malrotation may be unilateral or bilateral and may affect a normally positioned or ectopic kidney. The kidney is commonly rotated around its vertical axis, and in most cases the pelvis is aimed somewhat anteriorly somewhere between the fetal and normal adult positions (Fig. 47.5). Rarely, this situation can be reversed, with the pelvis pointing posteriorly. The renal vessels are usually normal when the kidney is malrotated but in its normal retroperitoneal position, which excludes a vascular cause for the anomaly.

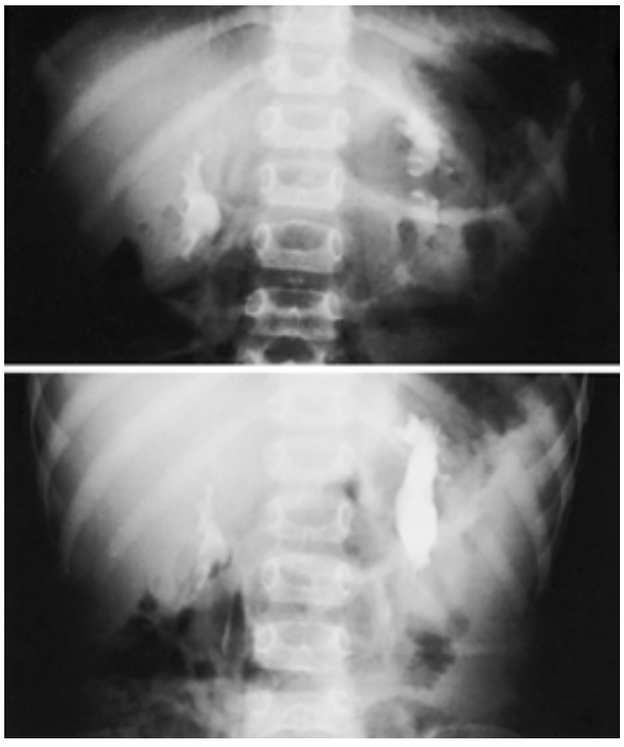

FIGURE 47.5. Excretory urogram of malrotated left kidney with pelvis pointed anteriorly demonstrates normal calyces **(top)** and slightly dilated pelvis **(bottom)**.

Although the malrotated kidney is generally no more predisposed to pathologic conditions than is the normal kidney, malrotation is often accompanied by dysmorphism of the pelvis and calyces, especially in the presence of renal ectopy and fusion. Consequently, the malrotated kidney and pelvis may look hydronephrotic or deformed or may have a bizarre shape that suggests extrinsic compression or the presence of tumor (Fig. 47.6). In most instances, these appearances are illusory. However, at times, special diagnostic studies may be needed to exclude obstruction and to establish a correct diagnosis.

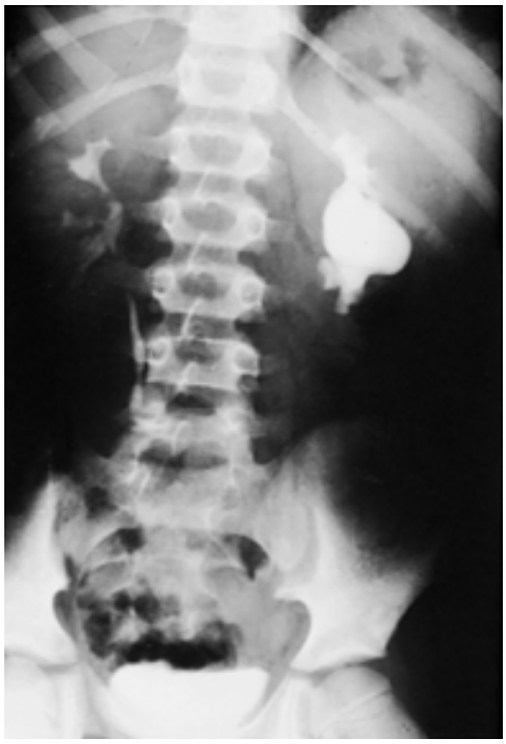

FIGURE 47.6. Excretory urogram of malrotated left kidney demonstrates dysmorphic renal pelvis and hydronephrosis, proved to be nonobstructive by diuretic radionuclide studies.

Renal Ectopy

When the kidney occupies a position outside of its normal retroperitoneal location, it is termed *ectopic*. Ectopy may be acquired, as in ptosis, where the renal vasculature and ureteral length are normal. In contrast, congenital renal ectopia usually represents a developmental arrest during renal ascent so that the kidney occupies a pelvic, iliac, or abdominal location (Fig. 47.4), having a shorter-than-normal ureter and an abnormal vascular supply. Malrotation is a usual accompaniment, with the pelvis typically directed anteriorly (Fig. 47.7).

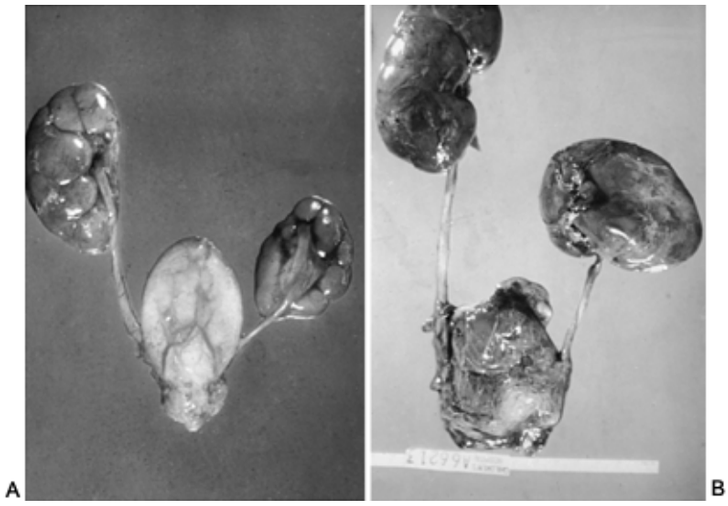

FIGURE 47.7. A: Ectopic left kidney shows incomplete rotation with renal pelvis aiming anteriorly. **B:** Ectopic left kidney, which has ascended higher than **A,** has completed normal medial rotation but has an abnormal axis.

Pelvic Kidney

In most cases of simple (ipsilateral) renal ectopy, the kidney is located within the confines of the bony pelvis and is often termed a *pelvic kidney* (Fig. 47.8). In this position, it overlies the pelvic bones and lumbosacral vertebrae, which makes its visualization on urography difficult even when renal function is well preserved. Diagnostic difficulty may be further compounded by poor renal function and by the renal pelvis and calyces assuming an abnormal and often unexpected attitude (Fig. 47.9). Many ectopic kidneys display a characteristic ultrasonographic appearance with absent or eccentric

renal sinus echo patterns that reflects this altered calyceal anatomy and the presence of an extrarenal pelvis.

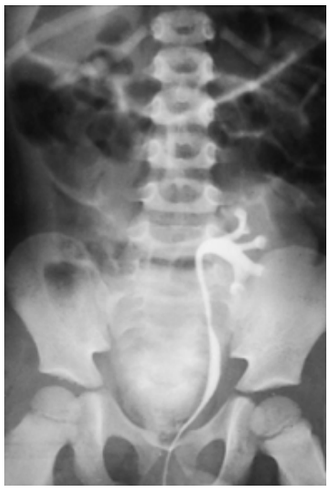

FIGURE 47.8. Retrograde study of normally rotated and formed pelvic kidney with short ureter.

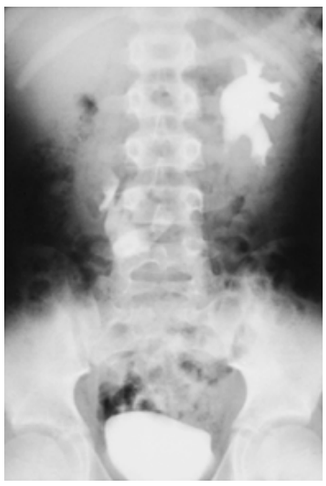

FIGURE 47.9. Right pelvic kidney overlies the lumbosacral spine and is difficult to visualize on excretory urogram.

Pelvic kidneys are more susceptible to calculus formation than normal ones. They are also more frequently observed to be hydronephrotic, the cause of which may be true obstruction or nonobstructive dilation due to vesicoureteral reflux, dysmorphism, malrotation, and so on. Because nonobstructive dilation occurs in over 50% of cases (41), careful assessment must be made before the dilated kidney is assumed to be obstructed and treatment is initiated. If reconstructive surgery is necessary, angiography occasionally may be helpful to characterize an unpredictable renal vasculature (Fig. 47.10). Also, the presence and status of the opposite kidney must be determined in case nephrectomy is required (3). In general, the prognosis in renal ectopia is primarily related to the presence of any associated urologic disease and not related directly to ectopia alone (41).

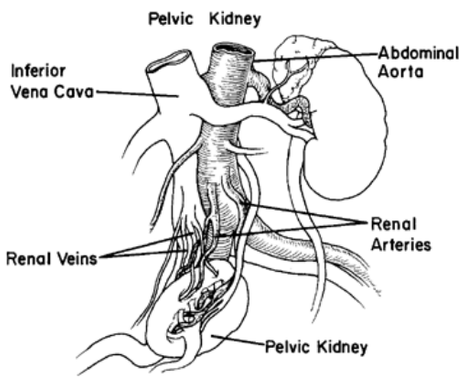

FIGURE 47.10. Unpredictable renal vasculature to pelvic kidney is derived from surrounding major vascular trunks.

In clinical series, ectopic kidneys are frequently symptomatic in up to 40% to 50% of patients (31). Symptoms are generally on the basis of urinary infection, abdominal mass, or pain simulating gastrointestinal disease. The autopsy incidence of this condition, 0.14% (17), is much greater than is the clinical expression, 0.008%, based on hospital admissions (61). This finding suggests that in many cases the anomaly is asymptomatic and remains unrecognized. Prognosis ultimately depends on whether the pelvic kidney is solitary and whether the contralateral kidney is normal, as reflected in the series by Downs and co-workers (31) in which renal disease developed in 40% of patients with a solitary ectopic kidney (representing approximately 10% of patients with pelvic kidney) and 15% did not survive early adulthood. The clinical significance of ectopic kidney is reinforced by the fact that in up to 50% of patients, the contralateral kidney may be abnormal (77).

Prognosis also depends on the severity of associated anomalies, which are particularly common with renal ectopy, and may coexist in up to 85% of patients (77). In addition to the high incidence (15% to 45%) of genitourinary tract anomalies, such as hypospadias, undescended testis, and vaginal agenesis, associated anomalies typically include the skeletal, cardiovascular, and gastrointestinal systems. This high incidence of associated abnormalities requires thorough investigation, particularly in young children found to have renal ectopy. Similarly, the presence of skeletal and especially vertebral anomalies should raise the level of suspicion for coexisting renal abnormality (29). Maizels and Stephens (75) have identified and defined an embryologic explanation for this close relationship between renal ectopy and vertebral anomalies in a series of elegant experiments. By deforming the developing caudal trunk of the chick embryo, they could regularly induce scoliosis, which, when present, was associated with a 62% incidence of renal ectopia. Equally important was the relatively high incidence of associated anomalies of the mesonephros, mesonephric duct, and müllerian duct comparable with that reported in the clinical literature. As a result of these studies, they have proposed that an environmental teratogen affecting the hind end of the embryo at a critical period of approximately 5 to 7 weeks' gestation may lead to abnormal growth of the spine. This abnormal growth of the spine in turn would limit renal ascent to produce ectopia and deflect the mesonephric duct away from the cloaca, leading to abnormalities of these structures or of the müllerian duct system. Such studies and their clinical correlates clearly indicate that the development of the lower end of the embryo is a highly complex process with multisystem interdependence. Therefore the clinician must keenly recognize the interrelationships between renal anomalies and other genitourinary and somatic abnormalities to provide the thorough investigation necessary to uncover their presence and to interpret their significance.

Thoracic Kidney

Thoracic kidney is a rare form of renal ectopy where the kidney protrudes or projects, at least in part, above the diaphragm. It is distinguishable from diaphragmatic hernia in which other abdominal viscera occupy the chest cavity as well. Embryologically, it is uncertain whether the kidney ascends before the diaphragmatic leaflets close normally or whether delayed diaphragmatic formation enhances the exaggerated renal ascent (16).

Because the thoracic kidney is typically asymptomatic and otherwise normal except for position, the diagnosis is usually made on routine chest roentgenogram. The ureter is longer than normal to reach the bladder, but unlike the pelvic kidney, the renal vasculature is not anomalous and typically arises as a single renal artery and vein. Once a diagnosis has been confirmed (Fig. 47.11), therapy is usually

not required because neither the ectopic thoracic kidney nor its contralateral mate are predisposed to pathologic disturbances.

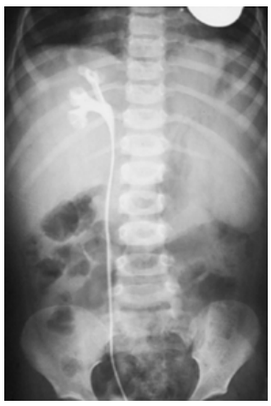

FIGURE 47.11. Thoracic kidney, evaluated by retrograde pyelography, is entirely normal but abnormally positioned.

ANOMALIES OF POSITION AND FUSION

Part of "47 - ANOMALIES OF THE KIDNEY "

Embryologic Considerations

Anomalies of position and fusion include kidneys that have migrated to become contiguous or fused with their contralateral mate and is subdivided clinically on the basis of whether both or only one kidney moves toward or crosses the midline. In horseshoe kidney, the most common fusion abnormality, both kidneys have migrated, whereas in crossed ectopia, usually only one kidney has crossed the midline. In both situations, the blood supply is unpredictably abnormal, arising from multiple sources, and the kidneys are malrotated to some degree because fusion usually prevents normal rotation from being completed.

Numerous eclectic embryologic theories have sought to provide an explanation for these different events, which occur very early in gestation. These explanations include faulty ureteral bud development, abnormalities of renal vasculature limiting ascent, and other teratogenic factors (61,79). More recently, Cook and Stephens (24) have proposed a more unified theory that relates the position and fusion anomalies to abnormal variations in growth or flexion of the hind end of the developing embryo and to the subsequent induction of one or two nephrogenic cords. They propose that horseshoe kidney and its variants may be due to midline fusion of the two renal blastemata while they are still confined to the true pelvis. This fusion results from excessive ventral flexion of the hind end of the embryo, which pushes the kidneys together (Fig. 47.12). Alternatively, a combination of exaggerated ventral as well as lateral flexion with rotation of the tail might carry the cloaca and its attached ducts across the midline to allow the development of a fused kidney from a single nephrogenic cord that has been intercepted by ureteral buds from both wolffian ducts.

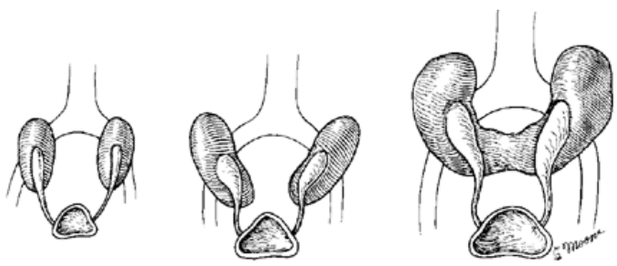

FIGURE 47.12. Presumed embryologic sequence in the formation of horseshoe kidney.

Crossed Renal Ectopy

Crossed renal ectopy is an uncommon condition with an autopsy incidence of approximately 1 in 2,000 and a slight male predominance (1,79). It occurs when the ureter occupies its normal position in the bladder but crosses the midline to join an ectopic kidney, which, in 90% of patients, is fused to its mate. In their comprehensive study, McDonald and McClellan (79) subdivided this condition into four groups: (a) crossed ectopia with fusion, (b) crossed ectopia without fusion, (c) solitary crossed ectopia, and (d) bilateral crossed ectopia (Fig. 47.13). Crossed renal ectopia with fusion, the most common of these entities, was further classified into six categories based on morphologic appearance (Fig. 47.14). Of these, the most common form appears to be fusion with the ectopic kidney placed inferiorly.

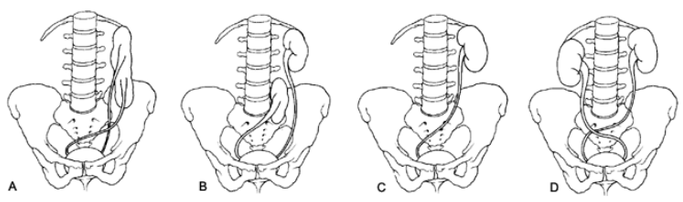

FIGURE 47.13. Types of crossed renal ectopia. **A:** Fused. **B:** Nonfused. **C:** Solitary. **D:** Bilateral. (Modified from McDonald JH, McClellan DS. Crossed renal ectopia. *Am J Surg* 1957;93:995, with permission.)

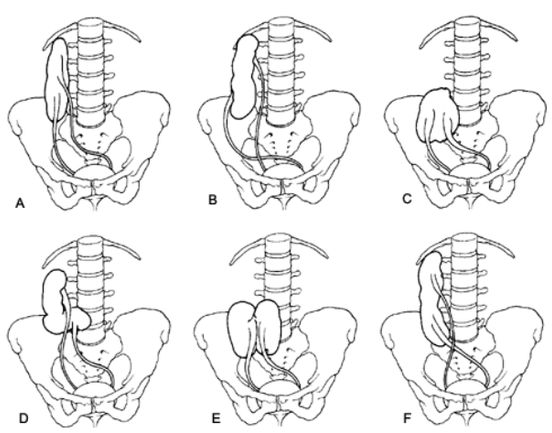

FIGURE 47.14. Six types of crossed renal ectopia with fusion. **A:** Ectopic kidney superior. **B:** Sigmoid or S-shaped kidney. **C:** Lump kidney. **D:** L-shaped kidney. **E:** Disk kidney. **F:** Ectopic kidney inferior. (Modified from McDonald JH, McClellan DS. Crossed renal ectopia. *Am J Surg* 1957;93:995, with permission.)

Although both urinary and nonurinary anomalies can be associated with this condition, their incidence is low and they are not as frequently seen as in unilateral agenesis or pelvic kidney. However, various abnormalities, including sacral agenesis, scoliosis, and cardiovascular and gastrointestinal anomalies, have been reported (61,79).

Many patients with crossed renal ectopia remain entirely asymptomatic. However, because of associated malrotation, a significant proportion of these kidneys displays pelvocalyceal dysmorphism that simulates hydronephrosis. In some instances, an abnormal ureteropelvic junction (UPJ) position and aberrant blood vessels may actually interfere with pelvic emptying to produce obstruction and predispose to

urinary infection and calculus formation. Also, reflux is commonly observed to be associated with this anomaly.

Although crossed ectopia can be appreciated by ultrasonogram, excretory urography is often required to precisely characterize the anatomy of the crossed ectopic moieties, especially if function or morphology is not normal (Fig. 47.15 and Fig. 47.16). However, because of the high incidence of reflux, voiding cystography and radionuclide studies that evaluate the functional significance of collecting system dilation are recommended. If surgery is required, angiography may occasionally be helpful because, as Rubinstein and associates (106) have shown, the vascular supply to both the ectopic and nonectopic kidney may be anomalous.

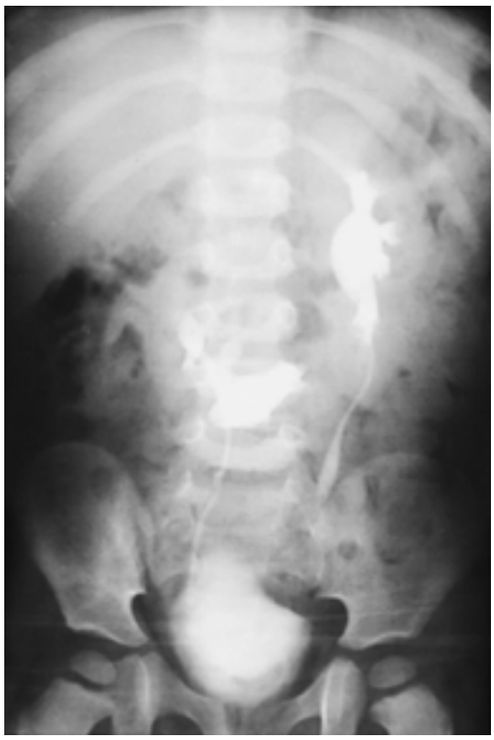

FIGURE 47.15. L-shaped crossed fused renal ectopia with renal pelvis overlying spine is visualized by excretory urography. Note malrotation of left kidney.

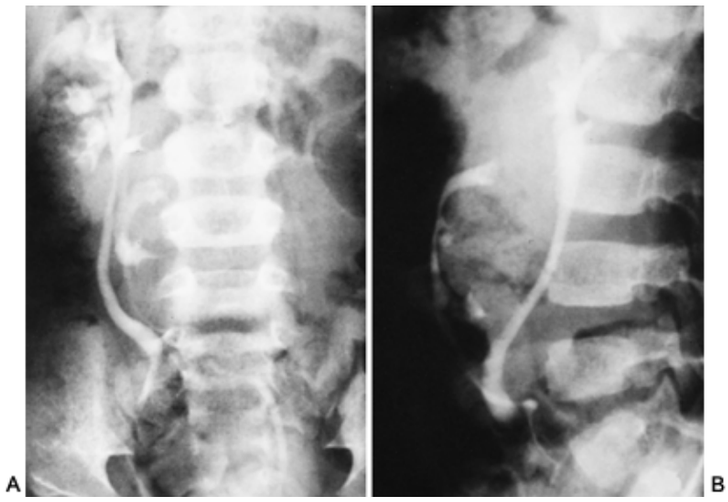

FIGURE 47.16. A: Crossed renal ectopia with crossed kidney fused inferiorly is demonstrated on excretory urogram. **B:** Lateral film shows orientation of collecting systems to be anterior for inferior ectopic kidney and posterior for superior kidney.

Horseshoe Kidney

Horseshoe kidney is the most common fusion anomaly, with an incidence of approximately 1 in 400 births and a

male predominance (42,112). It presents great variability in morphology, position, and vascular supply. In more than 90% of cases, there is true fusion of the lower poles, which form an isthmus and become medially directed (Fig. 47.17). The site of fusion may lie over the midline or may be asymmetrically positioned to one side. Depending on the degree of fusion, the isthmus may be composed of thick functioning parenchyma or merely be a fibrous band that serves to tether the lower poles. In most instances, the kidneys are located in their proper retroperitoneal positions, with the isthmus placed anterior to the great vessels at approximately the level of L-4 or L-5. The ureters typically course in front of the isthmus, descending from anteriorly facing renal pelves. Blood supply to the horseshoe kidney is variable, with the fused segment receiving a particularly unpredictable blood supply from branches of the common iliac, aorta, and at times, the hypogastric and middle sacral arteries (11). If large portions of the renal parenchyma fuse, the resulting kidney may lose its horseshoe shape and become a flattened disc or lump kidney, which often has a pelvic location (Fig. 47.18).

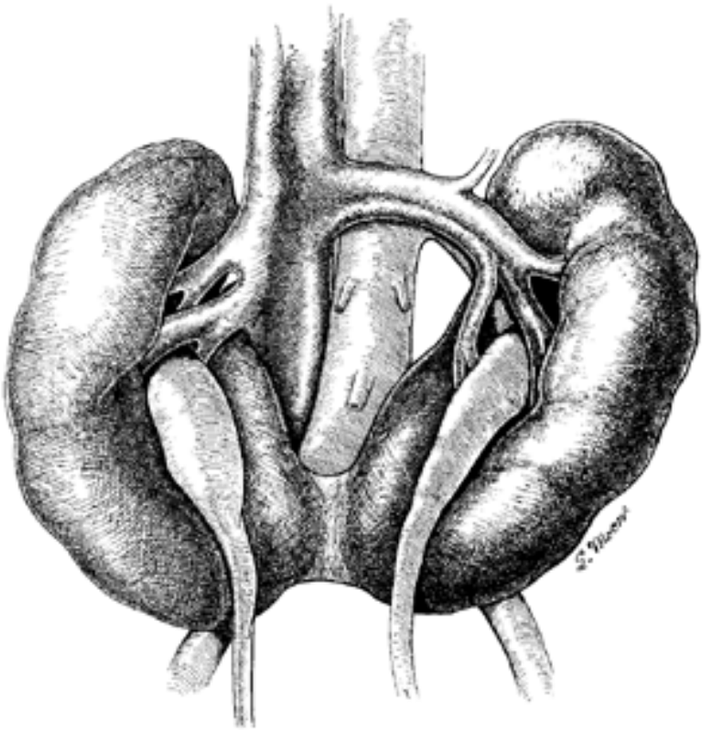

FIGURE 47.17. Classic features of horseshoe kidney. Fusion of lower poles produces an isthmus and shifts the axis of the kidneys toward the lumbosacral vertebrae.

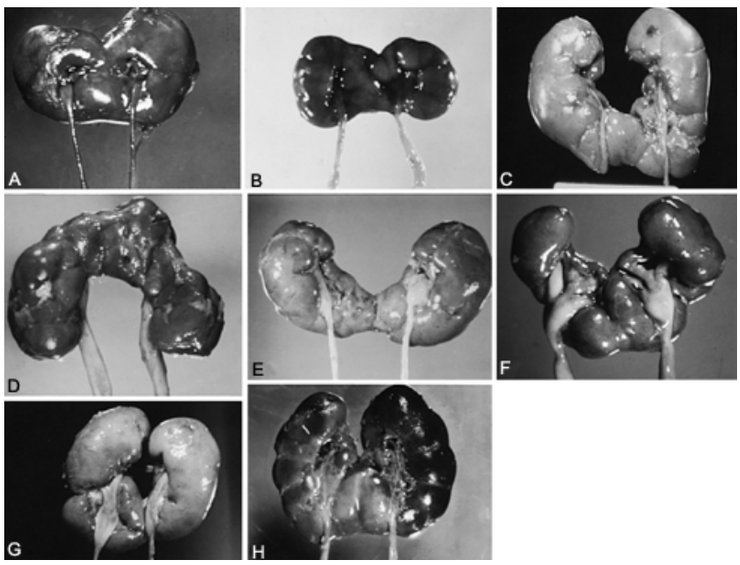

FIGURE 47.18. Horseshoe kidney. Specimens **(A-H)** show wide variation in degree of fusion, thickness of the isthmus, ureteral morphology, renal axis, and horseshoe appearance. Note fusion of upper poles in **D**.

Associated anomalies occur in at least one-third of patients regardless of whether the horseshoe kidney is itself symptomatic. These anomalies include multisystem disturbances of the skeletal and cardiovascular systems and gastrointestinal tract as well as genitourinary abnormalities. It appears that horseshoe kidneys are more common in infants succumbing to multiple congenital anomalies, but the kidney itself is rarely the cause for their deterioration. Boatman

and colleagues (11) documented an increased incidence of male and female genital anomalies with this condition. Also, an increased frequency of ureteral duplication with obstructive sequelae (e.g., ureterocele) and reflux has been reported (97,112).

A large proportion of patients with horseshoe kidney remain entirely asymptomatic. When symptoms are present, they typically relate to calculi, hydronephrosis, infection, or hematuria. A high incidence of calculus disease has been attributed to a combination of partial obstruction and stasis; however, Evans and Resnick (36) found that metabolic causes for kidney stone disease were no less frequent in patients with horseshoe kidney than in the general population. The treatment of calculi in a horseshoe kidney requires special consideration with regard to shock wave lithotripsy (SWL) therapy and endourologic techniques (25,35,113).

Hydronephrosis was present in approximately 80% of the children with horseshoe kidney (88,112). Hydronephrosis may be due to UPJ obstruction, which is commonly associated with a high insertion of the ureter into the pelvis as well as displacement by the fused isthmus. However,

hydronephrosis also may be consequent to vesicoureteral reflux or to pelvocalyceal dysmorphism consequent to malrotation, ectopy, and parenchymal distortion. Differentiation between obstructive and nonobstructive conditions is obviously essential for effective therapy (Fig. 47.19).

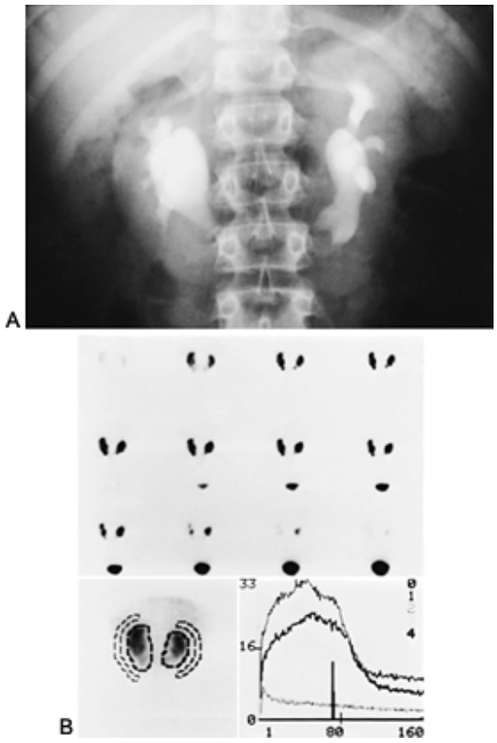

FIGURE 47.19. A: Excretory urogram shows horseshoe kidney with bilateral hydronephrosis greater on the right side. **B:** Diuretic radionuclide study indicates that isthmus has no appreciable blood flow *(bottom left).* Also, scintiscans *(above)* and histogram curves *(bottom right)* illustrate rapid nonobstructed tracer transit and exclude mechanical obstruction.

Dysplasia and neoplasia have been reported to occur in horseshoe kidney. Wilms' tumor, angiomyolipoma, teratoma, and transitional cell carcinoma all have been documented (19,37,39,109). Also, the incidence of transitional cell carcinoma appears to be increased (100).

The radiographic diagnosis of horseshoe kidney, although difficult with ultrasonography if the isthmus is not detected, usually can be made with excretory urography if the renal segments function well; the vertical line of axis through the kidneys will point toward the lumbosacral spine, and there will be ureteral deviation by the isthmus. However, in children with spina bifida and a thoracolumbar gibbus deformity, the axis of the kidneys may be distorted to simulate a horseshoe kidney (78).

The addition of diuretic radionuclide imaging may be helpful in patients with horseshoe kidney because it reliably establishes whether the isthmus contains functioning parenchyma (52), and it distinguishes true obstructive hydronephrosis from nonobstructive dilation (128) (Fig. 47.19). To these studies, voiding cystography should be added because of the predictably high incidence of vesicoureteral reflux. If surgery for a diseased horseshoe kidney is contemplated, angiographic study may be required to characterize the variable arterial supply to the kidney.

Treatment and prognosis for horseshoe kidney, particularly for associated hydronephrosis, have changed considerably over the years, reflecting both conceptual evolution and technologic advance. Historically, Smith and Orkin (116) believed that a horseshoe kidney was almost always diseased and in need of surgical therapy, especially division of the isthmus. Later, Glenn (42) provided evidence that nonoperative follow-up of horseshoe kidneys was compatible with a symptom-free course; fewer than 25% of patients required surgery for calculus or obstruction. Also, no patient required division of the isthmus for pain relief, a practice that has since lost favor. Division of the isthmus, however, was often thought to be necessary and was performed in conjunction with pyeloplasty or alone to improve drainage. However, symphysiotomy is not commonly performed today because the position of the kidneys and course of the ureters are not appreciably altered nor is the drainage pattern of the kidney improved by this maneuver (97). Standard pyeloplasty techniques are easily adaptable to the horseshoe kidney despite the presence of the isthmus whose division is not required for excellent surgical result (111). With the absence or elimination of obstruction many large series have reported a very favorable prognosis for these patients (42,97). The presence of a horseshoe kidney can significantly affect the management of other disease conditions involving the kidney and retroperitoneum such as renal and testicular neoplasm, aortic aneurysm, and renal transplantation. Special considerations and alterations in therapy may be required (51,89,99).

ANOMALIES OF THE RENAL COLLECTING SYSTEM

Part of "47 - ANOMALIES OF THE KIDNEY "

Calyx

Calyceal Diverticulum

A calyceal diverticulum is a cystic cavity located peripheral to an otherwise normal minor calyx with which it communicates through a narrow channel. It is lined by transitional epithelium, may be multiple, and can occur anywhere in the kidney, although the upper calyx is most frequently affected.

Because the incidence in children and adults is approximately the same, it is considered to be a defect in embryogenesis, although the embryology is unclear. One plausible explanation is based on persistence of later generations of the dividing ureteral bud that fail to degenerate and persist as calyceal diverticula, enlarging because of backflow of urine (82,129).

Diagnosis is usually suspected on ultrasonography and confirmed if necessary by excretory urography, although the neck of the diverticulum is best outlined on retrograde study (Fig. 47.20). In the evaluation, they must be distinguished from other acquired abnormalities such as cortical abscess, papillary necrosis, and tuberculosis. Calyceal diverticula may be entirely asymptomatic, but there is an increased incidence of milk of calcium and stone formation within the poorly draining cavity, which in turn may cause clinical symptoms and secondary complications of pain, infection, and hematuria (142). Percutaneous surgery may be required to treat the contents of the diverticulum, and if required, eradication can be achieved by dividing the calyceal neck and marsupializing the cyst.

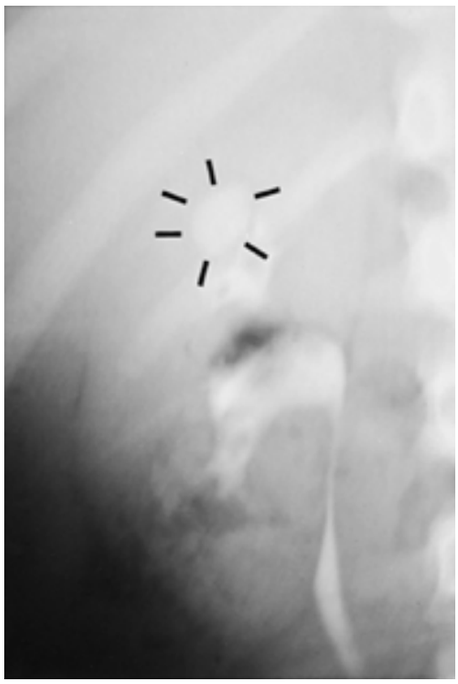

FIGURE 47.20. Excretory urographic demonstration of a calyceal diverticulum.

Megacalycosis

In this nonobstructive condition, the calyces are dilated, malformed, and often increased in number in the absence of UPJ obstruction or enlargement of the renal pelvis. Megacalycosis or megacalyces are much more common in males, and the usual presenting symptoms in children are urinary tract infections, which are not necessarily related. In adults, megaureter is associated in 10% to 20% of patients and must be proved to be nonobstructive before a diagnosis of megacalycosis can be made with certainty (40). Histologically, the renal cortex is normal, but the medulla is underdeveloped, which correlates with malformation of the renal papillae and an almost universally present defect in tubular concentrating ability.

The diagnosis of megacalycosis can be made only when there is no anatomically or functionally definable site of obstruction in the urinary tract. However, the etiology may involve a transient obstruction in fetal life during the period of early parenchymal development (40,55). The observations on transient fetal hydronephrosis and the similarity between megacalycosis and the postoperative appearance of successfully corrected UPJ obstruction give credence to this theory. Occasionally, the clinical features and radiographic findings of these two conditions appear to overlap, which leads to diagnostic confusion (93).

Megacalycosis must be differentiated from true obstructive uropathy and from acquired conditions that produce infundibular scarring and calyceal dilation. As a nonobstructive anatomic deformity, the overall prognosis is excellent.

Infundibulopelvic Stenosis

Infundibulopelvic stenosis is a rare form of congenital hydrocalycosis in which the narrowed and at times distorted infundibula drain variably dilated calyces into a small, nonobstructed renal pelvis (Fig. 47.21). Although the cause of this condition is unknown, it may have embryologic significance as a link in the spectrum of congenital upper urinary tract obstructive anomalies, which ranges from infundibulopelvic dysgenesis, hydrocalycosis, and calyceal diverticulum through UPJ obstruction to severe multicystic renal dysplasia (60,132). Clinically, infundibulopelvic stenosis must be differentiated from renal malignancy as well as from the more recognizable and correctable forms of hydronephrosis. Unless it is associated with significant renal parenchymal dysplasia, this abnormality rarely progresses (73,110).

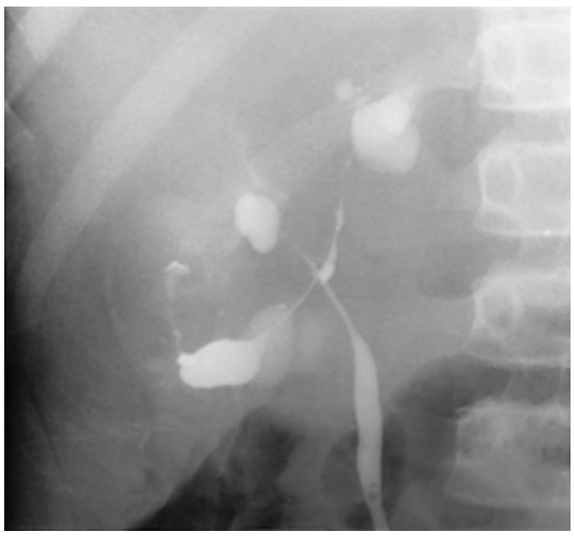

FIGURE 47.21. Infundibulopelvic stenosis. Excretory urogram demonstrates dilated calyces and narrowed, elongated infundibula, which fuse to form narrowed upper ureter; renal pelvis although almost nonexistent is not obstructed.

Ureteropelvic Junction Obstruction

Before the era of ultrasonography, hydronephrosis caused by obstruction at the UPJ was considered a common cause of hydronephrosis in children and adolescents. Although its overall incidence was difficult to estimate, presentation was often in younger children; 25% of cases were diagnosed within the first year of life and 50% recognized before the age of 5 years (56,139,140). With the use of routine perinatal ultrasonography, hydronephrosis suspected of being caused by UPJ obstruction is now recognized in nearly

1 in 500 live births (5,44). This condition occurs more commonly in males, especially neonates, with left-sided lesions predominating. Bilateral obstruction has been reported to occur in 10% to 40% of patients and, again, is more common in infants (71,135,140). Occasionally, true UPJ obstruction occurs in a duplicated kidney and usually affects the lower pole moiety (Fig. 47.22).

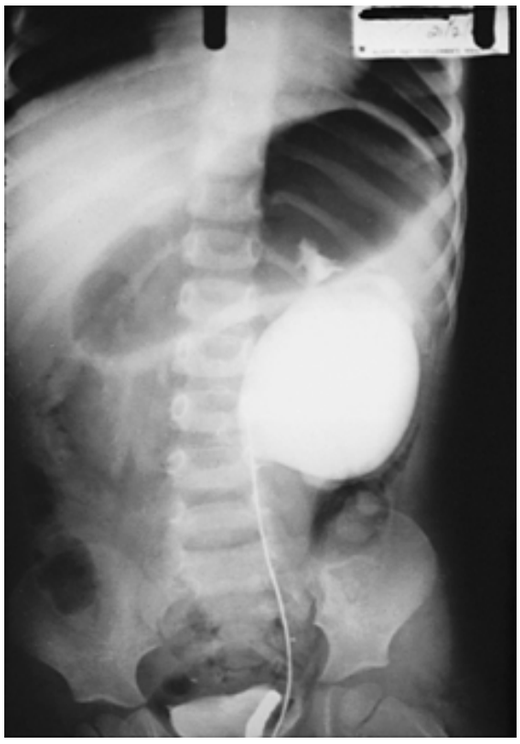

FIGURE 47.22. Sequential retrograde pyelograms of each moiety of a duplicated kidney demonstrates ureteropelvic junction (UPJ) obstruction affecting the lower pole.

Pathophysiology

Hydronephrosis may be caused by a variety of anatomic lesions or functional disturbances of the UPJ, which restrict urinary flow across this region either by compression of the UPJ and/or by interference with peristalsis. Because complete obstruction to the UPJ causes relatively rapid renal destruction, most clinical cases of hydronephrosis are thus suspected of being caused by a partial rather than a total obstruction. Although hydronephrosis associated with partial UPJ obstruction has a potential to cause progressive dilation and renal deterioration, such does not necessarily occur. In some instances, a state of equilibrium will occur, whereas in others improvement may even be spontaneous. These phenomena are recognized clinically both in patients with lifelong UPJ-type hydronephrosis who have no measurable reduction in renal function (Fig. 47.23) and in those adults and children followed nonoperatively who develop neither loss of renal function nor progressive urinary tract dilation (12,134). Also, the clinical observations that as many as 40% of patients show no measurable radiographic improvement after pyeloplasty for UPJ obstruction suggests

that partial obstruction was not functionally significant (32,49,56,140). Experimental studies support these clinical observations. Application of a ligature to the UPJ or burying the ureter in the psoas muscle in dogs produces initial hydronephrosis, but thereafter, not all kidneys progressively dilate; some reach an equilibrium, dilate no further, and maintain stable renal function (65,90).

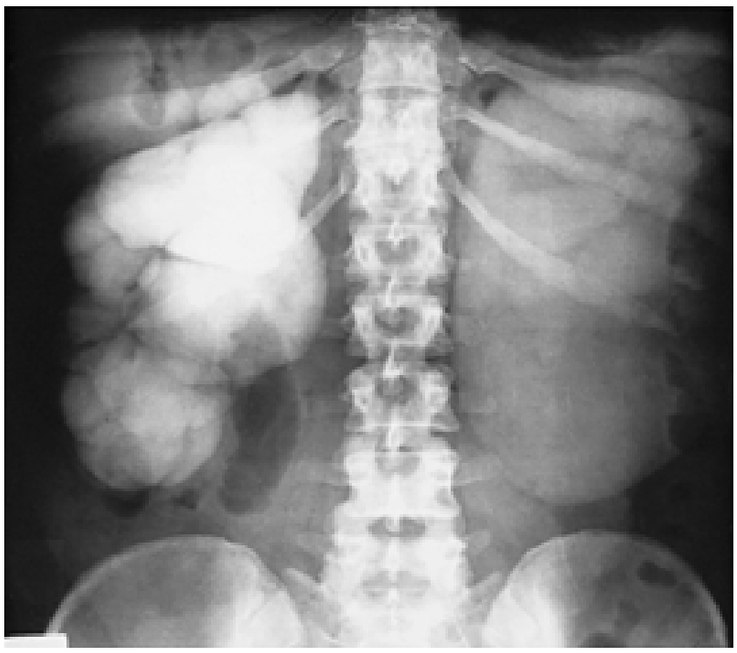

FIGURE 47.23. Incidentally discovered bilateral congenital UPJ-type hydronephrosis in a 72-year-old woman who had normal renal function and no symptoms attributable to the urinary tract.

The potential for progression or equilibration in hydronephrosis appears to be determined by several physiologic factors. These include (a) urinary output and flow rates during diuresis, (b) the anatomy and function of the UPJ, (c) glomerular and tubular renal function, and (d) pelvic compliance. Experimental pelvimetric studies have helped clarify the relative importance and interrelationship among these factors. Pelvimetric study of the renal pelvis involves temporarily occluding the UPJ while infusing saline into the pelvis and simultaneously measuring renal pelvic pressure and volume (63,65,91). This is analogous to a cystometric examination in which a pressure volume curve is generated that describes the visceroelastic properties of the renal pelvis. The results of numerous pelvimetric studies have shown that all kidneys, whether normal, obstructed, dilated but nonobstructed, or previously obstructed, are characterized by a similar shaped pelvimetric curve: Low-pressure filling or accommodation occurs until a critical pelvic volume, unique for each pelvis is reached—the "capacity volume" of the renal pelvis. This capacity volume is analogous to bladder capacity and represents the volume above which low-pressure accommodation is no longer possible and overstretching of pelvic smooth muscle and elastic and connective-tissue components occurs. Above this volume, pressures rise rapidly as volume expands further (Fig. 47.24). As the size of the pelvis increases, two important pelvimetric changes take place, which determine the likelihood for progressive hydronephrotic dilation and renal damage: (a) The pelvis stretches, and its "capacity volume" and compliance increase, causing (b) the slope of the pelvimetric curve above the "capacity volume" to flatten (Fig. 47.25). As a result, large hydronephrotic kidneys require proportionately greater volumes of urine to overdistend their pelves and to develop high intrapelvic pressures, and once the pelvis is overdistended, intrapelvic pressures rise at a much slower rate in kidneys with large pelves than in those with small pelves. These findings explain (a) why kidneys with a small intrarenal pelvis are more vulnerable to renal damage from obstruction (they will rapidly develop high intrapelvic pressures) and (b) why kidneys with large pelves are seemingly protected from obstructive injury (they can accept larger volumes of urine before pressures begin to rise and once overdistended, pressures rise at a much more gradual rate). Consequently, once kidneys develop a large extrarenal pelvis with relatively increased compliance as a result of partial obstruction, they may reach a state of hydronephrotic equilibrium and deteriorate no further (14,65).

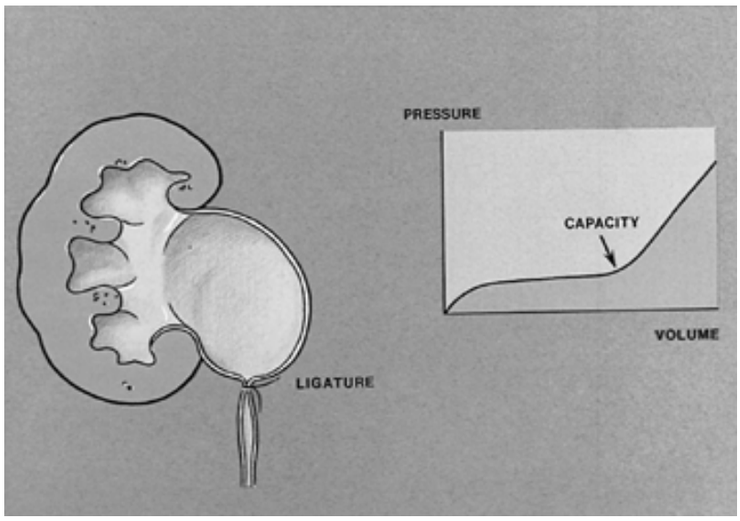

FIGURE 47.24. Pelvimetric study of the renal pelvis displays characteristic pelvimetric tracing, which defines the capacity of the renal pelvis and the slopes of the accommodation and filling phases below and above capacity.

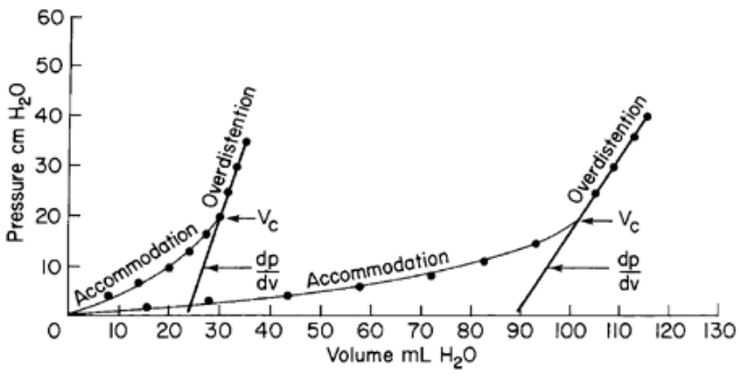

FIGURE 47.25. During progression of hydronephrosis, pelvimetric studies demonstrate an increase in pelvic capacity (V_c) and a decrease in the slope of the overdistention portion of the curve (dp/dv). (From Koff SA. the diagnosis of obstruction in experimental hydronephrosis: mechanisms for progressive urinary tract dilation. *Invest Urol* 1981;19:85, with permission.)

Experimental studies also have shown that a partial UPJ obstruction that is capable of causing a normal kidney to initially dilate and become significantly hydronephrotic may not be significant enough to cause the now dilated kidney to develop progressive hydronephrosis or renal injury. The kidney may no longer be able to induce a diuresis sufficient to overfill the renal pelvis and to cause intrarenal pressures to rise. In this setting because of acquired changes in pelvic size, compliance, renal function, and nephron mass, hydronephrosis may have become a beneficial compensatory mechanism that protects the kidney from further

injury (65,69). These interrelationships and observations have special importance in neonatal hydronephrosis, where the combination of a disproportionately large, stretchy, highly compliant renal pelvis, immature renal function, and reduced urinary output tend to minimize or eliminate completely the potentially harmful effects of partial UPJ obstruction and, in some cases, allow hydronephrosis to spontaneously improve. Witness the fact that reviews of the natural history of nonoperated UPJ-type hydronephrosis in newborn infants indicate that only approximately 25% of infants will actually be found to have an obstruction or display any evidence of renal deterioration or progression of hydronephrosis and require pyeloplasty (21,66,67,134).

Ureteropelvic Junction Anatomy

Various anatomic abnormalities can affect the UPJ to cause restriction of flow and obstruction. *Intrinsic* lesions are easily recognized during radiographic evaluation and at the time of surgery. Although true strictures at the UPJ are rare findings, the upper segment of the ureter is often visibly narrowed and thinned but probe-patent (Fig. 47.26 and Fig. 47.27). This narrowing may represent an arrest in development (2) which can be explained embryologically by the fact that during fetal life the ureter undergoes a continuous process of obstruction and recanalization, which, if incomplete, may produce narrowing and obstruction (105). The fetal ureter also may show intraluminal muscular invaginations, folds or valvelike structures, which can persist postnatally; ordinarily these are nonobstructive and disappear with time. However, if these folds become overdeveloped, they may produce obstruction to the upper ureter or UPJ (54) (Fig. 47.28).

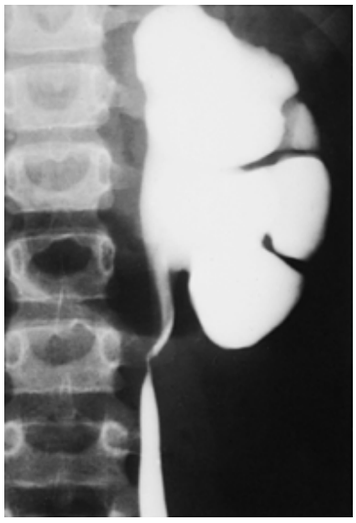

FIGURE 47.26. Ureteropelvic junction obstruction due to narrowed segment of upper ureter.

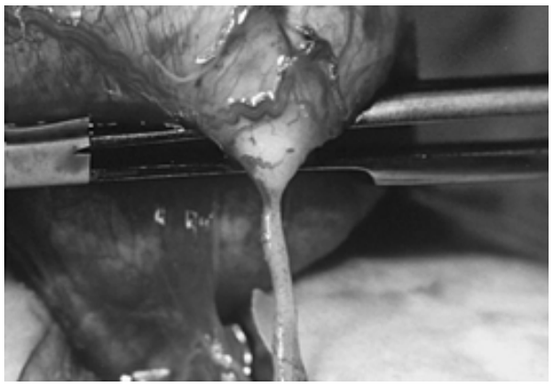

FIGURE 47.27. Anatomic appearance of intrinsic ureteropelvic junction obstruction caused by narrowed upper ureteral segment.

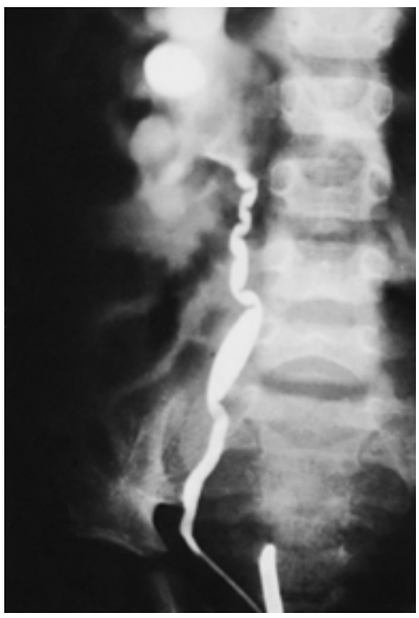

FIGURE 47.28. Ureteropelvic junction obstruction associated with prominent ureteral folds.

Although there is no histologic difference between the normal UPJ and the remainder of the upper urinary collecting system (62), histologic differences have been identified in cases of obstruction by several authors, but their findings and interpretations have differed. Abnormalities include a preponderance of longitudinal muscle fibers, excessive collagen fibers in and around muscle bundles, and compromised or attenuated muscle bundles (34,47,58,83,119). All of these changes can, to some extent, interfere with normal ureteral peristalsis and urine transport, but it remains genuinely unresolved as to whether these changes better represent the cause or are merely a histologic effect of the obstruction.

Extrinsic mechanical abnormalities at or below the UPJ may produce morphologic alterations and functional disturbances that impair pelvic emptying. This type of obstruction is commonly caused by an aberrant or accessory renal artery or early branching vessel to the lower pole of the kidney or a similarly positioned fibrous band that typically passes anterior to the pelvis and ureter to produce kinking, compression, or both. Although this type of ureterovascular

hydronephrosis has been reported to occur in up to 40% of patients, not all observers are convinced that the crossing vessel or band is the sole or inciting cause of the obstruction (56). Interestingly, in contrast to older children and adults, crossing vessels are rarely encountered in young children with prenatally detected hydronephrosis (104). This suggests that the mechanism for hydronephrosis and obstruction in the fetus and young child may be altogether different than for the older patient. In many instances, an underlying primary intrinsic disturbance of the UPJ may exist or coexist to produce obstruction, which results in pelvic overdistention and rotation. This rotation may then distort the normal anatomy and give the illusion that vessels or bands are the primary cause of obstruction. Stephens' (121) observations on ureterovascular hydronephrosis support this view by indicating that transient or permanent defects in medial rotation of the renal pelvis predispose the UPJ to vascular obstruction. Insertion of the ureter high onto the pelvis instead of in a dependent position may produce a similar type of mechanical obstruction that combines a deficiency in UPJ funneling with pelviureteral adhesions that can angulate and/or compress the ureter against the expanding pelvis (Fig. 47.29 and Fig. 47.30). Extrinsic obstructions of this type have important clinical implications, especially at the time of surgical repair. It must not be assumed that apparent extrinsic compressions or mechanical disturbances are the sole cause of impaired pelvic emptying and that their correction will relieve obstruction. The possibility that a coexisting intrinsic disturbance at the UPJ also exists must be considered, assessed intraoperatively, and if present, treated appropriately. In addition, it has been hypothesized that in some cases, UPJ obstruction may be caused entirely by a functional disturbance in the ability of the pelvis and upper ureter to function synchronously to initiate, form, or conduct peristaltic waves across the UPJ (23,138). This concept is obvious in those cases when no other cause for the obstruction is apparent, but it also may be operative in certain cases when after release of an obvious extrinsic obstruction, the now normally appearing UPJ does not

function properly and resection of an adynamic UPJ segment is required for complete relief of obstruction.

FIGURE 47.29. Ureteropelvic junction obstruction associated with high insertion of the ureter into the pelvis.

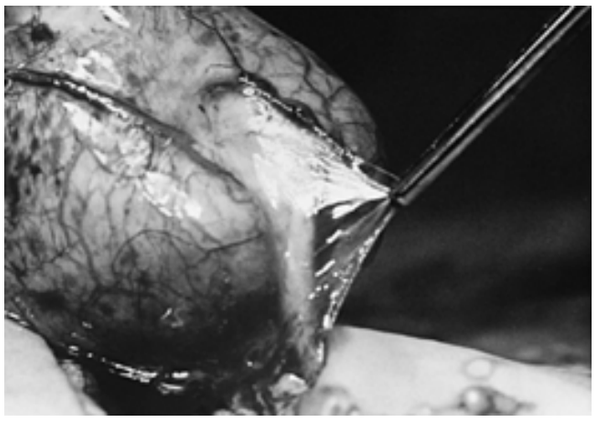

FIGURE 47.30. Anatomy of extrinsic ureteropelvic junction obstruction demonstrates adventitial tissue compressing the upper ureter against the overdistended renal pelvis.

Ureteropelvic Junction Function

The different forms of pathologic anatomy of the UPJ, intrinsic and extrinsic, not only produce dissimilar degrees of static compression and obstruction at the UPJ, but also they produce altogether different patterns of dynamic urinary flow across the UPJ, which has important clinical implications. These distinctive flow patterns determine to a great extent the potential for progression or equilibration of hydronephrosis and influence the accuracy of diagnostic tests that aim to assess obstruction in hydronephrosis (68). Intrinsic obstructions, such as ureteral narrowing or an adynamic segment tend to be fixed in severity, produce a constant degree of obstruction, and are characterized by a linear pressure-flow curve in which the rate of flow across the UPJ is determined and driven primarily by increases in intrapelvic pressure. This flow pattern has been termed *pressure dependent*. In contrast, extrinsic UPJ obstructions such as kinks, angulations, or compressing bands or vessels tend to vary in severity, produce a changing degree of resistance, and are characterized by a nonlinear pressure-flow curve in which flow rate depends primarily on renal pelvic volume and is determined by how tightly the ureter is kinked by or compressed against the overdistended renal pelvis. This flow pattern has been termed *volume dependent* because even at high pressures, flow may be low or absent. With this pattern, when pelvic volumes are small, resistance is usually low and obstruction may be absent altogether. However, during a diuresis when the pelvis enlarges to a sufficient volume, obstruction may be activated, produce ureteral compression, and thereby induce self-perpetuating progression of obstruction by causing further pelvic enlargement, which increases obstructive compression. This sequence of events may be recognized clinically and at surgery in cases in which adventitial bands bind the pelvis and ureter together and become more compressive as the pelvis overfills and the bands are drawn taut (Fig. 47.31).

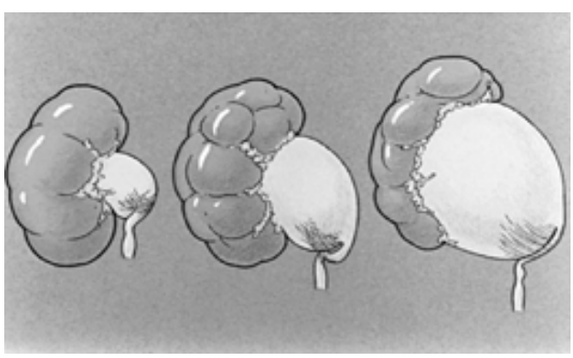

FIGURE 47.31. Representation of the sequence of events involved in activation of an extrinsic volume dependent obstruction by diuresis, which causes renal pelvic volume expansion and overdistention. This allows adventitial bands to tightly compress the ureter against the dilating renal pelvis.

In trying to relate the anatomy and function of the UPJ to its clinical behavior, it appears that intrinsic or extrinsic obstructions with pressure and volume-dependent flow patterns can explain many of the differences observed in the way kidneys respond to partial obstruction and the difficulties encountered in trying to diagnose obstruction. These discrepancies are related primarily to the intermittency of the obstruction. Intrinsic obstructions are almost always present, whereas extrinsic obstructions are not active at all times, but instead fluctuate depending on the renal pelvic volume. Renal function and the ability of the kidney to initiate and sustain a diuresis are thus major factors in determining the timing and extent of pelvic overdistention and if obstruction becomes activated.

The diagnosis of obstruction can be particularly difficult in cases of intermittent obstruction, especially if the pelvis is minimally or not dilated between episodes of overdistention because diagnostic tests may simply report that urine flows freely across the UPJ. In this setting, successful diagnosis often requires provocative testing during ultrasound or excretory urography with fluid loading to induce a diuresis; dynamic studies such as diuretic renography or Whitaker's pressure-perfusion test also may be particularly helpful in provoking or sustaining pelvic overdistention (68). Occasionally, testing must be performed during an episode of pain because this is the only way to actually prove the diagnosis (76).

Presentation

In cases of symptomatic UPJ obstruction, the presenting signs and symptoms depend on the age of the patient. Pain, hematuria, or urinary infection is more common in older children, whereas infants usually present with a palpable

abdominal mass (56,117,139). The pain often simulates gastrointestinal disease, especially if it is intermittent and associated with vomiting. Hematuria, which often occurs after mild abdominal trauma, is particularly significant because it reflects an increased susceptibility of the already dilated kidney to injury. Episodic intermittent flank pain associated with increased fluid intake is another recognizable presentation pattern that suggests sudden overdistention of the renal pelvis associated with diuresis. Congenital anomalies are commonly associated with UPJ obstruction and may occur in up to 50% of patients (71,102,135); however, genitourinary tract abnormalities usually are seen in only 10% of patients (56,117).

Diagnostic Evaluation

Most cases of perinatal hydronephrosis are not symptomatic and are detected initially by ultrasonography. UPJ obstruction is suspected when the pelvis is enlarged and the ureter is not dilated. In this age group, a voiding cystogram is required to exclude vesicoureteral reflux, which can produce renal pelvic and calyceal dilation indistinguishable from obstruction. In older patients, an excretory urogram is often the first study to identify hydronephrosis. The pattern of hydronephrosis caused by UPJ obstruction has a characteristic radiographic appearance; the pelvicalyceal system is dilated, contrast transitions abruptly at the UPJ and the ureter is either nonvisualized or of normal caliber (Fig. 47.32). These diagnostic findings also may be produced by (a) obstruction at the ureterovesical junction with incomplete visualization of a dilated ureter, (b) lower urinary tract obstruction, or (c) vesicoureteral reflux. To exclude these other causes, one should obtain delayed filming (during excretory urography) and perform voiding cystography. However, visualization of a normal ureter on delayed films does not exclude significant urinary obstruction, nor does identification of reflux or a dilated ureter exclude coexisting obstruction at the UPJ.

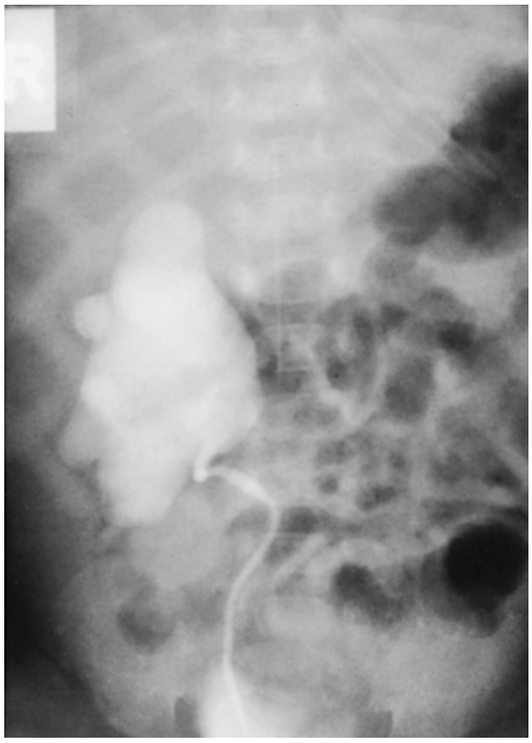

FIGURE 47.32. UPJ obstruction demonstrated by retrograde pyelogram illustrates characteristic features. Pelvicalyceal dilation and abrupt transition at ureteropelvic junction to normal-caliber ureter are noted.

Reflux associated with hydronephrosis may present particular diagnostic difficulty (Fig. 47.33). If there is trapping of urine in the pelvis following voiding and pelvic dilation persists, UPJ obstruction may coexist. In this setting, a diuretic renogram may be able to determine if primary UPJ obstruction also exists, but it must be performed using a continuously draining bladder catheter to allow the UPJ to be analyzed independent of the reflux by eliminating any reflux-induced pelvic overdistention. The use of diuretic renography and constant perfusion pressure flow testing also are required whenever the diagnosis of UPJ obstruction is equivocal (64,94,138). A more detailed discussion of the application of diagnostic tests in the diagnosis of hydronephrosis is presented in Chapter 48B .

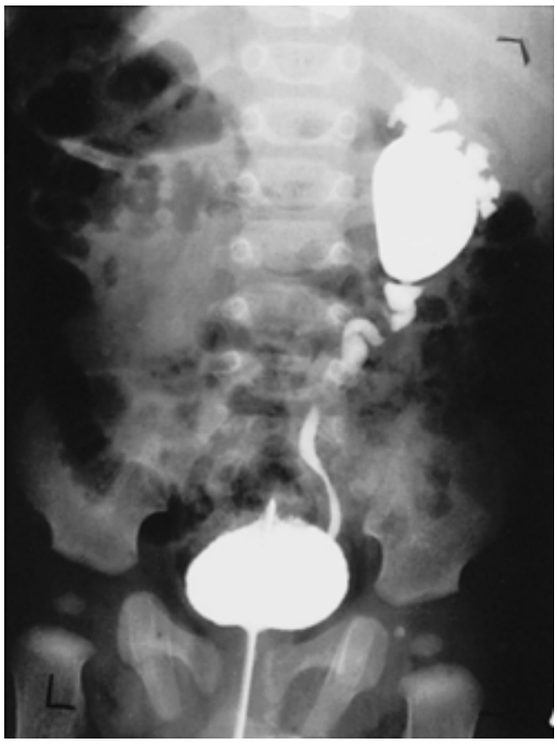

FIGURE 47.33. When mild reflux is associated with pelvic hydronephrosis, ureteropelvic junction (UPJ) obstruction may coexist even though refluxed urine crosses the UPJ. A postvoiding study is required. If hydronephrosis persists, diuretic renography performed with a continuously draining bladder catheter is required.

Before surgical treatment of UPJ obstruction, it is necessary to prove that the ureter is normal in caliber and not obstructed. In some cases this information can be obtained by visualization of a normal ureter on excretory urography

or noting normal ureteral transport and size at renography. When required, precise anatomic delineation of the ureter, pelvis, and UPJ before surgery may be obtained by retrograde or antegrade pyelography.

Prognosis

The prognosis for kidneys obstructed at the UPJ is generally good when surgery is performed in childhood. Anticipated renal recoverability generally correlates inversely with the age of the patient and with the duration and severity of obstruction and the extent of renal injury. Because of the unpredictably great potential for renal recoverability in young children, reconstructive surgery is almost always performed in childhood with nephrectomy reserved for only the most hopelessly damaged and dysplastic specimens.

RENAL VASCULAR ANOMALIES

Part of "47 - ANOMALIES OF THE KIDNEY "

Aberrant and Accessory Vessels

Normal vascular anatomy of the kidney and its variations are described and discussed in Chapter 1 . In addition to normal variations, two anomalies of blood supply must be recognized: aberrant and accessory renal vessels. The term *aberrant* should be reserved for arteries that originate from vessels other than the aorta or main renal artery (43). True aberrant vessels are rare except in association with anomalies of renal position and fusion such as renal ectopia and horseshoe kidney, in which they may arise from a number of nearby major arterial trunks.

Accessory renal arteries are multiple arterial branches supplying the same renal segment. They occur rather frequently (23%) and are more common on the left side (Fig. 47.34). Accessory arteries enter the lower pole twice as frequently as the upper pole and typically pass caudal to the main renal artery (4).

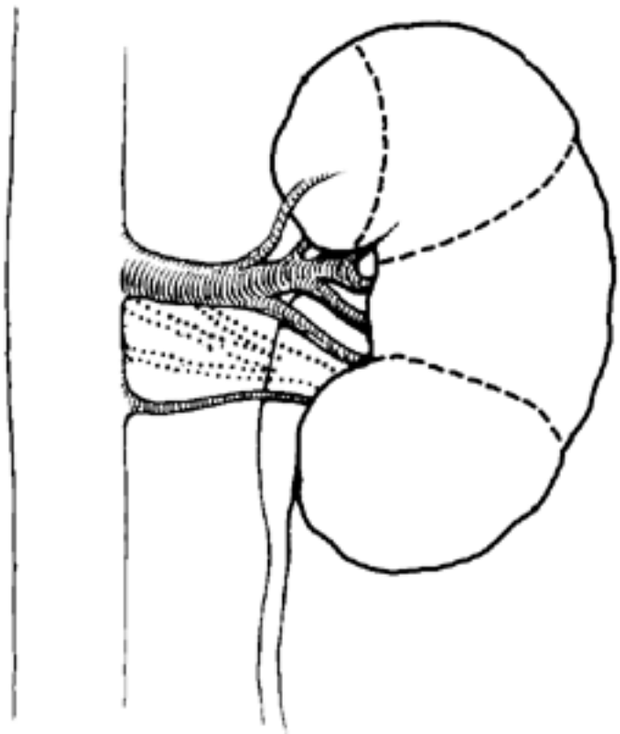

FIGURE 47.34. Accessory renal arteries more commonly supply lower pole of left kidney.

Vascular anomalies typically become clinically significant only when they interfere with urinary drainage to produce symptoms or to create unexplained filling defects on the excretory urogram. Characteristic vascular-induced patterns include UPJ obstruction due to an aberrant or accessory vessel to the lower pole and superior infundibular compression producing calyceal enlargement and pain.

Renal Arteriovenous Malformation and Fistula

Arteriovenous malformation (AVM) and fistula (AVF) of the kidneys are direct communications between the renal arteries and veins via enlarged, tortuous vascular spaces (123). AVF is most common and is usually acquired as a result of renal biopsy or trauma (Fig. 47.35). Congenital AVM of the kidney is rare and usually presents in adulthood, more commonly in women (3:1) and in the right kidney (133). Two types have been described: (a) *cirsoid* (resembling varices) with multiple vascular communications (38) and (b) *aneurysmal* with a single cavernous channel and a well-defined arterial and venous element (141). Congenital AVM accounts for 25% to 30%; the rest are acquired secondary to arteriosclerosis, neoplasia, fibrodysplasia, or trauma, especially renal biopsy (53,74,123). Although many AVM remain asymptomatic, their presentations reflect the local and system disturbances caused by each lesion. Hematuria is common and is probably related to the proximity of the anomaly to the pelvicalyceal wall.

As the lesion enlarges and shunting increases, the perfusion of renal parenchyma decreases, leading to renin-mediated hypertension. In addition, large fistulae can produce high output cardiac failure, an abdominal mass, or flank pain (74). On physical examination, a loud bruit is often heard in the abdomen. Some lesions have been reported to affect renal function and cause polyuria and electrolyte abnormalities (141).

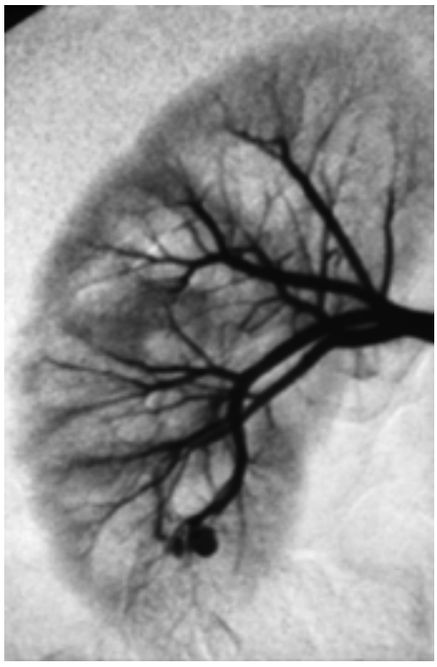

FIGURE 47.35. Selective renal arteriogram performed after renal biopsy demonstrates an arteriovenous fistula in the lower pole of the right kidney.

Intravenous urography may be normal in up to 50% of patients. In others it can show characteristic findings such as a segmental or generalized reduction in renal function, distortion of calyces or pelvis by an enlarging mass, and filling defects caused by clots. Renal ultrasonography of these lesions typically reveals anechoic structures located within the kidney in association with an enlarged renal vein (22). Ultrasound with color Doppler (USD), CT, and MRI also may suggest the diagnosis; however, arteriography remains the gold standard for diagnosis (74,123). The diagnosis of renal AVM is typically made by selective angiographic studies (137). Tortuous vascular channels, shunting with early filling of venous vessels, and an enlarged renal vein are pathognomonic (137,141) (Fig. 47.36). Visualization of the inferior vena cava within seconds of the arteriogram phase is considered the hallmark of renal AVM. Importantly, arteriography provides the opportunity not only to diagnose but also to simultaneously treat the lesion with transcatheter embolization (137).

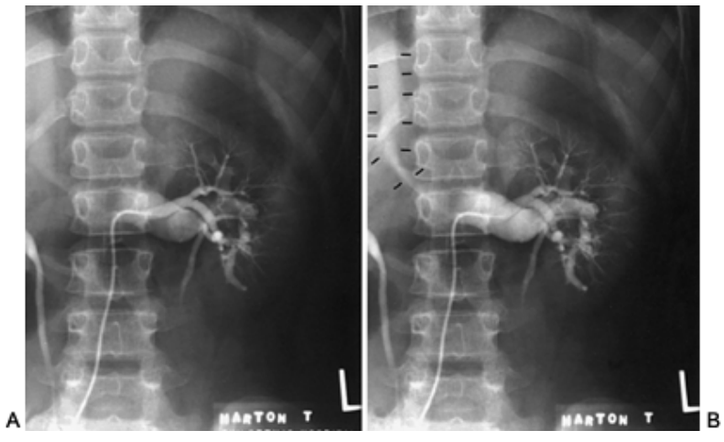

FIGURE 47.36. Arteriovenous fistula involving lower pole of left kidney visualized by selective arteriography. **A:** Early injection film shows tortuous vascular channels and early filling of enlarged renal vein. **B:** Later film shows prominent, dilated renal vein and contrast in inferior vena cava.

Treatment of renal AVM depends on the etiology, symptoms, size and location, and presence of associated renal artery disease (137). Small asymptomatic lesions can be managed nonoperatively, especially because angiographic evidence of spontaneous closure has been reported. Nonoperative management is especially suited for postrenal biopsy AVF, with embolization usually reserved for excessive bleeding requiring multiple transfusions. Medium and large symptomatic fistulae have been treated successfully with percutaneous transluminal embolization or surgical resection requiring partial or total nephrectomy (123,137). Recent reports with long-term follow-up of transcatheter embolization of cirsoid AVM describe excellent results (123). Excision may be more appropriate for large lesions with associated arterial disease, those that fail embolization, or if a malignancy is suspected.

Renal Artery Aneurysm

Renal artery aneurysms (RAAs) occur with equal frequency in both sexes and have been reported in all age groups (1 month to 82 years). Approximately 80% are unilateral, 17% are intrarenal, and in 30% of patients, the lesions are multiple. Two morphologic types of RAA are commonly described: saccular (most common type) and fusiform.

The clinicopathologic classification of pediatric aneurysms suggested by Sarkar and associates characterizes aneurysms into two broad categories, true aneurysms and false aneurysms (107). True aneurysms contain all three layers of the arterial wall and may be congenital or acquired. In false aneurysms, the wall contains fewer than the three normal layers, usually none (45). This classification is appropriate

for RAAs when true RAA can be further classified into aneurysms associated with (a) arterial infection, (b) giant cell aortoarteritis, (c) autoimmune connective-tissue disorders, (d) Kawasaki's disease, (e) Ehlers-Danlos and Marfan syndromes, (e) arterial dysplasia, (f) other forms of noninflammatory medial degeneration, and (g) congenital or idiopathic factors. The second main category, false aneurysms, are those associated with extravascular events causing vessel wall injury or disruption (107).

The incidence of RAA in children is less than in adults (15). Congenital RAA are usually recognized in children younger than 5 years of age. The presence of all three layers of the vessel wall without arteritis is necessary to confirm the diagnosis. However, most RAAs in children are of the acquired type and specifically represent renal artery dysplasia (45). This condition affects only the renal arteries and usually is associated with renal artery stenosis and hypertension. It is typically diagnosed by arteriogram performed to evaluate hypertension and is treated by surgical excision. Trauma and infection are also common causes of pediatric RAA, and even in children, some of these aneurysms can reach a large size (8 cm) (45,87).

The presentation of children with RAA is dependent on the size and location of the lesion. Most aneurysms are small and silent; however, when they are symptomatic they may be associated with hematuria, abdominal pain, or most commonly, hypertension. Arteriography remains the diagnostic test of choice for RAA, especially if surgical intervention is considered (72,87) (Fig. 47.37). However, because of the size and character of these lesions, less invasive imaging using USD, CT, and MRI is useful in the initial investigation of RAA because of the better sensitivity and specificity (15,87). USD typically shows a cystic (hypoechoic) lesion near the renal artery with arterial pulsation (59). CT findings include a cystic lesion that enhances simultaneously with the aorta.

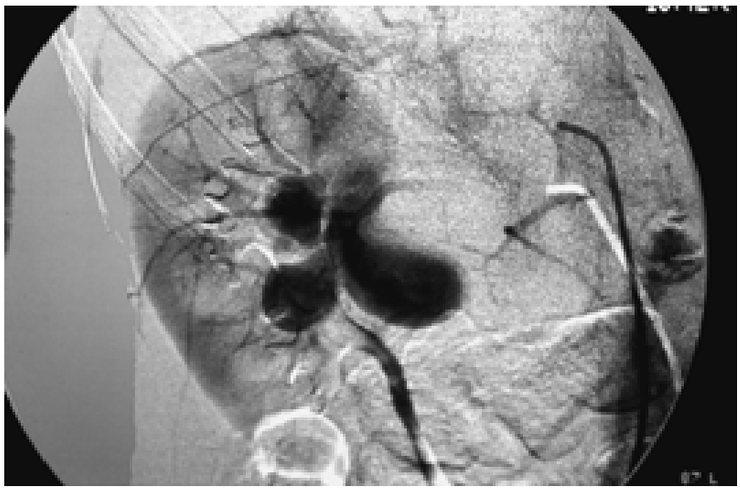

FIGURE 47.37. Selective renal arteriogram in a 12-year-old girl with severe hypertension reveals saccular renal artery aneurysms.

Treatment of RAA depends on symptoms, etiology, size, and location of the aneurysm as well as associated renal artery disease. Several authors recommend nonoperative management for asymptomatic RAA because the risk for rupture is extremely small and spontaneous cure (thrombosis) has been reported (50,70). In a study of more than 36,000 autopsies in Sweden, Tham and associates (126) found no case of death due to ruptured RAA. Small RAA due to vasculitis may be treated medically (45). Also, small intrarenal aneurysms have been treated with transcatheter embolization even in children (72). Most other types of RAA are usually treated by surgical resection using standard vascular techniques (15,87,107).

Renal Artery Stenosis

Renal artery stenosis (RAS) in children is one of the most common causes of pediatric renovascular hypertension (RVH), can have either a congenital or acquired etiology, and may occur as an isolated lesion or be part of a systemic disease. Neurofibromatosis and Williams syndrome are examples of systemic conditions that can be associated with congenital RAS (92). Acquired lesions include fibromuscular dysplasia, anastomotic stenosis, and renal artery trauma, whereas Takayasu's arteritis, Kawasaki syndrome, Marfan syndrome, Alagille syndrome, and midaortic syndrome (MAS) are systemic conditions associated with RAS (26,92,101).

The signs and symptoms of children with RAS reflect hypertension with headache, palpitation, irritability, epistaxis, encephalopathy, retinopathy, and congestive heart failure. An abdominal bruit may be heard on examination (101). Although no laboratory tests are specific for the diagnosis of RAS, selective renin sampling may be useful if the patient is hypertensive. Determination of the erythrocyte sedimentation rate (ESR) may help guide the timing of operative intervention in children with arteritis because it is recommended that surgery not be performed during the active inflammatory phase of the disease (92).

In hypertensive children with suspected RAS, several different imaging studies can be used initially, including USD, captopril renography, MRI, and CT with and without angiographic phases and arteriography (92). Currently, reports on the accuracy of captopril renography and color Doppler in diagnosing RAS in children are insufficient to draw conclusions. We recommend ultrasound initially because it is noninvasive, can detect other urologic anomalies, and in experienced hands, suggests the diagnosis of RAS in the majority of patients (46). However, the gold standard for the diagnosis of RAS is selective renal arteriography, which has a sensitivity of 98% (92) (Fig. 47.38). A large percentage of children with RAS have involvement of segmental or distal branches that are better defined with an angiogram. Angiography also allows for simultaneous transluminal balloon angioplasty (dilation) of nonostial lesions.

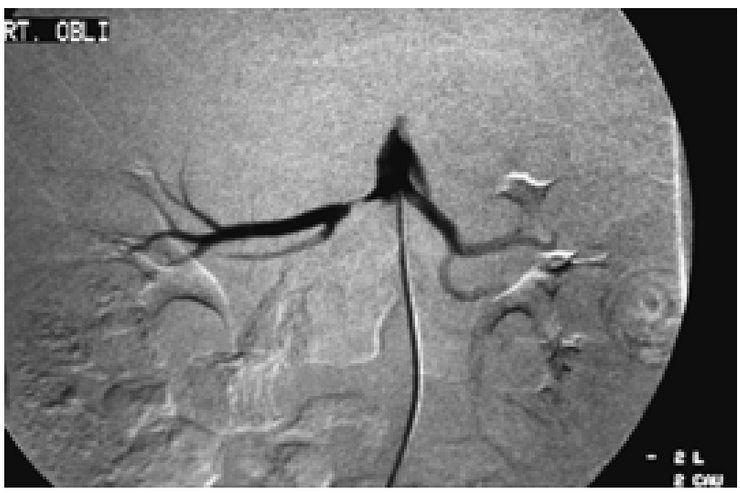

FIGURE 47.38. Arteriogram of a hypertensive child with proximal right renal artery stenosis.

In cases of medial fibrodysplasia producing arterial stenosis and hypertension, the treatment of choice is percutaneous transluminal angioplasty (PTA) or surgical bypass, depending on the specific arterial anatomy. The results of angioplasty are best when the lesions are in the midportion of the main renal artery or in its segmental branches. Angiography should be attempted when the lesion is in this favorable location. However **,** many children have lesions affecting the ostia, a location that is better treated with surgery (92,101). Angiography should be attempted when the lesion is in a favorable location or when associated with nonspecific aortoarteritis (114). Tyagi and co-workers (131) reported a 91% success rate in 35 children with renovascular hypertension treated with PTA.

Midaortic Syndrome

Midaortic syndrome (MAS) is a relatively rare condition that involves segmental narrowing of the distal thoracic and/or abdominal aorta, including the visceral and renal arteries. Other names have been given to this condition, including subisthmic coarctation, abdominal coarctation, mesenchymal disease of neurofibromatosis, and aortoarteritis (95). Typically, these patients present in their second decade of life with severe hypertension, an abdominal bruit, and absent or diminished femoral pulses (101). Diagnosis requires arteriography, and renal revascularization is required (Fig. 47.39).

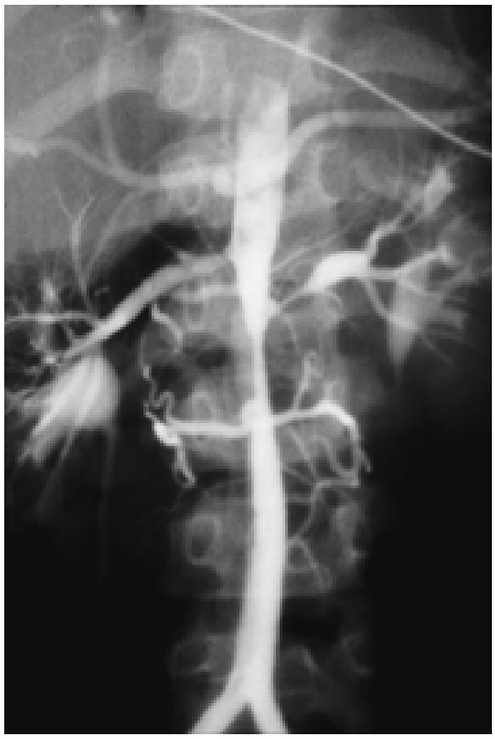

FIGURE 47.39. Preoperative aortogram in a child with midaortic syndrome demonstrates segmental narrowing of the infrarenal aorta and left renal artery stenosis.

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48

THE URETER

Contents

48A URETERAL ANOMALIES

Christopher S. Cooper

Howard M. Snyder III

Part of "48 - THE URETER "

C.S. Cooper: Department of Urology, University of Iowa College of Medicine; Children's Hospital of Iowa, Iowa City, IA 52242-1089.

H.M. Snyder, III: Department of Surgery, University of Pennsylvania School of Medicine; Division of Pediatric Urology, Children's Hospital of Iowa, Philadelphia, Philadelphia, PA 19104.

TERMINOLOGY

A standard set of definitions used to describe ureteral duplication anomalies was established by the Urologic Section of the American Academy of Pediatrics Committee on Terminology, Nomenclature, and Classification (64). A *duplex (duplicated) system* refers to a kidney with two pelvicalyceal systems. If this kidney has two ureters that empty separately into the bladder (double ureters), it is considered a *complete duplication.* A duplex system may also have a partial or incomplete duplication, in which case a single ureter enters the bladder. A *bifid system* is a form of duplication with two pelvicalyceal systems joining at the ureteropelvic junction (bifid pelvis) or before emptying into the bladder (bifid ureters).

The *upper* or *lower pole ureter* describes the ureter draining the upper or lower pole of a duplex kidney. The orifice associated with the ureter draining the upper or lower pole is known as the *upper* or *lower pole orifice,* respectively. A *laterally ectopic* ureter inserts lateral to the normal position and a *medially* or *caudally ectopic ureter* inserts medial and distal to the normal position on the trigone. An *ectopic ureter* drains to an abnormal site and generally refers to an orifice located medially or caudally.

A ureterocele consists of a cystic dilation of the intravesical submucosal ureter. Ureteroceles contained entirely

within the bladder are called *intravesical ureteroceles*. *Ectopic ureteroceles* contain a portion permanently situated at the bladder neck or urethra. A *single-system ureterocele* is associated with a kidney with only one ureter. A *duplex-system ureterocele* is associated with the upper pole of a kidney with a complete ureteral duplication. Ureteroceles can be characterized further as stenotic, sphincteric, sphincterostenotic, cecoureteroceles, blind, and nonobstructive, as suggested by Stephens (163).

EMBRYOLOGY AND PHYSIOLOGY OF THE URETER

An understanding of the embryology of the ureteral bud facilitates comprehension of the spectrum of ureteral anomalies to be presented in this chapter. Associated renal abnormalities result from differences in induction of renal tissue from the metanephric ridge produced by ureteral buds arising at various levels from the mesonephric duct. Normally, the ureter begins development at approximately the end of the fourth week of embryonic life as a bud originating from the mesonephric (Wolffian) duct where the duct bends sharply ventrally (the elbow) (Fig. 48A.1). The ureteral bud grows rapidly to penetrate the metanephric blastemal ridge. By 5 weeks of gestation, the renal pelvis can be discerned. As subsequent renal differentiation takes place, the ureteral bud produces the entire renal collecting system: ureter, renal pelvis, calyces, papillary ducts, and collecting ducts.

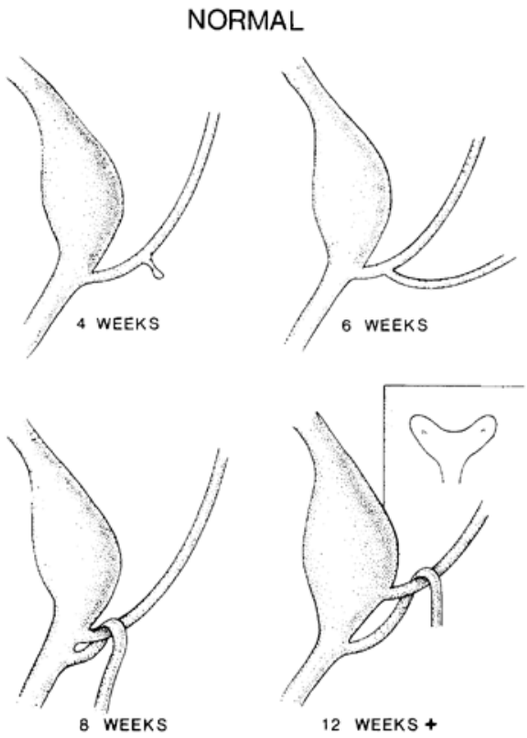

FIGURE 48A.1. Normal embryology of ureteral bud from the mesonephric duct.

The “common excretory duct” consists of that portion of the mesonephric duct between the origin of the ureteric bud and cloaca. This segment, along with a short segment above the ureteral bud, expands and inverts into the urogenital sinus by the eighth week of development forming half of the trigone. As development proceeds, the ureteral orifice migrates cephalad and laterally while the mesonephric duct moves distally and medially. By the twelfth week of gestation, the mesonephric duct reaches its final entry position in the posterior urethra at the level of the verumontanum in the male. The mesonephric duct becomes part of the epididymis, seminal vesical, and vas deferens in the male and becomes Gartner's duct in the female. This migration explains why the vas crosses over the ureter ventrally.

In normal embryology, the point at which the distal mesonephric duct joins the urogenital sinus indicates the eventual location of the bladder neck. As the common excretory duct (mesonephric duct below the point of origin of the ureteral bud) is incorporated into the expanding urogenital sinus, it forms the tissue of the bladder trigone. After ureteral bud and mesonephric duct migration is complete, the final positions of the ejaculatory duct and the ureteral orifice are roughly equidistant from the bladder neck.

Incomplete ureteral duplication results from a ureteral bud that bifurcates shortly after its origin from the mesonephric duct (Fig. 48A.2). If division of the ureteral bud

occurs late (fifth week), following the interaction of the ureter with the metanephric blastema, a bifid pelvis occurs. Before the fifth week, bifurcation of the ureteral bud will lead to varying degrees of ureteral duplication but with fusion distally to form a single ureter entering the bladder. A complete duplication with double ureters requires two ureteral buds arising from the mesonephric duct.

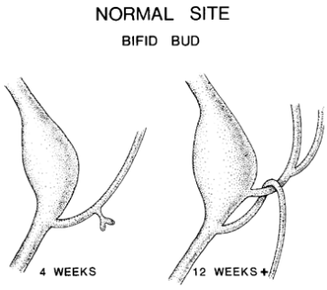

FIGURE 48A.2. Bifid ureteral bud at normal site leading to incomplete duplication of ureter.

A more lateral and cranial placed ureteral orifice is often associated with primary vesicoureteral reflux. This abnormal location of the ureter results from a ureteral bud originating at a lower-than-normal position on the mesonephric duct (Fig. 48A.3). A popular hypothesis holds that the early incorporation of this ureteral bud into the urogenital sinus permits it to migrate more laterally and cranially than normal. In this position, less trigonal support for the ureter might be expected, permitting vesicoureteral reflux. This embryologic explanation would account for what is found clinically in primary reflux: a lateral ureteral orifice with a shortened submucosal tunnel that permits vesicoureteral reflux (7,162,169).

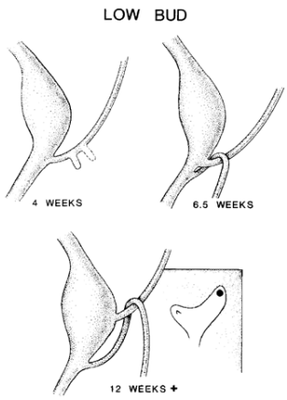

FIGURE 48A.3. Low origin of the ureteral bud from the mesonephric duct causing laterally ectopic ureteral orifice and vesicoureteral reflux.

When a ureteral bud originates slightly higher than normal on the mesonephric duct, it is incorporated into the urogenital sinus later than normal. This results in a shorter cranial and lateral migration resulting in a minor displacement of the ureteral orifice toward the bladder neck (Fig. 48A.4). However, if the ureteral bud originates very high on the mesonephric duct, it fails to be incorporated into the bladder altogether and ends in the urethra or mesonephric remnants (Fig. 48A.5). These remnants constitute the epididymis, vas, and seminal vesical in men and Gartner's duct in women. Gartner's duct runs from the broad ligament of the uterus along the lateral wall of the vagina to end at the hymen. A very high origin of the ureteral bud in the female could end anywhere along this duct and with secondary rupture of the duct into the vagina, resulting in a vaginally ectopic ureter. This explains the main sites of ectopic ureters in males and females. The important difference between the two sexes is attributed to the fact that in the male, all ectopic ureters terminate above the level of the external urethral sphincter so that urinary incontinence is uncommon. By contrast, in the female, ectopic ureters commonly exit below sphincteric control, which accounts for the history of constant wetting from the ectopic ureter despite normal voiding of urine from the ureter(s) terminating in the bladder.

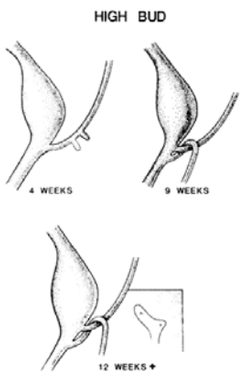

FIGURE 48A.4. High origin of the ureteral bud from mesonephric duct leading to mild degree of ureteral ectopia toward the bladder neck but still on trigone.

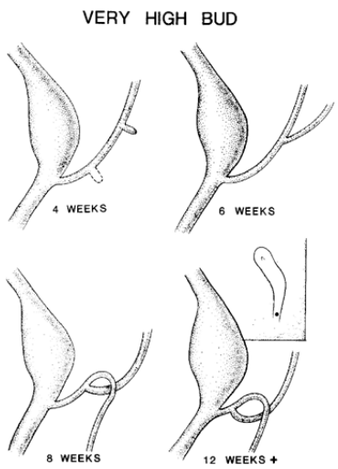

FIGURE 48A.5. Very high origin of ureteral bud from mesonephric duct causing ectopic ureter to maintain contact with mesonephric remnants (vas, epididymis, or seminal vesicle).

The presence of two ureteral buds having independent origin from the mesonephric duct explains some of the most fascinating of ureteral anomalies. If the two buds arise close

to the normal point of ureteral origin from the mesonephric duct, a complete ureteral duplication may result without any significant consequence (Fig. 48A.6). By contrast, if two buds are present, with one located normally and one low, the result would be complete duplication with vesicoureteral reflux into the ureter, which during migration was carried most cranially and laterally, that is, the lower pole ureter (Fig. 48A.7). This anomaly is a common clinical finding (8). With a duplication of the ureteral bud with one in a normal location and one high, the high ureter ends more caudally and medially than normal (Fig. 48A.8). Thus the upper pole ureter is the one that ends ectopically. This embryologic review explains the Meyer-Weigert law: When complete ureteral duplication exists, the medial and distal ureteral orifice is that of the ureter to the upper pole of the kidney (120,181). Occasional exceptions to this law have been reported (109).

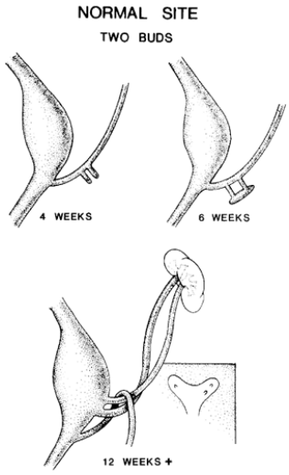

FIGURE 48A.6. Two ureteral buds at normal site on mesonephric duct leading to complete duplication of the ureter without pathologic sequelae.

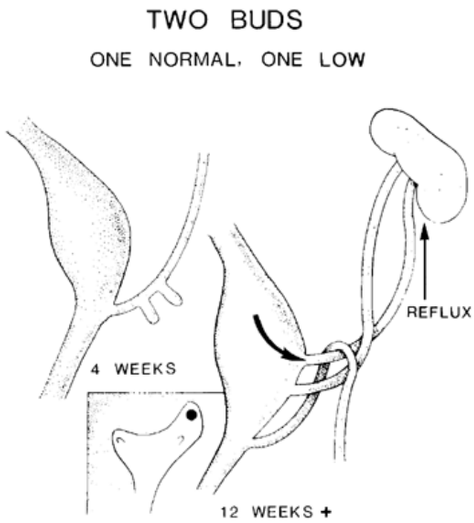

FIGURE 48A.7. Two ureteral buds, one normal and one low on the mesonephric duct, leading to complete ureteral duplication with lower pole vesicoureteral reflux.

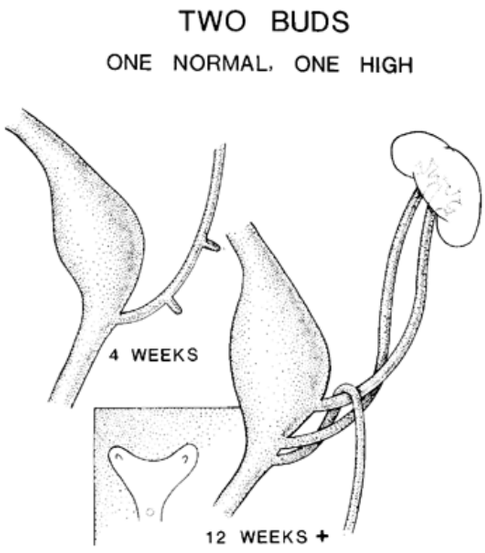

FIGURE 48A.8. Two ureteral buds, one normal and one high on the mesonephric duct, leading to complete ureteral duplication with ectopic upper pole ureter.

Ureteroceles can be defined as a cystic dilation of the terminal portion of the ureter. Ureteroceles associated with a single ureter are seen in children, usually as intravesical ureteroceles; however, ureteroceles associated with complete ureteral duplication are more common. In this situation, they are at the distal end of the ureter. They drain the upper pole collecting system and are most commonly ectopic ureteroceles, that is, a ureterocele with some portion situated permanently at the bladder neck or in the urethra.

The embryology of all ureteroceles cannot be explained by one hypothesis. Chwalla (34) pointed out in the embryo a two-cell-layer ureteral membrane that is present at the time the ureteral bud arises from the mesonephric duct. If this membrane did not completely break down, an obstructed ureteral orifice could result, leading to the formation of a ureterocele. Ureteroceles seen with stenotic orifices or associated with muscular hypertrophy of the ureteral wall support Chwalla's model. However, Stephens (164) and others have described cases in which ureteroceles are found to have large ureteral orifices. Alternatively, some suggest that the distal ureteral segment may be acted on by the same force that causes the expansion of the urogenital sinus to form the bladder (163,170,171). If this model were an adequate explanation for ureterocele formation, all caudal ectopic ureters should be associated with a ureterocele, which is not the case. Tanagho's hypothesis (Fig. 48A.9) suggests that delay in establishing the lumen of the ureteral

bud with that of the mesonephric duct could result in ureteral expansion secondary to the same process that results in expansion of the urogenital sinus into the bladder (170,171).

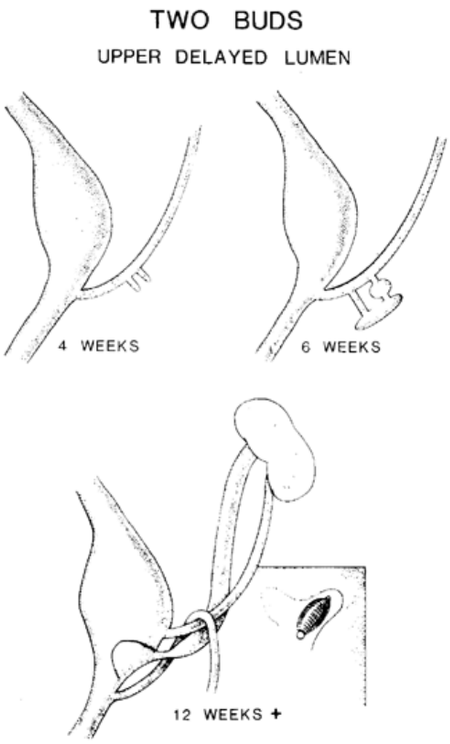

FIGURE 48A.9. Two ureteral buds with delayed establishment of lumen of upper ureteral bud leading to development of upper pole ureterocele.

Relation of Ureteral Bud Position to Renal Morphology

Renal tissue associated with ectopic ureters and ureters joining ureteroceles is often dysplastic or hypoplastic and has minimal, if any, function. In 1975, Mackie and Stephens suggested that this finding could be associated with an abnormal origin of the ureteral bud from the mesonephric duct, which, as we have seen, may account for the caudal embryologic explanation for ectopic ureters and ureteroceles (Fig. 48A.10). According to this theory, the metanephric ridge is made up of blastema with variable potential for the formation of normal renal tissue. The best potential exists in the central zone of the ridge, which would be the area

normally penetrated by a ureteral bud having origin from a normal location on the mesonephric duct. This normal ureteral bud would thus be expected to induce a kidney from the metanephric blastema with the best potential to form a normal kidney. On either side of the central zone of the metanephric ridge, the blastema may have a lesser potential to form normal renal tissue. Thus, if the ureteral bud is located above or below the normal point of origin, it may grow to induce renal tissue from blastema with an increased propensity for dysplasia or hypoplasia. This hypothesis appears to hold best for the upper pole ureters seen in complete duplications associated with ectopic ureters or ureteroceles. Less often, lateral ectopic ureteral orifices associated with vesicoureteral reflux may also be found attached to ureters draining dysplastic or hypoplastic renal tissue. Thus the Mackie and Stephens hypothesis provides an attractive explanation for abnormal renal tissue associated with a ureteral orifice, either cranial or caudal, from the location of a normal ureteral orifice at the corner of the trigone.

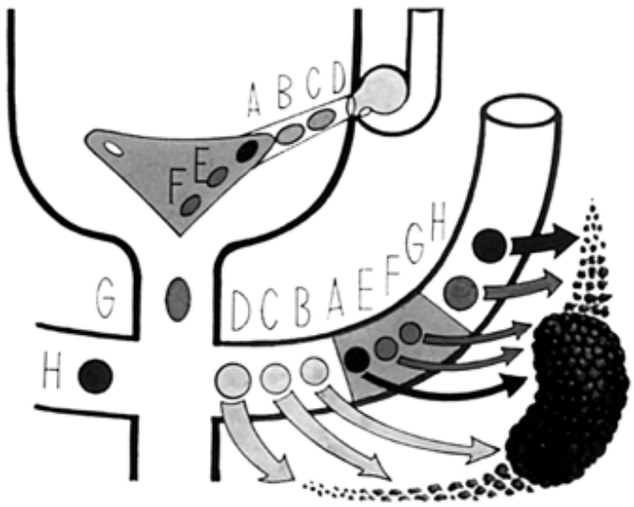

FIGURE 48A.10. Stephens' theory that an abnormal origin of the ureteral bud from the mesonephric duct leads to induction of metanephric blastema with limited potential for the formation of normal renal tissue. Composite diagram showing how a ureteral bud with near-normal origin *(A, E, F)* from the mesonephric duct will induce the kidney from the main mass of metanephric blastema and for a good kidney associated with a ureteral orifice on the trigone. Ureteral buds with an abnormal origin will induce blastema with limited potential and will be associated with an ectopic ureteral orifice.

PHYSIOLOGY OF THE URETER

The ureter consists of a syncytial type of smooth muscular tube with a urothelial lining that transports urine from the renal pelvis to the bladder. The normal ureterovesical junction prevents reflux of urine. The number of smooth muscle cells increases from birth at least to the age of 12 (44).

The transport of urine begins in the minor calyces, where pacemaker cells cause a contraction of the calyces. The smooth muscle cells of the ureter are in continuity with the calyces and renal pelvis. The contraction of the calyces is propagated along the smooth muscle cells to the renal pelvis. At normal urine flow rates, some of these contraction waves are blocked at the ureteropelvic junction (UPJ); however, most are propagated to the ureter. In children, the renal pelvis contracts an average of four times per minute, and ureteral contractions occur an average of 3.7 times per minute (52). In states of diuresis, there may be a 1:1 relationship between the pacemaker contractions of the calyces and the ureteral contractions (38). Although the nervous system may modulate the contractions, the fact that a transplanted kidney and ureter continues to contract demonstrates that peristalsis may occur without extrarenal innervation.

When a bolus of urine is pushed into the proximal ureter through the UPJ, it must be propagated to the bladder. The UPJ closes after a bolus of urine, preventing back-pressure and backflow of urine into the renal pelvis from the elevated ureteral contraction pressure (69). A contraction ring forms in the proximal ureter, and this ring of contraction migrates toward the bladder, pushing the bolus of urine distally. The pressure generated by this wave of contraction in children is approximately 30 cm H_2O (similar, but slightly less than in the adult), whereas the resting pressure in the ureter is 0 to 5 cm H_2O (52). In states of high urine output, the size of the bolus increases, and the pressure in the bolus may be greater than the contraction ring ahead of it, in which case the ureteral walls cannot coapt and urine is transported as a single column of fluid.

The intravesical ureter courses obliquely through the bladder wall. There is a normal elevation in resting pressure (10 to 15 cm H_2O) in this segment that increases with bladder filling and helps prevent reflux. In refluxing ureters, this pressure gradient has been shown to decrease (124,182). The histologic structure and autonomic innervation do not appear different in refluxing ureters relative to nonrefluxing ureters (50).

A decreasing compliance of the ureter with age suggests that more ureteral dilation occurs in neonates and young children in response to obstruction than in the adult. With dilation of the ureter, the intraluminal pressure generated by a given contractile force decreases inversely with the radius according to the Laplace equation (pressure = stress × wall thickness/radius). Therefore dilated ureters do not transport urine as well as nondilated ureters despite relief of obstruction (182).

URETERAL DUPLICATION

Incidence, Genetics, and Associated Anomalies

Ureteral duplication is the most commonly seen ureteral anomaly. In an autopsy population, ureteral duplication appears to occur in approximately 1 in 125 patients, or

0.8% (28,126). The right and left kidneys are affected equally. Bilateral duplication occurs in approximately 40% of cases (174). In clinical series, there are twice as many women with duplications as men. In series in which urography has been done for urinary symptoms, there is a much higher incidence of duplication: 2% to 4% (73). Urinary infection is the most common associated finding.

A genetic analysis of duplication indicates this anomaly may be transmitted as an autosomal-dominant trait with incomplete penetrance (35). When an index child with a duplication is found in a family, the frequency of a sibling being found with a duplication rises from 1 in 25 to 1 in 8 or 9 (11,13,185).

Patients with ureteral duplication have an increased incidence of other urinary tract anomalies. In the radiographic review of Privett and colleagues (139), 29% of the duplex units reviewed exhibited scarring, hydronephrosis, or both. Histologically, renal hypoplasia or dysplasia and pyelonephritic scarring occur more frequently. Clinically, one would expect to see an increased incidence of childhood urinary tract infections when duplications are present because of associated reflux or obstruction, and indeed, this increase is what has been found (28,101).

Incomplete Ureteral Duplication: "Y" Ureter

A ureteral bud that bifurcates early results in a partial duplication. A bifid renal pelvis is the result of the highest level of bifurcation and occurs in approximately 10% of the population. Of the other incomplete duplications, approximately 25% are found to divide in the distal or proximal third of the ureter and the remaining 50% divide in the middle section. Most partial duplications are discovered accidentally; however, with a "Y" junction in the ureter, it is possible for urine to be passed down to the junction and then, in a retrograde fashion, up the other side of the Y (27,176). This ureteral reflux, or "yo-yo," on occasion leads to stasis and ureteral dilation (Fig. 48A.11). It is most common when the bifurcation is at a low position but is rare if the duplication ends in the intramural portion of the ureter (106). It has been reported in a blind-ending bifid ureter (99). When ureteral reflux is present, there may be associated infection or flank discomfort.

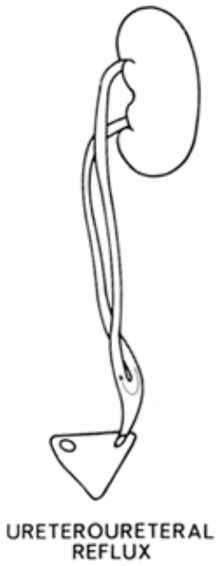

FIGURE 48A.11. Yo-yo reflux: incomplete ureteral duplication and ureteroureteral reflux.

Diagnosis is made by intravenous pyelography (IVP), particularly if fluoroscopic observation is used to observe the ureteral reflux (91). A voiding cystourethrogram (VCUG) is essential to eliminate ureteral dilation due to simple vesicoureteral reflux, which is much more common. When surgical treatment is required, the technique depends on the level of the duplication. With a low duplication, a reimplantation of the ureters into the bladder with separate ureteral orifices may be possible (5). When the duplication is higher, ureteropyelostomy or ureteroureterostomy at the renal level with excision of most of the distal duplicated ureter is curative (6).

On occasion, ureteropelvic junction obstruction may be found in association with incomplete duplex systems and may pose interesting reconstructive problems (131). Because the upper pole usually has no true ureteropelvic junction, it is almost always the lower pole collecting system that is obstructed. Usually, the lower pole ureter is short (Fig. 48A.12), and a side-to-side anastomosis of the obstructed lower pole pelvis to the upper pole ureter is required.

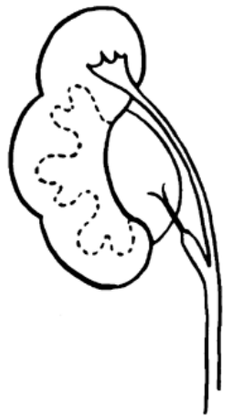

FIGURE 48A.12. Ureteropelvic junction obstruction in lower pole of duplex kidney. Usually, the lower pole ureter is too short for a ureteropyelostomy, and accordingly, a side-to-side anastomosis of the pelvis to the upper pole ureter is performed.

Incomplete Ureteral Duplication: Blind-ending Ureter

If a ureteral bud bifurcates, but only one limb induces the associated metanephric blastema, a rare form of incomplete duplication with a blind-ending ureteral stump is generated (2,135,151). Most of these duplications are in the middle or distal ureter. Women are three times more likely to exhibit this, and it is seen most frequently on the right side. A ureteral diverticulum may be confused with this entity (141). Culp's (43) somewhat arbitrary criteria help better define the true blind-ending bifid ureter: those blind-ending structures whose lumen joins that of the ureter at a clear angle, whose length is at least twice the width, and whose histologic characteristics resemble the ureter. Occasionally, a blind-ending ureteral duplication may end in the bladder and be confused with a periureteral diverticulum because of the frequent association of vesicoureteral reflux in this situation (116). The blind-ending ureter rarely causes symptoms but may generate flank pain associated with infection or calculi. A retrograde ureterogram may be required for diagnosis because the blind duplication may not fill on IVP. Treatment consists of surgical excision of the duplication.

Incomplete Ureteral Duplication: Inverted “Y” Ureter

The inverted “Y” ureter is the rarest of all anomalies of ureteral branching. The embryologic explanation presumably lies in two separate ureteral buds arising from the mesonephric duct but fusing before penetrating the metanephric ridge. This anomaly has been seen almost exclusively in females (97). If one limb is distally ectopic, urinary incontinence may result. Treatment is directed at problems caused by the ectopic limb. Usually resection of this limb is required. An inverted Y ureteral duplication with one blind-ending ureter has been reported (23).

Complete Ureteral Duplication and Vesicoureteral Reflux

When a complete ureteral duplication is present, vesicoureteral reflux is the most common cause of acquired renal disease. Reflux typically occurs into the lower moiety of a duplicated kidney (8). The upper pole ureter with its orifice medial (Meyer-Weigert law) has a longer submucosal tunnel and usually does not reflux. When reflux into both upper and lower pole ureteral orifices is seen, cystoscopy usually reveals that both orifices are side by side in a laterally ectopic position. This anomaly is embryologically explained by two ureteral buds close to one another, having an origin in a position caudal to normal on the mesonephric duct. Reflux into the upper pole ureter also may occur if its orifice is ectopic in the bladder neck or urethra. The child with duplication and reflux presents most commonly with urinary tract infection, as does the child with single-system reflux. Fehrenbaker and co-authors (59) found reflux in more than two-thirds of children with duplex systems who had a urinary tract infection. Renal Ultrasound or IVP and VCUG establish the diagnosis by showing a duplex renal system with vesicoureteral reflux usually only into the lower pole collecting system (Fig. 48A.13).

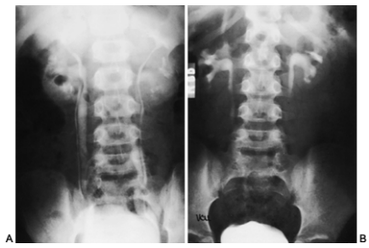

FIGURE 48A.13. Complete ureteral duplication and vesicoureteral reflux. **A:** Intravenous pyelogram showing completed duplication of ureters. **B,** Voiding cystourethrogram showing bilateral lower pole vesicoureteral reflux.

The treatment of duplicated ureters with reflux adheres to the same principles that govern the single-system ureter with reflux. When the grade of reflux is low, spontaneous resolution with linear growth of the child accompanied by lengthening of the submucosal tunnel of the ureter usually avoids the need for surgery (105,132,180). Antibiotic prophylaxis and radiographic monitoring intermittently suffice for treatment. Surgical management may be more appropriate when the grade of reflux is high and the likelihood of spontaneous resolution is small. In a complete duplication, the distal 2 to 3 cm of the two ureters usually is bound in a common muscular sheath, making their separation dangerous to one or both ureters. Surgical correction of reflux thus involves mobilization of the common sheath and reimplantation of the common sheath, even though reflux has been observed in only one ureter (14,87). The success rate for common sheath reimplantation is similar to that reported for single systems (55). When the lower pole parenchyma is very diminutive, a common sheath reimplant generally suffices unless there is major ureteral dilation. This approach avoids the need for a renal operation.

Ureteral Triplication

Ureteral triplication is one of the rarest anomalies of the upper urinary tract. In their review of the literature in 1978, Kohri and colleagues could find only 75 cases. The embryologic explanation for ureteral triplication would be the presence of three ureteral buds originating separately on the mesonephric duct. If the ducts divide early, partial triplication would result as has been reported. In most cases, all three ureters drain through a single orifice (98). The left side appears to be affected most commonly, and trifid ureters are seen more often in females (133). Symptoms may be infection, incontinence, or pain (108). Ureteral triplication in association with an ectopic ureter (192,194) and ureterocele (62) has been reported. Surgical treatment must be individualized. Ureteral quadruplication is most rare but has been described by Soderdahl and colleagues (161).

URETEROCELE

Terminology and Definitions

A *ureterocele* is a cystic dilation of the intravesical submucosal ureter. According to the Committee on Terminology of the Urologic Section of the American Academy of Pediatrics, ureteroceles contained entirely within the bladder are

intravesical ureteroceles, and a ureterocele that is partially situated permanently at the bladder neck or urethra, regardless of the position of the orifice, is an *ectopic ureterocele.* A *single-system ureterocele* is associated with a kidney with only one ureter, whereas a *duplex-system ureterocele* is associated with the upper pole of a kidney with a complete ureteral duplication. Usually, the wall of a ureterocele exhibits attenuated muscle and collagen (166,175). Ureteroceles vary greatly in size from ones so small that may be difficult to see to ones that are so large as to fill virtually the entire bladder (Fig. 48A.14). The orifice of a ureterocele may be stenotic, normal in size, or occasionally even patulous. They may be located intravesically or extravesically.

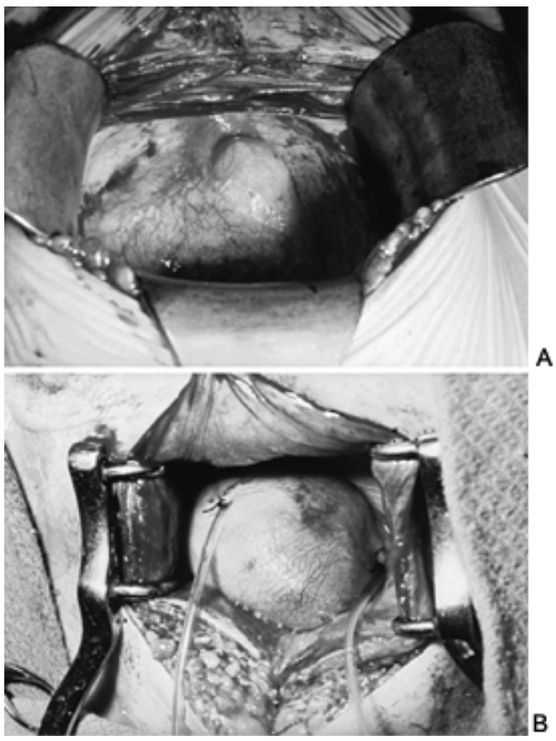

FIGURE 48A.14. A: Small ureterocele. Lower pole ureteral orifice is elevated by the ureterocele. **B:** Large ureterocele. Catheters are in the orifice of the ureterocele and ipsilateral lower pole ureteral orifice.

Incidence and Diagnosis

Campbell (29) reported the incidence of ureteroceles to be 1 in 4,000 autopsies of children. Malek and co-authors (114) report an incidence between 1 in 5,000 and 1 in 12,000 general pediatric admissions. Both of these estimates are probably low, suggesting that small ureteroceles were missed. Uson and colleagues (177) reported a much higher incidence of 1 in 500 autopsies. Ureteroceles occur most commonly in whites and are unusual in blacks. Although females are affected four to seven times more often than males, the malformation is often more complex in the male (53). Some series have demonstrated a slight left-sided predominance; approximately 10% are bilateral (144). Of ureteroceles, 60% to 80% are ectopic (25,56,115), and

approximately 80% are associated with the upper pole ureter of a duplex kidney (24,56,115,164). Intravesical ureteroceles associated with a single ureter are seen more in adults than in children and may be an acquired lesion (173). Although the severity of obstruction and hydroureteronephrosis is greater in children than in adults (140), single-system ureteroceles usually are associated with better function and less hydronephrosis than are duplex renal units and their more commonly associated ectopic ureteroceles. Single-system ectopic ureteroceles are rare, usually occur in men, and may be associated with cardiac and genital anomalies (85). Rarely, a ureterocele is associated with a blind-ending ureter (4). Associated urologic anomalies, especially renal anomalies of fusion and ectopia, often occur with ureteroceles. When the ureterocele arises from the upper pole of a duplex kidney, the upper pole frequently displays renal dysplasia (134,159).

Ericsson (56) was the first to try classifying ureteroceles. *Simple* ureteroceles were defined as ones contained entirely within the bladder, and *ectopic* ureteroceles were defined as ones that extended to the bladder neck or urethra. The clearer classification given earlier in the chapter eliminates the confusing term *simple.* Stephens (164) provided a more complex classification that was intended to better describe the pathologic anatomy of ureteroceles. He described *stenotic* ureteroceles (approximately 40%) as being located entirely within the bladder and having a small ureteral orifice. The orifice could vary from pinpoint size with a constantly tense ureterocele to larger orifices that permit some decompression of the ureterocele and with the ureterocele being visible only when a peristaltic wave fills it. The muscle is predominantly longitudinal in orientation. Stephens (164) classified *sphincteric* ureteroceles (approximately 40%) as ones with an orifice confined within the internal sphincter, making them a type of ectopic ureterocele. Compression by the internal sphincter obstructs drainage from the ureterocele, causing emptying to occur only during voiding. The size of the meatus may be normal or even large. This type of ureterocele may exhibit vesicoureteral reflux (9%) (154). Stephens' *sphincterostenotic ureteroceles* (approximately 5%) have a stenotic meatus located either at the bladder neck or more distally and are also a type of ectopic ureterocele. These ureteroceles tend to be large and tense. Because they do not decompress during voiding as sphincteric ones do, the tense ureterocele may act as a ball valve in the bladder outlet, producing urethral obstruction. In the female, it may prolapse through the urethral meatus. Stephens' fourth type of ureterocele is referred to as a *cecoureterocele* (Fig. 48A.15). Here, although the meatus of the ureterocele is in the bladder, a tongue of the ureterocele extends down the urethra. At the time of ureterocele excision, if this tonguelike projection is not carefully excised, a mucosal flap may be left capable of producing a valvelike obstruction of the urethra (9).

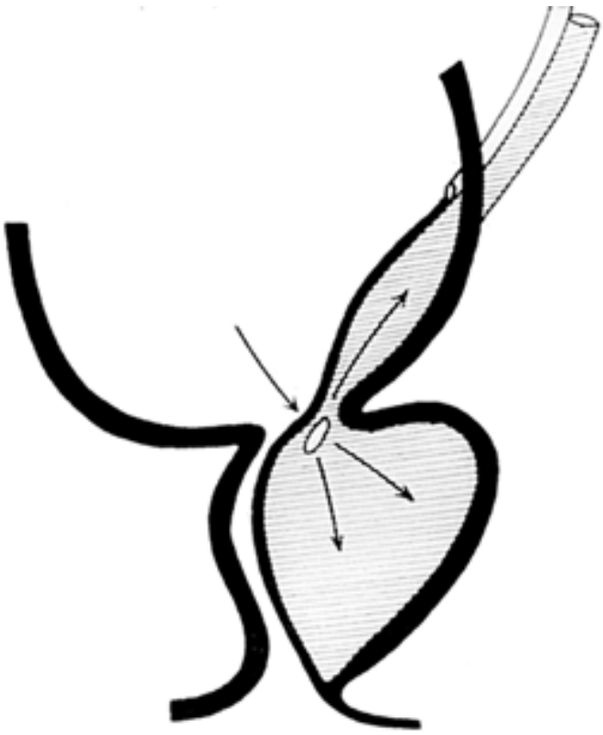

FIGURE 48A.15. Cecoureterocele: ureterocele with tonguelike projection extending down urethra submucosally.

The most common presentation of ureteroceles currently is by prenatal ultrasound, although infection continues to be a common presentation for ureteroceles after birth (26,71,88,113). This infected obstructed system may lead to the picture of full Gram-negative sepsis. At other times, infants may simply fail to thrive or show nonspecific gastrointestinal symptoms as seen with other obstructive uropathies in infancy. On occasion, an infant will have a palpable abdominal mass representing the bladder or the obstructed renal unit.

Prolapse of a ureterocele in the female may lead to bladder outlet obstruction, which constitutes the most common urethral obstruction seen in girls (96). Prolapsing ureteroceles can also occasionally obstruct the urethra in boys (49,127). Usually, this obstruction occurs with a duplex system ureterocele. The “ball-valving” obstructive ureteroceles tend to be tense large ones that Stephens would classify as stenotic. However, most ureteroceles are not

obstructive because they are compressible during voiding. Hematuria may occur from minor trauma to the dilated system or rarely from the presence of a stone. At times, the only symptom is abdominal or flank pain. When incontinence is a presenting symptom, it is usually secondary to infection. Occasionally, a large ureterocele with an abnormal lax bladder neck may lead to incontinence before or after the ureterocele is surgically treated (80,102).

Although historically, in the diagnosis of a ureterocele, the most useful study has been the IVP (18,6,49,71,79,88,96,102,113,127,134,155,186), today, the diagnosis of a ureterocele relies predominately on ultrasonography (10,71,129,167). Ultrasound may demonstrate a well-defined cystic intravesical mass along the posterior bladder wall (Fig. 48A.16). The ultrasound appearance of a ureterocele can be deceiving, and accurate diagnosis requires an experienced radiologist. Because many ureteroceles are compressible with bladder filling, observation when the bladder is very full may obscure the mucosal irregularity of the bladder base. A dilated ureter behind the bladder may also be confused with an ectopic ureter or primary obstructive megaureter (Fig. 48A.17).

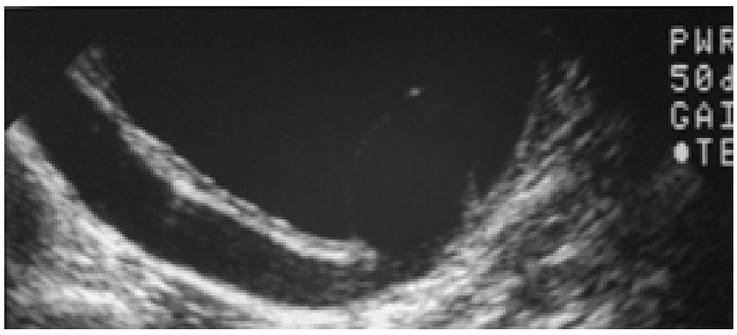

FIGURE 48A.16. Ultrasound demonstrating a dilated upper pole ureter posterior to the bladder, associated with a ureterocele.

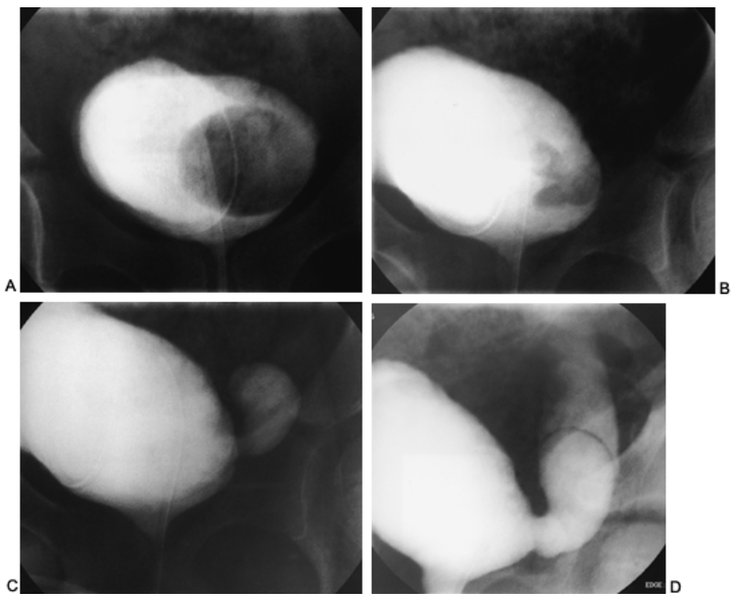

FIGURE 48A.17. Cystograms demonstrating large intravesical ureterocele **(A),** which prolapses through the ureteral hiatus **(B, C)** with subsequent reflux into more proximal ureter **(D)**.

When the associated renal unit exhibits good function, an IVP demonstrates a characteristic “cobra head” or “spring onion” deformity of the distal ureter that is produced when opacified urine in the ureterocele is surrounded by a radiolucent halo that represents the wall of the ureterocele (Fig. 48A.18). Renal function adequate to produce this characteristic image is most frequently seen with single-system

intravesical ureteroceles. Most ectopic ureteroceles are associated with the upper pole of a duplex kidney that exhibits minimal or no function, with reports of 74% to 90% (26). In these cases, the radiographic signs of a ureterocele are primarily negative, reflecting the displacement of the functioning lower pole renal unit and ureter by the hydronephrotic upper pole segment. The lower pole renal unit is often downward and laterally displaced, producing the characteristic “drooping lily” sign (Fig. 48A.19). The lower pole ureter may be tortuous and displaced away from the spine as it wraps around the dilated upper pole ureter. At the bladder level, a negative shadow may be seen, suggesting the presence of a ureterocele. The negative shadow can vary from a large, tense, round shadow occupying much of the bladder volume to a minor irregularity along the floor of the bladder. This negative shadow has to be differentiated from a bladder calculus, blood clot, bladder tumor, or gas in the rectum. In single-system ureteroceles, the absence of function or associated hydroureteronephrosis may help clarify the issue, but in a ureterocele associated with a duplex unit, especially if there is little hydroureteronephrosis, the diagnosis may be more difficult. The early films and the postvoid films from a urogram should be examined closely for the ureterocele because once the bladder is filled with contrast, the ureterocele may be obscured. Intravesical ureteroceles tend to be defined by contrast that nearly surrounds them as opposed to ectopic ureteroceles, which are poorly separated by contrast from the floor of the bladder.

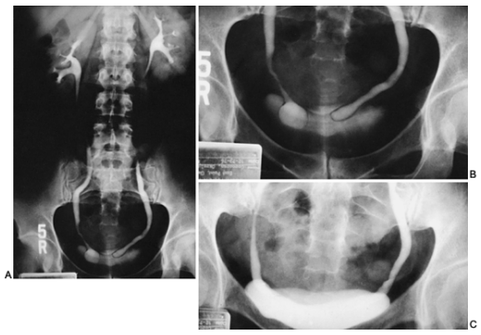

FIGURE 48A.18. Bilateral single-system simple ureteroceles. **A:** IVP showing normal kidneys and minimal obstruction. **B:** Bladder showing typical cobra head deformity of distal ureter with small ureterocele and good renal function. **C:** Bladder later in IVP showing how accumulation of contrast may obscure ureterocele.

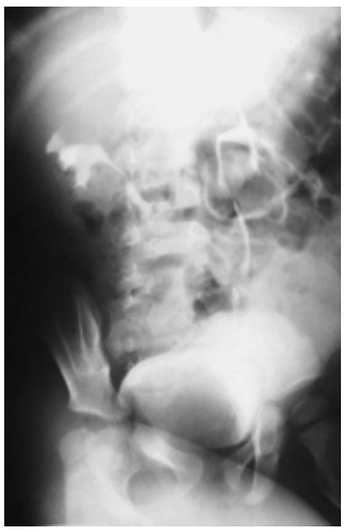

FIGURE 48A.19. Large ureterocele associated with nonfunctioning upper pole of duplicated right kidney. Intravenous pyelogram shows right lower pole is pushed down and out (the drooping lily sign). A paucity of calyces is evident, and the upper pole infundibulum is absent.

A good quality VCUG constitutes a critical component in the evaluation of all ureteroceles (Fig. 48A.20). With duplex ureteroceles, reflux occurs in the ipsilateral lower pole in approximately 50% of cases (24,26,154). Most often, they are compressible ureteroceles that provide poor support for the submucosal course of the lower pole ureter. In approximately 25% of cases, there is contralateral reflux, and in approximately 10% of cases, there is reflux into the ureterocele itself (92,107,154) (Fig. 48A.17). Reflux into a single-system ureterocele is less common but can occur. This usually occurs into a wide-mouth sphincteric ureterocele, a ruptured one, or a cecoureterocele (22,154).

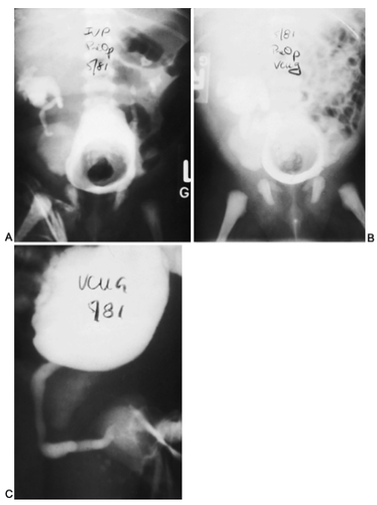

FIGURE 48A.20. Right renal duplication with ureterocele in infant presenting with sepsis. **A:** Intravenous pyelogram showing large ureterocele associated with nonfunctioning upper pole of right kidney. Lower pole shows drooping lily sign, and right lower pole ureter is tortuous as it wraps around the dilated upper pole ureter. **B:** Voiding cystourethrogram showing right lower pole vesicoureteral reflux. **C:** Voiding cystourethrogram showing that despite its size, the ureterocele does not obstruct the bladder outlet. Bladder full of contrast obscures the ureterocele.

The VCUG may help ascertain the degree of detrusor backing present for the ureterocele. If detrusor support is poor and the ureterocele prolapses through the detrusor with voiding, the ureterocele may mimic a bladder diverticulum (Fig. 48A.17 and Fig. 48A.21) (41,184). Prolapse may occur either into the dilated ureter associated with the ureterocele or through the hiatus paraureterally (100). Occasionally, following decompression of a ureterocele, detrusor backing may appear to improve. When tense, a ureterocele may obstruct the ipsilateral lower pole ureter or contralateral ureter as well as the bladder outlet. Occasionally, in males, an ectopic ureterocele can prolapse and produce an image that may be confused with posterior urethral valves (61).

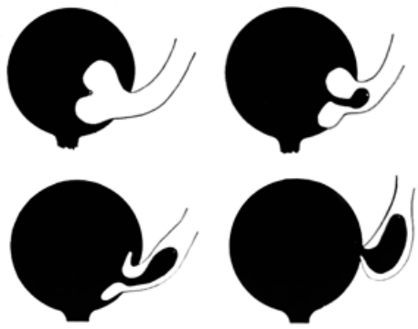

FIGURE 48A.21. Illustration of how prolapse of a ureterocele through the ureteral hiatus may mimic a bladder diverticulum.

Cystoscopic detection of ureteroceles can be quite variable and frequently confusing. When a ureterocele is small, it may not be apparent until a peristaltic wave or flank compression causes it to fill. With very large ureteroceles, identification of any ureteral orifice in the bladder may be impossible. With a large ureterocele causing bilateral obstruction, it can be difficult to tell from which system the ureterocele originated. In this situation, the use of a small needle wedged into the end of a fine ureteral catheter can be used to puncture the ureterocele under direct vision at cystoscopy, and injection of contrast medium may permit an intraoperative radiograph defining the anatomy. An alternative approach is to use a spinal needle passed transabdominally into the bladder and then into the ureterocele under cystoscopic guidance with an intraoperative radiographic examination.

A compressible ureterocele can resemble only a minor mucosal fold with bladder filling, and one must examine the bladder carefully when it is nearly empty as well as when it is full. When the ureterocele has poor detrusor support and prolapses, one can misdiagnose it as a bladder diverticulum at cystoscopy (Fig. 48A.17) (160). As the bladder is emptied and the flank compressed, the ureterocele may fill again, permitting the correct diagnosis. Conversely, when the bladder is empty, the redundant mucosa of a periureteral diverticulum may be mistaken for a collapsed ureterocele. Once again, examination of the area in question when the bladder is full should permit recognition of a true diverticulum. Trigonal cysts are very rare but when present can be confused with a ureterocele at cystoscopy (168). Injection of contrast into the cyst, as previously described, or ultrasound should help diagnose these rare cases. Occasionally, the dilated lower end of an ectopic ureter may elevate the trigone, causing a “pseudoureterocele” by ultrasound, VCUG, or cystoscopy (Fig. 48A.22) (63).

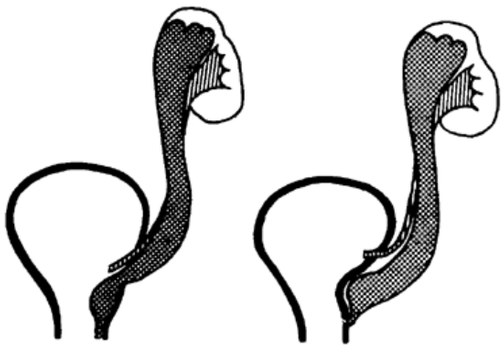

FIGURE 48A.22. Ureterocele **(left)** and “pseudoureterocele” **(right).** An ectopic ureter can occasionally elevate the floor of the bladder sufficiently to mimic a ureterocele **(right).** (From Gill B. Ureteric ectopy in children. *Br J Urol* 1980;52:257, with permission.)

Because contralateral duplications are common with ureteroceles, it is worth every effort to assess the contralateral anatomy at cystoscopy. In this way, possible damage to a nonapparent ureteral orifice may be avoided.

The Choice of Ureterocele Treatment

The goals of ureterocele treatment are control of infection, protection of normal ipsilateral and contralateral units, preservation of renal function, facilitation of subsequent reconstructive procedures, and maintenance of continence. Because the natural history of asymptomatic ureteroceles is unknown, the effect of any treatment option on asymptomatic neonatal ureteroceles remains difficult to determine. With the advent of successful ureterocele treatment by endoscopic incision, the algorithm for the management of ureteroceles has become more complex. A number of factors must be considered when determining which treatment approach is optimal for the child with a ureterocele. Treatment must be individualized because no one approach is appropriate for all ureteroceles.

The *age of the patient* is an important consideration. With a ureterocele detected antenatally, endoscopic incision has the advantage in the newborn of providing a simple and direct decompression of the obstructive uropathy. In the series reported from Great Ormond Street, there were no cases of urosepsis following decompression (57). An infant may tolerate a shorter, simpler endoscopic procedure better than a more complex upper pole partial nephrectomy. If excision of the ureterocele is later needed, this is facilitated by previous endoscopic decompression. After toilet training,

bladder neck surgery causes a considerable degree of postoperative discomfort, thus treatment is best accomplished before toilet training. At this age, the attractiveness of a “simplified” approach with an upper pole partial nephrectomy avoids bladder surgery but is often not definitive because of associated reflux (26,154).

The *amount of functioning parenchyma* is another issue commonly considered when choosing treatment. If a child has never had pyelonephritis, salvage of functional renal parenchyma may be more successful. It is important to remember that usually the upper pole system serving the ureterocele typically makes up only the parenchyma subserved by the upper pole infundibulum (139), so in most cases, one should not let preservation of function be a paramount part of decision-making. On the other hand, a poorly functioning renal unit that is serving a decompressed ureterocele with no reflux has little or no reason to be removed.

A more important point is *whether the kidney is single or duplex.* In a single-system ureterocele, it would appear that a primary endoscopic approach would almost always be appropriate because open surgery would be directed at the bladder level. After endoscopic incision, one would have the advantage of reimplanting a smaller decompressed ureter should postendoscopic incision vesicoureteral reflux require an open operation. When the renal unit is duplex, the decision is more complex. Some of the issues to be subsequently mentioned may be more critical in this setting.

Consideration of the ureterocele as *intravesical* or *extravesical* is important because both the endoscopic and open surgical reconstructions vary. The endoscopic treatment of ectopic ureteroceles has not been as successful for definitive treatment as for intravesical ones (20,37,39,71,136,157). With long-term follow-up of ureteroceles treated endoscopically, 18% of patients with an intravesical and 64% of patients with an extravesical ureterocele required a second operation (37,136). Thus it would appear that for intravesical ureteroceles, whether associated with a single or duplex renal unit, a primary endoscopic approach is preferred. The high percentage of second operations required in children with extravesical ureteroceles managed with initial endoscopic treatment has become well established (37,78,84,136,157). However, prior endoscopic decompression should permit definitive surgery to be done with one open operation done through an incision at the bladder level (71). The decompressed ureter serving a ureterocele can be reimplanted with results approaching that seen for ureters without a ureterocele (i.e., greater than 90% success rate).

Detrusor backing is an important consideration in that a poorly supported ureterocele that everts during voiding and becomes a bladder diverticulum may be more likely to require secondary reconstruction of the trigone than one that is well supported. However, after ureterocele decompression, the support occasionally appears to improve, making it impossible to say that poor detrusor backing of the ureterocele is a firm predictor of the need for subsequent open-bladder surgery.

The degree of ureteral dilation is another factor. When there is a small ureter running to a small intravesical ureterocele that is detected when one is operating for what is felt to be primary reflux, reimplantation of the ureter from the poorly functioning upper pole with the refluxing lower pole ureter serves as very good definitive treatment (15). If, on the other hand, the ureter associated with the ureterocele is massively dilated, as is so often the case, attempts at reimplantation of such a system will be fraught with a greater complication rate than an ablative operation aimed at the upper pole of the kidney. After endoscopic decompression,

the ureteral dilation will greatly diminish improving reimplantation results.

Associated vesicoureteral reflux appears to best predict the need for open surgery and emphasizes the importance of the VCUG . The review by Sen and colleagues (154) indicated that one can expect to see approximately 50% of ipsilateral lower pole ureters exhibit reflux. Approximately 25% of contralateral ureters reflux, and in about 10% of cases, reflux was seen in the ureterocele-bearing unit. In a review by Husmann and colleagues (80), it is evident that reflux was the major factor cause for subsequent surgery to decompress a ureterocele after an upper pole partial nephrectomy (the so-called “simplified” approach). In cases in which the ureterocele alone was present without reflux, no patient required additional surgery. If less than grade III reflux was present in only one ureter, 60% of patients did not require further surgery. In contrast, a higher grade reflux than this into one or more renal moieties almost invariably led to further surgery (96%). If high-grade reflux were associated with a ureterocele, it would appear that a primary endoscopic incision would be logical because subsequent surgery at the bladder level, while likely, will be facilitated by decompression of the ureterocele. The decompressed ureter to the ureterocele can usually be successfully reimplanted, and upper pole partial nephrectomy, even for a poorly functioning upper pole, is rarely needed. If there is no vesicoureteral reflux, then a “simplified” approach by an upper pole partial nephrectomy for an ectopic ureterocele is a reasonable treatment option. Unfortunately, ectopic ureteroceles without reflux are uncommon.

From this brief section, it can be deduced that there will not be one simple solution to all ureterocele problems. Minimizing the number of anesthetics and surgical procedures, as well as postoperative morbidity, becomes very challenging. With improved endoscopic techniques, one hopes when secondary open surgery is needed that it will be possible with one incision only, lessening surgical trauma to the child.

Endoscopic Treatment of Ureteroceles

Endoscopic decompression of ureteroceles was suggested initially by Zielinski (193) and by Hutch and Chisholm (81). Tank (172) advocated unroofing of ureteroceles without regard for reflux and found that 50% of patients showed improvement in function and that subsequent nephrectomy was not necessary. Lower tract reconstruction for recurrent infections was reported in only 10% of cases. Monfort and colleagues (122,123), Rich and colleagues (142), and Blyth and colleagues (20) suggested the current approach to ureterocele decompression: a small puncture placed low on the ureterocele to preserve a flap valve of the collapsed ureterocele and prevent reflux.

Several technical points concerning endoscopic treatment of intravesical ureteroceles may decrease complications. Because many ureteroceles are compressible with bladder filling, it may help to keep the bladder rather empty and massage the flank to distend the ureterocele to ensure a low incision on the front wall of the ureterocele just above the bladder neck. A 3-Fr Bugbee using the cutting current at a high enough level to ensure a clean incision is used. If a clean cut is not achieved, one may end up pushing the inner layer of the ureterocele away from the outer layer, thus not achieving decompression. A perpendicular approach to the ureterocele is important to avoid a skiving incision that may likewise miss the lumen of the ureterocele. Although a low incision is preferred in efforts to create a flap valve mechanism of the decompressed ureterocele, it must be borne in mind that if one incises too low, the incision can be below the level of the ureterocele floor. A 2- to 3-mm incision is adequate in most cases because the thermal effect of the incision leads to subsequent enlargement in the hole. Only when the ureterocele appears to be very thick-walled is an incision any larger than this appropriate (71). Confirmation of adequate decompression can usually be assured from seeing a jet of urine emerge from the incision site in the ureterocele. This can be augmented by massage of the ipsilateral flank.

There are *technical considerations* in the *endoscopic incision of an ectopic ureterocele* that are different from those for an intravesical ureterocele. With the objective of achieving decompression of the ureterocele, a low puncture of the ureterocele to maintain a flap valve of the collapsed ureterocele continues to be a fairly uniform approach among different authors (39,148,157). Controversy exists about the treatment of the extension of an ectopic ureterocele into the urethra. Concern has been expressed that following decompression, an obstructing distal portion might remain. However, Schlussel and colleagues (148) and Smith and colleagues (157) report no problems with the urethral extension of the ureterocele after puncture at the intravesical level only. Care was taken to make a low, transverse, small incision that was within the bladder with the bladder neck closed. Technically, this can be accomplished by sweeping the cystoscope along the bladder wall lateral to the ureterocele and picking up the edge of the ureterocele just inside the bladder neck. An angled Bugbee facilitates a puncture perpendicular to the ureterocele wall. If the ectopic ureterocele is decompressed by intravesical puncture, the urethral extension will usually be adequately decompressed and will thus be unlikely to cause any difficulty. When one uses the technique described by Blyth and co-workers (20) of incising the intraurethral extension of the ureterocele upward until the incision is clearly within the bladder, the opening of the bladder neck may open the orifice of the ureterocele, leading to a greater incidence of reflux. This may account for the increased incidence of postpuncture reflux seen in Blyth's versus Schussel's series. This concern about the distal extension of the ureterocele may be more germane to open ureterocele excision when the urethral extension could remain

as a cusp, catching urine during voiding and thus obstructing the urethra (9).

Follow-up after an endoscopic incision routinely involves a renal and bladder ultrasound 1 month after the procedure. Although residual hydroureteronephrosis often persists, a diminution of some degree indicates that decompression has been achieved. Subsequent imaging of the upper tracts and a VCUG 6 months following the procedure help direct further treatment.

Bladder-level Operation for Ureteroceles

In the open reconstruction of intravesical ureteroceles, if there is poor detrusor backing for the ureterocele, the bladder wall must be repaired at the time of ureterocele excision. In single-system ureteroceles that are decompressed, it is expected that the degree of ureteral dilation will go down to the point where a 5:1 ratio of submucosal tunnel length to diameter can be easily achieved to prevent vesicoureteral reflux. However, with massively dilated ureters associated with ureteroceles, even after decompression, a tailored reimplant may be required. Cohen's (36) technique of cross-trigonal advancement is generally used because it permits the reimplant to be done away from the area of bladder wall reconstruction.

In children who require ureterocele excision and lower pole ureteral reimplantation, it is usually delayed until the child is approximately 2 years old and is most commonly needed for persistent ipsilateral lower pole or contralateral reflux. As excision of the ureterocele and bladder neck reconstruction are considerably more symptomatic than a simple ureteral reimplant alone, it is preferable to perform the surgery before the age of toilet training. Several technical points in this procedure are worth bearing in mind. There are two basic methods for the intravesical excision for a ureterocele. If the detrusor backing for the ureterocele is solid, the back wall of the ureterocele can be left in place and the lower pole ureter tunneled beneath the mucosa. However, a bladder wall reconstructive procedure usually is warranted because of detrusor weakness behind the ureterocele. This may reflect an embryonic abnormality of the trigone, especially with ectopic ureteroceles (Canning DA, personal communication, 2000). It is usually possible to save a portion of the sidewalls of the ureterocele by separating the inner lining of the ureterocele to permit later mucosal coverage of the area of bladder wall reconstruction. If the ureterocele has a urethral extension, it is important not to leave a distal lip of mucosa that can be an obstructing flap valve. Either the entire urethral tongue of the ureterocele can be excised and the bladder neck area carefully reconstructed before closing the mucosa, or if the bladder neck and urethra have not been dilated by the ureterocele, merely removing the ureterocele roof as it extends down the urethra will suffice. It is technically a simpler procedure, but one must be certain that a functionally intact urethra and bladder neck are left behind because the primary reconstruction of these structures is easier than a secondary approach.

It is important to remember that in the series by Husmann and colleagues (79), 6% of the girls treated by an upper pole partial nephrectomy developed urinary incontinence after puberty, presumably due to a weakening of the bladder neck by the ureterocele, which persists after decompression. Because a ureterocele, especially ectopic ones, often widen the bladder neck, it is important to reconstruct this defect after ureterocele excision. The technique of “keeling” as described by Stephens (165) is particularly attractive (Fig. 48A.23). A series of sutures is used to evert the detrusor (“keeling”) until the bladder neck is reconstructed to a normal diameter. The mucosal edge of the ureterocele provides a good guide as to the amount of eversion needed. When the mucosa is reapproximated at the bladder neck, good bladder neck reconstruction can be ensured. To ensure that a small distal urethral mucosal cusp is not left to potentially obstruct the urethra (9), it is a simple matter at the end of the operation to use a small probe bent into a little hook and passed from the perineal end of the urethra to catch a distal lip of ureterocele, draw it externally, and nip it with a fine pair of scissors.

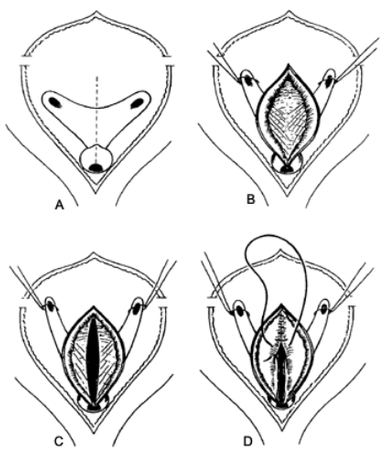

FIGURE 48A.23. Keeling repair of bladder neck after excision of ectopic (extravesical) ureterocele **(A, B).** Stephens' technique **(C, D)** involves a series of sutures placed to evert the detrusor at the bladder neck until the functional diameter of the bladder neck is restored to normal. The mucosal edge of the ureterocele provides a useful guide to the extent of eversion.

When one is operating at the bladder level for persistent reflux after upper pole partial nephrectomy (“simplified” approach), as the ureterocele is mobilized, the upper pole ureteral stump will be mobilized with the lower pole ureter. This dissection in most cases can be accomplished totally intravesically. After the lower pole ureter has been sufficiently mobilized for an adequate reimplant, the upper pole ureter stump is opened on its wall opposite the common one shared with the lower pole ureter. No effort is made to excise the portion of the wall of the upper pole ureter that is contiguous with the lower pole ureter. In this way, there should be minimal risk of injury to the lower pole ureter. A Cohen cross-trigonal reimplant is usually feasible and keeps the course of the ureter away from the area of recent bladder wall reconstruction. A ureteral stent is used only if the lower pole ureter is significantly abnormal.

On occasion, a surgeon will begin a ureteral reimplantation for what appears to be simple primary vesicoureteral reflux into a single system, and as the ureter is mobilized, a second small ureter is found running to a small nonobstructed ureterocele. It is the small size of the ureter and associated lack of function in the diminutive upper pole unit that may lead to this intraoperative discovery (15). Even though there is no function in the upper pole unit, treatment is usually satisfactory by a common sheath reimplant. The need for later removal of the upper pole renal unit is rare.

An intravesical ureterocele as part of a duplex unit rarely is associated with adequate function and a ureter small enough to permit ureterocele excision and a primary common sheath reimplant of the two ureters. More frequently, the associated ureter is too dilated to be reimplanted without

tailoring. Here, if function justifies salvage, a renal level ureteroureterostomy or ureteropyelostomy may be used effectively (Fig. 48A.24). Today, a primary endoscopic puncture of the ureterocele and later a possible bladder level operation make these previous renal level operations rarely appropriate.

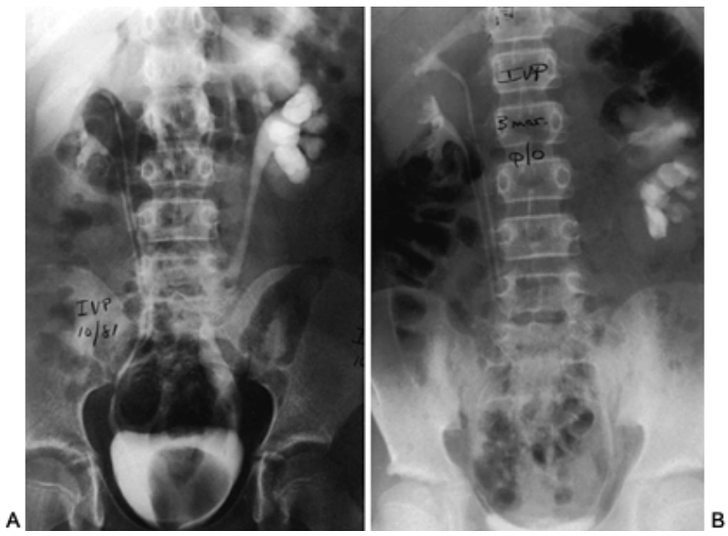

FIGURE 48A.24. Left ureteral duplication with ureterocele and function of upper pole treated by ureteroureterostomy. **A:** Preoperative intravenous pyelogram shows function of left upper pole and large ureterocele. **B:** After surgery, the left upper pole is well decompressed. The ureterocele collapsed and is no longer evident in the bladder.

If a bladder-level operation is needed after successful endoscopic incision of a ureterocele, it usually is for reflux associated with ectopic ureteroceles. An advantage of the endoscopic incision is that the decompressed ureter usually shrinks in diameter sufficiently to permit reimplantation into the bladder with results approaching that for normal refluxing ureters (71). Poor function of an associated upper pole renal segment is not an indication for a partial nephrectomy because when there is no associated persisting obstruction or reflux, follow-up has not demonstrated clinical problems.

Total Reconstruction

The first techniques developed for treatment of an ectopic ureterocele associated with a duplex renal unit was “total reconstruction” with excision of the ureterocele, reconstruction of the detrusor, and reimplantation of the ipsilateral lower pole ureter and the contralateral ureter if required. Following this bladder operation, a separate flank incision was made and an upper pole partial nephrectomy completed (75,76). If the upper pole had questionable function or the child was sufficiently ill to warrant a staged approach, the upper pole ureter could be exteriorized temporarily as a cutaneous ureterostomy. Monfort and colleagues (122) used this technique in 18 patients, with recovery of significant function in only 3, indicating that this approach is rarely indicated. Because most ureteroceles present in the very young, often before 1 year of age, the total reconstruction approach requires a technically challenging excision of a ureterocele, often with a urethral extension. Complications are not rare (46). As mentioned, the urethral extension of an ectopic ureterocele may act as a urethral valve and produce bladder outlet obstruction. Also, if the ureterocele is excised but the bladder neck imperfectly reconstructed, incontinence may follow (102). Incontinence can also rarely result from incomplete excision of a ureterocele that has an orifice beyond the sphincter mechanism, leaving a channel that bypasses sphincteric control (189). Proponents of this approach note that the majority of children can be treated with

one operation, albeit two incisions. In one series, 14% of children with extravesical ureteroceles that underwent total reconstruction required subsequent intervention (145), indicating the significant risk of complications from a one-stage total reconstruction. It is our view today that a one-stage total reconstruction is rarely necessary.

Upper Pole Partial Nephrectomy: “Simplified” Approach

Because of potential complications secondary to a total reconstruction early in life, alternative methods of treatment for ureteroceles were undertaken. In duplex renal units with an associated ureterocele, the upper pole unit usually has not demonstrated sufficient function to warrant salvage (154,159), and a partial nephrectomy leaving the upper pole ureter open effectively decompresses the ureterocele. Because of this, a simplified “approach” based on a primary upper pole partial nephrectomy with ureterocele decompression and later a staged approach to bladder-level surgery were tried in several centers (26,30,32,94). The upper pole ureter was excised down to the level of the iliac vessels and left open to facilitate decompression of the ureterocele. The expectation was that decompression would simplify bladder surgery that would be carried out when the child was older or possibly eliminate the need for an operation at the bladder level completely. Ureterocele decompression by this technique was found to have the additional benefit that frequently ipsilateral lower pole reflux or obstruction and contralateral reflux or obstruction would subside. The ureterocele generally collapses so completely that it is difficult to subsequently visualize by a VCUG (16,26,32,60). Occasional cases with poor detrusor backing for the ureterocele have been observed to have an improvement in bladder support after decompression.

Husmann and others (78) noted that 30% of children without reflux developed reflux following partial nephrectomy. Half of these children spontaneously resolved their reflux, and the other half (15%) required additional surgery for reflux. Other series have found the overall need for eventual bladder surgery to range from 25% to 50% (26,32,94). Thus it must be acknowledged that while the “simplified” approach of an initial upper pole partial nephrectomy provides very effective decompression, an incidence of subsequent bladder-level surgery is likely to be significant, especially if there has been initial high-grade reflux.

Husmann and colleagues (79) point out a rare complication of the simplified approach. They saw 6% of their patients treated with upper pole partial nephrectomy alone

develop a stress pattern of urinary incontinence after toilet training. In these cases, it would appear that the mass of the distended ureterocele distorted the bladder neck sufficiently to cause incompetence after decompression.

Experience with the simplified approach suggests that this approach to the treatment of ectopic ureteroceles with duplex systems permits the majority of children without reflux to avoid a secondary bladder procedure (Fig. 48A.26). Unfortunately, reflux is very common in association with ureteroceles, especially ectopic ureteroceles. As with endoscopic decompression of the ectopic ureterocele, most children with reflux treated by the simplified approach will require a second operation at the bladder level (78,79). The significant need for lower tract reconstruction has led some to suggest that in older children complete reconstruction may be a more definitive and efficacious treatment modality (78). However, many believe this is not necessary because endoscopic puncture for ureterocele decompression and possibly further operations at the bladder level constitute less surgical trauma for the child.

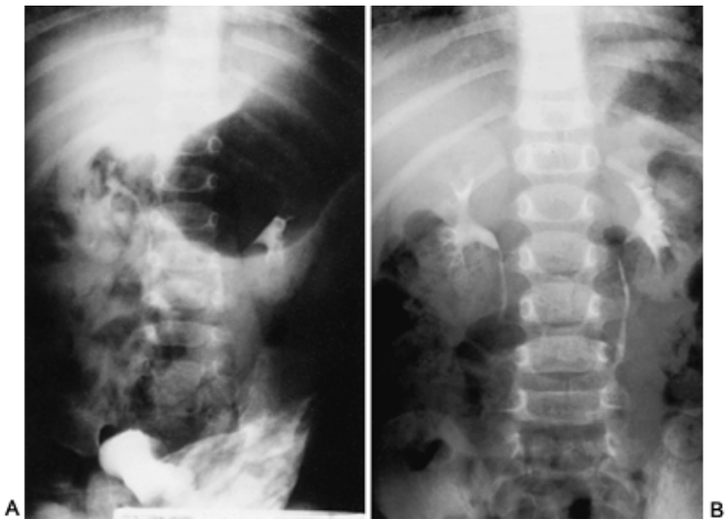

FIGURE 48A.26. Left ectopic ureterocele treated only by upper pole partial nephrectomy. **A:** Preoperative intravenous pyelogram (IVP) shows drooping lily sign, paucity of calyces, and absence of upper pole infundibulum. Ureterocele is just visible in the bladder. **B:** IVP 2 years after surgery shows an excellent left kidney. Voiding cystourethrogram shows no reflux.

Upper Pole Partial Nephrectomy

In the performance of an upper pole partial nephrectomy in a duplex renal unit, several technical points bear mentioning. A relatively short, transverse, flank incision just below the tip of the twelfth rib extending posteriorly to the erector spinal muscles permits complete mobilization of the kidney to facilitate surgery on the upper pole without difficulty in the majority of children. Because the upper pole renal vasculature is often anomalous and variable (21), when the kidney is mobilized, care should be taken to identify the small vessels that frequently course directly into the upper pole. If dissection is kept close to the upper pole, vessels running to this unit can be identified before their division. This will reduce the chance of damaging the blood supply to the lower pole. The ureter to the upper pole usually runs posterior to the renal vessels, and no attempt is made to dissect out the hilar vessels. Occasionally, an aberrant vessel will be located behind the ureter. After identification and division of the ureter to the upper pole, gentle traction guides dissection of the upper pole parenchyma (Fig. 48A.25A). The upper pole capsule may be stripped back for later use in closure if not too adherent from previous inflammation (Fig. 48A.25B). Complete removal of the upper pole collecting system is the most important aspect of an upper pole partial nephrectomy. We make the parenchymal incision just on the upper pole side of the line of demarcation from the lower renal unit, which is usually evident following the division of the upper pole vessels. The hypoplastic or dysplastic upper pole can then be excised (Fig. 48A.25C and Fig. 48A.25D). Manual compression of the kidney provides adequate vascular control, and blood loss should be minimal.

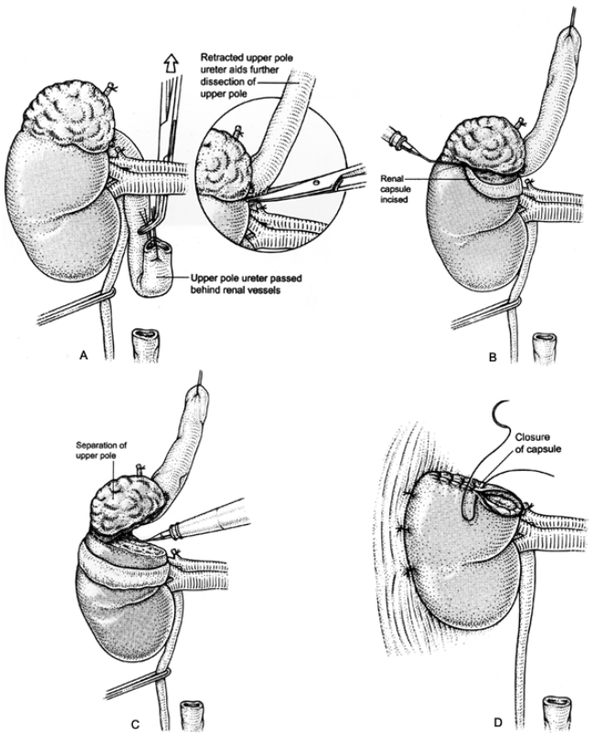

FIGURE 48A.25. A: Division and traction of upper pole ureter guide dissection of the upper pole along the collecting system. **B:** The upper pole capsule is incised and stripped back. **C, D:** Following complete removal of the upper pole collecting system, the capsule is closed.

Next, the distal end of the upper pole ureter should be dissected down to below the level of the iliac vessels, where it begins to assume a common adventitial sheath with the lower pole ureter. The upper pole ureter is usually dilated and tortuous; therefore it may appear to wrap itself around the more normal lower pole ureter. Dissection should be kept immediately on the wall of the upper pole ureter to prevent injury to the lower pole ureter. Patience with this often slightly tedious aspect of the dissection will gradually straighten the upper pole ureter, and the lower pole ureter will be well preserved. After dissection reaches the level of the iliac vessels, which is not difficult through the usual flank incision, the upper pole ureter is opened and the interior of the ureterocele gently irrigated with a feeding tube. If there is no reflux into the ureterocele, the stump of the excised upper pole ureter is left open. Occasionally, when the ureterocele is a large one, a small feeding tube may be left in the lumen of the upper pole ureter extending down into the ureterocele for a couple of days to act as a wick to help ensure that the ureterocele does indeed collapse. If reflux into the ureterocele is present, the upper pole ureter should be ligated. Here, there is an increased likelihood that a subsequent bladder operation to remove the ureterocele and upper pole ureteral stump may be required when the child is older. A small Penrose drain left in the area of the ureteral stump as well as one in the area of the removed upper pole renal parenchyma provides drainage.

Laparoscopic and Other Surgical Techniques for Treatment of Ureteroceles

The advent of the laparoscopic heminephroureterectomy presents another operative alternative that may be useful if partial nephrectomy is thought to be appropriate (72,82). It is our view, however, that with primary endoscopic incision it should be possible to carry out definitive open surgery with one procedure at the bladder level. Poor function of the upper pole does not require that it be removed. In rare cases in which the upper pole function is good and there is no initial vesicoureteral reflux present, a ureteropyelostomy or high ureteroureterostomy may be an alternative (Fig. 48A.24). This approach is less suitable if the lower pole pelvis is intrarenal or the lower pole ureter is nondilated. Today, endoscopic ureterocele puncture is typically the most appropriate primary approach.

Salvage of the upper pole renal unit by a primary bladder-level operation involving excision of the ureterocele and a common sheath reimplant has the disadvantage of requiring the reimplant of an often very dilated ureter into the small bladder of an infant. Amar and colleagues (3) have also suggested ureterocele excision, lower pole ureteral reimplantation, and a low ureteroureterostomy of the upper pole ureter into the lower pole ureter as alternative approaches. However, we propose that endoscopic decompression followed by an open operation at the bladder level with a duplex reimplant is preferable.

ECTOPIC URETER

An *ectopic ureter* is one that opens at the bladder neck or more caudally rather than at its normal location on the corner of the trigone. An ectopic ureter forms when the ureteral bud has an abnormally high origin from the mesonephric duct with delayed or no separation from the duct. There are multiple sites for an ectopic ureter in both males and females. However, in the male, the ectopic ureter is always above the external sphincter, which accounts for the prime clinical difference in presentation between the sexes (see later discussion).

Incidence of Single and Duplex Systems

Our estimation of the incidence of ectopic ureters may be low because not all cause symptoms. In autopsy series, the incidence of ectopic ureters is 1 in 1,900 (28). Occasionally, ectopy occurs in more than one family member (47,125). In 80% of cases, the ectopic ureter is attached to the upper pole of a duplicated renal system. The percentage of ectopic ureters associated with duplication in females is even higher than 80%. In males, an ectopic ureter drains a single system more commonly (86,150). Indeed, ectopic ureter is much more of a female clinical problem in general, with only approximately 15% of ectopic ureters having been reported in men (149). Approximately 10% of ectopic ureters are bilateral (54). When the ectopic ureter is part of a duplex system, the contralateral system is duplicated in approximately 80% of cases, and 21% will have duplication contralaterally with contralateral ectopy as well (114).

The most commonly encountered anomaly associated with an ectopic ureter is hypoplasia or dysplasia of the renal moiety. There is a fairly good correlation between the degree of ectopia and the degree of renal abnormality, although it appears to hold better for duplex systems with ectopy than for single systems with ectopy (147). Severe ectopia with an orifice in the genital system is almost always associated with nonfunctioning renal tissue (143,149). Some series (63) have shown a higher incidence of other associated anomalies, especially imperforate anus, in single-system ectopy.

A single ectopic ureter with a normal contralateral system usually does not result in any deficiency of the bladder neck. However, when two single ureters are ectopic, the bladder and bladder neck fail to form normally and incontinence is a problem (see later discussion). Interestingly, when one single ectopic system is at the bladder neck and one is more distal, an intermediate level of bladder neck abnormality is present. In the series from the Children's Hospital of Philadelphia (147), most of the children in this intermediate group were continent.

Ectopic Ureter in the Female

The fundamental difference between ureteral ectopia in the female and male is that in females, ectopic ureters can terminate at a level distal to the continence mechanisms of the bladder neck and external sphincter and thus may be associated with incontinence (Fig. 48A.27) (89,121). Approximately one-third of ectopic ureters open at the level of the bladder neck (Fig. 48A.28) or slightly more distally in the upper urethra (95). A higher orifice has a lower chance of associated urinary incontinence; however, obstruction is more common in higher ureters because they traverse a greater portion of the musculature of the bladder neck.

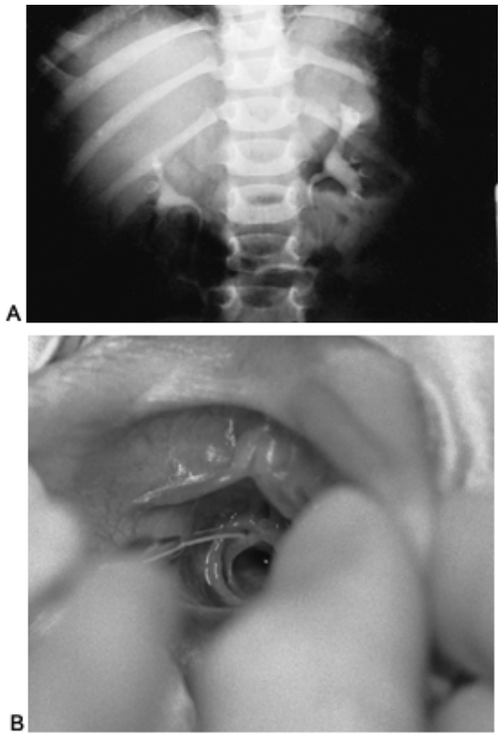

FIGURE 48A.27. Ectopic ureter in vaginal vestibule in female who presented with constant dribbling incontinence as well as normal voiding. **A:** Intravenous pyelogram shows right duplication with minimal upper pole function and down and outward displacement of lower pole (drooping lily sign). **B:** Ureteral catheter in ectopic ureter.

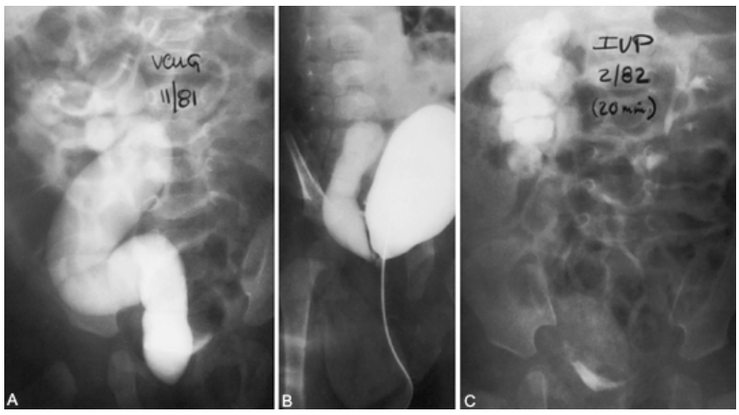

FIGURE 48A.28. Ectopic ureter at bladder neck in girl who presented at 4 months of age with sepsis. **A:** Voiding cystourethrogram showing vesicoureteral reflux into very dilated right ureter. **B:** Oblique view from cystogram showing ectopic ureter entering at bladder neck. **C:** Intravenous pyelogram 3 months following tapered reimplant of right ureter.

These more proximal ectopic ureters drain primarily during voiding when the continence mechanism is open. Vesicoureteral reflex occurs in 75% or more of these higher ectopic ureteral orifices, producing the paradox of both reflux and obstruction. By having the bladder neck repeatedly open, the cyclic VCUG described by Lebowitz and Wyly (190) provides an opportunity for the obstructed ectopic ureter to decompress before contrast is voided and thus increases the likelihood that the contrast will reflux into the ectopic system. When the ectopic ureter enters at the level of the external sphincter or more distally, reflux is less commonly seen.

One-third of ectopic ureters in the female terminate in the area of the vaginal vestibule immediately around the urethral orifice (Fig. 48A.27). This area marks the terminal end of Gartner's duct—the mesonephric duct remnant in the female. Occasionally, infant girls will present with an ectopic ureter entering what appears to be a urethral diverticulum but that is actually a Gartner's duct cyst (180). In approximately 25% of ectopic ureters in females, the orifice opens into the vagina. More rarely, an ectopic ureter can end at a higher site on Gartner's duct with an opening at the level of the cervix or even uterus (less than 5%). These uterine, cervical, and vaginal cases presumably are the result of a rupture of Gartner's duct into the urovaginal canal along their common wall. Ureteral ectopy into the rectum is rare and usually is noted incidentally at autopsy (178). Presumably, it must result from an abnormal division of the cloaca by the descent of the urorectal septum or from an abnormally placed mesonephric (Wolffian) duct that empties into the posterior half of the cloaca.

Historically, approximately half of females with ectopic ureters presented with a classic history of continuous dribbling incontinence despite what appears to be a normal voiding pattern (114,147,149). Today, antenatal detection of hydroureteronephrosis is increasing. If undetected, ectopic ureters in the female may go unrecognized until adulthood (68). If the associated ureter is very dilated, the child may be continent when supine, and the pattern may be one of daytime wetting only. This reservoir effect may lead to an erroneous diagnosis of stress incontinence. Occasionally, it is a persistent, foul-smelling, vaginal discharge that suggests an ectopic ureter. If the ectopic ureter ends in a Gartner's duct cyst, the child may present with a mass on the anterior vaginal wall. When the ectopic orifice is quite high and there is significant obstruction, reflux, or both, urinary infection is frequent and is a common form of presentation for an ectopic ureter in the small child. An infant may present with an abdominal mass resulting from a severely obstructed ectopic ureter (179) (Fig. 48A.29). There are well-documented cases of females with ectopic ureters entering the vestibule or distal urethra without incontinence, presumably due to obstruction of the ureter as it traverses the continence mechanism with emptying only during voiding (130). Flank pain may be the only symptom (48). In this type of case, incontinence has been reported to develop after puberty or childbirth (33,45).

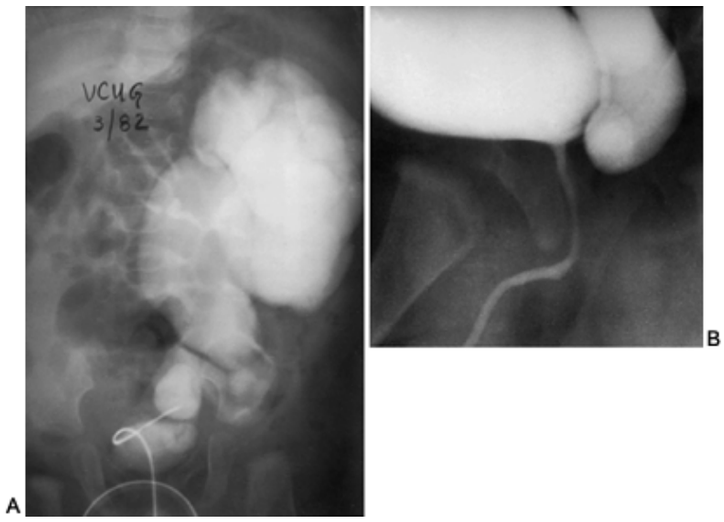

FIGURE 48A.29. Ectopic ureter to bladder neck in male infant who presented with an abdominal mass. **A:** Voiding cystourethrogram shows vesicoureteral reflux into massively dilated left renal unit. **B:** Oblique view shows ectopic ureter to bladder neck. Renal scan revealed the left kidney to constitute only 5% of total renal function. Treatment was by nephroureterectomy.

The diagnosis of an ectopic ureter in the female may be obvious or may be very difficult. Particularly when there is

ectopy into the external genitalia, there is likely to be nonvisualization of the associated renal unit (70). Ultrasound can be especially useful for detecting the dilated ectopic ureter behind the bladder (Fig. 48A.30). If there is little hydroureteronephrosis of the ectopic upper pole system, diagnosis may depend on recognizing the absence of an upper pole calyx or an apparent excessive thickness of the renal tissue on the medial aspect of the upper pole. Tomography during urography or a computed tomography (CT) image of the kidney may aid in making this diagnosis (104). Magnetic resonance imaging (MRI) has been used to delineate the fluid-filled ureter and its anatomy (12). Bilateral ectopic ureters occur in approximately 10% of cases, and the radiographic findings may be very subtle, permitting one side to be easily missed (Fig. 48A.31).

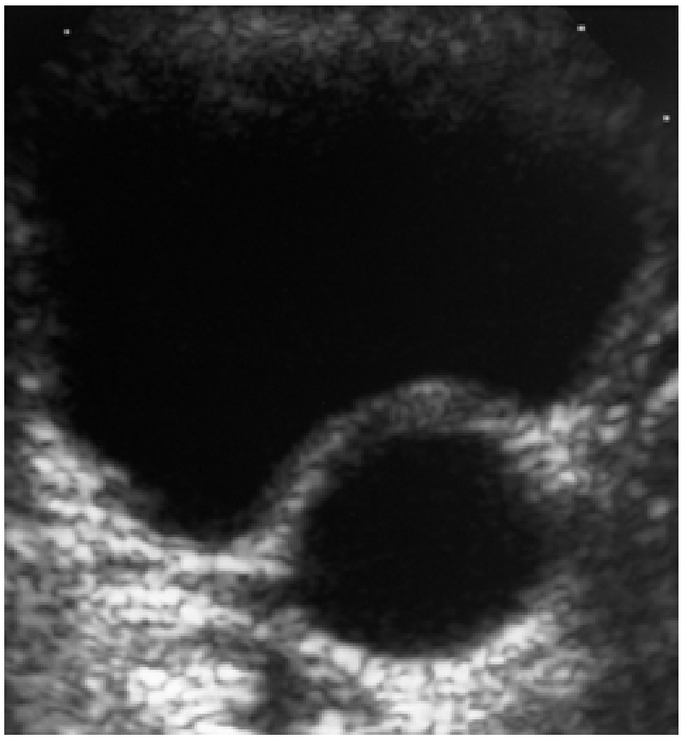

FIGURE 48A.30. Ultrasound demonstrating dilated ectopic ureter behind posterior bladder wall.

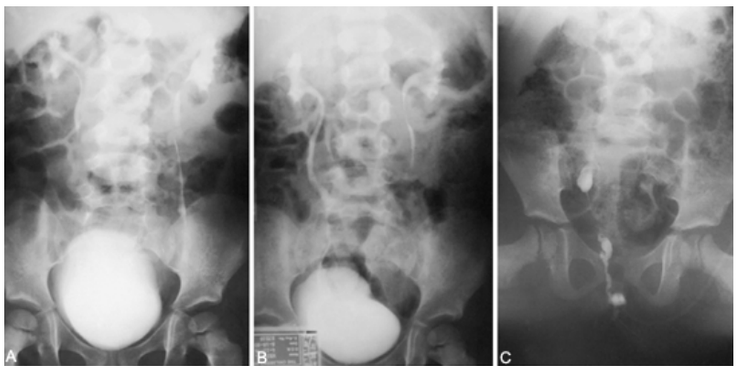

FIGURE 48A.31. Bilateral ectopic ureters in female who presented with constant incontinence as well as normal voiding. **A:** Initial intravenous pyelogram (IVP) shows down-and-outward displacement of left kidney and lateral displacement of ureter, suggesting duplication with ectopic ureter. Right kidney was not believed to be duplicated. Left upper pole partial nephrectomy did not correct incontinence. **B:** Follow-up IVP shows vertical axis to right kidney and mild tortuosity of right ureter, suggesting duplication with second ectopic ureter. **C:** Retrograde ureterogram of vestibular ectopic right ureteral orifice confirms suspicion of bilateral duplication with ectopia by showing upper pole ureter. Child was cured of incontinence by right upper pole partial nephrectomy.

If the ureter is single and beyond the continence mechanism, the associated renal tissue often is nonfunctional and the diagnosis may be made even more difficult by the fact that the associated kidney itself may be ectopic or even crossed and fused (183). Renal function may be inadequate to permit visualization by either intravenous urography or renal scan (152). The finding of a hemitrigone at cystoscopy may lead to the erroneous diagnosis of renal agenesis. Associated genital and anal anomalies occur in about one-third

of cases (93) and may mask the presentation of single ectopia. Ultrasound used to detect a dilated ureter behind the bladder may be particularly useful in this situation (117). Vaginograms carried out by occluding the introitus with a Foley balloon may demonstrate reflux into a vaginal ectopic ureter. The ectopic ureter alternatively may be identified at vaginoscopy. Today, MRI will sort out many questions involving pelvic anatomy. However, there are cases in which exploratory surgery is required. Once the ureter is found, it can be traced upward to its associated renal unit.

When the physician is confronted with suspected ectopic ureters, dyes used to stain urine, such as indigo carmine and methylene blue, have a role. Because function of renal tissue associated with ectopic ureters is usually poor, intravenous administration of dye often is not successful in demonstrating an ectopic ureteral orifice. However, in the investigation of an incontinent child, the presence of an ectopic ureter would be strongly suggested if the bladder is filled with indigo carmine or methylene blue–stained saline via a Foley catheter and observation of the perineum reveals a continued slow drip of clear urine. Phenazopyridine hydrochloride (Pyridium) appears to be a better color marker excreted by poorly functioning renal tissue than methylene blue or indigo carmine (183), and thus if a cotton swab is left high in the vagina overnight and it is stained orange, it may suggest the diagnosis of a vaginally ectopic ureter.

Meticulous observation during physical examination of the area around the urethral meatus and distal vagina will many times reveal a recurring drop of liquid over a very small opening that can be probed and then retrogradely injected to confirm the presence of an ectopic ureter (Fig. 48A.32). Vaginoscopy with attention to the superior lateral aspect of the vagina may reveal vaginal ectopia. Sometimes, the orifice is large and obvious; at other times, it is hidden in a vaginal fold. Pressure on the anterior vaginal wall may produce a jet of cloudy fluid or pus from the ectopic orifice, revealing its presence.

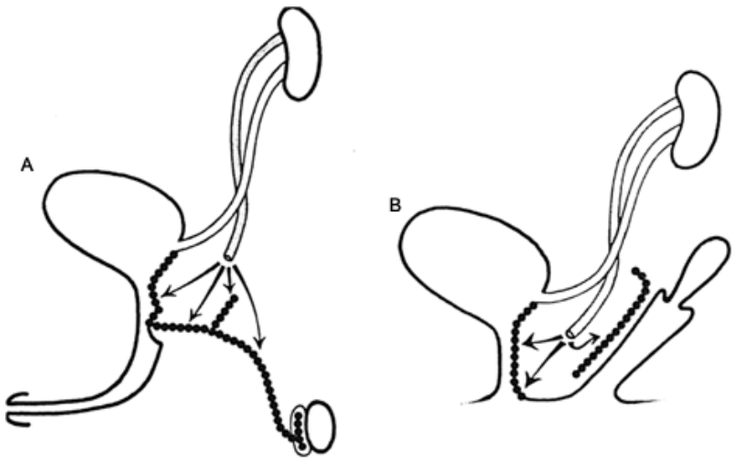

FIGURE 48A.32. A: Ureteral ectopia in a male. Possible sites of ectopic ureter are above the external sphincter. **B:** Ureteral ectopia in a female. Ectopic ureter may be located beyond continence mechanism and produce incontinence. (From Johnston JH. Problems in the diagnosis and management of ectopic ureters and ureteroceles. In: Johnston JH, Scholtmejer RJ, eds. *Problems in pediatric urology.* Amsterdam: Excerpta Medica, 1972:57, with permission.)

The choice of surgical treatment of an ectopic ureter in a female depends on the associated renal parenchyma. Single-system ureteral ectopia to the genital system usually has such poor parenchyma that a nephroureterectomy is appropriate, but when single-system ectopia is to the bladder neck or urethra, there is often adequate function to justify a reimplantation of the ureter into the bladder (147). When the ectopic ureter is associated with the upper pole of a duplex renal unit, function of the upper pole is usually inadequate to justify salvage and a partial nephroureterectomy is most often performed. Several studies have demonstrated the incidence of histologic dysplasia in the upper pole ranges from 23% to 43%, which is less common than previously assumed (66,158). With increased perinatal detection of duplicated systems with an ectopic upper pole ureter, it may now be possible to salvage more renal function than before when this anomaly was recognized following a urinary tract infection.

Twelve percent of patients with ectopic ureters managed by upper pole nephrectomy alone will require subsequent distal ureteral stump removal secondary to infections (137). With either duplex or single ectopic ureters, the entire distal ureter associated with ectopia into the introitus or vagina usually need not be removed. The distal ureteral segment is a rare source of later problems in these patients with genital ectopia (42,147). If the distal segment becomes a source of stasis and infection, marsupialization of the ureter, usually a Gartner's duct cyst, into the vagina will correct the problem. More recently, the use of laparoscopic heminephroureterectomy

for duplication anomalies has been reported to decrease postoperative discomfort and shorten hospital stay (72,191).

If, instead of ending genitally in the vagina or introitus, there is a urinary ectopic ureter ending in the bladder neck or urethra, reflux of voided urine into the residual ureteral stump is more likely to occur and require ureteral stump removal. This may present as a small amount of dribbling incontinence after micturition but more commonly presents with recurrent urinary infection. In a series of 23 ectopic ureters managed by upper pole nephrectomy, subsequent stump removal was required due to infections in all patients with reflux into the ectopic upper pole ureter and in 40% of those with reflux into the lower pole ureter (137). This stresses the importance of a preoperative cyclic voiding VCUG in any patient with an ectopic ureter to assess the need for distal ureterectomy.

Although the dissection behind the bladder can be tedious when removing the distal portion of an ectopic ureter, if dissection is kept immediately on the wall of the ureter, there is no reason for the bladder neck or external sphincter to be damaged. The transtrigonal approach can be very useful. In a postpubertal girl, excision may be accomplished transvaginally. If the ectopic ureteral stump is not too large, its lining can be destroyed endoscopically using a Bugbee electrode, leading to obliteration of the ureteral lumen.

When enough function is present to merit salvage of the upper pole, a ureteropyelostomy or ureteroureterostomy to drain an upper pole ectopic system into the lower pole system at the renal level may be appropriate, although this is less feasible if the lower pole pelvis is intrarenal. An alternative technique for treatment of an ectopic upper pole ureter consists of ureteroureterostomy performed near the bladder level. This technique has been used to treat obstruction of the upper pole ureter as well as reflux (19,77,110). The ureter–ureter anastomosis is performed 3 to 5 cm above the bladder proximal to the common sheath. The distal upper pole ureteral stump is ligated or excised if it ends in the bladder neck or urethra. The concern about creation of iatrogenic “yo-yo” reflux appears more theoretical than real with no reports of this as a complication. This approach has the advantage of avoiding an open bladder operation. The ectopic ureter can also be primarily reimplanted into the bladder, although it may be sufficiently dilated to warrant tailoring. Rarely, a temporizing low end ureterostomy for decompression (especially in an infant) may permit a more simple later reimplant and additionally permits in a marginally functional unit time to see if recovery of function will justify a further reconstructive approach.

Ectopic Ureter in the Male

The ectopic pathway in the male extends from the bladder neck down the posterior urethra to the verumontanum and can lead to ureters ending in the mesonephric duct derivatives: epididymis, seminal vesicle, and vas deferens (Fig. 48A.32). The most common location of an ectopic ureteral orifice in the male is the posterior urethra, where approximately half of ectopic ureters will be found (Fig. 48A.33) (54). In approximately one-third of male patients, the ectopic ureter joins the seminal vesicle (67,153). Other ectopic sites are seen more rarely. Jona and colleagues (90) have described a case of single ureteral ectopia to the epididymis. Ectopic ureters to the male genital tract may present as epididymitis. Accordingly, any prepubertal boy with epididymitis requires evaluation for an ectopic ureter (156). A urine culture should always be performed. A bacterial urinary tract infection (UTI) and epididymitis is very likely to demonstrate pathology on VCUG and ultrasound. In some males, symptoms caused by a genitally ectopic ureter do not present until the onset of sexual activity. At that time, the male may present with epididymitis, prostatitis, seminal vesiculitis, or occasionally, an infected seminal vesicle cyst that may lead to pain with a bowel movement or be tender on rectal examination (17). Because ectopic ureters in the male enter above the external sphincter, they generally do not produce incontinence as they do in the female. Symptoms of flank pain and urinary infection are more common. Occasionally, there may be urgency or frequency due to the constant drip of urine into the posterior urethra. An occasional case of male incontinence may be caused by reflux of urine into a dilated ectopic ureter with drainage after voiding into the posterior urethra and subsequent leakage out through a relaxed external sphincter (188). A dilated single-system ectopic ureter into the prostatic urethra may elevate the bladder neck, causing outlet obstruction (118).

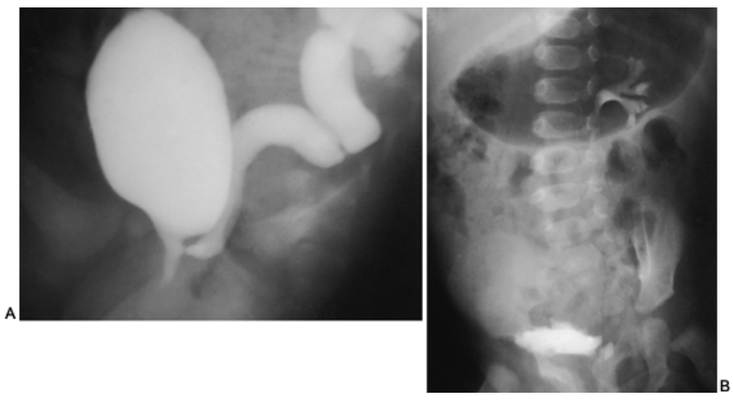

FIGURE 48A.33. Ectopic ureter to posterior urethra in a male who presented as an infant with sepsis. **A:** Voiding cystourethrogram shows vesicoureteral reflux into single ectopic ureter entering posterior urethra from solitary left kidney. **B:** Intravenous pyelogram after reimplantation of ectopic ureter into the bladder.

A high index of suspicion may be required to diagnose an ectopic ureter in the male. An ectopic ureter entering the genital tract is often single and drains a nonfunctioning renal unit (31,143,183). Ultrasound may show a dilated ureter and its associated renal element. In the case of an ectopic ureter associated with a duplex renal unit, the indirect signs of hydroureteronephrosis of the upper pole unit, described previously, with respect to ureteroceles again apply. The greatest diagnostic difficulties arise in duplex renal units when there is a tiny upper pole unit draining into a minimally obstructed ectopic ureter with little dilation (13).

Most ureters ectopic to the urethra or bladder neck will reflux (147), and thus careful examination of the oblique views from a VCUG and use of the cyclic voiding technique may enable the diagnosis to be made. In the male, as in the female, ectopic ureters at the level of the sphincters may demonstrate the paradoxical finding of both obstruction and reflux. Occasionally, when the ectopic ureter is outside the urethra, the ejaculatory duct will be so dilated as to permit reflux (188). MRI may be useful for diagnosing and demonstrating the ectopic ureteral anatomy (119).

The advent of fast-scan MRI technology should improve the utility of this diagnostic study in the pediatric population.

Cystoscopy and examination with the patient under anesthesia are useful in establishing the diagnosis. A mass in the area of the seminal vesicle or an elevation of the bladder floor over a cyst (pseudoureterocele) may be noted during cystoscopy. The ectopic ureteral orifice may be seen at the bladder neck or urethra, or there may be an enlarged ejaculatory duct, permitting a retrograde study that will establish the diagnosis. When there is single ureteral ectopia, a hemitrigone is present. Occasionally, a vasogram is useful in defining the anatomy (150).

Treatment of ectopic ureters associated with duplex units in the male usually involves removal of the associated poorly functioning renal unit. When function is adequate, a ureteropyelostomy or ureteroureterostomy as previously discussed may be performed. Because the ectopic ureter is usually dilated, a reimplantation of the duplex ectopic ureter into the bladder is a less attractive alternative. These issues come up only rarely in the male because most duplex ectopic ureters occur in females.

In the treatment of single ureteral ectopy in the male, a functioning renal unit worthy of salvage is more likely to be present if the ectopia is to the urinary tract, namely, the bladder neck or urethra (147). When an ectopic ureter enters the male genital duct, it may be unfit for the passage of sperm, and ligation of the vas may be required to avoid recurrent epididymitis.

Bilateral Single Ectopic Ureters

Bilateral single ectopic ureters are rare (40,128,146,187). When bilateral single ectopic ureters are present at the level of the urethra or more distally, there is usually a poorly developed bladder with an absent trigone and poorly developed bladder neck. Rarely, there is associated bladder agenesis (65). Associated genital and anal anomalies are common with bilateral single ectopic ureters (93).

Females most commonly are found to have bilateral single ectopic ureters located in the distal urethra. Infant girls usually present with urinary infection and are noted, incidentally, to have constantly wet diapers. Older girls most commonly present with incontinence. Women in general have worse bladder function and more severe renal anomalies than men with bilateral single ectopic ureters (40,187). Although enough urine may enter the bladder in the male to permit some voiding to take place, males may also present with incontinence. Because some urine enters the bladder in the male, it is often slightly larger than the bladder seen in females.

This description represents the cases at the worst end of the spectrum of bilateral single ectopic ureters when bothureters are very distal from their normal point of entry into

the bladder. When bilateral single ectopic ureters are present at the bladder neck level, the children may present with infection and upper urinary tract dilation from obstruction, reflux, or both, but the bladder neck is generally better formed and continence more likely. When one ureter is ectopic to the urethra and one is ectopic at the bladder neck, there is an intermediate condition, but here incontinence is usually present (147).

A carefully executed IVP or ultrasound and VCUG usually establishes the diagnosis (138,190). The associated renal units may show very poor function. The VCUG shows a small bladder with an open bladder neck. If the ectopic ureters are in the urethra, reflux is commonly present, and the VCUG usually makes the diagnosis. If the ureters are further down the ectopic pathway than the urethra, they usually are not demonstrated by VCUG. Again, an ultrasound examination may be useful. Saline into the vagina may enable reflux into a vaginally ectopic ureter to be recognized by the presence of refluxed air bubbles into the ureter, which can be picked up by ultrasound. A retrograde flush vaginogram with a Foley balloon occluding the introitus may similarly detect refluxing, vaginally ectopic ureters. During cystoscopy, a child with bilateral single ectopic ureters usually has a poorly defined, funnel-shaped bladder neck and a small bladder capacity. In the male, the ureteral orifices are usually located in the distal bladder neck or urethra, but in the female, they may be more ectopic and thus more difficult to locate.

A child who is incontinent with bilateral single ectopic ureters presents a major challenge to reconstructive surgery. In the rare case in which bladder capacity appears to be adequate, reimplantation of the ureters into the bladder and a Young-Dees-Leadbetter type of reconstruction of the bladder outlet may be appropriate (103). If bladder capacity is inadequate, a primary continent reconstruction with bladder augmentation by bowel is wise. If the ureters are dilated, implantation into the bowel in an antirefluxing fashion is less likely to succeed. Thus the use of an ileocecal augmentation anastomosing the dilated ureters to the ileum and creating a nonrefluxing ileocecal valve (74) or use of the serosal-lined ureter to bowel anastomosis (Mainz) (1) may succeed in producing a nonrefluxing reservoir. The difficulty of creating a continent bladder outlet in this patient population often leads to eventual bladder neck closure and appendicovesicostomy to achieve continence (83).

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48B THE WIDE URETER

H. Norman Noe

Part of "48 - THE URETER "

H.N. Noe: Department of Pediatric Urology, University of Tennessee; Department of Urology, LeBonheur Children's Hospital, St. Jude's Children's Hospital, Memphis, TN 38104.

The therapeutic approach to the widely dilated ureter varies regarding etiology and the pathologic significance associated with such dilation. The wide ureter lacks effective peristalsis owing to the inability of the ureteral walls to coapt, and thus it fails to properly propel a bolus of urine. This leads to urinary stasis and potential infection, predisposes to urinary calculi, and in the extreme, results in renal parenchymal destruction. However, not all wide ureters carry this poor prognosis, and in some cases, renal growth and development can proceed normally even in the presence of ureteral dilation. Because successful surgical therapy of the wide ureter is currently possible, it becomes important to identify patients with a dilated ureter who would benefit from such therapy. It also is equally important to identify those renal and ureteral units that will not benefit from surgery and can be safely observed. In this latter instance, surgical therapy can only serve as a source for potential complications and possible detriment without offering a significant change for benefit.

Much confusion has arisen as the debate regarding nomenclature for the wide ureter has continued. Caulk (8) first used the term *megaloureter.* His original term has been shortened to simply *megaureter,* but the term itself has come to mean different things to different observers. At its simplest, it means only “big ureter.” To achieve a more informed approach to the management of the widely dilated ureter, it is essential to clarify the terms used to describe such a ureter. Precise classification allows treatment based on etiology, thus permitting effective communication of the outcome of that treatment with colleagues. The term *megaureter* should not bring to mind a specific disease process nor imply an etiology, but rather it should be used as a general term for the wide ureter. Descriptive and modifying terms can then be applied as a classification scheme is adopted.

The precise definition of what constitutes an abnormally wide ureter can be elusive. The diagnosis of megaureter inevitably is established based on some form of radiographic demonstration. Technically, any ureter whose width exceeds that of the upper limits of normal for any particular age group can be designated a megaureter. Cussen (9) has established normal ureteral measurements in children from 30 weeks' gestational age to 12 years of age. Using this scheme, any ureter greater than 7 mm in diameter technically is a megaureter. However, practically speaking, there is little need to try to define megaureter in absolute diameter measurements. The radiographic appearance is usually striking, demonstrating more than just minimal ureterectasis. Marked ureteral dilation is the usual case. Ureteral tortuosity also may be present. Pelvocalyceal dilation is variable depending on the severity of the underlying disease process. Renal parenchymal scarring or loss may be present because of back-pressure atrophy or secondary to infection or calculi.

CLASSIFICATION

Several schemes for classifying the megaureter have been proposed (7,15,65). The most pressing practical matter has

been to define the obstructive from the nonobstructive forms of megaureter, given that obstructive forms need surgical correction as early as possible. Most observers easily accepted the difference between the obstructed and the refluxing megaureter, but it became less clear how to classify or categorize the so-called nonobstructive, nonrefluxing megaureter. Inherent in any discussion of the classification of megaureter is that one must accept that a wide ureter can exist without significant reflux or obstruction being present. Considerable confusion developed as this problem of classifying the megaureter was examined, and there was initial failure to accept a uniform terminology. As the understanding and experience with megaureters grew, it became possible for a more uniform terminology to be proposed and accepted.

In 1976, an international pediatric urologic seminar was held in Philadelphia. This was a combined meeting of the members of the Urological Section of the American Academy of Pediatrics, the Society for Paediatric Urological Surgeons, and the Society for Pediatric Urology. A committee was formed to develop a standard nomenclature and classification of wide ureters. This was accomplished and has been the classification scheme most widely adopted and used up to the present (56). Although many observers disagree regarding specific clinical instances for inclusion in this scheme, it offers the opportunity for all patients with wide ureters to be classified within the system. Many less complex systems are appealing but lack the ability to classify all patients clearly. It appears that some degree of complexity will have to be accepted to ensure completeness with any classification system.

The three major categories of classification in the aforementioned scheme are (a) the refluxing megaureter; (b) the obstructed megaureter; and as noted earlier, (c) the nonrefluxing, nonobstructed megaureter (Table 48B.1). Each major category can be further divided into primary and secondary subcategories. A few pitfalls already have been pointed out. It is possible to have a wide ureter that shows both reflux and obstruction (29). This represents a special situation and should be kept in mind and specifically sought when evaluating the refluxing megaureter. Iatrogenic megaureter, the residual ureterectasis following urethral valve ablation, the prune-belly ureter, and other instances have been offered as examples for which classification is difficult or incomplete. It seems that with appropriate testing, most dilated ureters usually could be properly classified. One also would have to accept that it would be possible for the classification of the ureters to change depending on the results of therapeutic intervention. An example would be the secondary obstructive megaureter caused by urethral valves that improves following valve ablation and remains as a nonobstructive, nonrefluxing megaureter. Another instance could be the residual nonobstructive ureterectasis seen after successful ureteral reimplantation. Many patients may be properly classified only following serial evaluation or long-term observation. One should also remember that the testing procedures used to evaluate the wide ureter are prone to certain inaccuracies and may have to be repeated before proper classification can be achieved. Although imperfect, the international classification scheme seems to be the most comprehensive and widely accepted at present. This scheme is used in the discussion of the wide ureter in this chapter.

Refluxing Megaureter	Obstructed Megaureter	Nonrefluxing, Nonobstructed Megaureter
Primary (congenital reflux)	Primary (e.g., adynamic segment, urethral valves)	Primary (idiopathic)
Secondary (e.g., urethral valves, neurogenic bladder)	Secondary (e.g., tumor, urethral valves, neurogenic bladder)	Secondary (diabetes insipidus, infection, residual dilation from surgery)

*Major categories within the international classification scheme for megaureter. Select examples are in parentheses. Note some conditions may appear in more than one category.

TABLE 48B.1. CLASSIFICATION OF MEGAURETER[a]

DIAGNOSTIC METHODS

General

All urologists are familiar with the fact that a ureter can appear normal on one testing circumstance and not on another. These differences can be accentuated further by different testing conditions; that is, the state of hydration, fluid load, or presence of urinary infection. The working party to establish the international classification agreed that any method that would demonstrate an abnormally wide ureter was sufficient to define the condition of megaureter. As mentioned previously, no definite measurement is used as an absolute point of definition for the diagnosis of megaureter because from a practical standpoint the diagnosis is usually quite clear radiographically.

The basic investigative procedure used by pediatric urologists today is the renal ultrasound to evaluate the upper tracts and the voiding cystourethrogram. If reflux is ruled out on the voiding cystourethrogram, the next two tests that can be used are the standard excretory urogram and/or the nuclear renal scan. The nuclear renal scan can define the severity of obstruction and the degree of renal function and

is particularly helpful in the infant or young child, where concentrating ability for the contrast media is not yet mature. The excretory urogram is especially useful to identify anatomic features of obstruction, particularly to localize that obstruction if fluoroscopy is used during the excretory urogram. Using the aforementioned tests in their proper sequence usually will be sufficient to identify the majority of causes of megaureter, both primary and secondary.

Endoscopic techniques generally are used only as secondary procedures; more informative studies, which are discussed further in the text, are relied on initially. Cystoscopy can be appropriate in the initial management of the entities, such as posterior urethral valves, urethral stricture, or the evaluation of primary reflux, or may be best deferred until the time of any planned definitive surgical procedure. In the past, retrograde ureteral catheterization noting any “hydronephrotic drip” has been used to help confirm a diagnosis or to add information in equivocal cases. This is now primarily of historic interest only. Retrograde pyelography with drainage films also can be beneficial, particularly if drainage is delayed for a substantial time. Drainage films following administration of a diuretic also can add useful information.

Once reflux has been excluded, the diagnostic dilemmas arise when it is unclear whether the wide ureter is truly obstructed or represents a nonrefluxing, nonobstructive megaureter. Two procedures are now widely used to help establish further information regarding the presence or absence of obstruction. These are the diuretic renogram and the pressure perfusion study as advocated by Whitaker (4,34,48,49,64). Each test has advantages, disadvantages, and sources of error. In most settings, they can be considered complementary rather than competitive.

Diuretic Renogram

The diuretic renogram or furosemide-assisted nuclear renal scan attempts to quantitate or measure the ability of a system to empty following a diuretic challenge. It should be performed in a consistent fashion with standard tracer and diuretic doses and with the patient well hydrated. The most widely used radiopharmaceuticals are technetium 99m diethylenetriamine pentaacetic acid (^{99m}Tc DTPA) and technetium-99m mercaptoacetyl triglycine (MAG3). Early images are recorded and interpreted as the angiographic phase of the study, with renal blood flow being estimated. During the first 3 to 4 minutes after injection, images are taken that reflect renal perfusion and can be used to calculate relative renal function. Over the next several minutes, images are made and data are gathered to generate a renogram curve. When the collecting system is well filled with isotope, images are then taken after intravenous (IV) administration of 1 mg/kg of furosemide (Lasix). When evaluating the megaureter, the clinician must remember that areas of interest should include both the kidney and the lower ureter (32). In general, half-time clearance after furosemide should be accomplished in less than 15 minutes. If clearance is greater than 20 minutes, obstruction is likely. Clearance between 15 and 20 minutes is thought by many to represent equivocal test results.

Four types of renogram curves generally are recognized (Fig. 48B.1). The normal pattern shows spontaneous washout of the tracer without the need for furosemide. The dilated, nonobstructive pattern shows progressive accumulation of the radionuclide before furosemide administration, but prompt washout after its administration. The obstructed pattern shows no washout or progressive accumulation within the ureter and upper collecting system following administration of furosemide. In the equivocal pattern, there is some degree of washout following furosemide, but the rate of clearance is much slower than that in the nonobstructive system. Simultaneous imaging of the bladder and the ureter can be particularly helpful to define the point of obstruction if an abnormality at the ureterovesical junction is suspected (Fig. 48B.2).

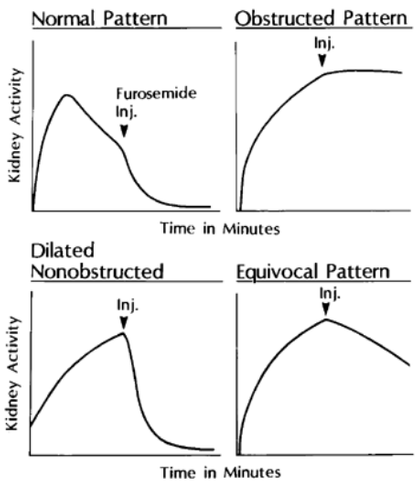

FIGURE 48B.1. Four major types of renogram curves generated during diuretic renography. Obstruction may be evidenced as a flat or even increased curve following furosemide injection.

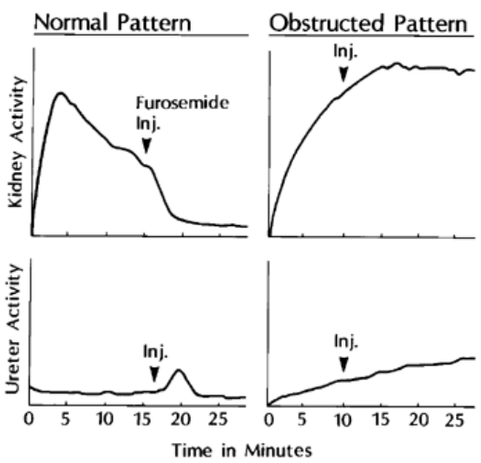

FIGURE 48B.2. Localization of the area of obstruction during diuretic renography by simultaneous renal and ureteral scanning. Note increased radioactivity in the ureteral region following furosemide injection when obstructed ureter is present.

Several factors affect the accuracy of this test. The doses of both tracer and furosemide should be standard so that adequate comparison of test results can be made. Adequate hydration is essential to ensure clearance of the tracer, and if the patient is not well hydrated, this can serve as a source of error for interpretation of the test. IV fluid administration can be helpful and is advocated by many as a routine part of the test to ensure adequate hydration. IV fluids are essential

when evaluating equivocal cases of obstructed megaureter. The degree of bladder filling influences the test; during the procedure, voiding should be initiated or catheterization performed to ensure evaluation with both an empty and a full bladder. This is especially important when evaluating specific conditions involving obstruction at the ureterovesical junction or determining whether a hypotonic, high-pressure bladder may be responsible for some degree of ureteral dilation. Poor renal function also can be an important source of error. The poorly functioning kidney may not generate enough of a diuresis to stimulate washout. By the same token, even a kidney with good function may not be able to diurese or empty an extremely capacious system if hydronephrosis is extreme (reservoir effect). In this situation, washout may be slow even if true anatomic obstruction is absent.

As we see increasing numbers of children with diagnosed prenatal hydronephrosis, it is especially important to remember that renal function immaturity in the newborn can significantly alter the results of the diuretic renogram. Low levels of glomerular function lead to slow diuretic responsiveness, and when the degree extends to the ureterovesical junction, it can make the timing of the diuretic and interpretation of the test difficult. When possible, it is best to obtain a diuretic renogram at 3 to 4 months of age, allowing time for renal maturity to occur and to avoid the possibility of a false-positive renal scan (31). This is especially important in the infant with either mild to moderate obstruction or an equivocal initial result as a newborn. The extraction factor component of the DTPA renal scan has been advocated as a means of measuring clinically significant obstruction (22). Although this appears to be a reliable test, broader experience is required to determine its usefulness in this setting.

The diuretic renogram has several advantages. It provides information for renal function measurement, is minimally invasive, can be performed with standard equipment, does not require anesthesia, and perhaps of greatest significance, can be easily used serially. The last advantage can be particularly useful in evaluation of the equivocally dilated-obstructed system or in the postoperative patient.

Pressure Perfusion Studies

The pressure perfusion study is an attempt to define obstruction in terms of pressures generated when subjecting the system to a set flow rate. By definition, in an unobstructed setting, a low pressure is maintained even when upper limits of normal flow are encountered. Thus a volume of fluid can move through the system without difficulty and without the requirements of high pressure. However, with obstruction, a high pressure is generated with the same flow rate when an attempt is made to move the same volume of fluid through the system. It is the high pressure required to move a volume of fluid through the system that is thought to produce renal damage. The pressure perfusion test was made popular by Whitaker (64) and is accepted as an accurate method of determining upper urinary tract obstruction. However, instances in which the results of the pressure perfusion study are difficult to interpret with certainty still remain.

The pressure perfusion study usually requires anesthesia in younger children, but it is possible with sedation and local anesthesia in the older, more cooperative child. It should be performed where the test can be monitored radiographically. The system is represented diagrammatically in Fig. 48B.3 . Access to the upper urinary tract is established by a percutaneous nephrostomy. An appropriate-sized urethral catheter is placed in the bladder. The system is then

connected through a length of manometer tubing and incorporates a pressure transducer and recording apparatus. A series of stopcocks allows measurement of renal pelvic and intermittent bladder pressure at different phases of filling of the urinary system. A dilute contrast agent is added to the fluid used to fill the system. This allows images to be taken during perfusion to ensure a completely filled system. A perfusion pump is used to establish a standard fast flow of 10 mL per minute, which is considered the upper limit of the physiologic range.

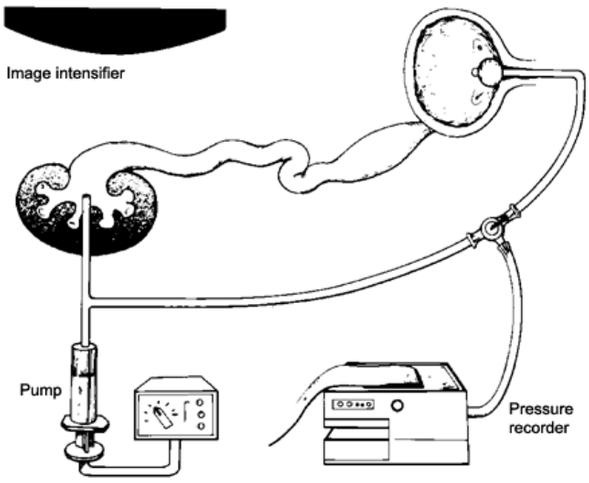

FIGURE 48B.3. Diagrammatic representation of pressure perfusion study.

Before perfusion of the system, a baseline pressure is established as that measured at the kidney level. The bladder pressure is then checked against a baseline and is usually somewhere between 3 and 5 cm H_2O pressure. Once perfusion of the urinary tract begins, spot radiographs are taken to afford anatomic information at various filling pressures; alternate renal and bladder pressures are recorded. When adequate measurements and radiographs have been obtained, the nephrostomy cannula can be removed or left, depending on the patient's therapeutic needs. To provide accurate calculation of the test results, the pressure generated when perfusing the cannula alone outside the body is measured and is subtracted from other readings. In essence, one obtains renal pelvic pressure as a relative value. This relative renal pelvic pressure is the recorded pressure minus the cannula resistance and minus the bladder pressure. A variation of the antegrade perfusion test is to fix the pressure in the renal pelvis and monitor the resulting flow into the bladder (fixed pressure perfusion). This ensures equilibrium and reduces artifact of rapid flows. In the unobstructed state, flow into the bladder is achieved at pressures below 7 cm H_2O.

A relative renal pelvic pressure less than 12 cm H_2O at a flow of 10 mL per minute is thought to be normal when assessing a point of potential obstruction, such as the ureterovesical junction. A pressure differential of 13 to 20 cm H_2O is thought to be equivocal and a greater-than-20-cm H_2O pressure difference is thought to represent true obstruction. The test usually is considered most helpful in instances in which impaired renal function and a large volume collecting system are present and the diuretic renogram is equivocal. When normal, the test is considered reliable. When equivocal or marginally elevated measurements are obtained, the results have to be interpreted with care.

Patients who are difficult to evaluate by this method are the same ones who are problematic by other methods. These include patients with noncompliant bladders, such as those with posterior urethral valves or refluxing ureters with residual ureterectasis following surgical correction. Such children may have normal relative renal pelvic pressures with the bladder empty but exhibit marked rises in pressure as the bladder fills. In these cases, the ureterovesical junction, by strict definition, is unobstructed; however, increasing bladder pressure with bladder filling results in a functional obstruction. The result is the same as localized obstruction, but the treatment is different and aimed at decreasing bladder pressures and increasing compliance as with augmentation cystoplasty. Occasionally, obstruction with filling also will be noted with little increase in bladder pressure. This can occur after reimplantation surgery with angulation of the ureter as it enters the bladder wall. Large-capacity systems also may have relatively low pressures even if obstruction exists. One must be certain that the urinary system to be tested is completely filled and at equilibrium (i.e., flow in equals flow out) to ensure accurate measurements. In addition, spot radiographs can ensure that no extravasation or leakage of fluid from the system has occurred, which could alter the accuracy of the results.

The main disadvantages of the pressure perfusion study are its invasive nature, the requirement for anesthesia in younger children, and that it is not easily applied in a serial fashion. It also gives no renal function information. As also noted previously, the results at times are difficult to interpret. It has been noted experimentally that renal pelvic pressures do not always accurately reflect obstruction (33). The determinants of the progression of hydronephrosis and possible renal damage include the rate of urine formation and the degree of duration of obstruction but, also importantly, must take into account the compliance of the pelvocalyceal and ureteral systems. A large-capacity collecting system can indeed tolerate larger volumes at lower pressures and thus give a certain measure of protection to an obstructed ureteral and renal unit once equilibration of urine formation and renal pelvic pressure has been reached. Thus low pressures can be measured within a compensated system even though obstruction does exist. In these instances, pressure perfusion measurements may not be able to predict whether hydronephrotic progression can or will occur.

Despite the drawbacks and inaccuracies mentioned, the pressure perfusion study still is considered to be a very sophisticated method of demonstrating obstruction and should be viewed as complementary to other methods, specifically the diuretic renogram. The test can be applied intraoperatively, although this seems to be applicable only in very selected instances to confirm a diagnosis or to check the immediate surgical result.

Comparisons of the diuretic renogram and Whitaker's pressure perfusion test have been made. Kass and associates (27) evaluated and compared the results of these two studies and found an excellent correlation. In their series of 42 kidneys, the majority could clearly be defined as obstructed or unobstructed by either study. False-positive and false-negative instances were encountered in both studies, although in less than 10% of the cases. Equivocal or indeterminate results also were obtained using both testing procedures, but again in less than 10%. It was through the complementary use of these tests and correlation with clinical, radiographic, and surgical findings that the final result could be established in these equivocal cases. Others have attempted to correlate the diuretic renogram and the pressure perfusion studies, with all investigators eventually concluding that there are certain limitations and technical

considerations for each method (17). Both methods seem to have their advantages, disadvantages, and sources of error. These must be kept in mind as test results are interpreted and surgical decisions are made.

Most agree, following the standard renal ultrasound or excretory urogram, to proceed with the diuretic renogram in evaluating possible obstruction. Its noninvasive nature and ready availability make it attractive. If the diuretic renogram shows prompt washout, obstruction is unlikely. Particularly in the face of good renal function, hydronephrosis and delayed washout on renal scan argue strongly for surgical approach to an obstruction without the need for further studies. However, if the results of the study are equivocal, if renal function is poor, or if an error is suspected because of a capacious collecting system, then pressure perfusion studies can be considered. If the diagnosis of obstruction is still uncertain, repeat studies might have a role in the clinically stable young patient. There will still be the occasional case in which test results may remain indeterminate. Management should be based on clinical judgment, with the final diagnosis sometimes being made only at the time of surgery.

REFLUXING MEGAURETER

Primary

As shown in the earlier classification scheme, the refluxing megaureter may be divided into two basic categories: the primary and the secondary groups. *Primary reflux* refers to the circumstance in which only a ureterovesical junction malformation exists. Ureteral tunnel length is inadequate and free reflux is demonstrated on a voiding cystourethrogram (Fig. 48B.4). Primary refluxing megaureters are more likely to be bilateral as opposed to the unilateral occurrence in the primary obstructed megaureter. Patients with refluxing megaureters most often present with signs and symptoms associated with urinary tract infection. Some will present with renal failure and azotemia, and a significant number of patients will be neonates and infants. Refluxing megaureters seem to be encountered more often in boys than in girls. In addition to the classic symptoms of infection, presentation in older children also can involve findings associated with hypertension. Whereas most patients present in the classic symptomatic manner, some have been found to have refluxing megaureters without obvious clinical signs or symptoms. This usually has occurred as an incidental finding during other medical investigations, in prenatal screening, or in conjunction with screening for familial reflux (45,46).

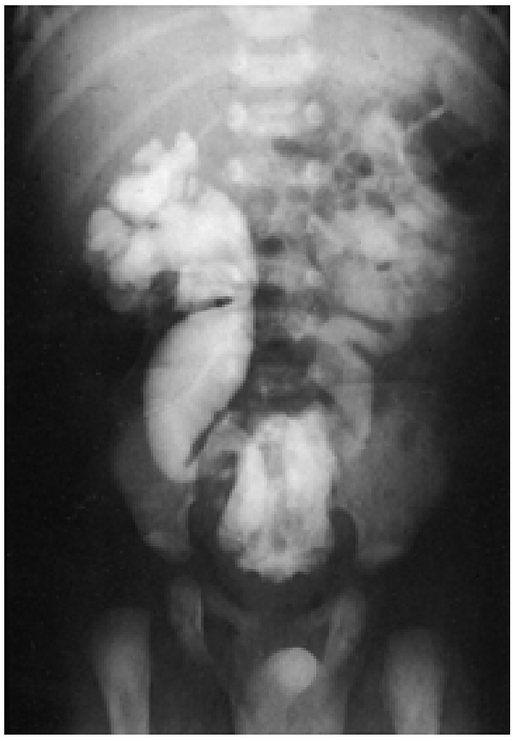

FIGURE 48B.4. Primary refluxing megaureter in a neonate presenting with urosepsis.

In many cases, the amount of renal parenchyma associated with the refluxing megaureter is reduced or renal scarring already is present at the time of discovery. Renal histology may show changes similar to those observed with obstruction, or it may demonstrate a degree of dysplasia. Secondary ureteropelvic junction obstruction can occur with severe reflux and a tortuous ureter (Fig. 48B.5).

A nuclear renal scan is sometimes helpful to diagnose concomitant obstruction, which requires surgical repair with pyeloplasty. If the dilation proves simply to be nonobstructive and secondary to the reflux alone, it will usually correct with resolution of the reflux.

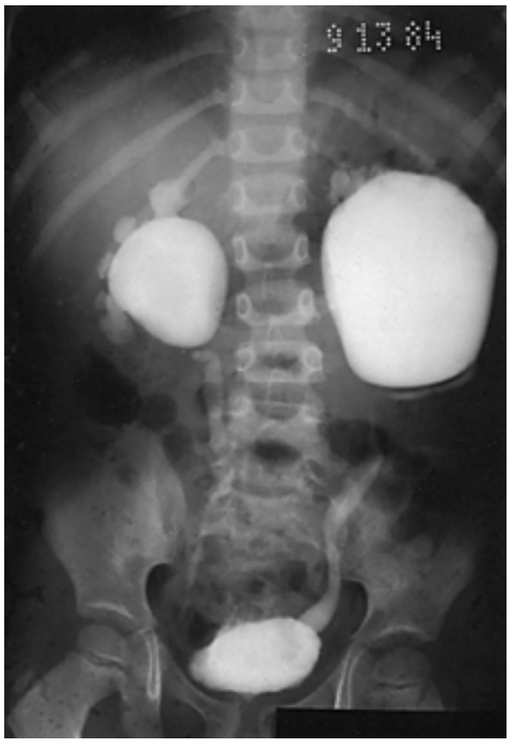

FIGURE 48B.5. Secondary ureteropelvic junction obstruction associated with reflux.

Management of the primary refluxing megaureter depends on several factors. Some children may be safely observed while on antimicrobial prophylaxis in hopes of spontaneous cessation. Realistically, however, with the more severe degrees of reflux (grades III to V), spontaneous cessation is less likely, particularly after the first year of life, and surgical management may be required. This is particularly true in children with associated abnormalities such as paraureteral diverticulum or gaping ureteral orifices.

Surgical management of the refluxing megaureter usually involves primary reconstruction. In the past, ureteral reimplantation was prone to a high level of complication and, for this reason, primary ureterostomy or permanent diversion was advocated. The latter is now thought to be inappropriate in most cases. Temporary diversion by cutaneous vesicostomy has proved useful in select situations because of its ready reversibility and ease of performance (3,12). This may be especially true in a sick neonate or in an infant with multiple congenital anomalies in whom definitive surgical correction is best delayed. Although it is possible for surgical correction and a reasonable success rate to be achieved even in neonates with high-grade reflux, experience has shown it is probably best to delay correction until the child is older. The bladders of neonates and young infants can present a hostile environment with high storage pressures and increase the likelihood of failure. Immediate or early surgery should be reserved for those children in whom breakthrough infections or deterioration of renal function is noted.

Older children with refluxing megaureters may present with severe renal compromise with or without hypertension. Ureteral reimplantation in these instances seems to offer little to improve renal function. However, surgery can be successful in controlling infection (by reducing postvoid residuals) and flank pain. Some have advocated this as a desirable alternative to later performance of pretransplant nephroureterectomy.

The unilateral refluxing megaureter can be associated with a degree of dysplasia or varying degrees of alteration of renal function, even to the point of nonfunction. A renal scan performed with an indwelling urethral catheter can determine the function in the kidney of a unilateral refluxing megaureter. If function is poor (less than 10%) and the contralateral kidney function is satisfactory, nephroureterectomy may be the therapy of choice in preference to ureteral tapering and reimplant.

Secondary

Secondary refluxing megaureters result from a functional or anatomic abnormality involving the bladder or urethra. The most common causes relate to neurogenic bladder dysfunction associated with myelodysplasia and outlet obstruction (and/or bladder dysfunction) associated with posterior urethral valves (Fig. 48B.6 and Fig. 48B.7). Other less common conditions resulting in secondary reflux include ureteroceles, urethral stricture, cyclophosphamide and radiation cystitis, and the “nonneurogenic neurogenic bladder.” The approach to the secondary refluxing megaureter is more complex and initiated with treatment of the primary etiologic factors. For example, in the case of urethral valves, 50% of patients will have high-grade reflux at initial

diagnosis (usually in the newborn period); more than one-third of these refluxes will spontaneously resolve following successful valve ablation, without the need for reimplantation surgery. Furthermore, persistent unilateral reflux following valve ablation, in many cases, is associated with a nonfunctioning kidney [vesicoureteral reflux dysplasia (VURD) syndrome]. The dilated ureter to a nonfunctioning renal unit can be used to augment a noncompliant bladder and potentially facilitate a complex reconstruction (43). In the patient with a secondary reflux megaureter, the character of the dilated megaureter may be highly variable—ranging from elastic with peristaltic activity to severely scarred with no elasticity or peristalsis and poor potential for reconstruction. Scarring is most common in the older patient with a history of urinary infections.

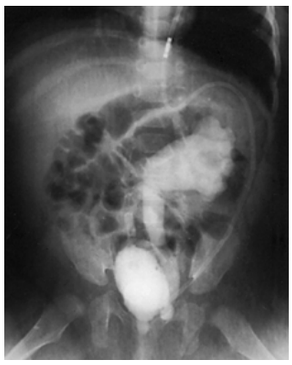

FIGURE 48B.6. Reflux associated with a neurogenic bladder.

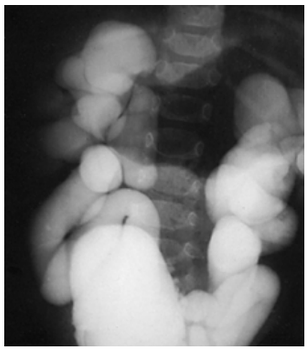

FIGURE 48B.7. Secondary refluxing megaureter attributable to posterior valves.

Similarly, management of severe reflux associated with a neurogenic bladder is initiated with a plan for bladder management. In the older child, this can involve clean intermittent catheterization with the appropriate pharmacologic manipulation and antimicrobial prophylaxis. In many cases, successful management of the bladder dysfunction will allow stabilization of the patient's condition and even lead to cessation of the reflux. In the neonate or infant, definitive bladder management may not be possible; in such cases, cutaneous vesicostomy has provided a temporary solution (3,12). Closure of the vesicostomy with management of the bladder by clean intermittent catheterization and pharmacologic means can then be attempted before a final decision is required regarding the reflux. Even the higher grades of reflux have been observed to cease in the neuropathic bladder after a period of vesicostomy drainage and with appropriate postvesicostomy bladder management (42). When required, ureteral reimplantation can be performed successfully in the presence of a neurogenic bladder. The success rate of ureteral reimplantation now has reached a level at which it plays an important role in the management of this situation (6,24,67). A cross-trigonal procedure is preferred because the trigone is usually less trabeculated and the chance of postoperative obstruction is minimized in these thickened, abnormal bladders (26). The improvement in the surgical management of even the refluxing megaureter in the neurogenic bladder makes it desirable, certainly in lieu of urinary diversion.

In the nonneurogenic neurogenic bladder or severe cases of voiding dysfunction with severe reflux, appropriate bladder or sphincter management (including voiding retraining and intensive counseling) should *precede* any attempt at surgical correction of reflux. Although the need for surgery is highly likely, this will allow the optimal chance of surgical success. Severe reflux associated with cyclophosphamide or radiation cystitis is usually best treated with augmentation cystoplasty or continent diversion because reimplantation alone has not proven successful (44).

Primary and Secondary Reflux with Accompanying Obstruction

One criticism of the international classification is that it provides no separate category for patients in whom reflux and obstruction coexist. Although this represents a small percentage of megaureters, this finding is of practical clinical importance in that ureters with both reflux and obstruction have been shown to be resistant to any form of treatment other than surgical correction (63). The obstructive component is thought to be more destructive because of chronic equilibrium with bladder detrusor pressure.

Subsequent obstruction results from ureteral wall fibrosis with muscle bundle disruption or fibrosis with fixed ureteral kinking as tortuosity develops. This process may be associated with paraureteral diverticula. This has been observed in both primary refluxing megaureters and in secondary refluxing megaureters associated with urethral valves.

The possibility of this entity of reflux and obstruction must be kept in mind by both the urologist and the radiologist during the evaluation of the wide ureter. At the time of the voiding cystogram, reflux may not be demonstrated until the patient voids or it may extend only into a dilated, tortuous lower ureter (Fig. 48B.8). Postvoiding films are important to obtain because they may show the rounded appearance of the distal obstructed ureter, with a space between this point and the bladder. This space usually represents the fibrosed or stenotic segment of the distal ureter (Fig. 48B.9). Other films may show a paraureteral diverticulum with reflux and poor drainage on delayed films. Diuretic renography or the Whitaker test may be necessary to define obstruction in selected patients.

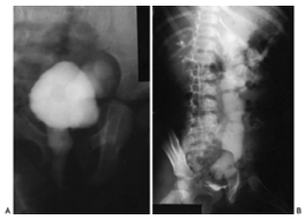

FIGURE 48B.8. A: Reflux into only the lower portion of a megaureter. **B:** Delayed intravenous pyelography film showing an obstructive element in addition to reflux.

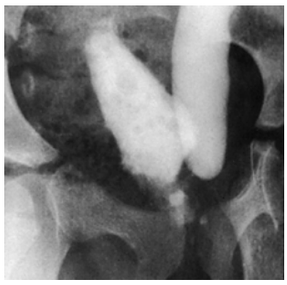

FIGURE 48B.9. Refluxing megaureter associated with secondary obstruction. (Note rounded appearance of the lower ureter characteristic of this finding on postvoiding film.)

OBSTRUCTIVE MEGAURETER

Primary

Primary obstructive megaureter has a congenital intrinsic form of obstruction at or above the ureterovesical junction. Causes include ureteral stenosis or stricture, valves, segmental atresia, ectopic orifice, and most commonly, an adynamic distal segment.

Congenital Ureteral Strictures

Congenital ureteral strictures or stenosis can occur throughout the length of the ureter. They occur primarily at the distal ureterovesical junction but are seen occasionally in the midureter in the region of the pelvic brim (Fig. 48B.10 and Fig. 48B.11). A ureteral stricture or stenotic area should be, by definition, an anatomic narrowing that is defined by calibration. Such areas have been shown histologically to contain normal transitional epithelium with sparse muscle and a relative increase in collagenous tissue. These strictures are thought to result from a vascular compromise in the

eleventh or twelfth week of gestation resulting in the development of abnormal mesenchyme leading to decreased ureteral muscularization (2).

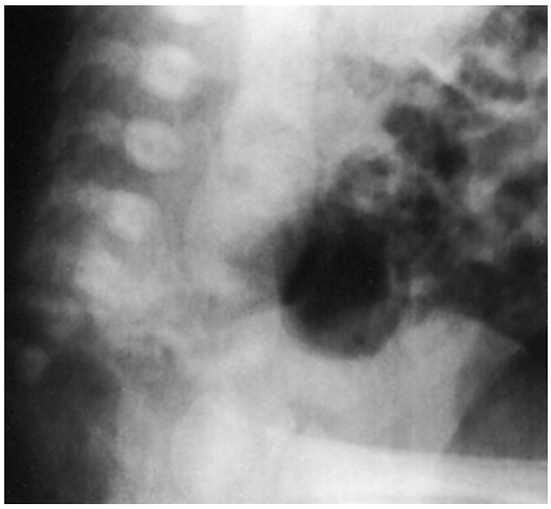

FIGURE 48B.10. Midureteral stricture in a solitary kidney discovered in a prenatal ultrasound. Lateral, delayed film during intravenous pyelography.

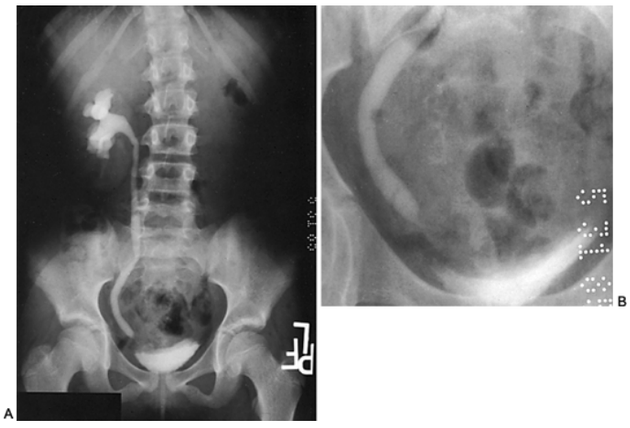

FIGURE 48B.11. A–B: Congenital distal ureteral stricture in child with solitary kidney. Child presented with flank pain and hematuria.

Ureteral Valves

Ureteral valves, like ureteral strictures, are rare. A true ureteral valve consists of a transverse fold of ureteral mucosa containing smooth muscle fibers above which are obstructive changes (Fig. 48B.12). These are annular valves that may occur in either the upper or the lower ureter.

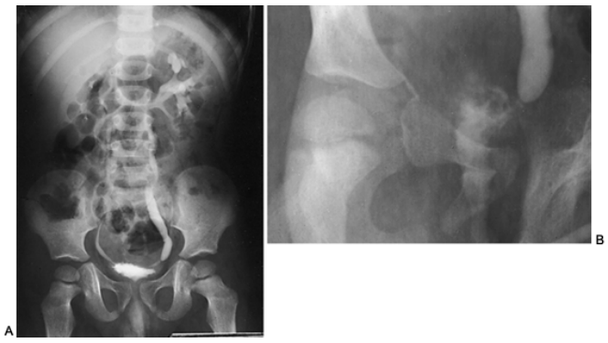

FIGURE 48B.12. A–B: Annular valve of distal ureter. (From Noe HN, Scaljon W. Case profile: ureteral valves. *Urology* 1979;14:411, with permission.)

In the upper ureter, multiple transverse folds occur during normal fetal development (50). These folds normally disappear with growth, but many believe that it is their persistence that is the source of valvular obstruction in the upper ureter (1). Valvular obstruction in the lower ureter has been suggested to be secondary to persistence of

Chwalla's membrane, but that theory will not account for the valves seen in the upper ureter.

Treatment of distinct ureteral valves will vary with the location. In the upper ureter, excision and either ureteropyelostomy or ureteroureterostomy is performed. Distal ureteral valves can be treated with excision and ureteral reimplantation.

In addition to the annular valves described previously, eccentric cusplike valves also have been described as possibly obstructive, particularly in the lower ureter (10). These cusplike folds are located at the junction of the proximal dilated ureter and the normal caliber distal ureter. Whether they are the primary source of obstruction or simply the result of a more distal obstruction is still unclear. A similar form of obstruction attributed to a tilt valve mechanism also has been described (14). This tilt valve occurs where the proximal dilated ureter joins a normal caliber juxtavesical ureteral segment. The distal ureteral lumen meets the proximal dilated ureter in an eccentric fashion. The portion of the wall of the proximal ureteral segment that overlaps the distal ureteral segment, including the lip of the eccentric distal lumen, acts as a flap and causes obstruction according to this concept. Once again, whether this is a primary process or a change secondary to more distal obstruction, as yet, is unclear. If indeed such a tilt valve mechanism exists, simple correction of the valvular obstruction could be performed and more extensive ureteral resection and reimplantation could be avoided because the distal ureteral segment may not be abnormal.

Ectopic Ureter

Ectopic ureters may prove to be obstructive. This is especially seen in the case of the ectopic ureter at the bladder neck in which compression of the ureteral orifice by the bladder neck musculature is obstructive (Fig. 48B.13). Intrinsic abnormalities of the distal ectopic ureter also may contribute to the obstruction.

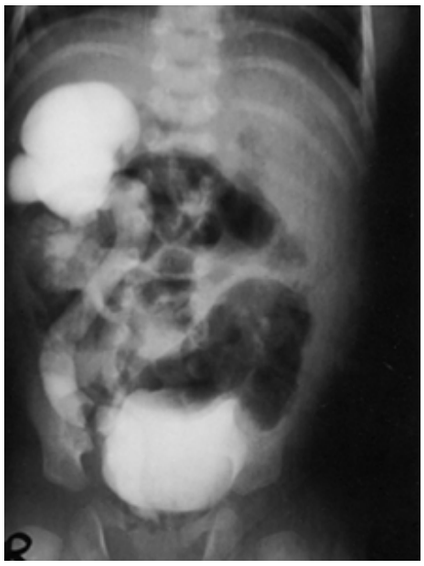

FIGURE 48B.13. Obstructive megaureter attributable to ectopic bladder neck insertion of upper pole ureter.

Distal Adynamic Segment

The distal adynamic segment is perhaps the best known of all the causes of primary obstructed megaureter. This segment consists of the terminal 3 to 4 cm of ureter that does not conduct a peristaltic wave and thus fails to allow passage of a bolus of urine through this portion of the ureter (Fig. 48B.14). This terminal ureteral segment is of adequate caliber anatomically and can be readily catheterized using the appropriate sized ureteral catheter. Thus the obstruction is functional rather than anatomic. Dilation appears proximal to this distal obstructive segment.

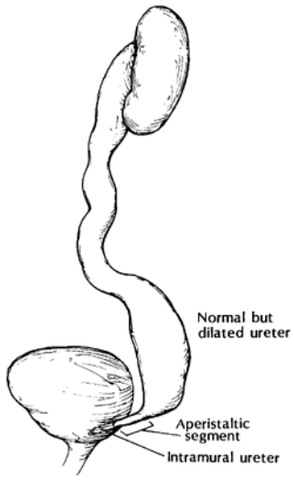

FIGURE 48B.14. Distal adynamic segment as found in primary obstructive megaureter.

Caulk's (8) original description likened this form of primary obstructed megaureter to Hirschsprung's disease. Although others attempted to further this concept, no neurologic deficit or absence of parasympathetic ganglia

analogous to Hirschsprung's has ever been demonstrated. However, several histologic studies have been successful in demonstrating abnormalities in this distal adynamic segment. Increased collagenous tissue in the distal segment has been described (18). Others have described an area in this distal segment that is devoid of musculature (37), and some have described predominantly circular muscle in this area (41). Because the ureter is basically a smooth muscle meshwork of opposing helices, many have thought that the predominant circular pattern represents an exceptional tight helix formation at the distal end of the ureter, which has the same effect as a circular muscle. McLaughlin and colleagues (39) reported histologic studies on light microscopy of 32 such ureters. In their study, five ureters were normal, two showed primarily circular muscle, and three showed mural fibrosis with essentially absent muscle. The largest single category in this study included 22 ureters that showed muscular hypoplasia or atrophy of widely separated muscle bundles interspersed with fibrosis (Fig. 48B.15).

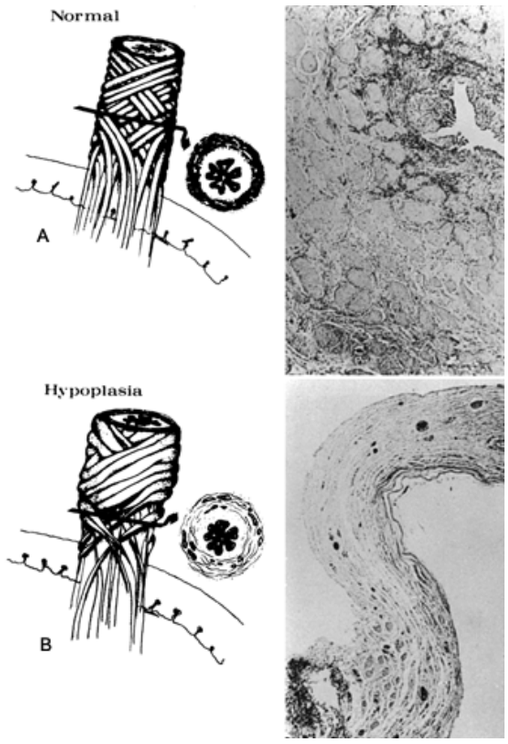

FIGURE 48B.15. Histopathologic findings in primary obstructed megaureter. **A:** Normal ureteral muscular orientation found in five ureters in McLaughlin's series. **B:** The most common abnormal finding of hypoplasia and atrophy of ureteral muscle seen in 22 patients in the McLaughlin series. (From McLaughlin AP III, Pfister RC, Leadbetter WF, et al. The pathophysiology of primary megaloureter. *J Urol* 1973;109:805, with permission.)

Electron microscopic studies of these ureters also have been performed (20,47,51,60,61). The early studies predominantly showed that collagenous tissue was observed in increased amounts between the muscle cells. It was thought that this would possibly alter the normal cell-to-cell contacts (intermediate junctions), thus disrupting electrical impulse propagation and peristalsis. More recently, quantitative histologic analysis of these dilated ureters has been performed (35). A color image analysis system was used to examine and compare collagen and smooth muscle components of the muscularis layers with more normal control ureters, primary

obstructed megaureters, and primary refluxing megaureters. In patients with primary refluxing megaureters, a twofold increase in the tissue matrix ratio of collagen-to-smooth muscle was seen when compared with patients with primary obstructed megaureter. In those with primary obstructed megaureters, the amount of collagen was increased but did not appear to be statistically different from the control ureters. These differences in the structural components (collagen and smooth muscle) may account for the difference in surgical outcomes as will be discussed later. In addition, these histologic differences have been suggested to be a function of time. Harada and associates (21) performed an experimental study in 35 mongrel dogs in whom ureteral compliance and its relationship to histologic changes were studied over 26 weeks following the establishment of partial ureteral obstruction. This study demonstrated the initial response to be muscle hypertrophy with increased compliance up to 8 weeks following obstruction. Thereafter, the compliance significantly diminished and was proportional to the amount of connective tissue proliferation. Although most of these studies have mentioned altered collagen-to-smooth muscle ratio, to date, no specific or consistent intracellular abnormalities of the individual muscle cells have been shown in any of the ultrastructural studies. The distal thickened ureteral sheath also has been suggested as being partially obstructive and usually associated with bladder distention (60). A recent study has shown that a qualitative increase in apoptosis is present in congenitally obstructed megaureters compared with normal control ureters. The presence of apoptosis following the vascular supply into the fibromuscular areas of the megaureter could account for the characteristic alteration in the circular and longitudinal muscle fibers as well as in collagen deposition seen in these children (57).

All of the aforementioned studies seem to point clearly to the fact that the predominant mechanism of obstruction of the ureter is disruption of muscular continuity and the prevention of proper muscular propulsion of a bolus of urine. Whether this results from a single anatomic cause or multiple anatomic and/or functional causes at a tissue, cellular, or molecular level remain to be clarified.

Embryologically, the explanation of the distal adynamic segment is thought to rest with abnormal development involving the distal ureteral musculature. Tanagho (58) noted that the distal ureteral musculature was the last to develop and, in particular, noted that the earliest development occurred primarily in muscle with circular orientation. Arrest later in development, such as by vascular pressure in the female or by the vas deferens in the male, could lead to diminished longitudinally oriented ureteral muscle and could result in the histologic changes noted (59).

The degree of ureteral dilation proximal to the obstructing segment is variable. In many instances, only terminal ureterectasis is seen. In other instances, dilation of both the renal pelvis and calyces also is present. As the bolus of urine reaches the obstructed segment, retrograde flow from that point leads to increased urine volume in the terminal portion of the ureter. This increased volume results in the variable degree of dilation seen in the affected ureter. The ability of the upper ureter and pelvis to dampen this retrograde flow and maintain antegrade emptying determine the effect, if any, on the renal parenchyma.

Currently, megaureter is diagnosed most commonly by prenatal ultrasound as an incidental finding. In the past, clinical presentation of patients with this entity was variable but usually owing to the symptoms accompanying urinary tract infection (13,51,52,53,54,66). In some instances, the infection is clearly related to the affected renal unit, but in others, cystitis symptoms also may be present. With the latter, no relation to the ureteral anomaly is obvious and megaureter may be an incidental finding. Hematuria, abdominal pain, or abdominal mass also may be symptoms at presentation. Discovery also may be incidental during investigation for urinary incontinence or medical investigation for a nonurologic disorder. Fortunately, the signs and symptoms of renal failure are unusual modes of presentation in this disorder. The lesion appears to affect males more commonly than females except in the first year of life, when they are roughly equal. The left ureter is affected more often than the right, and involvement is bilateral in approximately 25% of the cases. Children younger than 1 year of age are more likely to have bilateral megaureters than are older patients. Contralateral renal agenesis occurs in approximately 10% of the cases. No hereditary basis is currently recognized for this entity.

Excretory urography or renal ultrasound is the means by which the diagnosis of primary obstructive megaureter secondary to the distal adynamic segment is made. Because the narrow distal obstructive segment is close to the bladder, oblique and postvoiding films may be helpful in visualizing this area (Fig. 48B.16 and Fig. 48B.17). Videofluoroscopic studies usually demonstrate active ureteral peristalsis down to the distal adynamic segment, where the urine bolus then floods back up the ureter for a variable distance (Fig. 48B.18). Upper ureteral or renal pelvic dilation may or may not be present. The diuretic renogram or pressure perfusion studies can be useful in select cases in which the decision for treatment is unclear. Endoscopy performed at the time of surgery usually demonstrates a normal ureteral orifice and trigone. Retrograde ureteral catheterization is performed with ease, and a “hydronephrotic drip” can be noted when significant obstruction is present. A retrograde ureterogram can confirm the diagnosis demonstrating poor emptying of the ureter, but this procedure usually is not required. If instrumentation is performed, it should be performed at the time of anticipated surgical correction to avoid introducing infection into a static system.

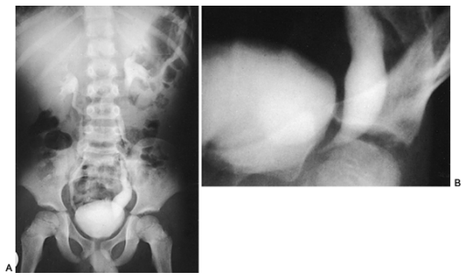

FIGURE 48B.16. Primary obstructed megaureter attributable to distal adynamic segment. **A:** Intravenous pyelogram showing terminal ureterectasis only, with otherwise normal renal unit. **B:** Oblique view of lower ureter showing area of distal adynamic segment.

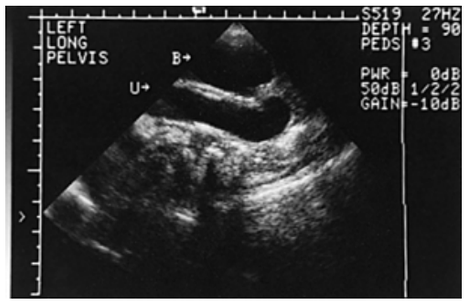

FIGURE 48B.17. Longitudinal ultrasound of an obstructed megaureter. Real-time image showed ureter clearly obstructed just at the ureterovesical junction. B, bladder; U, ureter.

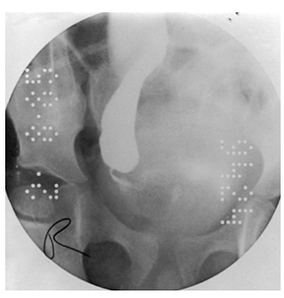

FIGURE 48B.18. Distal ureteral obstruction demonstrated on antegrade ureterogram at the time of percutaneous nephrostomy.

Treatment of these patients depends on the severity of the obstruction and the presence of symptoms. Those with only terminal ureterectasis and otherwise normal upper

urinary tracts can be safely observed and usually do not progress. Surgical correction should be reserved for those with progressive or generalized hydronephrosis, parenchymal loss, calculus disease, or persistent flank pain in patients with proven significant obstruction. Persistent or recurrent infections, particularly those that can be related to or lateralized to the affected renal unit, also form an indication for surgical treatment.

Secondary Obstructive Megaureter

Secondary obstructive megaureter occurs as a result of urethral obstruction, neurogenic vesical dysfunction, ureterocele, extrinsic compression, or fibrosis.

Urethral Valves

Urethral valves are the most commonly seen form of urethral obstruction leading to secondary obstructive megaureter. They can be due to poor bladder compliance, relatively small bladder, associated nephrogenic diabetes insipidus, ureteral fibrosis, or fibrosis and kinking often associated with a paraureteral diverticulum. It should be remembered that ureteral dilation can remain following valve ablation but not be associated with true obstruction. Marked improvement in ureteral dilation and tortuosity can occur in a relatively short time following valve ablation (Fig. 48B.19). Significant residual dilation must be evaluated further. The diuretic renogram with a draining bladder catheter is usually the first study obtained. If this study demonstrates a dilated but nonobstructed pattern, distal causes such as poor bladder compliance, high urine volume state, or persistent bladder outflow obstruction must be considered. Serial studies, primarily by ultrasound but including renal function evaluation, often are helpful to confirm efficacy of a nonoperative approach. If the diuretic renogram is equivocal, the Whitaker test may be used. High perfusion pressures with an empty bladder indicate a potential obstruction at the ureterovesical junction, and surgical treatment is indicated. One of the major difficulties in interpreting the Whitaker test in patients with urethral valves has been the effect of the degree of bladder filling on relative renal pressures (16). If pressures are low with the bladder empty but become rapidly abnormally elevated with bladder filling, the patient is potentially at risk for progressive renal damage because of poor bladder compliance. Anticholinergic therapy, and rarely, augmentation of the noncompliant bladder should be considered before megaureter repair. Urodynamic evaluation with fluoroscopy is critical in such cases. Often, it is necessary to combine lower tract dynamic evaluation with antegrade perfusion to specifically define the nature of the cause of the ureteral ectasia.

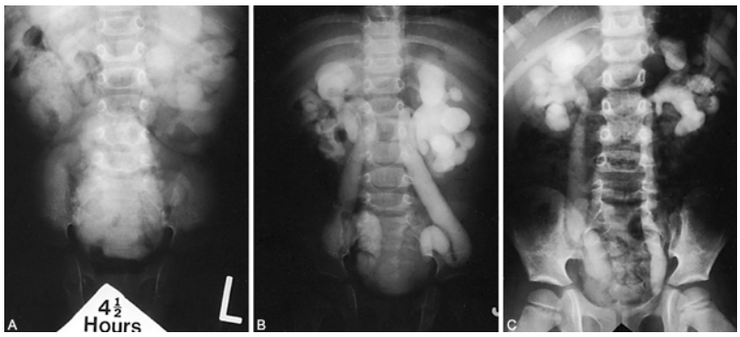

FIGURE 48B.19. A: Resolution of ureterectasis and hydronephrosis following valve ablation. Ureterectasis was present at diagnosis. **B:** Resolution of ureterectasis and hydronephrosis following valve ablation. Improvement was noted 12 months after valve ablation. **C:** Resolution of ureterectasis and hydronephrosis following valve ablation. There was further improvement 2.5 years later.

Neurogenic Bladder

Neurogenic vesical dysfunction can result in obstructive megaureter. Management of the bladder by vesicostomy, clean intermittent catheterization, or pharmacologic manipulation (anticholinergic and/or alfa-sympatholytic agents) usually results in resolution of the hydronephrosis without

the need for diversion. In older children, augmentation may be required for long-term treatment of the noncompliant or small bladder.

Successful ureteral reimplantation can be undertaken in the neurogenic bladder. It is important to have the bladder stabilized in terms of function and emptying capabilities before considering reimplantation.

Ureterocele

Obstructed megaureter can be secondary to ureterocele. Ureteroceles can involve the ipsilateral ureter or, in some cases, also can be secondary to a contralateral ureter causing an element of obstruction. Simple ureteroceles generally are not encountered in children but have been noted to occur. Ectopic ureteroceles can be associated with massively dilated ureters. Four major types of ectopic ureteroceles have been described (55). Although ureteroceles are included here as a secondary form of obstructive megaureter, it is obvious that ureteroceles also could be considered in the primary obstructed category.

Mass: Vascular Compression

Extensive compression occurs with retroperitoneal masses or tumors (Fig. 48B.20). Treatment usually consists of management of the primary condition with observation for resolution of the ureterectasis. Persistent ureterectasis following successful tumor treatment may require additional studies to be performed to determine if true obstruction remains.

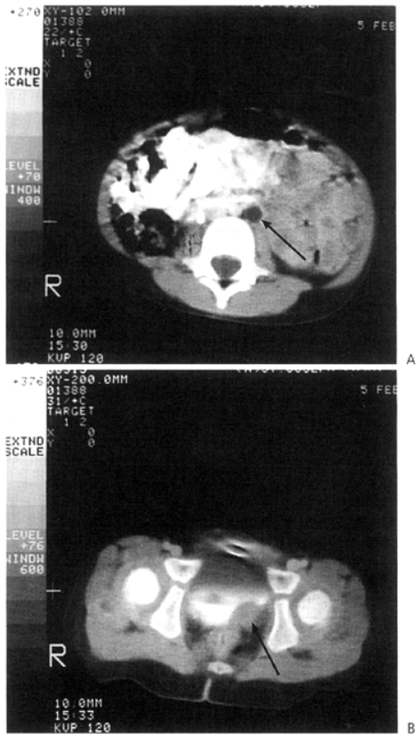

FIGURE 48B.20. A: Secondary obstructed megaureter owing to tumor. Computed tomography scan shows hydronephrosis and enlargement of left ureter *(arrow).* **B:** Tumor recurrent at bladder wall at ureterovesical junction *(arrow).*

Vascular compression can occur as a result of aberrant or accessory vessels. In these instances, treatment is influenced by the vessel involved and the degree and location of the obstruction.

Fibrosis: Iatrogenic Causes

Fibrosis can result in ureteral obstruction and can be caused by trauma or be associated with diverticula, but it is most often is the result of prior surgery, most commonly ureteral reimplantation. The assessment of postoperative residual ureteral dilation following reimplantation can be as challenging as in the similar situation involving posterior urethral valve patients. Diuretic renogram and/or pressure perfusion study and urodynamic evaluation should be utilized when the diagnosis is uncertain. As with valves, bladder compliance must be evaluated to ensure that accurate conclusions serve as a basis for treatment.

Occasionally, an unusual form of transient ureteral obstruction occurs following ureteral reimplantation. This is usually observed following surgery on the megaureter but also can be observed on ureters with less severe dilation. Although anatomically the distal ureter is open and can be catheterized, a very high-grade, if not almost complete, obstruction is observed postoperatively. This obstruction seems to be related more to ureteral dysfunction and altered peristalsis. A period of temporary drainage by double-J ureteral stent or short-term percutaneous nephrostomy usually allows a return of ureteral function and resolution of the abnormality. Once ureteral function has demonstrated recovery, tube removal is all that is required to allow proper return of function of the urinary system.

NONREFLUXING, NONOBSTRUCTED MEGAURETER

Primary

The cause of isolated primary nonrefluxing and nonobstructed megaureter is not known. It could represent an

intrinsic abnormality of ureteral development or perhaps a resolved obstruction leaving residual ureterectasis. The entire ureter usually is dilated from the bladder proximally. The degree of dilation and the presence of caliectasis is variable. The distal ureter is not stenotic, nor is the remaining ureter especially tortuous. The diagnosis of a ureter in this category is, by definition, one of exclusion. In the absence of infection and with stable renal function, it seems safe to observe these patients. A case representative of this entity is shown in Fig. 48B.21 .

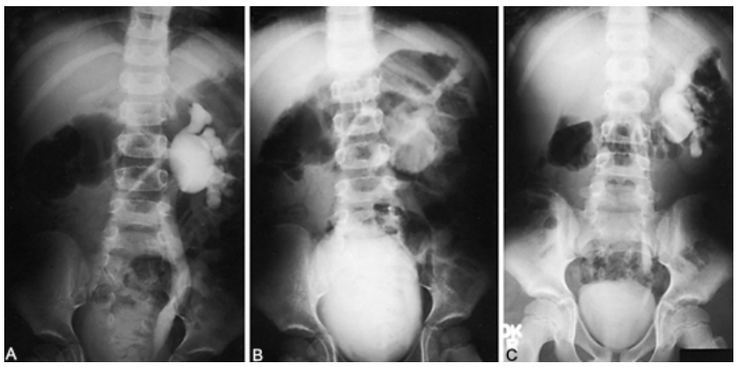

FIGURE 48B.21. A: Nonobstructive, nonrefluxing megaureter. Intravenous pyelogram (IVP) of solitary kidney with ureteral dilation discovered on evaluation for hypospadias. **B:** Prompt washout shown 10 minutes after administration of furosemide. **C:** IVP 5 years later showing adequate renal growth without progression of hydronephrosis. Follow-up diuretic renograms have shown the system to be nonobstructed, and the creatinine clearance has remained stable.

In some cases, the prune-belly syndrome can be considered in this category. Ureteral dilation in the prune-belly syndrome is secondary to abnormal ureteral development, and the radiographic picture represents a degree of dysmorphism. This dysmorphism appears to be at its greatest in the distal portion of the ureter with the proximal-most portion of the ureter usually being less dilated. However, it should be kept in mind that ureteral dilation in the prune-belly syndrome may also be demonstrated to be secondary to either obstruction or reflux, and merits a full investigation. The particulars of the prune-belly ureter are discussed elsewhere.

The concept of a dilated but nonobstructed urinary system has been brought keenly to the forefront with the advent and widespread use of fetal and maternal ultrasound. It has been shown that spontaneous resolution of antenatal and postnatal urinary tract dilation does occur commonly (19,23,25). It recently has been demonstrated that up to 60% of these children will have resolution of this dilation and can be safely followed to between the ages of 12 and 36 months (40). The concept of spontaneous resolution or improvement has been extended to several groups of neonates prenatally discovered with megaureter who have been followed and evaluated (5,36,62). Keating and co-workers (28) first reported a large number of patients with megaureter discovered prenatally or serendipitously who were followed without surgery. Many of those renal units improved and were managed nonoperatively with preservation of renal function as measured by the extraction factor (22). This now has been confirmed in several other series. Although initially this might seem to go against the advice of those advocating early surgical correction of obstruction (30,38), it seems on reflection that the real dilemma may be in truly defining obstruction in the neonate or infant. There are numerous problems with precisely defining obstruction in this patient group, including the concept of renal functional maturity, which proceeds within the first few months of life (31). Thus it seems that when an asymptomatic mildly to modestly dilated system is discovered either serendipitously or through prenatal ultrasound, early diagnostic studies attempting to define the degree of obstruction should be obtained. There appears to be no ill effect to at least a modest delay in reconstructive surgery in most of these children while waiting for renal function to mature (11). If renal function is maintained and only mild to modest or improving obstruction is found, careful but frequent follow-up can be offered as an alternative to surgical correction. It should be noted that when significant

obstruction with renal functional compromise is present, early surgical correction to preserve renal function and to prevent further damage is indicated. Whether the antenatally discovered, asymptomatic megaureter turns out to be a different entity than those discovered in the past because of symptomatic infections, stones, abdominal pain, mass, and the like, remains to be seen. It has been hypothesized that the fetal and neonatal ureter is more compliant with increased urinary output and that perhaps many of these children were simply unnoticed in the past because of their lack of symptoms. Only careful follow-up of such a series of patients such as those reported can shed new light on this problem.

Secondary

Ureteral dilation also can occur secondary to high urine flow and volume, as in diabetes insipidus or in the compulsive water drinker (Fig. 48B.22). Bacterial toxins also can affect ureteral muscular action leading to dilation and diminished peristalsis.

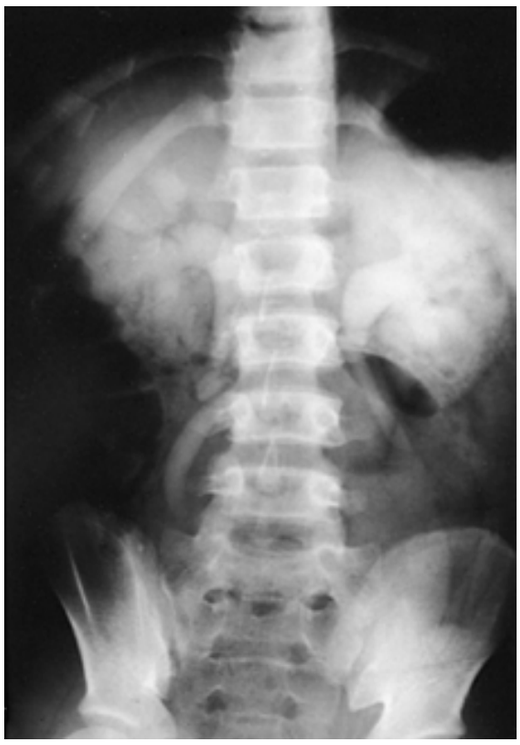

FIGURE 48B.22. Ureteral dilation secondary to high urinary output in patient with diabetes insipidus.

Other conditions included in this classification are the residual dilation following relief of the distal obstruction as in the patient with posterior urethral valves. Residual dilation following ureteral reimplantation also may be categorized in this designation (Fig. 48B.23). The classification of a dilated ureter can be a dynamic process. Successful treatment of the primary condition can still result in persistent ureteral dilation with no other clinical significance. However, these patients should definitely be followed over the long term to ensure that no late renal deterioration or increase in hydronephrosis occurs.

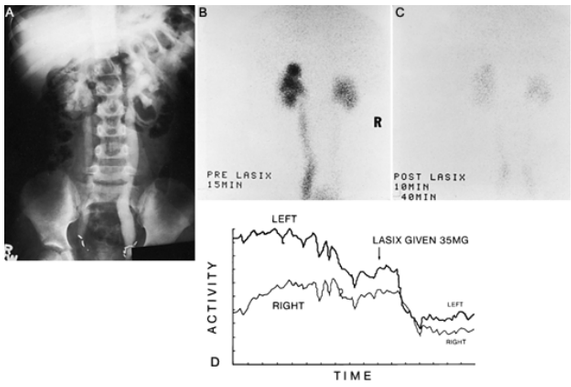

FIGURE 48B.23. A: Residual dilation following ureteral reimplantation. Intravenous pyelogram shows ureteral dilation postoperatively. **B:** Renal scan images before furosemide (Lasix) administration. **C:** Renal scan images showing prompt washout 10 minutes after furosemide administration. **D:** Renogram curves corresponding to images of the scan.

Urinary tract infection as a result of urinary stasis occasionally is seen in patients in this category. If this is true, nonrefluxing nonobstructive megaureter can serve as an indication for surgical treatment. If ureteral muscular failure is suspected or peristalsis is absent, surgical remodeling of the ureter may be of no benefit. In select instances, replacement of the ureter may be warranted.

MANAGEMENT OF THE MEGAURETER

The management of megaureter is evolving. In many cases, particularly those associated with prenatal hydronephrosis, simple observation may be warranted. Observation of children with dilation but no documented obstruction and good renal function may be appropriate, provided they are taking antibiotics. However, for children who exhibit persistent high-grade reflux, show proven obstruction, or have urinary tract infections, surgical management is the cornerstone of treatment. An intermediate response may be the placement of ureteral stents to temporize, as in the case of a sick neonate or young infant. However, in large part, if the megaureter secondary to either reflux or obstruction requires definitive treatment, it will require surgical correction. Such surgical correction usually takes the form of a tailored ureteral reimplantation directed at the lower ureter. The discussion of this treatment is provided in detail in the section of reconstruction techniques.

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48C PRUNE-BELLY SYNDROME

Douglas E. Coplen

Part of "48 - THE URETER "

D.E. Coplen: Department of Surgery, Division of Urology, Washington University-St. Louis; Division of Pediatric Urology, St. Louis Children's Hospital, St. Louis, MO 63110.

Prune-belly syndrome (PBS) consists of a constellation of three major findings and other commonly associated organ system anomalies. A deficiency of abdominal musculature gives the child's abdomen a wrinkled, prunelike, appearance (Fig. 48C.1). Bilateral, nonpalpable, undescended testes are present, and there is an abnormal urinary tract characterized by tortuous, dilated ureters, megalocystis, dilated prostatic urethra, and renal dysmorphism. Associated anomalies can involve the respiratory tract, gastrointestinal tract, cardiovascular system, and musculoskeletal system. Frolich first described it in 1839, and urologic interest began in 1895 with Parker's description (71).

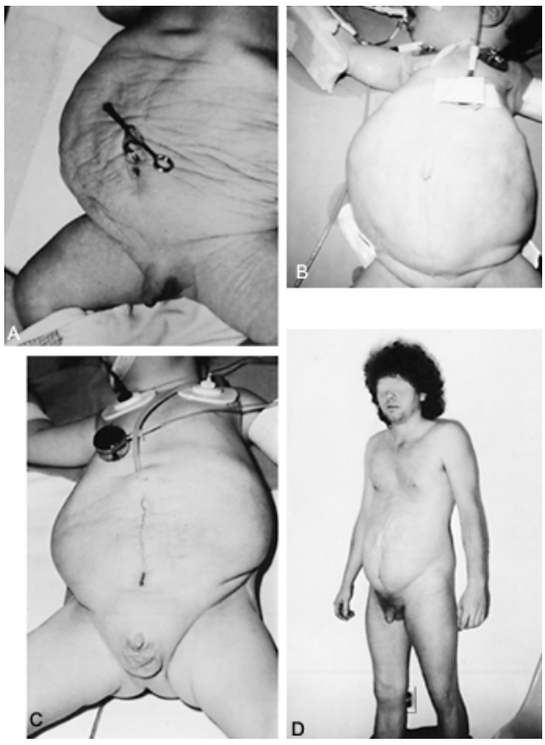

FIGURE 48C.1. A–B: Typical newborn abdominal appearance. Note wrinkling in **A** and laxity in **B. C:** A 1-year-old child with renal failure on chronic ambulatory peritoneal dialysis. **D:** A 24-year-old man with typical potbelly. No surgery was done except for bilateral orchiopexies. Note pectus excavatum and prominent midline cutaneous infolding.

This syndrome has been called by many other names, including *Eagle-Barrett syndrome* (23), *absence of abdominal musculature* (13,54,60), *triad syndrome* (67), and *mesenchymal dysplasia syndrome* (48). Despite these many terms, the name *PBS* is the most widely accepted for this constellation of major and minor findings (6,34,20,96,107,109,127).

SPECTRUM

The manifestations of PBS are widely varied. In some infants, the disease is so severe that kidney development and

urine production *in utero* are impaired. Subsequent oligohydramnios leads to pulmonary hypoplasia incompatible with life. These severely afflicted children may be stillborn or die shortly after birth. The most common postnatal cause of death is urosepsis. Before the 1970s, almost 50% of reported cases were postmortem reports (6,54,60). With aggressive management, including the judicious use of urinary diversion, peritoneal dialysis and transplantation, some of these children may survive. On the other hand, there are children with normal renal function even though the urinary tract has a markedly abnormal radiographic appearance. These children may grow up without much physical or physiologic impairment.

Attempts to correlate abdominal wall laxity with a degree of urinary tract abnormality or functional impairment have not been successful. The abnormal results of either the abdomen or the urinary tract imaging should not lead one to draw conclusions about long-term prognosis or treatment options without careful evaluation of the functional status of the child .

INCIDENCE

The incidence of PBS is estimated to be equal to that of exstrophy of the bladder (1 per 35,000 to 50,000 live births) (5,29).

There are little data to support this estimation, although approximately equal numbers of PBS patients and exstrophy patients are seen at large centers (118). The complete triad occurs only in males, but there is a subset of patients with two of three systems involved and some of these are female.

GENETICS

There is no evidence for a single gene or an autosomal-recessive inheritance in PBS (48). Riccardi and Grum (87) proposed a two-step autosomal-dominant mutation with sex-limited expression and also proposed that different gene abnormalities may result in an identical phenotype. Harley and colleagues (40) noted siblings with PBS and mosaicism, suggesting a genetic etiology. Subsequently, the occurrence of PBS in siblings has been reported many times. Frydman (27) reported a familial segregation of PBS anomalies that appeared to follow an X-linked inheritance. Amacker (3) and Hoagland (45) described an association between PBS and trisomy 21 and 18, respectively, whereas Watanabe (111) described two siblings with Beckwith-Wiedemann syndrome PBS. Despite the suggestion of chromosomal anomalies and associations with other syndromes, these still must be considered exceptions rather than the rule (29,37). However, parents should be counseled of the potential occurrence in subsequent offspring, and the chromosomal analysis of PBS patients is recommended.

There is a significant association between PBS and twin pregnancy. Among PBS patients, 1 of 23 is the product of a twin pregnancy (48). This is a much higher incidence than one would expect spontaneously (1 in 80). The majority of reported twins have been discordant for PBS, and this again speaks against a genetic etiology for PBS (48). The cause in twins may be the result of an uneven division of the mesenchyma at a critical time of primitive streak development during the third week of embryogenesis.

EMBRYOLOGY

The embryologic explanation for the development of PBS is unknown. Four theories have been suggested:

1. Wigger and Blanc (115) suggested that a primary myopathic or dysplastic process results in PBS. The predominant involvement of medial and lower abdominal wall muscles and the dysplasia that is observed histologically indicate a problem with the development and differentiation of mesenchyme into striated muscle. The lateral thoracic somites have migrated to the midline (i.e., midline defects like exstrophy and omphalocele are not present), but the somites either fail to differentiate into myoblasts or the myoblasts did not migrate ventrally and caudally. The bladder arises from the same lateral somites, so the same defect could lead to the bladder findings in PBS. Similarly, the deficiency of smooth muscle and fibrosis in the ureters might interfere with normal peristaltic propagation and result in ureteral dilation. This theory, however, does not explain the discrepancy in upper and lower ureteral dilation or the presence of undescended testicles.
2. It is possible that an intrinsic defect exists in the urinary tract that causes bladder and ureteral dilation. The consequent abnormal abdominal distention throughout embryogenesis would result in abdominal wall laxity and the characteristic appearance of a PBS patient. With this theory, the dilated bladder will mechanically block the testicle's descent into the scrotum. However, it does not explain the actual embryologic process of the urinary tract malformation, nor does the laxity of the abdominal wall necessarily correlate with the degree of urinary tract dilation.
3. PBS may result from an early, prostatic, membranous, urethral obstruction that causes bladder and ureteral dilation. Whether this is a functional (46,62) or anatomic (45) obstruction is unclear, but either might cause the abdominal musculature laxity and undescended testes, as explained previously. The overall incidence of urethral obstruction in reported cases is about 30% (58,115). I have seen a child with PBS abdominal wall and testicular findings but with a typical urethral valve urinary tract with a trabeculated bladder, bladder neck hypertrophy, and so forth. Prenatally, the fetus had ascites that may be a contributory factor in the development of abdominal wall laxity. Gonzalez and colleagues (1990) studied second trimester urethral obstruction in the fetal lamb. In one animal, this experimental manipulation resulted in musculoskeletal and genitourinary abnormalities and undescended testes as in PBS. It was hypothesized that the complete urethral obstruction in this model resulted in the findings that are distinctly different from the findings of the partial obstruction in posterior urethral valves. Outlet obstruction is clinically minimal in most patients at birth, so early urethral obstruction must recanalize later in development. This theory does not explain the more severe changes in the distal urinary tract and the milder changes in the proximal urinary drainage system.

Two histopathologic studies support an obstructive etiology for PBS. Serial sectioning of the intact bladder and urethra in infants with PBS (45) revealed a short segment of obstruction in the prostatic urethra just above the membranous urethra in some patients.

In another patient (46), the hypoplastic prostatic urethra was dilated and the angulation at the level of the internal sphincter caused a functional obstruction.

However, Workman's (129) histologic evaluation of bladders from patients with PBS revealed two distinct groups. One group had marked muscle thickness consistent with obstruction, while the other group had thin bladders with increased connective tissue inconsistent with obstruction. This suggests either an obstructive or mesenchymal defect.

4. Stephens (100) suggested that the yolk sac perhaps could be at fault because it has a key relationship to the lateral folds of the discoid embryo as it enlarges and infolds into the chorionic cavity. If the yolk sac does not shrink and constrict, some may be retained inside the embryo, giving the abdominal wall redundancy. This theory would also explain the bladder and urachal anomalies encountered because they arise from the allantois and yolk sac. This theory does not address the ureteral changes or the undescended testes.

CLINICAL EVALUATION

Antenatal Diagnosis

Antenatal ultrasonography detects anatomic urologic abnormalities that may or may not require subsequent intervention. Bilateral dilation of the upper urinary tract in association with a large bladder that does not empty completely on real time ultrasound is suggestive of PBS, but a similar presentation would also be seen with posterior urethral valves. Scarborough and associates (89) suggested that the presence of fetal ascites early in gestation is suggestive of PBS. These anatomic abnormalities may be found as early as 15 weeks of gestation. Some have recommended *in utero* intervention for placement of a vesicoamniotic shunt to decompress the urinary tract and alleviate oligohydramnios (28,41,32,66). Others, on the basis of antenatal ultrasonographic evidence of PBS, have recommended pregnancy termination (77).

Antenatal ultrasound is associated with both false negative and false positive findings that make *in utero* diagnosis uncertain . There is no proof that relief of a functional obstruction *in utero* will affect renal function (12), although pulmonary function may be salvaged if oligohydramnios is reversed. Antenatal intervention or pregnancy termination for PBS is not indicated in the absence of oligohydramnios. The urinary tract dilation in PBS is not caused by obstruction but more often is the result of nonobstructive dilation in a functionally balanced system. There may be unusual circumstances in which abdominal distention or urinary tract dilation causes dystocia that may necessitate urinary tract decompression (28).

Diagnosis in the Newborn

Because of the typical features of a child with PBS, the diagnosis is usually obvious. Initially these patients should be monitored closely, with particular attention to their respiratory and renal function.

ELEMENTS OF PRUNE-BELLY SYNDROME

Abdominal Musculature

The abdominal musculature is unevenly involved. The lateral and inferior abdominal wall musculature is diffusely deficient, whereas the upper abdominal musculature and trunk musculature may be normal (83). The musculature, however, may be totally absent in some cases (58). The affected lower abdominal wall may consist of skin, subcutaneous fat, and condensation of fibrous tissue onto the peritoneum without evidence of organized muscle tissue (2,61). The whole muscle may be simply thinned out within the fascia, replaced by thick bundles of collagen surrounded by fascia, or consist of fragments of muscle interspersed in collagen (115). The abdominal organs can easily be palpated through the abdominal wall in these infants.

Over the first year, the wrinkled abdomen of the infant smoothes. As the child begins to stand, there is a pear-shaped, or pot-bellied, appearance to the abdomen (Fig. 48C.1). The abdominal musculature weakness makes it difficult for these children to sit from a supine position. They typically roll over and use their arms to assist them. Developmental delays in other motor activities may be associated with their difficulty in axial balance when standing to walk.

Cryptorchidism

In PBS, the undescended testicles are usually found at the level of the iliac vessels in the peritoneum on a long mesorchium. Kaplan and associates (1986) suggested a role for intraabdominal pressure in the process of testicular descent; however, Hutson and associates believe that the high intraabdominal pressure and bladder distension block descent (47). The underdevelopment of the inguinal canal may also contribute to the testicular nondescent (36). The fact that pseudoprune patients can have normally descended testicles and severe abdominal laxity sheds some doubt that mechanical forces are singly responsible for the cryptorchidism.

Histologic findings on testes biopsies vary. Case reports have described these testes as Sertoli cell-only (108), hypospermatogonia with Leydig cell hyperplasia (68), and normal for age-matched controls (36). The most comprehensive review of testicular histology is the review from

Children's Hospital of Philadelphia (70). This study compared PBS testes, other intraabdominal cryptorchid testes, and testes of age-matched controls. There was no significant difference in germ cell counts, Adult Dark stem cell or Leydig cell counts found between intraabdominal testes in PBS and other intraabdominal cryptorchid testes. The observation that germ cell counts approach normal in PBS patients less than 1 year old suggests that PBS testes, like other cryptorchid testes, are not a congenital malformation but the outcome of a disease state.

Occasionally, the epididymis is detached from the testis, as noted in other circumstances of cryptorchidism. The ductus deferens may have a thickened wall of collagen with sparse musculature. The vas deferens may be tortuous and thin walled with atretic segments (105).

The risk of testis tumor in PBS patients is poorly defined. Certainly, the presence of germ cells in the young PBS patient testes places the patient at risk. Massad and co-workers (59) showed histologic similarities with intratubular germ cell neoplasia in three infants with PBS. Teratocarcinoma has been noted in intraabdominal testes after puberty (126), and a seminoma has been reported in a 30-year-old man who had undergone orchidopexy 6 years prior (72). Another PBS patient had a primary retroperitoneal embryonal cell tumor with normal testes biopsy results (88).

Orthopedic Anomalies

The oligohydramnios in PBS is believed to produce limited intrauterine space, which in turn leads to fetal compression and resultant musculoskeletal deformities. Some of these compression effects are mild (Fig. 48C.2). The incidence of orthopedic abnormalities ranges between 30% and 45%, and it is the most commonly affected system outside the genitourinary tract. The involvement may be congenital (clubfoot, limb deficiencies, hip dysplasia and dislocation, and vertebral anomalies) or developmental (renal osteodystrophy, scoliosis, and pectus deformities). Loder (1992) believes that the embryologic characteristics of the congenital musculoskeletal problems correlate with an aberration of mesenchymal development around 6 weeks of gestation, but Green (1993) believes that the anomalies are a direct result of the oligohydramnios based on the unilaterality of many of the deformities.

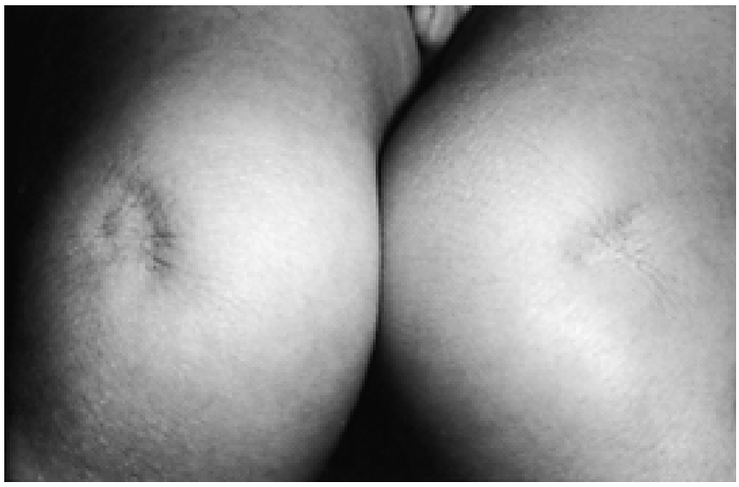

FIGURE 48C.2. Knee dimples seen in prune-belly syndrome. Dimples also may be seen on the elbows and are probably related to *in utero* compression.

Gastrointestinal Anomalies

Gastrointestinal anomalies are seen in 20% to 30% of PBS patients. Most anomalies (malrotation, volvulus, atresia, and stenosis) result from persistence of the wide embryonic mesentery with absent fixation to the posterior abdominal wall (94,130). The spleen has the same abnormal mesenteric attachment, and acute torsion has been reported in five patients (44,106). Gastroschisis (92,116), omphalocele (78), Hirschsprung's disease (11), and imperforate anus (64,110) have all been reported. PBS children may have problems with chronic constipation presumably secondary to the inability to generate intraabdominal pressure. This may require chronic intervention (30).

Respiratory Anomalies

Significant respiratory problems have been observed in PBS. These may result from a combination of pulmonary hypoplasia secondary to *in utero* oligohydramnios and disordered thoracic mechanics resulting from scoliosis, rib cage abnormalities, and abdominal weakness. Most patients have no baseline history of respiratory disease, although the majority had abnormal lung function when studied in a pulmonary function laboratory. Patients showed gas trapping secondary to poor expiratory effort, and half the patients showed significant restrictive lung disease that appeared to be secondary to musculoskeletal abnormalities rather than an interstitial lung problem. These pulmonary abnormalities must be considered before the elective treatment of PBS anomalies (i.e., musculoskeletal).

Cardiovascular Anomalies

Cardiovascular anomalies occur in approximately 10% of PBS patients (1). Atrial and ventricular septal defects as well as tetralogy of Fallot are the most common anomalies seen.

Cardiovascular, pulmonary, or other anomalies may have far greater significance in the newborn than the urologic manifestations of PBS. Urologists must individualize

the approach for each patient's specific needs, realizing that the urologic anomalies are seldom a pressing problem in the newborn.

RADIOGRAPHIC EVALUATION

The introduction of infection during radiographic procedures is a real possibility because the PBS urinary tract is dilated and urine may be stagnant. Studies that require instrumentation are avoided unless they will significantly influence management decisions. Antibiotic coverage is recommended for radiographic instrumentation of the urinary tract.

Imaging of the urinary tract may be done with a voiding cystourethrogram, which usually fills the upper urinary tracts as a result of reflux. Some information about bladder functioning and emptying can also be gained from this study. The dilated, tapered, posterior urethra, so characteristic of PBS, may also be demonstrated.

Ultrasonography can be helpful in evaluating the size of ureters and the degree of the upper urinary tract hydronephrosis. It may also aid in distinguishing the amount of normal parenchyma from dysplastic parenchyma.

Upper urinary tract imaging is beneficial, but in the newborn, it should be delayed for 2 to 4 weeks to allow for better visualization of the kidneys. A renal scan obtained with technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc DTPA) measures only gross function. Because of the dilation and tortuosity, furosemide (Lasix) administration and measures of half-time excretion are not valid in the PBS to demonstrate obstruction (33).

Kidneys

Renal dysmorphism is a common finding. Cystic calyces are characteristic of PBS without narrowing of the infundibula. Incomplete renal rotation and irregular renal outline may be present. Most kidneys display some degree of hypodysplasia. Because PBS is potentially a mesodermal abnormality, the metanephric mesenchyme may not be normal or may be inadequately induced by an abnormal ureteric bud (56). Early fetal obstruction to urine flow may also influence or cause these developmental changes.

In postmortem specimens, Stephens (100) found hypoplasia and renal dysplasia (defined as any disorganization of the renal parenchyma consisting of embryonic tubules, cartilage, cysts, and mesenchymal connective tissue) in the majority of PBS patients. Renal cystic dysplasia is most commonly associated with some degree of distal obstruction (115), and those patients with urethral atresia usually have solid dysplastic kidneys as described by Potter (80). The involvement of the kidneys is variable and may be segmental, thus renal biopsy may not be accurately predictive of outcome. The autopsy patients evaluated by Stephens and Wigger were severely affected by the syndrome, and the prevalence of dysplasia in PBS patients with “normal” renal function is unknown.

Ureter

A radiographic hallmark of PBS is the characteristic ureteral redundancy, tortuosity, and dilation, with the distal portion being more involved than the proximal ureter (8,35) (Fig. 48C.3). Segmental dilations of the midureter are occasionally found. Rarely, an obstructed ureteral segment is discovered. Fluoroscopic examination shows an ineffective churning peristalsis. Over time the ureters may straighten somewhat, and the peristaltic activity may improve. Most of these ureters have free vesicoureteral reflux. It is difficult to incriminate an obstructive cause when the distal ureter is so much more involved with these changes than is the proximal ureter. Maizels and Stephens (57) noted “pleat valves” in the caudal portion of these ureters, which may be obstructing at times (15).

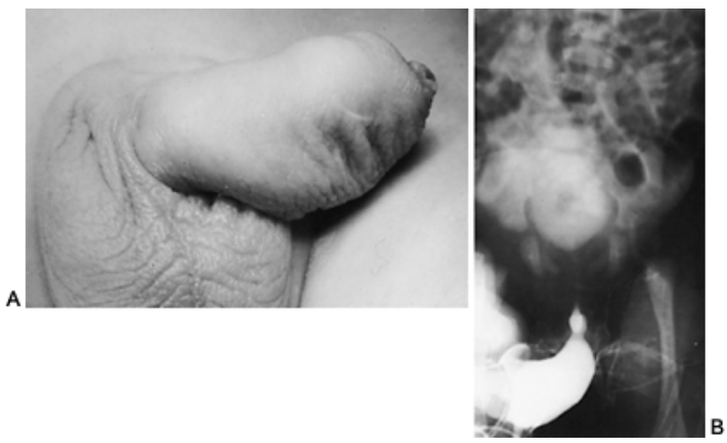

FIGURE 48C.3. A: Scaphoid megalourethra in a prune-belly syndrome (PBS) patient. **B:** Retrograde urethrogram of the scaphoid megalourethra in this PBS patient.

Histologic studies of the ureteral wall by Stephens (100) show fibrocytes, collagen, and smooth muscle in varying proportions. Other histologic studies show that the ureteral wall is composed primarily of a thick, hyaline ground substance that is acellular (24,38,69).

The poor quality of the distal ureter makes this segment a poor choice for reconstructive procedures or urinary diversion to the skin. Because the upper urinary tract dilation is nonobstructive, diversion is seldom required .

Bladder

The PBS bladder is enlarged and thick walled but not usually trabeculated. The dome of the bladder may have a pseudodiverticulum where the urachus is attached (Fig. 48C.4). Occasionally, the urachus is patent, especially when there is complete urethral atresia. The bladder is irregular, and diverticula may be present. The trigone is splayed, the ureteral orifices are laterally and superiorly displaced (100), and vesicoureteral reflux is present in 75% of the cases (20).

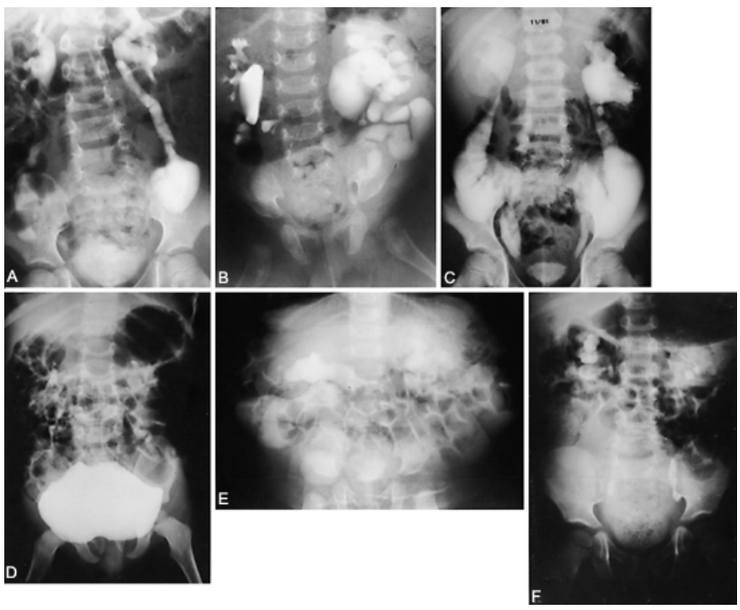

FIGURE 48C.4. A–E: Typical prune-belly syndrome urinary tract, representing a variety of cases with different degrees of dilation and tortuosity. All of these patients are being managed successfully without extensive reconstructive surgery. The patient in **B** is the same patient as in Fig. 48C.5. **B:** After excision of the urachal diverticulum and partial cystectomy. Note the typical distal tortuosity and more prominent dilation. **F:** Patient shows cystic changes in the calyces and a large bladder.

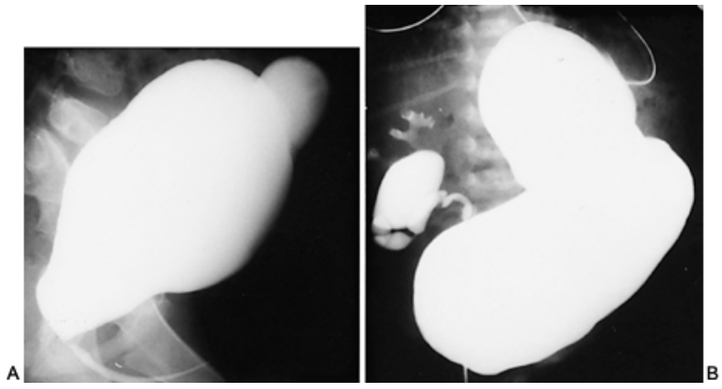

FIGURE 48C.5. A–B: Prune-belly syndrome bladders with urachal diverticula. Note the wide open bladder neck in **A** with narrowed area at membranous urethra.

The bladder has a variable histologic picture. Smooth muscle cells are intermixed with fibrocytes and collagen. Some portions of the bladder wall may be devoid of muscle cells completely. In some studies, actual muscle cell measurements show no evidence of hypertrophy (15,101). Workman (129) showed that some bladders display smooth muscle hypertrophy consistent with an obstructive etiology.

During voiding, the bladder neck opens widely and the intravesical pressures usually remain normal (67,98,119). Some patients are able to empty their bladders completely; however, many have significant post void residuals. The latter may indicate abnormal bladder dynamics or a relative outflow obstruction (98). In an analysis of 34 patients with PBS (51), three distinct uroflow patterns were identified.

These were normal initiation and peak flow, prolonged steady low flow, and an intermittent pattern. The pattern was not predictive of the ability to empty. Lee (55) found that some bladders improve their tone and emptying with age.

Prostatic Urethra

During voiding, the prostatic urethra markedly dilates, tapering down to the membranous urethra. These findings are characteristic of PBS (Fig. 48C.5). To the inexperienced observer, the PBS prostatic urethra may resemble posterior urethral valves (Fig. 48C.6). Valvular obstruction in conjunction with PBS is rare. Most of the prostatic urethral dilation is posterior, and there is occasionally evidence of a small utricle. The verumontanum can seldom be seen on the voiding studies. The membranous urethra is usually of normal caliber, and the distinct diminution of caliber from the prostatic urethra to the membranous urethra has led many to assume that there is obstruction at this point.

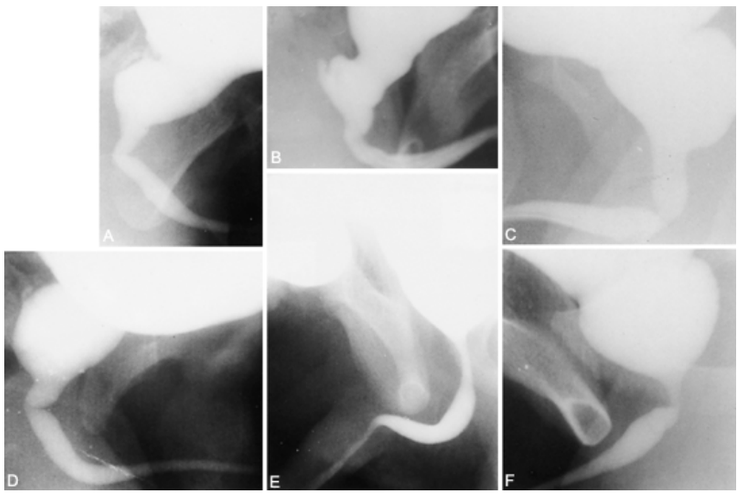

FIGURE 48C.6. Typical urethra of prune-belly syndrome. **A–F:** Six examples of the bladder neck, prostatic urethra, and anterior urethra.

Occasionally, obstructive lesions have been found in the prostatic urethra. An autopsy series search by Wigger and Blanc (115) revealed stenosis in 4 of 14 patients, atresia in 3 of 14 patients, and urethral valves in 4 of 14 patients. Manivel (58) found stenosis in 5 of 25 patients, atresia in 5 of 25 patients, and urethral valves in 4 of 25 patients. These findings are distinctly uncommon among living patients. Stephens (100) carefully studied the prostatic urethra and noted anterior folding of the mucosa, which in some cases overlapped the urethral outlet, having a valvelike effect.

Prostate

Prostatic maldevelopment in PBS is the rule. Few normal epithelial elements are found on histologic evaluation (16,62,79). The PBS patient also has an abnormal verumontanum and seminal vesicles. Because these structures are normal in urethral valve patients, this implies that the prostatic abnormality may be secondary to disturbed mesenchymal-epithelial development rather than obstruction (103).

Anterior Urethra

The anterior urethra in PBS patients is usually normal. Occasionally, a membranous urethral stenosis or atresia is present in the more severe cases; however, this is usually associated with a patent urachus. Without urethral or urachal patency, these patients usually are stillborn or die as newborns.

The occurrence of megalourethra is seen more frequently in PBS than in any other condition (4,65,93). Megalourethra occurs in two distinct types: fusiform and scaphoid (91,102). An absence of all three corporal bodies characterizes the fusiform type of megalourethra, which is the more severe defect. It results from a failure of the mesoderm in the urethral folds to develop, leading to an epithelium-lined urethra adjacent to a fibrous wall of the tunica albuginea (17). The fusiform type of megalourethra has been strongly associated with PBS and stillbirths (20,93). The scaphoid type of megalourethra is less severe (Fig. 48C.7) and results from failure of mesenchymal elements to invest the urethra.

This explains the absence of spongiosal tissue in these patients. In a review of the literature (93), nearly 50% of patients with scaphoid megalourethra had PBS.

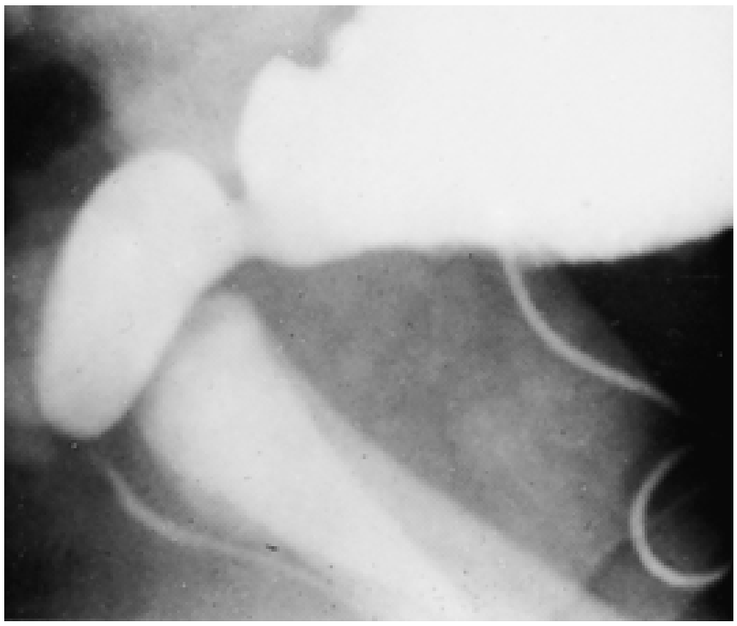

FIGURE 48C.7. Posterior urethral valve. This patient does not have prune-belly syndrome (PBS). This voiding study is shown to demonstrate the difference between posterior urethral valves and the typical PBS urethra.

Kroovand and associates (53) described milder urethral abnormalities, including a fusiform dilation of the bulbous urethra and similar dilation of the pendulous urethra. These abnormalities are usually not significant. In general, the phallus of PBS patients is long and slender with some curvature dorsally. Hypospadias has been reported.

MANAGEMENT

Therapeutic Considerations

Varied approaches to the management of the PBS patient have been advocated, ranging from watchful waiting with selective surgical intervention (20,120) to immediate newborn reconstruction without prior diversion (43,49,73,113,122).

In the 1950s, clinical outcomes with PBS were poor, and aggressive immediate surgical drainage followed by later reconstruction was the recommended management for PBS. This approach supposes that the urinary tract dilation is

secondary to obstruction and that massive reflux and residual urine leads to further renal damage or both. This reconstruction includes excision of the distal half of the ureters with tapering reimplantation of the healthier upper portion of the ureters into the bladder. In addition, the size of the bladder is reduced, and the testes are brought into the scrotum without division of the spermatic vessels. This approach has been successful in achieving radiographic improvement and perhaps stabilizes renal function and decreases the incidence of infection (49,121).

Early intervention to create nephrostomy drainage, ureterostomies, or tube cystostomies may change a balanced though dilated urinary tract into one that will require reconstruction. Intervention may be prescribed in patients with rising blood urea nitrogen (BUN) and creatinine and acidosis. Although high diversion is rarely indicated, a cutaneous pyelostomy may be performed if the systems are redundant and stagnant (82,90). Cutaneous ureterostomies should be discouraged in these patients because the upper ureter is more normal and should be used in subsequent reconstruction (123).

An approach of limited surgical intervention has been applied. The dilation in PBS is low pressure and nonobstructive, and reflux should not lead to renal damage without infection (19,21,97). This approach includes careful monitoring of the child during the first several days of life. The BUN concentration, creatinine level, and electrolyte values should be followed and should stabilize at acceptable levels (creatinine of 1.0 mg/dL or less). Spontaneous voiding should be observed for stream force and bladder emptying. Gentle bladder massage usually leads to a bladder contraction and allows evaluation of bladder function. With the urinary tract full of urine and easily palpable through a lax abdominal wall, it is difficult to avoid the temptation to achieve better drainage surgically. Catheter drainage should be discouraged because infection is likely to result. Selective surgical intervention is required if the child does not do well on prophylactic antibiotics.

A policy of watchful waiting can be very successful (Fig. 48C.8). The collecting system can distend to alarming proportions but without the significant pressure increase that would be associated with obstruction. Certainly, there are bona fide indications for surgical intervention. Before embarking on such a course; however, remember that there are quite a few reported and unreported technical failures leading to permanent diversion or rapid renal failure (18).

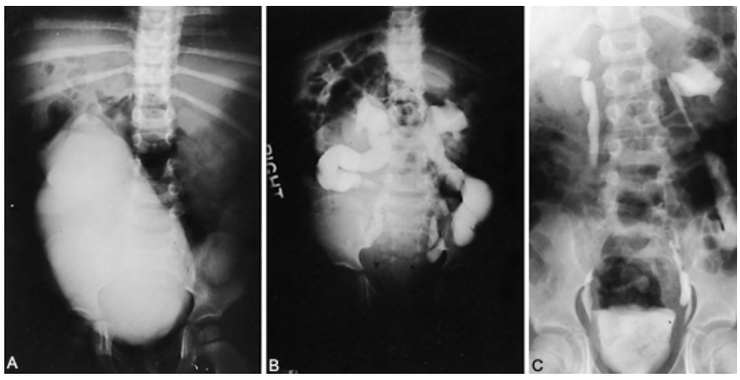

FIGURE 48C.8. A: Patient with prune-belly syndrome cystogram with large bladder but no reflux. **B:** Intravenous pyelogram with full bladder. **C:** Several years later when voiding dynamics balanced. No reconstruction was done.

There are several large clinical series showing that the management of PBS is variable and must be highly individualized with regard to timing and selection of surgical procedures (10,19,30,124,127). This probably reflects the spectrum of the PBS pathology. In general, the “good prunes” (good renal function and capacity for bladder emptying) do very well, but “bad prunes” (renal dysplasia, massive hydrouretero nephrosis, and poor bladder emptying) do poorly. As with posterior urethral valves, bladder function and emptying play an important role in upper tract outcomes. If bladder function is good, it is less likely that upper tract surgery will be required.

Infection

Infection can be devastating in the stagnant but balanced urinary tract of a PBS patient. Antibiotics in the neonatal period and long-term prophylactic antibacterial therapy with a sulfonamide or nitrofurantoin should prevent this complication. When urosepsis is present, the already poor ureteral peristalsis and bladder contractility are suppressed and surgical drainage may become necessary.

Anesthetic Considerations

These anomalies present particular problems with anesthetic management and sedatives (39,50). It is recommended that newborns have apnea monitors. A 25-year review of the Great Ormond Street experience (42) revealed a 6% incidence of postoperative upper respiratory infection. There were three postoperative deaths in 133 anesthetics. Only one of these was directly related to PBS. Normal doses of muscle relaxants may be used in these patients, but active physiotherapy is required postoperatively along with judicious use of analgesics.

Cutaneous Vesicostomy

When diversion of the dilated urinary tract is indicated, cutaneous vesicostomy is the diversion of choice (22). This procedure vents the entire urinary tract with a pop-off system of decompression. The dome of the bladder is secured to the abdominal wall through a small transverse incision midway between the symphysis and umbilicus. In PBS patients, in contrast to other patients with vesicostomies, a generous stoma is created because stenosis is a common occurrence. If a urachal pseudodiverticulum is noted, it is excised at the time of cutaneous vesicostomy. The urine is simply allowed to drain into a diaper, and prophylactic antibiotics are continued.

Reduction Cystoplasty

In some PBS patients, the bladder is enormous. Emptying is infrequent and incomplete. Some investigators have recommended a reduction in bladder capacity in hopes of improving bladder emptying (76). This procedure has been done in many ways. Generally, the dome and pseudodiverticulum of the urachus are excised, and the bladder is reapproximated in the midline (123). Williams and Parker (120) recommended bladder plication rather than excision, whereas Hanna and colleagues (38) proposed excision of bladder mucosa with overlapping detrusor flaps to augment the bladder emptying.

Urethrotomy

Despite the fact that the anterior urethra and membranous urethra in PBS patients are usually normal, a significant number of patients (30% to 50%) have difficulty with bladder emptying. Cukier (14) proposed urethrotomy of the membranous urethra (Fig. 48C.9) to improve bladder emptying. It is thought that the urethrotomy reduces the normal urethral outlet resistance that overbalances the diminished PBS detrusor contractile strength. Woodhouse (125) reported proper bladder emptying in four of five patients after urethrotomy, and Williams (117) reported

urodynamic improvement following urethrotomy in most patients.

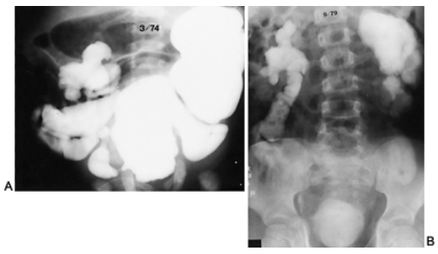

FIGURE 48C.9. A: Patient with prune-belly syndrome with cystogram at 1 month of age. **B:** Same patient 5 years later after a ureterocalycostomy of the left system and urethral sphincterotomy.

Anterior Urethra

PBS may be associated with either urethral atresia or megalourethra. Passerini-Glazel (75) reported the progressive soft dilation of the urethra (PADUA) resulting in a normal caliber urethra. When this is not successful or in cases of megalourethra, repair should be based on sound principles of hypospadias repair.

Vesicoureteral Reflux

Three-fourths of PBS patients demonstrate vesicoureteral reflux (20). However, the indications for antireflux surgery in the PBS patient should be different (21,114). Because the PBS patient has dilated ureters, the pressure from the vesicoureteral reflux is dissipated and does not reflect directly onto the renal papilla. It is technically difficult to prevent reflux and not cause some degree of obstruction at the ureterovesical junction because of the poor peristaltic function of the ureters. Reflux without infection does not lead to renal deterioration. If infection becomes a problem in the young patient, cutaneous vesicostomy is the preferred temporary surgical procedure.

If an individual patient requires antireflux surgery as a result of recurrent urinary tract infections, it is best to use the most proximal portion of the ureter that comfortably reaches the bladder and to excise the redundant distal ureter. If the reflux is unilateral, a transureteroureterostomy may be considered and can effectively bypass the ipsilateral reflux.

Abdominal Wall Plication

The abdominal wall laxity usually improves as the child matures. However, Ehrlich (25) and Parrott (74) believe that the appearance may be “psychologically crippling” in many patients. Children may wear a corset, but abdominal wall plication has been used to correct this deformity. Vertical abdominal wall plications are sometimes unsatisfactory because the laxity can return. Duckett (20) and Stephenson (104) reported that after vertical abdominal wall plication many of the patients returned to a more lax state. Ehrlich and colleagues (25) described a midline abdominal incision with plication of the fascia rather than excision. A subsequent modification by Monfort (63) allows preservation of the umbilicus.

Randolph and associates (83) studied the distribution of musculature and noted that the upper abdominal musculature was more normal. They used a transverse lower abdominal incision, removing the lower abdominal musculature, skin, and peritoneum. This technique nicely reconstitutes the patient's waistline, and in many patients has a pleasing cosmetic result (Fig. 48C.10). It can often be combined with orchiopexy or other reconstructive procedures when necessary.

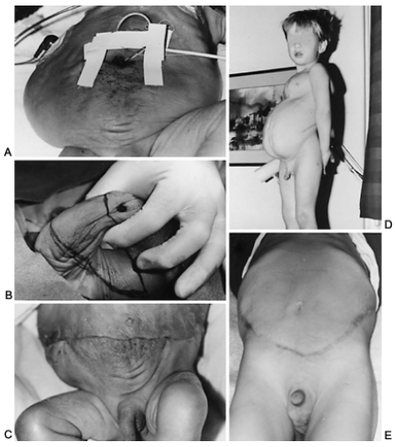

FIGURE 48C.10. Plastic repair of abdominal wall. **A:** Abdomen of neonate with prune-belly syndrome. **B:** Elliptic portion of the lower abdominal wall to be excised. **C:** Early postoperative result. **D, E:** Preoperative and postoperative appearance in an older child.

Smith and associates (95) reported that abdominoplasty resulted in improved urinary tract emptying; however, the procedure was performed in conjunction with major urinary tract reconstruction and tailoring, and the relative contribution of the abdominoplasty must be questioned. It is possible that in the presence of repeated problematic pulmonary infections, plication may support a more effective cough.

Orchiopexy

All male PBS patients have bilateral undescended testes. The testicles are usually found in the abdomen on a broad mesorchium overlying the iliac vessels but may be found at any point along the pathway of normal testicular descent. In some patients, the testes may be placed in the scrotum with conventional orchiopexy techniques. Woodard and Parrott (121,122) recommended a transabdominal neonatal orchiopexy in which the spermatic cord vessels can usually be mobilized to allow the testes to be positioned dependently in the scrotum without vascular compromise. It may be performed in conjunction with neonatal reconstructive surgery or at the time of vesicostomy.

Fowler and Stephens (26) described a technique wherein the spermatic vessels are divided and the testicle is placed in the scrotum on a vas and peritoneal pedicle blood supply. The success rate with this technique is approximately 75% (9,31). This procedure allows the high intraabdominal testicles to be brought into the scrotum when the vessels are too short. The decision to do this procedure must be made before dissection around the testicle, which would disrupt the vasotesticular collateral blood supply. It has been recommended that the contralateral spermatic vessels be ligated at the time of the ipsilateral orchiopexy so that when the second orchiopexy is done at a later time, collateralization will have already developed. Microvascular autotransplantation, anastomosing the spermatic vessels to the inferior epigastric vessels, is feasible once the spermatic vessels are of sufficient size (at 5 years of age) with a success rate of approximately 80% (9).

SEXUAL FUNCTION AND FERTILITY

Woodhouse and Snyder (128) studied the sexual function of adult male PBS patients and found that erectile

function was normal. Most patients had normal orgasm; however, seminal emission was absent in 7 of 8 patients. The fertility potential in these patients has always been in doubt (108,128). Before the advent of assisted reproductive techniques, no male PBS patient had documented fertility. This is most likely on the basis of poor prostatic function and seminal fluid, the abnormal configuration of the prostate and bladder neck, vasal anomalies and abnormal spermatogenesis. Both semen and postejaculate urine have been examined for the presence of sperm, and none was found (128). In the Woodhouse series, orchiopexy was done in late childhood or early adolescence The confirmation of germ cells in the PBS testes gives an indication for early efforts to place the testes in the scrotum (70). There is a reported case of sperm retrieval from a male with PBS, intracytoplasmic sperm injection, and twin live birth (52).

RENAL FAILURE AND TRANSPLANTATION

Approximately 25% to 30% of PBS patients will develop renal failure. This is either a developmental (renal dysplasia) or acquired (urinary tract infection and pyelonephritis) problem. A histopathologic evaluation (85,86) showed that the most severe renal changes in patients who developed

renal failure after infancy were those of chronic inflammation and reflux nephropathy with lesser involvement of the kidneys with dysplasia when compared to infant kidneys. This stresses the importance of vigilant prevention of infection in these patients.

Reinberg (84) reviewed the Minnesota experience with renal transplantation. There was no significant difference in patient death, graft survival, or graft function between PBS patients and controls. Urinary tract undiversion was performed prior to transplantation, and intermittent catheterization was routinely used in the presence of chronic urinary retention. These results are in contrast to the results with renal transplantation from the same institution that show an adverse effect on allograft survival and function in posterior urethral valve patients.

INCOMPLETE PRUNE-BELLY SYNDROME

By definition, PBS must have the triad of an abnormal urinary tract, abdominal musculature laxity, and undescended testes. However, there is an occasional patient who has two of the three elements required for the diagnosis. Most commonly the abdominal wall is normal and typical urinary tract findings are present in conjunction with cryptorchidism, although the testes are often palpable. These patients frequently have a similar clinical course to PBS patients and need the careful follow-up demanded for patients with this syndrome. Renal failure occurs in up to 50% in some series (7).

Female patients with deficient abdominal musculature and the characteristic findings of the urinary tract have been seen (81,85,86). The frequent occurrence of bladder outlet obstruction in the Reinberg series suggests a role in the pathogenesis of the syndrome. The occurrence of associated anorectal anomalies is high (40%), and the perinatal mortality was 40%. In addition, two of four surviving patients developed renal insufficiency.

PROGNOSIS

In the past, PBS portended a poor prognosis, but PBS represents a wide spectrum of disease. The outcome greatly depends on the amount of renal hypodysplasia and renal function and the degree of respiratory embarrassment. The urinary tract is dilated and rarely obstructed, and, with better management of urinary tract infections, the outlook is brighter. Each patient must be dealt with on an individual basis. A course of watchful waiting with selective surgical intervention has been successful in many centers. Early reconstruction is technically challenging but can be safely performed despite the increased risks associated with megaureters and abnormal bladder dynamics.

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48D VESICOURETERAL REFLUX AND URINARY TRACT INFECTION IN CHILDREN

R. Dixon Walker

Anthony Atala

Part of "48 - THE URETER "

R.D. Walker: Department of Surgery and Pediatrics, University of Florida College of Medicine; Shands Children's Hospital, Gainesville, FL 32610.

A. Atala: Department of Surgery, Harvard Medical School; Department of Urology, Children's Hospital, Boston, MA 02115.

In 1926, Keyes posed several questions that were prophetic in that they raised the same queries that we are faced with today in understanding the interaction of urinary tract infection (UTI) and reflux. These questions asked why some bacteria were pathogenic and others were not and how they get to and damage the kidney. Galen (147) in medieval times, recognized that reflux was abnormal when he observed the function of the ureterovesical junction in the dissected dog bladder. Others, including Pozzi (149), observed reflux in experimental animals and in humans but were unable to draw conclusions as to whether it was abnormal or not. Sampson (171) observed that the normal obliquity of the ureter through the bladder prevented reflux, and in one operated patient with an end-to-side ureterovesical anastomosis, reflux occurred. He further recognized that when reflux occurred, it could conceivably be a cause of renal infection. Sampson's work was reviewed by Young, who stated that he had come to a similar conclusion in 1898 regarding the normal ureter and that in patients who had a normal ureterovesical junction, there was no reflux, even when the bladder was forcibly distended through a catheter. It is of interest that, whereas reflux occupies a significant portion of a textbook on pediatric urology today, major texts on pediatric urology from the early 1950s from both the United States and Great Britain contained only one or two pages on reflux (32,68).

The point at which reflux became recognized as important had its genesis in Hutch's classic studies in 1952, demonstrating the effect of reflux in paraplegic patients and its relationship to chronic pyelonephritis. Before then, operations on the ureterovesical junction had been performed and the methodology of cystograms had been developed; however, the clinical implications of reflux were not recognized. This work of Hutch was followed by the observations

of Hodson (74) that reflux was more common in children with UTI and that there was a high correlation between reflux and chronic pyelonephritis as seen on intravenous urogram (IVU). These classic studies ushered in a modern era of the development of surgical techniques to treat this disease and extensive studies on the natural history of reflux. More important, they laid the foundation for the development of the specialty of pediatric urology.

PEDIATRIC URINARY TRACT INFECTION

Etiology, Incidence, and Classification

The incidence of UTI is highest during childhood and decreases steadily until adolescence (Fig. 48D.1). In the first 2 years of life, UTI is a common problem, with the cumulative risk of having a UTI almost equal between boys and girls: 2.2% versus 2.1% (85). In uncircumcised boys, the risk of UTI is greatest in the first 6 months.

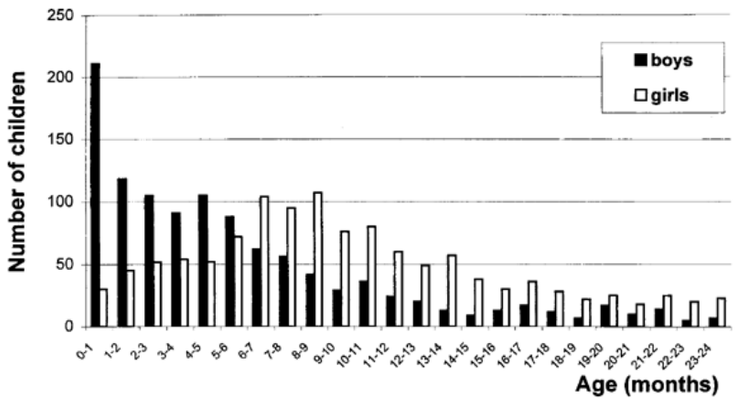

FIGURE 48D.1. Age and sex distribution of children presenting with first urinary tract infection. (From Jacobsson B, Esbjorner E, Hansson S. Minimum incidence and diagnostic rate of first urinary tract infection. *Pediatrics* 1999;104:222.)

UTI is a common presentation in children with abnormalities of the genitourinary tract. Indeed approximately 50% of children younger than 12 years of age who present with UTI are found to have such abnormalities (188). Traditionally, children have been classified according to whether they had a complicated or uncomplicated UTI, but the data that made this classification valid are changing. In the past, complicated infections were those associated with congenital abnormalities, most often reflux. The clinical symptoms associated with these infections included fever, lethargy, failure to thrive, and abdominal pain. Uncomplicated infections were not associated with congenital abnormalities and were more likely to be associated with lower tract symptoms. The primary factor in this changing classification has been the common use of newer imaging modalities that have altered the way we look at both UTI and reflux. The most important of these new modalities has been DMSA (dimercaptosuccinic acid with labeled technetium) scintigraphy, particularly when used with single-photon emission computed tomography (SPECT) imaging. Current data suggest that most patients presenting with a febrile UTI who have DMSA scintigraphy evidence of acute pyelonephritis will not have reflux (119). On the other hand, renal scarring, as determined by DMSA scintigraphy, is commonly associated with vesicoureteral reflux (VUR) (36). The relationship, however, is loosely correlated because renal scarring also occurred in neonates, suggesting that some of the lesions seen are a congenital dysmorphic process. Indeed, Anderson and Rickwood (8) found that 71% of uninfected neonates with grade III or higher VUR had renal scarring on DMSA scintigraphy similar to that seen with older children, suggesting congenital renal dysmorphism as the possible cause.

Perhaps the classification of UTI that is the most important is that associated with renal scarring, as opposed to that without renal scarring. In 1997, an expert group of panelists performed a meta-analysis of the VUR literature and decided that renal scarring was the most important endpoint in the treatment and that its presence was the principal factor in deciding management (48).

A number of host and bacterial factors have been proposed as important in the etiology of UTI (160). Many of these host factors are genetically determined and thus cannot be altered as a form of management. It is important to discuss with the family those etiologic factors that can or cannot be altered with management. A major factor in the etiology of UTI has been the discovery of its association with functional elimination syndromes (99). Dysfunctional voiding problems include bladder instability, infrequent voiding, lazy bladder, and Hinman syndrome. Bowel symptoms include chronic constipation and encopresis. These symptoms are associated with an increase in the number of UTIs, an increase in breakthrough UTIs while taking prophylaxis, and delayed resolution of VUR. They are also associated with a higher complication rate from antireflux surgery (137). Loening-Baucke (110) found that the incidence of UTI decreased after bowel dysfunction was treated. The treatment of dysfunctional voiding, discussed more fully in another chapter, includes measures such as timed voiding and anticholinergic therapy. Bowel retraining and treatment of bowel disorders are equally important in reducing the incidence of UTIs. Treatment includes dietary increases in raw vegetables, fruits, and fruit juices; use of whole wheat breads; and a limitation on milk and milk products. Stool softeners, mild laxatives, and enemas are also used to establish regularity.

A controversial area is the relationship of UTI in male neonates to the presence or absence of foreskin. In 1985, Wiswell and associates (228) presented their initial report of a decreased incidence of UTI in circumcised versus noncircumcised male infants. A follow-up study reviewing a larger number of patients showed a tenfold increase in UTIs in uncircumcised male infants: 1.12% versus 0.11% (227). Of interest was that a large number of these infected infants required hospital admission for management of clinical pyelonephritis. This study was the impetus for these investigators to look further at the relationship of UTIs and circumcision with the finding that decreased numbers of routine neonatal circumcisions were being done and that this correlated with a rising number of neonatal male UTIs (225). Winberg and co-workers (222) suggested that perhaps the prepuce was a “mistake of nature”; but rather than suggesting circumcision as a cure, it was suggested that the prepuce be colonized with a nonpathogenic anaerobic gastrointestinal bacteria from the mother. Wiswell and Geschke (226) also have looked retrospectively at the sequelae of UTIs in the noncircumcised male infant. They found a much higher incidence of bacteremia, renal failure, and death. This retrospective study has a serious flaw in that the results do not state whether these patients had any other associated risk factors, such as obstructive uropathy or VUR. The intact foreskin has also been suggested as an etiologic factor in acute epididymitis in boys (19). A large study from the Department of Public Health in Toronto found an increased risk of UTI and hospitalization in noncircumcised boys but much less than previously published data. The study questioned the efficacy of routine circumcision as a means to protect boys from UTI (205). The Fetus and Newborn Committee of the Canadian Pediatric Society (52) did an extensive review of 122 articles on circumcision and came to the conclusion that “circumcision of newborns should not routinely be performed.” The Task Force on Circumcision for the American Academy of Pediatrics (6) made a similar policy statement indicating that although medical benefits did result from circumcision, they were not sufficient to recommend routine neonatal circumcision. The British Journal of Urology (28) recognized the tremendous emotional concerns about circumcision and devoted an entire supplement to the subject.

Although less controversial, labial adhesions in young girls have raised similar questions as to the relationship with UTIs. The relationship has a theoretical scientific basis on the grounds that it might promote abnormal perineal bacterial colonization, but there are no data to support this. Labial adhesions in young girls with UTIs should be treated. The initial form of treatment is estrogen cream applied daily after the child's bath for 3 weeks and then some mild ointment daily to prevent recurrence. For the latter, one can use vitamin A and D ointment. If estrogen treatment is not effective, the adhesions can most often be broken down in the office by applying EMLA cream for 45 minutes and painlessly forcing the adhesions apart. One can then follow with A and D ointment as just described. It is rare for a child to require surgical therapy of labial adhesions.

Pathogenesis

Bacteria that cause UTI are most often aerobic Gram-negative rods that are normal inhabitants of fecal flora. These organisms reach the bladder and kidneys through ascent from the rectum to the perineum, vagina, and urethra. The anatomic differences between males and females account primarily for the difference in the incidence of UTIs. These differences include the longer urethral length and the absence of the moist perineal-vaginal area in the male.

Bladder infection is the result of the relationship between virulent bacteria and the mucosal surface of the bladder. Factors that make bacteria virulent include the presence of pili, which may allow adhesion with uromucoid surfaces, and the nature of bacterial cell wall antigens and their association with hemolysin and colicin, which gives it a competitive advantage against other bacteria. Mutations on the surface of pili also may allow bacteria to adapt to changing conditions in the bladder.

Bacterial adherence is theoretically a vital link in the development of pyelonephritis. The subject is reviewed in the monograph by Schaeffer (174). It has been common knowledge among bacteriologists for some time that bacterial adherence is a property that allows colonization of

surfaces. Recently, the role of adherence as a pathogenic phenomenon has been explored. Colonization of the alimentary tract and mucosa-lined orifices takes place within the first few weeks after birth. Colonization of the gut by pathogenic organisms is the first step in the process that eventually produces renal scarring. The adherence of pathogenic bacteria to the perineum, vagina, urethra, or bladder wall resists the natural action of those structures to wash the bacteria away. Adherence is, in part, due to the interaction between binding molecules on the bacteria (ligands) and receptors on the host cells. This bond between bacteria and host cells is so well developed that it is almost impossible to reverse. Bacterial ligands are located on fimbriae that provide the initial contact between bacteria and host cells. Fimbriae may be of several types, but any one bacterium will have only one type. Type 1, or mannose-sensitive fimbriae, are very common on nonpathogenic stereotypes of *Escherichia coli.* These fimbriae are so called because they react with a mannose sugar on the host cell surface. Mannose-resistant fimbriated bacteria are more likely to be pathogenic and have been implicated in pyelonephritis in children. Some mannose-resistant *E. coli* have fimbriae that possess P blood group bacterial adhesions and thus are referred to as *P pili bacteria.* The importance of these P pili bacteria is that they are implicated in a large number of children with clinical acute pyelonephritis. Kallenius and associates (90) found P pili *E. coli* in 91% of children with acute pyelonephritis. Acute pyelonephritis was defined as UTI with temperature greater than 38°C, elevated C-reactive protein level, and elevated erythrocyte sedimentation rate. Of the 150 strains of *E. coli* identified by O antigens, 9 are present in most UTIs (122).

The problem in relating this finding to renal scarring is that many of the children in both studies did not have reflux; conversely, the study by Lombard and associates (111) indicated that very few children with severe reflux and renal scarring have demonstrated infections with P pili bacteria.

Although renal scarring does occur in the absence of reflux (154), the rate at which it does so is unclear. Thus we are left with the conflicting data that suggest that the P pili *E. coli* is a very virulent strain, easily causing renal damage in experimental situations, and yet uncommonly is related to the renal scarring in children that is the focus of this chapter. Other types of adherence may occur in severely refluxing children and may account for the development of renal scars. It has been shown that both capsular K and cell wall O antigens can cause adherence, and these antigens are present in a large number of *E. coli* organisms. K antigen is present within the capsules of virulent Gram-negative organisms and is believed to protect against phagocytosis and inhibit host immune response.

These organisms also commonly have fimbriae that show mannose-resistant hemagglutination and fail to react with mannose on the host cell surface. Some mannose-resistant bacteria also express P blood group ligands on their fimbria, a property that further enhances bacterial adherence to the urothelium and renal epithelial cells (109,211). Some authors suggest that the adherence of bacteria to urothelial cells is independent of the P blood group antigen in the host (113), whereas others note that patients with the P1 blood group have a relative risk of pyelonephritis 11 times that of normals (159).

The ability of bacteria to adhere appears to also be affected by host epithelial cell surface receptors or soluble receptors in the urine. *E. coli* infections, for example, occur with greater frequency in children with Lewis (a-b-) phenotype, which is postulated to promote bacterial adherence (86). Tamm-Horsfall protein, which is secreted by the proximal renal tubules, binds to certain nonfimbrial adhesins and can prevent bacterial adherence to mucus (glycoproteins or glycosaminoglycans) that normally coats the urothelium (140). Differences in IgA (1), blood group antigens (25), and the amount of mucopolysaccharide (141) secreted by the bladder epithelium may also contribute to sexual and individual differences in the propensity to UTIs. However, no significant difference in genetic markers has been shown in children in the first year of life (3).

Other virulence factors, including hemolysin, aerobactin, and bacterial iron-binding capacity, contribute to the host inflammatory response and degree of tissue destruction (169). Bacteria that express three or more virulence factors are usually the cause of acute pyelonephritis in the absence of reflux. Less virulent bacteria can cause similar episodes in patients with reflux (112). In theory, once bacteria adhere to ureteral urothelium, endotoxins cause a decrease in ureteral motility, ureteral dilation, and an alteration in papillary configuration, thus allowing intrarenal reflux (158).

The bladder defense mechanisms include the mucosal surface of the bladder and the emptying capacity of the bladder. The mucosal surface of the bladder, its glycosaminoglycan layer, and its propensity for infection may be determined genetically. Surface cells produce secretory IgA that may help prevent bacterial colonization (1). Bladders that do not empty effectively leave urine behind; this promotes greater contact with bladder mucosa, which fosters bacterial growth. Many conditions may allow poor emptying of the bladder, including neurogenic bladder, VUR, and obstructive uropathy. In the normal individual, other factors inhibit the growth of bacteria, including the osmolarity and acidity of the urine.

Bacteria that reach the kidney and cause pyelonephritis have a similar relationship to the surface of the renal pelvis and collecting ducts of the renal medulla as bacteria do to the bladder. These bacteria reach the kidney more commonly when reflux or obstruction is present, but they also can reach the renal pelvis in a perfectly normal system. Pyelonephritis occurs when there is an inflammatory response in the medulla; leukocytes are mobilized to combat the infection, and the resulting phagocytosis of bacteria,

with the release of high oxygen radicals, is a factor in eventual renal scarring.

The renal scar may develop very quickly or take quite a long time. Ransley and Risdon (152) have proposed that some scarring in infants with intrarenal reflux takes place immediately after a severe pyelonephritic episode and have called it the “big bang” effect. They acknowledge that in some instances, the process takes longer, perhaps in a series of “little bangs.” Friedland (53) has indicated that the full growth of a renal scar may take place over as long as 2 years.

The actual process of scarring probably is due to the normal cellular response to the invading bacteria. The same processes that come into effect to kill the bacteria also damage the tubular cell wall. Roberts (156) has theorized that once bacteria adhere to renal tubular cells, an immune response is elicited. During phagocytosis, superoxide is released in a respiratory burst from the cell wall and damages both bacteria and tubular cells. This damage causes an interstitial inflammatory response that leads to renal scarring. In the monkey, administering superoxide dismutase (163) can block the scarring and inflammatory response. Furthermore, Roberts and co-workers (161) have been able to block adherence to tubular cells by immunization with an antifimbrial antibody. Immunization with a less purified *E. coli* mixture that had a mild protective effect against renal scarring also has been performed in piglets (207). New data from Langerman and colleagues (103) suggest that other factors might cause adherence against which immunization may provide protection. FimH, an adhesion, is necessary for colonization with *E. coli* of the bladder wall in some experimental animals, and immunizing with FimH may protect against repeat colonization. All of these findings suggest that immunization might be practical; however, in the long run, antimicrobial agents may provide less expensive and better protection (174).

Ischemic damage to renal tubular cells also can occur as a result of exposure to *E. coli.* Anaerobic metabolism of *E. coli* causes anoxia and consumption of the purine pool, leading to release of superoxide radicals. This process can be blocked by allopurinol (157). The complex mechanism of the development of renal scarring as described by Roberts is depicted in Fig. 48D.2 .

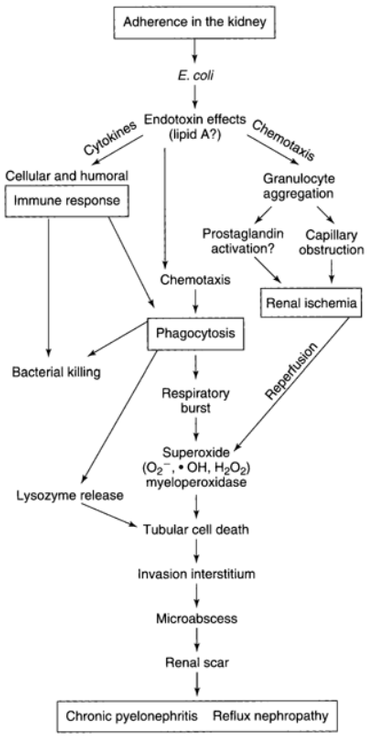

FIGURE 48D.2. Schematic representation of pathogenesis of pyelonephritis scar formation. (From Roberts J. Vesicoureteral reflux and pyelonephritis in the monkey: a review. *J Urol* 1992;148:1721, with permission.)

Diagnosis

The diagnosis of UTI can be made on a urine culture obtained from a clean catch or a catheterized specimen. Clean-catch specimens are more likely to be contaminated, but if the growth is a single pathogenic bacteria, it is likely significant. Urine can be obtained easily from infants with a suprapubic bladder puncture or catheterization with an infant feeding tube. Colony counts of 100,000 colonies in a clean-catch urine are usually required to be significant, but any positive culture must be correlated with the symptoms that the patient presents with. Any urine culture greater than 5,000 colonies from urine obtained on a suprapubic puncture or catheterized specimen is significant.

Presentation

Infants and young children with UTIs are more likely to have nonspecific signs or symptoms. The most common

serious presentation is with fever, which should trigger a strong suspicion of an underlying urologic abnormality. Other symptoms in young children include failure to thrive, vomiting, diarrhea, anorexia, and lethargy. Children of any age with renal scarring may present with hypertension. Older children and adolescents often have symptoms of bladder irritability, anorexia, or abdominal pain (186). Pain with sterile reflux may be colicky in nature. Older children may complain of flank pain with a full bladder. These symptoms are nonspecific as to localization of infection, but when associated with fever, they are suggestive of upper UTI.

Fever is a key presenting symptom that helps distinguish between children with pyelonephritis and those with cystitis, but it is not always a reliable determinant. Because children with pyelonephritis are more likely to have reflux, this presenting symptom, if reliable, would be helpful in predicting which children would have a positive radiologic evaluation. Woodward and Holden (230) evaluated 350 children with UTI and found that 90% of refluxing children had temperatures greater than 38.5°C, whereas only 40% of nonrefluxing children had similar temperatures. They noted that if only children with fevers had been evaluated, 10% of those with reflux would have been missed. Levitt and co-workers (105) examined the IVUs of children with upper or lower tract symptoms. Only 2 of 99 females with lower tract symptoms had abnormal IVUs, whereas 23 of 57 females with upper tract symptoms had abnormalities. The number of refluxing patients was not indicated in the study. Govan and Palmer (60) found a high correlation between historical evidence of pyelonephritis (presumably fever) and reflux; there was a positive history in 79% of refluxing patients but only 39% of nonrefluxing patients. In the refluxing patients, only 7% still had symptoms of pyelonephritis after successful antireflux surgery. In addition, it was noted that the children with reflux tended to present with UTI an average of 2 years earlier than those without reflux. Smellie and Normand (188) presented data that are in conflict with some of these findings. In their large series of children with UTI, there was no age difference in those with or without reflux. However, children with reflux were more likely to present with fever, and it was particularly evident if there was also renal scarring.

It is difficult to localize infection on a clinical basis, and although a number of laboratory tests have been suggested, most are not in standard use. These tests have included urine concentrating ability, leukocyte excretion rate, antibody-coated bacteria, lactate dehydrogenase (LDH), and the measurement of $ß_2$-microglobulin (134). The clinical diagnosis of pyelonephritis is best made with criteria of fever (greater than 39°C), flank or costovertebral angle tenderness, and elevated white blood cell count. The National Children's Hospital group has advocated DMSA renal scanning as a means of making the diagnosis with a high degree of specificity (7,119). The addition of SPECT imaging allows for even more accurate diagnosis (118,203).

Radiologic Evaluation

The evaluation and management of children with UTI should allow initial treatment of the infection, followed by evaluation after the urine is cleared. The exception is the child in whom it is difficult to clear the infection or when obstructive uropathy is strongly suggested by history; in these instances, an early ultrasound (US) is appropriate. Ferrer and co-workers (51) found that for 99% of pediatric urologists, the two standard radiologic examinations for the child with UTI were renal US and voiding cystourethrography (VCUG). Belman (18) has suggested that all girls younger than 5 years old with UTI should have a US and VCUG as the initial studies, as should any older child with a *febrile* UTI. US by itself is not sensitive enough to diagnose most cases of VUR, particularly with lower grades of reflux (26). It has also been suggested that many children should have DMSA scintigraphy to quantify renal scarring, particularly those with a history of febrile UTI (200). As indicated previously, the presence of renal scarring is the major determinant for long-term management of VUR. Stokland and co-workers (199) analyzed children 1 year after febrile UTI and found that 38% had renal scarring on DMSA scintigraphy; about 50% of these had VUR. There is no question that the sensitivity of DMSA scintigraphy with SPECT imaging allows for the most accurate diagnosis of renal scarring. In major centers, these studies have virtually eliminated the use of IVU for this diagnosis. The problem with DMSA scintigraphy remains the cost and the difficulty in separating the renal scars into those that are congenital in origin versus those that are acquired.

In addition to structural data, renal scintigraphy can also give functional information that can be used in following the patient or in comparing preoperative and postoperative function. Technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc DPTA) primarily is used to assess glomerular and tubular function; technetium-99m dimercaptosuccinic acid (^{99m}cDMSA) is best for visualizing cortical tissue and measuring renal function; and iodohippurate sodium ^{131}I is used to assess tubular function. MAGIII has recently been used to define renal function and obstruction but may not be as specific for renal scarring.

Nuclear cystograms provide an alternative for the patient who may require multiple or longitudinal studies annually. The study is also an alternative for the evaluation of the female with a first UTI. The methodology is similar to contrast studies and has the advantage of a lowered radiation dosage. Whether nuclear cystography is more sensitive than VCUG in detecting VUR is in question. A large study from

Scotland did indicate better sensitivity (127), but a study in which patients were followed to see if VUR resolved spontaneously found that nuclear cystography was not as dependable as contrast VCUG (17). This might be related to the inaccuracy of grading with nuclear cystography as compared with contrast VCUG. The Children's Hospital of Philadelphia outline of evaluation and management of UTI, as depicted in Fig. 48D.3, has been updated to include the role of DMSA scintigraphy.

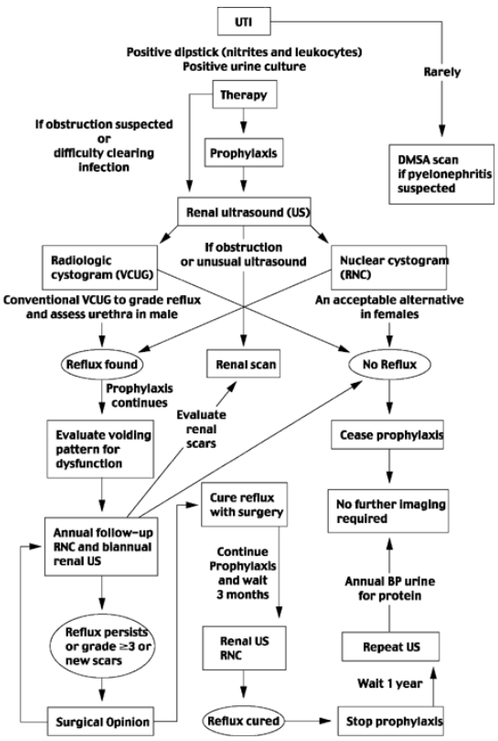

FIGURE 48D.3. Updated Children's Hospital of Philadelphia algorithm for urinary tract infection *(UTI).* BP, blood pressure; DMSA, dimercaptosuccinic acid with labeled technetium; RNC, radionuclear cystogram; VCUG, voiding cystourethrography.(Courtesy of John W. Duckett, M.D.)

Cystoscopy

In the past, cystoscopy has been considered part of the evaluation of UTI and the refluxing child, but this concept

is no longer valid. There are several reasons for the decreased emphasis on cystoscopy, including low yield and the added risk and cost of an anesthetic. The likelihood that low grades of reflux (grades I and II, International Classification) will disappear spontaneously is so great that cystoscopic information adds little to the diagnosis or management. For the higher grades of reflux with clear indications for surgical intervention, cystoscopy may be done at the time of reimplantation of ureters. The continued evidence against bladder neck or significant urethral obstruction in female patients obviates cystoscopy performed solely for the purpose of ruling out obstruction. Dilation of the urethra as a routine treatment of UTI or reflux has no place in our current armamentarium and should be left for specific indications (48). A recent meta-analysis of articles dealing with this subject found no data to support urethral dilation or cystoscopy in most patients.

What then are the indications for cystoscopy in the refluxing child, and what information can be gained by the procedure? There are no absolute indications for cystoscopy in the refluxing child. Observation of the contralateral ureteral orifice in unilateral reflux at the time of surgery may be of help in deciding whether any procedure needs to be done to the contralateral side. The child with duplex ureters and reflux or an ipsilateral periureteral diverticulum may represent an indication for cystoscopy. Children with multiple breakthrough UTIs may require cystoscopy before a decision can be made about continuing medical therapy. Cystoscopy may be indicated in select children who also are having urodynamic studies.

The information gained at cystoscopy includes information about the urethra, bladder wall, ureteral orifices, and submucosal tunnels as well as about the external genitalia and vagina. Even though urethral obstruction is rare, the urethra should be calibrated. Visualization of the bladder neck from the urethra may indicate the raised, small, cystic-appearing lesions that are consistent with cystitis cystica. Children with cystitis cystica may have lower tract symptoms, such as urgency, frequency, and incontinence; however, associated reflux still has an excellent chance of spontaneous resolution (29). One of the major problems with cystoscopy in infants and children with reflux is the lack of consistency of observed findings among different examiners. The description by Lyon and associates (115) of orifice configuration is still widely used, although it does not correlate with spontaneous resolution. Duckett (41) found orifice configuration of only minimal value and indicated that even in the most abnormal orifices there was spontaneous resolution of reflux in 15% to 20% of patients. The tunnel length-to-ureteral diameter ratio can be measured nicely by using a 4-Fr whistle-tip ureteral catheter. The submucosal portion of the tunnel can be measured and an estimate of width obtained by comparing the width of the orifice to the width of the catheter (approximately 1 mm). Data should be obtained with both a full and an empty bladder and should indicate whether the orifice is patulous, the degree of development of the trigonal muscle, the degree of trabeculation of the bladder wall, and whether the orifice moves laterally as the bladder fills. The position of bladder diverticula should be noted, particularly in relation to the ureteral orifice. Spontaneous resolution of reflux may occur with periureteral diverticula unless the ureter enters the diverticulum (106). Vaginoscopy and inspection of the external genitalia also should be done at the end of the procedure; the pelvic organs can be palpated effectively with a rectal examination.

Urodynamics

Urodynamics, including cystometrogram, perineal or periurethral electromyogram (EMG), and urinary flow studies, may be helpful in select patients with VUR. These studies are particularly helpful in children with dysfunctional elimination syndromes. Taylor and co-workers (204) showed that 75% of refluxing girls had evidence of uninhibited bladder contractions. Allen (4) has indicated that these uninhibited contractions yield higher intravesical pressures and that, when associated with reflux, may lead to greater renal damage. This assertion, however, is not supported by the data of Taylor and colleagues (204). Koff and Murtagh (98) have treated such patients with anticholinergic therapy and indicate that it may be helpful in resolution of reflux. Cystometric studies are more easily interpretable in the child with low grades of reflux. If uninhibited bladder contractions are detected, appropriate pharmacologic control will often arrest the reflux and associated infection. The cystometrogram is also difficult to do and may be difficult to interpret in the very young child or infant. However, practicality would dictate that urodynamics is not cost-effective.

DEMOGRAPHY OF REFLUX

The demographic information that we have comes from three sources: (a) cystographic evaluation in normal children, (b) cystographic studies in children with UTI, and (c) the study of other animals. The first of these sources of information is largely closed to use because of ethical constraints in obtaining studies in normal children. Studies of children with UTI allow us to look at not only that population but their siblings. Comparisons of experimental animals to humans let us look at those who are close phylogenetically and those that have close anatomic resemblance.

Incidence

The incidence of VUR in normal infants and children is not known and probably varies depending on race and perhaps

country of origin. Askari and Belman (10) have reported on the infrequency of reflux in African American children. In their studies of African American children investigated for UTI, the incidence of reflux was only 25% of that seen in infected white children. Extrapolating these data with the lowered incidence of UTI in African Americans, they concluded that the actual incidence of reflux in the normal African American population was 10% of its occurrence in a white population. Although the incidence of reflux was less in African American children, its natural history, once discovered, is the same. Skoog and Belman (184) described the distribution of grade of reflux and spontaneous resolution in African American children and found it the same as in a larger group of white patients. A recent study evaluated neonates who presented with prenatal hydronephrosis; 58 were African American and 51 non–African American. Of the former, VUR occurred in none and in 17.6% of the latter (78).

The incidence of reflux in other races or national groups is not known, although all of the large reported studies on refluxing patients seem to come from northern Europe, including the Scandinavian countries, Great Britain, and Ireland, as well as North America, Australia, and New Zealand. Manley (121) suggested that reflux occurs more commonly in children with fair skin, blond hair, and blue eyes. Urrutia and Lebowitz (210) refute this and believe that only red-haired children have a higher incidence of reflux.A number of cystographic studies were done in normal children before the time at which human experimentation committees rightly placed constraints. Despite these constraints, the previously gained information is valuable. These studies must be examined critically because there was often no standardization of cystographic technique and the patient populations were not well defined. We know now that it is particularly important because of the racial differences in incidence, and it is likely that in many of these studies, the population chosen for study was unlike the population with UTI. In 1949, Gibson (56) did 43 cystograms in children, using syringe injection of contrast, and found two cases of reflux. Iannaccone and Panzironi (83) evaluated 50 infants without urologic disease and found only one instance of reflux. Although the patient population was not defined, they were all likely of Mediterranean origin. Jones and Headstream (89) evaluated 100 children and found one who had reflux. Race was not defined, and 70% of the patients were males. Lich and co-workers (108) did cystograms on 26 infants less than 48 hours old and found no reflux. Politano (146) had similar findings in 50 normal children. Peters and associates (144) defined race in 66 premature infants studied with cystography. They found no reflux in their group, 56 of whom were African American. In contrast to these studies, all of which showed a very low incidence of reflux, is the study of Kollerman (100), who found that reflux was more common. He examined 161 children with cystography. The technique was admittedly unphysiologic and involved filling the bladder with a syringe to capacities of 40 to 200 mL. No child had a history of UTI or of any urologic problem. Of the group, 18.5% had VUR.

The incidence of reflux in children with UTI is suspected of being much higher than in the normal population, despite our difficulty in defining incidence in this latter group. Shopfner (181) reviewed a large number of children defined as having a UTI by the culture of at least 100,000 colonies of bacteria per milliliter of urine. Reflux was present in 14% of 1,695 females and 29% of 523 males. Baker and colleagues (13) had shown previously that reflux was most common in younger children with UTI, occurring in 70% of children younger than 1 year of age, 25% of children at 4 years of age, 15% of children at 12 years of age, and 5.2% of adults. Compilation studies in children with asymptomatic bacteriuria yielded similar results: 29% of preschool-age females and 23% of school-age females had reflux (213).

Reflux is a commonly occurring phenomenon in some animals (Fig. 48D.4). It occurs in almost all rats and many rabbit species. Christie (34) found reflux in 80% of 3-month-old puppies, but it disappeared spontaneously and was present in only 10% of adult dogs. It is not present in piglets or adult pigs. Roberts (155) indicated that its presence in monkeys is variable and is both age and species related. In his studies on infant rhesus monkeys, reflux

occurred almost all of the time in newborns but gradually disappeared, so by 36 months of age, it was uncommon. The disappearance curve was a gradual decline rather than a sharp change and was gone by the time the animal reached maturity. These studies are intriguing because the primates are close to us phylogenetically, and the disappearance curves closely parallel the disappearance of reflux in children with UTI. Figure 48D.5 depicts a comparison between the disappearance of reflux in infant and maturing rhesus monkeys (155) against the disappearance of reflux in a series of children with UTI (13).

FIGURE 48D.4. Incidence of reflux in mammalian species (percentages). (From Roberts J. Vesicoureteral reflux and pyelonephritis in the monkey: a review. *J Urol* 1992;148:1721, with permission.)

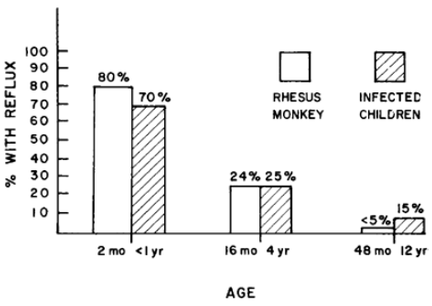

FIGURE 48D.5. Comparison of the disappearance of reflux in infant monkeys (162) to that of children with urinary tract infection (13).

Patterns of Inheritance

The observation that reflux occurs in siblings and parents of affected children has been known for the past two decades, but the actual mode of inheritance has not been determined. Stephens and colleagues (197) noted the occurrence of reflux in twins. Tobenkin (206) reported on a family in which three different generations had evidence of reflux. He suggested that the mode of inheritance might be sex linked, with incomplete penetrance. Mulcahy and co-workers (132) reported on three families in which two members had reflux and also noted that 18% of patients undergoing reimplantation had other family members with a history of UTI. Other investigators reported familial reflux in series ranging from 5 to 20 families (131,176,231).

Dwoskin (44) reviewed 125 families of probands with reflux and found that 26.5% of siblings had reflux. In a similar study, Jerkins and Noe (87) found 33% of siblings showing reflux. The conclusion from both of these studies was that the siblings of all children with reflux should be evaluated, particularly those younger than 2 years of age. This conclusion has been confirmed in studies that have gone on over a decade with the only change in recommendation being that aggressive screening should occur in all siblings younger than 5 years of age (135). A recent study from two centers evaluated siblings to 16 years of age and found largely low-grade reflux in 27% but evidence of reflux nephropathy in some older children. Their data supported screening children younger than 7 years of age (217).

Lewy and Belman (107) believed that a pattern of autosomal dominance was suggested by the occurrence of reflux in a large number of siblings, and that concept is actually supported by recent data (50). The wide variability of reflux in siblings actually gives credence to a polygenic or multifactorial mode of inheritance, as has been suggested by Burger and Burger (31). Polygenic modes of inheritance probably account for the variability of pathologic findings in many congenital urologic conditions, of which reflux and hypospadias may be two of the best examples. The variable factor determined by this mode of inheritance appears to be submucosal ureteral tunnel length. Experimental data in puppies with reflux have indicated that in addition to ureteral tunnel length, a paucity of adrenergic nerve fibers may relate to reflux. The suggestion was that with maturation of the autonomic nervous system and the increase in the adrenergic nerve fibers, there was a concomitant decrease in the incidence of reflux (96). The recent data from Noe and co-workers (136) indicate transmission of reflux from parent to child is significant in that 66% of the offspring of affected parents have VUR. These authors agree that the mode of transmission is almost certainly as a multifactorial genetic trait. However, reflux may be inherited as an autosomal-dominant trait in some instances.

CLASSIFICATION AND TERMINOLOGY

Classification of Reflux

The earliest attempts at classification of reflux tended to broadly quantify the amount of reflux to the kidney or to classify by what was happening physiologically in the bladder. Rolleston and associates (164) classified reflux as being slight, moderate, or gross. These investigators noted that gross reflux was almost always associated with renal damage. Hinman and co-workers (71) introduced the terms *high-pressure reflux* and *low-pressure reflux* to indicate reflux that occurred during bladder filling (low pressure) versus that which occurs during voiding (high pressure). The implication from this distinction was that low-pressure reflux was congenital and would not resolve, whereas high-pressure reflux was more likely to resolve with time. The pressure effect on the kidney was not an issue at that time.

More precise measures of reflux were proposed in both the United States and Europe and have provided the nucleus for the International Classification System that is in current use. Heikel and Parkkulainen (65) proposed a five-category classification system that gained use in northern

Europe, whereas in the United States, the Dwoskin-Perlmutter (43) classification system was commonly used. The International Classification System represented one of the first cooperative efforts of the International Reflux Study. It was the belief of the original members of the study group that there were deficiencies in both the Heikel-Parkkulainen and the Dwoskin-Perlmutter systems that could be addressed only by a new system. Rather than discard the other two systems, the best characteristics of each were incorporated in the new system. Particular emphasis was placed on the fornices and calyces, and the anatomy of these structures provided the basis for classification. The International Classification System is shown in Fig. 48D.6 . Despite the sophistication of this classification system, it was quickly recognized that clinical patterns of reflux were not neatly compartmentalized; the subtle variation in each grade is illustrated in Fig. 48D.7 .

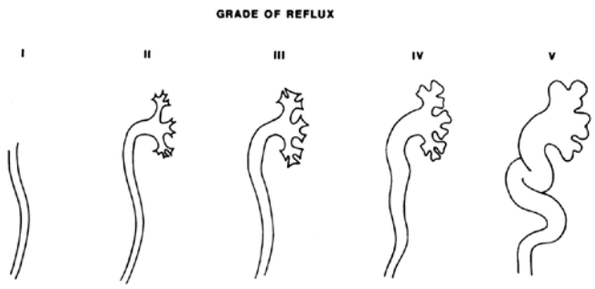

FIGURE 48D.6. International Reflux Classification.

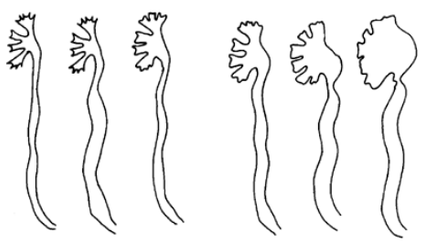

FIGURE 48D.7. Variations with grades III and IV of the International Reflux Classification.

Reflux also can be graded, although less precisely, by nuclear cystogram. Although many radiologists will extrapolate to nuclear cystography the International Grading System, there is no scientific basis for doing so. Indeed, there is no universally accepted grading system for nuclear cystography, with most radiologists simply using the terms *mild, moderate,* and *severe.* Majd and Belman (117) have indicated that the clear advantage of nuclear cystography is the lower radiation dosage, and because of this, it is an excellent tool for screening females and for follow-up studies in both sexes. The disadvantage is the difficulty in recognizing important associated bladder pathology, such as bladder diverticula, or in viewing the male urethra.

Classification of Orifice Shape and Position

The shape and position of the ureteral orifice is primarily of importance in assessing the contralateral ureteral orifice of a refluxing ureter to determine whether it may be incompetent in the future or have refluxed in the past. Paquin (142) has shown that the intramural tunnel is vital to the prevention of reflux. In normal nonrefluxing children, the tunnel length-to-ureteral diameter ratio was 5:1, whereas in refluxing children this same ratio was 1.4:1. It is likely that one needs at least a 3:1 ratio to prevent reflux, although this ratio is not satisfactory with ureters of a large diameter. Cussen (39) has done an exacting study measuring normal submucosal and intravesical ureteral lengths in children of different ages. These data are partially presented and extrapolated in Table 48D.1 .

Age (yr)	Intravesical Ureteral Length (mm)	Submucosal Ureteral Length (mm)	Ureteral Diameter at Ureterovesical Junction (mm)
1–3	7	3	1.4
3–6	7	3	1.7
6–9	9	4	2.0
9–12	12	6	1.9

Modified from Cussen LJ. Dimensions of the normal ureter in childhood. *Invest Urol* 1967;5:164.

TABLE 48D.1. MEAN URETERAL TUNNEL LENGTHS AND DIAMETERS IN NORMAL CHILDREN

Lyon and associates (115) described four basic orifice shapes: cone, stadium, horseshoe, and golf hole. These four shapes represent increasing levels of orifice incompetency. They believed that orifice shape, rather than tunnel length, determined valvular competency. Mackie and Stephens (116) developed a more complex classification of orifice position that was originally intended for duplex systems but now is generally used for single ureters as well. The system is a complicated one to remember because the authors have related orifice position to the original location of the ureteral bud on the wolffian duct. The three zones of urethral orifice position are depicted in Fig. 48D.8 . These classifications are primarily of historical rather than clinical importance because studies have shown poor correlation with cystoscopic findings and reflux resolution (41).

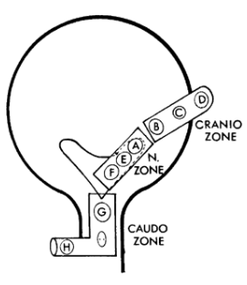

FIGURE 48D.8. Classification of the ureteral orifice position. (From Mackie GG, Stephens FD. Duplex kidneys: a correlation of renal dysplasia with position of the ureteral orifice. *J Urol* 1975;114:274, with permission.)

Classification of Renal Scarring

Renal scarring can take a variety of forms (187), as shown in Fig. 48D.9 . This classification has less validity today because it was based on IVU interpretation. Attempts to quantify the amount and character of renal scarring are important. Only if precise definitions of scarring and parenchymal thickness are made can one tell if the disease has progressed. This progression is important not only in investigatorial studies that compare treatments but, indeed, in the individual patient who is being followed with medical management. Equally important as the measurement of renal scarring is the measurement of renal growth. Some refluxing patients may exhibit only growth failure as an effect of their reflux. Renal growth is best measured by renal US (166), although Mesrobian and co-workers (128) have shown significant reader error in taking measurements. The results of the International Reflux Study in Children (IRSC) showed that there was another type of injury related to reflux—parenchymal thinning (139). Parenchymal thinning often preceded scar formation but, in some instances, was also reversible.

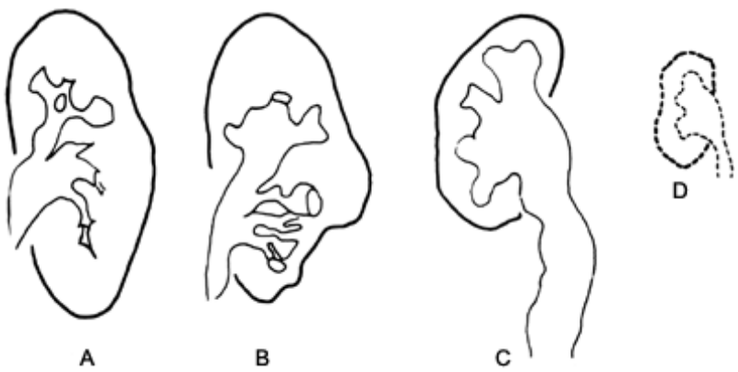

FIGURE 48D.9. A–D: Classification of renal scarring. [From Smellie JM, Edwards D, Hunter N, et al. Vesicoureteral reflux and renal scarring. *Kidney Int* 1975;8(Suppl 4)65, with permission.]

Recent evidence has indicated that DMSA scintigraphy is more sensitive than IVU in detecting renal scarring. ^{99m}CDMSA is an excellent isotope for visualizing the renal cortex. Elison and co-workers (49) evaluated a large number of patients with both IVU and DMSA renal scanning and found a significantly larger number of scars detected by the latter method. In a related study, Rushton and Majd (168) evaluated children with DMSA scanning after an episode of acute pyelonephritis and found that subsequent scarring occurred at the site of renal infection. These authors (168) reviewed an extensive array of studies and concluded that DMSA renal scanning is the most sensitive method of detecting renal scarring. It not only detects scars earlier than IVU but also detects smaller scars. Whether it will detect parenchymal thinning is as yet unclear, but studies in the piglet have suggested that it will (55). The disadvantages of DMSA scintigraphy are its cost and its current lack of availability worldwide and in many areas of the United States.

NATURAL HISTORY

Etiology

Primary VUR results from a congenital anomaly of the ureterovesical junction, wherein an inadequate valvular mechanism allows the retrograde flow of urine from the bladder to the upper urinary tract. Secondary reflux may be the result of several etiologies within the broad categories of anatomic or functional bladder outlet obstruction. However, both of these physiologies may be linked by embryology.

The inadequate valve in primary reflux is the shortened submucosal tunnel. When the intramural and submucosal ureter have an adequate tunnel, the submucosal roof of the tunnel will compress as the bladder fills and will act as a flap valve. The mechanism can be more passive than active, as demonstrated by the success of the cross-trigonal reimplants. The role that the trigone plays is unclear; however, there is an apparent contraction of Waldeyer's sheath and trigone with detrusor contraction, which preserves tunnel length and increases distal ureteral luminal pressure with bladder filling and voiding. Therefore the intrinsic antireflux mechanism is much more dynamic than that achieved by surgery.

The role that infection plays in reflux can be summarized by a review of both experimental and clinical data. Schoenberg and co-workers (178) produced reflux in apparently normal puppies by infecting them with *Proteus.* Roberts and Riopelle (162) observed that reflux resolved spontaneously in infected monkeys as often as in uninfected ones, but it took longer to do so. Their conclusion was that infection

delayed maturation. Furthermore, in adult monkeys, infection caused reflux only in damaged orifices, a finding that supported similar observations in humans. Shopfner (181) and Blank and Girdany (27) have stated that most nonobstructed reflux in humans was secondary to infection, but most observers have disagreed with such a sweeping statement. Gross and Lebowitz (61) could find no data in their large series of patients to suggest that infection causes reflux. Their conclusion was that both reflux and infection were independent variables that often coexisted and that the association was seen so often simply because the principal reason for doing a VCUG is UTI. Kaplan (91) has indicated that some children will reflux only if the cystogram is done during an acute infection and that these children remain an unstudied population that may have a worsened prognosis. One can conclude from these data that infection does not cause reflux of the normal mature orifice and would be a factor only for those orifices that are immature or damaged.

As previously defined, secondary reflux occurs in association with obstruction or neurogenic bladder. Virtually all of the reflux that occurs secondary to obstruction occurs in males. Reflux associated with bladder neck obstruction in females is of historical interest only, and that which occurs with urethral obstruction is hard to define because of the controversial nature of the latter. Despite the best efforts of many to deemphasize the role of urethral stenosis in the female, it is nonetheless a diagnosis commonly made by the urologist. The data regarding reflux in obstructed males are likewise unclear. The incidence of reflux in infants with posterior urethral valves is 50%. Much of it is associated with abnormal ureteral orifices (67). If obstruction causes reflux, a much higher percentage of valve patients should reflux. Several clinical investigators, including Hendren (66) and Kurth and associates (101), have tried to classify milder forms of urethral valves on the basis of degrees of reflux. The degree of reflux may alter the severity of bladder changes by offering a pop-off mechanism and reducing the pressure work done by the bladder.

Secondary reflux is common in both occult and true neurogenic bladders. Treatment is much more difficult and has a decreased success rate. Minimal voiding and urodynamic abnormalities are fairly common in primary reflux, and in some instances, the spectrum is such that it may be difficult to differentiate between the patient with nonneurogenic/neurogenic bladder (Hinman syndrome) and the patient with urodynamic abnormalities secondary to reflux. The incidence of dysfunctional voiding is certainly more prevalent and more of a factor than has been appreciated previously. Unfortunately, the true incidence is not known and varies widely between investigators. Sillen and colleagues (182) found elevated intravesical pressure in 17 of 18 infants with bilateral reflux of high grade as determined by urodynamic studies. On the other hand, the data from the IRSC showed evidence of dysfunctional voiding in 18% of children with reflux whose parents responded to a questionnaire regarding voiding patterns (212). Koff (97) indicated that these children with bladder instability had a different urodynamic pattern from those with nonneurogenic/neurogenic bladder in that the former had a pattern of high end-filling pressures, whereas the latter had high voiding pressures. Thus reflux in this situation should not be considered either primary or secondary, but rather is a combination of two factors—the high intravesical end-filling pressures and the immature ureteral orifice. The disappearance rate of this type of reflux is probably similar to that in children with normal bladder dynamics, but it may be delayed. Treatment with anticholinergics may be effective in decreasing uninhibited contractions and end-filling pressures while allowing the reflux to resolve spontaneously.

Renal Scarring

Hodson (74) was the first to recognize the relationship of renal scars in children with recurrent UTIs, and 97% of these children had VUR. This close relationship caused Bailey (14) to use the term *reflux nephropathy* to describe the radiologic changes, which included (a) focal thinning of the renal parenchyma overlying a clubbed, distorted calyx; (b) generalized calyceal dilation with parenchymal atrophy; and (c) impaired renal growth, either associated with focal scarring or global atrophy (76). The sequelae of such findings, including proteinuria, hypertension, eclampsia in pregnancy, and renal failure, can be devastating, although most scars never pose a health threat to the affected patient.

A number of questions have been raised over the years: Why are children more susceptible to scarring than adults? Is it the reflux or the infection that causes renal scarring? The development of scars is an age-related phenomenon. Just as the highest incidence of reflux is found in younger children, the risk of scarring is greatest in children younger than 1 year of age (223). Patients who experience their first febrile UTI before age 4 have a much greater likelihood of developing a scar than children whose first episode of pyelonephritis occurs at a later age (189). Reflux nephropathy occurs uncommonly after 5 years of age (164). Postinfectious scarring can develop in children of any age who are not properly treated (20). In the European arm of the IRSC, new scars developed in approximately 24% of children younger than 2 years of age, in 10% of those between the ages of 2 and 4, and in only 5% of those older than 5 (139). The clinical studies of Berg and Johannson (21) also suggest that the infant kidney is more vulnerable to damage by infection during the first 3 years of life. Immaturity of the immune system and a lessened ability to fight renal parenchymal infection may play a role.

The “big bang” theory of Ransley and Risdon (151) underscores the susceptibility of young children with reflux to UTIs and proposes that the most severe degrees of renal parenchymal injury occur with the first infection. Because

all susceptible segments of the kidney are simultaneously affected, sequential scar formation is unusual, although “little bangs” do occur (152). The theory supports two clinical observations. Most renal scarring in young children is as severe on initial imaging as is likely to develop in follow-up, unless severe episodes of pyelonephritis occur. In addition, the incidence of scarring is not significantly greater in children evaluated after their first infection than in those who present after multiple infections. There is evidence that the renal dysmorphism seen may represent both congenital and acquired lesions. Some renal dysmorphism presumably evolves on a congenital basis, although the pathophysiology undoubtedly differs from that of the more common acquired etiology of pyelonephritis. Such an etiology is likely in newborns with antenatally diagnosed disease. Despite being infection free, 30% to 35% of patients have kidneys that are diminutive and/or dysmorphic and scarred, especially with higher grades of reflux (30,124,133). Male infants are particularly prone to this occurrence because of their tendency to have high grades of reflux (72) and because they are much less likely to acquire scarring because they rarely have recurrent UTIs. One recent study reported primary (congenital) scarring in 86% of boys but only 30% of girls, who were more likely to acquire scars from repeated infections (220).

The histology differs between congenital and acquired lesions, although their radiologic appearance can be indistinguishable. In theory, the interplay between the ureteral bud and renal blastema during the first few weeks of gestation determines the development of the kidney as well as that of the ureterovesical junction. As Mackie and Stephens (116) have suggested, a ureteral bud that is medially (caudally) positioned from a normal takeoff from the mesonephric duct offers an embryologic explanation for primary reflux, whereas those laterally (cephalad) positioned are often obstructed (Fig. 48D.8). Variable degrees of renal dysplasia and caliectasis follow (193,194,198).

In addition to dysplasia, hypoplasia is commonly found in nephrectomy specimens of patients with reflux. Acquired cortical loss is often typically interspersed as a consequence of infection (69), although progressive renal scarring can be avoided if infections are prevented (11). Dysplasia has also been noted in patients with duplex collecting systems and upper ureteral ectopia (116), prune-belly syndrome (120), and posterior urethral valves, where the effects of high-grade obstruction early in embryogenesis may also contribute to renal dysmorphism. In fact, in one series, as many as 50% of infants with urethral valves and reflux had clinically significant renal insufficiency at a time too early in infancy to be caused by infection (80).

Countering the aforementioned information is the evidence that renal scarring is acquired. Hodson and associates' (75) early work implicated sterile reflux and a high-pressure “water-hammer” effect as a significant cause of renal scarring. Surgically creating reflux and occluding the bladder outlet allowed reflux nephropathy to be induced in miniature pigs, even in the absence of infection. High intravesical pressures caused intrarenal reflux, usually in the polar areas, and interstitial fibrosis, whose radiologic appearance was similar to that seen in children with postinfectious reflux nephropathy. Other work has also supported the concept of elevated bladder pressures causing reflux nephropathy (125). The proximal projection of pressure causes a decrease in postglomerular blood flow to the medulla and cortex that results in ischemic damage (158). This cause of nephropathy must be considered in the face of elevated bladder pressures and a high incidence of reflux associated with bladder dysfunction (97), urethral valves, or the high voiding pressures of newborns with antenatally diagnosed reflux (47).

Although abnormal bladder pressures may contribute to renal scarring in some children, the pathophysiology of most renal scarring was better defined by Ransley and Risdon (152), who were unable to create scars in a model similar to Hodson's by keeping the bladder unobstructed and the urine sterile. These findings were recently confirmed using magnetic resonance imaging (MRI), DMSA scans, and histopathologic analyses.

Clinical verification of the importance of infection is documented by a number of reports that cite new scars only in patients with reflux who have recurrent infections. In the combined series of Smellie and colleagues (185) and Huland and Busch (79), new scars developed in only 17 (4%) of 446 patients, all of whom had interval UTIs. The bulk of clinical and experimental studies underscore the importance of infection in the evolution of most renal scars.

Although pyelonephritis can commonly occur in the absence of VUR, reflux predisposes the kidney to ascending infections and may amplify the invasive effects of pathogens. For example, in one series, acute pyelonephritis was documented twice as often in patients with high-grade reflux than in those with low-grade reflux (119). In addition, most studies show a linear relationship between the grade of reflux and frequency of scarring (219,224). Primary renal dysgenesis could also contribute to the latter.

Papillary configuration also plays a role in protecting the renal parenchyma from urinary pathogens. Compound or concave papillae, which are flattened and whose ducts open at right angles to the calyx, are more likely to allow intrarenal reflux than simple or convex papillae. The convex papillae, which project into the renal pelvis and have ducts that exit obliquely into the calyx, provide a valvular action against the retrograde flow of urine into the collecting tubules of the renal medulla. The configuration and action are very similar to the flap-valve created by the ureter itself. Compound papillae are mostly localized in the polar regions of the kidney, where reflux nephropathy is much more likely to occur initially (75,151).

Further deleterious distortion of normal papillae architecture can result from adjacent scarring, hydronephrosis, and high-pressure voiding and eventually involve the entire collecting system. Early studies focused on intrarenal reflux

(Fig. 48D.10), which is observed in 5% to 15% of neonates and infants with reflux (164,165). When scarring occurred, it was always in the parenchyma overlying the segment with intrarenal reflux. Autopsy studies in newborns younger than 1 month of age demonstrate intrarenal reflux at pressures as low as 2 mm Hg. Later in development, greater amounts of pressure become necessary to produce the same effect (e.g., 20 mm Hg in a 1-year-old) (54). Intrarenal reflux, like new scarring, is rarely seen radiographically after the age of 5. Ransley and Risdon (150) demonstrated the crucial interplay of intrarenal reflux and urinary infection in piglets, whose renal papillary morphology is similar to that of humans. Scarring occurred only in areas exposed to both infected urine and intrarenal reflux. However, the presence of intrarenal reflux does not alter the likelihood of spontaneous resolution or management strategy if infections can be avoided.

FIGURE 48D.10. Cystogram shows the presence of intrarenal reflux in the upper pole.

Renal Growth

Small kidneys associated with reflux may have that morphology for a variety of reasons, including the congenital dysmorphism often associated with, but not caused by, reflux (30%); the number and type of urinary infections and their resultant nephropathy; the quality of the contralateral kidney and its implications for compensatory hypertrophy; and the grade of reflux in the affected kidney. Studies that could be used to evaluate this parameter do so unreliably. In addition to the variability in interpretation that occurs with excretory urography or US (77,153), the response of the kidney to scarring, with its polar contracture and intermediate hypertrophy, makes interpretation of renal length alone unreliable. Other methods used to measure growth have included parenchymal thickness, renal area and length, and bipolar thickness (64,95,114). Claesson and associates (35) used planimetry to measure urograms and formulate a nomogram that allows determination of renal mass in relation to somatic size.

With the exception of those kidneys that are developmentally arrested, most studies implicate infection as the cause for altered renal growth. Ambrose and colleagues (5) reviewed the pathologic findings from kidney specimens of 63 patients with reflux and found a histologic pattern consistent with pyelonephritis in 51 (81%). In their study, patients with long-term reflux had kidneys that did not grow as well as normal. It was subsequently shown that acceptable growth occurred if urinary infections could be controlled. Elder and colleagues (48), for the Pediatric Vesicoureteral Reflux Guidelines Panel, found no evidence that renal growth is impaired in *unscarred* kidneys exposed to *sterile reflux* of any grade or that surgical correction of reflux facilitates renal growth postoperatively.

In a study of 111 patients with reflux who were managed medically, Smellie and co-workers (190) found slow growth in 11, 10 of whom had documented UTIs. Successful antireflux surgery can accelerate renal growth but may not allow affected kidneys to return to normal size (130,221). In one study of 22 kidneys with reflux nephropathy, significant growth after reimplantation occurred in 15 (68%), 7 of which grew proportionally to its mate (33). The potential for renal growth was less optimistically portrayed by the studies of Hagberg and associates (63) and Shimada and co-workers (180), in which 75% of kidneys with significant nephropathy remained stunted despite reimplantation. In contrast, kidneys without radiographic evidence of scarring usually show rebound growth with the surgical correction of reflux or its spontaneous resolution. In addition, the results from the Birmingham Study Group (24) and International Reflux Study (139,218,219) show no significant difference in rates of growth or parenchymal scarring between patients who were managed medically or surgically.

Renal Function

Renal failure that develops with reflux and renal scarring occurs in a significant number of patients. Bailey (15) indicated that as many as 30% of children may have end-stage renal failure because of reflux. In the Children's Transplant Program at the University of Florida, between 7% and 10% of 110 children had scarred kidneys in which reflux may have been a factor. However, there were some who had reflux unrelated to their renal failure, presenting with diseases such as nail-patella syndrome or asphyxiating thoracic dystrophy. A review and update of infants with severe VUR followed for a long period indicates that 80% have either unilateral or bilateral renal scarring, with 29% of these having either renal insufficiency, proteinuria, or hypertension (16). It is likely that recurrent pyelonephritis associated with reflux may be responsible for the majority of patients with reflux who develop renal failure.

Chronic pyelonephritis was reported as the cause of end-stage renal disease in 15% to 25% of children and young adults in earlier studies (81,175,192), although the presence of active reflux is probably less common at an estimated 10% (170). In many of these patients, prior infection went unrecognized or became evident only with the diagnosis of end-stage renal disease. In a study by Jacobson and associates (84), every adult who had their first infection during infancy had decreased renal function; hypertension was found in approximately 33% and end-stage renal disease in 10%. Increased awareness has had a positive effect on this complication. For example, chronic pyelonephritis accounted for less than 2.2% of end-stage renal disease in a report from the North American Renal Transplant Cooperative (138). In addition, a better understanding and medical management of the renal nephropathy that accompanies scarring should further lessen the progressive nature of the disease.

The mechanism for renal insufficiency or failure might be focal glomerular sclerosis brought on by renal hyperfiltration (70). Preventive treatment may further retard the onset of disease. For example, the effects of therapy with an angiotensin-converting enzyme inhibitor (captopril) were studied in 16 patients with severe reflux nephropathy and microalbuminuria. After 2-year follow-up, proteinuria was decreased and blood pressure and serum creatinine were stabilized in each case (102).

Lesser degrees of renal impairment can also occur with reflux in a progression that has been likened to that with partial ureteral obstruction in that tubular function is affected earlier than glomerular function. Renal damage from reflux occurs in a retrograde fashion, and the increased pressure is felt first by the most distal nephron. The effect of reflux is difficult to distinguish from that of associated UTIs. Defects in concentrating ability have been demonstrated in refluxing children with sterile urine, although almost all have had histories of UTI (215). In experimental animals, the effect of infection on concentrating ability is felt no longer than 6 weeks after the infection is eradicated (92). The defects in concentrating ability in refluxing children are persistent even while the urine is sterile for long periods. Furthermore, the concentrating defect is inversely proportional to the grade of reflux (Table 48D.2). In many refluxing patients, concentrating ability improves after the reflux disappears. Impairment of concentration ability may be related to the anti-antidiuretic hormone (ADH) effect of increased medullary prostaglandin E (PGE) levels in patients with severe VUR (214). Other parameters of tubular function, such as fractional excretion of sodium and magnesium, also may be affected (93). Renal tubular acidosis was identified in 9 (50%) of 18 children with primary reflux, 16 of whom had scars. Four of the affected children also had short stature (62).

Grade of Reflux[a]	Fasting Concentration (mOsm/kg)	Creatinine Clearance (ml/min)
Control	1,001 ± 104	130 ± 28
Grades I–II	864 ± 135	136 ± 43
Grade III	808 ± 119	127 ± 16
Grade IV	744 ± 129	108 ± 15
All grades with significant parenchymal scarring	543 ± 126	102 ± 41

[a]International Classification.
Modified from Walker RD, Richard GA, Dobson D, et al. Maximum urinary concentration: early means of identifying patients with reflux who may require surgery. *Urology* 1973;1:343, with permission.

TABLE 48D.2. TUBULAR AND GLOMERULAR FUNCTION RELATED TO GRADE OF REFLUX

Glomerular function is usually not affected unless there has been parenchymal damage, and decreases in glomerular function are proportional to the amount of parenchymal loss. In the International Reflux Study, there was no deterioration in glomerular function as measured by serum creatinine nor was there any decrease in glomerular filtration rate when measured by chromium-labeled ethylenediaminetetraacetic acid. Berg (22) measured glomerular filtration rate and renal plasma flow in a large number of children with renal scarring and VUR. He found that decreases in renal function correlated with the degree of renal scarring, with decreased renal function being the most significant in those with bilateral, small, scarred kidneys. Surgical correction of reflux stabilizes the glomerular filtration rate, but it has not been shown to lead to long-term improvement (48).

Proteinuria accompanies significant renal insufficiency and scarring (209). Genetic markers, including HLA-B12 in females, B8 with A9or BW15 in males, and BW15 in both sexes, have been found with end-stage reflux nephropathy and may represent a genetic link to a susceptibility to renal damage (208).

Physical Growth

Dwoskin and Perlmutter (43) and Polito and colleagues (145) noticed in their series that children with reflux, especially those with a history of recurrent UTIs, tended to be in the lower-weight percentile groups. Eliminating infections with prophylactic antibiotics maintained normal somatic growth for 51 girls with known reflux (191). Surgically correcting reflux has also been shown to positively affect somatic growth (126). Sutton and Atwell (201) compared physical growth while children with reflux received medical therapy and also found that growth improved after subsequent reimplantation. It remains unclear whether one form of treatment offers preferential benefit to this aspect of development because a comparative prospective study in a large series of children with extended follow-up is lacking. The Pediatric Vesicoureteral Reflux Guidelines Panel (48)

found no evidence to substantiate an effect of reflux treatment on somatic growth.

Hypertension

Refluxing patients with scarred kidneys are at greater risk for developing hypertension (48). Although the actual incidence of hypertension secondary to reflux nephropathy has been reported to be as high as 38% (195,216,229), methodologic flaws can be found in many study designs (179). Patients without renal scarring are probably not at any greater risk of becoming hypertensive than the normal population. Arterial damage in the area of renal scarring presumably leads to segmental ischemia and renin-driven hypertension.

Abnormalities of Na^+-K^+-ATPase activity have also been described (59). Despite this, renin profiles have been measured in children with a history of reflux and many, but not all, were elevated (46,173). Elevated renins may be related to eventual hypertension for some patients, but others with high renins remain normotensive; a small group of patients, however, revert to normal with extended follow-up (172). In a 15-year follow-up of renin and blood pressure in a cohort of patients with reflux nephropathy, plasma renin levels were significantly higher than those in controls, but they were not predictive of the development of hypertension (58). Most patients who develop hypertension have nearly normal renal function, and the appearance of hypertension is rarely related to renal failure. In most series, hypertension is related to the grade of reflux and the severity of scarring, especially with bilateral involvement (69,209,224). However, in the study by Wolfish and associates (229), primary reflux was not associated with hypertension or the severity of scarring unless there was preexisting dysplasia. The implications of scarring can be subtle. In one provocative study, normotensive children with renal scars demonstrated similar renal function and levels of renin and aldosterone to controls. They also demonstrated the same expected drops in nocturnal blood pressure but significantly greater heart rates, a possible risk factor for future cardiovascular morbidity (148).

The elimination of reflux or its spontaneous resolution does not reverse the predisposition to hypertension once scarring is present (48). Wallace and associates (216), for example, reported hypertension despite successful ureteral reimplantation in 18.5% of children with bilateral scarring and 11.3% with unilateral scarring after more than 10 years of follow-up. Hypertension did not develop without scars. This type of data emphasizes the need for periodic checks of the blood pressure in any child with a history of reflux and scars. Removal of the offending renal parenchyma with partial or total nephrectomy can improve or correct hypertension in some patients (40). Patients with one small, scarred, poorly functioning kidney may be reasonable candidates. Confirmation with selective renal vein renins (ratio greater than 1.5) is instrumental to selection but may still not ensure success with ablative surgery. Global changes in vascular resistance may contribute to persistent hypertension. Those with diffuse bilateral scarring are less-than-ideal candidates because localization is difficult and sparing renal parenchyma assumes primary importance.

MANAGEMENT OF REFLUX

The appropriate management of VUR requires integration of multiple and often complex variables with the individualization of treatment for each patient and clinical scenario. Initially, any patient suspected of having VUR is placed on a prophylactic antibiotic regimen either immediately or after an appropriate course of antibiotic therapy if the latter is warranted by presentation. After therapy, if necessary, antibiotic prophylaxis is continued through diagnostic evaluation, which usually requires urethral catheterization for radiographic or scintigraphic study. If the suspicion of VUR is confirmed and the diagnosis established, a management plan is formulated based on many factors. These factors include but the etiology of reflux (primary versus secondary); mode of presentation; grade of VUR; and age, gender, and general health of the patient.

Surgical and endoscopic intervention, when indicated, are also part of the armamentarium of management options for VUR. More commonly, antibiotic prophylaxis is continued, and serial examinations are performed with knowledge of spontaneous resolution rates and anticipation of such. Medical or expectant management is not a treatment per se, but rather a concerted effort by the patient, the patient's family, and the clinician to protect a patient with VUR from initial or further complication of reflux during the period between its diagnosis and potential spontaneous resolution.

General Observations

One of the most difficult decisions regarding the child with VUR is deciding between medical and surgical management. Despite the many unanswered questions about the natural history of reflux, there are some reasonable observations, that if considered, allow the clinician to make a rational decision:

1. *Reflux will disappear spontaneously in many children.* VUR commonly resolves spontaneously, especially in patients who are young at presentation and when reflux is of low grade. Elongation of the submucosal ureteral tunnel and improved bladder characteristics, including increased compliance and capacity, are mechanisms believed to contribute to the resolution of reflux over time (196).

Spontaneous resolution of reflux is more likely when the diagnosis is made in the younger the child, regardless of grade of reflux. Burge and colleagues (30) reported a 54% resolution rate at 3 years of follow-up in patients with perinatally diagnosed VUR. This rate of resolution is approximately twofold greater than that observed at 5-year follow-up in the International Reflux Study of patients younger than 10 years of age (202,219). Skoog and associates (183) noted a significantly shorter time to resolution for reflux presenting before the age of 12 months compared with that presenting later (1.44 versus 1.85 years; p <.02). Others have reported no difference in time to resolution of grade III and IV VUR for patients younger than 1 year versus those older than 1 year at presentation (129).

Spontaneous resolution of VUR usually occurs within the first few years following its diagnosis, if it is to occur at all. With variation according to grade of reflux, the mean duration of reflux in those in whom it resolved was 1.69 years, with 30% to 35% resolving each year (183). If serial cystograms do not show an improvement in the degree of reflux, it is unlikely that reflux will resolve spontaneously. The appropriate duration of observation is poorly defined. McLorie and co-workers (129) noted that patients with grade III VUR who resolved, 92% did so within 4 years from the time of diagnosis. Spontaneous resolution of reflux beyond 5 years following diagnosis or with puberty is uncommon, especially if associated with little or no interval improvement in reflux degree (48).

Most cases of grade I and II VUR resolve spontaneously. Rates of 85% and 80% have been reported by Edwards and colleagues (45), and Smellie and Normand (187), respectively. During 5 years of medical management, the Southwest Pediatric Nephrology Study Group (9) reported reflux resolution rates of 82% and 80% for grades I and II, respectively. Duckett (41) reported a resolution rate of 63% for grade II reflux, and according to Skoog and co-workers (183), 90% of children with grade I to III VUR experienced resolution after 5. Several authors report resolution of grade III VUR in approximately 50% of patients followed for 5 years (9,41,129).

In general, higher-grade VUR is much less likely to resolve spontaneously. Patients with grades III and IV reflux were followed for 5 years in the International Reflux Study (218). Of patients randomized to medical management in the European arm, reflux resolved in 61% and 10% of patients with unilateral and bilateral VUR, respectively (202). In the American arm, resolution of reflux occurred in 25% overall in the 41 medically managed patients (219). Scholtmeijer (177) studied 93 children with 135 refluxing ureters of varying grades for at least 5 years. Spontaneous resolution was noted in 27 (57%) of 47 cases of grade III and IV VUR. VUR of grades III to V resolved spontaneously in 41% of patients according to Smellie and Normand (187). Skoog and associates (183) reported 9% resolution in grade IV reflux, and McLorie and co-workers (129) noted resolution in 30% of patients with grade IV and 12% of patients with grade V reflux.

2. *Sterile reflux is unlikely to cause renal damage.* Persistent reflux of infected urine causes renal damage. Despite the experiments in swine by Hodson and colleagues (77), renal scarring rarely occurs in refluxing children if a sterile urine is maintained. Recent studies in pigs showed that sterile reflux did not lead to renal scarring. The development of renal scarring in closely followed patients is almost always associated with breakthrough infections. Those incidents in which sterile reflux is implicated in children are almost always anecdotal and retrospective. The only exception may be in grade V reflux, and in this situation, the refluxing megaureter is more analogous physiologically and pathologically to obstructive uropathy.
3. *Long-term antibacterial therapy is usually safe and well tolerated by children.* This fact does not imply that there is no risk, but simply that the risk is small. The physician who implements long-term therapy must monitor the patient to see whether side effects occur. Nitrofurantoin often causes gastrointestinal distress in children and may be better tolerated in the macrocrystal form. Rare reactions include interstitial pneumonitis or pulmonary fibrosis, exfoliative dermatitis, hemolytic anemia, and peripheral neuropathies. Sulfa and trimethoprim-sulfamethoxazole combinations have been associated with blood dyscrasias, Stevens-Johnson syndrome, gastrointestinal symptoms, and central nervous system abnormalities. Both drugs may cause allergic reactions. Monitoring requires alerting the patient and family to possible side effects and promptly ceasing therapy should severe side effects occur. Despite the rare side effect in isolated patients, most patients tolerate long-term antibacterial therapy for years with no problem. This minimal risk of medical therapy must be compared with the real and demonstrated risk of renal scarring and sepsis if antibacterials are not instituted.

   Prophylactic antibiotics may be stopped in a highly select older population with low-grade reflux when the risk of developing a UTI may be small, although very careful follow-up would be necessary (38). In younger children with significant reflux, continuous antibacterial therapy will most likely provide protection against the development of renal scarring. Unfortunately, there is a high rate of noncompliance and being lost to follow-up in medically managed patients (218,219).

4. *Most associated bladder abnormalities do not preclude the possibility that reflux may disappear spontaneously.* Such abnormalities include bladder diverticula, duplex ureter, cystitis cystica (cystitis follicularis), urethral obstruction, and uninhibited bladder. Although any of these abnormalities

may lessen the chance for spontaneous disappearance, they do so in an unpredictable fashion and are not contraindications to medical management (2,143). *Ureteral reimplantation surgery has a high success rate.* One should expect surgical success rates of 95% to 98% in patients with normal-caliber ureters and normal bladders. Coleman and McGovern (37) have indicated that success rates decline as the ureter and bladder become more abnormal. In their large series, the success rate in females was 98% when both the bladder and ureter were normal, 54% when the ureter was markedly dilated, and only 40% when both the bladder and ureter were abnormal. The success rate for the American arm of the IRSC was 99% (42).

5. *Reflux that persists in adolescence or adulthood is unlikely to disappear spontaneously.* Reflux in male adults may or may not be associated with significant morbidity. Reflux in adult females may carry a significant morbidity, particularly during pregnancy. The implications of reimplantation surgery were studied by Austenfeld and Snow (12), who found an increased risk of urinary infections and fetal loss in 31 women who had undergone ureteral reimplantation as children, despite correction of the anomaly. In a follow-up study compared with a new cohort of historical controls, women with UTIs and reflux who underwent reimplantation (suggesting an initially higher degree of reflux and increased renal scarring) were still at significant risk of UTI during pregnancy (123). However, they were not at a higher risk of miscarriage than the general population. In a larger study of 77 pregnancies in 41 women whose ureters had been reimplanted, Bukowski and associates reported that the incidence of pyelonephritis during pregnancy was slightly higher than in the general population but that the fetus and mother were a significant risk when renal scarring or hypertension was present (29a).

Based on this information, one can reach an assessment of the individual patient in deciding the course of management. Certainly, for lower grades of reflux in infants and younger children, every opportunity should be given for the reflux to disappear spontaneously. In those in whom it has not disappeared by late childhood or adolescence, consideration should be given to surgical therapy, depending on the sex, likelihood of future infections, patient reliability for follow-up, and patient interest in a resolution to the problem. Patients with severe reflux that represents the more severe varieties of grade IV or V usually require surgical management as the initial form of management. An exception to this is in the neonate in whom dramatic improvement can occasionally occur in what appears to be severe reflux. This may be related to the increased compliance of the newborn collecting system. Patients with breakthrough UTIs, particularly when associated with fever and regardless of the grade of reflux, probably should have ureteral reimplantation. Patients with high-grade III and grade IV reflux who can be maintained with sterile urine can be followed for a time, but the failure of resolution in those with bilateral reflux is a strong factor in favor of earlier rather than later reimplantation.

Specific management decisions can also be made based on the American Urological Association Pediatric Vesicoureteral Reflux Guidelines Panel. The Guidelines Panel reviewed the reflux literature extensively and developed practice policy recommendations on the basis of evidence-based outcomes and panel opinion, reflecting its clinical experience. The Reflux Guidelines Panel made treatment recommendations based on the presence or absence of renal scarring and the child's age during the initial diagnosis (Table 48D.3).

Clinical Presentation (Age at Presentation)		Treatment Recommendations for Children Without Scarring at Diagnosis					
		Treatment					
		Initial (Antibiotic Prophylaxis or Open Surgical Repair)			Follow-up[a] (Continued Antibiotic Prophylaxis, Cystography, or Open Surgical Repair)		
VUR grade laterality	Age (yr)	Guideline	Preferred Option	Reasonable Alternative	Guideline	Preferred Option	No Consensus[b]
I–II Unilateral or bilateral	<1	Antiobiotic prophylaxis					Boys and girls
	1–5	Antiobiotic prophylaxis					Boys and girls
	6–10	Antiobiotic prophylaxis					Boys and girls
III–IV Unilateral or bilateral	<1	Antiobiotic prophylaxis			Bilateral: surgery if persistent[c]	Unilateral: surgery if persistent[c]	
	1–5	Unilateral antibiotic prophylaxis	Bilateral antibiotic prophylaxis			Surgery if persistent[c]	
	6–10		Unilateral antibiotic prophylaxis Bilateral surgery	Bilateral: antibiotic prophylaxis		Surgery if persistent[c]	
V Unilateral or Bilateral	<1		Antibiotic prophylaxis		Surgery if persistent[c]		
	1–5		Bilateral: antibiotic	Bilateral: antibiotic prophylaxis	Surgery if persistent[c]		
			Unilateral: antibiotic prophylaxis	Unilateral: surgery			
	6–10	Surgery					
I–II Unilateral or bilateral	<1	Antiobiotic prophylaxis					Boys and girls
	1–5	Antiobiotic prophylaxis					Boys and girls
	6–10	Antiobiotic prophylaxis					Boys and girls
III–IV Unilateral	<1	Antiobiotic prophylaxis			Girls: surgery if persistent[c]	Boys: surgery if persistent[c]	
	1–5	Antibiotic prophylaxis			Girls: surgery if persistent[c]	Boys: surgery if persistent[c]	
	6–10		Antibiotic prophylaxis		Surgery if persistent[c]		
III–IV Bilateral	<1	Antibiotic prophylaxis			Surgery if persistent[c]		
	1–5		Antibiotic prophylaxis	Surgery	Surgery if persistent[c]		
	6–10	Surgery					
V Unilateral or bilateral	<1		Antibiotic prophylaxis	Surgery	Surgery if persistent[c]		
	1–5	Bilateral: surgery	Unilateral: surgery			Surgery if persistent[c]	
	6–10	Surgery					

Recommendations were derived from a survey of preferred treatment options from 36 clinical categories of children with reflux.
The recommendations are classified as follows:
Guidelines = Treatments selected by 8 or 9 panel members, given the strongest recommendation language.
Preferred Options = Treatments selected by 5 to 7 of 9 panel members.
Reasonable Alternatives = Treatments selected by 3 to 4 of 9 panels members.
No Consensus = Treatment selected by no more than 2 of 9 panel members.
The treatment recommendations apply to both boys and girls with primary vesicoureteral reflux.
[a]For patients with persistent uncomplicated reflux after extended treatment with continuous antibiotic therapy.
[b]No consensus was reached regarding the role of continued antibiotic prophylaxis, cystography, or surgery.
[c]See Duration of Reflux in the text regarding the length of time that clinicians should wait before recommending surgery.
VUR, vesicoureteral reflux.

TABLE 48D.3. TREATMENT RECOMMENDATIONS

Prospective, Nonrandomized Reflux Studies

In 1984, the Southwest Pediatric Nephrology Study Group (9) initiated a closely monitored prospective study of the medical management of primary VUR. Entry criteria were age younger than 5 years, primary reflux of grades I to III/V, and radiographically normal kidneys after presentation with the first recognized UTI. Patients received medical therapy, including daily antibiotic prophylaxis, meticulous screening, and prolonged counseling, at each follow-up after the diagnosis of VUR was made. A total of 113 patients with 161 refluxing ureters were entered in the study. Preliminary results were published in 1992. Fifty-nine patients with 84 refluxing units had completed the protocol and were evaluable for analysis after 5-year follow-up.

Resolution of VUR was defined as no reflux on two consecutive voiding cystourethrograms performed annually during the 5-year study. VUR resolved in 82% of the 11 ureters with grade I, in 80% of the 40 ureters with grade II, and in 46% of the 33 ureters with grade III reflux. Bilateral VUR of all grades resolved in 54% of patients compared with 66% with unilateral reflux. Urine cultures were obtained every 3 months as well as if urinary symptoms and/or fever developed. Breakthrough UTIs occurred in 20 (34%) of the 59 evaluable patients over the 5 years of study. Standardized excretory urography was performed at 1, 3, and 5 years following diagnosis to assess renal growth, expressed as planimetric surface area, and to detect renal scarring.

Renal growth assessed at 5 years determined that 20 kidneys (9 with scar), associated with all grades of mild or moderate VUR, were more than 2 standard deviations smaller than the mean normal size. Each of these kidneys became progressively smaller during the study.

Several conclusions have been reached from the Southwest Pediatric Nephrology Study Group report. Renal scarring and impaired renal growth in infants and young children can be associated with any grade of VUR, with or without recurrent infection. Resolution of grade III VUR is

much slower than that with grades I and II, and the consequences of grade III reflux on the kidney are worse than those of grades I and II. There is a significant incidence of renal scarring associated with mild VUR (9).

Goldraich and Goldraich (57) have reported a prospective study of 202 children with 314 refluxing units and a mean follow-up of 68.7 months. Mean age at entry following investigation of UTI was 31.5 months. Data regarding spontaneous resolution of VUR were presented according to chronologic age, not the interval between diagnosis and resolution of reflux. Resolution of reflux was the patient's age at the time of the first of two consecutive radionuclide cystograms without reflux.

The diagnosis of VUR was made significantly earlier in males than in females. At entry, 44% of the 314 refluxing units had evidence of reflux nephropathy. At age 5 years, low-grade (grades I and II) VUR had resolved spontaneously in 55% and 60% of ureters in boys and girls, respectively. Resolution of reflux at 5 years was noted in 42% and 48% of ureters in boys and girls, respectively, with high-grade (grades III and IV) VUR. For patients followed for 10 years, spontaneous resolution was noted in 81% and 90% (low grade) and in 50% and 65% (high grade) of ureters in boys and girls, respectively. Although reflux lasted longer in boys than in girls, this difference did not reach statistical significance.

During follow-up, new renal scars developed in 7 (3.5%) of the 202 patients. All scars appeared in patients following a febrile breakthrough UTI and during the first 18 months of follow-up. Of note, in 3 of the 7 patients with new scars, reflux was of low grade. There was no significant gender predilection for prevalence of reflux nephropathy either at entry or during follow-up (57).

Rates of spontaneous resolution have also been studied in patients with high-grade (grades III, IV, and V) VUR (129). Between 1981 and 1987, 300 patients with high grade VUR were to be observed on prophylactic antibiotics. During the period of follow-up, 132 patients received observational therapy alone, and for specific indications, 168 required surgical correction after varying periods of observation.

Spontaneous resolution of reflux occurred in 3 of 26 patients with grade V VUR, but 23 required surgery. For patients with grade IV reflux, 17% and 30% resolved spontaneously by 2 and 5 years of follow-up, respectively. Rates of resolution for patients in the observation group with grade III VUR were 17% and 50% at 2 and 5 years, respectively. New renal scars developed in 8% of patients during the period of observation. Based on their data, the

authors recommend surgical correction of high-grade VUR if it has not spontaneously resolved during 4 years of uncomplicated observational therapy (129).

Prospective, Randomized Studies

Controversy persists regarding what constitutes the best treatment for moderate degrees of VUR. Three prospective, randomized studies comparing medical versus surgical management of patients with moderate to moderately severe reflux have reported results after 5 years of follow-up.

The International Reflux Study was a prospective, randomized investigation comparing the results of medical and surgical treatment of infants and children with grades III and IV (International classification) VUR. Patient recruitment began in 1980 and was completed in 1985. A total of 452 patients entered the randomized trial, 321 and 131 in European and United States arms, respectively. Radiographic requirements at entry included excretory urography and VCUG. Excretory urography was used to evaluate renal scar(s). Blood pressure was recorded, and glomerular filtration rate was estimated using creatinine clearance for all patients. After random allocation, the children were treated with either prompt antireflux surgery or managed medically with antibiotic prophylaxis until spontaneous resolution of reflux (218).

Patients randomized to medical management had similar rates of spontaneous resolution of VUR whether enrolled in the American or European arm of the study (202,219). One-hundred and fifty-five patients were randomized to medical management in the European arm. During the 5 years of the International Reflux Study, reflux resolved in 61% and 10% of patients with unilateral and bilateral VUR, respectively (202). Resolution of reflux occurred in 25% of the 41 patients randomized to medical management in the American arm of the study and followed for 5 years. Results of unilateral versus bilateral reflux were not designated (219).

Randomization to surgery was the fate of 151 patients with 237 refluxing units in the European arm of the International Reflux Study (73). Successful ureteral reimplantation, defined as the correction of VUR and absence of ureteral obstruction, was documented postoperatively in 92% of the refluxing units. Persistent reflux and obstruction was noted postoperatively in 9 and 10 ureters, respectively. Eighty-seven patients with 154 refluxing ureters were randomized to surgical management in the American arm (42). Of the 154 reimplanted ureters, a successful result was obtained in 99.4%. Persistent VUR was present in only one ureter postoperatively.

In the European arm of the International Reflux Study, breakthrough UTIs occurred in 38% of patients during the 5 years of medical management (88). UTIs developed in 39% of patients after ureteral reimplantation. However, the incidence of pyelonephritis was 10% and 21% during follow-up for the surgical and medical groups, respectively. In the United States, there was a threefold and statistically significant higher incidence of pyelonephritis in the medically versus the surgically managed patients (219).

Upon entry to the study, approximately 50% of patients in both the American and European arms had scarred kidneys and the patients were evenly distributed between the medical and surgical treatment groups (218). Over the 5 years of follow-up, no statistically significant difference was noted in the incidence of new renal scarring and parenchymal thinning between the American and European or medical and surgical arms (139,219). In addition, there was no significant difference with regard to renal growth for medical versus surgical management.

The principal conclusions of this study were as follows:

1. Bilateral grade IV reflux was unlikely to resolve within 5 years.
2. There was no difference in renal scarring between patients randomized to surgery or medical therapy at 5 years. There was a difference, however, in the pattern of scarring in that the scars in the surgical group occurred early, whereas those in the medical group were evenly distributed throughout the study. Also, the incidence of clinical pyelonephritis was much higher in the medical group. Thus, because a number of medically followed patients still had reflux, it might be expected that scarring would be higher in two similarly constructed groups followed for another 5 years.
3. The surgical success rate, particularly when done by an experienced surgeon, was quite high.

The Birmingham Reflux Study Group randomized children with severe VUR to receive medical or surgical therapy. Reflux was categorized as grade I, reflux into the ureter; grade II, nondilating reflux into the renal pelvis; and grade III, reflux causing dilated calices. Entry included all patients with grade III reflux and grade II reflux with renal scarring (23,24).

A total of 104 patients were recruited for this prospective study. Fifty-one and fifty-three patients were randomized to surgical and medical management, respectively. Resolution of VUR occurred in approximately 20% to 50% of patients treated medically during the 5-year follow-up period. A 98% success rate was achieved in those patients undergoing ureteral reimplantation. No statistically significant difference was noted between the medically and surgically treated groups with regard to development of new renal scars or renal growth. Their report showed no clear advantage to either surgical or medical therapy in patients with reflux.

In a third prospective study, patients with grade IV VUR were randomized to medical versus surgical management (177). Ninety-three children with 135 refluxing ureters were studied for at least 5 years. Of the 135 refluxing ureters, 35 had grade IV VUR; 24 underwent surgery, and

11 were treated with antibiotics alone. During 5 years of follow-up, VUR resolved in 6 (55%) of the 11 ureters managed medically. Reflux was cured in all ureters treated by reimplantation.

Medical Management

Choice of Antibacterial

Appropriate antibiotic prophylaxis for the purpose of maintaining sterile urine in the face of VUR is the cornerstone of medical management. Several different medications achieve high urinary concentrations and effectively control a broad range of uropathogens. Medications are usually given at half the standard therapeutic dose. Nighttime administration in toilet-trained individuals precedes the longest period of urinary retention and is most effective in prophylaxis.

The antibacterial agent chosen should be one that combines the following: is the least risk to the patient, has high urine concentrations, minimally alters vaginal-perineal flora, has a broad spectrum of action against most Gram-negative bacteria, is available and well tolerated in liquid forms, and is available at minimal cost to the patient. No one antibacterial agent satisfies all of these criteria.

Amoxicillin and ampicillin are well tolerated and are the recommended formulations for children up to 6 weeks of age. These medications have the fewest side effects in the newborn but do favor the development of resistant fecal flora. After 6 weeks of age, sufficient maturation of the biliary system makes trimethoprim-sulfamethoxazole preparations a viable alternative. This usually becomes the antibiotic of choice. However, awareness of side effects, including gastrointestinal symptoms, allergies, Stevens-Johnson syndrome, and leukopenia, is necessary. A complete blood count may be necessary before any surgery in patients using a trimethoprim-sulfamethoxazole preparation. After 2 months of age, nitrofurantoin becomes another acceptable alternative for the purpose of UTI prophylaxis. As an elixir or tablet (crushed, divided, and added to food), this is the best medication for minimizing resistance of and/or altering fecal flora. Rare, but well-recognized, complications of Macrodantin use include pulmonary fibrosis and interstitial pneumonia. Side effects, including nausea and vomiting, hemolytic anemia, peripheral neuropathies, and exfoliative dermatitis, have also been described. A written, summarized description of well-recognized antibiotic side effects should be available and given to the respective caretaker(s).

All antibacterial agents should be continued as long as the patient is refluxing. *Intermittent* treatment of infections is *ineffective.* With the practice of intermittent antibiotics, Lenaghan and associates (104) noted a 21% incidence of new renal scarring versus a report by Smellie and colleagues (185) of a 1% incidence with the use of continuous antibiotic prophylaxis. Progressive nephropathy is the course for patients who are treated only during symptomatic episodes.

Once the reflux has resolved, the antibacterial agents can be stopped. The patients will continue to require monitoring to make sure that infection does not recur. Recurrent infections are common after reflux resolves (60), although most will now be associated with lower tract symptoms rather than clinical pyelonephritis.

Clinic Visits

Children with reflux should probably be seen at no more than 6-month intervals. Clinic visits should establish any history consistent with intercurrent infection or of reaction to the antibacterial. Physical examination should record parameters of physical growth and blood pressure. Laboratory studies should include urinalysis and culture at each visit, and hemogram, white blood cell count, and serum creatinine clearance should be obtained as needed. These tests represent only the minimum studies and must be altered depending on the child's condition.

Frequency of Radiologic Studies

US or IVU should be performed initially in the infection-free patient and repeated at intervals of 18 to 24 months, but sooner if repeated infections occur. Contrast VCUG is used as the initial study to grade the reflux and ascertain any associated bladder pathology. Subsequent studies should be done at about 12- to 18-month intervals. After the initial study is used for grading, subsequent studies may be done with a radionuclide cystogram. Barthold and co-workers (17) have recommended two normal studies before the assumption that reflux is resolved; however, one study may be adequate unless the patient continues to have febrile infections.

DMSA scintigraphy is probably the most sensitive indicator of renal scarring and gives excellent assessment of differential renal function. It is indicated as both a baseline and for follow-up in patients with higher grades of reflux, after a febrile UTI, and when renal scarring is suspected on IVU or renal US.

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49

THE BLADDER

Contents

49A BLADDER DEVELOPMENT: CELLULAR SIGNALING

Laurence S. Baskin

Part of "49 - THE BLADDER "

L.S. Baskin: Chief, Pediatric Urology, University of California– San Francisco, San Francisco, CA 94143.

The urinary bladder has two major functions: (1) storage and (2) socially acceptable efficient emptying (55). A number of urologic diseases that affect both adults and children, males and females, are characterized by abnormal noncompliant bladders. For example, patients with interstitial cystitis, spinal cord injuries, myelomeningocele, tuberculosis, bladder exstrophy, and posterior urethral valves may all require treatment to normalize bladder function. When pharmacologic manipulation fails, the next step is surgical bladder rehabilitation, which typically requires enlargement with intestinal segments.

For the bladder to be a safe and effective storage chamber, the ideal cellular lining is urothelium. Epithelial cells from the gastrointestinal tract are not optimal for this purpose because they either secrete or absorb electrolytes (38,44). This can lead to chronic electrolyte abnormalities such as metabolic acidosis, which occurs with ileal augmentation cystoplasties. In the case of gastric augmentations, the stomach segment continues to act as a gastric secreting organ, which may predispose to hypochloremic hypokalemic metabolic alkalosis (12,31). Chronic electrolyte imbalance also may lead to abnormalities in calcium homeostasis, resulting in bone demineralization. The risk of tumors in bladder augmentation also is increased based on sporadic case reports and experimental studies (2,14). Intestinal segments also secrete mucus, changing the quality of urine in these patients. The use of bowel in the urinary tract also increases the chance of urolithiasis through unknown lithogenic properties (8).

A number of strategies have been devised to avoid the use of bowel in the urinary tract. Autoaugmentation, as described by Cartwright and Snow, has had success in a select group of patients whose compliance is poor based on abnormal pressures (16). This procedure is technically difficult in patients who have poor volumes secondary to small contracted bladders. The concept of creating a large bladder diverticulum composed of urothelium and lamina propria has been extended by attempting to support the inherently weak autoaugment with deepithelized bowel segments from the stomach or the sigmoid colon (15,45). The well vascularized deepithelized bowel segments can theoretically provide a vascularized stromal support to the urothelial diverticulum. What type of cellular interactions occur at this foreign interface between bladder urothelial cells and intestinal

stroma? Before we can answer this question, we first need to define what we mean by “normal” urothelium and “normal” stroma or mesenchyme.

Definition: Note that *mesenchyme* refers to the nonepithelial cellular elements (i.e., connective tissue, fibroblasts smooth muscle). Mesenchyme refers to the embryonic time period and stroma refers to the same non-epithelial elements postnatally.

DEFINING UROTHELIUM

As previously stated, the ideal goal of bladder augmentation is to have a urothelial cell–lined bladder. To accomplish this goal, we need to carefully define the phenotype of the urothelial cell. Presently, urothelium can be defined by morphology, protein expression, turnover, and function. Histologically, bladder urothelium is a stratified transitional epithelium consisting of basal, intermediate, and superficial cells. Functionally, these cells must accommodate rapid changes in volume and pressure (5). During bladder cycling, the urothelial cells function as an impermeable barrier to most solutes. The superficial urothelial cells have a highly specialized apical membrane consisting of thickened plaques of asymmetric unit membrane (AUM), which can be internalized to decrease the luminal surface area of the bladder during emptying. The AUM is composed of urothelial-specific proteins: the uroplakins I, II, and III (56).

It is possible to culture urothelial cells *in vitro* (3,25,28,36,51). Depending on the *in vitro* environment, the urothelial cells can form a monolayer or can be induced to stratify and mimic the *in vivo* phenotype. Southgate and colleagues have been able to show that long-term organ cultures of urothelium retain the same basic phenotype as normal urinary tract tissue *in situ.* The “normal” phenotype is based on the addition of exogenous calcium to the *in vitro* cultures as well as presence of the proper stroma (28,51).

Therefore it is possible to develop a table of antigen expression for urothelium *in situ* and compare the phenotype with urothelium during cell culture and with urothelium that has been placed in the environment of a different stroma such as is occurring in bladder reconstruction (Table 49A.1). Presently, the antigen expression of cytokeratins, uroplakins, integrins, and E-cadherin have been well described (9,36,57).

		Normal Urothelial Tissue			Cultured	Intact Organ Culture		
Antibody	Type/Specificity[a]	Basal	Intermediate	Superficial	Urothelial Cells	Basal	Intermediate	Superficial
Ld568	Monoclonal keratin 7	++	++	++	++			
Ld5103	Monoclonal keratin 7,8,18	++	++	++	++			
LP1K	Monoclonal keratin 7	++	++	++	++			
E3	Monoclonal keratin 17	++	++	++	++/+			
BA16	Monoclonal keratin 19	++	++	++	++			
LP2K	Monoclonal keratin 19	++	++	++	+++/+	++	++	+++
LE41	Monoclonal keratin 8	+	+	++	+	+	+	++
LE61	Monoclonal keratin 18	+	+	++	++	+	+	++
CAM5.2	Monoclonal keratin 18,19	+	+	++	+++/++			
2D7	Monoclonal keratin 13[b]	++	++	–	++			
IC7	Monoclonal keratin 13[b]	++	++	–	++			
KS13.1	Monoclonal keratin 13	++	++	–	++			
CK8.6	Monoclonal keratin 1, 10, 11	–	–	–	–			
KB37	Monoclonal basal, squamous	–	–	–	–			
6B10	Monoclonal keratin 4	–	–	–	–			
LL001	Monoclonal keratin 14	–	–	–	++			
AUM	Rabbit urothelial membrane antigen	+	+	+++	–	+	+	±
ASU	Rabbit asymmetric unit membrane	–	–	++	–			
AE31	Monoclonal uroplakin 1	–	–	++	–			
V9	Monoclonal vimentin	–	–	–	++			
L9	Rabbit fibronectin	–	–	–	++			
F4	Monoclonal fibronectin	–	–	–	++			
Lam	Rabbit laminin	–	–	–	+			

Note: Immunofluorescence on normal human urothelial tissue sections, cultured urothelial cells, and intact organ cultures.
The immunofluorescence reaction is scored subjectively from negative (–) to strongly positive (+++).
[a]Human keratin polypeptide numbers used as assigned by Moll and associates.
[b]Positive on only 2% to 5% of cultured cells.
Adapted from references 8, 36, and 51.

TABLE 49A.1. DEFINING UROTHELIUM

For example, cytokeratin expression in the rat bladder varied as a function of development and cell position (basal versus luminal) (9). Cytokeratin 5 was first detected at 19 days' gestation, whereas cytokeratin 14 was first detected in the newborn rat bladder (day 0). Cytokeratins 7, 8, 18, and 19 were detected in 15-day embryonic bladders, the earliest day studied. Cytokeratins 8 and 18 were localized to the luminal aspect of the epithelium, whereas cytokeratins 5, 7, 14, and 19 localized predominantly to the basal layer of the epithelium. Cytokeratins usually are expressed in pairs (5, 14 or 8, 18) (46,47). Interestingly, in the rat bladder, cytokeratin 5 appears before cytokeratin 14, an exception to the pairs rule. In the corneal epithelia, the expression of the basic cytokeratin 3 also has been found to be discordant with its acidic pair cytokeratin 12. In this case, neutrality is maintained by the simultaneous expression of cytokeratin 19 along with cytokeratin 3 (46). In the bladder, it may be that the discordant expression of the cytokeratin 5/14 pair is compensated by the earlier expression of another cytokeratin as occurs in the corneal epithelium (47). The localization of specific cytokeratins to either the basal or luminal layer of the urothelium suggests that the basal cells and luminal cells perform different functions. The pattern of expression of cytokeratins in the bladder epithelium is unique and can be used as a fingerprint to differentiate urothelium from other epithelium.

The uroplakins (I, II, and III) are known to be specific biochemical markers for urothelial differentiation (56). The uroplakins consist of three major proteins (15, 27, and 47 kDa), which form an asymmetric unit membrane in the superficial umbrella cells of the urothelium. These molecular markers are thought to represent an advanced stage of urothelial differentiation. These unique proteins are not expressed in any other epithelial cells. Uroplakins are thought to play a role in the impressive folding that occurs when the bladder lumen collapses during emptying. The uroplakins are unique markers for urothelium.

STROMA AND SMOOTH MUSCLE CELLS

Using the rat as an experimental model, the ontogeny of both epithelial and smooth muscle differentiation was defined using a panel of antibodies to smooth muscle and epithelial proteins (9). The smooth muscle proteins, a smooth muscle actin, myosin, vinculin, desmin, and laminin are sequentially expressed as a function of developmental stage. At 14 days' gestation, the rat bladder mesenchyme does not have any smooth muscle based on histologic criteria of smooth muscle cells such as a centrally located nucleus, spindle shape, and relatively small nucleus-to-cytoplasmic ratio. Based on immunohistochemical staining, the 14-day embryonic bladder mesenchyme does not express any of the smooth muscle proteins (Fig. 49A.1). The fact that the 14-day bladder of the fetal rat did not express any of the smooth muscle markers provided the opportunity to establish the required bioassay to test the hypothesis that cell–cell interactions between the epithelium and mesenchyme regulate smooth muscle cell differentiation (9).

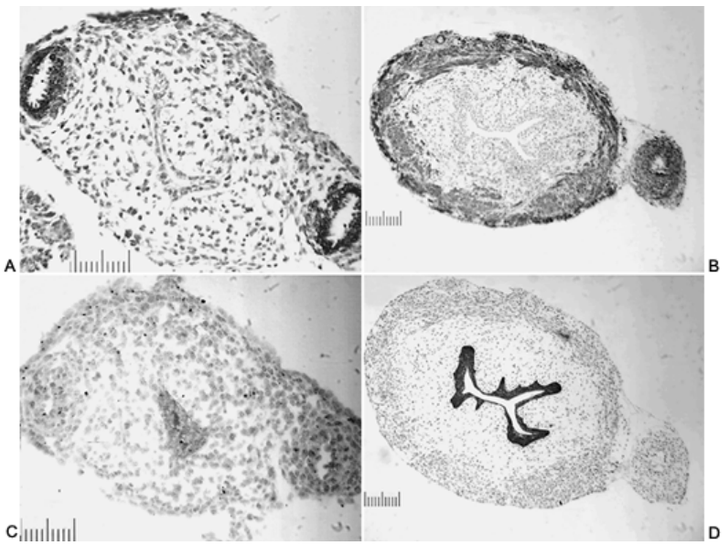

FIGURE 49A.1. Embryonic bladder development: smooth muscle and urothelium. Smooth muscle and epithelial development in the rat bladder. **A:** Embryonic bladder at 14 days' gestation showing α-actin smooth muscle immunostaining. Note the lack of localization in the bladder mesenchyme in contrast to the positive staining of the adjacent umbilical vessels. **B:** In contrast, at 17 days' gestation, well-defined smooth muscle bundles are localized in the outer layer of the bladder by α-actin smooth muscle. **C:** Cytokeratin epithelial immunohistochemistry at 14 days' gestation. Note the sparse localization to the epithelial cells. **D:** In contrast, there is intense localization to the urothelium in the 17-day gestation bladder.

The first mesenchymal marker to be detected during bladder development was vimentin at 15 days' gestation. With time, vimentin expression became localized exclusively to the fibroblasts of the lamina propria and connective tissue between the smooth muscle bundles. A similar pattern

of expression has been reported in the developing stroma of the rat prostate and seminal vesicle, where vimentin is initially widely expressed in the mesenchyme, but with time, it localizes to the interductal connective tissue and lamina propria (34). In the developing rabbit bladder, Chiavegato and associates have shown that vimentin and a nonmuscle isoform of myosin are initially expressed in the smooth muscle cells of the young rabbit bladder. With normal aging, these differentiation markers cease to be expressed in the smooth muscle cells of the young rabbit bladder but can reappear following experimental partial bladder outlet obstruction (18). Further work by Buoro and co-workers with the same experimental obstruction model showed that fibroblastic cells adjacent to the bladder serosa may transform into myofibroblasts and subsequently into fetal type smooth muscle cells based on the reexpression of smooth muscle markers (13). At 16 days' gestation, when smooth muscle is first noted by the previously defined histologic criteria, α-smooth muscle actin staining cells are detected in the periphery of the bladder. Subsequently, these actin-positive cells sequentially acquire the remaining smooth muscle markers, vinculin, laminin, myosin, and desmin. Smooth muscle protein expression is consistent with the temporal expression of the message for smooth muscle α-actin (43).

EPITHELIAL-MESENCHYMAL INTERACTIONS

Epithelial-mesenchymal signaling may be required for the smooth muscle differentiation to occur (8). To test this

hypothesis, 14-day embryonic rat bladders (before the differentiation of smooth muscle) were isolated, and the epithelium was separated from the mesenchyme following tryptic digestion, which degrades the epithelial basement membrane. The isolated bladder mesenchyme, bladder mesenchyme recombined with urothelium, and intact 14-day embryonic bladders were then grown underneath the kidney capsule of syngeneic hosts. The intact 14-day embryonic bladders underwent normal differentiation, defined by the expression of smooth muscle proteins. In contrast, when isolated bladder mesenchyme was grown alone underneath the kidney capsule, the tissue survived, but the mesenchyme did not differentiate into smooth muscle. However, when bladder mesenchyme was recombined with bladder epithelium, smooth muscle differentiation occurred, although this was less organized than if the epithelium was left intact in its natural state (Fig. 49A.2) (8).

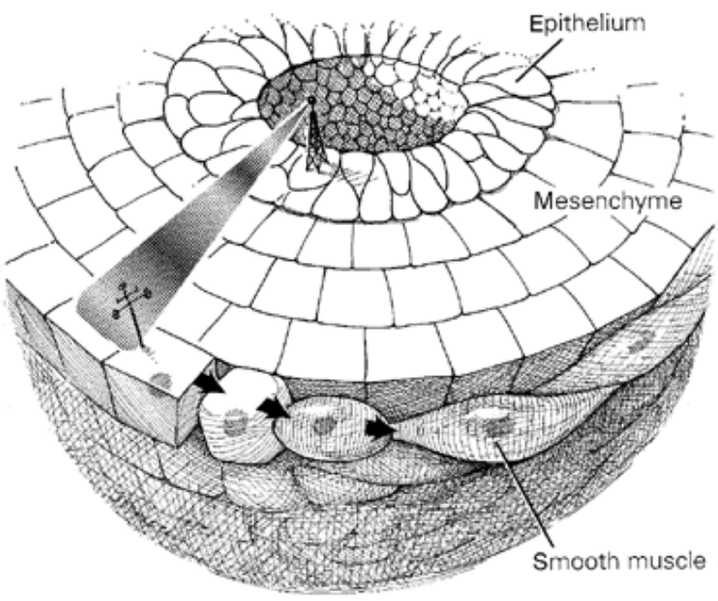

FIGURE 49A.2. Cellular signaling in the bladder. Epithelium is required for bladder mesenchyme to differentiate into bladder smooth muscle. Signaling occurs via an unknown mechanism, possibly diffusable growth factors. (From Baskin LS, Hayward S, Young P, et al. Role of mesenchymal-epithelial interactions in bladder development. *J Urol* 1996;156:1820, with permission.)

The same experiments were repeated *in vitro,* where intact embryonic bladders before smooth muscle differentiation were grown on top of filter paper nourished by standard tissue culture medium. Compared with bladder mesenchyme cultured alone, there was impressive growth of the intact organs. When epithelium was recombined with bladder mesenchyme, again the growth was greatly improved compared with the mesenchyme alone. Labeling of the organ culture with 3H-thymidine showed extensive cellular proliferation in the tissue recombinants composed of bladder mesenchyme plus bladder epithelium and in intact bladders, whereas in the mesenchyme alone, little DNA synthesis occurred. Histologically, tissue recombinants of bladder mesenchyme plus epithelium structures revealed healthy cellular histology, whereas the bladder mesenchyme alone showed evidence of cellular degeneration.

A final experiment determined whether urothelium from a different species could induce bladder smooth muscle differentiation. This hypothesis was tested by performing a unilateral nephrectomy in nude mice (8). Undifferentiated, 14-day rat bladder mesenchyme with the epithelium removed was then surgically attached to the severed mouse ureter. The bladder mesenchyme and mouse ureter were allowed to grow for 1 month *in situ,* with the idea that the ureteral epithelium would induce smooth muscle differentiation of the rat bladder mesenchyme. As expected, the mouse urothelium induced smooth muscle differentiation in the rat bladder mesenchyme, resulting in the expression of smooth muscle differentiation markers. Species-specific probes confirmed that the epithelium was of mouse origin and the smooth muscle was from the rat. These experiments strongly support the concept that cellular signaling between the bladder epithelium and undifferentiated bladder mesenchyme is required for the induction of bladder smooth muscle.

What happens if abnormal signaling occurs? (See Fig. 49A.3 .) For example, during bladder augmentation with bowel segments at the anastomotic site, the urothelium is receiving signals from the intestinal stroma and the intestinal epithelium is receiving signals from the bladder stroma. Might this abnormal signaling lead to cellular changes such as atypia and even cancer? Although relatively rare when cancer does occur in augmented bladders, the site is always at the junction between the native bladder and the intestinal segment.

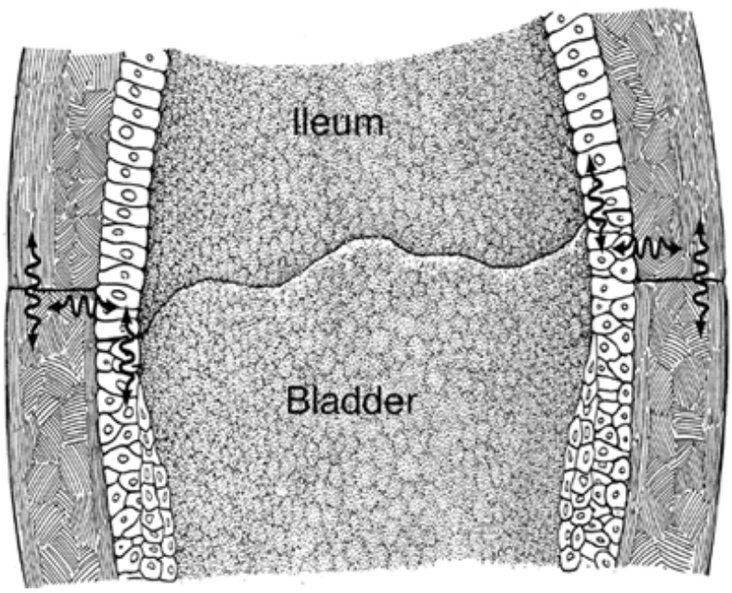

FIGURE 49A.3. Augmentation cystoplasty. Schematic of the heterotypic stromal-epithelial interactions that are created at the anastomotic site of intestinal bladder augmentations. [From Li YW, Liu WH, Hayward SW, et al. Plasticity of the urothelial phenotype: effects of gastro-intestinal mesenchyme/stroma and implications for urinary tract reconstruction. *Differentiation* 2000;66(2 and 3):126, with permission.]

GROWTH FACTORS

If diffusable growth factors play a role in bladder differentiation, one would expect to see differences in their expression during development. RNase protection assays were performed against a panel of growth factors at strategic times during bladder development and smooth muscle differentiation (10). Specifically, rat bladders were examined at the embryonic stage before smooth muscle development (14 days' gestation), at the time of first smooth muscle differentiation (16 days' gestation), and then at subsequent time points (18 days' gestation, newborn, 20 days postnatally, and adulthood). Transcripts for keratinocyte growth factor (KGF) and the KGF receptor, transforming growth factor-α (TGF-α) and epidermal growth factor (EGF) receptor, and the TGF-β family were assessed. TGF-β2 and TGF-β3 were regulated as a function of development, being expressed at a high level in early gestation and then decreasing as a function of time. TGF-α and KGF were expressed in opposite fashion, being minimally expressed in the embryonic period with a greater expression in the mature bladder (10).

A model of bladder outlet obstruction was created in the rodent to study the effect of obstruction on smooth muscle remodeling (52). This resulted in a sixfold increase in

bladder volume and a fivefold increase in bladder weight, as well as a doubling of smooth muscle cell diameter. The mRNA for the growth factor TGF-ß2 increased twofold, TGF-ß3 increased fivefold. The mRNA for TGF-α was elevated tenfold. In contrast, the transcripts for KGF and the receptors for KGF and EGF did not exhibit any changes. TGF-ßs are known to affect extracellular matrix synthesis, and it may be that the changes in the bladder wall and increased matrix deposition resulted from the upregulation of these growth factors. Other investigators have shown acute changes in growth factors during bladder outlet obstruction. For example, in an acute model of partial bladder outlet obstruction in the rabbit, transcripts for basic fibroblast growth factor (bFGF), c-myc, c-fos, and Ha-ras and Ki-ras oncogenes are elevated, whereas mRNA encoding TGF-ß1 is decreased (17,40).

EXTRACELLULAR MATRIX

The bladder also undergoes significant tissue remodeling as it increases in size and matures in function. In addition to maturation of smooth muscle and urothelium, much of the change in the bladder wall occurs within the extracellular matrix (ECM), which serves both structural and regulatory functions. The changes occurring in the ECM of the bladder during both normal development and in response to obstruction reflect a balance of synthesis and degradation of the fibrous (mainly collagen and elastin) and nonfibrous (proteoglycans and glycosaminoglycans) constituents. Both collagen types I and III are regulated as a function of development and bladder outlet obstruction (4,5,7). The expression and activation of type IV collagenases (MMP-2 and MMP-9) are developmentally regulated and play a role in bladder remodeling during obstruction (53).

BLADDER WOUND HEALING

Further evidence for cellular signaling via growth factors has been shown with a model of bladder wound healing (6). Using the rodent as a model, an incisional wound was created in the bladder and then sutured with primary closure. Histologic analysis revealed that the bladder epithelium regrew over the defect within 24 to 48 hours. RNase

protection assays of growth factors showed an eightfold increase in the expression of KGF as compared with sham-operated and control animals. Interestingly, this increased expression occurred in the first 12 to 24 hours corresponding to the period of intense epithelial proliferation noted histologically. At 5 and 7 days, when the epithelium had completely regrown, the expression of KGF returned to baseline.

Another interesting finding is that when the bladder wall was sampled at a distance from the injury, there was still an upregulation compared with sham and nonoperated animals, suggesting that global signaling occurs throughout the bladder in response to injury, which facilitates epithelial repair (Fig. 49A.4) (6). The proliferative activity of the urothelial cell is impressive as it is normally quiescent with turnover every 6 months to a year (35). However, following bladder epithelial injury, KGF released by the stroma binds to receptors on the epithelial surface to cause the urothelium to proliferate (1). Further support for the direct effect of KGF in the bladder was tested by injecting human recombinant KGF subcutaneously into neonatal mice. In comparison with saline controls, urothelial proliferation was greatly enhanced as judged by 3H thymidine labeling (6). A similar finding has been reported for the monkey bladder by Yi and colleagues (58).

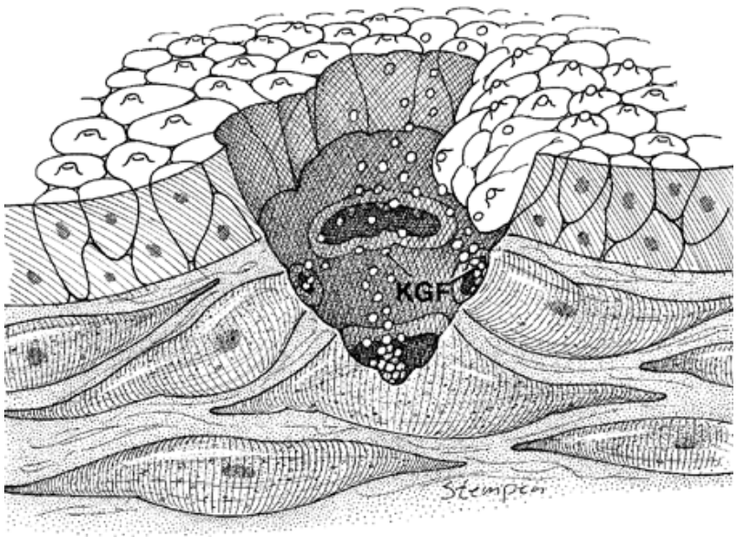

FIGURE 49A.4. Bladder wound healing schematic. Keratinocyte growth factor *(KGF)* is released from bladder stroma cells during bladder injury and directly acts through its urothelial located receptor to cause proliferation and regrowth of urothelial cells mending the bladder injury. (From Baskin L, Sutherland R, Thomson A, et al. Growth factors in bladder wound healing. *J Urol* 1997;157:2388, with permission.)

BLADDER REPLACEMENT

One of the most exciting areas of bladder research is development of new methods of bladder augmentation that avoid the use of intestinal segments. One model of bladder augmentation uses an acellular tissue matrix to elicit regeneration of bladder tissue (Fig. 49A.5) (54). In this model, the dome of the bladder is excised (again, this was first performed in the rodent model) and acellular tissue matrix made from either the bladder or the stomach is sutured to the surgical defect. The acellular matrix is prepared by incubating the bladders or stomachs of adult rats in distilled water for 1 hour to lyse the cells and to release intracellular contents. Tissues are then suspended in 40 mL of 40% sodium deoxycholate (Sigma Chemical Company, St. Louis, Missouri), for 2 to 4 hours, followed by treatment with 2,000 Kunitz units of deoxyribonuclease I (Sigma Chemical Company) in 1 M of sodium chloride solution for 1 to 2 hours. This process is repeated one to three times to extract all cellular material. Histologic confirmation shows an absence of cells. The preparation of the acellular matrix is designed to avoid complete removal of potentially important growth factors, as well as other extracellular matrix ligands. After suturing the acellular matrix patch in place, animals were sacrificed at serial time points to specifically study the interface between the native bladder and the acellular matrix tissue. Complete reepithelization with urothelial cells occurred by 4 days, and smooth muscle regenerated into the acellular matrix by 2 weeks after grafting. Interestingly, the smooth muscle grew in juxtaposition to the epithelial surface, which over time, matured into normal size bundles by 26 weeks after grafting.

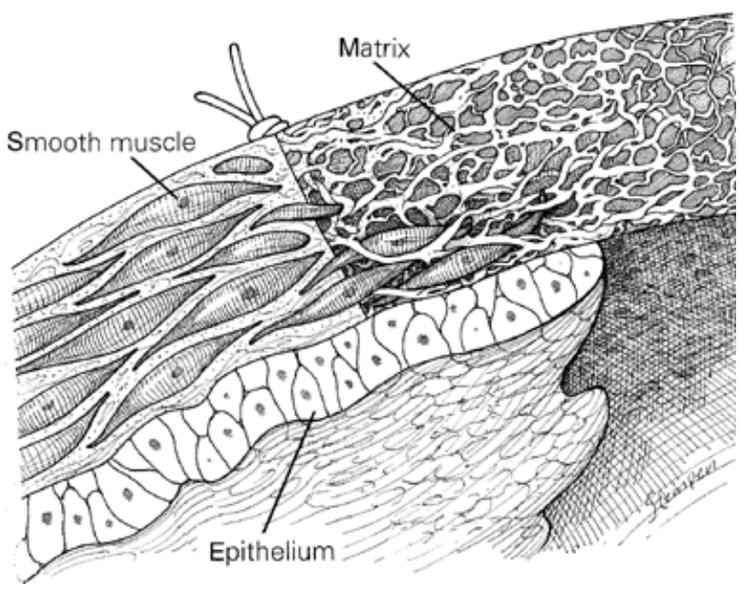

FIGURE 49A.5. Matrix experiment for bladder replacement. A model of bladder regeneration with an acellular tissue matrix shows that urothelium, smooth muscle, and nerves can grow into the tissue matrix, most likely under the influence of stromal-epithelial cellular communication. (From Sutherland RS, Baskin LB, Hayward SW, et al. Regeneration of bladder urothelium, smooth muscle, blood vessels and nerves into an acellular tissue matrix. *J Urol* 1996;156:571, with permission.)

Neovascularization was seen by 2 weeks, and neural elements from the native bladder formed around the developing

bundles of smooth muscle as early as 4 weeks. These animals were able to void and function normally. Careful histologic analysis showed that the acellular tissue matrix did not regenerate into completely normal bladder, but over time, smooth muscle bundles did organize into their appropriate position in the periphery of the bladder, and the urothelium itself covered this matrix, presumably under the influence of KGF from tissue injury (6).

ABNORMAL CELLULAR SIGNALING

Normally, the urinary bladder consists of three well-defined layers: (a) an inner layer of transitional epithelium approximately three to five cell layers thick, (b) an underlying connective tissue layer intimately associated with the epithelium, and (c) a surrounding thick layer of organized smooth muscle. The development and maintenance of the bladder, like other organs, depends on positive and negative feedback between these interacting groups of cells (8,20). In certain clinical situations, such as with augmentation cystoplasty, the interacting groups of cells are iatrogenically altered (Fig. 49A.3). In augmented bladders, for instance, foreign epithelia and/or stroma from organs such as the intestine and stomach are permanently placed in contact with bladder tissue. A plausible explanation for the higher incidence of intestinal cancers in the augmented bladder (29,49,50) is that the interactions of the foreign epithelium and/or stroma with the existing bladder epithelium and/or stroma result in abnormal cell–cell interactions that perturb regulation of epithelial growth.

There is a definite cause-and-effect relationship between augmentation and the development of malignancy because the incidence of primary adenocarcinoma of the small bowel in the general population is only 0.1% (42), yet most of the reported malignancies in augmented bladders are in ileal augments (48). Thus the risk of developing a “small bowel” malignancy in a patient with an augmentation cystoplasty is significantly increased (approximately tenfold) compared with the general population.

The pathogenesis of this benign to malignant transformation is not understood but may be secondary to a perturbation in cell–cell signaling caused by the introduction of nonbladder cells into the bladder. Three major arguments support this theory. First, of the 12 reported cases in the literature of primary malignancies in bladder augmentation in which the location of the tumor could easily be defined, 8 were noted at the junction of the bladder and bowel and 2 were located near this junction (48,49). Also, in animal models, it has been shown that when tumors do develop, they almost always occur at the site of the enterovesical junction (42). If cell–cell interactions are important, the malignancy would be expected to occur at the site of the anastomosis. Second, it has recently been shown that the presence of feces or urine is not necessary for tumor development (42,48). Finally, abnormal cell–cell interactions have been implicated in carcinogenesis in general. Both colon (39) and prostate (21) adenocarcinomas are

thought to result from perturbed stromal-epithelial cell–cell interactions.

Currently, there is no clear understanding of the cell–cell interactions that occur at the anastomotic site of an augmented bladder. We know that in normal bladder development, epithelium is necessary for the differentiation of embryonic mesenchyme into smooth muscle (8). Epithelium is also essential for the differentiation of mesenchyme into smooth muscle in other organs such as intestine and uterus (19,23,37). Thus a signal must be transmitted from the epithelium to the mesenchyme, which instructs the mesenchyme to differentiate into smooth muscle.

During normal bladder development, signaling from the epithelium is required for smooth muscle development (Fig. 49A.2) (8). Epithelium is also necessary for the differentiation of mesenchyme into smooth muscle in other organs such as the uterus and intestine (50). Recent studies have shown that the inducing signal for smooth muscle differentiation is not specific to the age of the urothelium or in fact dependent on the origin of the epithelium (26). For example, embryonic, newborn, and adult urothelium all have the capability to induce bladder mesenchyme to form smooth muscle. Furthermore, heterotypic epithelia such as ureteral, gastric, uterine, colonic, corneal, and ileal will induce the same effect, although the amount of smooth muscle induction varies according to the type of epithelia Fig. 49A.6 (26).

In general, the ability of heterotypic epithelia to induce smooth muscle differentiation in bladder mesenchyme was linked to the amount of smooth muscle with which the epithelium is normally associated. This was the case for gastric, ureteral, myometrial, and bladder epithelium, which all had the ability to induce extensive smooth muscle development in tissue recombination experiments (Fig. 49A.6). In contrast, epithelium not typically associated with smooth muscle such as corneal epithelium and epidermis showed little inducing capability.

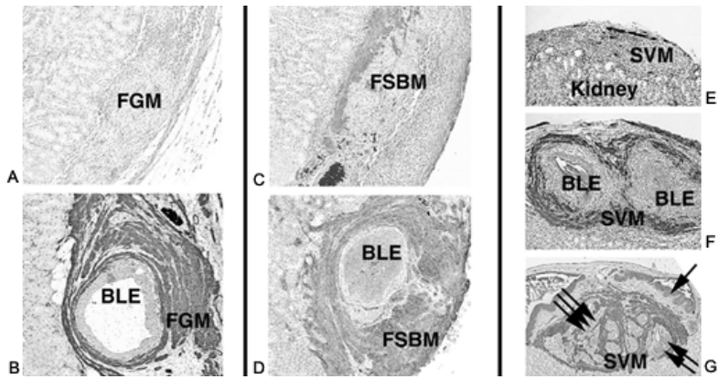

FIGURE 49A.6. Tissue recombination experiments illustrating stroma/mesenchymal-epithelial interactions. Three tissue recombinants using heterotypic fetal (gastric, ileal) and newborn (seminal vesicle) mesenchyme + adult bladder epithelium *(BLE).* When the fetal mesenchyme [gastric *(FGM)* and ileal *(FSBM)*] was grown alone (without epithelium, **A** and **C**), there was little evidence of smooth muscle differentiation (lack of α-actin smooth muscle immunostaining). However, when recombined with bladder epithelium, both gastric **(B)** and ileal **(D)** mesenchyme showed excellent smooth muscle differentiation [immunostaining (α-actin)]. Immunostaining for cytokeratin specific for transitional epithelium reveals a well-developed urothelial layer three to four cell layers thick in **B** and **D.** The entire morphology of the recombinant in **B** and **D** resembles that of bladder. When newborn seminal vesicle *(SVM)* is grown alone, there is evidence of smooth muscle differentiation **(E)** (which is to be expected because seminal vesicle mesenchyme has differentiated into smooth muscle by the time of birth). However, the smooth muscle is disorganized, and α-actin staining is scant **(E).** In contrast, when SVM is recombined with BLE in a female host **(F),** there is maximal smooth muscle differentiation and organization. Interestingly, when SVM is recombined with BLE in a male host **(G),** extensive smooth muscle organization is seen. Also, the epithelium in this tissue recombinant is transitional in some places (cytokeratin staining specific to transitional cells, *single arrow*), and prostatic in others (no pink staining, secretory morphology, *triple arrow*). There are some areas where the epithelium exhibits both transitional and prostatic morphology (*double arrow*). (From DiSandro M, Li Y, Baskin L, et al. Mesenchymal-epithelial interactionsin bladder smooth muscle development: epithelial specificity. *J Urol* 1998;160:1040, with permission.)

A large body of scientific evidence exists to support the concept that abnormal cellular signaling can lead to cellular changes. When embryonic or, even more surprising, adult bladder epithelium is placed in direct contact with urogenital sinus mesenchyme, the bladder epithelium is induced to differentiate into glandular epithelium that resembles prostatic epithelium histologically and ultrastructurally, expresses androgen receptors, and secretes prostate-specific proteins (Fig. 49A.6) (22,24,26). For example, both colon and prostate adenocarcinomas also are thought to arise from perturbed epithelial-stromal cell–cell interaction (21,32).

Changes in the stromal environment can profoundly influence adult epithelial morphology and function. This possibility has been tested by transplanting neonatal rat seminal vesicle mesenchyme *in situ* to the cut end of the mouse adult ureter. The adult urothelium was induced by the seminal vesicle mesenchyme to undergo seminal vesicle morphogenesis, to express seminal vesicle cytodifferentiation, and to produce the complete spectrum of major seminal vesicle proteins characteristic of the mouse. The induced seminal vesicle epithelium also expressed androgen receptors that are not seen in urothelial tissue. Staining with Hoechst dye 33258, which can distinguish cells of mouse and rat origin, further demonstrated that the induced seminal vesicle epithelium was indeed of mouse origin and not a contaminant of the inducing rat seminal vesicle mesenchyme. In addition, neonatal prostate-inducing mesenchyme grafted *in situ* beneath the bladder mucosa of adult male mice induced prostatelike acini, indicating that the aforementioned reprogramming of adult organs *in situ* is not an isolated occurrence. Thus it is clear that reciprocal epithelial-stromal interactions are important both in organogenesis and in adulthood in the homeostatic maintenance of normal tissue architecture and function and that adult epithelia retain a capacity to respond to stromal signaling. Further evidence that the stroma influences the epithelial phenotype is illustrated by recombination experiments in which urothelium is placed in an abnormal environment of rectal mesenchyme/stroma. In this case, the stroma causes the urothelium to change phenotype to a glandular mucous epithelium (Fig. 49A.7). Immunostaining of the tissue recombination experiments revealed a loss of uroplakin expression in the bladder cells, further evidence that the cellular phenotype of the urothelium had been changed. These data clearly support the concept of cellular signaling between the epithelium and stroma of the bladder (41). Theses data also illustrate the importance of normal signaling to maintain the normal phenotype of bladder cells.

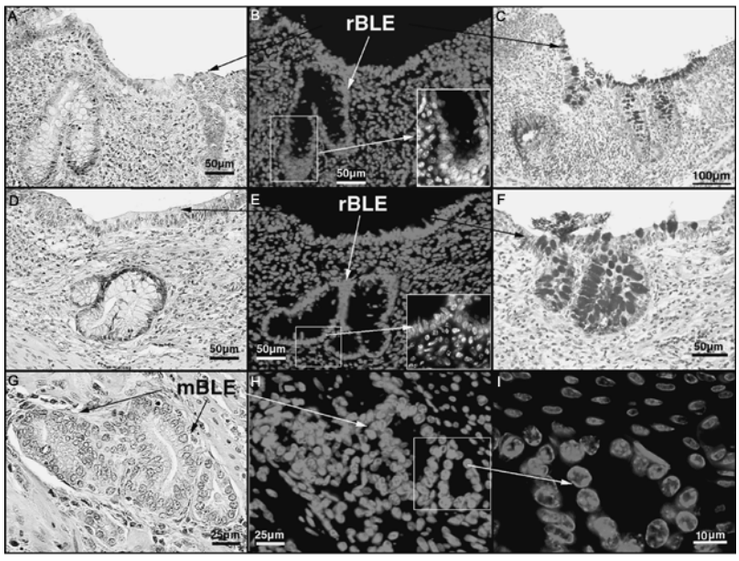

FIGURE 49A.7. Glandular epithelium induced from urothelium. Tissue separation and recombination experiment. **A:** Rat bladder epithelium combined with mouse rectal mesenchyme. Note that the epithelium has changed phenotype to glandular structures. **B:** Confirms that the epithelium is of rat origin. (Hoescht dye 33258 shows that the rat nuclei do not have speckles in contrast to the mouse nuclei in the stroma that have speckles.) The species-specific stain is useful to confirm that tissue contamination did not occur during separation of the epithelium and the mesenchyme. **C:** PAS stain showing mucin in the epithelial glandular structures. Note that some of the urothelium retains its histologic characteristics *(upper left).* **D:** Another example of rat urothelium changed to the glandular phenotype. **E:** Hoescht dye confirming the origin of the epithelium and mesenchyme. **F:** Note the positive mucin staining confirming glandular epithelium. **G:** The reverse tissue recombination experiment with mouse bladder epithelium and rat mesenchyme revealing that the mouse urothelium changed phenotype to a glandular epithelium. **H, I:** Hoescht dye showing origin of the epithelium and mesenchyme. *Arrows* relate area of magnification. [From Li YW, Liu WH, Hayward SW, et al. Plasticity of the urothelial phenotype: effects of gastro-intestinal mesenchyme/stroma and implications for urinary tract reconstruction. *Differentiation* 2000;66(2 and 3):126, with permission.]

It has been postulated that alterations of these interactions may play a role in the genesis of diseases such as benign prostatic hyperplasia and prostate cancer (21). It is also recognized that stromal changes occur in the genesis of many tumors. We have recently hypothesized that the reciprocal communication between incipient prostatic cancer cells and their surrounding stroma can promote of prostatic carcinogenesis (21). A similar scenario also may occur in the promotion of bladder tumors toward an invasive phenotype.

Epithelial-mesenchymal interactions during development continue as epithelia stromal interactions after birth. In numerous experimental systems, we have shown that the stroma regulates the epithelium, and the interactions are likely to be reciprocal (19,20,24). For example, it has been suggested that both normal prostatic development and prostate carcinogenesis are mediated by stromal-epithelial interactions. Recent evidence supporting this model comes from experiments in which the stroma surrounding prostatic tumors was analyzed by immunohistochemistry and shown to be dedifferentiated when compared with normal prostatic stroma. In another experiment, epithelial cells from the rat prostatic Dunning tumor were placed in contact with inductive mesenchymal environments (specifically with urogenital sinus and seminal vesicle mesenchyme). This resulted in a dramatic reduction in growth rate of the Dunning tumor cells and a loss of tumorigenicity (33). These findings demonstrate that the connective tissue environment can have profound regulative effects on neoplastic epithelial cells.

As previously noted, tumors in patients with bladder augmentations are primarily adenocarcinomas that originate at the anastomotic junction between the bladder and the intestine. It is known that nitrosamines are elevated in the urine of patients who have undergone enterocystoplasty. The nitrosamines in turn can cause mutagenic changes to the DNA. This hypothesis that nitrosamines are acting as carcinogens is supported by the increased incidence of cancer at the anastomotic site of patients who have had ureterosigmoidostomies (27).

We propose an alternative hypothesis that abnormal stromal-epithelial interactions at the site of bladder intestinal anastomosis lead to perturbations in reciprocal cell-cell signaling between the intestinal stroma and the urothelium. *In vitro* studies on bladder cancer cell lines support this hypothesis. Gordon and associates showed that altered extracellular matrices influence human bladder cancer cell lines possibly through regulation of the nuclear matrix (30). The authors conclude that the extracellular matrices derived from transformed stroma-producing cells may influence the proliferation, genetic regulation, and maintenance of the overlying urothelial tumor cells.

CONCLUSION

In conclusion, the bladder develops via coordinated signaling between the mesenchyme and the epithelium. Reciprocal cell–cell interactions maintain bladder function throughout life. Growth factors are likely mechanistic candidates that mediate the interactions between cells. Bladder wound healing, which is mediated by KGF, is a specific example of stroma-epithelial cellular signaling. Smooth muscle development, which is dependent on signaling from the epithelium, is another example of cell–cell interactions, although the specific causative growth factors remain to be elucidated. Abnormal cellular signaling may account for pathologic changes such as fibrosis secondary to bladder outlet obstruction or nerve abnormalities. Finally, abnormal stroma-epithelial signaling

such as occurs at the anastomotic site of intestinal bladder augmentations may account for the increased risk of cancer documented in these patients.

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49B EXSTROPHY AND EPISPADIAS ANOMALIES

Richard W. Grady

Michael E. Mitchell

Part of "49 - THE BLADDER "

R.W. Grady and M.E. Mitchell: Department of Urology, University of Washington; Division of Pediatric Urology, Children's Hospital and Regional Medical Center, Seattle, WA 98105.

Exstrophy and epispadias remain one of the most striking and challenging birth defects confronting physicians who specialize in the urologic care of children. With these anomalies, the anterior portion of the bladder and/or urethra and abdominal wall structures are deficient and the

pubis symphysis is widely separated from the midline. The deformity has been described as “if one blade of a pair of scissors were passed through the urethra of a normal person; the other blade were used to cut through the skin, abdominal wall, anterior wall of the bladder and urethra, and the symphysis pubis; and the cut edges were then folded laterally as if the pages of a book were being opened” (17). Interestingly, this defect often occurs in isolation so that other organ systems are affected only infrequently. Exstrophy is also a nonlethal defect; its natural history is known and has been described by various authors.

Formal descriptions of exstrophy date back to at least 1597 with Sherk von Grafenberg's description of this congenital defect. Probable depictions of exstrophy also exist on Assyrian tablets from 2000 B.C. Chaussier first coined the term “exstrophie” to describe this defect in 1780 following detailed descriptions of it by Mowat in 1748. Treatment of exstrophy was doubtlessly difficult during these earlier times and it remains challenging today.

Since the nineteenth century, various methods to treat exstrophy have been described. Because exstrophic conditions are rare, these early approaches were empiric and often unsuccessful. More focused efforts in this century have led to a better understanding and improved treatment of exstrophy. Currently, the exstrophic diseases are considered a spectrum of disease processes related by certain principle anatomic features. These diseases are referred to as the exstrophy–epispadias complex (60), which includes the following:

- Epispadias
- Classic bladder exstrophy
- Cloacal exstrophy
- Exstrophy variants

EMBRYOLOGY/PATHOGENESIS

Embryologically, components of the urinary system such as the ureteral buds first appear during the fourth week of fetal development and before the bladder has completely formed from the anterior urogenital sinus. Before this, the cloacal membrane separates the coelomic cavity from the amniotic space during the third week of development. By the fourth week of gestation, the cloacal membrane forms the ventral wall of the urogenital sinus at the root of the allantois. Before the bladder is completely formed, mesenchyme grows inward toward the midline between the bilaminar (ectoderm and endoderm) layers of the cloacal membrane. This ingrowth of mesenchyme later differentiates into the abdominal wall musculature and fascia of the bladder. Following this, the urorectal septum separates the bladder and rectum by growing downward between them to join the cloacal membrane in the primitive perineum. This occurs when Tourneaux's folds migrate craniocaudally to meet Rathke's plicae that merge together in a lateral-to-medial direction. The urinary bladder arises during the eighth week of fetal development when the ventral portion of the urogenital sinus begins to expand (126).

With bladder filling, the mesenchymal tissue surrounding this structure differentiates into smooth muscle, which eventually becomes the detrusor muscle. Ingrowth of neuronal tissue into this smooth muscle to form motor units is critical to the development of a functional bladder (100). Embryogenesis of the pelvic floor is also important in normal fetal bladder development and function; the pelvic floor acts as a dynamic support for the bladder, which aids in both continence and volitional voiding (56).

Genital development occurs simultaneously. The primordia of the genital tubercles develop cephalad and lateral to the cloacal membrane. These paired structures fuse in the midline above the cloacal membrane to create a single genital tubercle at the same time that mesenchymal ingrowth occurs into the cloacal membrane. The area between the body stalk and cloacal membrane subsequently lengthens to create an infraumbilical body wall.

Pathogenesis of Exstrophy

Early theories implicated trauma to the unborn child or ulceration of the abdominal wall and bladder between the second and third months of life as the underlying cause of exstrophy. In the nineteenth century, syphilis infection was believed to be a possible cause of exstrophy (222). Later, at the turn of the century, bladder outlet obstruction with rupture of the abdominal wall was implicated as the cause of exstrophy. This hypothesis explained the lack of fusion of the bony pelvis and abdominal wall but failed to adequately explain the pathophysiology of exstrophy. As our understanding of embryogenesis has improved, this idea subsequently has been abandoned (33).

Modern theories all implicate an error in embryogenesis rather than an event of arrested development as the cause of exstrophy because the developing human embryo does not normally pass through a stage that corresponds to an exstrophic state (163). Specifically, abnormalities in the appearance, timing, and function of the cloacal membrane are believed to be involved in the creation of exstrophy. Animal models suggest that exstrophy results from pathologic events involving the cloacal membrane. As described earlier, this membrane serves to separate the coelomic cavity from the amniotic space in early development and can first be identified during development at 2 to 3 weeks of gestation (216).

In 1962, Marshall proposed that exstrophy was caused by persistence of this cloacal membrane during fetal development based on autopsy studies of fetuses with bladder exstrophy done earlier in the century (144). Persistence of

the membrane would create a wedge effect that would keep the medially encroaching mesoderm from fusing in the midline. The persistent cloacal membrane would then later rupture because of its inherent instability to produce an exstrophic condition (163). To further study this hypothesis, Muecke subsequently created an animal model of cloacal exstrophy using the developing chick embryo. By placing a plastic graft in the region of the tail bud, he created cloacal exstrophy in these animals and concluded that exstrophy was due to persistence of the cloacal membrane as Marshall had originally postulated (163).

Other experimental models have implicated premature disappearance of the cloacal membrane in the pathophysiology of exstrophy instead. Johnston first proposed this mechanism for the development of exstrophy. However, it was not until Thomalla and Mitchell developed a model of cloacal exstrophy in the developing chick embryo by using a CO_2 laser to create an early dehiscence in the tail bud caudal to the omphalomesenteric vessels that the hypothesis was shown to have a valid animal model (118). Their results demonstrated that exstrophy may be caused by failure of the mesoderm to ingrow between the ectoderm and endoderm as the result of an absence of the cloacal membrane that also produces exstrophy. Simplistically, a hole in the anterior abdominal wall results in the herniation of the developing bladder, causing the structure to move anteriorly and to fail to close ventrally (Fig. 49B.1). Such an event could be caused by early hypoxemic infarction in the region of the tail bud with subsequent cellular loss of the mesoderm and herniation of the developing bladder or cloaca (212). This type of ischemic injury has been implicated as the cause of gastroschisis and can explain the spectrum of exstrophy–epispadias complex (211).

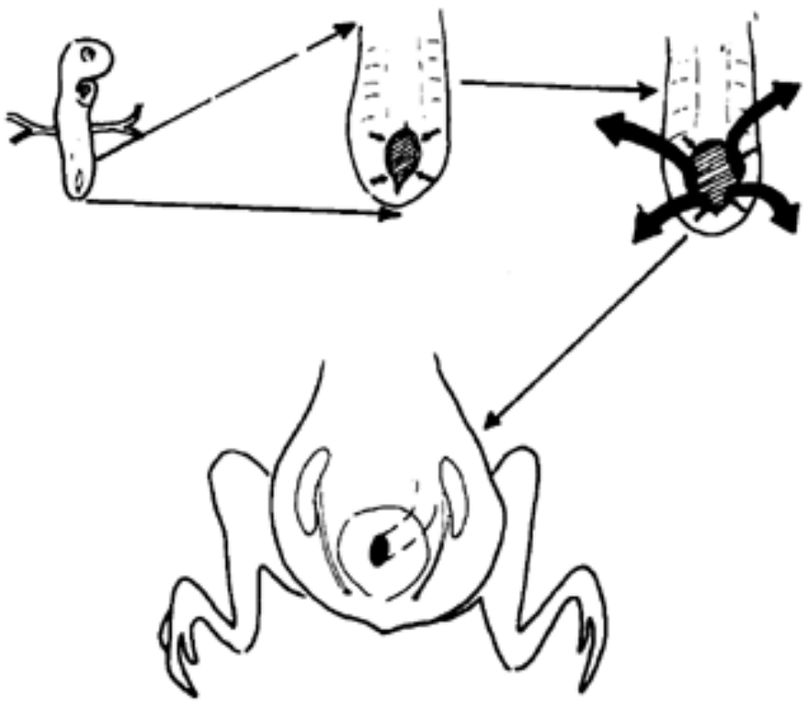

FIGURE 49B.1. Diagrammatic representation of cloacal exstrophy chick model. Defect in cloacal membrane induced by CO_2 laser. (From Thomalla V. Induction of cloacal exstrophy in the chick embryo using the CO_2 laser. *J Urol* 1987;134:991, with permission.)

Other proposed theories for exstrophy include caudal displacement of the paired primordia of the genital tubercles ("caudal displacement theory"). This hypothesis implicates caudal fusion of the primordia of the genital tubercles from their usual location relative to where the urorectal fold divides the cloaca into the urogenital sinus and rectum (172). This theory readily explains the spectrum of variation seen in the exstrophy–epispadias complex. Minimal caudal displacement of the primordia would produce epispadias; more significant caudal displacement would result in exstrophy. However, it fails to explain the higher incidence of exstrophy compared with epispadias; this hypothesis would predict a higher incidence of epispadias if caudal displacement were the underlying cause of exstrophy/epispadias because it represents the most trivial example of this phenomena (216).

Ultimately, the specific underlying cause of exstrophy remains unanswered because it is a rare birth defect and no naturally occurring animal models exist to facilitate research. The chick model to study bladder exstrophy has inherent limitations because chicks normally possess a cloaca so that only cloacal exstrophy can be created with this model. Other animal models to study bladder exstrophy have proven more difficult to create. Slaughenhoupt and colleagues have created an exstrophy model using sheep but have not published any data using this model to study the underlying mechanisms of exstrophy and its effects on bladder development (197).

ANATOMIC PATHOLOGY

The anatomic features of patients with exstrophy or epispadias can vary. The primary organ system—the genitourinary system—is always affected to a variable extent. Other organ systems also may be involved. The various anatomic features for all the exstrophic anomalies are discussed in the following sections (Table 49B.1).

TABLE 49B.1. AFFECTED ORGAN SYSTEMS IN THE EXSTROPHY-EPISPADIAS ANOMALIES

Malformation	Cloacal Exstrophy	Cloacal Exstrophy Variant	Classic Exstrophy	Epispadias
Bladder exstrophic	+	+	+	(–)
Bladder neck open	+	±	+	+ (varies)
Reflux	+	±	+	+
Genitalia		±	+	+ (can be minor)
Epispadias	+	+	(–)	(–)
Failure of müllerian duct fusion	Severe	(±)	(–)	(–)
Pelvis				
Lack of pelvic floor support	++	+ > ++	+	+
Pubis symphysis	++	+ > +++	+	+/(–)
				+
Renal				
Ectopia	++	+	(–)	(–)
Dysplasia	+	+	(–)	(–)
Spine				
Vertebral	++	+	(–)	(–)
Lipomeningocele	+	+	(–)	
Meningomyelocele	Rare	Rare	Rare	
Abdominal wall				
Omphalocele	++	++	(–)	(–)
Intestine				
Short bowel	++	±	(–)	(–)
Absent large bowel	++	++, (–)	(–)	(–)
Imperforate anus	++	+, (–)	(–)	(–)
Neurology				
Paraplegia	±	±	(–)	(–)
Limb deformity	±	±	(–)	(–)

Bladder Exstrophy

The primary features of exstrophy involve an absence of the anterior bladder wall and dorsal urethra with an associated absence of the anterior abdominal wall overlying it (Fig. 49B.2). The urothelium of the bladder and urethra is thus exposed to the environment. Considerable variation exists in the size and compliance of the bladder plate at birth; some bladders are quite small and inelastic, whereas others appear large and compliant. At birth, the urothelium is usually normal in appearance. However, ectopic bowel mucosa or polypoid lesions consistent with cystitis cystica and/or glandularis may be present. If left untreated and if not meticulously protected after birth, the exposed urothelium

will undergo squamous metaplasia in response to acute and chronic inflammation. Other inflammatory changes such as cystitis cystica and/or glandularis also will be seen. When left chronically exposed to the environment, the areas of squamous metaplasia often undergo malignant degeneration to adenocarcinoma or squamous cell carcinoma (85,168).

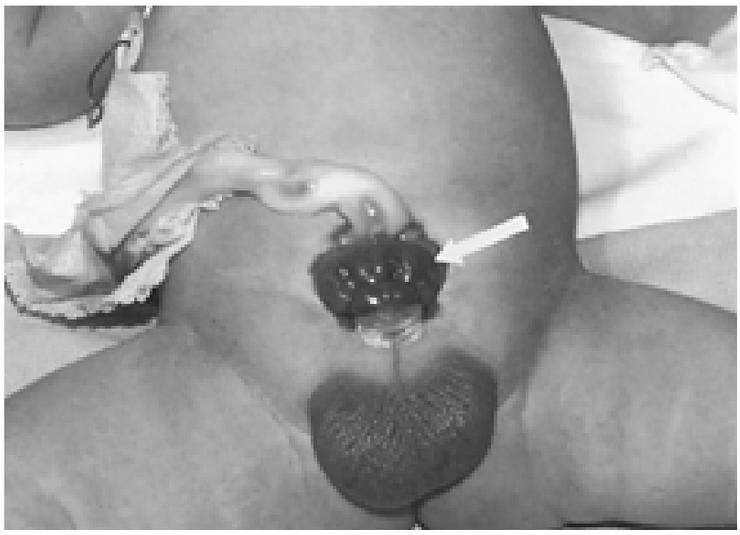

FIGURE 49B.2. Newborn male with classic bladder exstrophy.

Associated Anomalies

Classic exstrophy and epispadias share a low incidence of anomalies affecting organ systems other than the genitourinary tract and bony pelvis. In contrast, patients with cloacal exstrophy have associated anomalies more often than not (12,44). These anomalies can affect the upper urinary tract, intestines, skeletal system, and neurologic system. A possible reason for this is that the cloacal exstrophy defect occurs much earlier in development, affecting subsequent development of related structures including the spine, kidneys, and hindgut.

Kidneys and Upper Urinary Tract

Renal anomalies are not characteristic with bladder exstrophy. Associated renal abnormalities can include cystic dysplasia, ureteropelvic junction obstruction, pelvic kidney,

megaureter, renal hypoplasia, and horseshoe kidney (166). In contrast, vesicoureteral reflux occurs almost universally after exstrophy closure. This likely occurs because the ureteric migration into the bladder plate occurs after the anterior herniation of the bladder plate, resulting in an altered anatomy of the ureteric path such that its course is posterior and caudal, "J hooking" (Fig. 49B.3).

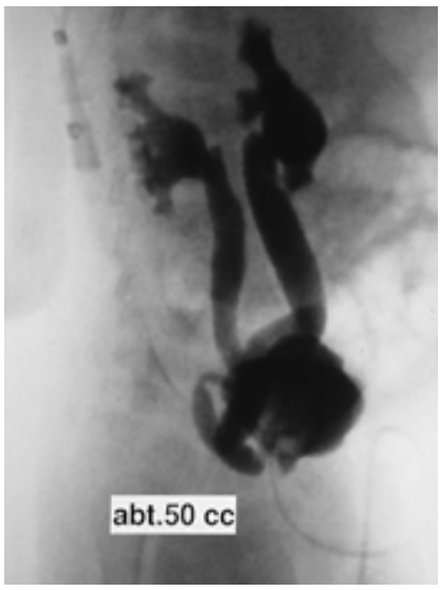

FIGURE 49B.3. Voiding cystourethrogram in 6-month-old boy with bladder exstrophy after closure demonstrating vesicoureteral reflux. The ureters approach the bladder inferiorly and laterally.

Genitalia

The male exstrophy patient has a broad and shortened penis. The penis is deflected dorsally and may have true intrinsic dorsal chordee. The corpora cavernosa are splayed laterally because of their attachment to the separated pubic bones. Because of the pubic diastasis associated with exstrophy, the penis appears variably foreshortened. Magnetic resonance imaging (MRI) evaluation of the penile length of adult male exstrophy and epispadias patients also reveals that the total corporal length is significantly shorter than in a control population. This corporal shortening apparently results from a foreshortened anterior segment (distal to the pelvic attachment). The posterior corporal segment is unaffected (195) (Fig. 49B.4).

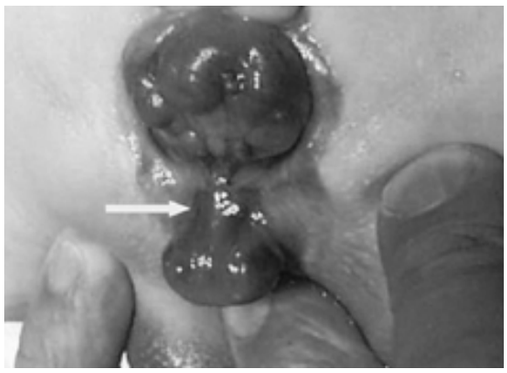

FIGURE 49B.4. The phallus of the exstrophic male. The proximal corpora splay laterally from their normal anatomic position and demonstrate dorsal chordee. *White arrow* points to the urethral plate.

The combination of the short urethral plate and dorsal chordee also creates the appearance of the glans penis lying in close approximation to the prostatic utricle. The ejaculatory ducts empty at the verumontanum exposed on the urethral plate. The vas and ejaculatory ducts are typically unaffected in classic exstrophy unless iatrogenically damaged (90). Innervation to the penis is preserved but the anatomic location of the nerves is affected. This has obvious implications for later surgical procedures. In the normal male, these nerves can be found on the dorsal aspect of the penis after they traverse the posterolateral aspects of the prostate and the membranous urethra (225). However, in the exstrophic male, the cavernosal nerves are located on the lateral aspects of the corporal bodies. The prostate is also incompletely formed (71,88). The scrotum usually is not affected, although most exstrophy patients have an increased distance between the base of the penile shaft and the scrotum and a broadening of the scrotum dependent on the degree of diastasis (Fig. 49B.2). The testes may be undescended with exstrophy. Because of the underlying bladder neck anomalies, exstrophic patients may have impaired fertility. A particular problem is retrograde ejaculation if the bladder neck does not close completely during emission following bladder reconstruction (9,15,134).

The exstrophic female has unique anatomic features affecting the genitalia as well (Fig. 49B.5). The mons pubis is absent. In association with a bifid clitoris, the anterior labia are laterally displaced although they fuse in the midline posteriorly. The vagina and introitus also are displaced anteriorly from their usual position and the introitus is tilted upward. The vaginal opening may be stenotic in these patients, but we have not found this to be a characteristic *de novo* feature. However, vaginal stenosis can result as a complication of surgical intervention. Internal genital structures (uterus, cervix, fallopian tubes, and ovaries) usually are unaffected in classic exstrophy although the cervical os often enters the superior wall of the vagina. Uterine prolapse due to deficient pelvic floor support can occur in the older exstrophy patient and poses particular problems with pregnancy (170). Early primary bladder reconstruction may decrease this risk. Uterine suspension procedures such as sacrocolpopexy can be used in these situations as well.

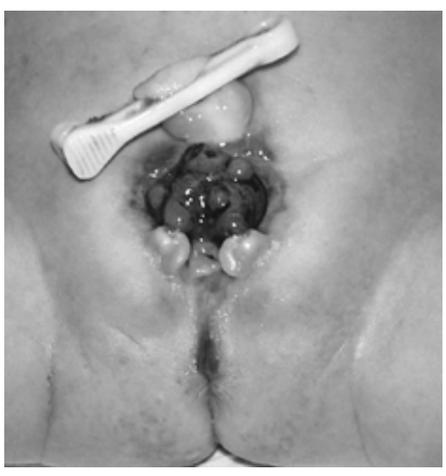

FIGURE 49B.5. Newborn female with classic bladder exstrophy.

Anorectal and Intestinal Abnormalities

The anus is often displaced anteriorly in the exstrophy complex. Some exstrophic patients have insufficient anal continence because of the underlying abnormalities of the pelvic floor support structures including the levator ani and puborectalis muscles. Anal sphincter weakness not only affects fecal continence but also may limit the use of ureterosigmoidostomy and its variants, that is, rectal bladder, ileocecal ureterosigmoidostomy, and so on. In untreated patients, rectal prolapse also can occur because of insufficient pelvic floor support. This can be treated with formal exstrophy repair that corrects the lack of anterior pelvic support. In the interim, most rectal prolapse is intermittent and reducible (60).

Skeletal Abnormalities

Diastasis of the pubic symphysis occurs as part of the exstrophy complex. The pelvis is open anteriorly and flattened in the anterior posterior dimension. This results from outward rotation of the innominate bones along both sacroiliac joints. Outward rotation of the pubic rami at the iliac and ischial junctions is seen as well. Sponseller has noted other differences in the pelvic anatomy of patients with exstrophy, including (a) increased distance between the triradiate cartilage, (b) external rotation and shortening (by 30%) of the anterior segment of the iliac bone, (c) external rotation of the posterior segment of ileum, and (d) retroversion of the acetabula (113,202) (Fig. 49B.6). These pelvic bone abnormalities contribute to splaying of the penis noted with exstrophy and epispadias and cause the penis to appear foreshortened. Gait abnormalities in these children arise as a consequence of these bone abnormalities. Many of these children initially learn to ambulate with a wide waddling gait that resolves as the children grow. Orthopedic procedures to reapproximate the pubis symphysis at the time of primary closure do not appear to offer any long-term benefits to these patients from an orthopedic viewpoint. Long-term follow-up of these patients clearly demonstrates that the pubic diastasis reoccurs over time despite osteotomies (190). Osteotomies to reapproximate the pubis symphysis do, however, increase the chance of successful primary bladder closure in selected patients and may have a significant role in securing continence and support of the pelvic diaphragm (1,14).

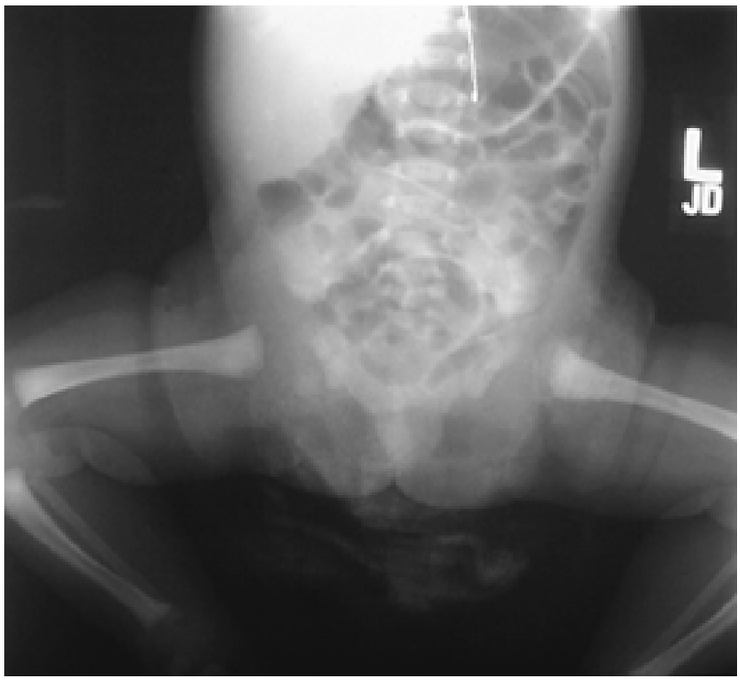

FIGURE 49B.6. The bony pelvis in exstrophy. Note wide pubic diastasis seen on this radiograph

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Fascial Abnormalities

Fascial abnormalities with exstrophy involve several factors in addition to the rectus fascial defect associated with the exposed bladder. Inferiorly, the pelvic floor support structures are compromised. In fact, the anterior portion of the pelvic diaphragm is actually thickened in the exstrophic patient. This thickened segment provides anterior support in the absence of the pubis symphysis and is often referred to as the intersymphyseal band or ligament. The remaining portion of the pelvic diaphragm lies completely posterior to the exstrophic bladder and urethra (Fig. 49B.7). The rectus muscles diverge laterally with the widened pubis symphysis. This abdominal defect is most severe in cloacal exstrophy.

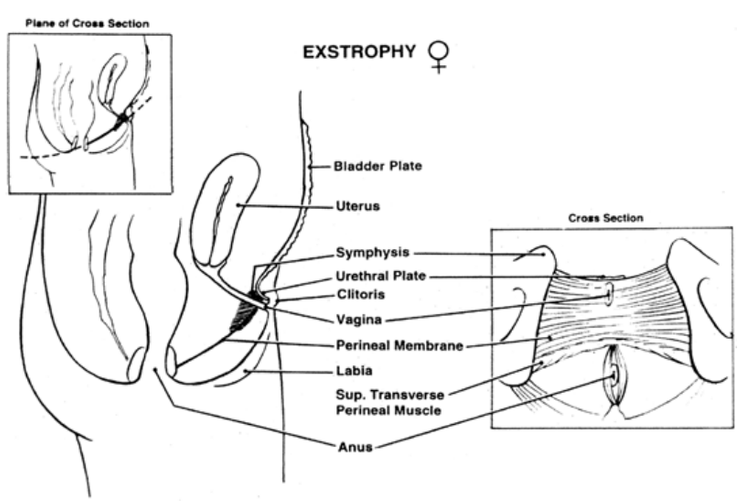

FIGURE 49B.7. Fascial anomalies. The pelvic support structures are compromised anterior to the bladder and urethra. This schematic diagram of a girl with bladder exstrophy illustrates the lack of anterior support.

Inguinal hernias commonly are associated with exstrophy in both male and female patients (34,207) (Fig. 49B.8). The majority of these hernias occur indirectly. They arise as a

consequence of enlarged internal and external inguinal rings combined with compromised fascial support and lack of obliquity of the inguinal canal (104). In a review of patients from Toronto Sick Children's Hospital, 56% of classic male exstrophy patients and 15% of classic female exstrophy patients developed inguinal hernias over a 10-year period. The authors recommended these hernias be repaired at the time of primary bladder closure to prevent incarcerated hernias that could affect up to 50% of these patients in the first 2 years of life (30). Reinforcement of the transversalis and internal oblique fascia during hernia repair decreases the incidence of later direct inguinal hernias. Umbilical hernias, as a contiguous defect with the bladder plate, also uniformly occur with exstrophy and are repaired at the time of the primary repair.

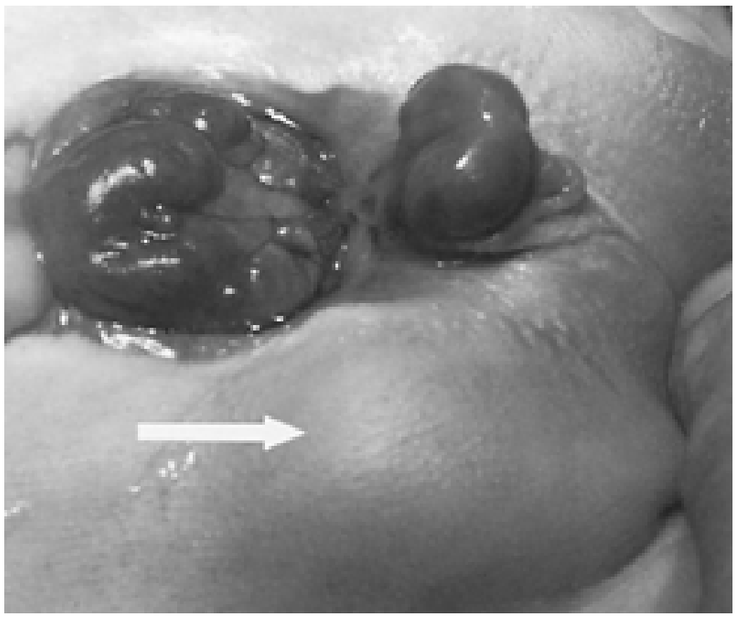

FIGURE 49B.8. Evidence of an inguinal hernia in this newborn male with bladder exstrophy as demonstrated by the inguinal bulge *(arrow).*

Omphaloceles also can be found in association with bladder exstrophy, although this rarely occurs in classic exstrophy (232). These are surgically corrected at the time of primary closure if they are small. However, cloacal exstrophy is typically associated with an omphalocele defect.

Neurologic System

Spinal cord abnormalities are the exception rather than the rule in bladder exstrophy. Occult spina bifida and even myelomeningocele can occur in combination with bladder exstrophy but this is a rare occurrence, especially in contrast to patients with cloacal exstrophy (20).

Epispadias

Epispadias is considered the least severe defect of exstrophy–epispadias complex and presents as a spectrum of severity as well. It does not involve the body of the bladder or the hindgut. Bladder function may be affected because of low urethral resistance during early development. This is the basis of the argument for early repair of epispadias with bladder neck involvement.

The defect in epispadias involves an absence of the dorsal aspect of the urethra and overlying skin extending to the bladder neck in the most severely affected proximal cases (Fig. 49B.9). The external genital anomalies described for the patient with exstrophy are noted with epispadias as well. These include lateral splaying of the penis and dorsal chordee in boys. In affected girls, the clitoris is bifid, the perineal body is broadened, and the vagina is anterior to its orthotopic position (Fig. 49B.10). Widening of the pubic diastasis occurs in epispadias as well although it is usually not as severe as that seen in classic exstrophy. Importantly, the bladder neck frequently is involved and is often wide and incompetent. This directly affects the continence mechanism of these children and their ability to achieve urinary continence. In untreated boys with epispadias, continence is

possible if the epispadias is located distally and the bladder neck is not involved. In girls, however, continence invariably is affected to some degree because of the urethral and bladder neck ectasia invariably involved in female epispadias. This is the basis of the argument for early repair of all girls with epispadias in an effort to maximize bladder function. Because of the shared features with bladder exstrophy, clinicians consider epispadias as part of a spectrum of exstrophy-epispadias complex.

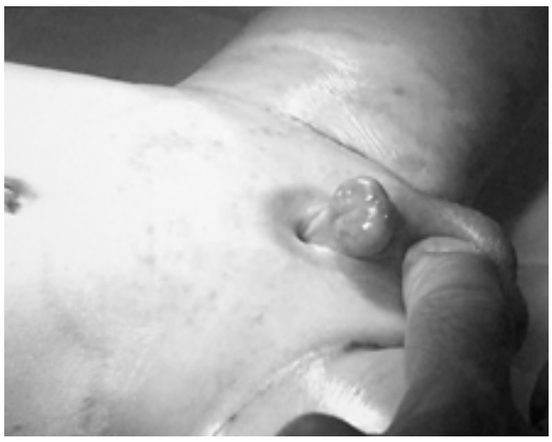

FIGURE 49B.9. Penopubic epispadias in 3-month-old boy. Skin demarcation is due to chronic urine contact dermatitis in this patient.

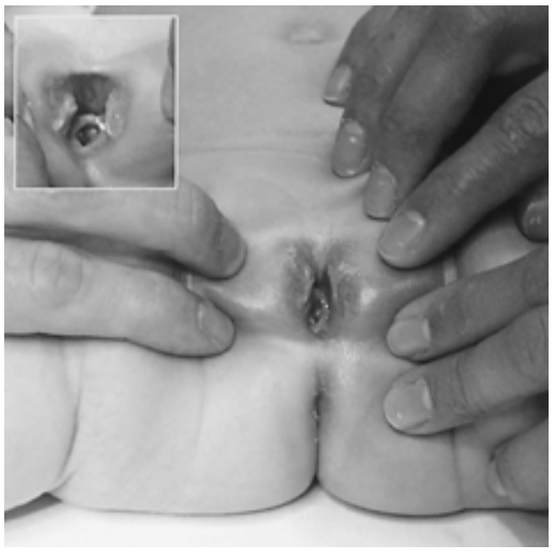

FIGURE 49B.10. Epispadias in 4-month-old girl. The anomaly affects the bladder neck and urethra. The clitoris is bifid.

Exstrophy Variants

Patients with atypical physical findings are categorized as exstrophy variant patients. These patients have some but not all of the typical features of bladder or cloacal exstrophy as well as other features not typically associated with classic bladder exstrophy or cloacal exstrophy. These include covered exstrophy and superior vesical fissure. Patients with exstrophy variants may have anatomically normal genitalia despite their bladder and colon anomalies (Fig. 49B.11).

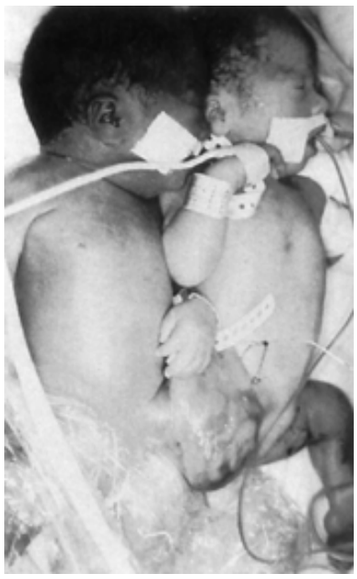

FIGURE 49B.11. Conjoined twins connected by membranous omphalocele sac containing a shared segment of distal ileum, cecum, and colon draining to a common exstrophic cloaca—an example of an exstrophy variant.

Bladder exstrophy variants include patients whose anatomic features resemble classic exstrophy in regard to the fascial and/or symphyseal defects but who do not have any significant anomaly associated with the urinary tract. These patients are considered to have pseudoexstrophy (125,144, 159,208). Some patients have an isolated ectopic bowel segment or anterior bladder wall defect in association with the previously mentioned findings; they are referred to as *covered exstrophy variants* (29). The sequestration phenomenon that occurs with these patients is not well understood embryologically. Other covered exstrophy variants include patients with overlying skin coverage of a bladder that possesses no anterior wall. These patients generally exhibit characteristics consistent with classic or cloacal exstrophy but initial evaluation is very deceiving. Therefore these patients invariably are incontinent of urine because the defect also involves their bladder neck.

Patients with superior vesical fissure also have the muscular and skeletal defects associated with bladder exstrophy, but only the upper portion of the bladder is affected so that the urethra may be intact and the genitalia are less affected than with classic exstrophy (125). In these patients, incontinence often is not a major problem.

A condition noted as duplicate exstrophy also has been described. Patients with this condition present with a duplicated lower urinary tract. However, one of the urinary tracts appears exstrophic. This duplication may not be recognized until the time of surgical exploration (194). Over nine cases of duplicate exstrophy have been reported in the literature since Marshall and Muecke's first description. Because the duplication anomaly can allow for a normal genitourinary system in one of the paired set of organs, treatment can be quite successful. However, these patients can have genital anomalies consistent with classic exstrophy as well; this association is variable. A subset population of this uncommon anomaly has been recognized and is more severely affected and more difficult to treat (3,164,176,194).

Possible etiologies for exstrophy variants include conjoined twinning or aborted conjoined twinning. Evidence of

conjoined twins with exstrophy variants has been described and would explain the duplication phenomena seen in some of these patients (78,81).

Incidence

Bladder exstrophy occurs at a rate of 1 per 10,000 live births to 1 per 50,000 live births (48,133). This anomaly has long been recognized to occur more commonly in males than females with a ratio of 2.3 to 4:1 reported in the literature (111,49). Cloacal exstrophy occurs even more rarely with an incidence of 1 in 200,000 to 1 in 400,000 live births (235).

Genetic factors involved in exstrophy remain incompletely defined. To date, eighteen familial cases of bladder exstrophy have been reported, the most recent of which describes a mother and son with bladder exstrophy (152). In 1984, a survey of pediatric urologists and surgeons, reported 9 cases related to 2,500 index cases of bladder exstrophy; this same series also reported on cases of twins and noted discordance in both fraternal and identical twinships (192). Furthermore, in a study population of more than 6 million births with 208 reported cases of exstrophy, no case had a family history for this anomaly (115). Current recommendations on counseling about risk of recurrence in a sibling of a patient with exstrophy cite an estimate of approximately 1% and a 1:70 chance of transmission to the progeny of an affected parent (152). Based on these findings, bladder exstrophy appears likely to be multifactorial rather than genetically based; environmental factors may play a significant role in the cause of the exstrophy-epispadias complex.

Antenatal Diagnosis

Prenatal identification of exstrophy is possible. The bladder may be visualized at 11 to 12 weeks of gestation and the kidneys at 14 to 15 weeks; both become more obvious with advanced gestational age so that ultrasonography can reliably detect exstrophy before the twentieth week of gestation (8,18,19,70,132,148,154,171,177). Absence of the bladder is a hallmark of exstrophy but several findings also suggest the diagnosis. These include the presence of normal kidneys in association with a low-set umbilical cord. Sonographic examination also may reveal a semisolid mass protruding from the abdominal wall in addition to the above findings (10,112) (Fig. 49B.12). Gearhart and co-workers reviewed the antenatal ultrasonographic studies of 25 women who delivered live infants with exstrophy. They noted the following:

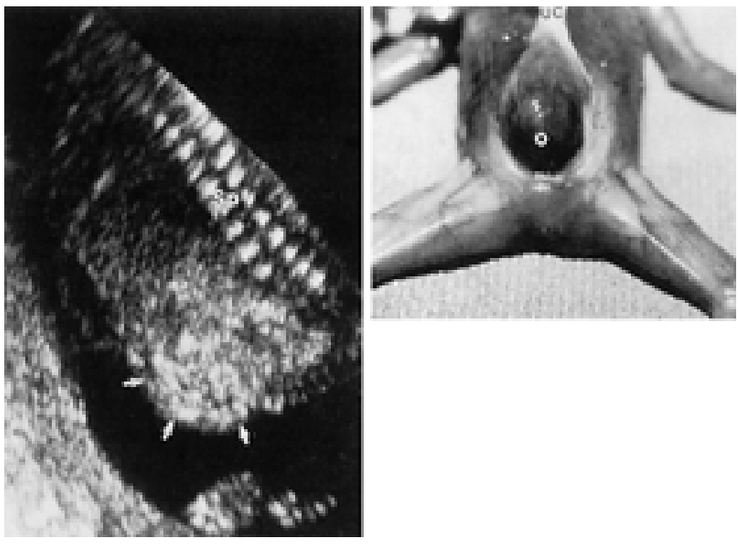

FIGURE 49B.12. Antenatal sonogram of fetus with exstrophy and photograph of fetus with confirmed exstrophy at autopsy. (Adapted from Mirk P, Calisti A, Fileni, A. Prenatal sonographic diagnosis of bladder exstrophy. *J Ultrasound Med* 1986;5:291, with permission.)

- An absent bladder in 71% of the studies
- A lower abdominal protrusion in 47% of the studies
- An anteriorly displaced scrotum with a small phallus in 57% of the male fetuses
- A low-set umbilical cord in 29% of the studies
- An abnormal iliac crest widening in 18% (70)

Because urine production is normal for these fetuses, amniotic fluid levels should be normal. Prenatal diagnosis allows optimal perinatal management of these infants, including delivery near a pediatric center equipped to treat babies with this unusual anomaly. Unfortunately, many affected fetuses are still not detected antenatally (196). In Gearhart's review of 29 antenatal studies of 17 children born with exstrophy, only 3 were identified before delivery despite the presence of findings to suggest the diagnosis (70). Subtle findings such as low umbilical cord insertion and the location of the genitalia will only be seen if the fetus is examined in a sagittal alignment with the spine (189). Because of the abnormal genitalia findings, the diagnosis is easier to make in males than females. Iliac crest widening also can be seen during the routine prenatal evaluation of the lumbosacral spine that is performed to evaluate for myelomeningocele. The iliac angle will be approximately 110 degrees rather than the 90 degrees normally seen (189).

Antenatal diagnosis allows the parents the opportunity to discuss early management of the patient. The early counseling should include the expertise of a pediatric urologist experienced in the treatment of bladder exstrophy. The overall prognosis of these children is excellent, if initial treatment is at medical centers with physicians experienced in the treatment of this disorder. Unfortunately, because of the rarity of bladder exstrophy, health care providers who lack insight and knowledge of this disorder often counsel prospective parents of these patients. The resultant counseling of these families by health care providers who are unaware of the true potential of patients with bladder exstrophy has led to an increase in the abortion rate of these fetuses. This is unfortunate in view of the very satisfactory long-term outcome and life expectancy that are possible with appropriate management (19).

THE NATURAL HISTORY OF EXSTROPHY

> Exstrophy of the bladder, unless the patient is willing to assume the (often mortal) risk of an autoplastic operation, is utterly irremediable; all that can be done is to palliate the patient's suffering by attention to cleanliness, and by the use of a closely-fitting flexible gutta-percha shield, furnished with a gum-elastic bottle for receiving urine… When this cannot be obtained, the part must be kept constantly covered with a thick, soft compress, renewed as often as it becomes wet and disagreeable. The skin around may be protected, if necessary, with pomatum, simple cerate, or zinc treatment" (84).
>
> —Samuel Gross, 1876

Because the bladder exstrophy–epispadias complex is not a lethal condition, children with bladder exstrophy or exstrophy can survive untreated. Before the modern era of surgery and anesthesia, some patients with bladder exstrophy survived untreated into adulthood. Reports exist of such patients with classic bladder exstrophy living into their eighth decade (169). In contrast, until recently, patients born with cloacal exstrophy died shortly after birth from electrolyte abnormalities and malnutrition. However, the morbidity bladder exstrophy patients experienced was often severe as a result of bladder and kidney infection, skin breakdown, and tumor formation in the bladder plate. Patients left untreated often covered the exposed bladder with various undergarments, including liniment soaked rags, cotton, and wool bolsters, resulting in chronic bladder plate irritation. The surrounding skin around the exstrophic bladder was often inflamed secondary to urine contact dermatitis, loss of skin integrity from constant wetness, and secondary infection. D.I. Williams noted in the 1960s that "inevitably, most untreated exstrophy children are very irritable and bad-tempered and their crying only serves to accentuate their umbilical hernia, their inguinal herniae, and their rectal prolapse"(220). These patients are often social pariahs because of associated odor and hygiene problems. This sad state of affairs prompted these patients to seek treatment and physicians who used heroic measures to help these patients.

Surgical Reconstruction—Early Efforts

The morbidity of exstrophy led surgeons to begin empiric approaches to the operative correction of this anomaly. Surgeons in the nineteenth century attempted urinary reconstructive or diversion procedures to treat these patients. Initial efforts were directed at partial reconstruction of the abdominal wall to allow the application of a urinary receptacle to collect urine. The first successful record of this form of repair is attributed to Dr. Pancoast in 1859. He used skin flaps from the abdominal wall:

> In the treatment of exstrophy of the bladder the principal objects aimed at are either to establish a channel for the conveyance of the urine to the rectum or perineum, or to cover its exposed and sensitive mucus membrane with flaps of skin, thereby protecting it from contact of the clothing, and preventing excoriation of the surrounding parts, as well as facilitating the adjustment of an apparatus for receiving the urine (84).
>
> A flap is taken from one side of the abdomen or groin, dissected up, and turned over like the leaf of a book so that the epidermis comes into contact with the mucous membrane. A second flap is then taken from the groin on the opposite side and its raw surface applied to the raw surface of the former flap…thus a thick bridge is formed over the cleft (36).

Dr. John Wood and F.F. Maury also described variations on the use of skin flaps to reconstruct the abdominal wall (84,221). Wood used a full thickness skin graft from the abdominal wall followed by a lateral, pyriform flap from each groin held in place with hare-lip pins, wire sutures, and broad straps of adhesive plaster, which were removed 6 to 8 days after surgery (Fig. 49B.13). In contrast, Maury created perineal and scrotal skin flaps to repair bladder exstrophy. These procedures represented early attempts at anatomic closure but did not address the functional reconstruction of these bladders—namely to achieve satisfactory storage and emptying of urine. V.H. Van Buren aptly stated the common sentiment of the time:

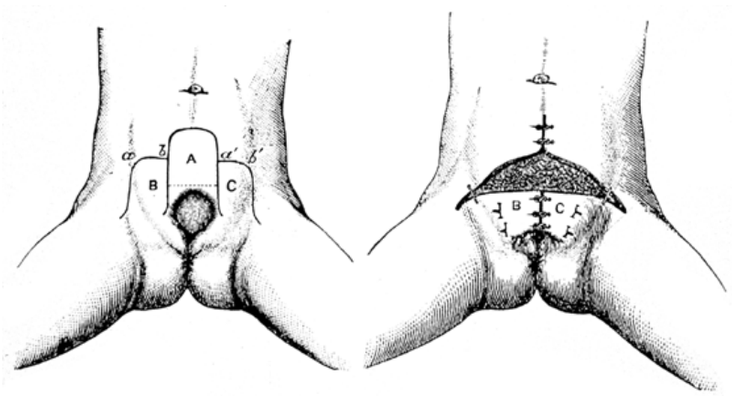

FIGURE 49B.13. Early operation for bladder exstrophy as proposed by Maury in the midnineteenth century. This operation was designed to create skin flaps to narrow the urinary outlet so that an appliance could be applied to collect urine.

> The most that can be promised by operative interference is to leave behind a fistula, more or less large, over which a urinal must be constantly worn. The patient's virility is not returned to him, nor is his condition very materially bettered. A less dangerous and equally efficacious mode of treatment seems to be to adapt a suitable urinal to the parts as they are left by Nature, such a one as shall shield them from injury, and keep the patient dry and clean (214).

Others, such as Simon, approached the surgical treatment by attempting urinary diversion in these patients through the creation of a ureteral sigmoid fistula. Results were poor: one patient died of peritonitis in the immediate postoperative period, and the other died of renal failure secondary to chronic pyelonephritis (84).

These early efforts suffered from lack of understanding of the physiology of the urinary tract and bladder and subsequently how these operations would affect urine storage and

emptying, kidney function, electrolyte homeostasis, the propensity for urinary tract infection (UTI) or calculus formation, fertility, and sexual function. Complications from these operations were often life threatening. That patients were willing to assume this risk in the treatment of this anomaly demonstrates the impact it had on their lives.

SURGICAL RECONSTRUCTION OF EXSTROPHY/EPISPADIAS—THE MODERN ERA

Modern objectives for reconstruction in the treatment of exstrophy can be placed broadly in the categories in Table 49B.2 .

TABLE 49B.2. MODERN OBJECTIVES FOR RECONSTRUCTION IN THE TREATMENT OF EXSTROPHY

Primary Goals	Secondary Goals
Preservation of kidney function	Minimization of urinary tract infections
Urinary continence	Adequate pelvic floor support
Low pressure urine storage reservoir	Minimization of the risk for malignancy associated with the urinary tract
Volitional voiding	Minimization of the risk for urinary calculi
Functionally and cosmetically acceptable external genitalia	Adequate abdominal wall fascia

Although these goals are straightforward and interconnected, successful achievement of them often remains elusive. In fact, many of the secondary goals address complications that can arise as a result or complication of surgical procedures used to treat exstrophy. Numerous operations have been devised for the treatment of bladder exstrophy testing the ingenuity of the physicians involved in the care of these patients as well as the resilience of the patients themselves. The objectives underlying these operations have expanded since the first operations were proposed and attempted beginning in the 1800s. These objectives address the primary pathology and problems associated with exstrophy and its management (Table 49B.3).

TABLE 49B.3. PRIMARY PATHOLOGIES AND PROBLEMS ASSOCIATED WITH EXSTROPHY AND ITS MANAGEMENT

Primary Pathophysiology (Untreated)	Complications (Associated with Management of Exstrophy)
Urinary incontinence Bladder malignancy	Malignancy (related to the use of intestine in bladder reconstruction), hydronephrosis
Urinary tract infection, reflux	Pyelonephritis, stones
Chronic bladder irritation	
Pelvic floor insufficiency	Cystocele, uterine prolapse
Symphyseal diastasis, pelvic flattening	Abnormal hip dynamics, back pain
Abdominal wall defect	
Severe penile shortening with dorsal chordee Ventral and inguinal hernias	Inadequate phallus in males with subsequent social and psychologic sequelae

Modern Operative Approaches to Exstrophy

Despite the innumerable operations that have been applied to the treatment of exstrophy, operations for exstrophy currently fall largely into two strategies. The first includes operations designed to remove the exstrophic bladder and replace it with a form of urinary diversion. The second includes reconstructive procedures designed to reconstruct the bladder either in multiple stages or in a single stage. Surgeon preference, patient anatomy, previous surgical procedures, availability of tertiary care facilities, and access to medical care all play a role in which operative procedures are chosen. No standard of care exists for this patient population. However, because of the complexity of exstrophy, specialists with an interest in the exstrophy–epispadias complex best manage these patients by tailoring their care to each patient's situation.

Perioperative Care

Preoperative Care

To prevent trauma to the exposed bladder plate after delivery, the umbilical cord should be ligated with silk suture rather than a plastic or metal clamp. The exstrophic bladder should be protected against the elements by whatever means are available. We prefer a hydrated gel dressing such as Vigilon. This type of dressing protects the bladder plate and stays in place to allow handling of the infant with minimal risk of trauma to the bladder. We have used this dressing for over 2 months for infants who could not undergo immediate repair because of severe prematurity; we noted minimal inflammation of the bladder at the time of total primary repair. The exposed bladder may be covered with plastic wrap as an acceptable alternative. Either dressing should be replaced daily. The bladder should be irrigated with normal saline with each diaper change. Other authors have advocated the use of a humidified air incubator with no dressing at all to minimize bladder trauma (30).

Routine use of intravenous antibiotic therapy in the preoperative and postoperative periods decreases the chance

for infection. We also routinely perform ultrasonography to assess the kidneys preoperatively and to establish a baseline examination for later ultrasonographic studies. A spinal sonographic examination also should be obtained if sacral dimpling or other signs of spina bifida occulta are noted on physical examination.

Operative Considerations—Initial Closure

In the newborn period, we perform primary exstrophy closure using general inhalation anesthesia. We advise against the use of nitrous oxide during primary closure because it may cause bowel distention, which decreases surgical exposure during the operation and increases the risk of wound dehiscence. Some authors advocate the use of nasogastric tube drainage to decrease abdominal distention in the postoperative period (59). We do not use nasogastric suction in most patients, but routinely use a one-time caudal block to reduce the inhaled anesthetic requirement during the procedure.

For patients older than 3 days or newborns with a wide pubic diastasis, pelvic osteotomy will facilitate closure and strengthen the anterior pelvic support that may potentiate later urinary continence (1,14).

Several groups of investigators have reviewed their patient series in an effort to identify factors that increase the success of the initial reconstruction. These include several factors that are important in the operative period:

- Use of osteotomies in selected cases and for newborn closures more than 24 to 48 hours after birth
- Ureteral stenting catheters placed intraoperatively for use in the postoperative period to divert urine
- Avoidance of abdominal distention
- Use of intraoperative antibiotics (107,140)

Postoperative Considerations

After a primary reconstructive procedure for exstrophy, the patient must be immobilized to decrease lateral stresses on the closure. Use of a spica cast for 3 weeks to prevent external hip rotation and optimize pubic apposition can facilitate early discharge and home care (Fig. 49B.14). Modified Buck's traction has been used by many groups for a period of 3 to 4 weeks. A posterior lightweight splint can be used in newborns when the child is out of traction to facilitate home care and early removal of traction. Over the years, we have tended not to use Buck's traction to facilitate earlier discharge and ease of care. External fixation devices also have been advocated by several centers. Fixator pins for these devices should be cleaned several times a day to reduce the chance for infection. Internal fixation may be necessary in older patients. “Mummy wrapping” should *not* be used to immobilize the pelvis because it is unreliable (59).

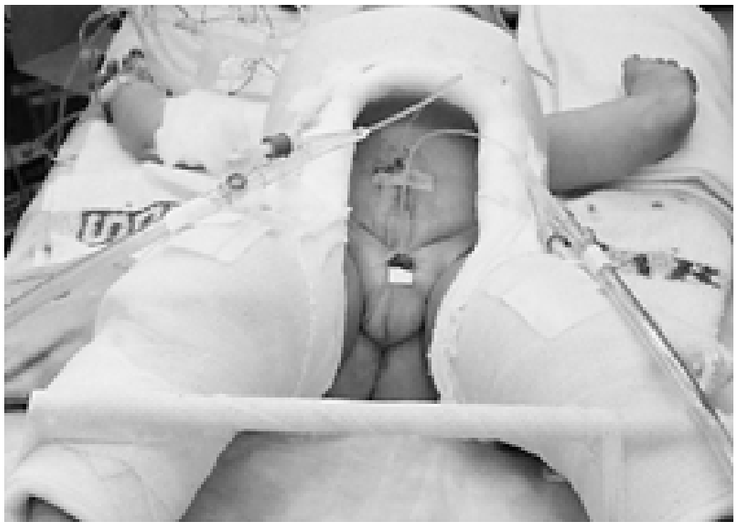

FIGURE 49B.14. Use of Spica cast following complete primary repair for exstrophy to reduce tension on the closure by preventing hip abduction in the postoperative period.

Because of the high incidence of vesicoureteral reflux, we prescribe low-dose suppressive antibiotic therapy for all newborns after bladder closure. This is continued until vesicoureteral reflux is corrected or is proven to resolve spontaneously. Postoperative factors that appear to directly affect the success of initial closure include the following:

- Postoperative immobilization
- Use of postoperative antibiotics
- Ureteral stenting catheters
- Adequate postoperative pain management
- Avoidance of abdominal distention
- Adequate nutritional support
- Secure fixation of urinary drainage catheters (107,140)

APPROACHES TO FUNCTIONAL RECONSTRUCTION

Reconstruction of the exstrophic bladder to achieve normal function and anatomy remains the primary goal in treatment. This end point defines the current surgical challenge of exstrophy. Canning and colleagues stated it well: “Both the surgeon and the parent feel tremendous excitement when a child voids to completion following a successful reconstruction”(23).

The first efforts at anatomic reconstruction of the exstrophic bladder usually are attributed to Trendelenburg who described his efforts to reconstruct a boy with exstrophy at the turn of the century (213). He emphasized the importance of pubic reapproximation in front of the reconstructed bladder to achieve continence and prevent dehiscence. Unfortunately, his patient ultimately did not achieve urinary continence despite initial urinary control following his operation. Discouraging results such as this led most surgeons in the first part of this century to abandon functional reconstruction of exstrophy. Instead, most surgeons advocated cystectomy and urinary diversion. Ureterosigmoidostomy became the preferred approach to the treatment of exstrophy with no attempt made to salvage the

exstrophic bladder. Ureterosigmoidostomy remains the first treatment choice in some areas of the world and offers a reliable means to achieve urinary continence for patients who may not have reliable access to health care facilities or who have not achieved urinary continence despite attempts at functional reconstruction (205).

Despite the common use of urinary diversion to manage bladder exstrophy in the early twentieth century, some surgeons still attempted functional reconstruction for these children. However, successful results were not achieved reproducibly. H.H. Young reported a successful primary bladder closure in 1942, when he achieved urinary continence after reconstructing the exstrophic bladder of a young girl (233). Since Young's report in 1942, other investigators have intermittently achieved a satisfactory result with a one-stage reconstructive effort to repair the exstrophied bladder. Ansell, an early advocate for primary reconstruction of the newborn with exstrophy reported on a one-stage closure in 1971 with a successful outcome in a newborn female (4). He eventually reported 28 cases closed in this fashion (5). Montagnani also described a one-stage functional bladder reconstruction in two female babies, aged 8 and 13 months. His bladder reconstruction procedure included innominate osteotomy, bladder closure, an antireflux procedure, and narrowing of the bladder outlet followed by pubic reapproximation. Continence was achieved in one of the two patients. The second patient required further bladder neck reconstruction (BNR) to achieve continence (162). Fuchs achieved urinary continence in 8 of 15 patients who also were repaired in a single-stage effort (55). However, several large series of patients who underwent single-stage reconstruction in the 1960s and 1970s reported continence rates of only 10% to 30%. Specifically, continence rates ranged from 0% to 45%, with an average of 17% for single-stage reconstruction (28,47,51,149,119,124,145,219). Renal damage was as high as 90% in these series, generally because of bladder outlet obstruction (124) (Fig. 49B.15).

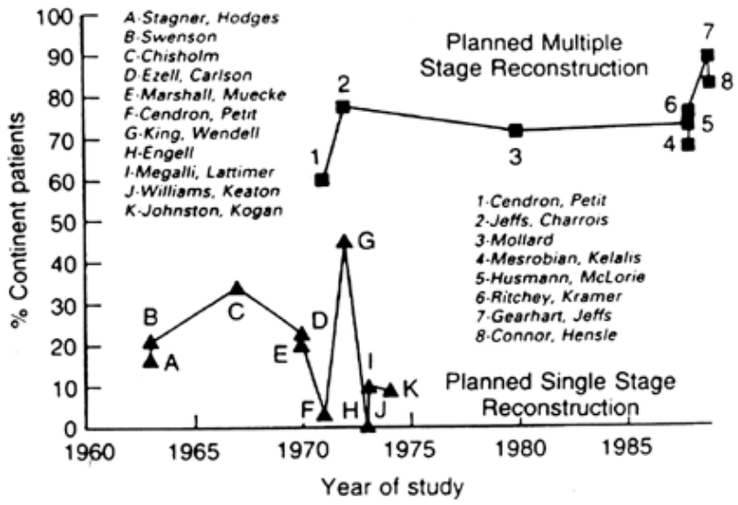

FIGURE 49B.15. Historical data on continence rates in planned multiple-stage versus planned single-stage reconstruction. (Adapted from Churchill B, Merguerian PA, Khoury AE, et al. Bladder exstrophy and epispadias. In: O'Donnell BA, Koff S, eds. *Pediatric urology,* 3rd ed, vol 1. Oxford: Reed Elsevier, 1997:495, with permission.)

Because of these complications and the low rate of urinary continence, reconstructive surgical efforts subsequently were directed toward staged bladder reconstruction, an approach pioneered and advocated by Dr. Robert Jeffs and others (116,188). More recently, Mitchell, Fuchs, Kelly, and others have advocated new techniques of single-stage reconstruction for exstrophy that appear to be safer than techniques used in the past. Continence rates in these series approach or equal those reported in series using a staged surgical reconstruction approach (55,82).

Staged Reconstruction

In contrast to the high rate of renal damage reported by multiple centers using a single-stage reconstructive effort to bladder exstrophy in the 1970s, the complication rate from a staged reconstruction approach appeared significantly better at that time. Jeffs and colleagues reviewed their results with staged reconstruction at Toronto Sick Children's Hospital and noted normal upper urinary tracts in 87% (42). Later series from Johns Hopkins also achieved low rates of renal damage (12% and 17%, respectively) (136,167).

Continence rates for the patients treated with a staged reconstructive approach at selected medical centers have been reported as high as 88% (volitional voiding with 2- to 3-hour continence intervals). In particular, initial and subsequent reports of staged reconstruction, most notably by Jeffs and co-workers, demonstrated continence rates of 60% to 88% (61,107,117,151,160,186). These results prompted a shift from single-stage reconstruction to planned multiple stage reconstruction in the reconstructive approach to bladder exstrophy. Planned staged reconstruction (the Jeffs approach) subsequently became the gold standard to reconstruction of the exstrophic bladder.

Unfortunately, the success using the staged approach to functional reconstruction has not been reproducible at other centers, even centers experienced in the care of children with exstrophy. Rates of urinary continence are as low as 9% with the need for CIC to achieve urinary dryness in as many as 60% of these patients (23,97,120,226). These series reflect the variable success of staged reconstruction. Conversion rates to urinary diversion for patients with a failed repair after staged reconstruction range from 7.4% to 59.4% (151,161,226). Nonetheless, the staged approach to exstrophy reconstruction currently remains the most common method used to treat bladder exstrophy in North America and many other parts of the world.

As currently described, the staged approach to bladder exstrophy reconstruction includes the following steps:

1. *Initial bladder closure*—ideally in the newborn period.
2. *Epispadias repair*—usually performed at 12 to 18 months of age but may be combined with initial bladder closure,

especially if initial bladder closure is delayed beyond 6 months of age.

3. *BNR*—usually performed at 4 to 5 years of age or when age appropriate for toilet training and bladder capacity is adequate.

Single-stage Reconstruction

Mitchell, Kelley, and others have recently repopularized a single-stage approach to the functional reconstruction of exstrophy. The goals of this approach include bladder closure, optimization of urinary continence, and correction of epispadias in a single operative procedure. Single-stage reconstruction of the exstrophied bladder is best done in the newborn period for several reasons. The procedure is technically easier in the newborn period than when done in an older child. It also offers theoretic advantages because it may maximize the opportunity for normal bladder development and the potential for urinary continence. The delayed use of the total disassembly technique with primary reconstruction (Mitchell technique) in older children with untreated exstrophy has been shown to be less successful than when used in the newborn period (86). The bony pelvis also remains pliable in the newborn period so that osteotomies may be avoided in some cases, usually if closure can be performed within the first 72 hours of life. While single-stage reconstruction currently remains the surgical approach of a minority of surgeons, several centers have reported the successful use of the total disassembly approach with primary reconstruction for exstrophy (82,87,129).

We favor the total disassembly technique with complete primary exstrophy repair (CPER) for single-stage reconstruction of exstrophy, which is the single-stage technique described in this chapter (82,83). This technique corrects a problem inherent in a primary closure using a staged technique. The principle defect in exstrophy is the anterior position of the bladder plate, bladder neck, and urethra. Closure of only the bladder without moving the urethra posteriorly into the pelvic diaphragm results in a compromise in the restoration of normal anatomy. CPER moves the bladder, bladder neck, and urethra posterior in the pelvis. This positions the proximal urethra within the pelvic diaphragm in an anatomically normal location to maximize the effect of the pelvic muscles and support structures in the achievement of urinary continence. Posterior movement of the bladder neck and urethra also facilitates approximation of the pubic symphysis that, in turn, helps prevent anterior migration of the urethra and bladder neck and provides a more anatomically normal muscular pelvic diaphragm.

In the male, total penile disassembly as part of the exstrophy closure reduces anterior tension on the urethra because the urethra is separated from its attachments to the underlying corporal bodies. These attachments otherwise pull the urethral plate anterior, preventing posterior placement of the proximal urethra and bladder neck in the pelvis. Tension reduction decreases the risk of bladder dehiscence and also reduces the dorsal tension on the corporal bodies that may contribute to dorsal chordee in males. Combining the epispadias repair with primary closure allows for the most important aspect of primary closure—deep incision of the intersymphyseal ligament or band located posterior to the urethra in these patients. To incise this ligament, the urethra must be separated from the corpora cavernosa, tubularized, and relocated within the pelvic diaphragm.

Neonatal closure using this technique seems to optimize the chance for early bladder cycling and consequent normal bladder development. It also may obviate the need for a multistaged repair of the exstrophied bladder, including further BNR, bladder augmentation, and penile reconstructive surgery.

INITIAL BLADDER CLOSURE

Initial bladder closure may be performed using either a staged approach or a single-stage reconstructive effort, such as the total disassembly technique described by Mitchell or the technique described by Kelly. The operative techniques for each are different. The goals of initial bladder closure using a staged approach include a secure closure with a patent bladder outlet to allow drainage of urine from the bladder at low pressures. In the staged approach, no attempt is made to address lack of bladder neck continence or epispadias. In contrast, a single-stage reconstruction intentionally addresses every anatomic component affected by exstrophy. Certain principles remain constant. The use of osteotomies, if indicated; effective urinary drainage; use of antibiotics; and postoperative immobilization appear important to the success of both approaches (67,82).

Primary Bladder Closure—Staged (Jeffs) Approach

For any reconstructive surgical procedure, careful planning and attention to technique are important. To begin the initial bladder closure, ureteral catheters are placed to aid in ureteral visualization before making the initial incision. These may be secured with 5-0 or 6-0 chromic suture. Initial dissection begins with a circumferential incision around the bladder plate. This can be initiated at the umbilicus. The underlying detrusor muscle is mobilized from the rectus sheath to expose the peritoneum. Extraperitoneal dissection lateral to the bladder exposes the retroperitoneal space and identifies the intersymphyseal band. This band should be incised on each side of the prostatic urethra to allow the bladder and bladder neck to be placed deep into the pelvis (Fig. 49B.16). The inferior portion of the dissection is carried distally to the level of the verumontanum in boys and to the vaginal orifice in girls. After a suprapubic tube has been placed, the bladder is closed in the midline in layers with a running 3-0 absorbable suture (Fig. 49B.17).

The posterior urethra also is closed onto the base of the penis over a 14-Fr catheter. The urinary outlet should be located at the base of the penis in boys or above the vaginal orifice in girls (Fig. 49B.18). To reapproximate the pubis symphysis, 0 PDS or no. 2 nylon suture also has been used; a figure-of-eight suture with the knot placed anteriorly decreases the chance for suture erosion into the bladder. The umbilicus may be used as the site to bring the urinary drainage catheters out to the skin. Paraexstrophy flaps and division of the urethra should be avoided during primary closure because of the high rate of complications associated with their use (68). Some surgeons also discourage the use of urethral catheters during the postoperative period. Instead, ureteral catheters are used to divert urine and avoid postoperative urinary retention (63).

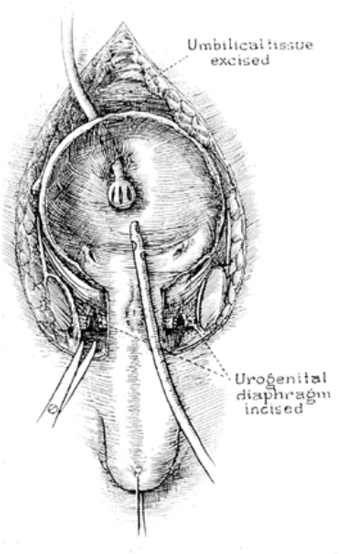

FIGURE 49B.16. In the staged closure of bladder exstrophy, the bladder is mobilized from adjacent structures. The urogenital diaphragm (intersymphyseal band) must be incised to allow the bladder to be positioned posteriorly. However, the proximal penile dissection is incomplete. (Adapted from Gearhart J, Jeffs R. Surgical repair of exstrophy/epispadias. In: Marshall F, Peters C, eds. *Textbook of operative urology.* Philadelphia: WB Saunders, 1996:900, with permission.)

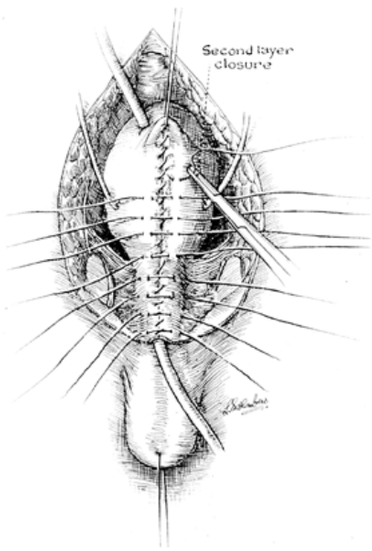

FIGURE 49B.17. The bladder and proximal urethra are closed in continuity over a urethral catheter that will be removed at the end of the operation. (Adapted from Gearhart J, Jeffs R. Surgical repair of exstrophy/epispadias. In: Marshall F, Peters C, eds. *Textbook of operative urology.* Philadelphia: WB Saunders, 1996:900, with permission.)

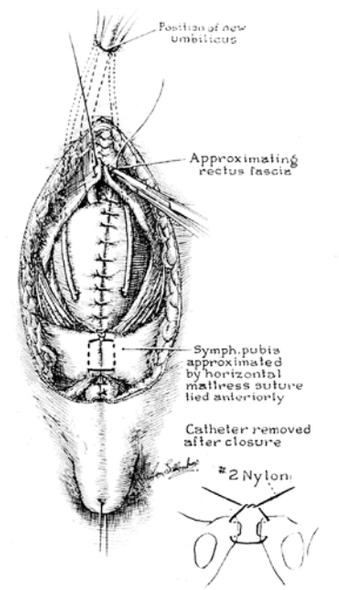

FIGURE 49B.18. After bladder and urethral closure, the pubis symphysis is reapproximated. The urethral opening is left at the base of the dorsum of the penis. (Adapted from Gearhart J, Jeffs R. Surgical repair of exstrophy/epispadias. In: Marshall F, Peters C, eds. *Textbook of operative urology.* Philadelphia: WB Saunders, 1996:900, with permission.)

Bladder Closure—Total Disassembly Technique with Complete Primary Exstrophy Repair (CPER or Mitchell Repair)

The basic concept of this repair is that the bladder, bladder neck, and urethra (entire urethra) should be considered as a

unit. Therefore the bladder neck and bladder cannot be effectively moved posterior without also mobilizing the *entire* urethra. Care in performing this technique is paramount to success. Before initiating the dissection, we place 3.5-Fr umbilical artery catheters into both ureters and suture them in place with 5.0 chromic suture. To aid in dissection, traction sutures are placed into each hemiglans of the penis (Fig. 49B.19). These sutures are initially oriented transversely in the hemiglans. They will rotate to a parallel vertical orientation as the corporal bodies rotate medially after dissection of the corporal bodies and urethral wedge (urethral plate plus underlying corpora spongiosa) from each other. Initial dissection is directed at separating the bladder plate from the adjacent skin. This dissection is then carried inferiorly (Fig. 49B.20). Fine-tip (tungsten) electrocautery (Colorado tip) is used in performing this dissection. Because the bladder and urethra including spongiosa are moved posteriorly in the pelvis as a unit, the urethra cannot be divided. However, in some cases, the urethra may be too short in the male patient; therefore he would be left with a hypospadias that will require later urethroplasty. The use of paraexstrophy flaps are never necessary or appropriate in this repair (68).

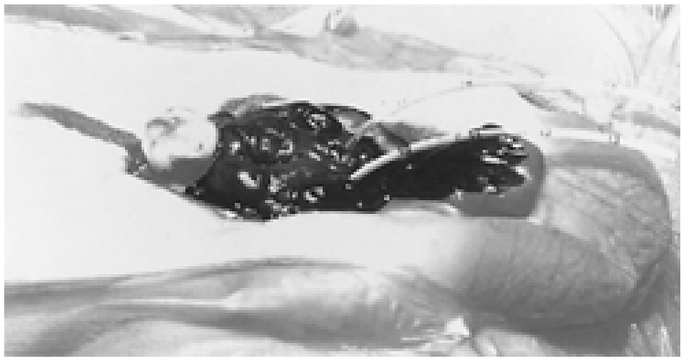

FIGURE 49B.19. Colored markings indicate lines of initial dissection for total disassembly technique with complete primary exstrophy repair (Mitchell repair). A 3.5-Fr umbilical artery catheter is secured in each ureter. The incision will be carried above the umbilicus to allow the umbilicus to move to a more anatomically normal position. The highlighted region represents the area of dissection.

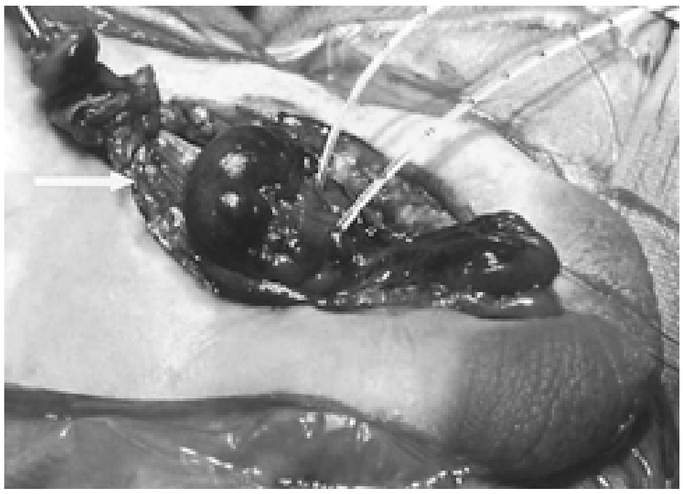

FIGURE 49B.20. The dissection begins at the superior aspect of the bladder plate *(white arrow)* and continues toward the bladder neck. The bladder is dissected from the attachments to the fascia laterally. The bladder neck is then dissected from its lateral attachments and the intersymphyseal band is divided to allow the bladder, bladder neck, and urethra to move posteriorly.

We begin the penile dissection along the ventral aspect of the penis as a circumcising incision (Fig. 49B.21). This should precede dissection of the urethral wedge from the corporal bodies because it is easier to identify Buck's fascia ventrally. The plane of dissection is between Buck's fascia and the overlying tissue on the lateral and ventral aspect of the penis. Staining the dorsal urethral plate with methylene blue or brilliant green facilitates dissection of the urethral wedge. Injection of the surrounding tissues with 0.25% lidocaine and 1:200,000 U/mL epinephrine also improves hemostasis, which assists the dissection. The plane of dissection is on the medial aspect of the corpora cavernosa on the tunica albuginea. There is no Buck's fascia on the medial aspect. One should take care not to narrow the urethral plate because this will be tubularized later. The urethral plate is actually a wedge of spongiosa tissue that extends between the corpora cavernosa. Urethral wedge dissection is carried proximally to the bladder neck. Careful lateral dissection of the penile shaft skin and dartos fascia from Buck's fascia on the corporal bodies is very important because the neurovascular bundles usually are located in this lateral position on the corpora (225) (Fig. 49B.22).

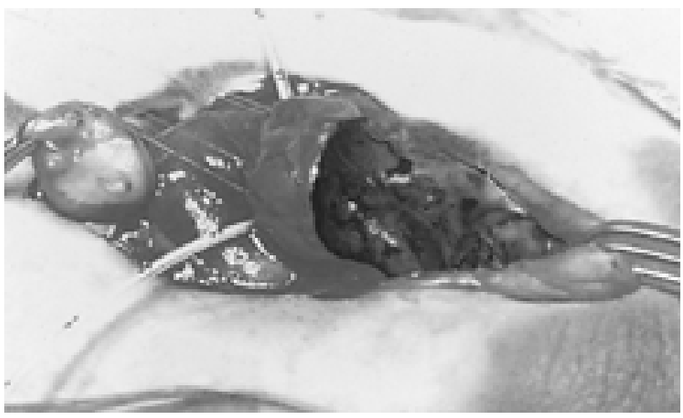

FIGURE 49B.21. During the initial dissection, performing a circumcising incision degloves the penis. The ventral approach seen here (retractor pulling tissue back) is the most efficient way to identify a plane between the corporal bodies and the urethral wedge. The highlighted area represents the ventral aspect of the corporal bodies.

FIGURE 49B.22. Separation of the corporal bodies from each other and the urethral wedge. The highlighted area represents the urethral wedge as it is dissected away from the corporal body. Care must be taken with lateral dissection to avoid damage to the neurovascular bundles.

As described by Mitchell and Bagli (157), the penis is ultimately disassembled into three components—the right and left corporal bodies with their respective hemiglans and the urethral wedge (urothelium with underlying corpora spongiosa) (157). This dissection is easiest to initiate proximally and ventrally. The plane of dissection should be at the level of the tunica albuginea on the corpora. Once a plane is

created between the urethral wedge and the corporal bodies, the dissection is extended distally to separate the three components from each other. The hemiglans may be completely separated from each other because they depend on a separate blood supply based on the paired neurovascular bundles. It is important to keep the underlying corpora spongiosa with the urethral plate: The blood supply to the urethral plate is based on this corporal tissue, which should appear wedge-shaped after its dissection from the adjacent corpora cavernosa (Fig. 49B.23). This urethral/corporal spongiosal component later will be tubularized and placed ventral to the corporal bodies.

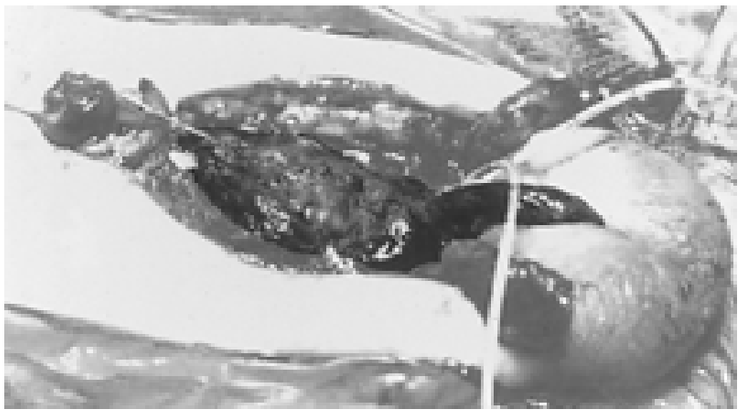

FIGURE 49B.23. This dissection is then carried proximally to separate the proximal corpora from the bulbar urethra. The phallus and urethra can then be separated into three components—the corpora with hemiglans and the urethral wedge. The bladder and a portion of the urethra have been reapproximated here. They have been highlighted in this photograph. The corporal bodies remain separate.

Proximal dissection of the urethral wedge from the corporal bodies is critical to the posterior placement of the bladder neck and proximal urethra. Bilateral deep incisions of the intersymphyseal band lateral and poster to the distal prostatic urethra are absolutely necessary to allow the bladder, the bladder neck, and proximal urethra to achieve a posterior position in the pelvis. Failure to adequately dissect the bladder and urethral wedge from these surrounding structures creates anterior tension along the urethral plate and prevents posterior movement of the bladder in the pelvis.

Once the bladder and urethral wedge are adequately dissected from the surrounding tissues, they can be closed (usually the peritoneum is not entered in this process). Before reapproximating the bladder, a suprapubic tube is placed and brought out through the umbilicus, which is usually moved cephalad to a more anatomic position. The bladder is closed using three layers of monofilament absorbable suture. The urethra is tubularized using a two-layer running closure with monofilament suture as well. We have not performed ureteral reimplantation at this time, although this may be considered. However, the bladder is not normal at this point, and antireflux surgery may negatively affect the potential for development (i.e., scarring rather than transition to normal detrusor).

At this point, the bladder, bladder neck, and urethra can be moved posteriorly deep into the pelvis and incised pelvic diaphragm. The symphysis can be closed *without* pressure on the urethra or bladder neck because these structures are moved posterior within the pelvis (Fig. 49B.24 and Fig. 49B.25). It is critical that the symphyseal sutures (usually

2 to 3 figure-of-eight 1-0 PDS) be placed firmly into the symphyseal tissues and tied anterior to the symphysis. Once the symphysis is reapproximated, the blood supply to the corpora cavernosa of the penis should be carefully assessed. If there is any question of reduced corporal perfusion, either the symphysis sutures need to be replaced and/or osteotomies considered. This occurs rarely in newborn classic exstrophy closures, but can happen in a larger patient with wide symphyseal diastasis and is particularly common in cloacal exstrophy patients. Do not try to do too much because staging the initial closure can be effective in these patients. Rectus fascia is reapproximated using a running 2.0 polydioxanone suture. The tubularized urethra is located ventral to the corporal bodies following pubic reapproximation. The corporal bodies tend to rotate medially; this rotation assists in correcting the dorsal chordee and can be readily appreciated by observing the vertical lie of the previously horizontally placed glans traction sutures. Occasionally, significant discrepancies in the dorsal and ventral lengths of the corpora will require dermal graft insertion. However, this is rarely needed in newborns. The corpora are reapproximated with fine interrupted sutures along their dorsal aspect.

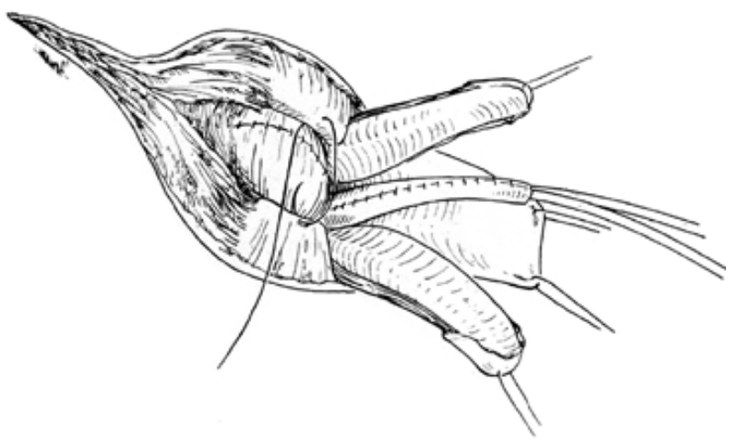

FIGURE 49B.24. Schematic drawing of bladder and urethral closure demonstrating continuity of these structures. The bladder and urethra are reapproximated using running absorbable suture material before the pubis symphysis is reapproximated.

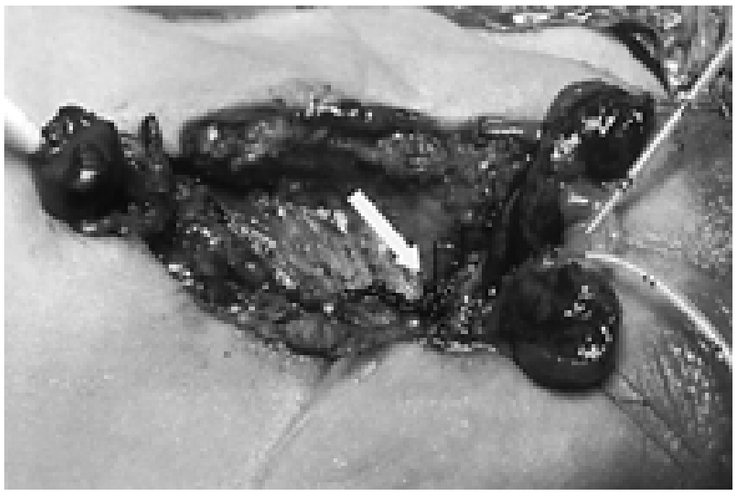

FIGURE 49B.25. Reapproximation of pubis symphysis occurs before penile reconstruction. The corpora cavernosa are still separated at this point. Penile reassembly takes place after the symphysis closure. PDS is used to approximate the pubis symphysis *(arrow).*

The urethra can then be brought up to each hemiglans ventrally to create an orthotopic meatus. The glans is reconfigured using interrupted mattress sutures of polydioxanone suture (PDS) followed by horizontal mattress sutures of 7.0 braided polyglactin suture (Vicryl) to reapproximate the glans epithelium. The neourethra meatus is matured as in a standard hypospadias repair. Some glans tissue is usually excised from the dorsum of the glans to create a conical appearance. Occasionally, the urethra lacks enough length to reach the glans. In this situation, the urethra may be matured along the ventral aspect of the penis to produce a hypospadias. This can be corrected at a later date as a second-stage procedure. We often leave redundant shaft skin ventrally in these patients to assist in later penile reconstructive procedures.

The penile shaft skin is reconfigured using either a primary dorsal closure or reversed Byars flaps if needed to provide dorsal skin coverage. Skin covering the abdominal wall is reapproximated using a two-layer running closure of absorbable monofilament suture.

Osteotomies

Regardless of whether one approaches the functional reconstruction of the exstrophic bladder in a staged or complete primary approach, use of osteotomies is an important component to achieve a successful result in many cases. Trendelenburg first recognized the importance of osteotomies in exstrophy closure at the turn of the century (213). In 1958, Schultz described a successful functional exstrophy reconstruction that used bilateral posterior iliac osteotomies (191). Osteotomies optimize pubic symphysis apposition and anatomic placement of the bladder, bladder neck, and urethra in the pelvis. They also improve the approximation of the corporal and clitoral bodies. Finally, osteotomies may decrease the chance for later uterine prolapse because the anterior closure brings the pelvic diaphragm into a more normal anatomic position to offer more support.

The need for osteotomy is best determined before closure, but sometimes the decision is made at surgery (see previous discussion). Candidates for osteotomy include those more than 72 hours old, newborns with a wide pubic diastasis, newborns with cloacal exstrophy, and patients who have had a previously failed closure. Osteotomies usually are performed at the same setting as bladder closure to help secure the closure. Although staging osteotomies and closure has been advocated at some centers in the past, this seems to be rarely necessary.

Osteotomies may be performed by an anterior or posterior approach or a combination of approaches (Fig. 49B.26). Posterior iliac osteotomies are performed with the patient in a prone position. The patient is then repositioned for the bladder closure. Anterior iliac osteotomies offer the advantage of a single position and sterile field preparation. Compared with posterior iliac osteotomies, an anterior approach also has been shown to result in less blood loss and better apposition and mobility of the pubic rami (53,54). The group at Johns Hopkins uses combined anterior innominate and vertical iliac osteotomies because of superior initial and long-term results compared with anterior iliac osteotomies alone (203). Both osteotomies may be performed through the same anterior skin incision. McKenna also has described the use of a diagonal midiliac osteotomy performed through the same incision as the exstrophy closure (147). Division of the superior pubic ramus also has been described; although not as effective as the other methods described, it may be used in the newborn period (153,190). Others advocate the use of bilateral anterior

pubic osteotomy because it does not require any particular orthopedic skills and therefore can be performed readily by a pediatric surgeon or pediatric urologist. Frey reported on 16 patients using this technique. Preliminary results appear satisfactory although one patient in this series experienced an obturator nerve injury directly related to this technique (53,54). However, it has been our experience that pubic and pubic ramus osteotomies do not serve to correct the real pelvic deformity and create more problems than they solve by weakening rather than strengthening anterior pelvic support.

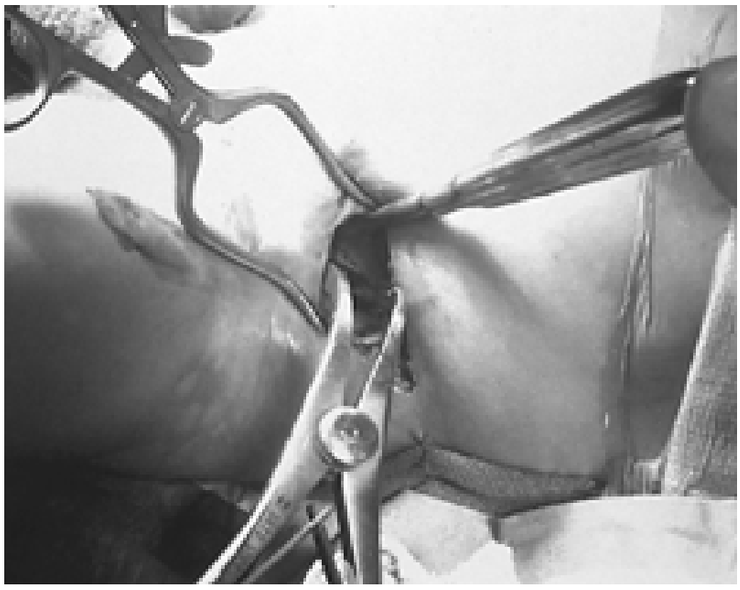

FIGURE 49B.26. Use of anterior iliac osteotomies as part of the initial bladder closure

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Complications associated with the use of iliac osteotomies include transient femoral nerve palsy, abductor atrophy, transient perineal nerve palsy, and osteomyelitis (201). Transient nerve palsies appear to occur less commonly with the combined anterior and posterior approach. The pubic diastasis generally recurs when these children are followed over the long term. However, older children may maintain better correction over time, especially when managed in the postoperative period with external fixation. More recently, the reseparation of the symphysis has been reduced by aggressive posterior mobilization of the urethra by deep incision of the intersymphyseal ligament.

EPISPADIAS REPAIR

Since Jeffs' initial description of the staged reconstructive approach to exstrophy, the timing of the epispadias repair has undergone change. Originally, Jeffs advocated epispadias repair as the last stage of reconstruction. However, he later recognized that earlier epispadias repair increased the success of later continence procedures by stimulating bladder growth and increasing bladder capacity (66). Epispadias repair is now typically performed at 12 to 18 months of age as a second-stage procedure when a staged approach to exstrophy repair is used. Various methods can be used. These include Cantwell-Ransley techniques and their modifications or CPER (Mitchell technique) or its variants. These procedures are discussed in more detail later. Both use dissection of the corporal bodies and transposition of the urethral plate to the ventral aspect of the penis. Lack of length of the urethra may result in hypospadias with either of these techniques. This can be corrected later in various ways using operations described for hypospadias repair.

More recently, Gearhart and colleagues (62) have accepted a nonstaged approach and reported on combining bladder closure and epispadias repair in 15 boys. They performed this combined approach as the initial procedure for one boy and used it as a salvage procedure for 14 boys who had previous closure failures. They found that combining a repeat bladder closure with epispadias repair optimized the use of osteotomies and was as successful as staging these operations. Furthermore, two boys who underwent combined repair became continent without further BNR, which has been observed by many groups using a complete primary repair technique. They now recommend combined bladder closure and epispadias repair as the preferred management of patients who have had previously failed bladder closure. Of note, some surgeons advocate the use of topical or intramuscular testosterone to increase the size of the phallus before performing the epispadias repair (74,175).

The approach to epispadias repair should consider the following goals:

- Correction of dorsal chordee
- Creation of a straight urethra to allow easy negotiation during catheterization or cystoscopy
- Satisfactory cosmesis
- Minimal complications, especially regarding urethrocutaneous fistulae
- Maintenance of normal erectile function

Reported rates of success for epispadias repair vary. The degree of epispadias, the age of the patient, surgeon experience, and the presence of previously operated tissues all affect the successful outcome of epispadias repair. Furthermore, penile cosmesis is a subjective measurement. A satisfactory appearance to the surgeon may not equal that of the patient's expectations and vice versa. So, success rates of reported series are difficult to validate and compare for this repair.

Complications involved in epispadias repair, independent of the specific repair used, include the development of urethrocutaneous fistulae. These typically occur dorsally at the base of the penis, where tissue coverage is most tenuous. The corporal bodies do not yet cover the reconstructed urethra. Fistula rates for the Cantwell-Ransley repair range from 5% to 15% (43,64). Fistula rates using the total penile disassembly technique are 10% to 20% (157,175). Other complications include persistent chordee, difficulty with urethral catheterization, and erectile dysfunction.

A recent review of the Cantwell-Ransley technique in 40 patients revealed a successful anatomic and functional result in 90% of the patients at a mean follow-up period of 3 years. These authors also reported complications requiring further procedures in 45% of the patients in their series. Complications were more common in those patients who underwent this procedure as part of a staged exstrophy closure versus isolated epispadias (138). The high rate of reoperation reflects the technical difficulty involved in epispadias repair even in experienced hands.

Zaontz and colleagues (234) reported on a multicenter experience using the total penile disassembly technique and found that 16 of 17 boys had straight erections following repair. Three patients developed pinpoint fistulae of which two closed spontaneously. Perovic (174) has described variants of this technique for epispadias that may be used in selected circumstances as well.

Although both the Cantwell-Ransley and total penile disassembly techniques can be used as salvage procedures for

the older child, these children also may require dorsal dermal grafts to achieve a straight penis. The neurovascular bundles may require mobilization to allow graft placement in this situation. Otherwise, it is more prudent to avoid excessive mobilization and handling of these nerve bundles.

Finally, the popularization of the Mitrofanoff principle has significantly improved the management of those patients with tortuous neourethras following urethral reconstruction. Creation of a Mitrofanoff channel allows patients who require CIC (CIC) of their bladders to do so easily. Most patients with bladder exstrophy that require CIC prefer to do so through a Mitrofanoff rather than per urethra even if urethral catheterization is technically straightforward**.**

OPERATIVE APPROACH TO EPISPADIAS

Various surgical procedures have been devised to correct this anomaly and achieve the goals of epispadias repair including a straight penis and urethra, easy urethral catheterization, normal erectile function, and a cosmetically satisfactory phallus. These goals allow the patient to stand while voiding and to have intromission during intercourse. Epispadias repair can prove challenging. Two of the more successful and popular procedures are described subsequently. Both types of repair can be used as salvage procedures for patients who have undergone previous operations for epispadias.

Modified Cantwell-Ransley Repair

Cantwell first described mobilization and ventral movement of the urethra for epispadias repair at the turn of the century (25). Ransley subsequently successfully modified this technique (179). The modified Cantwell-Ransley repair has been widely used since then by various surgeons (Fig. 49B.27).

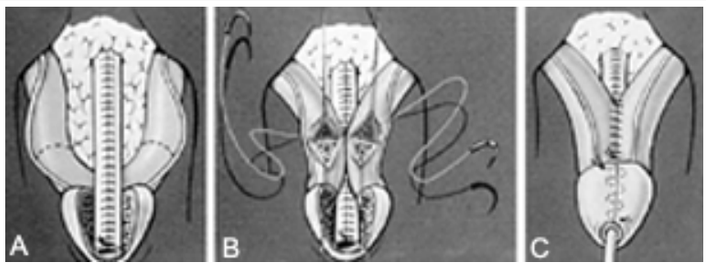

FIGURE 49B.27. Line drawing illustrating the steps for the Cantwell-Ransley repair for epispadias. **A:** The tubularized urethral plate is placed in a dorsal groove incision in the glans penis. The *dotted lines* indicate the site of incision for the cavernosa-cavernostomies. **B:** Approximation of the corpora cavernosa and performance of cavernosal anastomosis. **C:** Glans closure over urethra and skin closure. (Adapted from Brock J III, O'Neill J Jr. Bladder exstrophy. In: O'Neill JA Jr, Rowe MI, Grosfeld JL, et al. *Pediatric surgery,* 5th ed, vol 2. St. Louis, Mosby, 1998:1709, with permission.)

Initially, a traction suture is placed into the glans penis. A marking pen is then used to outline the incisions for a reverse meatal advancement glanuloplasty (MAGPI) or IPGAM procedure at the distal urethral plate. This advances the urethral meatus onto the glans. Skin incisions are then made on the lateral edges of the urethral plate and around the epispadiac meatus. This plate is dissected from the corporal bodies up to the level of the glans distally and to the prostatic urethra proximally. Lateral flaps or wings should be developed in the glans penis as well. The corporal bodies are then separated from each other to allow them to rotate medially. The urethra is then tubularized over a 6- or 8-Fr urethral catheter, typically using running absorbable suture. The corporal bodies are rotated over the urethra and reapproximated using absorbable suture in an interrupted fashion. Cavernostomies may be performed before reapproximating the corporal bodies to help correct persistent chordee. These are performed at the point of maximal angulation. The neurovascular bundles may require mobilization to avoid injuring them if cavernostomies are performed. The glans wings are then closed over the urethra dorsally using interrupted absorbable suture. Penile shaft skin can be trimmed and tailored to cover the penis. Z-plasties at the level of the pubis may decrease the chance of a dorsal retractile scar at the base of the penis.

Complete Penile Disassembly Technique

We have exclusively used the complete penile disassembly or Mitchell technique for epispadias repair since 1989. Bagli and Mitchell reported their results in 1996 (157). Complete penile disassembly offers several advantages compared with the modified Cantwell-Ransley technique. The planes of dissection extend anatomically to the bladder neck (Fig. 49B.28). This facilitates its use with BNR. Complete mobilization of the urethral wedge from the corporal bodies by disassembly also creates a more normal appearance of the penis by allowing ventral placement of the urethra. This technique is based on the unique anatomy of the epispadias. The blood supply of each hemiglans depends on the paired unique dorsal complex found on the lateral aspect of the corpora. Because the corpora are separated, there is no crossed blood supply and the primary circulation of each corpora cavernosa is based on the central artery. Similarly, the urethral plate and spongiosa have their unique blood supply and innervation from the proximal urethra (versus the distal urethra). Therefore the corpora cavernosa with hemiglans can be separated completely from each other and from the spongiosa and urethra complex without potential to damage ultimate function (Fig. 49B.29). This disassembly maximizes potential for anatomic reconstruction. It is important to note the dorsal complex is *not* dissected from the corpora cavernosal bodies. A detailed description of the surgical technique is included in the section on CPER (total disassembly technique for bladder exstrophy).

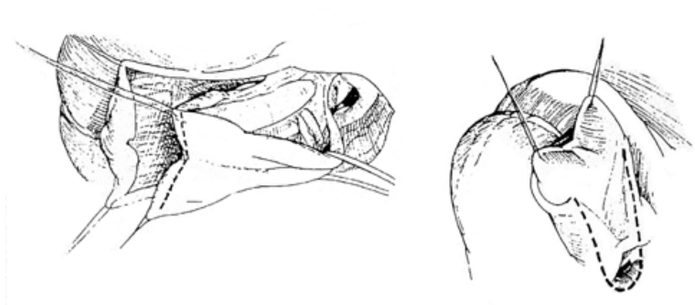

FIGURE 49B.28. Complete penile disassembly technique. On left, lines of initial dissection circumscribing the urethral plate and bladder neck. On right, careful dissection of the urethra from the underlying corporal bodies. *Dotted line* indicates site of distal incision to free the urethra entirely from the glans. (Adapted from Mitchell ME, Bagli DJ. Complete penile disassembly for epispadias repair: the Mitchell technique. *J Urol* 1996;155(1):300, with permission.)

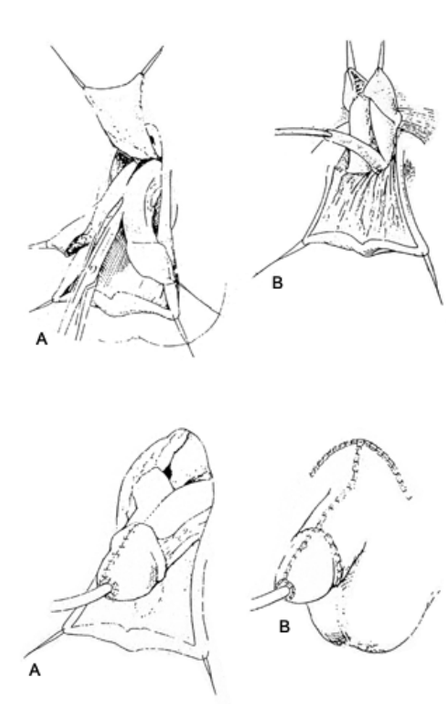

FIGURE 49B.29. Complete penile disassembly technique. **A:** Corporal bodies and two hemiglans are separated by a longitudinal midline incision. **B:** The urethra is tubularized and brought to the ventrum. The corpora are reapproximated dorsally. They will rotate medially when adequately dissected from each other. [Adapted from Mitchell ME, Bagli DJ. Complete penile disassembly for epispadias repair: the Mitchell technique. *J Urol* 1996;155(1):300, with permission.]

BLADDER NECK RECONSTRUCTION

BNR originally arose out of efforts to improve the functional reconstruction of the exstrophic bladder. Often, BNR was performed at the same time as the initial bladder closure and epispadias repair. Surgeons who popularized and championed these techniques include Herbert Johnston, D.I. Williams, J. Lattimer, and T. Chisholm (131). Jeffs arrived at the concept of using BNR as part of a staged approach to exstrophy repair in the early 1970s. At that time, Jeffs was inspired by a report of a series of patients with incontinent epispadias followed by O. Culp who had undergone BNR and later achieved a continence rate of 50% (38). Using a staged approach, Jeffs planned to transform the anatomy of bladder exstrophy into complete epispadias during the first staged reconstruction and use BNR later to achieve urinary continence.

With a staged approach to exstrophy repair, BNR is performed when the child is at an appropriate age for toilet training. This is typically at 4 to 5 years of age. Advocates of staged reconstruction emphasize the importance of achieving adequate bladder capacity before performing BNR. A bladder capacity less than 60 mL under anesthesia or during urodynamic evaluation decreases the success of BNR (117,136). Factors that may increase the potential for the bladder to achieve adequate capacity before BNR include the following:

- Avoidance of UTIs
- Complete bladder emptying with institution of CIC if bladder emptying is incomplete
- Epispadias repair (through increase in urethral resistance)
- Avoidance of bladder prolapse (30)

To reconstruct the bladder neck for exstrophy most surgeons use a Young-Dees or a Leadbetter approach or a modification of these techniques. These BNR techniques offer the best chance to create volitional voiding with

continence. They are described in detail later. Ureteroneocystostomy is usually required at the time of BNR to correct vesicoureteral reflux and to move the ureters from the lower bladder where BNR will occur. The Cohen technique is often used. However, others have described a cephalotrigonal technique that is particularly applicable to exstrophy patients because of the angle of ureteral entry into the bladder in exstrophy (24). The Marshall-Marchetti-Kranz bladder neck suspension or a bladder neck wrap using rectus muscle, bladder muscle, or fascia may be combined with BNR as well. BNR requires adequate bladder capacity because using some of the bladder reduces detrusor volume. It must be emphasized that the primary objective of these procedures is to restore anatomy to achieve continence with voiding (versus continence anticipating CIC).

Bladder Neck Reconstruction Procedures

Preoperative Assessment

Following a careful history and physical examination, we perform cystourethroscopy for all patients before proceeding to open BNR. Cystoscopy provides information regarding bladder capacity and the status of any previous repairs, including correction of epispadias.

Preoperative urodynamic evaluation also should be considered because it allows preoperative detection of detrusor hyperactivity or atony as well as assessment of functional bladder capacity and leak point pressures. However, the urethra of these patients may be difficult to catheterize. In these situations we combine our cystourethroscopic examination with suprapubic placement of a urodynamic catheter to be used later that day for the urodynamic evaluation. Preoperative urodynamic testing is often necessary before surgery. For example, results from urodynamic studies performed on exstrophy patients at Boston Children's Hospital before and after BNR indicate that approximately 60% of patients have relatively normal function before BNR and that most developed a hypertonic or hyperreflexic bladder following BNR (11). Urodynamic studies help guide decisions regarding the need for augmentation cystoplasty and the use of anticholinergic agents.

Mitchell Repair

The Mitchell repair uses a modification of the Leadbetter procedure in a previously described technique (120). We currently use this modification as our preferred method of BNR in patients with bladder exstrophy who require bladder outlet repair because it preserves the chance for volitional voiding. In this modification, the anterior urethra is incised transversely and the incision is extended cephalad (Fig. 49B.30A). The urethral incision is full thickness. After cross-trigonal ureteral reimplantation, the urethral strip is tubularized in two layers using Vicryl or Monocryl suture (4-0 or 5-0) over an 8- to 10-Fr urethral catheter, depending on the size of the patient. The bladder may be closed in continuity with the urethral closure. This procedure effectively narrows and lengthens the urethra (Fig. 49B.30B and C). It also moves fibrotic tissue at the level of the original bladder neck away from the new bladder neck. Dissection around the new bladder neck may be performed if a combined bladder neck wrap or sling is anticipated. Although this procedure has been applied to various clinical situations, it is best used in the exstrophy/epispadias patient.

FIGURE 49B.30. Mitchell bladder neck reconstruction. From left to right: *Dotted lines* indicate planned lines of incision. Following this, the urethra is lengthened and narrowed. The urethra and bladder then are closed in continuity with a two-layer closure. [Adapted from Jones JA, Mitchell ME, et al. Improved results using a modification of the Young-Dees-Leadbetter bladder neck repair. *Br J Urol* 1993;71(5):555, with permission.]

Postoperatively, urine is drained through a combination of ureteral stents, a suprapubic tube, and a 6-Fr (Kendall) urethral catheter. The urethral catheter remains for 7 to 10 days after the operation. Ureteral stents are removed at 10 to 14 days after surgery. The suprapubic tube remains for 3 weeks. We routinely clamp the tube before removing it and measure postvoid residual urine volumes to assess for urinary retention before removing the suprapubic tube. As with any BNR procedure (without augmentation), we anticipate that several months of adjustment will be required before the patient develops adequate bladder awareness, capacity, and control to achieve prolonged intervals of urinary continence.

Occasionally, trigonal tubularization must be combined with bladder augmentation because of small bladder capacity; most bladder neck repairs decrease bladder capacity because bladder is used to create the continence mechanism (142). Stomach offers the best potential to preserve spontaneous volitional voiding in this group, but places these children at risk of hematuria-dysuria syndrome, which can be especially troubling in the face of persistent urinary incontinence and normal sensory innervation (57). Other intestinal segments also may be used according to surgeon preference. If augmentation is required, a catheterizable stoma for bladder catheterization (Mitrofanoff operation) also should be strongly considered as urethral catheterization may be difficult.

Young-Dees-Leadbetter Procedure

To perform a Young-Dees-Leadbetter (YDL) procedure, a strip of bladder mucosa approximately 1 to 1.5 cm wide and

3 to 4 cm long is mobilized and constructed into a tube over an 8- or 10-Fr urethral catheter, using interrupted or running polyglycolic acid sutures (4-0 or 5-0) (Fig. 49B.31A). Use of an epinephrine-soaked sponge during this dissection may aid in hemostasis and visualization. Triangular flaps of demucosalized detrusor muscle are developed on either side of the mucosal tube and subsequently wrapped over the mucosal tube in a double-breasted technique using 3-0 polyglycolic acid sutures (30) (Fig. 49B.31B). This reinforces the neobladder, decreases the risk of fistula, and augments the outlet resistance (13).

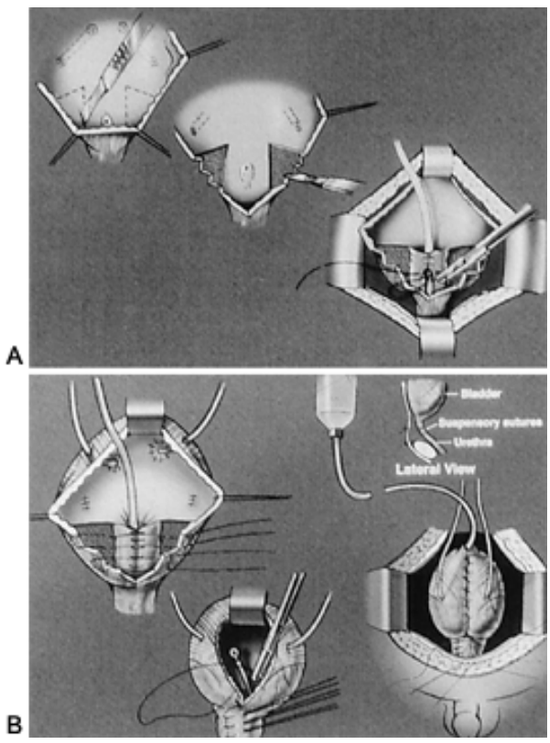

FIGURE 49B.31. The principles of the Young-Dees-Leadbetter procedure. This is performed as the third stage of a staged reconstructive approach to exstrophy. **A:** The ureters are reimplanted as shown here to prevent vesicoureteral reflux and move them out of the area of the bladder neck reconstruction. The base of the bladder is reconstructed to lengthen the urethra and reinforce the bladder neck. **B:** The bladder neck closure is reinforced with a pants-over-vest closure. Drainage catheters are brought out superiorly. (Adapted from Brock J III, O'Neill J Jr. Bladder exstrophy. In: O'Neill JA Jr, Rowe MI, Grosfeld JL, et al. *Pediatric Surgery,* 5th ed, vol 2. St. Louis, Mosby-Year Book, 1998:1709, with permission.)

Gearhart (60) advocates the use of intraoperative urodynamic studies. Retrospective studies have shown that intraoperative closure pressures of 70 to 100 cm H_2O will prevent urinary leakage at 50 cm H_2O intraoperatively (24). Postoperative management is similar to that following the Mitchell repair. Some surgeons recommend avoidance of a urethral catheter in the postoperative period because of concerns that it may adversely affect later urinary continence. Urinary drainage is achieved by the use of ureteral catheters and suprapubic tube drainage (60).

Results

BNR in YDL procedures and its variants has yielded success rates of 30% to more than 80% urinary continence for patients with bladder exstrophy (72,120,160). Many factors influence the outcome of surgery. For instance, an initial failed bladder closure or prior failed BNR reduces the chance to achieve subsequent urinary continence in these patients (73). Use of iliac osteotomies to provide a tension-free anastomosis and patient immobilization through the use of spica casting or Bryant's traction in the postoperative period increases the success of bladder closure and subsequent continence (73,139). Delayed bladder closure increases the likelihood of eventual need for bladder augmentation due to inadequate bladder capacity that, in turn, reduces the chance for volitional voiding.

Woodhouse and Redgrave also have reported that 8 of 13 patients with initially successful bladder closures and BNR required further surgery in their second decade of life because of the gradual development of poorly compliant, low-capacity bladders that caused urinary incontinence (223). Surgeons who care for these patients must be committed to the long-term follow-up of this complex group of patients because late complications such as this may develop.

THE FAILED REPAIR

The results of functional reconstruction for exstrophy can fall short of perfection. As a consequence, surgeons involved in the care of these patients must be well versed in the options available to manage treatment failures. Appropriate clinical perspective is also helpful.

> As in any operation for exstrophy, the results must be viewed in the light of the gruesome condition it is designed to correct.—H.M. Spence, M.D.

Failed Initial Bladder Closure

The following factors can affect the ability to achieve urinary reconstruction via bladder reconstruction in exstrophy patients:

- Primary failure (dehiscence) of the initial bladder closure
- Outlet obstruction
- Bladder prolapse
- Chronic UTI

Failure of the primary closure, the first stage of the staged repair, decreases the chance for eventual continence with volitional voiding (73,140). Gearhart and colleagues (72) reported that only 40% to 60% of patients after a failed primary closure attempt will ultimately achieve a bladder capacity adequate for BNR. If more than two closure attempts are required, chances for continence decrease to 20% (73). With a staged reconstruction, the initial closure is performed to prevent bladder prolapse but avoid outlet obstruction. The use of osteotomies and postoperative immobilization improves the success of initial bladder closure along with the other postoperative factors previously listed. Several investigators have noted the strong relationship between successful primary closure and the appropriate use of osteotomies, an observation also recognized more than 100 years ago by Trendelenburg and later by Schultz (23,69,191,213).

Gearhart and Jeffs (60) have noted that patients who are not initially continent (defined by a 3-hour dry interval) after BNR may achieve urinary continence later. However, such patients rarely improve if they remain wet 1 to 2 years after surgery. Kelalis and Kramer (127) also have observed some male patients who became continent after puberty and postulated that prostatic enlargement may have created enough additional resistance to achieve urinary continence (127). Although this observation appears valid in patients who have undergone epispadias repair, exstrophy patients do not achieve continence with puberty alone. Based on MRI studies in exstrophic patients, prostatic volume is equivalent to age-matched controls, but the configuration of this gland remains abnormal so that it does not surround the urethra (60).

Urinary outlet obstruction is one of the potentially dangerous failed outcomes of bladder closure because it can cause renal deterioration and increase the risk for chronic UTI. It is typically diagnosed when postvoid residuals are greater than half the actual bladder capacity. Outlet obstruction increases the risk of renal damage especially if unrecognized for several months or more because it can raise the maximum typical storage pressure in the bladder to dangerous levels (108). Outlet obstruction also increases the difficulty of clearing a UTI. Outlet obstruction also may decrease the chance to achieve urinary continence. Following the first stage of a staged repair, the bladder outlet following initial bladder closure should be assessed with sounds or bougies 4 to 6 weeks after closure to detect obstruction.

Following total disassembly with complete primary repair technique, the urethra should be assessed at 6 to 8 weeks postoperatively. Routine ultrasonography of the bladder and upper urinary tracts also should be performed frequently after closure to detect hydronephrosis that may indicate outlet obstruction. Evidence of hydronephrosis in combination with high postvoid residual urine volumes requires further evaluation with cystoscopy and urethral dilation or the institution of intermittent catheterization as indicated. In a review of 68 patients at Toronto Sick Children's Hospital, 23% developed hydroureteronephrosis following the initial closure and were then successfully treated with dilation of the bladder outlet or institution of CIC (108). Of note, some children will develop transient hydronephrosis following their initial surgery, which may be related to gradual accommodation of the bladder as it cycles urine. Some of these children may require CIC to assist them in bladder emptying even though there is no evidence of outlet obstruction. Some of these children will show spontaneous improvement, but it is currently not possible to predict this.

Failed Bladder Neck Reconstruction

Patients who fail to achieve continence after BNR should undergo urodynamic evaluation. Some patients will demonstrate bladder hyperreflexivity and/or hypertonicity likely due to increased resistance after BNR. Treatment with anticholinergic agents such as oxybutynin hydrochloride can significantly improve the continence of many of these patients.

If urodynamic evaluation reveals a bladder with adequate capacity but low detrusor leak point pressure, BNR can be performed again. However, this is an unusual occurrence. More commonly, patients demonstrate an inadequate bladder capacity and a low detrusor leak point pressure and usually require bladder augmentation (60).

After failed BNR, several other options are available. Because of the variable success of BNR in the exstrophy population, various treatment options have been explored and reported in the literature. Treatment choice depends on the results of urodynamic studies and other clinical and social factors.

Augmentation Cystoplasty

Indications for bladder augmentation can vary by degree, depending on surgeon preference and commitment to functional reconstruction. However, some patients will not achieve adequate bladder capacity or compliance as a result of postoperative complications and sometimes despite technically successful reconstruction efforts. Lack of adequate capacity and poor compliance can both contribute to urinary incontinence in this patient group. Preservation of the native bladder in these situations rather than continent urinary diversion offers several advantages. The native bladder offers a convenient substrate for ureteral and Mitrofanoff reimplantation that has a lower complication rate than when intestine or stomach is used for this purpose. Gastrointestinal segments used for bladder augmentation in the exstrophy population include stomach, ileum, cecum, and sigmoid colon (58,114). Stomach has proven to be as equally effective as small or large intestine in this population

and offers the possibility of spontaneous voiding (58). The Arap procedure represents an augmentation technique unique to the management of exstrophy. Arap (7) described this novel form of colocystoplasty in 1968. For this procedure, the ureters are implanted into the sigmoid colon, which is then fashioned at the skin as a conduit. Later, the native bladder plate is tubularized to create a neourethra. The sigmoid conduit is then taken down at the skin level and an anastomosis is created to the neourethra to allow CIC per neourethra. Currently, this procedure is infrequently used (7). Augmentation also may be performed with urothelial-lined tissue such as a dilated ureter if this is present. Often, bladder augmentation is combined with a bladder neck procedure to optimize the chance for urinary dryness. Most patients who undergo bladder augmentation will require CIC to empty their bladders of urine following this operation (46).

Artificial Urinary Sphincter

An artificial urinary sphincter (AUS) may be used to achieve urinary continence in patients who have adequate bladder capacity and compliance but an incompetent bladder neck after BNR (40). This device preserves the ability to volitionally void, but because of its current lack of durability and the dexterity required to use it, it is generally not a first choice for younger patients. Others have described its use in combination with bladder augmentation. In one series of 11 patients who underwent sigmoid augmentation with AUS placement, 9 are continent. However, these patients required multiple operative revisions to achieve this degree of continence (137). Sphincter erosion into the bladder neck or bowel segment also can occur (65).

AUS placement may be technically challenging in these patients. The plane of dissection around the bladder neck following BNR may be difficult to establish. A posterior and anterior approach to the bladder neck is useful in these cases. Other surgical options should be available at the time of AUS placement in case of accidental entry into the posterior bladder neck. In this situation, it is also possible to primarily repair the injury and place omentum between it and the AUS cuff. The AUS cuff should not be placed on the bulbar urethra in the exstrophy-epispadias patient. Cuff placement at the bladder neck will be more complicated if there has been previous bladder neck surgery.

Bladder Neck Wrap/Sling

Bladder neck wraps and slings also may be considered. However, series reporting on the use of bladder neck wraps suggest that this procedure does not consistently maintain long-term urinary continence especially in male patients who constitute the gender majority in exstrophy (41,130). Hanna and Stock also have described a bladder neck wrap using a gracilis muscle flap in a “cinch” technique as a procedure for BNR. They reported the achievement of urinary control in 5 of 11 patients with this technique (89).

Submucosal Collagen Therapy

Several authors have used collagen injections at the bladder neck to treat patients with stress incontinence after BNR (16,21). Its use in these situations has been compared with the treatment of intrinsic sphincter deficiency urinary incontinence. Ben-Chaim (16) reported an improvement in continence in 53% of patients after collagen therapy, although most required multiple injections. It can be used as an adjunctive procedure for those patients who demonstrate slight leakage due to stress incontinence after BNR. Submucosal collagen injection also may be used before BNR. Caione (21) advocates use in this situation to increase outlet resistance so that the bladder may increase in capacity.

Patients should undergo collagen skin testing 4 weeks before use to evaluate for possible hypersensitivity reactions. The possibility of multiple treatments with collagen also should be emphasized. Submucosal injections are typically carried out at three different locations at the level of the bladder neck. Collagen should be injected until visual occlusion of the urethra is seen. This usually requires 7.5 mL of collagen per patient (22).

The most significant problem with submucosal therapy at this time is its lack of durability. Volume reduction occurs over time, resulting in coaptation failure and subsequent urinary incontinence. As new endoscopic agents become available, this may become a more popular technique. In general, injection therapy has been disappointing in this patient group.

Bladder Neck Closure

Bladder neck closure in conjunction with appendicovesicostomy is also an option in those patients who have failed multiple attempts at BNR (92). This is a last resort measure because it eliminates the chance to void per urethra and commits the patient to CIC.

URINARY DIVERSION

> The bitter truth is that there is no completely satisfactory substitute for the unique qualities exhibited by a normal bladder and urethra… Patience is required since continence may be slow to develop in even a successful repair but at the same time one must have the wisdom to recognize what McGovern calls ‘failure staring you in the face' such that a course of action, no matter how politically correct it may seem, can be abandoned and replaced with an assault from another direction.—Terry D. Allen, M.D.

Approaches to Urinary Diversion

Methods to construct urinary diversions include those listed in Table 49B.4 .

TABLE 49B.4. METHODS TO CONSTRUCT URINARY DIVERSIONS

External Diversions (Continent Reservoir)	Internal Diversions (Anal Sphincter-based Continence)	Incontinent Diversions
Indiana pouch	Ureterosigmoidostomy	Ileal conduit
Penn pouch	Sigma pouch	Colon conduit
Koch pouch	Ghoneim reservoir	Ileocecal conduit
Miami pouch	Gersuny	Cutaneous ureterostomies
	Heitz-Boyer-Hovelacque	
Others	Rectal bladder with proximal colostomy	
	Ileocecal ureterosigmoidostomy	

Proponents of urinary diversion for the treatment of exstrophy argue that the varying continence rates achieved with functional reconstruction demonstrate the unreliability of this approach (94). The use of the native bladder often requires later bladder augmentation with intestinal segments to achieve a functional bladder storage capacity. Certainly, some centers report poor rates of continence after primary reconstruction and some urodynamic studies do demonstrate low urine flow rates and poor contractility in patients following primary bladder reconstruction (98,165).

Primary urinary diversion may avoid some of the complications associated with functional reconstruction including urinary retention and subsequent kidney damage, a predisposition to UTI, and later dependence on CIC to empty the bladder with its own possible complications of urethral stricture formation, epididymitis, and UTI (94,96). Advocates of early urinary diversion cite a decreased risk of epididymitis and obstruction of the vas deferens by the creation of a receptacle with a suprapubic window at the level of the prostatic urethra (94). Diversion can be combined with cosmetic operative procedures for the external genitalia.

Urinary diversion is used to provide urinary continence for patients who have failed multiple attempts at functional reconstruction. Some also advocate primary urinary diversion for patients with bladder plates deemed too small to close. However, because we cannot accurately predict which bladder plates will increase significantly in size after primary closure, we do not use this as a criterion for primary diversion and do not divert the urine primarily in exstrophy patients. Arap (7) has described preserving the very small bladder by tubularizing it as the continence mechanism after anastomosing the ureters to a sigmoid conduit in an antireflux manner. Final reconstruction involves attachment of the sigmoid conduit to the neourethra and reconstruction of the abdominal wall (7).

Because of the difficulties encountered with functional bladder reconstruction in exstrophy, advocates of early urinary diversion argue that their approach achieves the primary goals of surgical intervention for bladder exstrophy with fewer operations and higher success rates than those achieved with bladder closure and urethral reconstruction. Ureterosigmoidostomy became the treatment of choice for bladder exstrophy patients as a primary and secondary treatment because of the dismal results associated with primary bladder reconstruction at the turn of the century and well into the 1970s. The long-term complications including hyperchloremic metabolic acidosis, chronic pyelonephritis, and a 250- to 500-fold increased risk of colonic adenocarcinoma formation at the site of anastomosis dampened enthusiasm for this procedure despite the reduction of the metabolic complications after improvements in ureteral reimplantation were developed (102,135,199). Ureterosigmoidostomy subsequently was replaced by incontinent urinary diversions such as the colonic and ileal conduits. In the 1960s ileal urinary diversion was the treatment of choice for bladder exstrophy at many institutions (47). A significant disadvantage to these forms of urinary diversion is the incontinent abdominal stoma associated with conduits. The popularization of CIC allowed the development over the last 15 to 20 years of continent urinary diversions like the Indiana pouch, which was developed for the exstrophy population and is now the preferred method of urinary diversion to the abdomen in the this population.

Rectal Reservoirs

Various investigators have made significant improvements on the use of the rectum as a urinary reservoir including the Mainz II pouch and the Sigma pouch (76,95) (Fig. 49B.32A and Fig. 49B.32B). Use of a rectal reservoir permits urinary continence without reliance on CIC required with other forms of continent urinary diversion. Hohenfellner and Stein report a 92% rate of renal preservation in their series of children treated primarily with a urinary rectal reservoir (Mainz II pouch since 1991). Continence rates of 97% in school-age children are reported in using this technique (96). The Heitz-Boyer-Hovelacque procedure involves isolation of a rectal segment for ureteral implantation followed by posterior sagittal pull-through of the sigmoid colon through the anal sphincter to achieve both urinary and fecal continence. A small series using this procedure reported continence rates of 95% with acceptable complication rates in 1977 (209). This technique, however, is currently not popularly used.

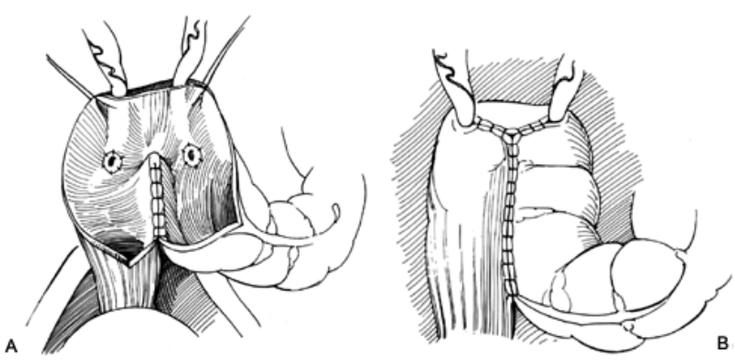

FIGURE 49B.32. Detubularization of the rectosigmoid colon to create a large pouch for urine storage (Sigma rectum pouch). **A:** The ureters are reimplanted in a tunneled fashion in the tenia of the colon. **B:** The pouch is closed to create a large urinary reservoir in continuity with the colon. (Adapted from Hohenfellner R: Sigma rectum pouch. In Hinman F, ed. *Atlas of pediatric urologic surgery.* Philadelphia: WB Saunders, 1994:427, with permission.)

Complications of this form of diversion continue to include fecal-urinary incontinence in patients with impaired anorectal sphincter control (60). Metabolic electrolyte imbalances

can be treated with complete frequent emptying of the rectal reservoir, which reduces the contact time between urine and the absorptive rectal mucosa along with oral bicarbonate replacement. Oral bicarbonate replacement is recommended for all patients who have a base deficit of 2.5 mmol/L or greater (94). The risk of malignant degeneration also still remains with this use of a rectal urinary reservoir. Various modifications of the rectal reservoir to prevent admixture of feces and urine may theoretically decrease the incidence of adenocarcinoma formation if it is due to conversion of urinary nitrates into carcinogenic nitrites by fecal bacteria (37). Long-term results are not yet available.

LONG-TERM CONCERNS IN EXSTROPHY

Psychosocial Concerns

Children with exstrophy face significant challenges in the development of their psychosocial identity. Reiner and co-workers have noted that delays in psychosocial and psychosexual development are commonplace (182). Unfortunately, this area of development has been poorly studied to date. A detailed sexual and social history is rarely part of the routine evaluation of these children as they become adults (184). Other studies have shown that adolescent males with exstrophy were psychosexually delayed 2 to 4 years compared with their peers and delayed 4 to 6 years in their activity. Data on teenage girls with exstrophy are incomplete, but Reiner (182) has noted that these girls struggle with sexual self-esteem issues such as body image, genital perception, and genital appearance.

Current recommendations include early psychiatric intervention at birth so parents of these children may be educated about the typical concerns these children will have and how to effectively approach these issues. Serial assessment at 12 to 18 months of age, late preschool period, in the third or fourth grade, at the beginning of middle school, during early, mid-, and late adolescence, and before any surgical interventions should be considered to help the child cope with his or her psychosexual and psychosocial concerns at these times. With early and routine education for parents and patients, exstrophy patients will likely better cope with sexual and social issues that profoundly affect their quality of life. Reiner (184) has found that anxiety and psychosexual disorders are universal in the patients he has evaluated to date. Routine patient and parental education is critical (184).

Woodhouse (231) noted in his series of adult patients with exstrophy that many of them do develop stable partnerships. He found 33 of 43 patients married or living with a partner. However, sexual counseling in these patients is paramount because of the difficulties they face in this regard. A strong network of support groups made up of families with exstrophy is a resource for new parents of children with exstrophy. Later support groups can provide very important cohort support structure for children with exstrophy. The World Wide Web has a number of websites that can prove very helpful to parents and patients. These include the following sites:

1. Seattle Children's Hospital and Regional Medical Center

www.seattlechildrens.org/surgery/exstroph_new/exsuppgrp.htm

www.seattlechildrens.org/surgery/exstroph_new/exstrophy.htm

2. The Johns Hopkins Urologic Institute

   www.med.jhu.edu/pediurol/pediatric/exstrophy/index.html

3. Boston Children's Hospital

   web1.tch.harvard.edu/urology/support.html

4. The Association for Bladder Exstrophy Children

   www.bladderexstrophy.com/support.htm

Andrology, Gynecology, and Fertility

As exstrophy patients age, sexual function becomes a major concern along with urinary continence and physical appearance. Libido for patients with exstrophy is characteristically present with or without surgical correction. For male patients, erectile function is usually intact (228,230). However, variable degrees of chordee can create difficulty in achieving intercourse for some patients (230). In these situations, a female superior position provides closer apposition of the genitalia for intercourse. For female patients, sexual function is usually intact (228). In Woodhouse's series, 14 of 23 patients had normal intercourse (227).

For men with exstrophy, ejaculation is often present as well despite the extensive reconstructive procedures done for these patients. Fertility varies for men with exstrophy. The seminal emission may be slow and continue several hours after orgasm. Further, sperm quality and quantity is often impaired (134). This may be due to partial obstruction or recurrent UTIs. Transrectal ultrasound (TRUS) findings in a small group of adult male exstrophy patients revealed an abnormally distal insertion of the seminal vesical/ejaculatory duct complexes into the prostate. Semen analysis of these same patients revealed abnormally high seminal fluid pH (91). Despite this, some male patients are fertile and do not require assisted reproductive techniques (ART) to father children (151). However, with improvements in ART, even patients with impaired fertility can successfully achieve fatherhood.

Fertility is unimpaired in female patients with exstrophy, but maintenance of a pregnancy is significantly more difficult (110,193). These pregnancies are more often complicated by uterine or vaginal prolapse, recurrent UTIs, preterm labor, malpresentation, and hydronephrosis. In a 1958 literature review of pregnancies carried by women with exstrophy, Clemston noted 49 live births from 64 pregnancies. Complications in this series included two maternal deaths as well (31). More recent series have demonstrated significantly better outcomes with only one obstetric complication out of 32 pregnancies (231).

Prolapse occurs more commonly because of the lack of pelvic floor support structures and failure of pubic symphysis fusion (128). Often, this results from posterior incision of the pelvis diaphragm without anterior closure (symphyseal approximation); widely opens the pelvic outlet; and reduces support leading to potential for severe uterine, bladder, and rectal prolapse. This can be debilitating for a young, active woman. Unfortunately, because the vaginal introitus is above the pelvic diaphragm (intersymphyseal band) there is a tendency to incise posteriorly to “open the vagina.” This is often done by gynecologists who are inexperienced with the anatomy of the exstrophic pelvis in young adult women. Sling procedures using nonresorbable mesh can be used to correct the prolapse. Bed rest is necessary in the later stages of pregnancy for most of these patients (229). Urinary incontinence and prolapse may develop after pregnancy as well. Elective cesarean section should be performed for any patient with a functioning bladder or with an AUS. Cesarean section may help avoid some of the later problems with prolapse as well. Prolapse, in particular, can be a difficult problem to treat because of the technical challenge involved in correcting the prolapse. Sacrocolpopexy has been successfully used to correct prolapse in these patients (187). Hysterectomy is not advised in this situation because the uterus is acting as the only solid organ supporting the pelvic floor in these patients (224).

Risk for Malignancy

The exstrophic bladder possesses an increased potential to undergo malignant transformation (123,169,173) (Fig. 49B.33). Patients with untreated bladder exstrophy are at greater risk for this than patients treated early in life. However, early reconstruction does not eliminate the risk of malignancy. Justrabo and co-workers (122) estimated that the untreated exstrophic patient is 235 times more likely to develop bladder cancer than someone in the general population. Latency periods range from 40 to 50 years on

average. More men than women are affected by a ratio of 2.5:1. The underlying mechanism of tumor development is not known. Hypotheses include chronic inflammation. This may induce a precarcinogenic metaplastic response. Others have suggested that ectopic glandular epithelial tissue in the bladder plate may later serve as the focus of tumor formation. Interestingly, of 53 exstrophic patients with intestinal metaplasia followed for an average of 12 years, none developed adenocarcinoma in their bladders (35). Histopathologically, most bladder tumors in this population are adenocarcinomas. Some have elements of squamous cell or transitional cell carcinoma. The adenocarcinomas resemble adenocarcinomas of the colon. These tumors elaborate sialomucin type mucins and express antigens KL1, ACE, and EMA. Notably, they do not possess the normal urothelial cytokeratins 8, 18, and 19. Adjacent glandular metaplasia is common (122).

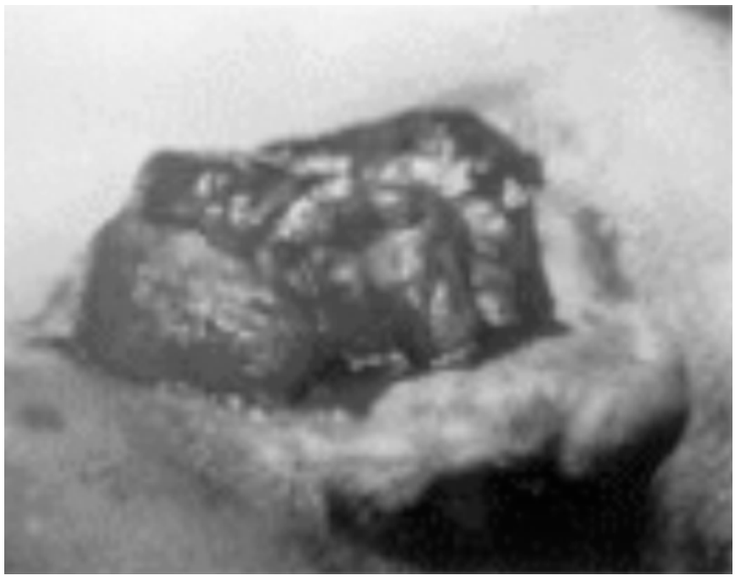

FIGURE 49B.33. Photograph of gross lesion that was identified as adenocarcinoma associated with an exstrophic bladder. [Reprinted from Paulhac P, et al. Adenocarcinoma in the exstrophic bladder. *Urology* (online) 1999;54(4):744, with permission.]

Patients who have undergone urinary diversion with ureterosigmoidostomy are also at risk for developing adenocarcinomas at the ureterosigmoid anastomosis (50,77). Latency periods range from 40 to 50 years on average. More men than women are affected by a ratio of 2.5:1. Routine surveillance by sigmoidoscopy is mandatory because the risk for tumor formation is several hundred times greater than in the general population. Latency periods for tumor development are on the order of decades (217). The risk of tumor development for those patients who have undergone augmentation cystoplasty using intestinal segments is not known, but case reports of tumors developing in the augmented segment following augmentation cystoplasty have been described in the literature (26,79,206). Theoretically, these patients should be at increased risk for malignant degeneration in these segments as well as in the native exstrophic bladder plate and should be followed routinely.

All patients with bladder exstrophy should undergo surveillance throughout their lives. The mortality rate from malignancy of the exstrophic bladder plate was reported as high as 67% in 1926 (215). With modern endoscopic techniques and close follow-up, this rate should be significantly lower. Some investigators also suggest the use of periodic acid–schiff (PAS) staining to screen for digestive tract cells in the urine as a screen for adenocarcinoma or glandular metaplasia (32). Treatment options include radical cystectomy with urinary diversion. Radiation and chemotherapy play a limited role in the treatment of adenocarcinoma of the bladder (173).

MANAGEMENT OF CLOACAL EXSTROPHY

Of the disease entities in this chapter, cloacal exstrophy represents the most challenging condition to manage (Fig. 49B.34A and Fig. 49B.34B). Cloacal exstrophy is rare. It occurs in 1 in 200,000 to 1 in 400,000 births. Although cloacal exstrophy has been recognized as a disease entity for at least several hundred years, Spencer became the first surgeon to report the successful repair and survival of an infant with this anomaly in 1965 (200). Mortality rates of infants with cloacal exstrophy remained high for years following this initial success. These affected infants routinely died of malnutrition and sepsis. In 1979, the mortality rate from this anomaly stood at 50% (218). The popularization of intravenous hyperalimentation in the 1970s significantly changed the survival rate of patients with cloacal exstrophy (103). Because of continued improvement in total parenteral

nutrition and neonatal management, mortality rates currently are less than 10% (39). Issues of quality of life are now paramount in this patient group.

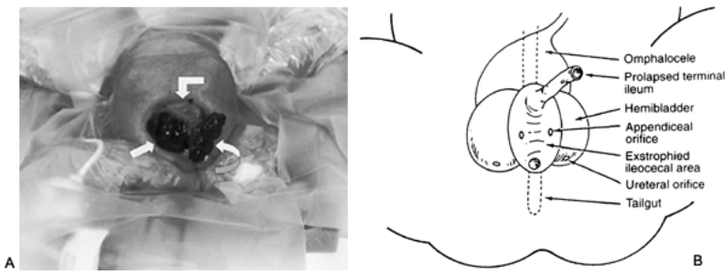

FIGURE 49B.34. Newborn male with cloacal exstrophy. **A:** The right lateral hemibladder plate can be seen here *(short arrow)* along with the central hindgut plate *(curved arrow)* and omphalocele *(right angle arrow)*. **B:** Schematic diagram of patient with cloacal exstrophy. [From Hurwitz RS, et al. Cloacal exstrophy: a report of 34 cases. *J Urol* 1987;138(4 Pt 2):1060, with permission.]

Antenatal diagnosis of cloacal exstrophy is possible. Austin (8) reported the typical findings associated with cloacal exstrophy *in utero* (Fig. 49B.35A and Fig. 49B.35B). These include the following:

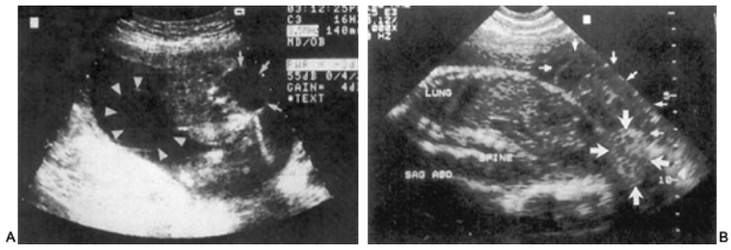

FIGURE 49B.35. Antenatal ultrasonogram of fetus with cloacal exstrophy. **A:** At 22 weeks of gestation, this transverse image reveals a cloacal membrane anteriorly *(arrowheads)* and lumbar myelomeningocele posteriorly *(arrows). B:* At 30 weeks of gestation, an omphalocele may be seen *(small arrows)* along with an exstrophic bladder and bowel inferiorly *(large arrows).* (Reprinted from Austin P, Homsey YL, Gearhart JP, et al. The prenatal diagnosis of cloacal exstrophy. *J Urol* 1998;160:1180, with permission.)

- Nonvisualization of the bladder
- A large midline infraumbilical anterior wall defect
- Omphalocele
- Myelomeningocele
- Widened pubic arches
- Lower-extremity defects
- Renal anomalies

In a review of 22 patients with cloacal exstrophy, all or some of these findings could be identified antenatally for 19 patients. As with classic exstrophy, antenatal diagnosis allows expectant parents to anticipate and plan for a child who will have significant anomalies at birth. Discussions regarding treatment options including therapeutic abortion should include pediatric surgeons and urologists familiar with the care of these children. Antenatal identification also permits parents to have these children delivered at a tertiary medical center equipped to provide multidisciplinary consultation and services.

Anatomic Issues

Patients with cloacal exstrophy routinely have multiple organ systems affected. As a result, cloacal exstrophy also is referred to as the OIES complex (*o*mphalocele, *e*xstrophy, *i*mperforate anus, and *s*pinal defects). Other organ systems may be affected as well, including the extremities; the upper urinary tract; and the cardiovascular, pulmonary, and craniofacial systems (103) (Table 49B.1). Because of the broad extent of organ involvement in cloacal exstrophy, a thorough physical examination should be preformed for all these children, and appropriate imaging studies should be obtained before proceeding with reconstructive surgery.

Cloacal exstrophy variants do occur. The anatomic findings for these patients vary from those typically found in the OIES complex. Some cloacal exstrophy variants have anatomically normal genitalia, whereas other authors have reported variants with aphallia (27). Erlich proposed a classification system for cloacal exstrophy and its variants (143).

Lower Urinary System

The hindgut plate separates the hemibladder plates found in cloacal exstrophy; the hindgut plate represents the deformation in the development of the colon that occurs with cloacal exstrophy. Ileum enters and intussuscepts into the middle of the hindgut creating the “trunk of an elephant's face” appearance with appendiceal appendages located laterally to give the impression of “tusks on the face of the elephant”(216) (Fig. 49B.34A).

With cloacal exstrophy, the bladder neck (internal urethral sphincter) and external urethral sphincter are not fully developed because of the failed development of the bladder and urethral remnant located on the anterior and dorsal surfaces of the body wall and penis respectively. Because the innervation to these structures may not be intact because of associated central nervous system defects in many of these patients, the possibility of achieving urinary continence after

functional reconstruction is less predictable than with bladder exstrophy (106). The urethral plate is characteristically short as well.

In contrast to classic exstrophy, the herniation defect (deformation) occurs earlier in development during the cloacal stage of the embryo. This results in multisystem involvement. It may be that the early herniation of the cloaca anteriorly prevents the curving of the tail bud ventrally, which ultimately prevents normal spine, renal, and intestinal development.

Kidneys and Upper Urinary Tract

Husmann and Vandersteen reviewed the available series of patients with cloacal exstrophy. They found a 67% incidence of renal anomalies in these patients, including anomalies of location such as pelvic kidney or crossed fused ectopia. Complete ureteral duplication, renal agenesis, and location anomalies represent the most common anatomic problems seen in patients with cloacal exstrophy. Horseshoe kidneys, single system ureteral ectopia, and ureteropelvic junction obstruction may occur as well (103,170).

Genitalia

For male patients with cloacal exstrophy, the penis is often separated into two hemiphalli because of the wide pubic diastasis (Fig. 49B.36). Furthermore, the phallus may be compromised by complete absence or absence of one of the corporal bodies. In many of these cases, the tissue available for penile reconstruction is significantly less than that found in a normal male infant This can make subsequent reconstructive efforts technically more challenging if a male phenotype is preserved (109). Historically, because of the difficulty in reconstructing the phallus in these patients, the prevailing opinion has been to perform gender reassignment for these male patients (210). However, gender conversion is now more controversial in this population because of recent information that suggests that patients who have been virilized *in utero* continue to gender identify as males even after gonadectomy. The lack of outcome data in this patient population and the lack of consensus among physicians that currently care for these patients continue to fuel this debate (103,182). The majority of these patients have a bifid or rudimentary scrotum, and cryptorchidism is the rule with cloacal exstrophy (103).

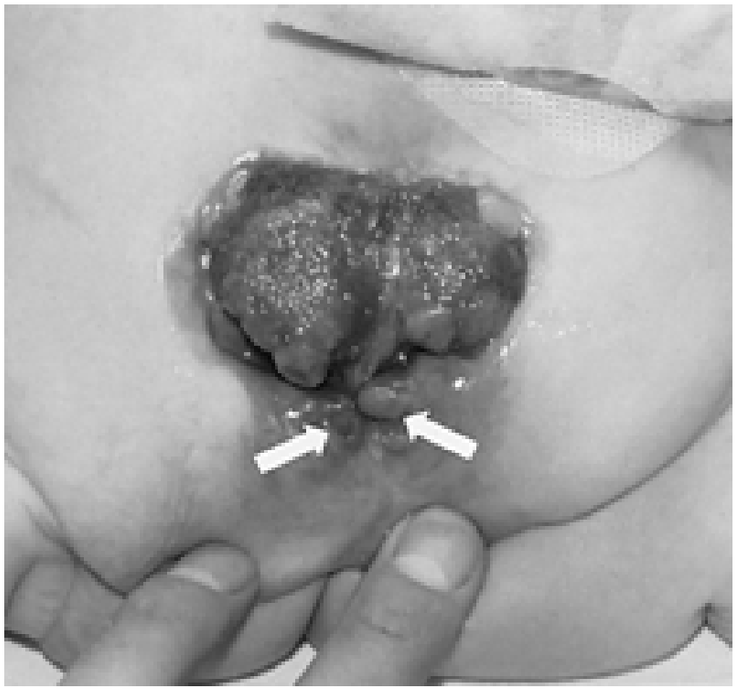

FIGURE 49B.36. Newborn male with cloacal exstrophy. The bifid phallus *(arrows)* in the male patient in association with the bifid scrotum below.

For genotypic girls with cloacal exstrophy, one typically notes a bifid clitoris, wide separation of the labia majora, and anterior displacement of the vaginal vault. These findings are shared with girls who have bladder exstrophy. Gynecologic abnormalities are common as well. These include uterus didelphys (94%), vaginal duplication (54%), and other fusion anomalies of the müllerian duct structures. Vaginal (20%) and clitoral agenesis (17%) are also common (103). Outcome data regarding sexual function and satisfaction toward body appearance for these patients are lacking at this time.

Anorectal and Intestinal Abnormalities

Associated intestinal abnormalities specific to cloacal exstrophy include imperforate anus, foreshortening of the midgut, bowel duplication, malrotation, intestinal atresia, inguinal hernias, and Meckel's diverticulum (103,170). These are in addition to the exstrophy of hindgut, omphalocele, ileal intussusception and exposed appendices that are considered part of the primary pathology of cloacal exstrophy.

Skeletal Abnormalities

In addition to the pubic diastasis associated with exstrophic conditions, patients with cloacal exstrophy can have other skeletal abnormalities. Skeletal anomalies are seen in as many as half of patients with cloacal exstrophy. Anomalies include congenital hip dislocation, talipes equinovarus, and a variety of limb deficiencies (202) (Fig. 49B.37).

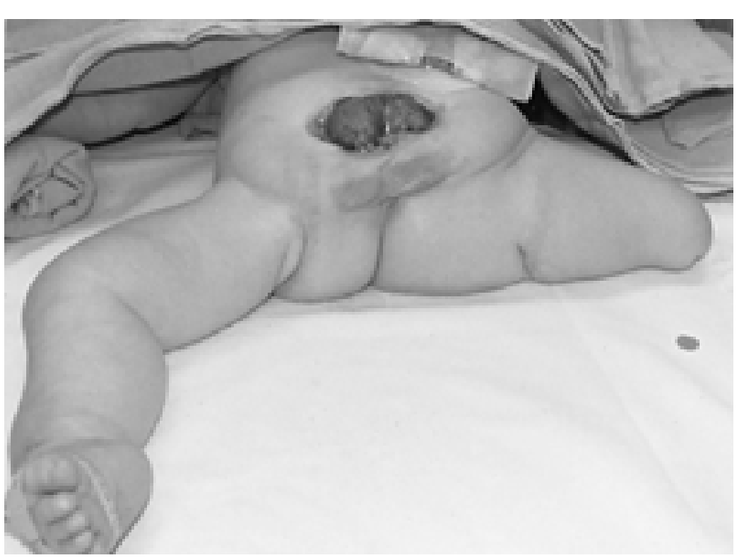

FIGURE 49B.37. Skeletal and limb anomalies associated with cloacal exstrophy. This patient has an underlying limb anomaly of his left lower extremity along with a myelocystocele not pictured here.

Fascial Abnormalities

The fascial anomalies associated with cloacal exstrophy include those previously described for bladder exstrophy. Further, omphaloceles almost always are present with cloacal exstrophy (93,141). If the omphalocele is small, it can be closed during the initial bladder closure. If the omphalocele is large, it may require closure as a primary procedure with the reapproximated bladder halves acting as a silo to decompress intraabdominal pressure. Alternatively,

the omphalocele may be treated with antiseptic paint to promote skin overgrowth. We prefer to correct the omphalocele surgically if the infant is a surgical candidate. We remove the hindgut and reconstruct it during the initial operation if possible and then proceed with primary reconstruction of the bladder at that time or at a later date, depending on whether the patient can tolerate a complete reconstructive procedure in one setting. In our experience, intraabdominal pressure following omphalocele closure determines whether we may proceed with primary bladder closure at the same time as the omphalocele repair or whether these operations must be staged. Aggressive one-stage closure of a cloacal exstrophy can lead to organ ischemia from increased intraabdominal pressure. Rupture of an omphalocele clearly requires immediate attention in these patients and would take precedence over other considerations. Fortunately, this occurs rarely.

Neurologic Abnormalities

Neurologic involvement of the lower spinal cord in the cloacal exstrophy population is reported between 50% to 100% (99,101,141). Most of these patients have lumbar or sacral cord involvement, but thoracic level myelodysplasia has been reported (141). In a review of the literature, 70% of patients with cloacal exstrophy had myelodysplasia, and 33% developed symptomatic tethering of the spinal cord (103). Because of the high incidence of neurologic abnormalities, management of patients with cloacal exstrophy must include neurosurgical input.

The high incidence of neurologic abnormalities in this patient population also affects the potential for these patients to achieve urinary continence (6,106). This factor also must be considered when counseling patients' families and when choosing the reconstructive technique to use to provide these children with a functional and safe urinary tract.

Perioperative Management

Because the care of patients with cloacal exstrophy involves multiple organ systems, these patients are optimally cared for at a tertiary medical center. As a result of the advances in neonatal care and intravenous nutrition, the survival of neonates with cloacal exstrophy is quite high. Mortality in this time period is usually due to concomitant anomalies affecting the cardiovascular or pulmonary systems in these patients rather than as a direct result of the cloacal exstrophy. In the past, mortality was high because of the poor nutritional and fluid support. With hyperalimentation and surgical sparing of the hindgut to preserve salt and water, the cloacal exstrophy patient has a good prognosis. The length of stay for the initial hospitalization may be significant, however.

In the neonatal period, the bladder and hindgut plate should be covered with a hydrophilic gel (e.g., Vigilon) dressing to protect these structures. The umbilical cord should be ligated with a silk suture because an umbilical clamp will abrade the bladder or hindgut plate. We also routinely administer antibiotic prophylaxis to these patients.

Preoperative studies include ultrasonography and karyotyping. Sonographic examination allows the evaluation of the upper urinary tracts, internal genital structures, and spinal cord. MRI may also evaluate spinal abnormalities. MRI of the pelvis is also useful to characterize the anatomy in the pelvis (150). Because the genital anomalies associated with cloacal exstrophy may cause confusion in accurately identifying the sex of the baby, karyotyping is indicated to define the chromosomal sex. The decision to gender reassign usually is based on the assessment of reconstruction potential. This should only be done by a team very experienced in the care of the cloacal exstrophy patient. However, antenatal imprinting may result in behavioral patterns that follow the genetic sex. This has resulted in sex conversion to the genetic sex in later years for some of these children who previously had been sex reassigned.

Management Strategies

Management of the genitourinary system for patients with cloacal exstrophy remains challenging. Many factors affect the surgical approach to these patients, including the severity of the underlying anatomic anomalies, availability of tertiary care facilities, surgeon experience with cloacal exstrophy, and the effects of previous surgical procedures. A specific standard of care does not exist for this patient population. Because of the complexity of exstrophy, specialists

with an interest in the exstrophy-epispadias complex should manage these patients so that their care may be optimized.

As with the management of classic bladder exstrophy, physicians caring for these patients approach the surgical management of the lower urinary tract of these patients with a strategy of functional reconstruction or urinary diversion. Urinary diversion involves excision of the exstrophic bladder plates and creation of a urinary reservoir from the gastrointestinal system. Functional reconstruction of the urinary tract may proceed in a staged or single-stage approach, depending on the physician team responsible for care and patient anatomy.

The goals of urinary reconstruction or urinary diversion include those listed in Table 49B.5 .

TABLE 49B.5. GOALS OF URINARY RECONSTRUCTION/URINARY DIVERSION

Primary Goals	Secondary Goals
Urinary continence	Minimization of the risk for urinary calculi
Volitional voiding (functional reconstruction only)	Minimization of the risk for malignancy associated with the urinary tract
Low-pressure urine storage reservoir	Adequate pelvic floor support
Preservation of kidney function	
Minimize infection	
Abdominal wall closure	
Functionally and cosmetically acceptable external genitalia	

Initial Closure

Closure of a cloacal exstrophy should involve a team of pediatric surgeons and pediatric urologists experienced in the care of cloacal exstrophy. If the baby is medically stable, we prefer to perform the initial reconstructive procedures within the first 48 hours of life. This allows us to take advantage of the pliable bony pelvis if closure of the entire exstrophy is possible. The size of the omphalocele and the size of the hindgut plate and bladder plates largely dictate the extent of the initial closure. A large omphalocele containing liver will preclude any attempt at complete closure (170). In this situation, the omphalocele and plates should be appropriately protected until reconstructive procedures can be undertaken. Usually, the omphalocele is first closed and a colostomy constructed. The bladder plate will function as a silo (all hindgut should be used in the gastrointestinal tract).

Before beginning the dissection, we place ureteral catheters in the ureteral orifices and secure them in place with 5.0 chromic suture. We first approach the omphalocele associated with the cloacal exstrophy. The omphalocele should be repaired first. The initial dissection is begun superiorly (Fig. 49B.38). The umbilical vessels are ligated and the bladder plates are separated from the adjacent skin using sharp dissection. We use Colorado tip electrocautery to do this. We then separate the medial hindgut plate from the paired, separated bladder plates during this stage of the closure (Fig. 49B.39). The ileum should be detached from the hindgut plate. The hindgut is then tubularized and reattached to the ileum to form a large intestinal segment (Fig. 49B.41). The distal end of this segment will be used as a colostomy at the end of the procedure.

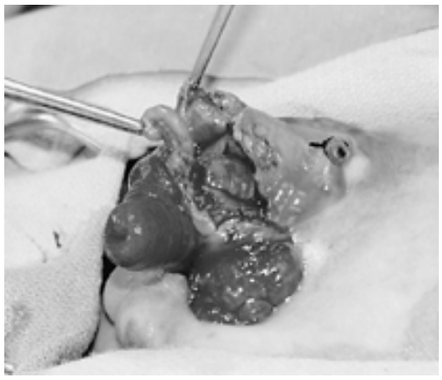

FIGURE 49B.38. Initial dissection used for repair of cloacal exstrophy. The dissection is begun superiorly. The omphalocele should be addressed first before deciding to proceed with hindgut separation from the bladder plate.

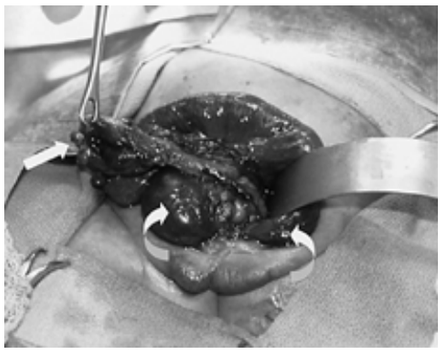

FIGURE 49B.39. The bladder halves *(curved arrows)* are separated from the hindgut *(straight arrow).*

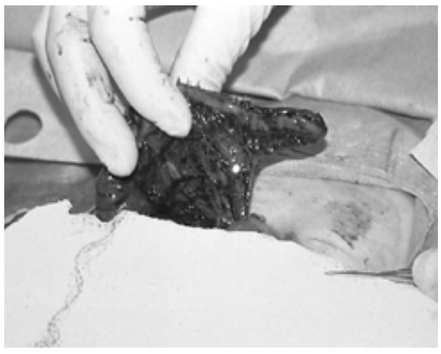

FIGURE 49B.41. The hindgut is separated from the lateral bladder plates and tubularized to allow it to remain in continuity with the rest of the gastrointestinal system.

After the hindgut has been separated from the bladder plates, these plates are reapproximated. Primary bladder closure may be performed at this time if the intraabdominal pressure remains low after omphalocele closure. This can be determined clinically by assessing ventilatory effort following the omphalocele closure. Increased abdominal pressure also may result in organ ischemia following closure.

Single-stage Reconstruction with Total Disassembly Technique and Complete Primary Repair

When possible, we perform a one-stage closure using the complete primary repair technique described for classic exstrophy. The decision to proceed with one-stage closure versus staged reconstruction must be weighed carefully. The importance of including surgeons experienced in the care of these patients cannot be overemphasized. Factors that effect a decision to proceed with a single-stage reconstruction include the size of the omphalocele, the extent of the pubic diastasis, and coexisting medical conditions. In most cloacal exstrophy patients, the bladder and genital repair can be performed several weeks to months after the omphalocele repair without apparent compromise to the primary closure. The bladder, however, must be carefully protected during this period.

When it is not possible to perform a single-stage reconstructive approach for these babies, we prefer to remove the hindgut in its entirety from the exstrophic bladder and then reapproximate the bladder plates (Fig. 49B.42). This, in essence, recreates the anatomy of classic bladder exstrophy. Once the baby has recovered sufficiently to tolerate another surgical procedure, we proceed with functional reconstruction of the bladder, bladder neck, and genitalia using the total disassembly technique previously described in this chapter (178). We have reported on this approach in six patients with cloacal exstrophy. Two patients void volitionally with urinary continence, two patients have dry intervals, and two patients are incontinent of urine and await further reconstructive procedures (82).

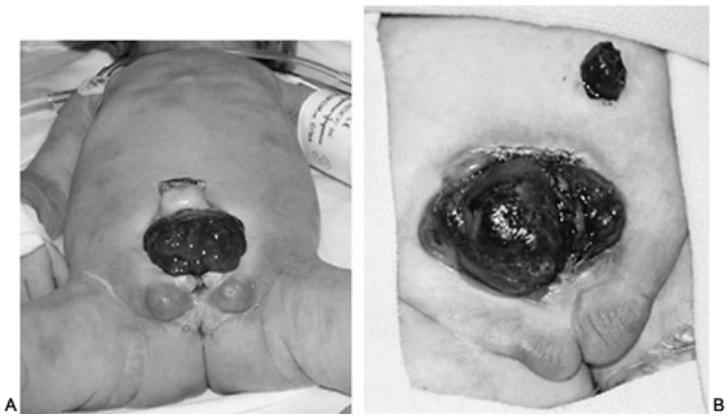

FIGURE 49B.42. A: Photograph before hindgut removal from cloacal exstrophy in a newborn male. **B:** Photograph after removal of hindgut from the bladder halves. The anomaly now appears similar to classic bladder exstrophy in gross appearance. A colostomy is present in the left upper quadrant.

Because of the wide pubic diastasis in cloacal exstrophy, pubic reapproximation often requires iliac osteotomies even if the closure is performed within the first 48 hours of life. We determine the need for osteotomies by assessing the lower extremities and external genitalia for ischemia during pubic reapproximation before osteotomies are performed. We have used osteotomies to assist in the reconstruction of the majority of these patients. Other authors prefer to avoid the use of osteotomies because they believe that osteotomies make the abdominal closure more difficult (103). This has not been our experience.

Staged Reconstruction

A staged reconstructive approach as popularized by Jeffs also has been used to reconstruct the lower urinary system of patients with cloacal exstrophy. Matthews and Gearhart (146) reported on a series of 37 patients managed with a staged approach: 1 patient is continent, 16 patients are dry with CIC, 3 patients have undergone urinary diversion, and 12 patients remain incontinent (146). The results of this series are similar to that reported by Husmann (106) and reflect the difficulty in achieving true urinary continence in this patient population.

The *staged approach* to cloacal exstrophy reconstruction involves the following stages:

1. *Initial bladder closure* ideally is performed in the newborn period. Patients with a wide pubic diastasis may require a staged pelvic closure.
2. *Epispadias repair* is usually performed at 12 to 18 months of age but may be combined with initial bladder closure, especially if initial bladder closure is delayed beyond 6 months of age.

3. *BNR* usually is performed at 4 to 5 years of age or when age appropriate for toilet training and bladder capacity is adequate.

Postoperative Considerations

To increase the success of functional reconstructive procedures, patients must be immobilized adequately following surgery either with a spica cast, external fixators, or Bryant's traction.

Other factors that may affect the success of functional reconstruction include the following:

- Use of postoperative antibiotics
- Ureteral stenting catheters
- Adequate postoperative pain management
- Avoidance of abdominal distention
- Adequate nutritional support
- Secure fixation of urinary drainage catheters (107,140)
- The severity of underlying neurologic anomalies (6,106)

Urinary Reconstruction and Diversion

Because patients with cloacal exstrophy lack a normal functioning anal sphincter, the option of a rectal reservoir is not available. Other forms of urinary diversion may be used including both incontinent and continent forms of urinary diversion. Many of these patients lack adequate intestinal length, especially large intestine. This may preclude the use of colon in urinary reconstruction for diversion or augmentation. Use of stomach for augmentation in these patients is often appropriate; stomach usually is not affected in cloacal exstrophy and its use will not compromise the remaining intestinal system unlike other forms of gastrointestinal urinary reconstruction (2,156,158). Other innovative procedures to avoid the use of intestine for reconstruction in this patient population include ureterocystoplasty and the double tunnel ureteral technique. In this latter procedure, the ureter is reimplanted in the bladder and then used to create a catheterizable channel to the perineum or umbilicus (121) (Fig. 49B.40).

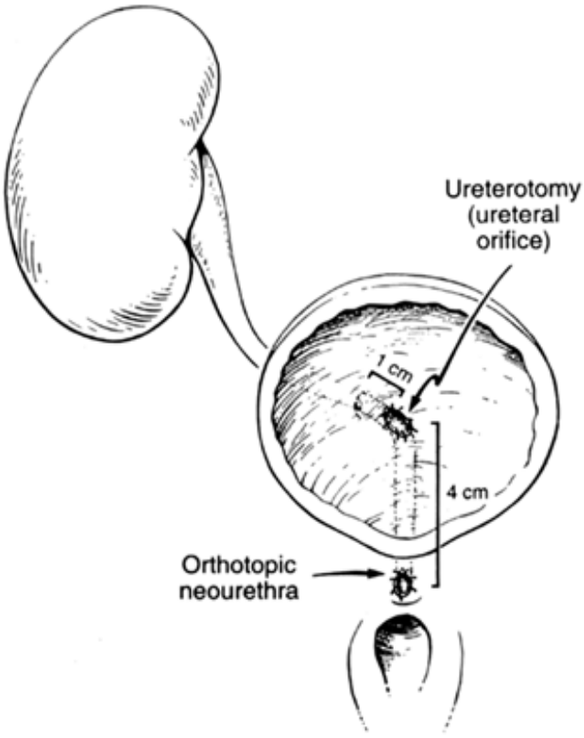

FIGURE 49B.40. Double tunnel ureteral reimplantation and continent catheterizable channel technique. Line drawing of technique. [From Joyner B, et al. A continence procedure using a single ureter as a nonrefluxing ureter and catheterizable neourethra . *J Urol* 1997;157(3):968, with permission.]

Genitourinary Reconstruction/Gender Issues

Currently, the gender issues involved with cloacal exstrophy remain one of the greatest challenges facing physicians who care for these patients. The genitalia of patients with cloacal exstrophy are severely affected. Reconstruction of male patients, in particular, can be quite challenging. Anecdotal accounts of early attempts to reconstruct the genitalia of these patients have been described to result in “the creation of an impotent, psychologically disturbed infertile male.” So, genotypic male patients with cloacal exstrophy have undergone sex conversion in infancy because of these concerns that the small, paired male phalluses in these patients were inadequate for reconstruction. This approach was supported by anecdotal data of unsatisfied patients following reconstruction of the male phallus (141). Furthermore, medical authorities have traditionally recommended a female

sex assignment for male patients when reconstruction of the genitalia appears impossible. This strategy is referred to as an “optimal gender policy” (180).

However, sex assignment for patients with cloacal exstrophy is currently under scrutiny both by the medical profession and by the lay public. Woodhouse and coinvestigators (181) have shown that postpubertal males with microphallus can have normal sexual function. Previous notions that humans were gender neutral at birth and therefore could undergo sex conversion safely in infancy have recently come into question (45). Recent evidence suggests that gender imprinting may occur during fetal development (80). Gender identity now appears to be a much more complex issue than previously thought. Questions about gender identity development in these patients currently fuel a debate about the best policy for sex of rearing of male patients. Beyond this, because patients with cloacal exstrophy are rare and have routinely survived only over the last two decades, little is known about their psychosexual development.

Recent support to preserve a male sexual identity for 46XY cloacal exstrophy patients comes from various sources. Because males with cloacal exstrophy have normal gonads, they experience prenatal androgenization, including the putative effects of this on the central nervous system. Some male-to-female sex-assigned patients also appear to maintain male gender activity and identity. Reiner reported on a cohort of genotypic males who underwent gonadectomy at birth for reasons including cloacal exstrophy and were raised as females. One-third of them still identified themselves as male or engaged in male gender role play (183). Others have found that some of these patients have marked shifts in gender role behavior as well (204). In contrast, Meyer-Bahlberg and co-workers have reported that although these patients may show girlhood masculinity, they do not experience any gross gender dysphoria (153). Husmann reported on a series of 15 postpubertal genetic male patients raised as males. Four of these patients were married and engaged in vaginal intercourse successfully. Nine patients had attempted vaginal intercourse but were unsuccessful as a result of inadequate phallus size, and two patients reported erectile dysfunction but refused evaluation (103).

Because of the lack of data and standardized assessment of these patients, current recommendations are influenced largely by anecdotal evidence. Many questions remain to be answered about this psychologically and emotionally sensitive topic. The consequences of growing up with a cosmetically and functional suboptimal penis are not well understood. Self-esteem issues are evident as noted by Reiner's studies of male exstrophy patients (182). However, patients assigned to a female sex role also appear to struggle with sexual and gender identity. Clearly, standardized evaluation of these patients with rigorous psychosexual assessment and improved support networks will improve our understanding and the care of gender development in these patients. At the present time, most institutions perform selective gender assignment of genotypically male patients with cloacal exstrophy. Importantly, routine assignment of these patients in a female sex role should no longer be considered the standard of care.

Our institutional experience with external genital reconstruction in this patient population covers a period of time when patients were gender converted and later when male gender was maintained. We now reconstruct these patients as males whenever technically possible. Our comparison of these two groups suggests that many gender reassigned individuals will later identify themselves in a male gender role in adolescence and adulthood (155). Technically, however, reconstruction of external male genitalia in the cloacal exstrophy population can be quite difficult. The wide pubic diastasis and small phallic size contribute to the technical complexity; these findings make it more difficult to bring the two phallic halves together in the midline.

Gastrointestinal Reconstruction

Short-gut syndrome usually is present in patients with cloacal exstrophy at birth. The effects of malabsorption and fluid loss from this entity appear to be clinically most significant early in life (105). Many such children require parenteral nutritional support in early infancy (52,75). Because of this, we share the belief that the hindgut should be constructed and placed in continuity with the intestine during initial reconstruction. This will perhaps improve nutrition and also preserve intestinal tissue that may be used in later reconstruction of the urinary tract or to form a vagina, if this is eventually needed. It is interesting to note that Rickham noted the importance of preservation of the hindgut in the intestine in his report of the first surviving neonate with cloacal exstrophy (185). Although hindgut can be preserved with the bladder to augment bladder capacity, we prefer to reconstruct these patients with the goal to provide maximal bowel length.

Preservation and incorporation of the hindgut into the gastrointestinal system also decreases the morbidity of malabsorption, dehydration, and nutritional deficits in patients with cloacal exstrophy. Advances in intravenous hyperalimentation have significantly decreased mortality due to short-gut syndrome in the cloacal exstrophy population. Before the era of hyperalimentation, patients who underwent excision of the hindgut and creation of a terminal ileostomy had a mortality rate of 68% compared with a mortality of 24% for patients who had the hindgut incorporated and brought out as a terminal colostomy. Currently, the mortality rates between patients managed with a terminal ileostomy compared with a colostomy are similar at 5% to 10%. However, the morbidity of patients with a terminal ileostomy remains higher, especially in the first 3 years of life. These patients are admitted more frequently with

dehydration and are dependent on intravenous hyperalimentation for longer periods (39,105).

For the reasons cited above, we rarely leave the hindgut with the exstrophic bladder. Instead, at the time of the initial procedure, we separate the bladder plates from the hindgut segment. The hindgut is then tubularized with the terminal portion of the ileum and exteriorized as a colostomy. In the event of colonic duplication, we attempt to preserve all intestinal segments and place them in series. We also try to preserve appendiceal segments in these patients for possible use in later reconstruction of the urinary tract as for a Mitrofanoff procedure.

Most patients with cloacal exstrophy are managed throughout their lives with a colostomy. Anecdotal experiences with pull-through procedures in this population have led to the belief that this procedure has an unacceptably low success rate. However, Soffer and co-workers recommend the use of a pull-through procedure for those patients with cloacal exstrophy who can achieve solid stool formation and who respond favorably to an enema program. Using this approach he reported complete fecal continence in 3 of 25 patients and 11 patients who were clean with occasional soiling. Success with this approach appears to depend on preservation of as much hindgut as possible in the gastrointestinal system and the ability to form solid stool. Neurologic impairment does not appear to affect the success of this approach (198).

Exstrophy represents a complex problem because of its severity and dimension. Although results of therapy are far from perfect, they reflect remarkable accomplishments from many physicians. There is great potential for further improvement such that one day children born with exstrophy will be treated early and completely and never know that they had a major problem. It is appalling that in the face of the many current successes in the treatment of exstrophy, it is the uninformed who are often making the decision to terminate a pregnancy based on information relating to treatments two or three decades old. The result is unfortunately unborn patients who will never benefit from treatments that can result in healthy, happy, and productive individuals.

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49C THE VALVE BLADDER

Clare E. Close

Part of "49 - THE BLADDER "

C.E. Close: Department of Surgery and Pediatrics, University of Nevada School of Medicine, Las Vegas, NV 89102.

"The primary lesion of posterior urethral valves is a simple one which might be expected to respond readily to simple transurethral resection. Nevertheless, the total care of the boy with urethral valves can be a complicated undertaking."

D.I. Williams (35)

Obstructive uropathy caused by posterior urethral valves is a complex disease process with the potential for life-threatening consequences. In the 30 years since Williams made his comments, there have been remarkable advances in the diagnosis, treatment, and survival of boys with urethral valves. With the increasing incidence of prenatal diagnosis by obstetric ultrasound, early postnatal intervention is available for most infants in the developed countries. Modern pediatric endoscopic equipment combined with high-resolution video imaging makes primary valve ablation safe and effective in almost all neonates with posterior urethral valves. There is growing evidence that with relief of urethral obstruction in early infancy the normal anatomy and function of the bladder, ureters, and urethra can be restored and that in many patients the steady degradation of the urinary tract can be avoided (4).

In 1982, Mitchell (23) introduced the concept of the valve bladder syndrome with his description of a recognizable complex of physiologic and anatomic changes in certain patients with valves. In a series of 70 boys with a history of severe posterior urethral valves, 16 patients demonstrated polydipsia and polyuria, incontinence and constipation, hydroureteronephrosis without vesicoureteral reflux, and poorly sensate bladders with high pressures at low urine volumes. These patients all had in common a delayed diagnosis of valves made after infancy or a history of treatment by urinary diversion with subsequent undiversion.

A number of significant disorders relating to the urinary tract are found in the valve bladder syndrome (Table 49C.1). At the renal level, there is significant renal tubular dysfunction secondary to congenitally abnormal parenchyma and damage from ongoing high bladder pressures transmitted to the upper tracts. Even with fluid restriction, these patients demonstrate a concentrating defect that results in a high obligate urine output. Urinary volumes as high as 3 L per day are typical even in young boys. Because polyuria from end-stage renal disease can cause bladder decompensation and incontinence even in patients with normal bladders, it is not surprising that valve patients with poorly compliant bladders often are incontinent (29). The concentrating defect also results in chronic dehydration that contributes to constipation in these patients.

Renal	Dysplasia, renal tubular dysfunction	High urine output
	Urine concentrating defect	Increased volume work for ureters and bladder
Ureters	Dilated with poor peristalsis	Large dead space
	Scar and fibrosis secondary to infections or previous surgery	Poor emptying
		Possible obstruction after reimplant
Bladder	Poor compliance, small volume, reduced sensation to high pressure	High bladder pressure most of time
	Myogenic failure in end stage	Progressive renal damage
		Progressive bladder damage
Urethra	Voiding dysfunction: functional bladder outlet obstruction	Difficulty with bladder emptying
		Magnified bladder pressure effect

TABLE 49C.1. ANATOMIC CHANGES AND CLINICAL CONSEQUENCES IN THE VALVE BLADDER SYNDROME

The second component of the valve bladder syndrome is ureteral dysfunction. Normal ureteral peristalsis is impaired because of ureteral dilation and ureteral wall scarring secondary to previous diversion surgeries and infection. Many of these ureters have no potential for peristalsis because the muscularis of ureteral wall is replaced with collagen. Furthermore, with urinary retention, which is common in these patients, the upper tracts and bladder pressures equalize and the normal falling pressure gradient from renal pelvis to bladder is lost. Therefore the full bladder acts as an impediment to ureteral drainage and, if noncompliant, exerts pressure on the upper tracts. This is because the only way there can be flow from the kidney to the bladder is from a higher pressure point to a point of lower pressure. Therefore

the energy for flow from the upper tracts is generated entirely by the kidney. Once the bladder pressure exceeds renal perfusion pressure, there will be no flow. If there is reflux, the situation is worse as the bladder and kidney equilibrate at the bladder pressure, which can be very high (16). After the patient voids, the bladder rapidly fills from the drainage of the upper tracts. This results in rapid return of the functional obstruction of the upper tracts. Inefficient upper tract drainage can be even more pronounced after ureteral reimplantation, which increases distal ureteral resistance.

The bladder is the third major component of the valve bladder syndrome and is the focus for both preventing and treating valve disease. Although it is often described as a small bladder, it is the high pressure and poor compliance of the valve bladder that are fundamental to the syndrome. These patients learn to tolerate high intravesical pressures without discomfort. As a result, they tend to delay voiding and suffer incontinence as well as continuing renal damage secondary to the high, transmitted back-pressures. Furthermore, polyuria causes volume stress and contributes to chronic overdistention of the bladder.

Complete bladder emptying is difficult to accomplish because of poor detrusor function, abnormal urethral dynamics, and rapid refilling of the bladder from the dilated upper tracts. Double or triple voids are necessary to empty the bladder and upper tracts. Understandably, patient compliance to such a voiding chore typically is poor, so complete bladder emptying rarely occurs. Of all components of the valve bladder syndrome, the bladder is the most amenable to intervention. Anticholinergic therapy combined with timed voids or clean intermittent catheterization can decrease bladder pressures and facilitate upper tract drainage by routine bladder emptying. Interestingly, anticholinergics also appear to increase sensation in the valve bladder. Mitchell (22) demonstrated a lower pressure threshold for pain from bladder distention in patients treated with anticholinergics and noted that a sensation of bladder fullness at a lower pressure correlates with effective therapy as the patient becomes aware of minor increases in bladder pressure (Fig. 49C.1).

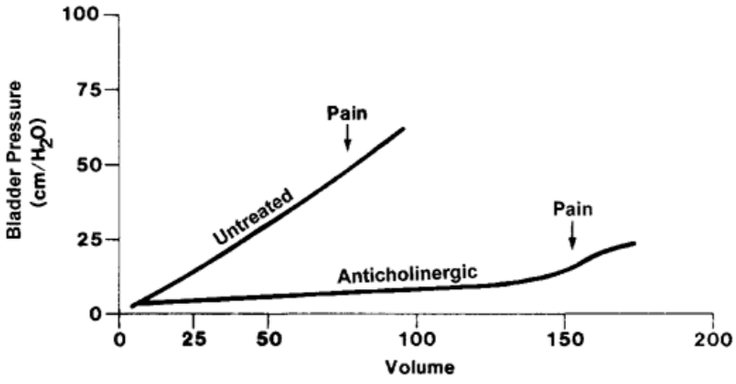

FIGURE 49C.1. Cystometrogram on patient with valve bladder without and with anticholinergic treatment. Without anticholinergic therapy, the filling curve demonstrates low bladder compliance (volume/pressure) and poor sensation to high intravesical pressure. Anticholinergic therapy improves compliance and sensation.

Although the patients originally described by Mitchell represent the severe end of the spectrum of valve disease, there is recognizable dysfunction in the urinary tracts of countless adolescents and young adults with a history of valves. The question remains as posed by Duckett (9) in 1997: “Are valve bladders congenital or iatrogenic?” Two types of variables in valve patients affect the outcome of bladder function: those that are inherent to the bladder's development and those that result from postnatal management. Can the valve bladder syndrome be avoided by changing our approach to the care of these children in infancy?

URETHRAL OBSTRUCTION: A SPECTRUM DISEASE

There is general agreement that posterior urethral valves result in a spectrum of changes in infants' urinary tracts. Variability is in part secondary to the degree of obstruction. Some valves are severely obstructing, leaving only a pinhole

opening in the posterior aspect of the urethra, whereas other valves leave a more generous urethral lumen (7). In a postmortem study Stephens and associates (31) reported the urethral lumen at the level of the valves to measure from 3 mm to more than 1 cm in the anterior–posterior dimension (31). In addition to the degree of obstruction, the gestational timing of the abnormality also affects the urinary tract morphology. Very early obstruction of the urethra occurs in prune-belly syndrome and results in urinary tract distention with irreversible dysmorphic development of the bladder, upper tracts, and abdominal wall (7). The obstruction from posterior urethral valves is known to occur later in gestation and results in bladder wall hypertrophy that may be reversible. Severe upper tract and bladder wall changes seen in patients with mild-appearing valves suggests that in some fetuses the obstructive lesions may partially resolve.

Clinical studies support the protean nature of posterior urethral valves. In 1971, Hendren (11) reported the incidence of secondary anatomic problems in 182 boys with posterior urethral valves. High-grade urethral obstruction occurred in 30% of patients and presented early in life with urinary sepsis, renal insufficiency, and pulmonary hypoplasia. About half of these patients demonstrated severe hydronephrosis, megaureter, and renal insufficiency. Mild obstructive disease was diagnosed in older children who presented with incontinence and urinary tract infections. Controversy still surrounds the classification of patients with apparent urethral valves and minimal or no upper tract changes. Hendren reported normal upper tracts with or without associated low-grade vesicoureteral reflux or paraureteral diverticula in 70% of the patients. Some believe that this end of the spectrum may represent normal urethral variation or the functional obstruction of voiding dyssynergia. Pieretti (25) reported mild valves in 41% of 87 boys studied. These patients had no upper tract dilation, vesicoureteral reflux, or paraureteral diverticula. Diurnal or nocturnal enuresis, urinary tract infection, and urinary frequency were the most common symptoms reported. The resolution of symptoms in 34 of the 36 boys after valve ablation seems to validate the significance of these minor lesions.

Mild cases of valves have also been described in boys who do not demonstrate the expected radiographic signs of obstructive changes in the posterior urethra and bladder on voiding cystourethrography (2). These patients demonstrate abnormal urodynamic findings suggestive of obstructive damage to the bladder, including high filling and voiding pressures and detrusor instability. The authors found minor valve leaflets on cystoscopy and reported improvement in symptoms after valve ablation. Because timed voiding and efforts toward complete bladder emptying often parallel surgical intervention in these patients, it is unclear whether these minor urethral lesions exist because of functional urethral obstruction from dysfunctional voiding or from true anatomic obstruction.

PRESSURE POP-OFF MECHANISMS AND VALVES

The anatomy of the trigone and upper tracts also affects the outcome of bladder function and renal function in patients with valves. In 1986, Duckett and colleagues introduced the concept of pressure pop-off mechanisms in valve patients. Contralateral renal function is preserved in patients with high-grade unilateral reflux into a nonfunctioning kidney. This phenomenon, known as the VURD syndrome (posterior urethral valves, unilateral reflux, and renal dysplasia), suggests that mechanisms that relieve bladder pressures may have a protective effect on renal function. Other pressure pop-off mechanisms include large bladder diverticula, bladder rupture with urinary ascites, and renal urinary extravasation. There is some evidence that decompressive mechanisms may protect bladder development and ultimate function. Rather than the typical thick-walled trabeculated bladder, patients with upper tract pop-off mechanisms may demonstrate a smooth-walled bladder on voiding cystourethrogram. In a series of 85 valve patients, Kaefer and co-workers (17) found 63 boys (67%) with a pressure pop-off. Most patients were not diagnosed prenatally but rather presented with urinary tract infection or voiding symptoms. Almost half of the patients without pop-off mechanisms had poor bladder function with mean end bladder filling pressures greater than 40 cm H_2O and small bladder capacities. Because this was a retrospective review, these data also reflect the effects of late diagnosis and prolonged postnatal pressure work by the bladder. Half the patients without pressure pop-off mechanisms had good bladder function, possibly reflecting other favorable parameters, including less severe obstruction or early treatment. Bladder function has not been reported for valve patients with pressure pop-off mechanisms and a history of early valve ablation.

PRIMARY TREATMENT OF POSTERIOR URETHRAL VALVES

To appreciate the potential effect of postnatal management on development of the valve bladder, it is necessary to understand the wide range of treatments used for patients with posterior urethral valves. Throughout the twentieth century, issues of patient survival and limitations in pediatric endoscopic instrumentation have compelled urologists to use a variety of surgical techniques to treat the congenitally obstructed bladder. It is important to appreciate the swings in treatment philosophies relative to the clinical challenges and the available technologies of the past to understand the change in thinking that has occurred with valve treatment.

Hugh Hampton Young (36), who provided the widely used, albeit challenged, classification of posterior urethral

valves, should be credited with recommending primary valve ablation (6). After endoscopic ablation of the valve leaflets, Young and McKay (37) advocated bladder drainage via a urethral catheter to allow decompression of the distended urinary tract. The duration of bladder drainage depended on the improvement in renal function. Although this treatment often was feasible, many patients were treated by complete bladder decompression through a suprapubic catheter, resulting in urinary tract infections and poor survival (28). Chronic catheter drainage with total decompression of the bladder also raised concern about a functional ureteral obstruction caused by compression by the thickened bladder wall. In an attempt to avoid these difficulties, in 1963, Johnson (14) popularized supravesical urinary tract diversion by temporary cutaneous ureterostomy. Without indwelling tubes to cause infection, Johnson argued that upper tract stasis would be relieved and bladder function preserved by the high diversion procedure. A decade later, however, there was evidence in the literature that urinary diversion in valve patients is detrimental to the bladder. Lome and associates (20) studied the bladders of children undergoing upper tract diversion by ureterostomy. Unlike normal bladders or bladders with acquired obstruction, congenitally obstructed bladders develop severe, irreversible hypertonicity when defunctionalized. All of his patients showed normal bladder capacity before the diversion. After diversion, all but one patient with valves showed reduced bladder capacity with poor bladder distention and compliance. Likewise, Tanagho (32) demonstrated permanent contraction of bladders in valve patients defunctionalized for 10 to 48 months. Two infants who underwent undiversion after 2 and 3 months had return of normal bladder capacity, although bladder compliance and subsequent function were not reported.

In response to the growing concern over bladder function in diverted patients, Duckett (9a) argued that if urinary diversion was necessary, creating a vesicostomy was preferable because it allowed upper tract decompression while preserving bladder function. He believed that the vesicostomy drainage occurred intermittently, thereby permitting normal bladder distention at low pressure volumes (9a). Hendren (10) addressed the bladder's role in the valve patient and suggested a bold shift away from any urinary diversion for severe valve obstruction. For mild valve cases, he believed that primary valve ablation was sufficient treatment. For cases with more severe obstructive changes such as massive vesicoureteral reflux, hydroureter, and bladder neck hypertrophy, Hendren (10) advocated complete early reconstruction of the megaureter and bladder neck in addition to endoscopic valve ablation. With or without upper tract reconstruction, Hendren's practice of early definitive valve treatment allowed the bladder to fill and empty normally in the newborn period.

Despite the surgical advances in valve treatment advocated by Duckett and Hendren, the belief that upper tract diversion preserves or improves renal function continued to drive the practice of performing routine pyelostomies or ureterostomies in infants with even mild, early postnatal creatinine elevation. In 1990, high diversion was once again recommended for newborns with valves and a nadir creatinine of more than 0.8 mg/dL after 5 days of bladder drainage by urethral catheter (3). It can be argued that such a sweeping recommendation for diversion fails to recognize the inherent difficulties in assessing renal function reliably in newborns and that many infants with valves have concomitant primary renal dysplasia and will suffer chronic renal failure regardless of bladder treatment. Serum creatinine, urea nitrogen, and electrolyte values that are routinely used to evaluate older patients are not dependable in newborns because of the normal delay in renal maturation. Even at 4 weeks of age, the renal function of a normal term baby is only 40% of normal (34).

Supravesical urinary diversion is still driven by concern about hydroureteronephrosis persisting after bladder decompression. Although other models of upper tract dilation such as primary megaureter or persistent pelvocaliectasis after pyeloplasty persist without obstruction, it is commonly held that hydroureteronephrosis after valve ablation indicates obstruction at the ureterovesical junction. Tietjen and colleagues (33) used the Whitaker test to challenge this concept and demonstrated fixed ureterovesical junction obstruction in only 4% of renal units in valve patients who had undergone proximal urinary diversion for newborn renal insufficiency. In support of proximal diversion, Aliabadi and associates (1) reported renal biopsy evidence of obstruction in 60%, dysplasia in 25%, interstitial fibrosis in 25%, and infectious change in 15% of valve patients studied. However, because biopsies were performed in these patients after the newborn period, these findings may reflect secondary or postdevelopmental influences and not the basic histology of *in utero* obstruction. Histopathologic data from newborns with ureteral obstruction are limited. Tietjen and colleagues (33) reported renal dysplasia in 85% of renal units from babies treated by proximal diversion for renal insufficiency at birth. In an autopsy study of fetuses surviving to 14 to 37 weeks of gestation with bilateral renal obstruction, Diakha-Dalmane and co-workers (8) found that all fetuses at more than 20 weeks of gestation showed renal dysplasia with blastema cells, interstitial fibrosis, and an arrest of nephrogenesis. These findings support the irreversibility of obstructive change that occurs early in gestation.

The impression that high urinary diversion can restore renal function in valve patients with newborn renal insufficiency is not supported by the recent data. In a review of the long-term outcome of patients treated by primary valve ablation, vesicostomy, or high diversion, Smith and associates (30) found no evidence that urinary diversion delayed the onset of end-stage renal failure. Thirteen percent of patients overall progressed to end-stage renal failure by age

15 years. Likewise, a multicenter study of 178 infants treated for valves in the first year of life found no long-term renal benefit with proximal urinary diversion (27). Addressing the same question, we evaluated newborns with posterior urethral valves and renal insufficiency, defined as postbladder drainage nadir creatinine levels greater than 1.2 mg/dL. The patients were treated with primary valve ablation or upper tract diversion, depending on the surgeon's preference. Progression to end-stage failure occurred with either treatment when renal insufficiency was present after creatinine stabilization at birth. Three of six children in each treatment group needed dialysis before age 3 (4). If there is no hope of reversing the primary renal dysplasia and *in utero* damage already suffered by these kidneys, diversion can be avoided and treatment can focus instead on bladder function preservation.

BLADDER FUNCTION AND POSTERIOR URETHRAL VALVES

To date, bladder function in boys with valves has been studied only through historical reviews. The conclusions reached by these authors must be examined carefully because confounding factors including severity of obstruction, age at treatment, and posttreatment bladder management may affect bladder function. The common patterns of bladder dysfunction associated with valves are those reported by Peters and co-workers (24) in 1990. In a urodynamic evaluation of 41 valve patients, the authors found myogenic failure, hyperreflexia, and small, poorly compliant bladders. Furthermore, some of the patients had more than one of these abnormalities. These data add to our understanding of the range of voiding dysfunction in valve patients, but because all patients were referred for voiding abnormalities (35 of 41 patients referred for incontinence), little can be concluded about the incidence of normal bladders in valve patients. Using serial urodynamic evaluations, De Gennaro and associates (5) found similar types of bladder dysfunction with an apparent progression from hypercontractility in infancy to hypocontractility or even myogenic failure in adolescence. Because the authors do not specify the age or type of initial treatment, these data may reflect the influence of a variety of primary valve treatments and the effect of years of dysfunctional voiding and ongoing pressure and volume work by the bladder.

The data presented by Kim and associates often are cited as evidence that urinary diversion in valve patients is not deleterious to ultimate bladder function even though only 4 of 36 patients were treated with proximal diversion, and statistical significance could not be determined because of the small sample size (18). These authors state that patients undergoing diversion by vesicostomy or pyelostomy demonstrated better compliance than those treated with primary valve ablation, although there was no difference in the number of patients with normal compliance in the different treatment groups. The demographics of the treatment groups are dissimilar, with urinary diversion being performed in newborns and valve ablation being delayed to a median age of 7 months. The age at the time of initial valve ablation in patients demonstrating poor compliance is not reported. Furthermore, the valve ablation group includes boys treated as adolescents. The effect of years of probable dysfunctional voiding in the older patients may well contribute to loss of compliance, as would persistent urethral obstruction in infants with treatment delayed beyond several months of life. In our review of patients treated in the first year of life with primary valve ablation, the only patient with poor compliance was the patient whose treatment was delayed until 5 months of age because of a missed diagnosis (4).

Reports of urodynamic findings in valve patients can be misleading if actual bladder pressures and volumes are not presented. High bladder compliance usually is interpreted as a normal bladder with good storage potential and therefore a good prognosis for continence and preservation of the upper tract function. A very large bladder volume can result in a normal volume-to-pressure ratio (good compliance) but still have high end filling pressures that could be detrimental to preservation of upper tract function. This would be magnified in a patient who tended to be inefficient in bladder emptying. In the older valve patient, in whom bladder volumes of 1 L are possible, bladder compliance can be “normal” (greater than 20 mL/cm H_2O) even though bladder pressures are greater than 30 cm H_2O (Fig. 49C.2).

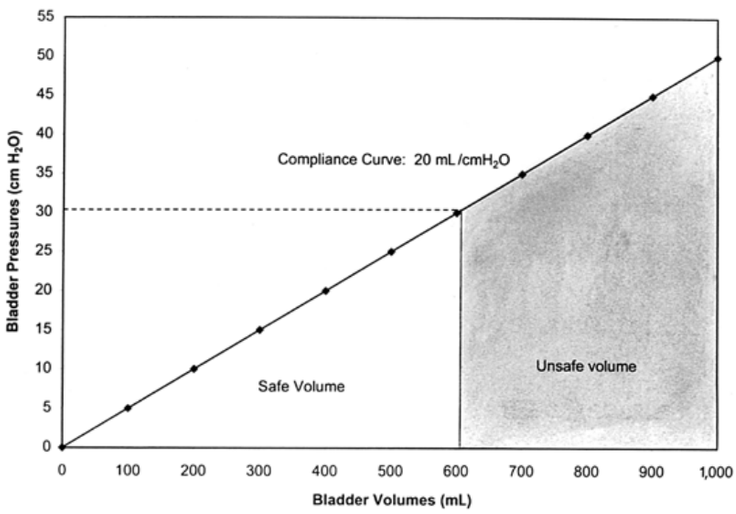

FIGURE 49C.2. Cystometrogram on valve bladder patient with bladder compliance calculated at 20 mL/cm H_2O. Note that because of high urine volume, dangerous intravesical pressures can develop at the high end of bladder volumes even with apparent normal compliance.

Several authors have published retrospective urodynamic evaluations of valve patients treated during infancy. Holmdahl and associates (12) evaluated boys with serial urodynamic studies performed over several years. Although these patients were diagnosed early (mean of 1.3 months), 75% of the patients had prolonged bladder decompression by a suprapubic tube before valve ablation. The authors reported initial hypercontractility and small-capacity bladders that improved slowly over time. Interestingly, the patients with the history of the longest diversions ultimately needed clean intermittent catheterization.

Podesta and colleagues (26) reported urodynamic findings on infants and toddlers treated by valve ablation or vesicostomy in comparison to age-matched controls. Again, this is a historical review, with all patients diagnosed after presentation with urinary tract infection or retention. Valve ablation was performed later than was urinary diversion, with only one primary valve ablation being performed in the first month of life. Three years after treatment, patients treated with valve ablation demonstrated bladder capacities larger than those in age-matched controls but with safe end filling pressures. Decreased compliance and bladder capacity were noted in patients treated by vesicostomy. Dangerously high end filling pressures developed in two of these patients, necessitating bladder augmentation in one patient.

Jaureguizar and colleagues (13) compared urodynamic outcomes for patients treated with high urinary diversion or primary valve ablation. They reported poor compliance in 4 of 30 patients treated with primary valve ablation, with one-third of this treatment group treated after 2 months of life. Poor compliance was similarly found in 5 of 29 patients managed with high diversion, with all patients treated before 2 months of age. Unfortunately, there are no longitudinal studies of bladder function in valve patients treated as newborns and followed closely with appropriate bladder management and evaluation.

THE POTENTIAL FOR BLADDER HEALING: CAN THE VALVE BLADDER BE PREVENTED?

In the fifth month of gestation, the human fetal bladder begins to cyclically fill, with a minimal increase in intravesical pressure. The filling and emptying *in utero* provides stretch forces on the components of the developing bladder wall to produce a compliant organ that can store urine at low pressures and empty effectively. Normal bladder function depends on smooth muscle cells, in addition to elastin and collagen, integrated as the active and passive components of the bladder wall.

With fetal bladder outlet obstruction by posterior urethral valves, the developing bladder carries out pressure work to empty. To overcome outflow resistance, the muscle mass of the bladder expands with an increase in contractile proteins and a significant alteration in the composition and distribution of collagen in the bladder wall. In unobstructed animal models, compliance improves with gestational age as the ratio of type III to type I collagen decreases. In bladder tissue from pediatric patients with anatomic or functional obstruction and poor bladder compliance, the type III-to-type I ratio is increased, with type III collagen infiltrating the detrusor muscle bundles. These aberrations in normal bladder wall architecture appear to be reversible only if the obstruction is relieved before the fibrotic process is too advanced (21). The chronically obstructed bladder in patients with a history of late diagnosis and treatment of valves cannot be rehabilitated and is therefore the focus of long-term management. In contrast, in developed countries obstetric ultrasound and modern pediatric endoscopic equipment are readily available, so early valve ablation should be possible. This would restore normal cycling to the postnatal developing bladder and maximize the potential for bladder healing.

Clinical data support the premise of bladder healing in the newborn. In babies treated with valve ablation alone in the first days of life, normal bladder morphology in previously trabeculated bladders is evident on cystourethrograms performed at age 1 year (Fig. 49C.3). Improvement in bladder function is further implied by the resolution of vesicoureteral reflux in infants after early valve resection (4,15). This is well documented in multiple studies and is consistent with other data showing reflux resolution with improving bladder function in children without valves (19).

We found improvement in reflux grade in 18 of 19 refluxing renal units in infants 1 year after primary valve ablation (Fig. 49C.4). Complete resolution of reflux occurred within 2 years of valve ablation in 12 of 14 patients (86%) (4). Urodynamic findings of good compliance and successful potty training in patients treated with early valve resection also attest to bladder healing after immediate postnatal bladder cycling. Urodynamic evaluation comparing children treated with newborn valve ablation and newborn urinary diversion demonstrated better bladder volumes and compliance in the valve ablation group. Furthermore, by age 4 more than 90% of patients treated by valve ablation were potty trained, whereas only 17% of the diverted patients had achieved day and nighttime continence. However, this was not a prospective randomized study, and doubt still exists as to the actual potential for bladder healing. It should be noted that in other models, in infant neurogenic bladder, and in exstrophy, normal bladder cycling seems to stimulate normal bladder development. Abnormal bladder cycling results in an abnormal bladder. Obstruction or diversion may significantly reduce the potential for normal development.

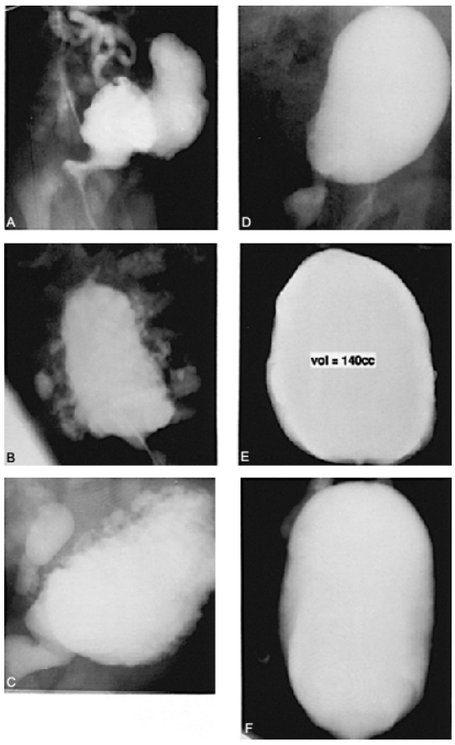

FIGURE 49C.3. A–C: Voiding cystourethrogram in three newborn infants with posterior urethral valves. Note bladder wall trabeculation and diverticula before valve ablation. **D–F:** Voiding cystourethrogram of same patients 1 year after newborn valve ablation, demonstrating healed bladder with smooth wall and normal capacity.

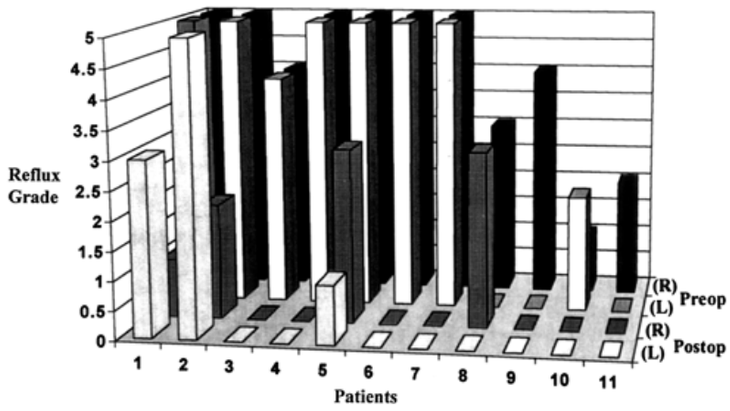

FIGURE 49C.4. Spontaneous resolution of vesicoureteral reflux 1 year early valve ablation alone. Results from 19 refluxing units in 11 patients are depicted. Persistence of reflux is associated with a nonfunctioning renal unit in two patients and upper tract duplication in one patient. L, left; Postop, 1 year postoperatively; Preop, before valve ablation; R, right.

Today, most infants with posterior urethral valves are diagnosed *in utero,* allowing ablation of the urethral obstruction

in the first days of life and in some circumstances temporary diversion *in utero.* Although underlying primary renal dysplasia cannot be altered by postnatal intervention, bladder function often can be preserved, thereby avoiding the cascading effects of the valve bladder syndrome. Careful follow-up of these boys is necessary to assess and manage elimination dysfunctions that may contribute to functional bladder outlet obstruction after potty training. Serial ultrasounds, urodynamic studies, and electrolyte evaluations should continue through adolescence. With this careful management after newborn valve ablation, there is a significant chance of preventing the valve bladder syndrome.

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49D NEUROVESICAL DYSFUNCTION AND DISORDERED MICTURITION IN CHILDREN

Mark F. Bellinger

Francis X. Schneck

Part of "49 - THE BLADDER "

M.F. Bellinger and F.X. Schneck: Department of Surgery/Urology, University of Pittsburgh; Department of Pediatric Urology, Children's Hospital of Pittsburgh, Pittsburgh, PA 15213.

Normal function of the lower urinary tract is the result of coordination of many interrelated neural and muscular structures. Balanced reflex activity of the detrusor and periurethral striated musculature is essential to allow the bladder to achieve low-pressure storage, voluntary micturition, and complete emptying. Sensation of bladder fullness acts as both a trigger for voluntary micturition and a protective mechanism against vesical overdistention. Neurologic,

infectious, structural, and psychologic processes that alter normal bladder activity may both jeopardize renal function and become a source of incontinence, urinary tract infection (UTI), and renal injury. In addition, unique congenital and developmental problems frequently are associated with neurovesical dysfunction in children. These all challenge the physician caring for such patients to preserve kidney function and secure urinary continence.

DEVELOPMENT OF NORMAL BLADDER CONTROL IN CHILDREN

The normal lower urinary tract provides low-pressure storage and voluntary elimination of urine, functions regulated by somatic, sacral parasympathetic, and thoracolumbar sympathetic nerves (62). Coordinated neuromuscular activity normally results in urethral pressure that is greater than vesical pressure at all times and during all forms of activity that increase vesical pressure. Bladder filling normally results in a negligible rise in intravesical pressure. The sequence that initiates micturition involves total relaxation of the striated sphincter, a decrease in urethral pressure, detrusor contraction, and opening of the bladder neck and urethra.

In the infant, neural pathways involved in micturition remain incompletely developed, and micturition is the end result of an involuntary spinal reflex. Detrusor and sphincter act in a coordinated fashion, voiding occurs frequently, and the bladder is completely emptied (136). This phase of bladder development has been termed detrusor micturition (184). Gradual maturation of the central and peripheral nervous systems brings the act of micturition under voluntary control, the first conscious awareness of bladder function usually occurring between 1 and 2 years of age (136). During the second year of life, normal development enables most children to sense bladder fullness, to communicate recognition of the need to urinate, and to hold increasingly larger volumes of urine for longer periods of time. Micturition therefore occurs less frequently. Between 15 and 24 months of age, most infants become fully aware of voiding, and toileting habits begin to develop with parental encouragement. During this first phase of maturation, reflex micturition ceases as the child begins to exert conscious control, first evident as a voluntary tightening of the bladder outlet in response to the sensation of bladder fullness. In most children, this brief phase of discoordinated micturition rapidly gives way to the normal adult mechanism of suppressing detrusor activity to maintain continence. However, pathologic persistence of the earlier stage may be seen in dysfunctional voiding of minor degrees and is most severe in the Hinman-Allen syndrome (nonneurogenic neurogenic bladder) (106). Further development of neuromuscular coordination between the pelvic floor, abdominal muscles, and diaphragm allows the voluntary initiation or interruption of micturition to be initiated at any stage of bladder filling. This final phase of development usually occurs between 3 and 4.5 years of age. During this period, nocturnal dryness is achieved in most children, although persistent enuresis is common (99,164). Bloom and co-workers (23) retrospectively surveyed the development of bladder control in 1192 children. They found that toilet training was achieved at ages ranging from 9 months to 5.25 years (mean 2.4 ± 0.6 years) in this group. Hellstrom and others (99) performed a similar survey in 7-year-old children. They found nocturnal enuresis in 7.1% of girls and 11.9% of boys, diurnal incontinence in 6% of girls and 3.8% of boys, and urgency in 21% of girls and 18% of boys, underscoring the spectrum of bladder control development in this age group.

Bladder capacity increases gradually with age, playing an important role in the development of urinary continence. Rather than being a primary cause of bladder development, however, increased capacity likely is both a reflection of maturation of the nervous system and behavioral adaptation. During childhood, bladder capacity increases approximately 30 mL per year (136). Muellner (184) documented a rapid increase in voided volume from age 2 to 4.5 years, with a gradual increase through childhood. Several authors have offered guidelines for estimation of appropriate bladder capacity in children. Berger and others (20) estimated bladder capacity in childhood as “age in years plus 2 equals bladder capacity in ounces.” Houle and associates (111) reviewed 923 urodynamic studies in children, using as an end point for bladder filling one of the following: desire to void, sensation of fullness, discomfort, or leak. They defined the minimal acceptable bladder capacity for age as “16 (age in years) + 70 mL” (Fig. 49D.1).

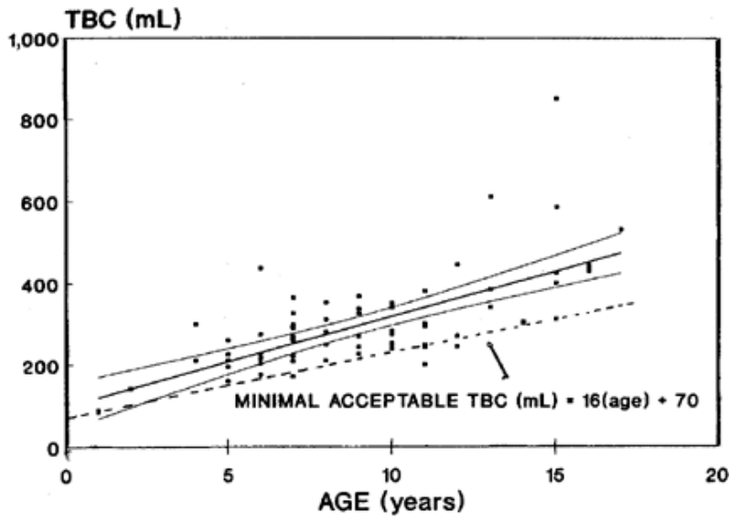

FIGURE 49D.1. Linear regression between age (years) and total bladder capacity [TBC (mL)] with 95% confidence interval for regression. *Dashed line* represents minimal acceptable total bladder capacity (mL) equals 16(age) + 70. (From Houle A, Gilmour RF, Churchill BM, et al. What volume can a child normally store in the bladder at a safe pressure? *J Urol* 1993:149:561, with permission.)

The development of normal continence is a complex process involving neurologic, developmental, and social factors. It also has been shown that emotional factors may influence the development of normal bladder control (65). As a result, many factors must be considered when evaluating a child with abnormal bladder function. This is especially critical during the period of transition from a functionally “reflex” infant bladder to conscious control of urination, a time when the assessment of bladder function is most difficult. The urologist must be prepared to consider all available historical data and to use multiple methods of clinical assessment to determine whether bladder function is normal or abnormal in this age group.

CLASSIFICATION OF NEUROVESICAL DYSFUNCTION

Dysfunction of the lower urinary tract may result from congenital or acquired lesions and may be expressed clinically as urinary retention, frequency, urgency, interrupted urination, incontinence, or UTI. Lower tract dysfunction

may alter ureterovesical dynamics and impair ureteral motility. Hydronephrosis or vesicoureteric reflux (VUR) may result. The complexity and heterogeneity of neurovesical dysfunction has lead to the description of several clinically useful classification schemes, several of which are described in the following text.

In 1971, Bors and Comarr (26) classified neurologic lesions that affect bladder function into sensory or motor, complete or incomplete, and according to location above or below the level of the sacral reflex arc. Lapides (154) built upon this foundation to outline a classic description of neuropathic bladder dysfunction, which included five categories: sensory paralytic bladder, motor paralytic bladder, autonomous bladder, reflex bladder, and uninhibited bladder. Many other systems of categorization have replaced this simplistic classification scheme that is outmoded by newer nomenclature that is based on functional derangement and is familiar to most urologists. The *sensory paralytic bladder* describes intact motor function without normal sensation. The absence of sensation may allow chronic overdistention to the point of detrusor decompensation. Bladder rehabilitation by timed voiding may prevent overdistention and preserve normal detrusor function. This type of neuropathic dysfunction is uncommon in childhood. A *motor paralytic bladder* results from loss of motor function, while sensation remains intact. Causes are trauma, poliomyelitis, and lumbar disc disease. *Autonomous bladder* dysfunction results from loss of both sensory and motor innervation leading to a large-capacity bladder with no detrusor contraction. Causes are spinal trauma below the cauda equina, radical pelvic surgery, and meningomyelocele or sacral agenesis. A *reflex bladder* results from complete injury above the level of the sacral reflex arc, commonly from spinal cord injury, tumor, or transverse myelitis. Unchecked sacral reflex activity results in a hyperreflexic bladder. Sensation is absent. *Uninhibited neuropathic bladder* dysfunction reflects incomplete inhibition of reflex activity by suprasacral inhibitory centers, and may be caused by central nervous system lesions (vascular, tumor, degenerative, traumatic). Sensation is present, extreme urgency is seen, and urgeincontinence may result from uninhibited detrusor contractions. Although the Lapides classification is descriptive, few patients fall into a single category, and in clinical practice, most demonstrate mixed lesions with various degrees of severity. For these reasons, urodynamic classification systems as described by Krane and Siroky (146) (detrusor: hyperreflexic, normoreflexic or hyporeflexic; sphincter: coordinated, dyssynergic, or nonrelaxing) and the International Continence Society (115) (detrusor: normal, overactive, underactive; urethra: normal, overactive, incompetent; sensation: normal, hypersensitive, hyposensitive) have appeal. For practical purposes, the end result of neurovesical dysfunction may be classified as either *failure to store* or *failure to empty* (69).

CLINICAL PRESENTATION OF NEUROVESICAL DYSFUNCTION IN CHILDHOOD

Dysfunction of the lower urinary tract may result from both congenital and acquired lesions, and may be expressed clinically as incontinence or retention, interrupted urinary stream, hesitancy, frequency, urgency, UTI, renal failure or a combination of symptoms. Many children with congenital causes of neurovesical dysfunction simply never gain normal urinary control. UTI, typically recurrent, is a common reason for urologic consultation. Constipation and/or fecal soiling are common. Hydronephrosis and/or VUR are common radiologic findings.

EVALUATION OF THE CHILD WITH SUSPECTED NEUROVESICAL DYSFUNCTION

History

Urologists are frequently called upon to evaluate children with known, suspected, or unrecognized neurovesical dysfunction. When neurovesical dysfunction is suspected, it is extremely important to review the child's medical and developmental history to determine whether the dysfunctional pattern is acute or chronic, stable or progressive, and primary or secondary to a period of normal urinary control. It should be noted whether other symptoms that frequently accompany neurovesical dysfunction are present, such as

changes in bowel habit or gait, back or leg pain, seizures or neurologic complaints, and erectile dysfunction in the older child. It is important to review the history of prior management of urinary symptoms, including medical and surgical interventions. *Incontinence* is a common presentation of urologic disease in childhood, and an accurate history is perhaps the most important aspect of its differential diagnosis. Incontinence should be categorized as primary or secondary, continuous dribbling or occasional leakage (large or small volume), stress or urge, prevoid or postvoid, and nocturnal or diurnal. Is the urinary stream weak or strong? Is there sensation of fullness or any sensation of voiding, or is the wetness noticed only after it occurs? Is voiding spontaneous, or merely associated with Valsalva maneuver? Hinman (104), Allen (5), Galdston and Perlmutter (81), and others have documented that psychologic, psychosocial, and behavioral disturbances can seriously alter voiding dynamics. A brief review of social history should therefore assess family dynamics, stress, school performance, and peer relationships. This assessment usually can be accomplished superficially with a few probing but nonthreatening questions, and is particularly important in cases of secondary incontinence or in the face of what appears clinically to be neurovesical dysfunction but without signs of an obvious neurologic cause. It is important to assess parent–child interaction during the interview and examination. Strained relationships and affective disorders may suggest social problems in the home, a possible additional factor in the development of dysfunctional voiding. The possibility of sexual abuse as the basis of significant bladder dysfunction should be considered in every patient.

Physical Examination

Physical examination may either confirm or refute the suspicion of neurovesical disease. A complete physical examination should include an assessment of gait, balance, muscular symmetry, and general neurologic status. Reflexes should be tested for symmetry and the presence of either hyperreflexia or hyporeflexia. The back should be examined for the presence of skin tags, dimples, hemangiomas, overlying hair patches, or other signs of dysraphism (4,97) (Fig. 49D.2) Examination of the abdomen is performed to detect bladder distention or a colon filled with stool. The ability to either stimulate bladder emptying by gentle bladder “massage” or to express urine by suprapubic compression or Credé's maneuver should be noted. The genitalia are examined to note the presence of skin excoriation (as a result of incontinence); hypospadias or meatal stenosis; cryptorchidism; and labial, introital, perineal, or anal anomalies. Rectal examination should assess perianal sensation and tone, the presence of hard stool (indicating possible bowel dysfunction), and the presence of a normal sacrum. The

bulbocavernosus reflex can be elicited by squeezing the glans penis or clitoris and evaluating the anal wink, indication of an intact sacral reflex arc.

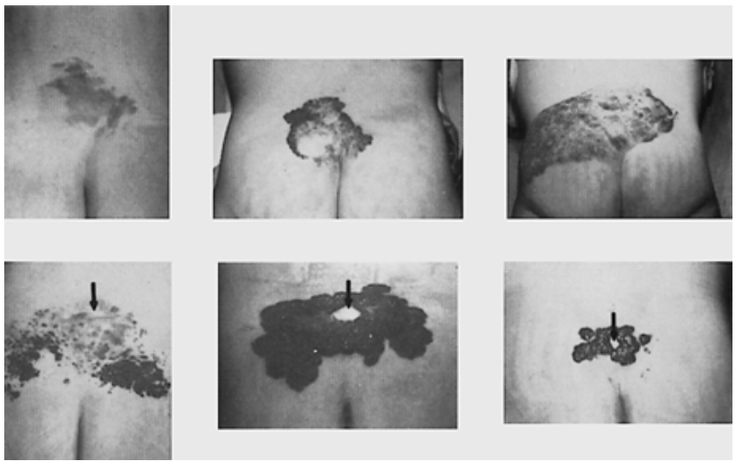

FIGURE 49D.2. Lumbar cutaneous hemangiomas associated with tethered spinal cords. *Arrows* point to transparent membranes. (From Albright AL, Gartner JC, Wiener ES. Lumbar cutaneous hemangiomas as indicators of tethered spinal cords. *Pediatrics* 1989;83:977, with permission.)

Laboratory Examination

Urinalysis is an important part of the initial examination of all children with suspected urinary tract disease. In the infant, urine can be obtained by a bag technique and occasionally by stimulating the voiding reflex by gentle suprapubic massage, in which case a midstream specimen may be obtained in both boys and girls. In older children, clean-catch specimens are generally reliable for culture when proper instruction is provided to the child and parents. When contamination is a concern, urine may be obtained by urethral catheterization or by suprapubic aspiration. All urines with abnormal sediment suggestive of infection should be plated for culture and sensitivity.

Once neurovesical dysfunction has been diagnosed, serum creatinine should be measured. If either elevated serum creatinine or renal scarring is present, glomerular filtration rate (GFR) may be determined by measurement of creatinine clearance. Infants and children who are incontinent may have GFR determination by radionuclide clearance techniques that do not require urine collection (234), or they may be estimated using the method described by Schwartz and associates (218). If significant proteinuria is documented, urinary protein excretion should be quantified.

Radiologic Examination

Radiologic examination of the urinary tract is an integral part of the evaluation of children with neurovesical

dysfunction because disordered bladder function may be associated with renal injury secondary to either hydronephrosis or VUR (245). The plain abdominal film should be examined for bony abnormalities (spina bifida occulta, sacral agenesis, and widened interpedicular distance). In addition, the degree of constipation can be assessed and the presence or absence of urinary calculi noted, especially in patients with longstanding neurovesical dysfunction and relative immobility (Fig. 49D.3).

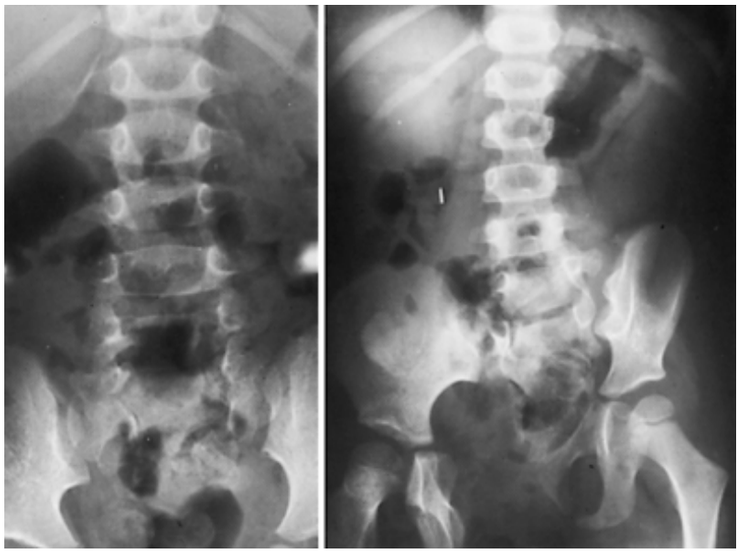

FIGURE 49D.3. Lumbosacral anomalies associated with neurovesical dysfunction.

The upper urinary tract may be imaged by ultrasound, intravenous pyelography (IVP), or radionuclide scan, depending on the age of the child, a knowledge of preexisting renal pathology, and the information desired. Most children are screened adequately with diagnostic ultrasound, which may assess renal size, upper tract dilation, gross renal scarring, bladder capacity, bladder wall thickness, and postvoid residual urine volume (76). When abnormal findings are documented by ultrasound, follow-up urography or radionuclide studies may be indicated. Although the IVP is used less commonly for routine imaging in children with neurovesical dysfunction since the advent of diagnostic ultrasound, it may be particularly useful in specific instances. Common indications for the use of intravenous urography include evaluation of children with severe kyphoscoliosis in whom ultrasound imaging of the kidney is technically difficult, anatomic delineation of ureteral and calyceal anatomy in the patient with calculus disease, evaluation of the patient with urinary diversion, and delineation of the renal anatomy in children with rotational or fusion anomalies of the kidneys. Intravenous urography should be tailored to answer particular questions asked by the urologist while minimizing radiation exposure to the patient.

Radionuclide renal imaging has assumed an ever-increasing role in the evaluation of children with neurovesical dysfunction. Because a multitude of radionuclides are currently in use, the urologist who orders or interprets radionuclide images must understand something about both the characteristics of the radionuclide and the important technical aspects of patient preparation and handling during the imaging process (239). Each study should thus be tailored to answer the clinical questions being asked.

Diuresis renography is usually performed to confirm or exclude the diagnosis of supravesical obstructive uropathy and is most helpful in the assessment of chronic hydronephrosis or hydroureteronephrosis when the question of dilation versus true obstruction arises (Fig. 49D.4) (53). Technetium-99m-diethylenetriamine pentaacetic acid (DTPA) (193) or technetium-99m-mercaptoacetlytriglycine (MAG3) (55) is used most frequently for these studies because they offer rapid renal clearance and tubular excretion. The renogram is performed after oral hydration, and frequently after a period of intravenous hydration as well. This aspect of the study is critical because furosemide acts on the ascending limb of the loop of Henle to promote diuresis, and the results may be invalid if the patient is dehydrated or renal function is poor. An indwelling bladder

catheter should continuously drain the bladder during the study. This is extremely important in patients with neurovesical dysfunction, VUR, and other causes of poor bladder compliance (i.e., posterior urethral valves) because a poorly compliant bladder, when even partially full, may generate high enough intravesical pressure to hinder upper tract drainage (167). Diuresis renography is one of the most technically demanding imaging studies both to perform and analyze, and many pitfalls exist (53). The Society for Fetal Urology and the Pediatric Nuclear Medicine Council have described a "well-tempered" renogram that attempts to standardize the many aspects of this study (54).

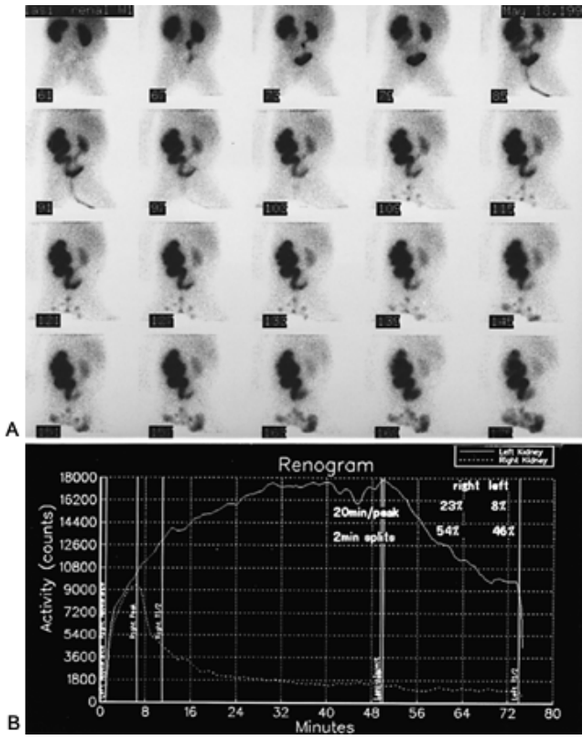

FIGURE 49D.4. A: Diuresis renogram images. Right kidney drains well, left kidney slowly. **B:** Washout curves from diuresis renogram of same patient. Right kidney drains readily, while left kidney takes longer to accumulate radionuclide and drains slowly after furosemide administration.

Static renal imaging using technetium-99m dimercaptosuccinic acid (DMSA) has played an increasingly important role in several clinical scenarios. DMSA images may provide information about differential renal function in children with disordered renal anatomy and renal parenchymal scarring (213) (Fig 49D.5B). DMSA imaging also has proven helpful in the delineation of acute parenchymal inflammation (pyelonephritis) (Fig 49D.5A) (117). This diagnosis is not always easy to make on clinical grounds alone, especially when a child who is managed by intermittent catheterization and who has chronic bacteriuria presents with a fever and lack of other localizing symptoms. In this clinical setting, UTI is frequently considered the source of fever, even though the differential diagnosis may include a viral syndrome. A positive DMSA scan, confirming pyelonephritis, allows the physician to begin appropriate treatment, while a negative scan may prevent unnecessary treatment and even hospitalization. A high degree of interobserver agreement has been found in the reliability of interpretation of DMSA imaging (197).

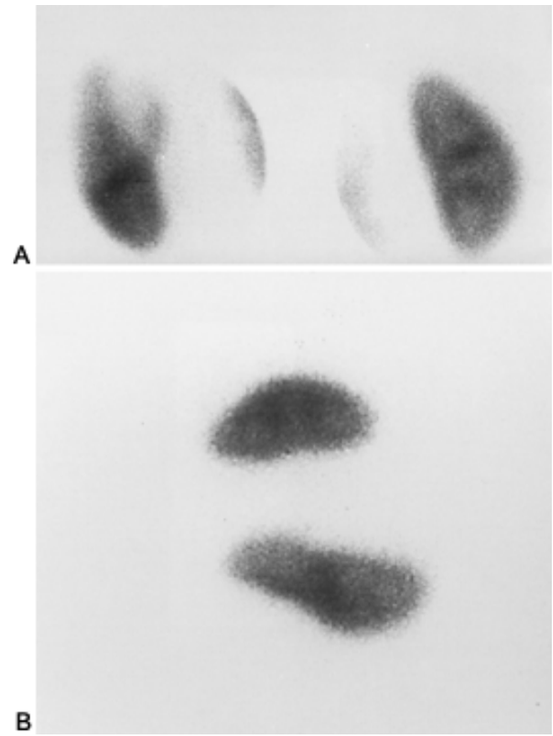

FIGURE 49D.5. A: DMSA scan showing acute pyelonephritis of upper pole of left kidney. Right kidney appears normal. **B:** DMSA scan 6 months later showing scar in upper pole of left kidney.

The voiding cystourethrogram (VCU) plays an important role in the evaluation of children with neurovesical dysfunction and should always be performed in infants, in patients with newly diagnosed neurovesical dysfunction, and when upper tract imaging documents the new onset of hydronephrosis or renal scarring. Likewise, pyelonephritis in a child without known VUR demands that a VCU be performed, preferably after infection has been eradicated and the child has been given suppressive antibacterial therapy for several weeks. Voiding cystourethrography is easily performed with a small catheter (8-Fr feeding tube in most infants). The bladder is filled with room-temperature contrast until voiding occurs. Bladder capacity and configuration, bladder neck and external sphincter competence, and urethral anatomy should be documented in addition to documenting the presence and grade of VUR. VUR should be graded using the standard criteria of the International Reflux Study in Children (115). A carefully performed VCU may offer, in addition to anatomic detail, a gross assessment of bladder capacity, an assessment of postvoid residual urine (assessment of the completeness of bladder emptying), voiding dynamics, and detrusor-sphincter coordination. Although the radionuclide VCU is preferred as a follow-up study for the assessment of VUR (157), the fluoroscopic VCU offers a great deal of anatomic, structural, and functional information not seen in nuclear cystography. Routine fluoroscopic voiding cystourethrography is thus preferred in most cases even for follow-up study in children with neurovesical dysfunction. The VCU and urodynamic evaluation may be combined in a videourodynamic evaluation.

Urodynamic Evaluation

Urodynamic evaluation of children must be tailored to fit both the ability of the individual patient to understand and cooperate with testing, and the information desired by the urologist (10). Although a complete urodynamic assessment might potentially assess bladder capacity and compliance, detrusor function, bladder neck and urethral dynamics, detrusor/pelvic floor coordination and voiding dynamics, these complex urodynamic studies are invasive and require extraordinary cooperation that may be achieved only by adults and a few very cooperative children. However, limited studies designed to elicit specific information may be

successful in children. It is extremely important that, before testing, the urologist have in mind specific questions to be answered. Success also necessitates that both parents and child understand the reason for the study, the nature of the testing, and the fact that all possible attempts will be made to minimize discomfort and anxiety. In this context, it is important to realize that not all children with either presumed or documented neurovesical dysfunction require urodynamic evaluation. It is also important to realize that not every urodynamic study will yield useful data.

Although urodynamic studies frequently are performed on infants with neurovesical dysfunction who have limited bladder and urethral sensation, many children presenting for evaluation are grossly neurologically intact. These children require even more intense preparation for the discomfort that may be caused by urethral catheterization. Children must be approached gradually, in a friendly and nonthreatening manner, as an atmosphere of trust is created. Meaningful urodynamic data rarely can be obtained until several visits with the child have taken place. These examinations will allow the physician to make an assessment of patient cooperation and a realistic determination of which urodynamic studies may be best suited for the individual problem in question. Because many children referred for urodynamic study will have had previous radiologic, endoscopic, or surgical procedures, the physician should try to assess the child's reaction to and cooperation with this testing. Pediatric urodynamic studies are best performed and interpreted by the physician or an extremely well-trained and experienced observer who is able to assess the child's response to testing in order to separate fact from artifact and to modify the procedure to suit the cooperation of the child and the needs of the examiner (10). Although children may be sedated for urodynamic evaluation, little more than basic cystometry can be achieved in a deeply sedated child. In many cases, urodynamic testing is best abandoned if the child is unable to cooperate. When formal urodynamic study is deemed infeasible, the state of bladder function must be inferred from other available data (voiding cystourethrography, postvoid residual volume determination, and voiding or catheterization diary).

Noninvasive urodynamic tests include uroflowmetry and electromyographic (EMG)/uroflow studies (49). Uroflow studies are the least invasive and most limited urodynamic studies that can be performed. Uroflow allows the examiner to assess (a) the flow rate (a balance between detrusor contraction and outlet resistance) and, using an electronic flowmeter, (b) the character of the urinary stream. An adequate volume of urine must be voided to allow an accurate assessment of urinary flow rate. Uroflow can be used to assess voided volume, time to maximum flow, peak flow rate, flow time, mean flow rate, and flow pattern. In children with voiding dysfunction, assessment of the pattern of flow may prove revealing, although uroflow by itself may not allow an accurate judgment of the nature of the abnormal voiding mechanics. This is because a low flow rate may be a reflection of either outlet obstruction or impaired detrusor function. We have used a simple flowmeter designed by Drake (66) in some clinical situations to evaluate voided volume, peak urinary flow rate, and a visual assessment of the character of the voided urinary stream in boys.

Micturition studies (uroflow combined with pelvic floor electromyography) are aimed at assessing the function and coordination of the periurethral striated musculature during voiding (78). Anal plug and urethral catheter electrodes may be used, but are liable to introduce artifact because of patient discomfort. Direct measurement of periurethral striated muscle activity can be achieved by the insertion of small needle or wire electrodes into the periurethral area in girls and into the prostatic apex in boys. Bauer (12) has demonstrated the usefulness of the oscilloscope in recording action potentials from the sphincter musculature, thus aiding optimal electrode positioning. Electrodes may be inserted under anesthesia and testing performed later, or may be inserted at the time of testing using local or topical anesthesia in a cooperative child. Insertion of a small trocar cystostomy catheter may facilitate bladder refilling for repetitive urodynamic study, especially if biofeedback training is desired. However, even small cystostomy catheters may introduce a considerable amount of discomfort and artifact in children. In an effort to achieve noninvasive monitoring of pelvic floor activity, Maizels and Firlit (166) described the use of perineal skin patch electrodes. These nonspecific electrodes require skin preparation with alcohol or acetone and tincture of benzoin adhesive to achieve good contact and prevent dislodgment. Because surface electrodes are less specific than electrodes placed directly into the paraurethral musculature, they may be associated with more artifact than is seen when needle electrodes are used. In children, however, the trade-off in gaining patient cooperation may make the noninvasive technique preferable.

During normal micturition, the internal sphincter, pelvic floor, and external urethral musculature relax to allow complete bladder emptying. Detrusor/pelvic floor dyssynergia (discoordination) is documented when pelvic floor musculature fails to relax and EMG activity persists during detrusor contraction (166). Such activity may be particularly difficult to separate from artifact generated by abdominal straining. The use of abdominal EMG patch electrodes to detect abdominal straining (140) or a rectal balloon to subtract abdominal pressure is especially important in children so that the diagnosis of dyssynergia is not made inappropriately (138).

The performance of cystometry in children requires patience, understanding, and adequate preparation of both the patient and his or her parents. Patient assessment is important, since a child who balks at catheterization is unlikely to be cooperative enough to provide meaningful

cystometric data. Sedation is usually not beneficial. However, lidocaine jelly instilled into the urethra before catheterization may diminish discomfort and allow improved cooperation. When cystometry is to be performed, catheterization is best performed immediately after voiding so that a determination of postvoid residual volume can be made. A small 7- or 8-Fr double- or triple-lumen urodynamic catheter or microtip transducer catheter is appropriate for most studies. A balloon catheter placed into the rectum is used to subtract abdominal pressure and negate artifact produced by straining. It is important to avoid latex catheters and balloons in all patients with spina bifida, even those with unproven latex allergy (216). If pelvic floor electromyography is to be performed, catheterization should take place after the micturition urodynamic study is completed. Cystometry may be performed using water or gas. Gas cystometry, although quicker and more convenient, is less physiologic and perhaps less accurate than studies using water (86). Slow-fill cystometry using body temperature water is preferred for most pediatric studies. Bladder filling should be approximately 10% to15% of expected bladder capacity per minute or approximately 3 (age + 2) = mL per minute (bladder capacity in ounces = age in years + 2) (20). During bladder filling, EMG activity may be monitored. In cooperative children, documentation of bladder capacity, sensation, and uninhibited bladder activity can be measured. The pressure (leak-point pressure) and volume at which urine leaks around the catheter during filling should be noted. If the child is capable of spontaneous voiding, the pressure generated in the bladder (voiding pressure) is measured. Cystometry and voiding cystourethrography may be combined in videourodynamic studies because it has been shown that contrast medium does not adversely influence urodynamic findings (125).

Static urethral pressure profilometry measures the passive resistance of the urethra along its length. The side-hole catheter may be positioned at any location in the urethra that requires study, but the measurement has little practical use in children with neurovesical dysfunction unless the efficacy of an artificial urinary sphincter cuff, bladder neck sling, or reconstructed bladder neck is being evaluated. Urethral pressure may vary at the same position in the urethra and is affected by bladder volume, the characteristics of the catheter itself, and infusion parameters (12).

Pediatric urodynamic data are extremely valuable when thoughtfully and carefully obtained. The data are useful in diagnosis, for estimation of the probability that upper tract deterioration may occur in the future, and for biofeedback training, particularly in children with nonneuropathic voiding dysfunction (162). In many cases, a repeat study is helpful, either to confirm suspected findings or to determine whether a change in bladder management programs or pharmacologic manipulation has resulted in a measurable change in measurable neurovesical parameters.

CONGENITAL NEUROSPINAL DYSRAPHISMS

Spina Bifida (Myelodysplasia)

The term *spina bifida* includes a group of developmental anomalies that result from defects in neural tube closure (231). Lesions vary in severity: spina bifida occulta, a generally incidental finding in which only a bony defect is present; meningocele, with a meningeal sac but intact neural elements; spina bifida cystica (myelomeningocele), with an intact skin-covered sac containing neural elements; and spina bifida aperta, in which the sac is open. Myelomeningocele is by far the most common defect seen and the most devastating. Spina bifida is a disease of variable prevalence, ranging from 4.5 in 1,000 births in Belfast to 0.12 in 1,000 births in Singapore (232). In the United States, the prevalence is estimated at 1 in 1,000 births but varies geographically, being more common in the eastern states. Stein (228) reported a steady decline in incidence in all ethnic groups in the northeastern United States from 1930 to 1980 and a progressive decrease in incidence in the United States as a whole from 1970 to 1980, while a significant decline was noted in Liverpool, England, between 1974 and 1979 (194).

The incidence of neural tube defects in England and Wales has, in fact, decreased from 3.2 per 1,000 births in the early 1970s to 0.1 per 1,000 births in 1999. More specifically, data documented a 96% drop in the incidence of neural tube defects between 1970 and 1997. Morris and Wald (182) analyzed this data and concluded that the decline in incidence should be apportioned as follows: 40% decreased incidence was due to antenatal diagnosis and elective termination of pregnancy, and 56% was due to a decline in incidence, perhaps in part because of an increase in dietary folate.

The etiology of neural tube defects appears to be multifactoral (231,232). Epidemiologic data incriminate environmental factors because the birth prevalence has varied over time and by geographic location and because epidemics of neural defects appear to have taken place at different times and in different locations worldwide (182). Genetic factors are incriminated by studies showing female preponderance, ethnic variability, and increased familial tendencies. Sibling incidence has varied from 1.4% to 6.0%, and when two siblings are affected, the risk rises from 4.8% to 12% (238). Neural tube defects likewise are associated with Meckel's syndrome (autosomal recessive), trisomies 13 and 18, and cloacal exstrophy (possibly on a local developmental basis) (238).

Growing evidence over the past several decades that periconceptional supplementation with multivitamins (190) might diminish the risk of neural tube defects correlates with the higher incidence of these anomalies found in areas with lower socioeconomic levels (183). A decade of debate has been resolved by two multicenter randomized

controlled studies. The first found a 72% reduction in the recurrence of neural tube defects among women who received a 4-mg daily supplement of folic acid in the periconceptional period (183) This study lead the United States Public Health Service to recommend in 1992 that all women of childbearing age consume 0.4 mg of folic acid daily. These data were given further significance by a second randomized controlled trial, which found the risk of the occurrence of first-time neural tube defects to be reduced by 60% by the use of periconceptional folic acid supplementation (249). A Canadian study, carried out to determine the efficacy of information dispersion concerning the importance of folic acid in preventing neural tube defects, found that most women studied were unaware of the importance of folic acid and were ingesting an amount far below the protective level recommended (79). The U.S. Food and Drug Administration is reportedly considering the fortification of a food staple with folic acid to further diminish risk to the general population (184).

Spina bifida is a disease that has dramatic impact on the involved child and family. Lessons learned from management of the urologic consequences of spina bifida have provided urologists with a significantly expanded armamentarium with which to treat neuropathic bladder dysfunction of all causes. Goals of management for the patient with neurovesical dysfunction are to preserve, or at least stabilize, renal function; to prevent complications of UTI; and to provide socially acceptable continence. The perception of what constitutes acceptable continence may vary among parent, child, caretakers, and peers. The child's age, mental and physical abilities, and socioeconomic status also influence this perception. In addition, normal developmental processes, schooling, and peer pressure may gradually alter his or her personal concept of what represents an acceptable bladder regimen. When continence and social acceptance (rather than medical concerns) become the main goals of urologic therapy in the child with neurovesical dysfunction, particular care must be taken to individualize treatment to fit the needs of the child and not to treat merely for treatment's sake. It is imperative that the urologist have an appreciation for other related problems—orthopedic, neurosurgical, neurologic, psychologic, social, developmental, endocrinologic, and sexual—that may occur as a result of spina bifida because these may influence or be altered by urologic management (186).

Perinatal Evaluation

Spinal dysraphism is usually found unexpectedly at birth but may be detected during prenatal ultrasound examination (109). A detailed examination of the entire spine by an experienced ultrasonographer is necessary to rule out neural tube defects, and even in ideal situations errors may be made (246). The presence of a neural tube defect is suggested when amniocentesis reveals an elevated level of α-fetoprotein (30). Controversy, however, surrounds the use of maternal serum screening for α-fetoprotein because both false-positive and false-negative determinations have been reported and the distribution of normal values of maternal serum α-fetoprotein overlaps values seen in the presence of neural tube defects (249).

The optimal perinatal management of the fetus with myelomeningocele remains the subject of debate. Elective caesarian section has been thought to be beneficial in diminishing trauma to neural elements (48). This conclusion, however, was based on the review of older series of deliveries and has been called into question. Benson and associates (19) reviewed the route of delivery and outcome of 75 babies and concluded there was no difference in outcome, independent of which route of delivery was chosen. These data also have been called into question, and the final answer awaits a more controlled study (110). Recent experience with prenatal surgical correction of myelomeningocele awaits long-term outcome analysis.

Neonate

The initial examination of a neonate with spina bifida should proceed along guidelines noted earlier for the child with suspected neurovesical dysfunction. Because back closure and ventriculoperitoneal shunt placement may have been performed before initial urologic evaluation, the child's general neurologic status should be documented. Abdominal wall tone, lower-extremity function, anal sphincter tone, and function of the sacral reflex arc (bulbocavernosus reflex) should be assessed. It is important to note that the level of the bony defect will not determine the functional cord level, which may be altered by the degree of involvement of the spinal cord and nerve roots, intracranial anomalies (hydrocephalus, Arnold-Chiari malformation), and perhaps the surgical trauma of sac closure (149). Each child represents a unique neurologic status, and each therefore requires a complete urologic evaluation. Observations of spontaneous voiding, continuous dribbling, or a forceful stream may provide valuable information about bladder capacity and function that, when added to information provided by the radiographic appearance of the bladder, may provide data similar to that provided by the cystometrogram. Abdominal examination is performed to assess renal size, detect bladder distention and assess the efficacy of bladder massage or the Credé maneuver to induce bladder emptying. The Credé maneuver, which is commonly taught to parents of children with spina bifida, is extremely limited in both effectiveness and applicability and, in fact, should be avoided in most cases because the majority of infants spontaneously void enough to provide adequate bladder emptying. Barbalias and associates (8) documented that the Credé

maneuver actually produced increased urethral resistance in 98% of patients studied. This maneuver thus may elevate intravesical pressure significantly and is particularly contraindicated when outlet resistance is high or VUR is present because the increased hydrostatic pressure will be transmitted directly to the renal parenchyma. When spontaneous voiding does not occur or is ineffective, intermittent catheterization should be instituted. However, urethral dilation and/or medications to reduce urethral resistance (phenoxybenzamine) have been used effectively in this patient group to limit the need for catheterization in the very young patient.

All neonates with spina bifida should have a complete urologic evaluation performed during the neonatal period. Urinary tract ultrasonography is performed to document the state of the upper tracts and assess bladder wall thickness. Postvoid sonography also can assess the completeness of spontaneous voiding. Although fewer than 10% of neonates with spina bifida exhibit hydronephrosis, Stafford (226) studied ten consecutive neonates of whom six had hydronephrosis. Using IV urography, Gaum (83) studied 68 neonates and found abnormal upper tracts in 13 (19%), bilateral hydronephrosis in 7, ureterectasis in 3, pyelectasis in 1, dysplastic kidney in 1, and horseshoe kidney in 1. Of the group with normal urography, 69% had an abnormal VCU, and of the group with abnormal urography, 92.3% had an abnormal VCU. Cystographic abnormalities included reflux (16%), bladder diverticula (23.5%), and subjective abnormalities of bladder wall thickness or bladder shape seen in the majority of patients. Given these data, it is mandatory that voiding cystourethrography and urodynamic evaluation be performed as part of the initial evaluation of all infants. Both studies should be repeated whenever new-onset hydronephrosis is detected by sonography or when there is a significant change in bladder function or continence. Once a complete urologic evaluation has been performed, an appropriate bladder regimen is designed for each individual patient. For many infants, spontaneous voiding into diapers represents optimal care. The Credé maneuver should generally be avoided. Transient urinary retention or elevated residual urine volumes immediately after back closure may require at least temporary management by intermittent catheterization. If prolonged catheterization is necessary, cystourethrography should be performed to determine the presence or absence of VUR. All neonates started on intermittent catheterization should be placed on prophylactic antibiotics at least until the absence of VUR is documented.

Urodynamic Assessment of the Neonate

Traditionally, urodynamic evaluation of children with spina bifida has been carried out in the late preschool or early school-age years in conjunction with the initiation of a bladder-training program, with the studies serving as a guide to bladder management and pharmacologic manipulation (206). McGuire (173) evaluated urodynamic findings in 42 children studied over a 7-year period and found urodynamic testing to be of prognostic value in determining which patients were at risk for upper tract deterioration. In the low intravesical pressure group (intravesical pressure 40 cm H_2O or less at the time of urethral leakage), no patient had VUR, and only 2 of 22 had ureteral dilation. In the high intravesical pressure group, however, 68% showed VUR, and 81% had ureteral dilation. More recently, Bauer (13) studied 36 neonates with spina bifida soon after sac closure and in follow-up for 18 to 48 months. In the group demonstrating detrusor-external sphincter dyssynergy, 72% had or developed hydronephrosis during the period of study; whereas only 22% with synergy and 11% with absent sphincter activity showed upper tract deterioration. In a subsequent study, hydronephrosis developed in less than 10% of infants considered to be at risk for upper tract deterioration who were placed on a program of prophylactic intermittent catheterization and anticholinergic therapy. These data confirm that early urodynamic evaluation is helpful for both guiding therapy and determining which infants are in need of more closely spaced follow-up studies or aggressive bladder management regimens such as intermittent catheterization, urethral dilation, or cutaneous vesicostomy.

Urodynamic findings also are helpful when counseling parents about the long-term prognosis for both upper tract preservation and the management of urinary continence. Landau and co-workers (153) more specifically analyzed urodynamic data in a group of children with neurovesical dysfunction. They commented on the fact that many of their patients achieved a normal total bladder capacity at the expense of elevated storage pressures. This experience underscores the significance that a catheterization diary can play in children with marginal bladder compliance. By comparing the record of urine volumes obtained at catheterization with the urodynamic data obtained from the same patient, it is possible to assess whether the bladder management program is effective in achieving reasonable bladder pressures during both day and night. If catheterized volumes are in the high-pressure range, a change must be made to the patient's bladder management regimen.

It is important to remember that a great deal of artifact can be introduced into urodynamic studies when performed in infants and children, and that voiding cystourethrography and a voiding or catheterization diary can provide a great deal of information about bladder function. This adjunctive information should not be overlooked in any patient and may prove to be particularly important when urodynamic testing is not available. Adjunctive data should be compared with urodynamic studies when both are available so that any discrepancy between the two can be

reconciled when a plan for bladder management is formulated.

GENERAL PRINCIPLES OF MANAGEMENT

One of the most important aspects of the urologic care of patients with neurovesical dysfunction is periodic reevaluation. A well-designed lifelong plan for follow-up should begin in infancy. If neonatal sonography demonstrates normal upper tracts, urodynamic studies are favorable, and urine is sterile and bladder emptying adequate, the infant may be discharged to be managed in diapers by spontaneous voiding. Parents must be counseled that close urologic follow-up is necessary both to prevent renal damage and to provide for periodic reassessment of the efficacy of the child's bladder program. When initial urodynamic and radiographic findings are favorable (good bladder compliance, absence of reflux and hydronephrosis), appropriate follow-up may only necessitate sonography in 3 to 4 months, at 1 year, and at yearly intervals thereafter. If hydronephrosis or urinary infection is documented, a VCU and urodynamic evaluation should be performed as soon as infection is cleared, as a part of the evaluation of the efficacy of the current bladder management regimen. When hydronephrosis, urinary retention, VUR, poor bladder compliance, or detrusor-sphincter dyssynergia is documented in infancy, a plan of action other than spontaneous voiding must be formulated. Intermittent catheterization with or without pharmacotherapy, urethral dilation (22,245), or temporary cutaneous vesicostomy (67) may be appropriate in specific settings for any of the previously noted urodynamic indications.

In children with low leak-point pressure, stable bladder function, and normal upper urinary tracts, close urologic surveillance also is necessary until a formal bladder management program is instituted. This group of children (with favorable bladder dynamics) will eventually have bladder manipulation performed for social indications only. Therefore the determination of what is the most appropriate time for the initiation of a formal bladder management program must be made, based not on chronologic age, but on factors such as the child's desire for continence; his or her manual dexterity; and family dynamics, support, and resources. Not all children or families share the same concept of dryness, and motivation may play a crucial role in determining the success or failure of any proposed regimen of bladder management.

For practical purposes, therapy for incontinence may be aimed at correction of either failure of the bladder to store urine or failure of the bladder to empty effectively, most patients demonstrating a deficit in both functions. Failure of adequate urine storage may result from detrusor hyperactivity or diminished detrusor compliance, inadequate outlet resistance, detrusor-outlet dyssynergy, or, in most cases, a combination of factors. In some instances, these causes of incontinence also may result in UTI secondary to inadequate bladder emptying. However, incontinence secondary to either diminished vesical compliance with elevated intravesical pressure at small bladder volumes or to detrusor hypertrophy secondary to detrusor-sphincter dyssynergy also may be associated with upper tract deterioration from either hydroureteronephrosis or VUR (172).

The management of inadequate urine storage must be aimed to correct or compensate for the source of dysfunction. Detrusor hyperactivity may be managed with anticholinergic agents or by diminishing smooth muscle tone (Table 49D.1). Combination therapy may prove beneficial. Transurethral electrical stimulation has demonstrated some promise for increasing bladder capacity, but the effect is only transient in many cases (130). Failure of pharmacologic therapy may necessitate a consideration of sacral rhizotomy (230) or bladder denervation (227) therapy, both of which have been performed rarely in children with spina bifida. Augmentation cystoplasty (179) may be required in severe cases with significantly diminished bladder capacity or compliance. Augmented bladders thus will be converted to the failure-to-empty category and managed as such. Pharmacologic agents that stimulate α-sympathetic receptors in the bladder neck and posterior urethra may modify insufficient bladder outlet resistance (Table 49D.1). Surgical reconstruction or compression of the bladder neck may

be necessary in severe cases. The newest approach to intrinsic sphincter deficiency involves transurethral or periurethral injection of bulking materials (polytetrafluoroethylene, collagen) (127,243). Limited success should be expected in children with bladder neck incompetence due to neurovesical dysfunction.

TABLE 49D.1. COMMON PHARMACOTHERAPY OF PEDIATRIC NEUROVESICAL DYSFUNCTION

Action	Drug	Maximum Dosage	Frequency
Cholinergic	Bethanechol	0.6 mg/kg/day	3–4 times daily
Anticholinergic	Propantheline	1.5 mg/kg/day	3–4 times daily
	Oxybutynin	0.2 mg/kg/dose	2–4 times daily
	Dicyclomine	5–10 mg/dose	3–4 times daily
	Hyoscyamine	0.0625–0.125 mg/dose	6 times daily
	Tolterodine	0.5 mg/kg/dose	2 times daily
Sympathomimetic	Ephedrine sulfate	1 mg/kg/dose	3–4 times daily
	Phenylpropanolamine (in combination drugs)	2.5 mg/kg/dose	2–3 times daily
Miscellaneous	Imipramine	0.7 mg/kg/dose	2–3 times daily

Failure of bladder emptying may result from ineffective detrusor function. Since it is generally considered that bethanechol is ineffective on a long-term basis, pharmacologic agents are rarely useful in clinical practice to improve detrusor function (248). Electrical stimulation (bladder pacemaker) has proved to be of very limited usefulness, particularly in the pediatric population (250). Transurethral electrostimulation has appeared to be beneficial in some children, although conflicting data have been reported (25,59,130,163). Myogenic failure may result from chronic overdistention, and in this scenario, intermittent catheterization may improve detrusor contractility.

Outlet resistance (bladder neck and proximal urethra) may be diminished pharmacologically by α-sympatholytic agents. Striated muscle relaxants may lower outlet resistance at the level of the pelvic floor (dantrolene, baclofen), but side effects related to generalized striated muscle relaxation (generalized weakness, dizziness, drowsiness) are common and have severely limited the usefulness of these agents when used systemically (250). Pharmacologic interruption of nerves responsible for increased outlet resistance (pudendal block) has been used infrequently in children (206,208,237). Johnston and Kathel (122) and Shochat and Perlmutter (219) described overdilation of the bladder outlet in females, therapy that has been reintroduced by Bloom (22,244). Surgical destruction of outlet resistance may be accomplished by transurethral incision of the bladder neck or external sphincter, Y-V–plasty of the bladder neck, or bladder flap urethroplasty. These procedures result in incontinence that is reversible only by surgical means (Table 49D.2).

TABLE 49D.2. THERAPEUTIC OPTIONS FOR THE MANAGEMENT OF NEUROVESICAL DYSFUNCTION

Failure to Store	Failure to Empty
Detrusor	Detrusor
Pharmacologic therapy	Pharmacologic therapy
Anticholinergic	Cholinergic
Smooth-muscle relaxant	Electrical stimulation
Imipramine	Intermittent catheterization
Neurologic therapy	Bladder outlet
Sacral rhizotomy	Pharmacologic therapy
Bladder denervation	α-Sympatholytic
Bladder augmentation	Smooth-muscle relaxant
Bladder outlet	Neurologic therapy
Pharmacologic therapy	Dilation
α-Sympathomimetic	Surgical
Imipramine (Urinary diversion)	Y-V–plasty of the bladder neck
	Transurethral incision of bladder neck
	External sphincterotomy
	Mechanical
	Valsalva maneuver
	Credé maneuver
	Intermittent catheterization
	Urinary diversion

The Valsalva or Credé maneuvers may produce mechanical bladder emptying. It has been demonstrated that Credé's maneuver may simultaneously increase both outlet resistance and intravesical pressure and may produce harmful effects on the upper urinary tract (7). Intermittent catheterization is of proven benefit in managing incontinence and may be used in conjunction with pharmacotherapy or appropriate surgical intervention. Although temporary diversion (i.e., cutaneous vesicostomy) often has proven beneficial in the management of the child with renal deterioration due to neurovesical dysfunction (225), permanent urinary diversion has been relegated to a position of last resort (40,242). It must be kept in mind that incontinence associated with sterile urine and normal upper tracts may be best managed conservatively in small children, older children unconcerned with wetness, and in social situations where diminished functional capacity or noncompliance to pharmacologic and catheterization regimens is a problem.

SPECIFIC OPTIONS FOR THE MANAGEMENT OF NEUROVESICAL DYSFUNCTION

Clean Intermittent Catheterization

Although indwelling catheterization has been used to manage neurovesical dysfunction, many adverse sequelae of long-term indwelling catheterization have been reported, particularly in boys. In 1966, Guttman and Frankel (95) introduced sterile intermittent catheterization to the care of patients with neurovesical dysfunction. The subsequent popularization of nonsterile clean intermittent catheterization (CIC) by Lapides (154,155) has allowed this technique to become the mainstay of management for neurovesical dysfunction in both children and adults, its popularity aided by the poor experience with bladder management by both the Credé maneuver and long-term indwelling catheterization. Cass (39) documented UTI in 72%, upper tract dilation in 45%, and incontinence in 100% of children managed by Credé maneuver. When managed with long-term indwelling catheterization, 100% of children were infected and 57% showed upper tract dilation. In contrast, Plunkett and Braren (200) described stable upper tracts in 82% and improved upper tracts in 15% on intermittent catheterization, with 6% incidence of pyelonephritis. Cass (39) documented an 87.5% incidence of stable upper tracts, improvement in 12.5%, and stable or improved VUR in 75%, and persistently sterile urine in 90% of patients. Nonsterile self-intermittent catheterization, especially in children who

may be less concerned about cleanliness in performance of catheterization, is associated with a significant incidence of bacteriuria. Although Cass (39) achieved a 90% incidence of persistently sterile urine on suppressive antibiotic therapy, Plunkett and Braren (200) documented persistent infection in 80%, yet pyelonephritis occurred in only 6%, each episode occurring in a patient with significant VUR. Crooks and Enrile (57) documented that asymptomatic bacteriuria in children on a CIC program was not a problem unless VUR was present, a finding confirmed by Lewis (161).

Nonsterile intermittent catheterization

may be initiated to manage VUR, upper tract deterioration, UTI, or incontinence. The aim of an intermittent catheterization program is to provide periodic, complete bladder emptying. The success of the program depends highly on the compliance and motivation of the parents or caretakers, the child, and the professionals caring for the child. When self-catheterization is instituted, a great deal of responsibility is thrust on the child. This responsibility is best undertaken when he or she displays interest in personal hygiene and self-image, a stage that coincides with the acknowledgment of peer pressure and social interaction. This stage in growth and development cannot be measured in years and may vary tremendously with the child's individual needs and abilities. Nor can it be assumed that all children will be able to quickly master the techniques of catheterization; in fact, some may be physically unable because of motor deficits, incoordination, skeletal deformity, or orthotic appliances. Time invested in bladder training at the outset will prove to be invaluable in helping both parents and child cope with setbacks and occasional or persistent wetness, especially when repeated urodynamic assessments and alterations in pharmacologic therapy are necessary. If self-catheterization proves unsuccessful, interaction with school personnel, caretakers, and other family members may be necessary to devise an adequate catheterization program. Each child successfully enrolled in a self-catheterization program will eventually come to design a personalized program that allows an unobtrusive catheterization schedule and technique. Catheters are carried in a small plastic bag and reused. They are simply rinsed under running water before and after use. Many girls can manipulate short plastic or stainless steel catheters more easily than catheters of standard length. Catheterization can be performed while standing at or sitting on the toilet, and micturition will appear close to normal as far as others are concerned.

The likelihood of achieving total continence using a program of intermittent catheterization and pharmacologic therapy greatly depends on bladder storage characteristics and patient compliance and motivation. Wolraich and co-workers (252) achieved 49% total daytime continence with CIC and pharmacotherapy. Cass (39) documented 17% slight dampness but dryness in only 34%, while Purcell and Gregory (201) reported 24% total dryness, 33% wet primarily because of poor patient compliance, and 30% wetness in spite of total patient compliance. Knoll and Madersbacher (137) found an overall continence rate of 40%, but this was as high as 55% in the group whose detrusor hyperreflexia was controlled by pharmacotherapy in association with a competent bladder outlet. These data must be taken into consideration when goals of a CIC program are discussed with patients and family. Adjuncts to CIC and pharmacotherapy should be considered when adequate continence is not achieved.

Pharmacologic Therapy of the Child with Neurovesical Dysfunction

Drug therapy may effectively alter bladder or outlet function and provide continence in milder cases of neurovesical dysfunction. More commonly, however, drugs are used as an adjunct to intermittent catheterization to modify the function of the detrusor or bladder outlet in an effort to provide both adequate storage capacity and adequate emptying. In children, the dosage and side effects of pharmacologic agents must be monitored carefully. Medication is best prescribed per kilogram of body weight. It is common practice to begin with a single agent at a low dose. As efficacy is monitored, dosages are increased and drugs combined in a stepwise fashion to achieve a desired clinical effect while minimizing adverse side effects (Table 49D.1).

Urethral Dilation

Johnston and Kathel (122) were the first to report that urethral dilation could both improve bladder emptying and diminish hydronephrosis in patients with myelomeningocele, a finding confirmed in a small series by Schochat and Perlmutter (219). Little attention was paid to this technique until the report by Bloom in 1990 (22), which detailed the urodynamic and radiographic effects of urethral dilation in 18 children with meningomyelocele and high vesical pressures who underwent dilation as an alternative to cutaneous vesicostomy. The urodynamic effect of dilation in this group of patients resulted in a decreased leak-point pressure from an average of 55.75 cm H_2O to 31 cm H_2O soon after dilation and 19.3 cm H_2O at later evaluation. Longitudinal studies demonstrated a persistent improvement in bladder compliance after dilation, and suggest that the ability to diminish adverse compliance at an early age by any technique may have salutary effect on long-term bladder function. Dilation may be performed in girls using urethral dilators and in boys using balloon dilation under fluoroscopic control. General anesthesia is used in most children, but may be unnecessary in girls who have little or no urethral and perineal sensation.

Cutaneous Vesicostomy

CIC is the most widely used intervention for the management of vesical dysfunction (32). Intermittent catheterization may be instituted as part of a bladder management program to treat incontinence or to manage hydronephrosis, VUR, or recurrent UTI resulting from poor bladder compliance or inadequate bladder emptying. Although intermittent catheterization can be performed safely even in infants, Blocksom's technique for cutaneous vesicostomy, popularized by Duckett (67), has become an effective alternative for dealing with the poorly emptying neuropathic bladder and its secondary effects on the urinary tract. The Blocksom technique utilizes a small transverse skin incision placed halfway between the pubic symphysis and umbilicus; exposure and isolation of the bladder dome from peritoneum, urachus, and umbilical vessel remnants; and creation of a small stoma after resection of a button of detrusor. The vesicostomy in effect acts as a pop-off valve, lowering intravesical volume and pressure, while allowing the bladder to maintain some urine storage and in many instances to allow voiding per urethra. The decision as to whether vesicostomy drainage will provide satisfactory bladder and upper tract decompression can be made by visualizing marked improvement of the radiographic appearance of the upper urinary tracts after bladder catheterization (a vesicostomy equivalent) (Fig. 49D.6). The decision to perform a cutaneous vesicostomy in preference to intermittent catheterization or when catheterization fails to effectively decompress the upper urinary tract must be made on clinical grounds and seems most warranted in the infant or small child with moderate or severe hydronephrosis or reflux and worrisome urodynamic parameters. Management is simple with routine diapering, and the demands of a catheterization program are not imposed on caretakers. The vesicostomy can be managed in children with orthoses, even those with scoliosis jackets or braces with pelvic bands, if minor orthotic adjustments are made. Adequate continence may be achieved with a pad and belt combination in older children if urethral leakage does not occur. Routine stomal appliances may be used effectively, although occasional leakage may be problematic because the vesicostomy is located in an area of skin that may crease when the child sits or bends.

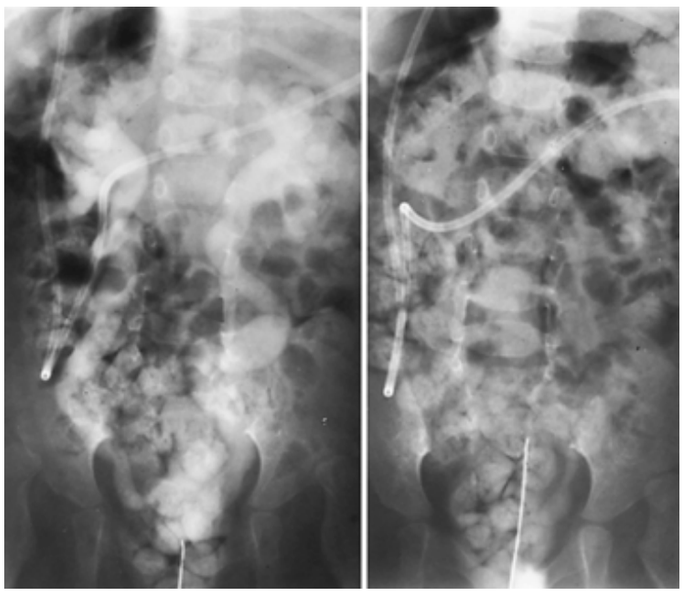

FIGURE 49D.6. Intravenous pyelogram with full bladder and after bladder catheterization.

Cutaneous vesicostomy and intermittent catheterization have been equated in terms of upper tract preservation. Plunkett and Braren (200) described stable upper tracts in 82% and improved upper tracts in 15% of patients managed by intermittent catheterization, with pyelonephritis in only 6%. Cass (39) documented an 87.5% incidence of stable upper tracts, improvement in 12.5%, stable or improved VUR in 75%, and persistently sterile urine in 90% of patients on intermittent catheterization. A report by Duckett (67), however, showed that 54% of patients on a regimen of CIC developed upper tract deterioration (most by 3 years of age), while 85% of patients managed with vesicostomy had complete resolution of hydronephrosis and stabilization in the remainder. No patient with a functioning vesicostomy showed upper tract deterioration. It is likely

that the failure of CIC in many cases is failure of the patient, parents, or caretakers to comply with the rigorous catheterization schedule. Finding a caretaker to provide these services in school or when the parents work may be an additional source of stress for a family already struggling with the demands of a handicapped infant.

Complications of vesicostomy are not uncommon but are generally minor and easily managed (112). Snyder and others (225) reported 3 patients with bladder calculi, 6 patients who required reoperation for stenosis or prolapse, and 1 patient requiring stomal catheterization for stenosis among a group of 48. Severe prolapse is extremely rare, but minor mucosal prolapse that does not require surgical revision occurs frequently. Stomal stenosis, even to a severe degree, usually continues to allow adequate urinary tract decompression, with revision being unnecessary. Unless the vesicostomy is created during an acute episode of cystitis, bladder capacity is maintained during the period of diversion (225). Vesicostomy closure combined with ureteral reimplantation and/or bladder augmentation, timed to coincide with institution of a planned self-catheterization program, is the outlook for most patients who undergo cutaneous vesicostomy (51). Long-term vesicostomy drainage has been used in patients unable to perform self-catheterization, usually severely handicapped individuals with poor bowel control who must be managed in diapers. In these individuals, the vesicostomy, although not providing continence, may provide upper tract stability and ease of management.

BLADDER AUGMENTATION

Enterocystoplasty

Children with hydronephrosis, reflux, or incontinence due to diminished vesical compliance and/or capacity may fail to achieve continence or stabilize upper tracts in spite of an optimal trial of intermittent catheterization and pharmacotherapy. Treatment options include bladder augmentation (with or without continent diversion, bladder neck revision, and/or without ureteral reimplantation) or cutaneous urinary diversion (Fig. 49D.7). When bladder augmentation is being considered, several prerequisites are important. Urodynamic studies should confirm diminished capacity and/or compliance. If hydronephrosis or reflux is thought to be secondary to bladder dysfunction, catheter drainage should diminish upper tract fullness. An accurate assessment of the function and adequacy of the bladder outlet should have been completed, and an effective intermittent catheterization program should be in place before surgery.

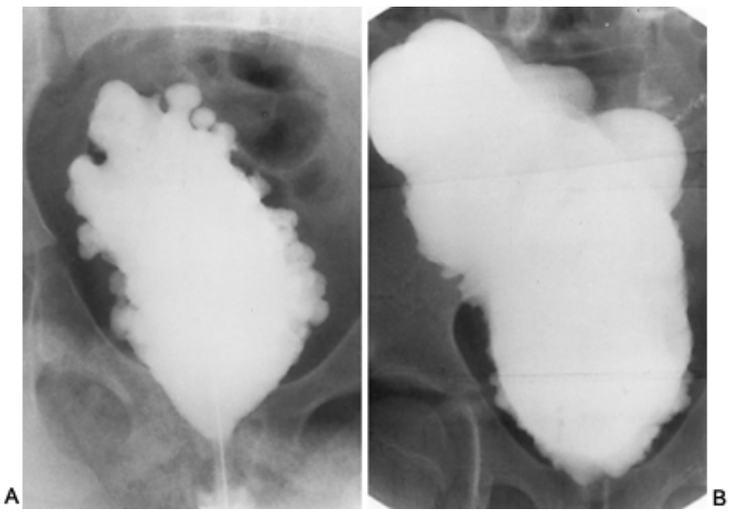

FIGURE 49D.7. A: Cystogram before enterocystoplasty. **B:** Cystogram after enterocystoplasty.

Patients being considered for enterocystoplasty must have adequate bowel length and function to permit exclusion of a segment sufficiently long enough to satisfy the need for increased bladder capacity. Small bowel, colon, and stomach have been the material of choice for bladder augmentation, which gained popularity for the treatment of neurovesical dysfunction after the introduction of intermittent catheterization eliminated concerns about bladder emptying (205,224). Although the choice of bowel segment to be used for augmentation remains controversial, it is

imperative that the native bladder be either widely bisected (from just above the bladder neck to trigone), or must be resected to a level just above the trigone. Failure to prepare the bladder base in this manner before augmentation may cause the intestinal segment to act as a diverticulum of the bladder, minimizing the effectiveness of the procedure. Sufficient bowel must be used to provide both adequate capacity and low intravesical pressure. Making optimal use of the shortest bowel segment that will be adequate for the patient's specific needs not only ensures a successful augmentation but also reduces the potential for malabsorption and electrolyte disturbances. Detubularization of bowel segments produces geometric changes, which modify the capacity, accommodation, and compliance of the bladder reservoir in a manner that improves both its storage characteristics and effect on the upper tracts. The geometric advantage of detubularization depends on the geometry of the volume of a cylinder (μpr^2 length) (171) compared with the volume of a sphere ($4/3\ \mu pr^3$) (138). Koff (139) has tabulated the theoretic increase in bladder volume that can be expected when various lengths of small and large bowel are detubularized before augmentation (Table 49D.3).

Bladder Volume ~ (mL) +	Bowel Length ~ (cm)	Bowel Radius (cm) =	Augmentation ~ Volume (mL)
50	20	1	250
50	30	1	382
50	40	1	532
50	50	1	697
50	60	1	877
50	10	2	250
50	20	2	532
50	30	2	877
100	10	1	203
100	20	1	327
100	30	1	470
100	40	1	630
100	50	1	804
100	10	2	327
100	20	2	630
100	30	2	992
150	10	1	380
150	20	1	530
150	30	1	695
150	40	1	875
150	10	2	530
150	20	2	875

From Koff SA. Guidelines to determine the size and shape of intestinal segments to be used for reconstruction. *J Urol* 1988;140:1150.

TABLE 49D.3. ULTIMATE AUGMENTATION VOLUME OF SMALL BLADDERS ENLARGED WITH BOWEL SEGMENTS OF DIFFERENT DIMENSIONS

Detubularization produces additional beneficial effects on the bladder reservoir. Hinman (105) has shown that accommodation, compliance, and contractility also are altered. Accommodation (increase in bladder volume without a significant increase in pressure) is related to the radius of the reservoir. At any given pressure, a reservoir with a larger radius will accommodate more volume. Compliance (change in pressure/change in volume) is an important facet of bladder augmentation in most cases. Compliance is related to the viscoelastic properties of the reservoir wall, and thus may change over time as the wall stretches and relaxes. Peristaltic activity of intestinal smooth muscle is both phasic and tonic and may be a cause of incontinence after intestinocystoplasty in some patients. Detubularization effectively interrupts the normally coordinated activity of the intestinal musculature. The more complicated the folding process that is carried out, the more disorganized and blunted the bowel contractions become. Sidi and associates (222) compared the clinical and urodynamic results of enterocystoplasty in patients with tubular sigmoid, intact ileocecal, and sigmoid cup-patch augmentations, and found better continence and lower pressures in the cup-patch (detubularized) group, a finding confirmed by others using ileum. Persistent incontinence secondary to peristaltic activity of the bowel segment may be treated with anticholinergic medication or smooth muscle relaxants. In severe cases, enteroplasty, using a second bowel segment as a patch to interrupt the peristaltic activity of the primary bowel reservoir segment, may be considered.

Gastrocystoplasty has been advocated as an alternative form of enterocystoplasty to minimize electrolyte imbalance and urea reabsorption especially in patients with chronic renal failure (1). The net excretion of hydrogen and chloride into the urine from gastric segments is beneficial in the face of metabolic acidosis due to renal failure, which may be worsened by the use of small or large bowel segments that absorb hydrogen and chloride ions. Gastrocystoplasty, however, is not free from complications. Gosalbez (92) reported two patients with severe intractable hypochloremic hypokalemic metabolic alkalosis, one with an intractable seizure disorder and one with respiratory depression and alteration in mental status. Hypergastrinemia has been reported in other patients (236). Nguyen and others (189) described the syndrome of dysuria and hematuria in 36% of 57 patients after gastrocystoplasty. The syndrome is defined as one or more of the following symptoms: bladder spasm or suprapubic, penile, or periurethral pain; coffee-colored or red urine without infection; skin irritation or excoriation and dysuria without infection. Patients particularly at risk are those with diminished renal function and those with incontinence. Treatments have included observation, baking soda, and omeprazole, an inhibitor of the hydrogen-potassium ion adenosine triphosphate (ATP) pump (189).

Mucus production, alteration of bowel function, diarrhea, electrolyte imbalance, the formation of bladder calculi, spontaneous bladder rupture, and malignancy are other reported complications of enterocystoplasty, the incidence varying with the intestinal segment used. Mucous production, generally considered to be a minor nuisance, has been

linked to outlet obstruction, calculus formation, and spontaneous bladder perforation (98). Daily irrigation with saline is usually sufficient to prevent complications, although acetylcysteine has been administered orally (700 mg four times daily) and intravesically (30 mL of a 20% solution) (18), and urea has been used (30 mL of a 40% solution left indwelling overnight) with success (34). Diarrhea may be a transient effect of enterocystoplasty, engendered by both the removal of absorptive surface and intense preoperative bowel preparation. In patients with neuropathic bowel dysfunction, the function of the ileocecal valve is particularly important because intractable diarrhea has been reported after ileocecal cystoplasty. The use of the ileocecal segment should be avoided in these patients.

Urinary calculus formation is reported in between 30% and 52.5% of patients after enterocystoplasty, with most stones occurring in the bladder (24). Risk factors appear to be UTI, mucous formation, and the use of both absorbable and nonabsorbable staples (98). Recurrent calculus formation seems to be most problematic in patients after continent urinary diversion, perhaps in part because of the increased likelihood that catheterization from a stoma at the top of the bladder will be less effective in emptying sediment from the bladder floor. Palmer and associates (195) have implicated hypocitraturia as a contributing factor, and in a preliminary statement, believe that oral citrate supplementation has diminished the risk of new and recurrent stone formation. Bladder stones may be managed by both bladder irrigation and transurethral or open surgical techniques. Some authors think that the open surgical technique lessens the risk of recurrent stone formation due to stone fragments remaining in the bladder after crushing or fragmentation by any available technique (24). The surgical treatment of bladder calculi can be particularly vexing for patients with reconstructed bladder necks who are managed by intermittent catheterization via continent stomas. Endoscopic access to these reconstructed bladders for stone manipulation may be severely limited.

Although bladder perforation secondary to intermittent catheterization has been reported, incidents rarely occur in the nonaugmented bladder. However, a growing body of literature has documented delayed “spontaneous” bladder rupture after enterocystoplasty (75). Bauer and others (15) reported 15 spontaneous perforations in 12 of 264 children who underwent enterocystoplasty using small bowel, large bowel, and stomach. All sites of rupture were located in the bowel itself, at or near the junction of the bladder and the enteral patch. Ischemic necrosis is thought to play a role in the mechanism of rupture, and suture granulomas were found in the reservoir wall near the site of rupture. Rosen and Light (212) reported similar findings, and concluded that a common factor was high outlet resistance. Crane and others (56) postulated that chronic overdistention leads to vascular compromise and ischemia. The lack of sensation of bladder filling, mucous plugs, and failure to comply with routine catheterization schedules may contribute to reservoir rupture. A significant percentage of patients suffering spontaneous rupture have died. Recommendations for prevention include daily bladder irrigation and prevention of overdistention, especially in patients who have a competent bladder outlet or who have undergone a surgical procedure to increase outlet resistance. Spontaneous bladder rupture should be part of the differential diagnosis of the acute abdomen in all patients after enterocystoplasty. Differential diagnosis may be difficult because of abnormal abdominal and visceral sensation. Sonography may demonstrate increased peritoneal fluid. Although cystography should be performed, a normal cystogram, even when the bladder is filled with considerable pressure, does not rule out rupture. If spontaneous rupture is suspected as a cause of an acute abdominal catastrophe, prompt laparotomy is often indicated.

The occurrence of neoplasia at the ureterocolonic anastomosis is a recognized risk of ureterosigmoidostomy (229) Occasional reports of malignancy after bladder augmentation have raised new concern about the long-term outlook for children after enterocystoplasty. Filmer and Spencer (77) tabulated 14 cases of malignancy arising between 5 and 29 years after augmentation. Patient ages were from 42 to 69 years at the time of tumor discovery. Tumor types were transitional cell carcinoma (3), adenocarcinoma (8), signet ring carcinoma (1), sarcoma (1), and oat cell carcinoma (1). The pathogenesis of these lesions is likely multifactorial, and surveillance cystoscopy appears to be warranted, beginning approximately 10 years after augmentation.

Two clinical concerns face the urologist considering bladder augmentation in patients with neurovesical dysfunction: assessment of the bladder outlet and the treatment of VUR. Assessment of the bladder outlet is particularly important in patients with myelodysplasia who commonly display bladder neck incompetence (86). If bladder augmentation is to be performed in these children, preoperative assessment is important to determine whether a simultaneous continence procedure should be carried out at the bladder neck. Appropriate evaluation of bladder neck competence can be made by fluoroscopic examination of the bladder neck during videocystography or videourodynamic evaluation with the patient in the upright or semiupright position (Fig. 49D.8) (147). Valsalva's and Credé's methods should be used as provocative maneuvers if the bladder neck is closed during filling. An open bladder neck indicates the potential need for a simultaneous continence procedure. Cher and Allen (47) prefer to assess the need for bladder neck revision urodynamically and have found that a bladder outlet resistance which exceeds 25 to 30 cm H_2O will be sufficient to prevent postoperative incontinence after enterocystoplasty. VUR that occurs as a result of poor bladder compliance may be refractory to intermittent catheterization and pharmacotherapy and is seen in many patients who become candidates for bladder augmentation. Whether or not to perform simultaneous ureteral reimplantation is an important decision because reimplantation can be technically

difficult in abnormal bladders, and yet may resolve spontaneously after bladder augmentation. Historical data are important because reflux, which develops secondary to abnormal bladder function, can be expected to reverse following augmentation (188). Conversely, when historical data document primary reflux; when cystoscopy or operative examination reveals disordered ureterovesical anatomy, parautereric weakness, or nonexistent submucosal tunnels; and when indications for reimplantation are marginal, simultaneous reimplantation should be performed.

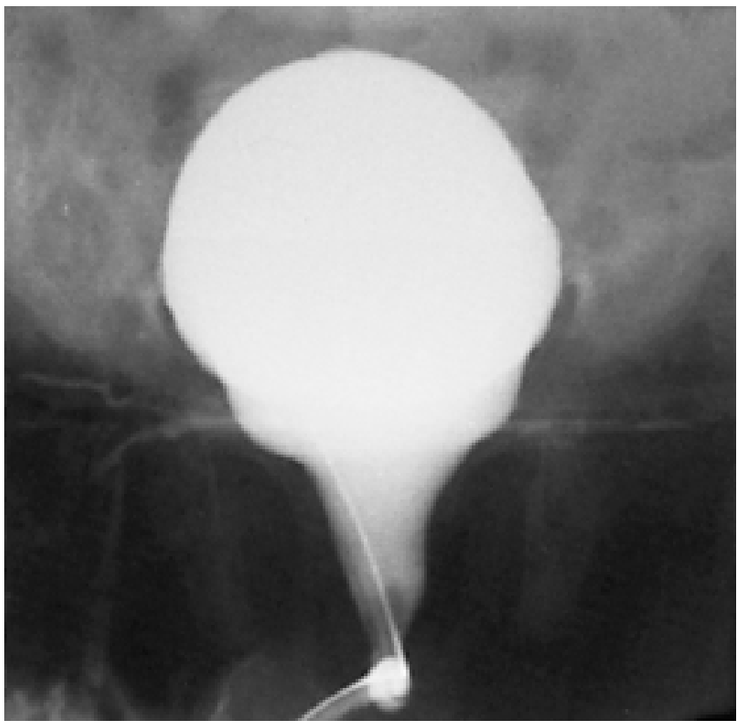

FIGURE 49D.8. Voiding cystourethrogram in a boy with myelomeningocele demonstrates an incompetent bladder neck (intrinsic sphincter deficiency).

When enterocystoplasty has been performed in childhood, long-term follow-up is important. A concern has been the effect of augmentation on the management of pregnancy and delivery. Hill and Kramer (102) surveyed 15 pregnancies after enterocystoplasty. UTI or pyelonephritis occurred in 60%, independent of the presence of reflux. Four patients experienced preterm labor. No incontinence occurred in patients who were delivered vaginally if there had been no prior bladder neck continence procedure. Caesarian section is recommended for patients who have previously undergone bladder neck reconstruction.

Autoaugmentation and Ureterocystoplasty

The reported complications of enterocystoplasty have lead researchers and clinicians to continue to search for viable alternative means of increasing bladder capacity and compliance. Patches of peritoneum, skeletal muscle, de-epithelialized bowel, bowel adventitia, and others have been reported. However, it seems that autoaugmentation (38) and ureterocystoplasty (16,50) have had some reproducible clinical success. Autoaugmentation (detrusor myotomy) is best suited for bladders with reasonable capacity that require a modest improvement in capacity and compliance (Fig. 49D.9). The procedure can be performed extraperitoneally and involves using cautery and sharp and blunt dissection to tease muscle fibers from the mucosa. Surgery is performed with a bladder catheter in place, varying the degree of bladder filling to assist dissection. When one-half to two-thirds of the detrusor has been teased off, the muscle is excised. Although not successful in all cases, autoaugmentation does not interfere with subsequent enterocystoplasty if

this procedure becomes necessary. It thus seems to be a reasonable procedure to attempt if there is reasonable consideration that it will improve bladder dynamics. Autoaugmentation has been performed laparoscopically in a small number of patients.

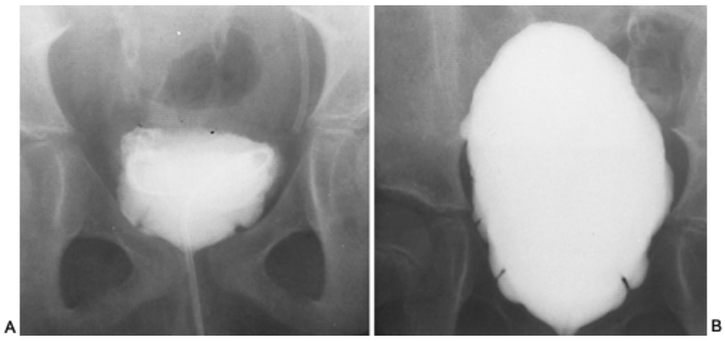

FIGURE 49D.9. Cystogram before autoaugmentation **(A)** and after autoaugmentation **(B).**

Ureterocystoplasty is a procedure that by its very nature is appropriate for only a limited patient population. Prerequisites are either a dilated ureter with a significant volume that is estimated to provide a significant additional increment to bladder capacity or a refluxing megaureter that has already proven its ability to serve as a pop-off mechanism to protect the contralateral kidney from the development of hydronephrosis or reflux (Fig. 49D.10). The technique of ureterocystoplasty may include nephrectomy if the refluxing kidney has poor function, or transureteroureterostomy if function is salvageable. The donor ureter (and renal pelvis if it is large) is mobilized carefully, preserving all adventitial and collateral vessels. The ureter is then divided along its antimesenteric border, the incision taken through the ureteral orifice and continuing to bisect the bladder in the midline or diagonally, as in enterocystoplasty. The detubularized ureter is then folded upon itself and sewn into the bladder defect as in enterocystoplasty. Simultaneous procedures such as contralateral ureteral reimplantation or appendicovesicostomy may be performed. As with autoaugmentation, a significant advantage of ureterocystoplasty is the ability to avoid incorporating extraurinary mucosa into the urinary tract. If, however, the ureter is inelastic because of scarring and fibrosis, the augmented segment may not be as useful as anticipated. Similarly if autoaugmentation results in scar formation rather than regrowth of bladder wall the anticipated results may not be appreciated. The inadequacies

of present techniques for bladder augmentation have stimulated efforts to regenerate new bladder tissue that will function as native tissue. The efforts are in early stages of development, but bladder muscle and epithelial cell cultures on either a synthetic matrix or acellular collagen matrix (SIS) have experimentally resulted in bladder regeneration.

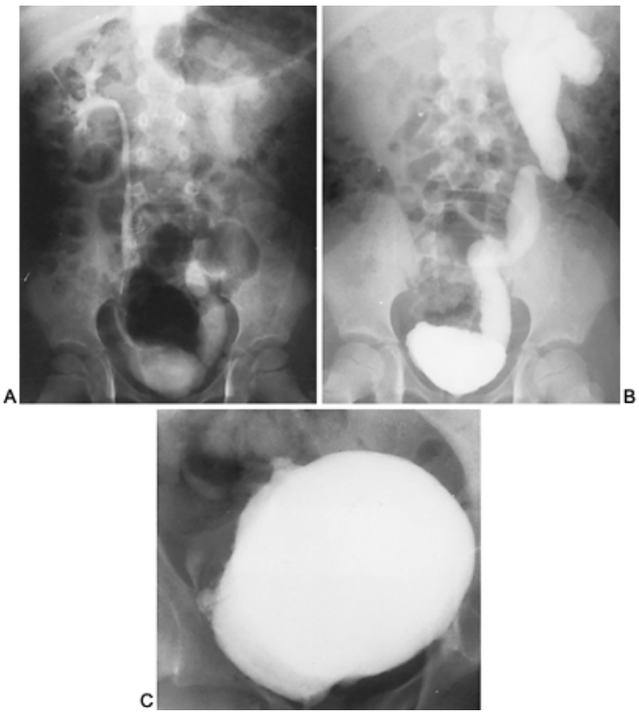

FIGURE 49D.10. A: Intravenous pyelogram before ureterocystoplasty: poorly functioning left kidney. **B:** Cystogram before ureterocystoplasty. **C:** Cystogram after ureterocystoplasty.

TREATMENT OF DETRUSOR HYPERREFLEXIA

Sacral Rhizotomy

Selective sacral rhizotomy became popular as a treatment for detrusor hyperreflexia after early experience with bilateral rhizotomy demonstrated an unacceptable incidence of impotence and bowel dysfunction. Although selective dorsal rhizotomy has received little attention in the daily management of detrusor hyperreflexia, several centers have developed an expertise and long-term data are now becoming available. Gasparini and others (82) reported follow-up over a mean of 32 months in patients with cervical and thoracic spinal cord injury. They found no adverse effects and a 94% improvement in continence. Storrs (230) combined untethering of the cord with selective posterior rhizotomy in two children with myelomeningocele and reported success in both. The role of sacral rhizotomy in the treatment of detrusor hyperreflexia is still uncertain.

Intrathecal Baclofen

Oral therapy for spasticity resulting from neurologic disease has proven unsuccessful, in large part because the systemic actions of the medications produce generalized weakness but are unable to sufficiently diminish spasticity. Intrethecal baclofen has been used successfully for patients with cerebral palsy or spinal cord injury (3). Investigators have been encouraged by this experience, and some data are available on the effect of intrathecal baclofen on bladder and sphincter function. Nanningia (187) studied seven patients with spasticity secondary to spinal cord injury, and found a decrease in sphincter activity that paralleled a general decrease in spasticity. Six of the seven patients demonstrated an increased bladder capacity, and improved continence was seen in a majority.

INCONTINENCE: INCREASING OUTLET RESISTANCE

Diminished outlet resistance is a common problem for patients with neurovesical dysfunction, especially in cases of myelodysplasia. Appropriate evaluation of bladder neck competence can be made by upright fluoroscopic examination of the bladder neck during cystography or videourodynamic evaluation (91). Valsalva's and Credé's methods should be used as provocative maneuvers if the bladder neck is closed during filling. Electromyographic studies also can be used to assess neuromuscular activity of the pelvic floor and periurethral musculature. An open bladder neck may indicate that intrinsic sphincter weakness is the cause of incontinence, but diminished bladder compliance and capacity also must be taken into consideration as the etiology of or as a contributor to incontinence.

When diminished outlet resistance is a contributor to incontinence, a trial of pharmacotherapy should be initiated before considering surgical intervention (Table 49D.1). Ephedrine, phenylpropanolamine, and imipramine are the most common agents used in the pediatric age group, and they are commonly used in conjunction with anticholinergic agents to achieve continence together with a program of intermittent catheterization. A catheterization trial, even when ineffective in promoting dryness, affords the urologist an interval of observation before surgical intervention to ensure that the child and family are committed to a rigorous program of catheterization that in all likelihood will be a permanent adjunct to surgical therapy. Many surgical options are used to correct an incompetent urethral sphincter. These procedures can be classified as effecting urethral lengthening, urethral suspension, or urethral compression. Several possible alternatives and modifications exist within each category of surgical procedure (Table 49D.3). The sheer number and variety of procedures that have been proposed, each with its proponents and detractors, attest to the fact that a perfect continence mechanism has yet to be described. It is important to recognize that detrusor function may be unfavorably altered after bladder neck reconstruction. This may result in diminished compliance and instability with secondary upper tract deterioration (185). Preoperative urodynamic evaluation of all patients with neurovesical dysfunction who are being considered for bladder neck reconstruction should include a provocative cystometrogram. Woodside and McGuire (254) described the use of a balloon catheter to occlude the vesical neck during the cystometry if urethral leakage occurs around the urodynamic catheter. After performing a routine cystometrogram, the study is repeated using a balloon catheter inflated at the bladder neck to simulate increased outlet resistance. Increased detrusor pressure or instability in the face of bladder neck occlusion is worrisome and raises the question of whether pharmacologic (anticholinergic) or surgical (bladder augmentation) intervention to improve detrusor compliance will be necessary in conjunction with or subsequent to the bladder neck procedure.

Young (255), Dees (61), Leadbetter (156), and Kropp (150) have described commonly used urethral lengthening procedures. The Young-Dees-Leadbetter procedure incorporates proximal reimplantation of the ureters and tubularization of the trigone to afford additional urethral length. A urethral length of 3 to 4 cm should be obtained, the mucosa tubularized over a small 5- or 8-Fr catheter with a pants-over-vest or modified closure of the muscularis. Jones (124)

reported a 9% continence failure rate and a 27% reoperation rate after using a modification of this technique. This procedure is rarely applicable to the neurogenic bladder patient but is very useful in the short dilated urethra such as found in epispadias and exstrophy. Normal voiding can be achieved with this procedure. Bladder neck suspension may be performed in conjunction with these urethral lengthening procedures.

Kropp (150) described a novel procedure using a detrusor tube reimplanted into a submucosal trigonal tunnel. He reported continence in 20 of 24 (80%) patients. Belman (17) reported a 78% success rate with this technique. Salle (214) reported improved continence in 70% of patients using another modification that utilizes an anterior bladder flap. The continence mechanism of these procedures is dependent on a flap valve that requires intermittent catheterization to empty the bladder. The procedures are applicable to the neurogenic bladder population and incompatible with normal voiding. The most common postoperative problem in this group has been difficult urethral catheterization.

Urethral suspension for outlet deficiency is commonly performed for incontinence of many types, including neurovesical dysfunction. Common techniques include suprapubic suspension (84,209) and variations of the periurethral and puboprostatic fascial sling. Bauer (14) reported dryness in 72% of girls after a sling procedure and Elder (73) achieved dryness in 9 of 10 girls and 4 of 4 boys after a combined sling and augmentation procedure. Decter (58) found 90% immediate postoperative dryness, but some increased wetness with time. There was no difference in success whether rectus fascia or fascia lata was used. Three patients had difficulty catheterizing postoperatively, and three required bladder augmentation because of postoperative upper tract deterioration.

Urethral compression to achieve incontinence is most often accomplished by artificial sphincter implantation or submucosal injection therapy. The artificial urinary sphincter has proved valuable in achieving continence in a highly select group of children with neurovesical dysfunction. Before sphincter placement is considered, it is mandatory to have a low pressure, compliant bladder. This may be achieved by pharmacologic therapy or may require augmentation cystoplasty (185). Gonzalez and Sheldon (90) implanted sphincters in ten boys and five girls, aged 5 to 17 years. Nine boys achieved continence over an average of 51 months, but only one girl was continent. Erosions occurred in girls whose bladder necks were violated during surgery. Kroovand (148) noted that 37 of 44 (84%) of his patients were dry, 5 of 44 (11%) had stress incontinence, and 3 of 44 (7%) developed erosions. In this group, 20 sphincter replacements were necessary because of mechanical failure, and the 44 patients underwent a total of 99 surgical procedures during the period of study. Bosco and co-workers (28) followed 36 consecutive children for at least 5 years after artificial sphincter implantation and found 75% of the sphincters still functioning. The most common complication requiring reoperation was leakage of fluid from the device. The overall continence rate was 84% at 2 years and 62% at 5 years. The success rate was best with the newest model sphincters. Jumper and others (126) found no evidence that the artificial sphincter cuff interfered with sexual development or function, or prostate growth and morphology in the growing child with myelodysplasia.

Barrett (9) demonstrated that particle shedding from implanted silicone devices occurs, with foreign body granuloma formation seen in local tissues and regional lymph nodes, Reinberg and co-workers (210) studied six children after artificial sphincter implantation and found silicone particles in the perisphincteric tissue but not in the regional lymph nodes. The clinical significance of this phenomenon is uncertain because no adverse effects have been encountered from migrated silicone particles.

Endoscopically guided submucosal injection therapy can be used to treat intrinsic sphincter deficiency. The purpose of injection therapy is to provide a mechanism for coaptation of the bladder neck and proximal urethra in patients whose open proximal urethra allows increases in intraabdominal pressure to be transmitted directly to the urethra and external sphincter. Polytetrafluoroethylene (Teflon paste), collagen, and autologous fat have been utilized. Teflon is an inert substance that cannot be broken down by the body. Vorstman (240) reported on 11 children who were treated with one or more periurethral or transperineal injections of Teflon paste. Four girls had neurovesical dysfunction, and two became dry on intermittent catheterization after injection therapy. In this series, large volumes of Teflon paste (5 to 21 mL) were used. Other series have found similar results, but the use of Teflon in children has come into disfavor because of the local inflammatory reaction at the injection site and migration of Teflon particles to distant organs. Brown (31) carried out histologic examination of 32 ureters subjected to ureteral reimplantation after submucosal injection of polytef paste to treat VUR. Four ureters were subsequently found to have granulomatous polyps at the site of injection. When the Teflon had been injected into the proper submucosal plane, it remained encapsulated, inciting a minimal foreign body reaction. However, this occurred in only 3 of 27 ureters that had persistence of VUR and were examined histologically at the time of ureteral reimplantation, while the remainder were found to have diffusion of the Teflon and an increased inflammatory reaction. Malizia and others (168) injected polytef paste periurethrally in female dogs and male monkeys. At pathologic examination 10 months later, polytef particles were found at the injection site and in lymph nodes, lungs, kidney, and brain. The pathologic finding at these sites was characterized as a pronounced chronic inflammatory reaction with giant cells. Based on these data, the authors

advised against use of this material in children, a point of view held by many urologists in this country.

Glutaraldehyde cross-linked collagen also has been used for the treatment of intrinsic sphincter deficiency. Animal experiments have shown that the collagen becomes integrated with the surrounding tissue and produces no foreign body reaction. Wan (243) reported on eight children treated with collagen, six of whom had neurovesical dysfunction. A total of 17 injections were required (average of 2.1 injections per patient) at an average volume per treatment of 10.9 mL. Continence was produced in 63% of patients, and another 25% improved. Shortliffe and others (220) saw similar improvement. Collagen seems to be a safer material in terms of migration, but sensitivity to the material is reported, and all patients must undergo skin testing 1 month before injection therapy. If the skin test is reactive, implant placement is contraindicated. Collagen seems to be less durable than Teflon and many patients have noted a gradual decline in urethral resistance with time.

Santarosa and Blaivas (215) reported on the use of autologous fat for injection in adults with intrinsic sphincter deficiency. No data are yet available on long-term results or the use of this procedure in children.

CONTINENCE ALTERNATIVES

Although intermittent catheterization has become the primary mode of bladder management for many children with neurovesical dysfunction, institution of a bladder catheterization program provides dryness in only 24% to 49% of reported series (41,201,252). Modern urologic management has provided an excellent outlook for renal function in most children, and social acceptance and freedom from odor, wetness, and embarrassment have now become realistic goals for most children and their families, with an overall social continence of 80% (174,186). Lindehall and associates (162) found that, even when complete dryness was not achieved, adolescents and young adults were encouraged by diminished wetness and less likelihood of embarrassing incontinence. Individualized and sometimes innovative continence alternatives have now become part of the urologic armamentarium, and it is extremely important that the urologist separate medical from social indications for bladder manipulation, particularly when major surgical procedures will be involved.

Diapering is standard management for infants, and may be appropriate for older children who are severely handicapped and unable to provide self-care, especially if effective bowel control is lacking. Institutionalized children frequently are managed in this way. An older child who is incontinent in spite of an adequate intermittent catheterization program may prefer changing diapers to either catheterizing and still being wet, or to dryness if being dry entails surgical intervention and long-term intermittent catheterization. As long as normal upper tracts are maintained, spontaneous voiding into diapers may be a reasonable alternative if wetness can be managed to the satisfaction of the child and caretakers. The only contraindication to this management scheme is the child with an elevated leak-point pressure and poor vesical compliance who might be subject to upper tract deterioration if a catheterization regimen was curtailed or discontinued.

Aggressive management of urinary incontinence requires that a satisfactory program for bowel continence be established before or in conjunction with bladder training. The establishment of an effective bowel regimen cannot be an overnight process and should be started in all infants with neurovesical dysfunction. Once established, however, an effective bowel program may provide tremendous impetus for the child to participate in a bladder management program.

The definition of an appropriate program for the management of urinary continence depends on the desires, social awareness, and individual concerns of each patient and his or her caretakers. Children on a catheterization program with minimal dampness between catheterizations should be encouraged to discard diapers. Occasional dampness may be managed by underwear and a sanitary napkin worn in case of accidents, avoiding the use of a bulky diaper. Condom urinary drainage is feasible in boys with adequate penile length and diameter and may provide socially acceptable continence when bladder emptying is adequate and bowels are well managed. Skin irritations and major penile trauma may occur, and the caretaker and child must be admonished against tight application or prolonged application of condom devices without skin examination (118). Ideally, the condom should be changed daily. In small boys with persistent incontinence who do not want immediate surgical intervention, we have devised a modified condom drainage that has been successful using stomal adhesive at the base of the penis. External sphincterotomy has been used in conjunction with condom urinary drainage in boys with spina bifida, but this creates permanent incontinence that can be corrected only surgically. As a result, this procedure is rarely used in children (144). External urinary collection devices have been designed for the female, although satisfactory dryness has been achieved in a small number of adult patients in few clinical series. Data in children are anecdotal.

The creation of a continent vesicostomy using a detrusor tube as a catheterizable stoma has never achieved a significant degree of success in adults or children. The description of appendicovesicostomy by Mitrofanoff (180) and its subsequent popularization by several authors (70,233) however, has made continent urinary diversion immediately applicable to the care of many children with neurovesical dysfunction. The Mitrofanoff “P’principle,” using a small caliber conduit such as the appendix or distal ureter in an antireflux fashion to provide a tiny catheterizable stoma, has been applied to the native bladder and to bladder replacement

reservoirs (70,233) The Mitrofanoff technique was originally used in conjunction with surgical closure of the bladder neck. In most cases, however, it is offered as an alternative to urethral catheterization when catheterization is painful or difficult because of urethral stricture, introital anatomy, or physical handicap which makes access to the urethral meatus difficult. Many other applications of continent urinary diversion have been applied to the pediatric population (101,203). When the appendix is unavailable, inadequate, or is to be used for an antegrade continence enema (ACE) procedure, creation of a small-caliber ileovesicostomy by the technique described by Monti may provide a satisfactory catheterizable continent stoma (36). Laparoscopic techniques have been utilized for the creation of continent stomas in children (35). Paradoxically creation of a continent catheterizable channel to the bladder facilitates bladder neck reconstruction in many patients because the need for urethral catheterization is obviated.

Urinary Diversion and Undiversion

Permanent cutaneous urinary diversion has become a therapy of last resort in the management of the child with neurovesical dysfunction. Ileal conduit diversion, once considered a panacea to salvage kidneys from reflux and infection, has proved hazardous over time. Schwarz and Jeffs (217) followed 96 patients 2 to 16 years after diversion, finding that radiographic evidence of deterioration correlated with the interval of diversion and that stomal stenosis, excessive conduit length, and ureteroileal obstruction contributed to accelerated deterioration. Cass (39) found upper tract deterioration in 16.5% of 50 children followed longer than 10 years. Crooks and Enrile (57) found transient upper tract improvement after ileal diversion with subsequent deterioration in 80% of patients. This was contrasted with stabilization or improvement in the upper tracts of children managed by intermittent catheterization. Nonrefluxing colon conduit diversion has been advocated to prevent the long-term effects associated with ileal conduits (6). Hill and Ransley (103) reported stomal stenosis in 34%, upper tract dilation in 36%, and an overall complication rate of 81% in 47 children with colon conduit diversion. Husman found an acceptable rate of upper tract preservation, but voiced concern about the long-term effects of chronic bacteriuria (113). Clearly, permanent cutaneous diversion should be considered a therapy of last resort in children with neurovesical dysfunction.

Urinary undiversion was initially made feasible by the application of bladder augmentation and innovative reconstructive principles to urinary tracts previously subjected to either temporary or permanent urinary diversion. These innovative and often extremely complex procedures have become less commonplace as the primary management for neurovesical dysfunction has become more effective and obviated the need for urinary diversion (100). The evaluation of a child for undiversion may include urography and/or radionuclide renal imaging, cystography, retrograde conduit (loopogram) studies, determination of creatinine clearance, and urodynamic evaluation (176). However, the single most important aspect of evaluation, above and beyond that of the assessment of bladder function, is the evaluation of the child's and his or her family's expectations for continence, and their motivation to undergo major surgery and pursue long-term intermittent catheterization (120).

Bladder storage capacity may be assessed before undiversion by intermittent bladder filling (cycling) via suprapubic or urethral catheter. An intermittent catheterization trial carried out at home for several weeks or months allows the urologist to assess not only the child's technical ability to perform catheterization but also his or her motivation to persist with lifelong bladder management. To proceed with undiversion without commitment from the patient and caretakers may risk lifelong incontinence or rediversion. The unique psychosocial stresses that bring children to consider undiversion and the expectations they hold for continence also must be weighed strongly before proceeding with undiversion. Urinary undiversion or reconstruction may be carried out in carefully selected patients as preparation for renal transplantation (89).

Transurethral Electrical Bladder Stimulation

In 1958, Katona and Berenyi (132) first used transurethral electrical bladder stimulation (TEBS) for the treatment of neurovesical dysfunction secondary to spinal cord injury. In 1975, he reported on a group of 100 children with myelodysplasia of whom 71% had attained day and night continence. Kaplan and Richards (130) have popularized TEBS in the United States for neurovesical dysfunction in children with myelomeningocele (130). It is postulated that TEBS stimulates mural receptors that have remained dormant because of a lack of afferent innervation to the bladder. Activation of the receptors triggers small detrusor contractions. Vegetative afferentation progresses, efferent pathways are facilitated, and both motor and sensory function improves. Biofeedback training is then used to link sensation to detrusor contraction as micturition is learned. Reported beneficial effects have included improvement of bladder sensation, stimulation of detrusor contraction, increased bladder capacity, and the establishment of urinary continence. Ebner (71) and associates have studied TEBS in a neurologically intact animal model and found that stimulation involved direct activation of mechanoreceptor afferents, which in turn elicited detrusor contractions.

TEBS therapy is time-consuming, necessitating daily 90-minute sessions. At least 30 sessions are needed to determine whether the patient might respond to therapy, and many patients require more than 100 stimulation

sessions to achieve maximal results. Therapy is initiated after performing a baseline urodynamic evaluation and an initial test stimulation. Stimulation is performed after filling the bladder to half capacity with saline via a special electrode catheter. Electrical impulses are passed through the saline. Frequency, intensity, duration, and waveform of the impulse are varied over multiple sessions to produce an optimal result (detrusor contraction) (Fig. 49D.11).

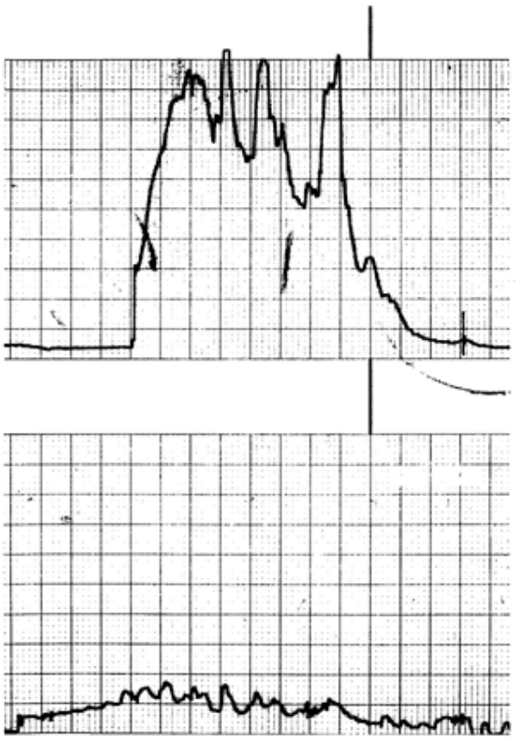

FIGURE 49D.11. Bladder pressure tracing demonstrating a detrusor contraction in response to transurethral intravesical bladder stimulation (upper tracing). Lower tracing reflects intraabdominal (rectal) pressure.

Clinical experience with TEBS has been limited to a small group of patients at a few centers, and the results of therapy were initially encouraging. Lyne and Bellinger (163) reported on a series of 17 patients who had undergone a total of 618 sessions of TEBS. All patients demonstrated detrusor contraction and 88% had some degree of sensation of the contractions. Six patients showed a significant (14% to 158%) increase in bladder capacity during therapy, but in half of these a return to near baseline capacity was noted after therapy was completed. No patient achieved voluntary micturition after therapy, 29% experienced some improvement in bladder parameters, and one patient has had continued improvement in fecal continence. Decter (60) reported a similar experience in 21 patients with neurovesical dysfunction, with initially encouraging results, but in a later report has abandoned offering this therapy to patients because of a lack of significant improvement in bladder function (59). Boone (25) carried out a prospective randomized clinical trial in 36 children over a 3-week period. He found no statistically significant increase in bladder capacity, detrusor activity, or bladder sensation during this short trial period. Further clinical experience with TEBS is in progress in a limited number of centers. Cheng and others (46) reported on a multiinstitutional trial. Of 335 evaluable patients, 53% demonstrated increased bladder capacity of 20% or greater over a period of 1.9 years after the initiation of treatment.

MANAGEMENT OF VESICOURETERIC REFLUX

VUR is found in 3% to 5% of neonates with myelomeningocele and may develop in as many as 30% to 40% by 5 years of age secondary to high intravesical pressures and detrusor-sphincter dyssynergia. Bauer (11) has shown that reflux is rarely seen in neonates unless abnormal bladder dynamics are found. Although Levitt and Sandler (160) failed to find VUR in infants less than 6 weeks of age, Stafford (226) found reflux in 3 of 10 neonates studied. Gaum and others (83) studied 68 consecutive neonates. Of 55 patients with normal urograms, 14.5% had VUR, and when urography was abnormal, 23% were found to have VUR. These data support the view that both urography and sonography are insufficient to screen for VUR in the neonate with neurovesical dysfunction. Cass (39) followed 210 children over 15 years. Although 21% initially had reflux, 38% eventually were found to reflux in subsequent studies, pointing out the importance of periodic reevaluation. Reflux always should be suspected when new-onset hydronephrosis is found on ultrasound examination in a child with abnormal bladder function.

Nuclear cystography is commonly used for the follow-up evaluation of VUR in children with primary VUR and normal bladder function. However, the anatomic detail offered by a routine contrast VCU makes it more applicable to patients with neurovesical dysfunction, for both the initial and follow-up examinations. The ability to assess detrusor trabeculation, bladder neck incompetence, posterior urethral dilation, and function of the external sphincter and bladder outlet during voiding are only a few of the effects of discoordinated voiding dynamics that would not be evaluable by nuclear cystography. These radiographic findings, however, might be important pieces of information for the urologist caring for a child with neurovesical dysfunction. The VCU may be combined with urodynamic assessment in a fluorourodynamic study (videocystometrogram).

The management of VUR in neurologically intact children includes antimicrobial prophylaxis; repeated urine cultures; periodic reevaluation; and, in many cases, surgical intervention when breakthrough urinary infection occurs or when the child fails to outgrow reflux within a reasonable period (116). Management of VUR in children with neurovesical dysfunction also must include meticulous attention to abnormal bladder and urethral dynamics, which, if uncorrected, may cause or promote secondary reflux (2).

Although elevated pressures generated in the neuropathic bladder may be transmitted to the kidney in the presence of VUR, infection remains the primary mediator of renal damage in patients with moderate VUR (207). All children with VUR must be maintained on long-term suppressive antibiotic therapy (72,158). In the young child with minimal reflux, adequate spontaneous bladder emptying, and persistently sterile urine, only antibiotic prophylaxis and close surveillance are necessary. Moderate VUR (grades 3 and 4, International System) (115) in children with neurovesical dysfunction demands aggressive evaluation and management. Urodynamic evaluation should be performed to detect the presence of detrusor hyperreflexia or noncompliance and to assess whether anticholinergic pharmacotherapy may be needed in an effort to improve detrusor compliance. In most cases, intermittent catheterization is begun. If the social situation prohibits an effective catheterization program or if intermittent catheterization in combination with anticholinergic therapy fails to effectively alter bladder dynamics, cutaneous vesicostomy is performed. Kass (131) documented spontaneous resolution of VUR in 31% of ureters once CIC was instituted (100% in nondilated ureters and 0% in dilated ureters), and Kaplan and Firlit (128) found resolution of VUR in 62% of 200 children when CIC was instituted. Close bacteriologic surveillance and periodic radiologic follow-up are necessary in this group because intermittent catheterization adds an increased risk of UTI. If VUR does not resolve in patients after the institution of a catheterization regimen with or without pharmacotherapy, surgical intervention is warranted.

The surgical management of VUR in the child with neurovesical dysfunction demands an in-depth assessment of bladder capacity, compliance, and emptying. The poor results of reimplantation in many early series (108,119,126) have improved dramatically once bladder rehabilitation with antibiotics; pharmacologic therapy; intermittent catheterization; and bladder augmentation, if necessary, have been achieved. In the severe case with massive reflux, temporary cutaneous vesicostomy may prove extremely valuable. Subsequent vesicostomy closure combined with ureteral reimplantation may be necessary if VUR persists. In many cases, bladder augmentation is necessary to provide adequate bladder capacity and compliance. In general, indications for reimplantation are alike in normal and neuropathic bladders: persistent VUR in spite of adequate pharmacotherapy and intermittent catheterization, recurrent infection (which may be a significant problem for the child on CIC), and upper tract deterioration. Technically, any reimplantation technique may be used, but the technique of Cohen (52) has been advocated because a long cross-trigonal tunnel can be achieved. However, postoperative obstruction may be difficult to deal with if the Cohen technique is used. Suprapubic diversion and ureteral stents are used routinely when one is reimplanting in thickened neurogenic bladders. Using careful bladder management, Jeffs (119) corrected reflux in 33 of 37 children (89%) using the Paquin or Cohen technique. Kaplan and Firlit (128) achieved 96% success in 40 ureters, and Woodard (253) accomplished successful reimplantation in 76% (83% in nontapered ureters and 33% in tapered ureters). Clearly, optimal bladder management is an important contributor to success in reimplantation.

Submucosal injection therapy for VUR was introduced by O'Donnell and Puri in 1986 (192), and subsequently was applied to children with neurovesical dysfunction by Puri (202). Kaplan (127) reported a success rate of 84% after one injection and 87% after two injections. Although Kaplan found no evidence of microscopic migration of Teflon particles to lymph nodes sampled at open surgery after Teflon injection (127), concern has been raised in animal studies (168) (see Incontinence), and many authors have abandoned the use of this material for injection in children (33). Cendren and others (44) reported an overall success rate at 1 year of 65% using cross-linked bovine dermal collagen injection for reflux. Although this material is currently available for the treatment of intrinsic sphincter deficiency, it has not been released for the treatment of VUR. The long-term efficacy of collagen in treating VUR is still to be determined. Tissue reaction is much less than seen with Teflon.

URINARY TRACT INFECTION

Although close surveillance of UTIs is an important part of the management of children with VUR, data conflict regarding the utility of chronic antibacterial prophylaxis in children without VUR who are maintained on a program of nonsterile intermittent catheterization. Bakke and Vollset (7) studied 262 patients on intermittent catheterization and found persistently sterile urine in 28%, occasional bacteriuria in 44%, and chronic bacteriuria in 28%. Among those using chronic antibacterial prophylaxis, fewer episodes of bacteriuria but a greater number of clinical UTIs were noted. Factors related to the presence of bacteriuria included high catheterization volumes and a low frequency of catheterization. Johnson and associates (121) studied the efficacy of short-term nitrofurantoin prophylaxis in 56 children during a 24-week double-blinded placebo-controlled crossover study. They found a diminished incidence of UTI in the treated group, but only a 76.9%

compliance with medication usage and a 0.62% incidence of symptomatic UTI. It appears that routine antimicrobial prophylaxis is not indicated in patients managed with intermittent catheterization in the absence of VUR.

ASSOCIATED CONCERNS

Bowel Incontinence

Bowel and urinary incontinence together present a tremendous handicap to normal social interaction for the child with spina bifida. Although a great deal of effort is commonly expended to provide adequate urinary control, failure to provide a good bowel program may leave the child diaper dependent. The purpose of establishing a bowel routine is to provide a method of periodic, effective bowel evacuation while preventing accidental soiling. An effective program must combine diet, controlled evacuation, and a well-regimented schedule (45).

Diet is extremely important for management of fecal incontinence. Although infants generally have loose or soft stools, the addition of table foods to the diet commonly results in hard stool. In general, a high-fiber diet is successful in preventing hard stools, and this diet should be started in early childhood to encourage a lifetime dietary regimen. When necessary, medications may be added to provide increased stool water.

Manual stimulation, reflex stimulation by suppositories, or mechanical stimulation by enemas may be necessary to trigger evacuation of the colon. As with bladder management programs, each child is an individual, and trial and error may be necessary to design an effective bowel program. For many children, saline or soapsuds expansion enemas given via a rubber ear syringe are remarkably effective, simple, and inexpensive (45). Independent of which program is chosen for bowel management, it is important to begin a regimented schedule early in childhood when the child can sit on a potty chair. Successful evacuation may be timed to occur after a meal at the same time each day, in an unhurried atmosphere.

Anorectal manometry has been described as a method of assessing the effect of neuromuscular dysfunction on the lower bowel and sphincters, and biofeedback training has been used with some success in myelodysplastic children (174,241,247). Malone (169) reported on an innovative modification of the Mitrofanoff principle to provide a nonrefluxing catheterizable stoma for ACE. Many reports have confirmed the efficacy of this procedure in providing optimal bowel management for patients with neuropathic bowel dysfunction (21,37,74,145,181).

Sexuality

The normal timetable of sexual development may be altered in children with hydrocephalus. The recognition that precocious puberty may occur in both male and female patients has been made by Meyer and Landau (177) using hormonal data to document true isosexual precocity, although the endocrinologic mechanisms involved are incompletely understood. Because of the potential for the early development of secondary sex characteristics, all children with spina bifida and their parents and caretakers will benefit from early discussion of normal adolescent development and menarche. Data on sexual function in spina bifida are poorly documented, much having been inferred from the spinal cord injury literature (204). Shurtleff (221) described 80% erectile ability and 40% ejaculation in a survey of older spina bifida males. Eighty percent of women were sexually active, all describing satisfactory orgasms. In Cass' series, 12 of 17 women having intercourse had become pregnant (42). Sexual counseling for the preadolescent and adolescent is a valuable part of any total rehabilitation program, and children should be encouraged to attend regular sex education courses in school, from which they may otherwise be excluded because of the mistaken impression that all handicapped children are nonfunctional or sterile. Girls in particular must realize that their fertility is normal and that normal sexual function is possible. Thus, knowledge of effective birth control is essential. Routine gynecologic examination should be encouraged in all girls beginning at puberty.

MISCELLANEOUS UROLOGIC CONCERNS

Circumcision offers two significant advantages for many boys with neurovesical dysfunction: diminished risk of UTI and increased ease of performing catheterization. Human foreskin is known to show a propensity for adherence and colonization by pathogenic bacteria. Wiswell confirmed the significance of bacterial adherence in boys, finding a tenfold increased incidence of UTIs in uncircumcised boys in a group of 209,399 infants. He also reviewed the findings of other authors who showed an increased risk of UTIs in uncircumcised boys, ranging from 5 to 89 times greater than seen in circumcised boys (251). Removal of the foreskin thus not only exposes the meatus for technically easier catheterization but also removes a contiguous source of periurethral skin colonization.

Cryptorchidism in spina bifida males is not uncommon (151). The management of these children should not differ from treatment plans for other boys.

Inguinal hernias (communicating hydroceles) may appear or worsen soon after ventriculoperitoneal shunting in infants. Kaufman and Carmel (133) noted hydroceles in 7% of girls and 23% of boys younger than 1 year of age with shunts. They postulated that a combination of increased abdominal fluid and pressure, an alteration in peritoneal membrane characteristics, and proximity of the shunt tubing to the inguinal canal influenced hydrocele

formation. In some instances, the shunt tubing may migrate into the scrotum (Fig. 49D.12). Surgical repair is indicated in these children, and bilateral exploration should always be carried out in young children. Rarely, spinal fluid pseudocysts may present as abdominal masses and may cause urinary tract obstruction (199).

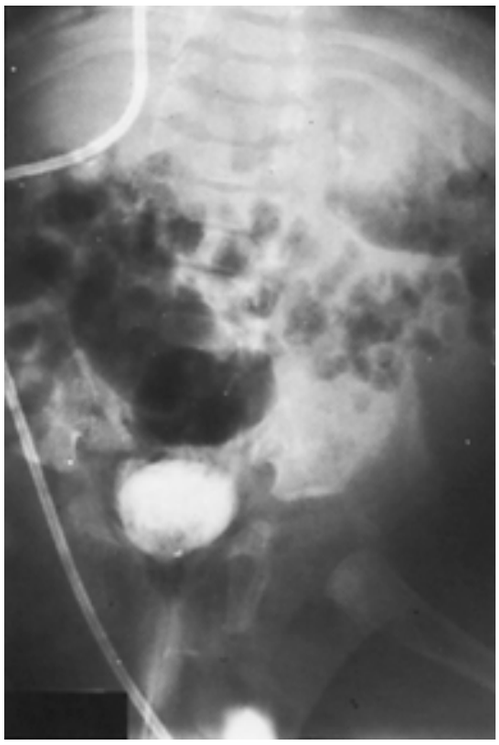

FIGURE 49D.12. Three-month-old boy with large communication hydroceles. At surgery, shunt tubing was found in processus vaginalis.

Tethered Spinal Cord

In children with spina bifida, the spinal cord, fixed abnormally by deformity and postsurgical scarring, may be placed on stretch with growth as the trunk elongates, causing neurologic changes (Fig. 49D.13). Normal somatic growth may thus produce alterations in gait, lower-extremity strength and function, and bowel and bladder control and may result in orthopedic deformities (scoliosis) as a result of neuromuscular imbalance. This “tethered cord syndrome” may progress silently (211). Tethering of the cord also may be seen with diastematomyelia, intraspinal lipomas, and dermoid tumors. Changes in bowel pattern, incontinence between catheterization, or unexpected changes in urinary control or bladder function should raise concern about development of a tethered cord. Urodynamic studies should be performed to document change in bladder dynamics, and neurosurgical consultation should be requested to assess other neurologic changes and to obtain consultation as to whether imaging of the spinal cord and surgical repair are indicated (152). Several series have shown that surgical correction of a tethered spinal cord may result in an increased bladder capacity in some patients, while others may

show no change in bladder function, and some may continue to show deterioration in spite of untethering. In many cases, transient postoperative urodynamic changes may be seen (129).

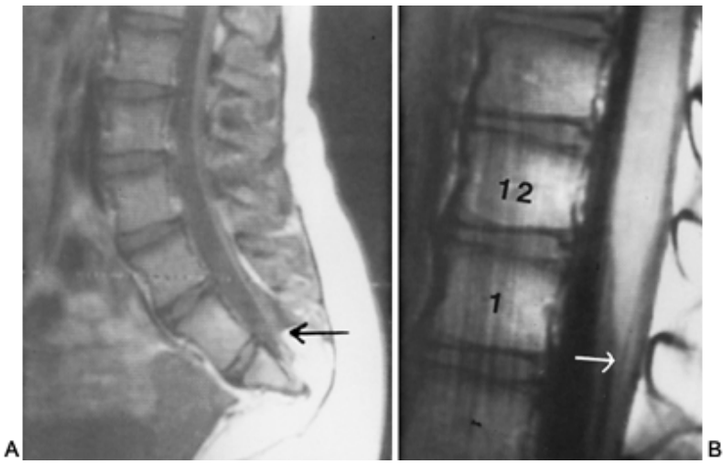

FIGURE 49D.13. A: Magnetic resonance imaging (MRI) scan of normal lumbosacral spine. Conus *(arrow)* ends at L-1. **B:** MRI scan of patient with tethered cord and partial sacral agenesis. Conus *(arrow)* ends at L-5.

Latex Allergy

IgE-mediated immediate hypersensitivity to latex is now a well-documented phenomenon that has been reported most often in children with myelodysplasia during surgery or other exposures to latex. Although delayed (type IV) hypersensitivity may be manifest as an eczematous contact dermatitis, immediate hypersensitivity to a yet undefined component of furosemide has ranged in severity from rhinitis and conjunctivitis to bronchospasm, anaphylaxis, and cardiovascular collapse (88). The almost epidemic reporting of latex reactions in children with myelomeningocele is not readily explained. [Schneck and Bellinger (216) found 45% of patients tested to have hypersensitivity.] It appears likely that previous allergic or cardiovascular episodes were attributed to other allergens or unknown causes. Because physicians are now attuned to the probability of latex hypersensitivity, many children undergo prophylactic skin testing. It is assumed that recurrent exposure to latex-containing gloves, catheters, and other medical devices (Table 49D.4) during multiple medical and surgical procedures sensitizes children at an early age, although many nonmyelomeningocele children are exposed to latex via baby bottle nipples and pacifiers and have an apparently much lower incidence of hypersensitivity. It is speculated those exposures of peritoneal and mucosal surfaces as well as direct tissue exposure during surgery may heighten the development of hypersensitivity.

TABLE 49D.4. COMMON LATEX-CONTAINING MEDICAL DEVICES

Electrocardiogram pads	Tourniquets
Tape	Face masks
Foley catheter	Ventilators, hoses, and bellows
Dilating catheters	Injection ports of IV tubing and IV bags
Surgical drains	Stoppers in medication vials and syringes
Nasogastric tubes	Floating disc valves on some IV burette chambers
Surgical/examination gloves	
Reservoir bags	
Blood pressure cuffs	

IV, intravenous.
From Pasquariello CA, Lowe DA, Schwartz RE. Intraoperative anaphylaxis to latex. *Pediatrics* 1993; 91:985.

In the absence of a confirmed negative latex allergy test, all patients with myelomeningocele or other forms of spina bifida should be considered to have the potential for latex hypersensitivity. A high index of suspicion is important, and the identification of patients at risk begins with the medical history, including a history of urticarial reactions to common latex-containing products, such as crib pads, rubber balls, and balloons. Patients at risk should undergo further definitive testing. Skin testing using colloidal suspensions of rubber particles is sensitive, but severe anaphylactic reactions may result. RAST (radioallergosorbent) testing, which measures the binding of IgE antibodies has been used in many series. RAST testing has sensitivity ranging from 53% to 86%, with specificity of 76% (223). Schneck and Bellinger (216) found reactivity to 3-antigen radioimmunoassay (RIA) latex-specific IgE to be a more sensitive test.

The identification of patients at risk, prophylactic avoidance of latex-containing products, and prompt treatment of hypersensitivity reactions are important to avoid life-threatening complications of latex allergy. When possible, children with spina bifida or other congenital anomalies who will be required to undergo multiple surgical procedures should be placed on a protocol of latex avoidance from birth. When latex hypersensitivity is documented, avoidance of latex-containing material should be practiced and special precautions taken during medical and surgical procedures. If early signs of latex allergy are detected, removal of the latex device should occur immediately and systemic treatment of anaphylaxis should be begun (143).

Team Approach to Spina Bifida

The consequences of spina bifida may be medical, social, psychologic, economic, and educational in scope (64,159). The medical consequences concern growth—developmental, general pediatric, neurologic, orthopedic, and urologic—to name only the most basic. With such major concerns, the interdisciplinary approach to the child and family has advantages, the most practical being that one area will not be neglected inadvertently by the patient or family, resulting in a major handicap for the child. Although the interdisciplinary concept has detractors (198), it offers the urologist the nursing skills necessary to initiate and manage a bowel and bladder program and to integrate this program with care of the child's other neurologic and orthopedic disabilities both at home and in school. Institutions committed to the care of children with significant birth defects will develop multidisciplinary clinics to provide the coordinated expertise of urologists, orthopedic surgeons, neurosurgeons, rehabilitation medicine, pediatricians, nursing, and social services. These facilitate and orchestrate the complex care and attention demanded by these young patients and their families.

Sacral Agenesis

Complete or partial sacral agenesis is a rare anomaly that may occur as an isolated lesion or in conjunction with imperforate anus, cloacal anomalies, and the syndromes of caudal regression (29,196). Maternal diabetes mellitus is found in 12% to 18% of cases of sacral agenesis, and 1% of

diabetic mothers have infants with sacral agenesis. Although affected children are usually evident as neonates, Guzman (96) found only 50% in the newborn period. It is not unusual for children to present at later ages with a lifelong history of urinary incontinence and encopresis.

Physical findings may include an absent gluteal cleft and abnormal contour to the buttocks. Sacral agenesis may be confirmed by anteroposterior and lateral spine films (Fig. 49D.14), but the neurologic deficit may not correlate well with the bony defects noted. Many patients with isolated sacral agenesis have symptoms related only to bladder and bowel control. The high incidence of hydronephrosis or reflux in cases presenting late in childhood demands an early and complete uroradiologic and urodynamic evaluation of all children with documented sacral deformity (29). Urodynamic findings are extremely variable. Guzman (96) studied 16 patients, finding detrusor areflexia in 7 and hyperreflexia in 9, whereas sphincter EMG showed considerable variation in activity and variable dyssynergia. Therapy is based on clinical and urodynamic findings.

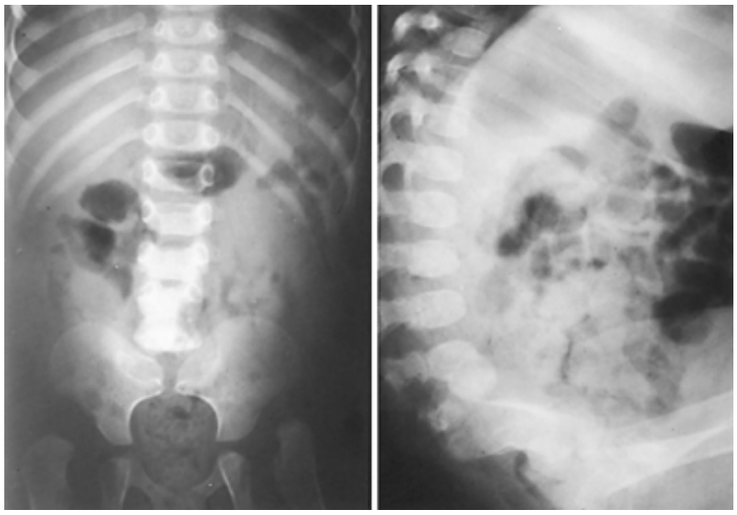

FIGURE 49D.14. Sacral agenesis.

Occult Spinal Dysraphism

Anterior meningocele, lipoma, lipomeningocele, diastematomyelia, ligamentous bands, dermoid cysts, and congenital anomalies of the spinal cord itself may produce variable neurologic deficits, many primarily of neurovesical dysfunction (27). Such lesions should be considered when plain films display abnormal lumbosacral anatomy. Conversely, it is mandatory that the spine be examined carefully on radiographs of all children studied for incontinence or UTI. The physical examination of all children with urinary disorders should include a search of the lower back for skin tags, abnormal tufts of hair, lipomas, dermal sinuses, or pigmented lesions that may be associated with underlying pathologic conditions (4,97). Urodynamic studies may be necessary to document neurovesical dysfunction, because other neurologic tests may be completely normal. MRI of the spine may be helpful in evaluating a lesion of the cord. Foster (80) found abnormal urodynamic findings to be the only sign of spinal cord tethering in 42% of 31 patients with lipomeningocele. If surgery is performed, postoperative urodynamic follow-up is important to document functional improvement or deterioration from the neurosurgical procedure itself. Gross and others (94) found an increase in bladder capacity in 10 of 17 patients, overall improvement in bladder function in 13, no change in 5, and deterioration in 3. In Rigel's series, after release of cord tethering, 3 patients originally thought to have permanent neurologic deficit improved, 5 of 9 with recent loss of bladder function recovered, and 17% lost bladder function (211). Khoury (134) reported on a controversial group of 31 patients with secondary urinary incontinence who had resection of a thickened filum terminale. Incontinence resolved in 72%, urodynamic evidence of detrusor hyperreflexia improved in 59%, and bladder compliance improved in 66% after surgery, but theindications for surgical intervention were unclear. Clearly, appropriate urologic and urodynamic evaluation is extremely important in children with incontinence, and neurosurgical evaluation may be appropriate if urologic findings indicate the possibility of neurovesical dysfunction.

Spinal Cord Injury/Transverse Myelitis

Transverse myelitis and traumatic spinal cord injuries are causes of neurovesical dysfunction that are uncommon in infants and small children, but not rare in adolescents. Infants may suffer spinal cord injury during traumatic delivery, and most other spinal cord injuries are secondary to automobile accidents, gunshot wounds, and diving accidents.

The child with an acute spinal cord injury commonly displays urinary retention, which may be a transient phenomenon, may persist for weeks or months, or may be permanent. Because most spinal cord trauma occurs above the level of the sacral reflex arc, however, urinary retention is usually temporary. An indwelling bladder catheter is placed in most patients with spinal cord injury soon after the injury. This should be replaced by intermittent catheterization as soon as the patient has been medically and surgically stabilized. Catheterization should be performed frequently enough to prevent bladder overdistention, which ultimately may result in myogenic failure. McGuire and Savastano (172) have shown that long-term intermittent catheterization in patients with spinal cord injury is effective in preservation of the upper urinary tract and prevention of pyelonephritis, while allowing both spontaneous voiding to occur and an ongoing assessment of the efficacy of spontaneous detrusor. Because detrusor hyperreflexia and detrusor-sphincter dyssynergia are common findings after spinal cord injury, urodynamic and radiographic studies should be carried out as a baseline and in follow-up of all patients. Evaluation and management of these children parallels that of children with spina bifida and other causes of neurovesical dysfunction.

Head Trauma

Trauma to the spinal cord is a leading cause of neurovesical dysfunction and morbidity (247). Head trauma may result in minor degrees of neurovesical dysfunction that may be an added aggravation during the rehabilitation process. Incontinence and urinary frequency and urgency are common symptoms in this group of patients. UTI, urethral stricture from prolonged catheterization during the acute phase of management, and bladder calculi from indwelling catheters should be considered as possible etiologies for bladder dysfunction and appropriately evaluated. Uninhibited bladder contractions may be discovered on urodynamic evaluation. Treatment must be individualized to meet both the needs and functional abilities of the child.

Cerebral Palsy and Miscellaneous Neurologic Diseases

Cerebral palsy and many stable or progressive neurologic disorders may be causes of bladder dysfunction and urinary incontinence (114,175). In many cases, generalized spasticity is a common finding. The child may be incapable of communicating much useful information about the level of sensation or type of incontinence present. History and physical examination are extremely important in these cases, and one frequently must seek information from the child's caretakers about frequency of urination, force of the urinary stream, bowel habits, and other aspects of history that may be important in terms of differential diagnosis and aspects of management.

Evaluation should begin with history and physical examination and include whatever testing seems appropriate for the level of concern that has arisen. If UTI is a concern, renal sonography, VCUG, and urodynamic evaluation are appropriate. If incontinence is the sole issue, evaluation should begin with a renal and postvoid ultrasound to determine the efficacy of bladder emptying. Urodynamic studies are indicated in many children with incontinence, and in many cases, detrusor hyperreflexia will be found. Anticholinergic therapy may prove beneficial in many cases, but intermittent catheterization may be required if a large postvoid residual urine volume secondary to incomplete bladder emptying is the cause of incontinence. Although many children with cerebral palsy are challenged with urinary control issues, it is rare that the upper tracts are jeopardized.

Nonneuropathic Voiding Dysfunction and the Hinman-Allen Syndrome

Voiding dysfunction in the neurologically intact child may be seen in a group of children with a wide spectrum of abnormal voiding patterns ranging from frequency to enuresis to severe incontinence and with radiographic and urodynamic findings from mild detrusor hyperreflexia to severely disordered bladder function, reflux, hydronephrosis, and renal failure. Many of the more severely afflicted children share many clinical, radiologic, urodynamic, and psychosocial characteristics that have been variously termed nonneurogenic neurogenic bladder, occult neurologic bladder, subclinical neurogenic bladder, or the Hinman-Allen syndrome (5,63,104,106,107) Although originally thought to represent true neurovesical dysfunction related to occult spinal dysraphism, it has been accepted that acquired behavioral and psychosocial disorders may be reflected in bladder and bowel dysfunction, mimicking neurologic disease.

The symptom complex associated with dysfunctional voiding varies from mild dampness to severe daytime frequency (the frequency syndrome of childhood) (256) to day and nighttime enuresis, encopresis, and constipation, recurrent UTI, hydronephrosis, reflux, and renal failure. Bladder and bowel dysfunction usually are preceded by the development of continence and a recognized period of normal bladder and bowel control, as opposed to primary neurovesical dysfunction in which urinary continence may have never developed. When seen by the urologist, many of the most severely dysfunctional children have a history of recurrent

UTI and may have undergone endoscopy or failed urologic surgery for reflux or hydronephrosis.

The initial consideration of dysfunctional voiding is usually raised by the past medical, urologic, and social developmental history. A history of UTIs should be noted, as dysfunctional voiding may trigger or be triggered by acute and chronic cystitis. A thorough evaluation of the child's voiding pattern and social history, both present and during the period of toilet training, must then be obtained. Geist and Antolak (85) noted a high incidence of emotional problems in children with symptoms of interstitial cystitis. Galdston and Perlmutter (81) have shown that anxiety in children may be manifested by alterations in urinary frequency and voiding characteristics. Hinman and Baumann (107) likewise noted shyness, timidity, and an attitude of failure, with some children displaying hyperactivity and general anxiety. Family and social histories frequently reveal strained relationships, separation, or divorce. The child who wets may have been punished repeatedly or ridiculed both at home and at school. Peer interaction is often strained, and many children dislike school, performing poorly. Parent–child interaction during the interview and examination may provide important clues to social problems in the home. Physical examination is generally normal, although a distended bladder may be palpable, and impacted stool may be noted on rectal and abdominal examination. Postvoid bladder ultrasound studies may reveal a large postvoid residual urine volume. Neurologic examination is normal. Many children with severe dysfunctional voiding are withdrawn and uncooperative to examination.

The level of concern raised by dysfunctional voiding and the intensity of evaluation it deserves should be related less to the severity of symptoms than to the clinical, radiographic and urodynamic findings that result. Likewise, the intensity of therapy should be related to the degree of dysfunction and the severity of bladder and upper tract dysfunction that results.

Daytime urinary frequency (the frequency syndrome of childhood) is an increasingly common complaint that brings children to urologic evaluation. The typical symptoms of this disorder are daytime frequency out of proportion to what may be perfect nocturnal dryness; occasional nocturia; and rarely, an episode of enuresis. Children rarely complain of symptoms, but parents, teachers, and caretakers are commonly distressed by the voiding pattern. UTI is not found, and radiographic findings are normal. Zoubek and Bloom (256) found that the average length of symptoms in this group was 7 months; that pharmacologic therapy did not improve symptoms in most cases; and that observation, lack of intervention, and benign neglect were the most effective means of assuring resolution. Screening sonography in the urologist's office will rule out significant bladder wall thickness or hydronephrosis, and reassurance can be given that resolution will occur in the majority of cases. In many cases, this reassurance and visual evidence of normal renal and bladder anatomy is all that is necessary to instill parents with the confidence that they need to deal with the annoyance of urinary frequency.

Moderate dysfunctional voiding is frequently associated with UTI in either a cause or effect relationship. Moderate voiding dysfunction is frequently classified clinically as either the small-capacity bladder, hyperreflexic bladder, or lazy bladder syndromes. Urinary frequency, incontinence, UTI, and constipation are seen in varying degrees in these syndromes, which have fittingly been termed *dysfunctional elimination syndromes.* Renal ultrasonography; voiding cystourethrography; and occasionally, urodynamic evaluation are important to characterize the nature of voiding dysfunction and document whether or not VUR or hydronephrosis is present. Reflux, in particular, may be a worrisome finding and requires close observation. Koff (141) first related abnormal vesical function to VUR in 1979. They studied 53 neurologically intact children with UTIs, urinary frequency, urgency, and/or nocturnal enuresis. All children demonstrated uninhibited detrusor contractions, and 50% were found to have VUR. Taylor (235) confirmed the correlation between the unstable bladder and VUR. Koff and Murtagh (142), in a later prospective study, documented that anticholinergic therapy, when added to a complete program of nonsurgical management of VUR, resulted in a tripled rate of spontaneous resolution of VUR when compared

with controls. Treating UTI and antibiotic prophylaxis in some cases results in resolution of both the dysfunctional voiding and reflux, while improvement in the dysfunctional pattern of voiding may conversely diminish the risk of UTI. This appears to be the result of improving the typical pattern of stop-and-start micturition seen with bladder hyperreflexia that allows milk-back of urethral contents into the bladder. Anticholinergic therapy is beneficial in many cases, and timed voiding regimens, treatment of constipation, and attention to stress-related factors are important aspects of therapy. Overall, the treatment of constipation, usually a relatively silent problem, will pay the biggest of dividends in improving bladder function.

The Hinman-Allen syndrome (nonneurogenic neurogenic bladder) represents the most severe end of the spectrum of voiding dysfunction. Uroradiographic studies are generally abnormal. Hydronephrosis (generally bilateral) is found in 66% to 70%, with significant VUR in 50% to 57%. VUR may have been absent in prior studies, and there may be evidence that VUR was acquired secondary to abnormal voiding mechanics (5,104). The bladder may appear large in capacity and may be smooth or trabeculated. A significant postvoid residual may be seen (Fig. 49D.15 and Fig. 49D.16). Voiding films may demonstrate persistent narrowing at the level of the external sphincter, mimicking posterior urethral valvular obstruction. The urinary stream

may be intermittent, associated with intermittent closure of the external sphincter during voiding. Voiding may be produced by abdominal straining. Ochoa has described a distinctive urofacial syndrome (the Ochoa syndrome), which is seen in children with nonneurogenic vesical dysfunction who display a unique facial inversion or grimace during the act of smiling (191). He postulates the existence of a lesion somewhere in the reticular formation of the brainstem to account for both aspects of neurologic dysfunction.

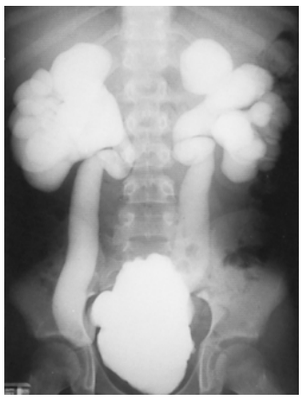

FIGURE 49D.15. Cystogram of 13-year-old boy with Hinman-Allen syndrome.

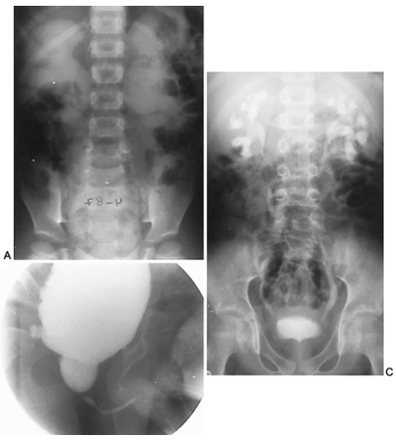

FIGURE 49D.16. A: Intravenous pyelogram (IVP) of 10-year-old boy with Hinman-Allen syndrome. **B:** Voiding cystourethrogram of same boy mimics posterior urethral valves. **C:** IVP of same boy after cutaneous vesicostomy, psychotherapy, family counseling, and vesicostomy closure 3 years later.

Both VCU and urodynamic evaluation may be extremely difficult to carry out in children with nonneuropathic voiding dysfunction because of a lack of patient cooperation. In some instances, insertion of a small trocar cystostomy and external sphincter electrodes or patches must be carried out under anesthesia, with urodynamic study after recovery. This technique is especially helpful when repeated study or biofeedback training is anticipated, although some children tolerate even small urodynamic catheters poorly and a great deal of artifact may result. Urodynamic findings may reveal increased bladder capacity and resting pressure, occasionally with uninhibited detrusor activity during filling (172). It is imperative to detect straining to void with abdominal EMG or intraabdominal pressure monitors. During voiding, the external urethral sphincter fails to relax and may show increased activity (detrusor-sphincter dyssynergy). These abnormal urodynamic findings appear to represent learned disorders of micturition, either as persistence of habits acquired during transition from the infantile bladder to normal continence or as a response to social or psychologic stress. Once wetness occurs, the child may further strain to tighten pelvic floor muscles and prevent leakage, a habit that may be difficult to unlearn.

Treatment of the child with dysfunctional voiding must be highly individualized. As in any functional disorder, therapy must be aimed not only at the bladder dysfunction and improved bladder emptying but also at constipation and the psychosocial stresses contributing to the dysfunction. In this context, psychotherapy, behavior modification, and biofeedback training may be extremely important, and the urologist must work closely with a child psychologist or psychiatrist who fully understands the nature and significance of nonneuropathic voiding dysfunction. In some cases, hypnosis has been used successfully. Biofeedback training can be extremely rewarding if the child will cooperate, and learned responses may significantly diminish external sphincter contraction during voiding (165). Double and triple voiding may help reduce residual bladder urine. The child with severe hydronephrosis or reflux may benefit from intermittent catheterization to provide bladder drainage while psychotherapy is in process, but many children are so uncooperative that catheterization is impossible. In such severe circumstances, temporary urinary diversion (cutaneous vesicostomy) may be necessary to prevent further renal damage. In severe cases with end-stage bladder dysfunction and fibrosis, bladder augmentation and even continent urinary diversion may be necessary. Whatever treatment plan is chosen, family counseling and stress reduction are of paramount importance. Long-term follow-up and periodic reassessment are mandatory (106).

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50

THE URETHRA

Contents

50A THE FEMALE URETHRA

Douglas A. Canning

Harry P. Koo

Part of "50 - THE URETHRA "

D.A. Canning: Department of Urology, Hospital of the University of Pennsylvania; Division of Urology, Children's Hospital of Philadelphia, Philadelphia, PA 19104.

H.P. Koo: Department of Surgery, Virginia Commonwealth University, Medical College of Virginia, Richmond, VA 23298.

Knowledge of the normal development of the urethra and adjacent structures in the female fetus is important to a thorough understanding of the various anomalies recognized in the female urethra. The urinary and genital systems in the female are closely interrelated in regard to their embryologic origin and their final anatomic location. To appreciate the great diversity of congenital urogenital malformations, knowledge of the normal embryogenesis of this area is essential.

EMBRYOLOGY OF THE LOWER UROGENITAL TRACT

Classical Theories on the Development of the Cloaca and the Urogenital Sinus

Our understanding of the embryology of lower genitourinary tract and the structures of the posterior perineum is based on embryonic theories that date from more than a century ago. In the traditional teaching, the caudal end of the embryo is partitioned by the fusion of the lateral walls of the cloaca (61) and cranio-caudal descent of the urorectal septum (75). Together, these embryologic events subdivide the cloaca into the urogenital canal anteriorly and the anorectal canal posteriorly. This process occurs between the fourth and sixth weeks of embryogenesis.

In the past, it has been assumed that the distal aspect of the cloaca fused with the urogenital canal and the anorectal canal and formed openings for these systems to the exterior (71). The urorectal septum was believed to fuse with the cloaca during the sixth week, forming the ventral urogenital membrane and a dorsal anal membrane. The area where the urorectal septum and lateral mesodermal folds fused with the cloacal membrane became the perineal body, which represented the partition between the digestive and urogenital systems (5). The anterior portion of the cloaca eventually developed into the bladder and urethra.

New Theories on the Development of the Cloaca and the Urogenital Sinus

Recently, there has been growing evidence that our previously accepted theories about the development of the caudal end of the embryo may be incorrect. Animal models (39,78) and human studies (49,52), along with technological advances, are providing detailed information about the changes occurring in early embryogenesis. With the use of computer-assisted three-dimensional reconstruction of human embryos (49,52) in combination with an image-processing technique called *morphing* (2,52), novel approaches have become available for analysis of the embryologic processes occurring in the caudal region.

The concept of a dynamic movement or change of configuration of cloacal structures better explains the observed changes in the embryo. The growth of the caudal region of the human embryo is accompanied by dramatic shifts in the morphology; positioning; and relative sizes of the primitive urogenital sinus, anorectum, and cloaca. Contrary to the traditional embryologic theories, the "descent" of the urorectal septum occurs as a passive process as a result of the rotation of the embryo. By a process called *transformation,* the structures of the caudal region elongate from the axial growth of the neural tube and the expansion of the embryo. The entire external and internal contour of the embryo is transformed, producing a total rotation of approximately 150 degrees during of the entire embryogenesis (Fig. 50A.1).

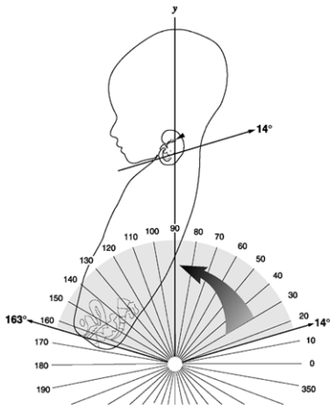

FIGURE 50A.1. Counterclockwise rotation of the embryo as shown through the morphing process. A line through the upper cervical vertebrae (C-1 to C-4; *arrow*) forms the y-axis. An axis during the developing stages was defined by passing from the anus to the urogenital sinus and its angle was measured from the established x-y coordinate system. Starting with the embryo at 29 days of age (angle of 14 degrees), the counterclockwise rotation is completed to an angle of 163 degrees in a term fetus. Total counterclockwise (dorsal) rotation was approximately 150 degrees. (Modified from Paidas CN, Morreale RF, Holoski KM, et al. Septation and differentiation of the embryonic human cloaca. *J Pediatr Surg* 1999;34:877, with permission.)

The urorectal septum thus passively subdivides the cloaca during rotation. Interestingly, the position of the septum with respect to the primitive urogenital sinus and anorectum does not change; it remains static. The apparent decrease in the distance between the tip of the urorectal septum and the cloacal membrane is due to the unfolding process of the embryo, which changes the spatial relationship between the involved structures. Because the urorectal septum does not grow in the direction of the cloacal membrane, the fusion of the septum with the cloacal membrane is never observed. Instead, the cloaca remains until the cloacal membrane ruptures by apoptotic cell death. Eventually, the ventral part of the cloaca will be incorporated into the definitive urogenital sinus (i.e., the vaginal vestibule in the female) (80).

Development of the Genital System, Urethra, and Vagina

The development of the female urethra is closely related to vaginal development. However, our understanding of the embryology of the vagina remains controversial. There are theories that suggest that the vagina is derived from the müllerian ducts (76), whereas others suggest it is derived from the wolffian ducts, the urogenital sinus, or a combination of these structures (45,83). The most generally accepted theory suggests that the superior part of the vagina derives from the fusion of the müllerian ducts and that the inferior part arises from the urogenital sinus; however, this theory assumes the inductor function of the wolffian ducts stimulates adequate müllerian development (6,11,51).

Below the caudal tip of the uterine primordium and above the dorsal wall of the urogenital sinus, a collection of müllerian duct cells forms the müllerian tubercle (1). At this point, the sinovaginal bulb forms as a solid mass between the caudal aspect of the fused müllerian ducts and the dorsal wall of the urogenital sinus to later envelop the müllerian tubercle (Fig. 50A.2A). These cells proliferate to produce a vaginal plate, which elongates to increase the distance between the uterus and the urogenital sinus. The urogenital sinus remains open as the vestibule, into which both the urethra and vagina open. The female urethra, which develops from the more cranial part of the urogenital sinus, is equivalent to the prostatic urethra in the male. The apparent downward growth of the sinovaginal bulb in the direction of the fetal perineum occurs between the tenth and twentieth weeks and has the effect of separating the vagina from the urethra. Later, the central cells of the vaginal plate break down, forming the lumen of the vagina (Fig. 50A.2B).

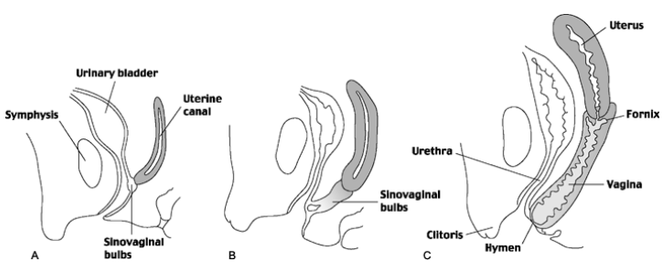

FIGURE 50A.2. A–C: Schematic sagittal sections showing the formation of the distal urethra and vagina at various stages of development. (Modified from Sanders RC, Blakemore K. Lethal fetal anomalies: sonographic demonstration. *Radiology* 1989;172:1, with permission.)

Until late in fetal life, the lumen of the vagina is separated from the cavity of the urogenital sinus by a membrane called the *hymen.* The hymen is formed by invagination of the posterior wall of the urogenital sinus, resulting from expansion

of the caudal end of the vagina (Fig. 50A.2C). The hymen usually ruptures during the perinatal period and remains as a thin fold of mucous membrane just within the introitus of the vagina (46). Outbuddings of the most cranial portion of the urethra form the paraurethral (or Skene's) glands in females, whereas homologous buds in the male lead to formation of the prostate. The labial swellings grow posterior and lateral to the vestibule to form the posterior commissure and the labia minora. Bartholin's glands (homologous to Cowper's glands in the male) grow into the labia majora as invaginations of the vestibular endoderm.

The association between the wolffian duct and the müllerian duct is so close that müllerian duct development cannot proceed in the absence of the wolffian duct. However, besides the inductor role of the wolffian ducts on the müllerian ducts, studies have also demonstrated the participation of the wolffian ducts in the formation of the vagina. Bok and Drews (3), using explants of the genital tract of mouse embryos in organ culture at the undifferentiated stage of development, have demonstrated that the sinovaginal bulb observed during the development of the vagina are in fact the caudal segments of the wolffian ducts. This work demonstrates the direct participation of the wolffian duct in the formation of the vagina.

Molecular Approaches to the Mechanisms of the Embryologic Processes of the Caudal Region

The elucidation of the molecular events in the embryologic process of the caudal region in the human embryo is unknown. Differentiation of the caudal region is induced in animals by growth factors, including fibroblast growth factor and transforming growth factor. The Wnt gene family of signaling molecules is also involved in the process (74).

The homeobox gene complex is a phylogenetically well-conserved set of instructions for the longitudinal development of higher animals. There is spatial cephalocaudal organization of the expression of these genes. In humans, the hand-foot-genital (HFG) hereditary syndrome was shown to result from disruption of *Hoxa-13* gene (47). HFG syndrome, which is considered genetically dominant, includes subtle digit abnormalities as well as genital tract malformations of variable expressivity. The most severe defects are found in females and consist of uterine duplication anomalies, abnormal urethra development, and ureteral ectopia (21,73).

Evidence from the mouse indicates that homeobox genes play a role in the mesenchymal development of the genitourinary system (7,82). Using gene targeting experiments, Warot and associates (82) have shown the effects of murine *Hoxa-13* and *Hoxd-13* mutations on morphogenesis of the hindgut and the urogenital tract. Various mutation combinations of *Hoxa-13* and *Hoxd-13* fetuses showed severely impaired development of the urogenital sinus, failure of the distal fusion of the müllerian ducts to form the upper vagina, poor separation of the cloacal cavity into urogenital sinus and rectum, and poor development of the genitalia. These defects exhibited by *Hoxa-13/Hoxd-13* mutant mice presumably result from developmental abnormalities similar to those occurring in HFG patients (82).

ABNORMAL DEVELOPMENT OF THE UROGENITAL TRACT

Numerous theories have been put forth to attempt to explain the various developmental anomalies. Recent observations of the normal embryologic development of the caudal region are in the process of modifying the understanding of the traditional concepts of normal development.

The presentations of the varied urorectal septal defects (i.e., persistent urogenital sinus, persistent cloaca and their associated urinary, reproductive and lower gastrointestinal tract anomalies and communications) reflect the varied degrees of abnormal development and growth of the urorectal septum between the fifth and eighth week of development. The cause or causes of these urorectal septal defects are not known. *In utero* cocaine exposure has been associated with a variety of urogenital anomalies (34). Spinal cord and column anomalies have been associated with urorectal septal defects. These may represent different manifestations of a broader, regional defect in embryologic development. Hartwig and co-workers (23) hypothesized that malformations of the cloaca, abdominal wall, and spinal cord result from a disturbance of the cell deposition process in the caudal end of the fetus.

Cloacal Malformation

A cloacal malformation occurs when there is a common canal into which the bladder, uterus, and rectum empty. Any variation in the arrest of development of the urorectal septum probably reflects the spectrum of anomalies ranging from urogenital sinus to complete persistent cloaca. There is a high incidence of other urologic defects, including vesicoureteral reflux, ureterocele, ectopic ureter, renal agenesis, and uterine and vaginal septations. There may also be associated anomalies of the gastrointestinal tract, the cardiovascular system, and the spinal cord.

Urogenital Sinus

A common drainage outlet of the uterovaginal secretion and urine is present. This condition may be associated with other abnormalities of the urinary tract, such as absence or duplication of the ureters, renal agenesis, or renal ectopia. A urogenital sinus abnormality may also be the result of female pseudohermaphroditism due to congenital adrenal hyperplasia.

The abnormality in the role of the urorectal septum and the differentiation of the vesicourethral canal from the true urogenital sinus has yet to be discovered.

In general, any child with anomalous-appearing genitalia, impalpable gonads, and an absent or anteriorly dislocated anus should be suspected of being a female with a urorectal septal defect. It is impossible to predict the internal anatomy from the external examination alone. These patients must be approached as an unknown in whom the spine, urinary, genital, and lower intestinal tracts should be thoroughly and individually assessed. Because these children are at great risk for major complications, this should be done as quickly and expeditiously as possible.

Urethral Anomalies

Congenital anomalies of the urethra are rare in females. Hypospadias may occur but is generally asymptomatic, with only occasional complaints of a sprayed voiding pattern. The urethra and vaginal introitus are common sites of ectopic ureteral orifices. Urethral diverticula are usually acquired phenomena, occurring most commonly with local abscess formation in Skene's glands. They may also occur congenitally in association with blind ending ureters.

Urethral Diverticula

There is no agreement about the nature of urethral diverticula. They have been considered orifices of ectopic ureters or portions of Gartner's duct. Many appear to be infected paraurethral glands or mucosal crypts. Traumatic origin following parturition has been suggested, but about 33% occur in nulliparous women. They are rare in infants and children (17,53).

Developmental Anomalies of the Müllerian Duct System

Various types of uterine duplication and vaginal anomalies result from arrest of development of the uterovaginal primordium during the eighth week: (a) incomplete fusion of the müllerian ducts, (b) incomplete development of the müllerian ducts, (c) failure of parts of one or both müllerian ducts to develop, and (d) incomplete canalization of the vaginal plate (46).

Wolffian Duct Remnants

By the seventh week of gestation, the wolffian ducts begin to degenerate in the female fetus. The degeneration is never complete, however, and a number of structures persist to various degrees. The remnant may persist in females as a thin cuboidally lined nonsecretory system parallel to the fallopian tube in the broad ligament. Tubules in the lateral portion of the broad ligament are referred to as the *epoophoron,* and those more medially are known as the *paroophoron.* Benign cysts occasionally arise from these structures but usually are of no clinical significance. The caudal extent of the regressing wolffian duct lies within the muscular wall of the cervix and vagina. Cystic lesions of varying size may form in these sites in up to 1% of the women and are referred to as *Gartner's duct cysts.* These cysts are typically asymptomatic and benign, although they may cause symptoms such as dyspareunia or irritative voiding symptoms.

Anatomy

The female urethra in the adult averages about 4 cm from the bladder neck to the vaginal vestibule. The epithelial lining changes from transitional to nonkeratinized stratified squamous epithelium as the urethra extends from the bladder neck to the urethral orifice. A series of small mucous glands opens into the urethra. Distally, these glands group together on either side of the urethra as Skene's glands and empty through two small ducts to the urethral meatus. The layers of the submucosa of the distal urethra form a cushion that contributes significantly to urethral closure pressure. These layers are estrogen dependent. A thick layer of inner longitudinal smooth muscle continues from the bladder to the external meatus to insert into periurethral fatty and fibrous tissue. There is no circular smooth muscle sphincter within the female urethra. A rather thin circular smooth muscle envelops the longitudinal fibers throughout the length of the urethra. The striated urethral sphincter in the female invests the distal two-thirds of the female urethra (4,50). Contraction of these fibers (the compressor urethra) closes the urethra against the fixed interior vaginal wall. Near the vaginal vestibule, the fibers completely surround the urethra and vagina to form a urethral vaginal sphincter. Contraction of this muscle group, along with bulbospongiosus, tightens the urogenital hiatus.

The suspensory ligament of the clitoris (anterior urethral ligament) and the pubourethral ligaments (posterior urethral ligament) form a sling that suspends the urethra beneath the pubis. There is apparently little sympathetic innervation in the neourethra. Parasympathetic cholinergic fibers are found throughout the smooth muscle. It is thought that the longitudinal smooth muscle of the urethra contracts coordinately with the detrusor during micturition to shorten and widen and therefore open the urethra (4,16).

The perineum lies between the pubis, thighs, and buttocks and is limited superiorly by the levator ani. Seen inferiorly, the symphysis pubis, the ischial tuburosities, and coccyx line the diamond shape of the perineum. The inferior ischiopubic rami and sacrotuberous ligaments form its bony ligamentous walls. A line drawn from the ischiotuberosities divides the perineum into an anal and a urogenital triangle. In the female, the vestibule of the vagina runs vertically throughout the length of the urogenital triangle (Fig. 50A.3).

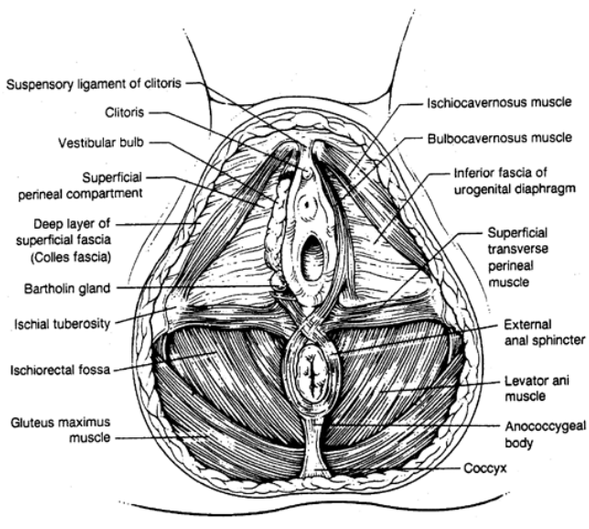

FIGURE 50A.3. The female perineum. Note the ischiocavernosus and bulbospongiosus and their relationship to the vagina and urethra. (From Danforth DN, et al, eds. *Danforth's obstetrics & gynecology.* Philadelphia: Lippincott Williams & Wilkins, 1999, with permission.)

The structure of the superficial pouch in the female is similar to that in the male. The crura of the clitoris attach to the inferior ischiopubic rami. They are surrounded by the ischiocavernosus muscles and converge to form the body of the clitoris. The vestibular bulbs lie to either side of the vaginal vestibule covered by the bulbospongiosus muscles. As homologues of the corpora cavernosus, they are composed of erectile tissue that meets anteriorly at the glans of the clitoris. The vestibular glands are deep to the vestibular bulbs and, unlike the bulbourethral glands in the male, are superficial to the perineal membrane. Their ducts travel to open in the vaginal vestibule on the either side of the labia minor.

History in the Female with a Urethral Anomaly

A large number of the children are referred with voiding complaints. The ability to place children in categories based on the voiding history will help focus the rest of the evaluation and guide further therapy. The time and duration of the voiding disorder must be identified early in the interview. Did symptoms begin before or after toilet training? Is wetting associated with pain, urgency, or frequency? What is the character of the voiding? Is the urinary stream steady from beginning to end, or is it a “staccato” or stop-and-start pattern suggestive of dysfunctional voiding? Are the symptoms worse at a particular time of the day? Does the child void frequently during the day yet sleep through the night without wetting? Is wetting confined to the nighttime, which is suggestive of primary nocturnal enuresis?

The voiding history is incomplete without a record of the child's eating and drinking pattern. Does the child consume small amounts of water during the day and large amounts of alternative liquids such as soft drinks and juices, which tend to be laden with salt and sugar and low on free water? What is the stooling pattern? Does the child have firm, chunky, or pebblelike bowel movements, which are suggestive of a retentive pattern of stooling or does the child have soft, well-formed bowel movements more suggestive of a normal stooling pattern? Very few children hold the urine and not the stool. Conversely, children who retain stool nearly always retain urine. All of these are indicators of a dysfunctional voiding pattern, which may lead to urinary tract infection.

Occasionally, children are referred with symptoms with history of “urethral discharge or vaginal discharge.” Perineal

pain or urethral discomfort may be associated with constipation, bladder holding, or vaginal irritation associated with leakage of urine into the vagina with secondary inflammation. A careful history will help elucidate these symptoms and separate urinary from vaginal abnormalities.

Examination of the Female Perineum

The perineal examination in the female is similar to that in the male. In a teenaged girl, the examination should be performed in the absence of the father but may be performed with the mother present, as long as the adolescent agrees. In general, bimanual examination in an adolescent is best performed in the operating room. The girl is placed in a frog-leg position or in a knee–chest position. The clitoris is examined for evidence of hypertrophy, which may be suggestive of an intersex condition. Gently spreading the labia majora in an inferior direction will allow inspection of the clitoral area and usually the introitus. The vestibule is assessed for any evidence of discharge. An easy way to examine the perineum is to gently grasp the labia majora and pull inferiorly. This maneuver tends to better define the various perineal folds and provide for a consistent examination in nearly all cases. The hymen and introitus should be inspected. An imperforate hymen may result in hydrometrocolpos and a lower abdominal mass. In older girls, a small speculum may be used to evaluate the cervix and interior of the vagina. Palpation of the vaginal walls and cervix and bimanual examination of the uterus complete the examination. Having the child perform the Valsalva maneuver may allow adequate assessment of the introital vaginal area. Vaginal discharge is often associated with vaginal voiding and is particularly common in children who hold the urine and subsequently dribble urine into the vagina. Treatment of dysfunctional voiding results in reduced vaginal drainage. Vaginal bleeding in the preadolescent may result from foreign bodies such as wadded toilet paper trapped in the vagina. Occasionally, other foreign bodies may have been inserted intentionally or accidentally.

Blunt injury to the perineum may result in hematoma beneath the perineal skin. The presence of hematoma or contusion alone does not usually require treatment. Penetrating injuries of the vaginal area warrant further careful evaluation, including radiologic evaluation of the urethra and bladder. Benign and malignant tumors of the vaginal area should be considered when vaginal bleeding occurs in young girls. A broad spectrum of entities, including from capillary hemangioma, rhabdomyosarcoma, neuroblastoma, or carcinoma, may be associated with vaginal bleeding. Labial masses may be associated with hernia or hydrocele of the canal of Nuck (37). Adhesions of the labia minora are common. In most cases, they are not symptomatic. Occasionally, a girl with labial adhesions will complain of vaginal irritation from pooled urine. If not separated, the irritation may progress to irregular voiding, which may exacerbate the problem. In some girls, a short course of estrogen creme applied to the labia may be effective. In many, however, separation of the adhesions in the office with local anesthetic creme may be required. Following separation, the child or her mother must apply a barrier ointment within the labia minora to prevent recurrence until the inflammation of the labial membranes has resolved. Labial fusion may be associated with congenital adrenal hyperplasia, gonadal dysgenesis, or cloaca. A genitosinogram is indicated when the urethra cannot be distinguished from the vaginal orifice.

It is absolutely critical to visualize the urethral meatus during the female examination. Incomplete visualization of the urethra, particularly in a small child, may result in inadvertent catheterization of the cervical os (64).

CONGENITAL ANOMALIES OF THE FEMALE URETHRA

Periurethral Masses

Two different types of periurethral masses can be commonly seen in the infant girl. The paraurethral or Skene's duct cysts may be present just lateral to the urethral meatus. In most cases, these present as a white or yellowish swelling of the orifice of Skene's duct that usually displaces the urethral meatal wall medially (Fig. 50A.4). These may resolve on their own over the first few months following birth. In some cases, needle aspiration of the cyst with incision of the superficial membrane may be therapeutic (40).

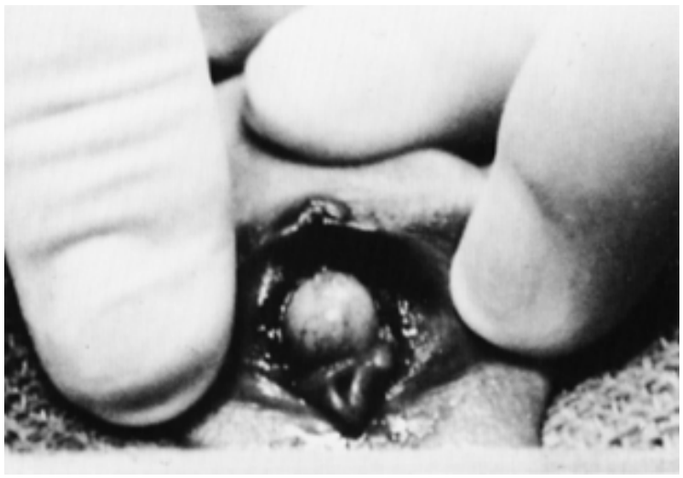

FIGURE 50A.4. Paraurethral (Skene's duct) cyst in a 1-year-old girl. (Photo courtesy of Dr. Terry Hensle.)

As the wolffian ducts begin to degenerate in the female by the seventh week of gestation, a number of structures may persist to various degrees. A “Gartner's duct cyst” may develop if the wolffian duct persists as a blind-ending limb, usually ending along the lateral margin of the anterior wall of the vagina. The cysts are usually asymptomatic but may result in dysuria. In most cases, a Gartner's duct cyst is found in prepubertal girls in association with an ectopic ureter that is blind ending and is proximal or one that is

connected to a rudimentary dysplastic kidney (27). These have been identified prenatally with sonography (70) and with magnetic resonance imaging and can achieve considerable size (20). Although Gartner's duct cysts may displace the bladder neck and result in bladder outlet obstruction (48), most are small and rarely affect voiding. The diagnosis of the cyst is deduced from the location of the cyst on the inferior lateral wall of the vagina, usually near the upper end. No treatment is required for small asymptomatic cysts. Large cysts, however, may protrude through the introitus and may cause local discomfort or difficulty with voiding. Transvaginal marsupialization or perineal marsupialization may be performed for large symptomatic cysts. Rarely, a large Gartner's duct cyst may displace the distal ureter upward over the cyst wall. This may occur in cases of a duplex ureter where the upper pole is dysplastic or absent. In these cases, obstruction of the lower-pole moiety may occur. Occasionally, these systems may require removal. This can be performed through a paravesical or intravesical procedure with or without reimplantation of the associated ureter.

Ureteroceles are covered in more detail in Chapter 48 ; however, a brief discussion in this chapter is warranted because a ureterocele that prolapses through the bladder neck may present as a mass at the introitus in an infant girl (Fig. 50A.5). Treatment includes incision and drainage in the newborn period and subsequent reconstruction or removal of the ureterocele and the associated upper-pole ureter and kidney. In many cases, however, particularly if the ureterocele is thin walled, the incision may provide a definitive therapeutic result (19). Single-system ureteroceles that prolapse are extremely rare in girls. A prolapsing uterocele that extends through the bladder neck and the urethra and presents as a vaginal mass in girls is also relatively uncommon. In most cases, this mass can be distinguished from other intralabial masses (e.g., rhabdomyosarcoma, urethral prolapse, hydrometrocolpos, periurethral cysts) by its location at the lateral wall of the introitus or along the posterior lateral wall of the urethra (30).

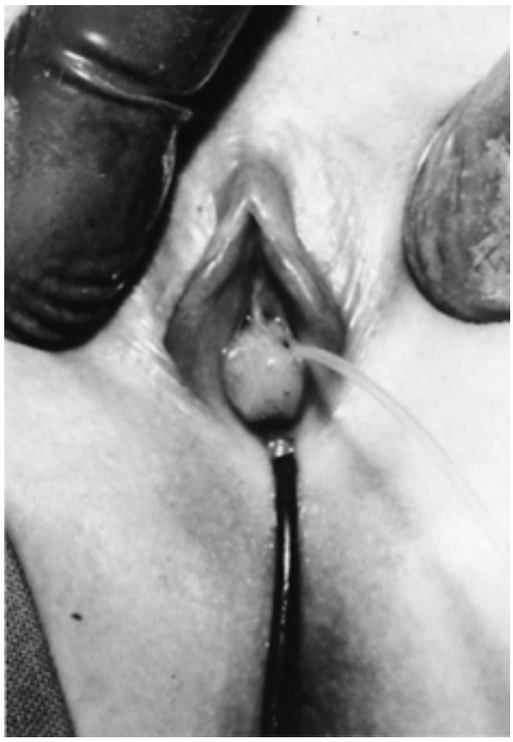

FIGURE 50A.5. Prolapsed ureterocele in a 3-year-old girl. (Photo courtesy of Dr. Terry Hensle.)

Urethral Duplication

Complete duplication of the bladder and urethra is rare and particularly rare in females. In most cases, duplication of the bladder involves two bladder halves, each with a full-thickness muscular wall and each with its own associated urethra. An accessory urethra in the female is also rarely found communicating with the urachus (41). The cause of the condition is unknown, and the malformation varies so widely from case to case that it is unlikely that the same embryologic explanation can apply to all cases (61). In one report of three girls with complete duplication of bladder, urethra, vagina, and uterus, the associated anomalies were different in each child. The first had a symphysis diastasis creating an abdominal hernia, with two bladders dislocated into this space. The second had an anal atresia with colon duplication, and the third had cloacal exstrophy with one open bladder and a second closed with persistent urogenital sinus. Treatment is individualized but generally involves preservation of the ureterovesical attachments with anastomosis of the bladder or urethra as appropriate with excision of redundant tissue (12).

Urethral Atresia

An association between urethral atresia and prune-belly syndrome in females has been recognized, but few reports discuss the outcome of treatment in these gravely ill infants (65). Of 34 patients with prune-belly syndrome noted at the University of Minnesota, 6 had urethral atresia, 3 of these were female. Half of these patients died in the newborn period. Of the three surviving infants, all had vesicocutaneous fistula. As neonates, two suffered from pulmonary insufficiency due to oligohydramnios. Most of these children will come to renal transplant due to severe renal damage that occurred in the neonatal period. However, in at least one case, normal renal function followed decompression of the urinary tract. In males, progressive catheter dilation has been used with reasonable success and would be similarly affective in males (66).

Urethral Stricture

Urethral stricture or stenosis in the female was considered much more common in the past than currently. The “spinning

top" urethra (Fig. 50A.6) was initially believed to be an indication of distal urethral narrowing or stenosis is probably more the result of bladder instability and discoordinate voiding than a true stenosis. In the past, when a voiding cystourethrogram (VCUG) demonstrated urethral narrowing distal to the bladder neck during voiding, it was assumed that bladder neck obstruction was the cause (9). It was believed that the urethra was wide because of poststenotic dilation or that habitual voluntary contraction of the striated sphincter resulted in dilation of the segment of the urethra between the urethral meatus and the bladder neck. Following Y-V advancement of the posterior bladder neck, or urethral dilation, as many as 50% of patients were improved. Subsequently, Kaplan and associates (35) compared urethral dilation, internal urethrotomy, and antibiotic prophylaxis in girls with urinary tract infections and found no significant differences in treatment results. The spinning top urethra probably results from a tendency for the female to hold the urine from time to time during development and normal toilet training. The most recent studies suggest that the spinning top urethra may indicate bladder instability in some girls, but bladder instability in "staccato" or intermittent voiding with dysfunction cannot be identified in all girls with an apparent dilation of the proximal urethra. The finding of a spinning top urethra on the VCUG should alert the examiner to functional disorders of the lower urinary tract. However, if no instability can be found with a thorough physical examination and appropriate testing, spinning top urethra should probably be considered a normal variant (24). From a practical standpoint, when we are evaluating girls with urinary tract infections or voiding disorders, we look for the spinning top urethra, and if that is combined with incomplete voiding or significant symptoms, we will enroll these children in biofeedback treatment. It is not known whether urethral dilation is any more effective than training for dysfunctional voiding and may in fact be harmful (22). There is rare indication for urethral dilation in the female child today.

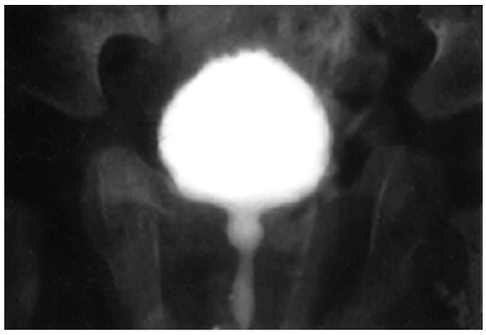

FIGURE 50A.6. "Spinning top" urethra in a 6-year-old girl with recurrent urinary tract infections and wetting. Note dilation of the proximal urethra during voiding.

Urogenital Sinus

A *urogenital sinus* is a common channel into which both the urethra and genital tracts open. There is a wide spectrum of urogenital anomalies caused by lack of development of the urogenital sinus derivatives. The common urogenital sinus is a normal stage of embryonic development in both sexes. Although many of these cases are associated with intersex, others are more characteristic of anorectal anomalies following agenesis of Rathkes plicae and failure of migration of müllerian ducts to the vestibule (72). With ambiguous genitalia, masculinization of the perineum results in closure of the urethral folds distal to the introitus, resulting in an abnormal development of the urethra in the female. Conversely, a urogenital sinus in the absence of ambiguous genitalia occurs as a result of defective caudal migration of Muller's ducts and failure of the distal sinus to evert. In the normal female, an arrest in the development of the müllerian ducts at 9 weeks of gestation after they have been fused with the urogenital sinus can manifest as a urogenital confluence or common urogenital sinus. The variations of the common urogenital sinus as a normal stage of embryonic development occur as a result of arrest and development of the müllerian ducts at 9 weeks of gestation after they have fused with the urogenital sinus. Early arrest may lead to a long urogenital sinus with a short vagina and a high urethral opening. A low or short urogenital sinus occurs with an almost normal vaginal vestibule and low urethral orifice if the arrest occurs late in development (Fig. 50A.7). Early, more severe defects are often associated with anterior placement of the rectum along the continued spectrum toward the cloaca (26).

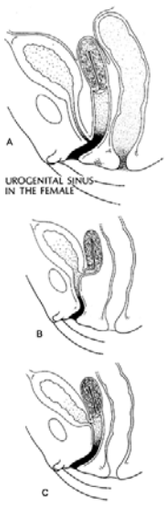

FIGURE 50A.7. A: Urogenital sinus anomaly. **B:** High or early arrest of the müllerian ducts results in short vagina with high confluence of the urogenital sinus. **C:** Low or late arrest of the müllerian ducts results in longer vagina with low confluence.

Ultrasonic suspicion of hydrometrocolpos in the fetus may represent indirect evidence of a persistent urogenital sinus or cloaca. On physical examination, the persistence of a urogenital sinus is usually obvious in that the vaginal opening and urethral opening are not distinct. Anterior displacement of the anus may also be present. Absence of the anus in cases of persistence of the cloaca or enlarged clitoris and rugated labial folds in cases of intersex is characteristic findings. Excluding the intersex cases that are covered in Chapter 52, the goals in the evaluation of the child with a urogenital sinus include assessment of the anatomy and detection of associated anomalies within the wolffian and müllerian systems (15).

In the newborn, a thorough abdominal examination with particular attention to palpation of the kidneys, bladder, and uterus may yield clues suggestive of the internal anatomy. A mass superior to the bladder or a palpable uterus may suggest hydrocolpos. A genitourinary sinogram to identify the point of confluence between the urethra and vagina will be important for surgical planning (Fig. 50A.8).

It also often provides information about the internal müllerian anatomy. Laparoscopy and exploratory laparotomy with or without biopsy of the gonads may also be important. Ultrasonography should be an initial study to identify the presence or absence of significant hydrometrocolpos. Stabilization of the infant may require temporary tube drainage of the dilated bladder or vagina while awaiting definitive repair. If the urogenital sinus is short but stenotic, dilation alone may be effective as an adjunct to tube drainage of the uterus and vagina. This may be required regularly. Careful monitoring with ultrasound and frequent examinations are required to ensure effective drainage to prevent urinary tract infection and sepsis.

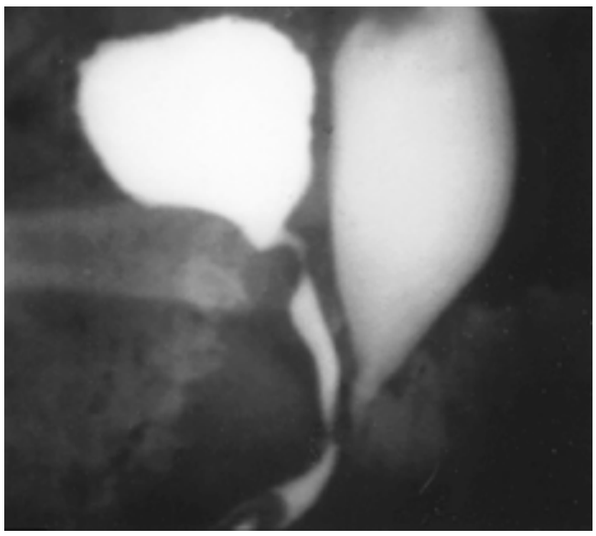

FIGURE 50A.8. Genitourinary sinogram in a newborn girl with 21-hydroxylase deficiency and a low confluence of the urogenital sinus. The urethra meets the vagina at a point only 2 cm from the perineum. This child underwent posterior flap reconstruction. In a child with a more anteriorly placed anus, anterior sagittal transrectal advancement of the urogenital sinus would be more appropriate.

Surgical Management

The surgical management of urogenital sinus and cloacal anomalies has been simplified considerably thanks to the work of innovative specialists who have focussed on anorectal disorders and their application to the urogenital sinus (25,32,54,57,59,60). If a simple urogenital sinus is shorter than 3 cm (Fig. 50A.9), the entire urogenital sinus may be mobilized and advanced as a unit to the perineum. If the urogenital sinus is extremely short, a simple U-flap vaginoplasty will be effective. However, in most cases, the perineal body is shortened because of the anterior placement of the anus that tends to minimize the available tissue with which to support a posteriorly based flap.

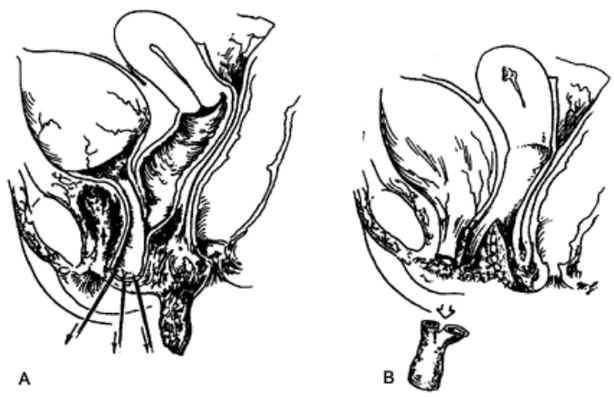

FIGURE 50A.9. When the urogenital sinus is less than 3 cm, the urethra and vagina may be mobilized as a unit through a posterior approach. **A:** A posterior inverted U-flap with the apex at the level of the opening of the sinus is outlined. Alternatively, a midline incision from the anal verge to the sinus may be used. The incision is continued around the orifice of the urogenital sinus, and the dissection is carried superiorly to the prevesical space anteriorly and to the peritoneal reflection posteriorly. **B:** The sinus is pulled down and excised. The posterior vaginal wall is incised to accommodate the flap. Alternatively, the posterior sinus may be incorporated into the repair as augmentations of the labia minora. Separate vaginal and urethral openings are created in the vestibule. (From Gonzalez R, Barthold JS. Urogenital sinus and cloaca. In: Gonzales ET, Bauer SB, eds. *Pediatric urologic practice.* Philadelphia: Lippincott Williams & Wilkins, 1999:676, with permission.)

If the urogenital sinus is between 1 and 3 cm in length, either mobilization via a perineal flap may be made or the anterior sagittal transrectal approach (ASTRA) may be used (8).

The patient is placed in the prone position with the pelvis elevated (Fig. 50A.10). The incision extends from the middle portion of the sacrum through the anus and the perineum and down to the urogenital sinus opening. The entire sphincter mechanism of the rectum and anus may be divided, or alternatively, only the anterior rectal wall is

opened along with the perineum from a point from the anterior anal verge to the posterior margin of the labia majora (8). An electrical stimulator helps determine where the midline is by checking the magnitude of the muscle contraction on both sides. The perineal fat also is divided; the posterior wall of the urogenital sinus is identified and opened. Rather than mobilizing the vagina from the urethra, as had been done in the past, because the urethra and vagina share a common wall, in a urogenital sinus shorter than 3 to 4 cm, the vagina and urethra are advanced as a unit to the perineum.

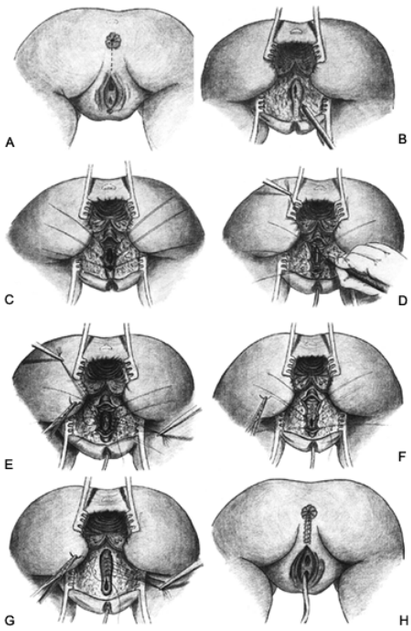

FIGURE 50A.10. Anterior sagittal transrectal approach to the urogenital sinus. **A:** An incision is made from the anal verge to the posterior margin of the labia. **B:** Incision is deepened on the midline through the perineum (and if necessary through the anterior wall of the rectum) to expose the urogenital sinus. **C:** Holding sutures are placed along the site of anastomosis. **D:** Margins are exposed and closed **(E, F)** in two layers of anterior vaginal (urogenital sinus) wall. Posterior wall of vagina **(G)** and rectum **(H)** are closed. (From Domini M, et al. Recurrent posttraumatic urethro-vaginal fistula: a new application for ASTRA. *J Pediatr Surg* 1999;34[12]:1865, with permission.)

This procedure may be done in infants as young as 4 months of age, and in our experience, it may be easier in the younger child because the distance for mobilization is shorter before the child has grown significantly linearly. In this technique, the goal of the treatment of the urogenital sinus is to create a urethral opening separate from the vaginal opening (56). Multiple sutures are placed in both edges of the open urogenital sinus in the vagina and along the vaginal edges. These sutures are used to exert traction and to allow dissection and mobilization of the entire urogenital sinus. There is a natural plane of separation between the urogenital sinus and the posterior aspect of the pubis. After dissecting the urogenital sinus away from the pubis, the suspensory ligaments are divided and an average of 3 cm of length is gained with this advancement. The dissection is carried circumferentially, and the urogenital sinus tissue is sutured back on itself to provide and extend the labial minoral folds. Considerable operative time is saved if the urethra is allowed to remain intact as a unit with the vagina. In addition, the risk of urethral stenosis or vaginal stenosis as a result of ischemic loss of the tissue is minimized.

If there is a long common channel, additional techniques must be used to complete the separation of the vagina from the urinary tract. The vagina must be separated from the urethra. In many cases, however, this maneuver is facilitated after mobilization of the urethra and vagina. Separation after total mobilization will allow the vagina to be brought down as a unit to the perineum following closure of the posterior urethra.

When the urogenital sinus is longer than 4 cm, after the initial posterior approach, the posterior sagittal wound is packed and the patient is turned to perform a midline laparotomy. The bladder is opened in the midline, and feeding catheters are placed into the ureters to protect them during the separation from the vagina and the bladder. Because the ureters pass through the junction between vagina and bladder, there is significant risk of injuring the ureters during the separation of the vagina from the bladder, hence the need for the catheters. The bladder is then mobilized anteriorly as the vagina and uterus are separated from the bladder base posteriorly. In many cases, there are two hemiuteri and hemivaginas. If one is particularly small, it may be removed at this point. If the presence of hydrocolpos required vaginal or uterine drainage early in the baby's life, significant scarring may be present, which may further impede an easy dissection. With a combined inferior and superior dissection, the vagina may then be mobilized and brought to the perineum in most cases. If the vagina is particularly small or high, vaginal replacement with intestine may be indicated. In these cases, sigmoid colon may be used, but a segment of small bowel that has been reconfigured may also be appropriate (55,59).

In practice, the urogenital sinus is usually short enough to allow for an ASTRA or an anterior approach that does not open the anterior rectal wall. When the rectum must be opened and in nearly all cases when a combined anterior and posterior approach must be used, a protective colostomy is used. Following mobilization of the vagina from above, the perineal orifices are then brought to the perineum and sutured in place with absorbable suture. If a bowel interposition is used, it is important not to bring the colon all the way to the skin's surface but to use perineal flaps to prevent an unsightly appearance (15).

Cloacal Anomalies

A cloaca exists when the rectum, vagina, and urinary tract meet and fuse into a single common channel. This group of defects appears in the female as a separate spectrum of malformations of anorectal anomalies.

The length of the common channel varies from 1 to 12 cm. If a short channel is present (less than 3 cm), a well-developed sacrum and favorable neurologic and muscular function to the levator ani complex will likely be present. A longer channel, however, indicates a more complex defect with a poor sphincter mechanism and an abnormal sacrum. The rectum and vagina share a common wall, as do the vagina and urethra (Fig. 50A.11). In more than 50% of these cases, the vagina is partially obstructed and filled with mucous secretions (hydrocolpos). As in the case of urogenital sinus, variations exist, which may suggest severity of the defect and fetal age at failure of the müllerian ducts and urorectal septum to complete (Fig. 50A.11). Approximately 50% of the time a duplicated vagina and uterus are present. This may be manifest by just a septum between the two vaginas or two completely separated structures. A distended vagina will often compress the trigone and lead to hydroureteronephrosis (57).

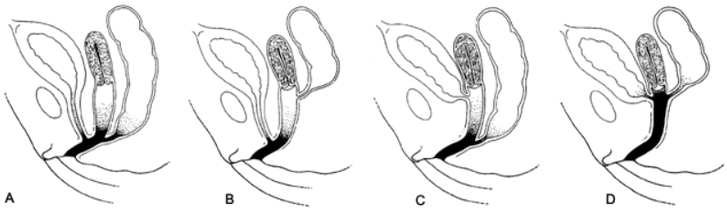

FIGURE 50A.11. A–D: Various forms of cloacal anomaly. Longer cloacal segments (higher confluence of urethra, vagina, and rectum) are associated with higher risk of urinary and rectal incontinence. (From Hensle TW. Genital anomalies. In: Gillenwater JG, et al, eds. *Adult and pediatric urology.* St. Louis, Mosby, 1996, with permission.)

Associated Defects

In persistent cloaca, there is a 90% frequency of associated urogenital defects (67). Hydronephrosis, urosepsis, and metabolic acidosis with poor renal function represent the main sources of mortality in neonates with anorectal malformations. Other malformations include esophageal atresia, duodenal atresia, and cardiovascular defects, especially tetralogy of Fallot. The sacral anomalies correlate with the degree of functional prognosis. More than two absent sacral vertebra represent a poor prognostic sign.

The presence of a single perineal orifice is pathognomic of a cloaca. These patients have a typically phallic-looking structure with flattened labioscrotal folds. The proboscis of tissue has no erectile bodies present. The single opening of the cloaca may be at the base of the phallus or can be channeled to the tip. There may be some rudimentary glans tissue. Rarely, these children inappropriately are designated males at birth. A feminizing genitoplasty is required later.

Once the diagnosis is made, abdominal ultrasound is carried out. This often shows hydroureteronephrosis. At this point, a catheter with a coude tip may be passed into the bladder and a cystogram performed. The catheter often will be directed into one of the dilated hydrocolpos and give a false impression of a bladder. Double-contrast studies, such as iodinated contrast in the bladder with air in the vagina, will often delineate the two chambers.

SURGICAL CORRECTION

Colostomy

A colostomy must be performed after the genitourinary evaluation. When significant urologic problems are present, a divided colostomy is more appropriate than a loop colostomy (Fig. 50A.12). This prevents contamination into the urinary tract with feces spilling into the distal limb of the colon.

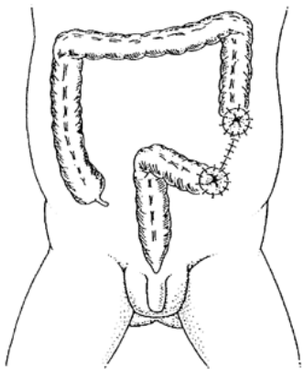

FIGURE 50A.12. The colostomy: The proximal stoma is placed at the supero **l** ateral margin of the wound. The mucous fistula is opened minimally to prevent prolapse and taken to the inferomedial margin of the wound. (From Pena A. Anorectal anomalies. In: Spitz L, Coran A, eds. *Rob and Smith's operative surgery.* London: Chapman and Hall Medical, 1995, with permission.)

Cystoscopic evaluation of the urogenital sinus with dilation of the vaginal openings into the urogenital sinus may provide adequate drainage of the mucus in the hydrocolpos if the vaginal introitus is low and the stenotic segment is short. Urine may be voided from the bladder into the vagina with stasis, which often leads to urinary infection and sepsis. A urethral sound passed posteriorly often will dilate the membrane that deflects the urine into the vaginas. It may be appropriate to perform a vesicostomy at the time of the colostomy to drain the urinary tract effectively.

Recovery after colostomy and appropriate urinary diversion is usually uneventful. The final repair of this defect is a posterior sagittal anorectovaginourethroplasty, which is usually performed at 4 to 6 months of age.

Before the definitive repair, a distal colostography is carried out with water-soluble contrast. This identifies the precise site of the rectourinary fistula located in the most distal part of the rectum. Sometimes, considerable hydrostatic pressure will be required to fill out the distal colon and locate the fistula. This may be done with a Foley catheter, inflating the balloon and applying distal pressure. This will overcome the muscle tone of the striated muscles surrounding the rectum (58).

Posterior Sagittal Anorectal Plasty

In posterior sagittal anorectal plasty (PSARP), the patient is placed in the prone position with the pelvis elevated (Fig. 50A.13A). Electric stimulation elicits muscle contractions throughout the operation so that no paralysis is used with anesthesia. A long incision starting at the middle of the sacrum extends anteriorly to the single perineal orifice. The anatomic relationship of the rectum to the genitourinary structures is complex. When all muscle structures have been divided in the midline, the rectum can be seen, as can the sphincter fibers of the external anal sphincter.

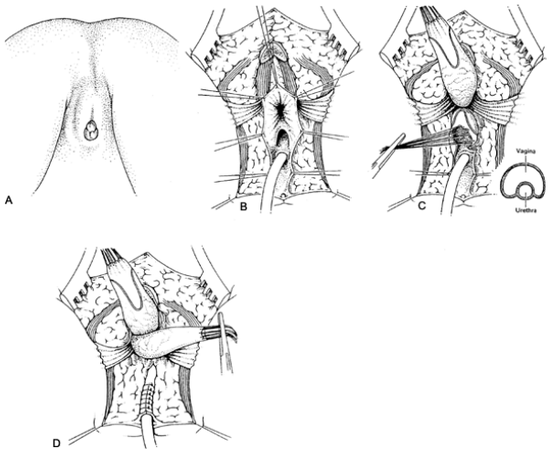

FIGURE 50A.13. A: Usual positioning for posterior sagittal anorectal plasty. **B:** Muscles have been separated carefully at the midline using electrostimulation to identify the appropriate incision line. Carefully placed sutures help separate the opened rectum from the sinus. The plane must be initially made in the common wall between the rectum and vagina; there is no definite line of dissection at this level. Catheter is in the urethra. **C:** The vagina surrounds the urethra for a variable distance. If the vagina is high and the channel is longer than 3 cm, vaginal elongation will be necessary to prevent injury to the vagina or urethra from overzealous dissection. **D:** In cases of common channels of less than 3 cm, the urethra is reconstructed using the whole common channel. (From Pena A. Anorectal anomalies. In: Spitz L, Coran A, eds. *Rob and Smith's operative surgery.* London: Chapman and Hall Medical, 1995, with permission.)

The urogenital sinus is incised posteriorly up to the confluence of rectum/vagina. Traction sutures are carefully placed on the rectal wall and lifted superiorly so that the three openings can be identified. A catheter is in the bladder (Fig. 50A.13B). The rectal wall is separated from the vagina, and the vagina is separated from the bladder neck area and urethra (Fig. 50A.13C). The urethra can be extended out to the perineum by rolling a tube of the urogenital sinus (Fig. 50A.13D).

The vagina surrounds the urethra and the bladder neck for approximately 2 to 3 cm of the dissection (Fig. 50A.13C, inset). This dissection must be carried cranial enough to mobilize the vagina to reach the perineum without injury to the blood supply of the bladder neck and vagina.

If the length of the cloaca is less than 3 cm, a similar technique to that used in the medium-sized urogenital sinus may be used to repair the cloaca (56). In these cases, following separation of the rectal wall from the vagina, no attempt is made to separate the vagina from the urinary tract; rather, the entire urogenital sinus is dissected and mobilized as a unit. A well-defined fat-containing space anterior to the urogenital sinus separates the sinus from the pubic symphysis. A dissection can be made along this space to reach the retropubic space. Traction is then exerted on the vaginal edges as the dissection continues in a circumferential manner to include the vagina and urethra. In this way, the two structures are separated from the rectum and advanced together. The common channel of the urethra and vagina is then mobilized, and the dissection continues circumferentially around the lateral and posterior walls of the vagina and the anterior wall of the bladder and urethra until enough length has been gained to connect the vaginal edges to the perineum. Thus a urethral and vaginal opening of near-normal appearance is accomplished. The vaginal and urethral edges are sutured to the skin and become a urogenital sinus channel that may be used to augment the labia minoral tissue.

For a urogenital sinus longer than 3 cm, some form of

vaginal elongation or replacement should be chosen; otherwise, overzealous dissection may result in devascularization and urethral injury. Vaginal replacement can be done with a segment of small intestine with preservation of its mesentery. After the end-to-end anastomosis of the small intestines, the upper segment of a small bowel segment is connected to the upper vagina while the lower part comes to the perineal skin (Fig. 50A.14).

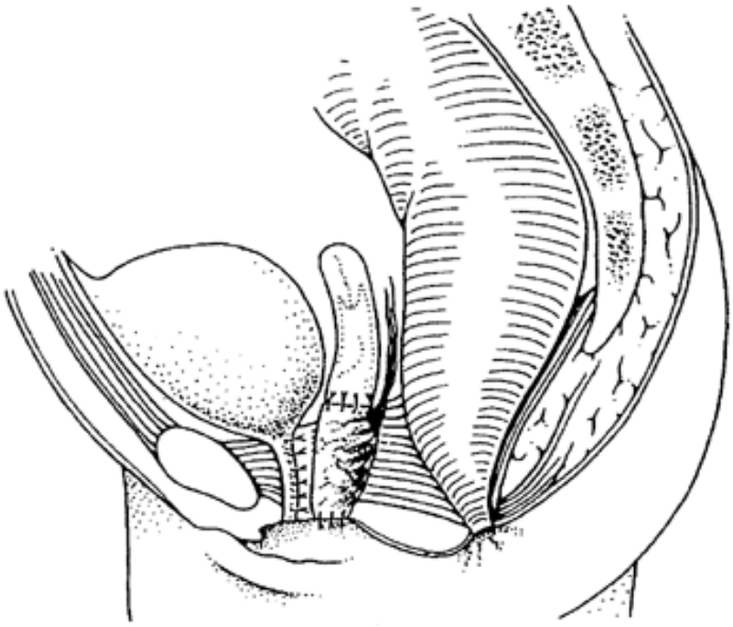

FIGURE 50A.14. When a long channel exists, a segment of intestine is used to bridge the defect from the high vagina and the perineum. (From Pena A. Anorectal anomalies. In: Spitz L, Coran A, eds. *Rob and Smith's operative surgery.* London: Chapman and Hall Medical, 1995, with permission.)

Two large hemivaginas divided by a midline septum may provide enough vaginal wall to reach the perineum. This can be done by removing the rudimentary uterus on one side and rotating the vagina from that side down into the perineum, dividing the septum in between (55). The perineum is reconstructed in such a way that there is a perineal body between the vagina and the new anus. The rectum is tapered so as to locate it into the internal and external sphincter complexes, which can be readily seen from the careful posterior sagittal dissection. The incision is closed carefully to reapproximate the sphincter muscles.

Postoperative Bowel Management

Two weeks after the procedure, anal dilations are started twice daily by the parents. Once the desired rectal size is reached, the colostomy is closed. For a period of time, frequent bowel movements are a problem, but this pattern usually improves by 6 months after closure of the colostomy. If the baby has one to three bowel movements each day and remains clean between bowel movements, this indicates that there is feeling during the defecation process and, in general, a good functional prognosis. On the other hand, if stool is passed constantly, colonic irrigations must

be instituted for cleansing purposes. Constipation may become the major postoperative problem. Some patients will benefit from the antegrade colonic enema program (ACE). A cecal attachment to the skin, either through the appendix or through a tubularized portion of cecum, permits the patient to catheterize the stoma and irrigate the colon. This situation is usually preferred by the patient to a high rectal colonic irrigation (18,44)

Neurogenic Bladder

If sacral anomalies occur or if the urogenital sinus is greater than 3 cm in length, it is likely that bladder function may be impaired. A plastic catheter can be used for intermittent catheterization in the postoperative period to manage urinary drainage intermittently. A coude tip may be helpful. In a more inclusive report of 1,192 patients from a single series with anorectal malformations, 75% of all have voluntary bowel movements yet urinary incontinence is relatively common after the repair of cloacae (60). Most patients will require intermittent catheterization to empty the bladder completely, and many will require augmentation cystoplasty to provide for adequate compliance of the bladder to preserve low-pressure storage.

ACQUIRED LESIONS OF THE FEMALE URETHRA

Urethral Prolapse

Urethral prolapse is relatively common, particularly in African-American females. The prolapse is through the meatus, forming a hemorrhagic, often sensitive mass that bleeds with palpation or with contact of the undergarments (Fig. 50A.15). Girls may have difficulty with urination, depending on the size of the prolapse and whether it includes the urethral meatus. Urethral prolapse may respond to topical application of estrogen and may be managed expectantly as long as voiding is normal (64).

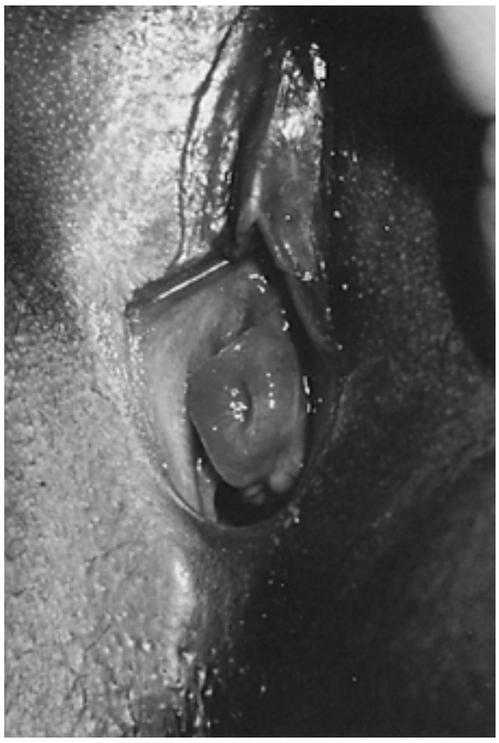

FIGURE 50A.15. Urethral prolapse in a 7-year-old African-American girl. (Photo courtesy of Arnold Colodny, M.D.; from Smith GHH, Duckett JW. Urethral lesions in infants and children. In: Gillenwater JG, et al, eds. *Adult and pediatric urology.* St. Louis: Mosby, 1996, with permission.)

Multiple etiologies have been proposed to describe urethral prolapse. It may be due to excessive urethral mobility, excessive mucosal redundancy, increased abdominal pressure, infection, neuromuscular deficiency, or poor attachment between the muscle layers of the urethra (42). Vaginal bleeding is normally the first symptom, but vaginal discharge or perineal discomfort may also be prominent symptoms. On physical examination, there is characteristic circumferential prolapse of the mucosa. The differential diagnosis includes urethral caruncle or papilloma, urethral polyps, prolapsed ureterocele, sarcoma, botryoides (rhabdomyosarcoma), and periurethral abscess.

An ultrasound of the bladder and upper tracts is needed if there is question about the presence of ureterocele or sarcoma (69). Conservative treatments with estrogen cream can be successful in as many as half of the patients. The rest require excision of the prolapsed lesion. Before excision, cystoscopy is performed, and infiltration of the lesion with 1% lidocaine and 1 to 100,000 epinephrine reduces bleeding during the excision (10,68,77).

Urethral Polyps

Urethral polyps in girls are rare but do occur. The most common presenting symptom is hematuria. Occasionally, a urethral polyp is identified at the urethral meatal orifice in a female, but most often it is identified as a filling defect of the urethra or bladder neck on VCUG or during cystourethroscopy. Urethral polyps may be managed with transurethral resection, with nearly universal success. The biologic activity of these polyps is uniformly benign, and there have been no recurrences following complete excision (13,38).

Urethral Caruncles

Urethral caruncles are most commonly found in the postmenopausal period but have been reported in children. They characteristically present as a red and tender mass protruding from the inferior portion of the urethral meatus. Symptoms may be nonspecific but usually include dysuria or urinary frequency or hematuria. On histologic examination, a caruncle is composed of a highly vascularized fibroplastic connective tissue stalk heavily infiltrated with leukocytes. Overlying the mass is an epithelium that is either transitional or squamous (28). A few have had colonic mucosal-like intestinal heterotopia, suggesting that a few of these caruncles may be congenital (29). These small tumors are readily incised, and the treatment is similar to that of a urethral polyp.

Malignancy

Virtually the only malignant tumor that occurs in the female urethra in children is rhabdomyosarcoma. These tumors may occur at any age but are most common in young children. Embryonal rhabdomyosarcomas characteristically produce polypoid lesions at the base of the bladder that have given rise to the descriptive term *sarcoma botryoides.* These “grapelike clusters” may grow out through the lumen of the urethra, forming a mass that may be identified at the urethral meatus in the female (Fig. 50A.16). This appearance occurs only in hollow organs such as the bladder or vagina, which allows unimpeded growth of the tumor into the lumen. The treatment of this tumor is discussed in more detail in Chapter 54 . Current therapy, however, includes chemotherapy with excisional biopsy only if the tumor can be excised without crippling surgery; otherwise, chemotherapy follows a diagnosis made through incisional biopsy and surgery is confined to resection of the residual tumor (33).

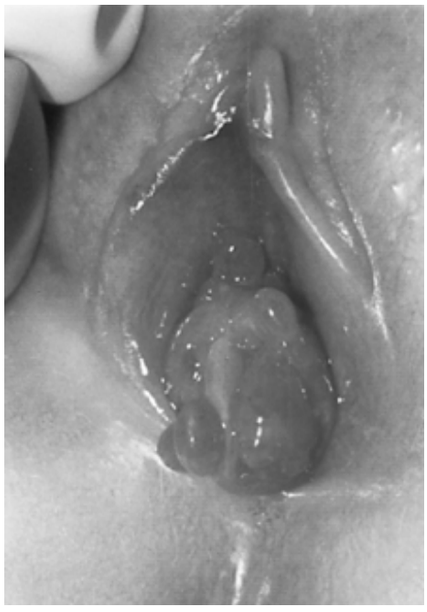

FIGURE 50A.16. Mass protruding from the vaginal introitus in a young girl with rhabdomyosarcoma. (From Ritchey ML, Andrassy RJ, Kelalis PP. Pediatric urologic oncology. In: Gillenwater JG, et al, eds. *Adult and pediatric urology.* St. Louis: Mosby, 1996, with permission.)

Trauma

Traumatic injury to the female urethra in children is unusual. In the vast majority of cases, treatment is the same as outlined in Chapter 12 for the adult woman. However, a few specifics to the female urethra in children and trauma should be mentioned. First, because the urethra in the female is short, pelvic fracture of urethral injuries occur less commonly in females than in males. Second, the female urethra, because it is relatively less well attached to the pelvic diaphragm, requires a more severe injury before significant damage is suffered, compared with the male. The most severe injuries seem to be associated with complete rupture of the urethra and a distraction defect suggesting an avulsion type of injury. These injuries, although rare, may be difficult to reconstruct with preservation of continence (79).

The urologist needs to have a high index of suspicion for urethral and vaginal injury following blunt traumatic injury to the urogenital region, particularly in the prepubescent girl. The emergency room evaluation, both by emergency physicians and pediatric urologists, of young girls who have suffered blunt urogenital trauma seems to grossly underestimate the severity of injuries that would be apparent if an examination under anesthesia was performed. Most girls will have findings in the operating room under anesthesia that are more extensive than those perceived during routine physical examination in the emergency room (43).

Pelvic fracture following an automobile accident is the most common source of major trauma to the urethra in females, as in males. After stabilization of the pelvic fracture

and resuscitation, in most cases, attempts should be made to surgically reconstruct the urethra and the associated vaginal laceration. Appropriate urinary drainage for 10 to 14 days following repair usually results in reconstructive success (14). Unfortunately, sexual assault and other penetrating injuries are also relatively common sources of injury in children. Because urethral and bladder injuries as well as renal injuries are also present in many cases, nearly all girls with significant external genital trauma should be evaluated for possible coexisting renal or ureteral injury. In severe injury, the child should be stabilized with urinary diversion via suprapubic catheterization with later reconstruction. If a urethral vaginal fistula occurs after trauma, it can be repaired using the anterior sagittal transrectal approach (Fig. 50A.10) (8).

Sexual Abuse

Sexual abuse includes any activity with a child before the age of legal consent that is for sexual gratification of an adult or a significantly older child. Sexual abuse includes oral–genital, genital–genital, genital–rectal, hand–genital, hand–rectal, and hand–breast contact; exposure of sexual anatomy; forced viewing of sexual anatomy; and the showing of pornography to a child or use of a child in the production of pornography. Sexual intercourse includes vaginal, oral, or rectal penetration. Penetration is entry into an orifice with or without tissue injury. Younger perpetrators tend to have younger victims but are more likely to have intercourse with older victims. Sex acts perpetrated by young children are learned behaviors and are associated with experiencing sexual abuse or exposure to adult sex or pornography. Without detection and intervention, sexual abuse may progress from touching to intercourse. Sexual play, on the other hand, may be defined as viewing or touching of the genitals, buttocks, or chest by preadolescent children separated by not more than 4 years in age in which there has been no force or coercion. Sexual abuse is surprisingly common. From 12% to 38% of adult women were sexually abused by age 18. The incidence of sexual abuse of males ranges from 3% to 9% of the population; males account for up to 20% of the reports. About one-third of sexual abuse victims are younger than 6 years of age, one-third are 6 to 12 years of age, and one-third are 12 to 18 years of age. Reported offenders are 97% male (31).

The abuse of daughters by fathers and stepfathers is the most common form of reported incest, although brother–sister incest is considered the most common type. Pedophiles have indicated that they seek positions and opportunities where they can be in contact with potential victims. The vulnerable children they describe include those with mental and physical handicaps, unloved and unwanted children, previously abused children, and children in single-parent families. Children of drug abusers and children with low self-esteem and poor achievement are also at risk. A father's desire for sexual gratification and a daughter's need for affection and nurturing may lead to incest when the mother is unavailable and there is longing to maintain the family unit. Violence is not common in sexual abuse; however, its incidence increases with the age and size of the victim.

The possibility of sexual abuse should be considered as a result of associated physical symptoms, including (a) vaginal, penile, or rectal pain, discharge, or bleeding, or (b) chronic dysuria, enuresis, constipation, or encopresis. Behaviors likely to be associated with sexual abuse include sexualized activity with peers, animals, or objects; seductive behavior; and age-inappropriate sexual knowledge and curiosity. Investigating the possibility of sexual abuse requires supportive, sensitive, and detailed history taking. Many hospitals have a sexual abuse team that can be readily consulted if sexual abuse is suspected. The key is to be aware of the possibilities when they might exist and to invite the team in early. The pediatric urologist will likely be asked to evaluate the abdomen and perineum (31). Examination of the female genitalia with the patient in the frog-leg position for young children or the knee–chest position for older children expedites the examination with minimal touching. Sexual abuse should be considered when the vaginal mucosa is bruised or injected, the vaginal opening is dilated, or the hymen is damaged, showing a V notch or cleft (81). Despite these guidelines, the diagnosis of sexual abuse is made by the history and not by the physical examination. In one review of 157 children referred to a sexual abuse clinic with only a physical complaint without a history of abuse, only 16% had examination findings suggestive of sexual abuse (36). If abuse is suspected, it must be reported to the police. If the perpetrator is a caregiver of the child or a parent, the state child welfare team must be contacted as well.

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50B THE MALE URETHRA

John W. Brock III

Mark C. Adams

Part of "50 - THE URETHRA "

J.W. Brock, III and M.C. Adams: Department of Urologic Surgery, Department of Pediatrics, Vanderbilt University Medical Center; Division of Pediatric Urology, Vanderbilt Children's Hospital, Nashville, TN 37212.

Abnormalities of the male urethra are varied and may be both acquired and congenital. The most common congenital problem, hypospadias, is covered in Chapter 52B . Posterior urethral valves is the most common anomaly associated with significant obstruction of the bladder. Anterior urethral valves and urethral atresia may have just as much effect on the bladder and upper tracts. Urethral polyps and congenital strictures may also cause obstruction. Urethral stricture disease in children is usually acquired, secondary to previous hypospadias surgery or trauma.

Over the past decades, many advances have occurred in the management of boys with congenital urethral problems. Urologists are better aware of their presentation and natural history, and radiographic evaluation is improved and generally definitive. More sophisticated instrumentation allows safer and more effective treatment of many of the lesions. However, despite those advances, progression to renal failure remains a potential problem for those patients with significant obstruction.

The symptoms of urethral lesions remain nonspecific; most children have frequency, urgency, incontinence, or terminal hematuria. When questioned, few parents and children denote a decrease in force or an abnormal stream. This is probably because most have never had a normal void

with which to compare. The diagnosis of urethral anomalies is usually made with a properly performed voiding cystourethrogram. Retrograde studies of the urethra are sometimes helpful, with endoscopy occasionally required for diagnosis. Ultrasound has assumed a major role in assessing the upper urinary system in such patients and may also be helpful in evaluating bladder function by examining residual urine or bladder wall thickness.

EMBRYOLOGY OF THE MALE URETHRA

The embryology of the urethra is not completely understood, particularly as it pertains to pathologic anomalies. The proximal or posterior urethra is formed by differentiation of the urogenital sinus, and the anterior urethra results from tubularization of the urethral plate. The urethra is usually divided into four sections:

1. The prostatic urethra, which is defined from the bladder neck to the proximal portion of the urogenital diaphragm
2. The membranous urethra, or that portion that traverses the diaphragm
3. The bulbar urethra, that segment from the membranous urethra to the penoscrotal junction
4. The penile urethra, which traverses the penile shaft and glans

Between the fourth and seventh week of gestation, the cloaca subdivides into a posterior portion (anorectal canal) and an anterior portion (primitive urogenital sinus) (Fig. 50B.1). The urogenital sinus then develops into a cranial portion that dilates to form the urinary bladder and pelvic portion that forms the proximal prostatic urethra and the membranous urethra. The anterior urethra is formed from the urethral folds on the genital tubercle. That portion of the urethra, unlike the posterior urethra, is dependent on 5α-reductase. The persistence of posterior urethral valves was first described by Tolmatschew (146) in 1870 as a simple enlargement of the folds and ridges seen in the posterior urethra. Bazy (9) in 1903 recognized them as incompletely resorbed membranes in that area. Lowsley (105) followed in 1914 with a description of a valvular formation related to abnormal development of the wolffian and müllerian ducts. It was 1919 when Young and colleagues (157) gave a clear description of valves. In their original essay, they recognized three variations of congenital urethral obstruction. They classified those as types 1, 2, and 3 (Fig. 50B.2). The classic type 1 valve is a membrane that billows with voiding and creates obstruction. The membrane

begins on each side at the posterior base of the verumontanum and inserts anteriorly at the level of the membranous urethra. This in effect creates two leaflets of tissue with an aperture of varying size located posteriorly. With voiding, the leaflets billow like a sail and create various degrees of obstruction (Fig. 50B.3).

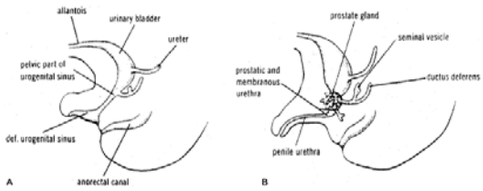

FIGURE 50B.1. A: Development of the urogenital sinus into the urinary bladder, the pelvic part of the urogenital sinus, and the definitive urogenital sinus. **B:** In the male, the urogenital sinus develops into the prostatic, membranous, and penile portions of the urethra. The prostate gland is formed by outbuddings of the urethra, and the seminal vesicles are formed by an outbudding of the ductus deferens. (From Langman J. *Medical embryology,* ed 2. Baltimore: Williams & Wilkins, 1969:157, with permission.)

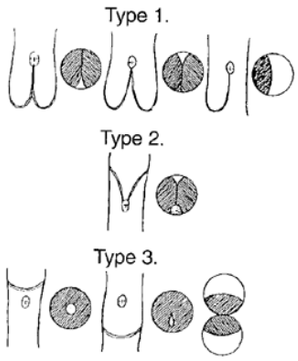

FIGURE 50B.2. Original diagram of Young and colleagues' (157) classification of posterior urethral valves. (From Young HH, Frontz WA, Baldwin JC. Congenital obstruction of the posterior urethra. *J Urol* 1919;3:289, with permission.)

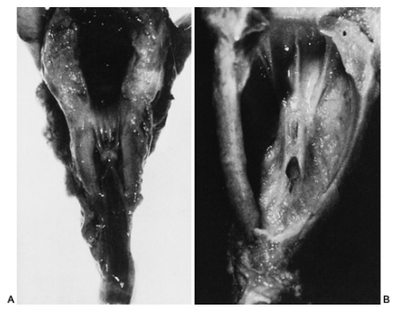

FIGURE 50B.3. Photographs of two type 1 posterior urethral valves. **A:** Posterior urethra opened in the midline; it give the impression of leaflets. **B:** Posterior urethra unroofed; it gives the impression of a membrane. However, it is attached to the veru. (From Robertson WB, Hayes JA. Congenital diaphragmatic obstruction of the male posterior urethra. *Br J Urol* 1969;41:592, with permission.)

Several different theories have been generated in regard to the development of posterior urethral valves. In the normal male, the mesonephric ducts insert laterally into the cloaca. As the cloaca folds inward in its midportion to separate the anorectal canal from the urogenital sinus, the ostium of each mesonephric duct migrates posterolaterally and cranially to assume a final position at the verumontanum. In a normal male, this pathway of migration appears to persist as plicae colliculi. Type 1 valves have been thought to result when the mesonephric ducts enter the cloaca in a more anterior portion than normal. As a result, when the cloaca undergoes separation and infolding, the mesonephric duct migration is impeded in midline fusion. Of note is that children with type 1 valves typically do not have plicae colliculi (Fig. 50B.4).

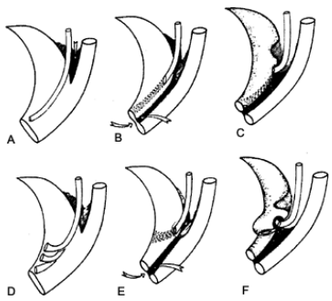

FIGURE 50B.4. Development of type 1 valves. **A–C:** Development of the normal urethral crest. Migration of the orifice of the wolffian duct from its anterolateral position in the cloaca to the site of the Müller tubercle on the posterior wall of the anorectal septum occurs synchronously with cloacal division. (Dots denote pathway of migration.) This wolffian remnant is more lateral and posterior and remains as the normal inferior crest and the plicae colliculi. **D:** Abnormal anterior positions of the wolffian duct orifices. **E:** Abnormal migration of the terminal ends of the ducts. **F:** Circumferential obliquely oriented ridges that compose the valve. (From Kelalis PP, King LR, eds. *Clinical pediatric urology.* Philadelphia: Saunders, 1976, with permission.)

Type 2 valves were initially described as folds radiating proximally in the urethra from the veru to the posterolateral bladder neck. It is now generally accepted that such valves are not obstructive and do not exist. Young and colleagues' classification system, however, remains imprinted on most urologists.

Type 3 valves are thought to represent an incomplete dissolution of the urogenital membrane. The resulting membrane is typically found distal to the veru at the level of the membranous urethra with a central aperture. Depending on its elasticity, it may create various appearances on fluoroscopy, including the wind-sock variety described by Field and Stephens (54a). Their embryonic explanation for such valves includes abnormal canalization of the urogenital membrane with subsequent slight constriction at the level of the perineal membrane. This causes varying degrees of obstruction (Fig. 50B.5).

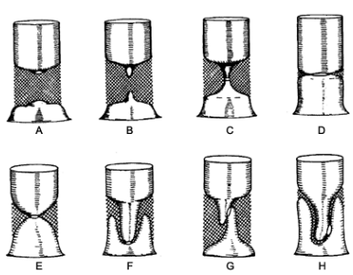

FIGURE 50B.5. Development of congenital urethral membranes (type 3 valves). **A–D:** Normal canalization of the urogenital membrane. **D:** Normal slight constriction at the level of the perineal membrane. **E:** Stricture formation. **F:** Canalization by central downgrowth and circumferential ingrowth resulting in building membrane with a central stenotic orifice. **G, H:** Side openings creating valvular wind-sock membranes. (Drawings and descriptions supplied through the courtesy of Dr. F.D. Stephens. From Kelalis PP, King LR, eds. *Clinical pediatric urology.* Philadelphia: Saunders, 1976, with permission.)

Field and Stephens (54a) also suggested the existence of an additional type of proximal urethral obstruction, which they called type 4 valves. This is an obstruction most often seen in boys with the prune-belly syndrome where the

poorly supported prostatic folds telescope into the urethra, creating relative outlet obstruction.

Type 1 valves make up 95% of the valves noted in newborns. Despite potential differences in embryologic derivation, there is no difference in the clinical presentation among children with type 1 and 3 valves. Both may have significant obstruction and effects on the kidneys and bladder. Rosenfeld and colleagues (129) suggested that type 3 valves may be associated with a worse prognosis.

The classification system described by Young and colleagues (157) has recently been challenged by Dewan and colleagues (35). In their description titled “Congenital Obstructing Posterior Urethral Membrane,” they noted that if endoscopy was performed before any instrumentation, a membrane was seen in all cases. They postulated that a membrane could be converted to a type 1 appearance by passing a catheter through the membrane or disrupting it with a hook. Debate continues because Young and colleagues (157) did not describe any attachment of the type 3 posterior urethral valve to the verumontanum as is seen with virtually all type 1 valves.

POSTERIOR URETHRAL VALVES

Historical Perspective

Review of the diagnosis and treatment of posterior urethral valves in boys reflects an interesting evolution in pediatric urology. Langenbeck in 1802 is credited with the first description of valves. However, it was not until Young and colleagues (157) described 36 cases that it was identified as a true entity. Treatment originally focused not only on the valves themselves but also on the bladder neck. That concern initially led to unnecessary bladder neck surgery. Severely ill infants were sometimes treated with cystostomy tubes, which were associated with infection, severe bladder spasms, and contracture of the bladder (89). Those children often succumbed to overwhelming sepsis. Treatment options then included many different types of supravesical diversions. Attempts at improving upper tract drainage and recovery began with low loop ureterostomy diversions and gradually were followed by high loop ureterostomy (87). Proximal loop ureterostomies were often done in the face of sepsis or when small bladders and markedly tortuous ureters were found. They did often lead to a difficult course of reconstruction because the bladder was defunctionalized and sometimes contracted further.

Supraurethral diversion in the form of vesicostomy was promoted by Duckett (42) at the Children's Hospital of Philadelphia in the 1970s. Primary valve ablation at the time was limited by the instrumentation for newborns. The caliber of the sheaths was too large for many neonatal urethras, and options were poor. If primary valve ablation was undertaken, it was often done by open valve resection through a perineal urethrostomy as described by Johnston

in 1966 (88). He used an otoscope to visualize and resect the valves. At about the same time, Hendren (69) described immediate and total reconstruction of the urinary tract in young patients with posterior urethral valves. He included not only valve ablation but ureteral tapering and reimplantation.

In the 1970s, a major advance in the treatment of these patients occurred with the introduction of a new Hopkins-Storz lens system. Primary valve ablation for newborns by endoscopic means became a viable option and treatment. It rapidly became evident that it was not necessary to reconstruct all children completely and that renal function, as well as the pyelographic appearance, improved in many children after primary valve ablation alone. Effective treatment of the obstruction immediately after diagnosis would seem to be the end of the story; however, patients continued to develop renal failure, and some surgeons suggested that better drainage of the kidneys might be ensured by upper tract diversion.

The Philadelphia group reviewed 100 patients followed for a median of 11.2 years after valve ablation. Thirteen percent had end-stage renal disease by 15 years of age. They also reported ten patients who underwent initial high diversion, only one of whom appeared to have improvement in renal function related to the diversion. At the same time, Krueger and Churchill (98) in 1980 reported that high diversion seemed to decrease renal failure and improve somatic growth in their patients. Controversy remains over the role and effectiveness of high diversion in patients with valves, primarily because numerous studies have not noted similar improvement. In 1997, Tietjen and colleagues (145) confirmed suspicions that segmental renal dysplasia could be found in many patients at the time of high diversion and often resulted in little improvement in renal function despite the diversion. The authors stated that they thought that fixed ureterovesical junction obstruction was rare, as was the need for supravesical diversion.

The widespread use of prenatal ultrasound has now provided the opportunity to identify many patients with valves well before birth. It makes intuitive sense that such diagnosis might allow earlier relief of obstruction and greater recovery or protection of renal function. The exact role of fetal intervention remains to be determined, although thus far it has not been possible to prevent early dysplasia.

Much early interest centered on the association of valves and the function of the kidneys. It has become clear that bladder outlet obstruction also affects the development and function of the urinary bladder. Persistent bladder dysfunction can then clearly cause secondary effects on the upper tracts. The urologist caring for patients with valves typically cannot change developmental renal dysplasia. It is imperative, however, that the urologist recognize bladder dysfunction and avoid secondary insult to the kidneys. Such bladder dysfunction can affect the native kidneys or a transplanted one. Marshall and colleagues (109) did not think that the valve bladder after relief of the obstruction affected a transplanted kidney. Churchill and colleagues (27) and Reinberg and colleagues (126) did suggest that the valve bladder significantly compromised renal transplantation. The Philadelphia group, evaluating their 100 patients managed with primary valve ablation, thought that bladder function was preserved in most. This was confirmed in a study of transplant patients in Birmingham (84). With 10-year follow-up, the study's authors noted no statistically significant difference in graft survival in posterior urethral valve patients with the native bladder intact.

Incidence

Posterior urethral valves are the most common cause of infravesical obstruction in the male child. It is also the most common cause of obstructive uropathy leading to childhood renal failure (148). The incidence ranges from 1:8,000 (21) to 1:25,000 (6) live male births. Valves may be associated with up to 10% of severe prenatally diagnosed hydronephrosis (16).

Developmental Renal Physiology

To better understand and evaluate renal functional outcomes and the role of urologic intervention in patients with valves, it is imperative that developmental renal physiology be well understood. Many babies are presently delivered prematurely either because of problems or recommendations for early relief of obstruction. To understand the fall of serum creatinine, particularly in respect to treatment, one must know the limitations for a specific child at a given age or gestational period.

Wilkens (150) confirmed that the glomerular filtration rate (GFR) quadruples from 26 to 40 weeks of gestational age. At 40 weeks of gestation, the GFR is typically 20 to 30 mL per minute. The GFR increases to approximately 50 mL per minute by 2 weeks of age and to 100 mL per minute by 1 year. Normal adult GFR is usually reached at approximately 2 years of age (Fig. 50B.6). From 80% to 90% of nephrons, however, are formed by 26 weeks of gestational age. Subsequent improvements in GFR may be due to changes in renal vascular resistance with redistribution of renal blood flow in the kidney (Fig. 50B.7). There is also a marked increase in capillary surface area with a resultant increase in total surface area for filtration. Changes in the permeability constant that lead to a change in the basement membrane permeability also improve function (154).

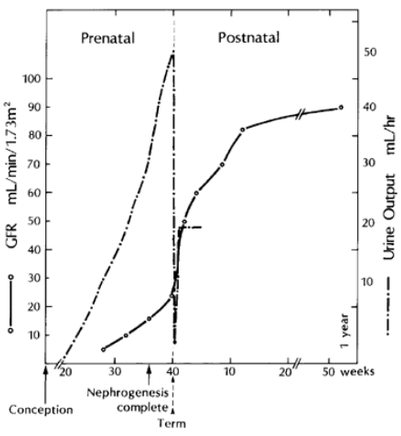

FIGURE 50B.6. Changes in glomerular filtration rate *(GFR)* and urine output during fetal development and infancy. A report by Rabinowitz and colleagues (122a) suggests that urine output at term may be 50 mL per hour.

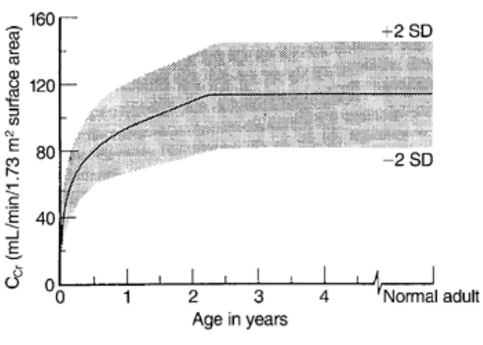

FIGURE 50B.7. The change in glomerular filtration rate with age. (From McCory WW. Regulation of renal functional development. *Urol Clin North Am* 1980;7:243, with permission.)

In addition to GFR, the tubular function of the kidney changes rapidly in the fetus and neonate. At birth, the normal neonate can concentrate the urine to 400 to 600 mOsm/L. The concentrating ability of the kidney gradually achieves adult status by 3 to 6 months of age.

The inability of the newborn to concentrate urine is related to an inefficient countercurrent mechanism, with decreased urea in the medulla, increased medullary blood flow, decreased tubular responsiveness to antidiuretic hormone, and a relatively short loop of Henle (155). Premature infants are likewise unable to acidify their urine as well as full-term infants (140). This results not only from an inability to excrete hydrogen ions well but also from a lower renal threshold for bicarbonate reabsorption.

With the knowledge of the normal fetal to neonatal progression of renal function, one must take into consideration the ability of the previously obstructed urinary tract to respond to being unobstructed. Standard treatment protocols have been based in the past on drainage of the bladder with achievement of certain renal parameters necessary to identify the next proper step in management. Historically, we believe that the rapid leap to upper tract diversion resulted from an approach that did not fully take into consideration the developing anatomy and the time required for an abnormal immature system to respond to treatment. It has become increasingly clear that upper tract diversion is not helpful in most cases due to the fact that lower tract treatment has provided adequate drainage if given time for the renal system to recover and mature. Furthermore, those who have not improved with high diversion did not because dysplasia plays a significant role (145).

Pathophysiology of Congenital Obstruction and Posterior Urethral Valves

The early obstruction of the urinary tract is associated with a variety of abnormalities. This includes ascending problems related to bladder storage and function and ureteral motility and drainage. It also has a great impact on proper renal development with resultant dysplasia, which impairs glomerular and tubular function. Unfortunately, depending on the timing and the severity of the obstruction, with the resultant increase in intraluminal pressure, the embryologic maldevelopment is so severe that even with prompt relief of obstruction, function does not return to acceptable levels. This leads to long-term clinical and pathologic problems. We will discuss the impact that posterior urethral valves and obstruction have on the development of glomerular and tubular function, vesicoureteral reflux, and bladder function.

Glomerular Function with Valves

The treatment of boys with posterior urethral valves is focused on preserving renal function. Unfortunately, there are many potential insults to renal function with a wide spectrum of etiologies. Clearly, problems can occur at the embryologic level and result from abnormal ureteral bud inducement of metanephric blastema (71). Mackie and Stephens' study (106a) suggested that abnormal position of the initial ureteral bud and eventual ureteral orifice is associated with resultant renal dysplasia or hypoplasias and that this same phenomenon exists in patients with valves. Their concept fits nicely with later recognition of the VURD syndrome (valves, unilateral reflux, and dysplasia); the refluxing kidney has profound dysplasia and the contralateral one is relatively spared or normal (78) (Fig. 50B.8).

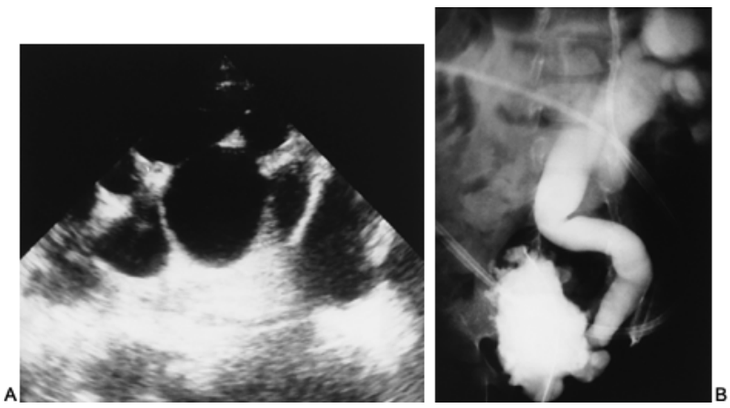

FIGURE 50B.8. Vesicoureteral reflux and dysplasia (VURD) syndrome demonstrated on ultrasound **(A)** and VCUG **(B)**.

One cannot ignore, however, the potential pressure effect of obstruction on the primitive developing kidney. Beck (10) thought that dysplasia could result from high intrapelvic pressure during nephrogenesis. Controversy arose when *in utero* ligation of animal ureters resulted in severe hydronephrosis but not consistent dysplasia (3,61,62,63). Maizels and Simpson (107) noted that the timing of ligation of the ureter in chick embryos was important in inducing dysplasia, as was the amount of metanephric blastema associated with the ureteral bud.

It is clear that the development of renal dysplasia is the single most influential factor with respect to the ultimate outcome of renal function in boys with valves. Despite early diagnosis and in some cases even early appropriate treatment, it does not appear that urologists at this point are capable of preventing its development. However, there are numerous secondary insults to renal function in patients with valves or any obstruction that can be affected by aggressive medical and surgical management. The first of these is obstruction, which must be relieved. Obstruction not only results from the valves themselves, but also potentially high intravesical bladder pressure resulting from either bladder noncompliance or uninhibited contractions. There is some evidence that satisfactory relief of obstruction may lead to an increase in parenchymal mass and GFR in the newborn or very young infant (110).

Recurrent urinary tract infections may cause decreased renal function. These children are at greater risk for infection secondary to increased intravesical pressure, nonemptying, diverticula, vesicoureteral reflux, and urinary stasis. They have the same risk of renal scarring with urinary tract infection as patients with primary reflux; however, their risk may be even more pronounced secondary to the association with increased intravesical pressure in many patients. Aggressive prevention of urinary tract infection by promoting emptying, decreasing the intravesical pressure in those patients with poor compliance or uninhibited contraction, and chemoprophylaxis can significantly lower the ongoing renal damage secondary to urinary tract infection. Selected use of surgery for those with reflux and poor bladder compliance also plays a role in protecting the upper tracts in some patients.

It is interesting to note that renal function seems to be better preserved in select valve patients with a pop-off mechanism. These vents include large diverticula, urinary ascites secondary to bladder or forniceal rupture *in utero,* and massive unilateral reflux with preservation of the contralateral renal mass (30,115,127). The pressure pop-offs are thought to dissipate the increased intraluminal pressure and allow renal development (Fig. 50B.9).

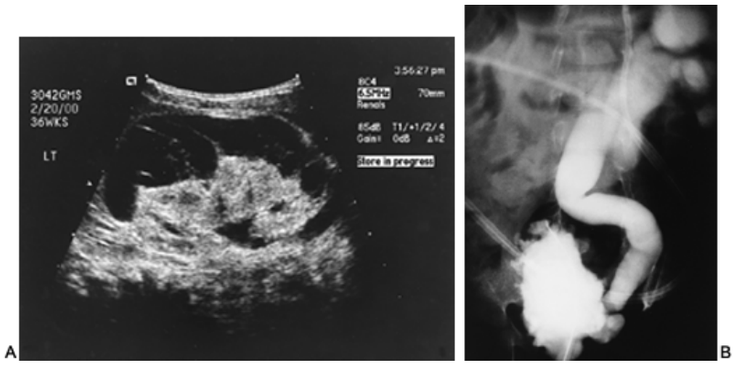

FIGURE 50B.9. A: Perirenal urinoma.

CHRONIC RENAL FAILURE

Chronic renal failure remains a final endpoint for a number of these patients. Unfortunately, the definition of chronic renal failure varies. Parkhouse and colleagues (116) defined *chronic renal failure* as a plasma creatinine concentration of 150 μmmol/L. *End-stage renal disease* is easily defined as a requirement for dialysis, renal transplantation, or death from renal failure.

The cause of progression to renal failure is multifactorial (40). On the one hand, there is the predetermined child with severe renal dysplasia at birth. A significant number of these babies either are stillborn or die soon after birth unless heroic measures with dialysis are instituted. The next group includes those with progressive renal damage secondary to ongoing obstruction, infection, or delayed diagnosis (13). Finally, there is the group who has adequate GFR and renal function to allow growth until puberty. At that time, however, the acceleration of somatic growth outstrips the ability of the kidneys to keep up and the renal reserve is overloaded. The hyperfiltration theory proposed by Brenner and colleagues (14) may play a role in these patients.

End-stage renal disease occurs in 25% to 40% of patients with posterior urethral valves. This also appears to occur with a bimodal age distribution with one-third manifesting end-stage renal disease after birth and two-thirds after puberty irrespective of surgical treatment (133,137) (Fig. 50B.10).

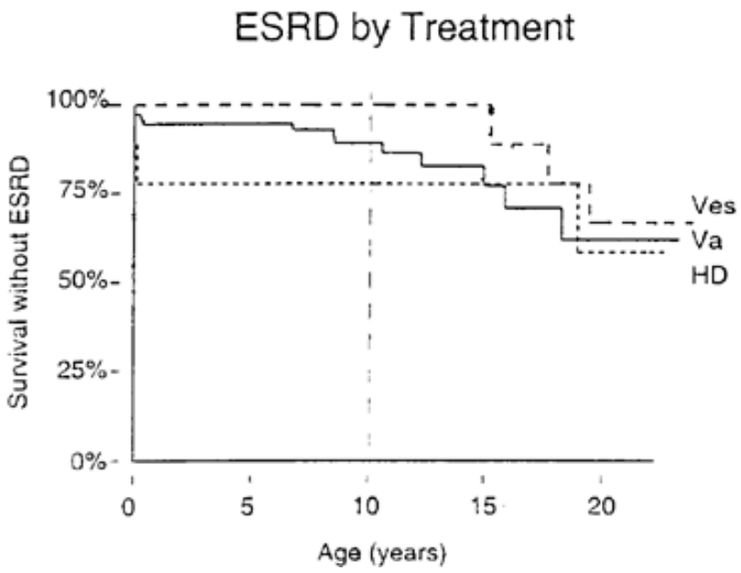

FIGURE 50B.10. Survival curve of the timing of renal failure in posterior urethral valves. Note that end-stage renal disease *(ESRD)* occurs in two peaks: the first few months of life and during the late teenage years.

TUBULAR FUNCTION

Experimentally, obstruction of the urinary system primarily affects the medullary portion of the tubule first. Clearly, there is washout of the medullary gradient necessary for resorption of water from the distal tubule, thus leading to an inability to concentrate urine (37). Work by Parkhouse and Woodhouse (117) suggested that renal tubular injury occurs before glomerular injury and that the tubule is more easily affected. Of 11 patients with a GFR less than 80 mL/ 1.73 m^2, all had evidence of tubular injury, whereas only 6 of 13 patients with a GFR greater than 80 mL/1.73 m^2 had abnormal concentrating ability.

This type of injury is potentially quite significant in the neonate. In spite of a reasonable glomerular filtration rate, the child must drink vigorously to keep up with urinary output. The child is very susceptible to severe dehydration with other minor illnesses associated with vomiting and diarrhea. The increased urine output also affects the lower urinary tract. The ureters and bladder must handle the volume, and resultant dilation may be physiologic. Increased

volume can eventually result in increased pressures in the abnormal bladder that can then secondarily harm the kidneys. Unfortunately, this nephrogenic diabetes insipidus is usually not responsive to hormonal therapy. Changes in diet and careful fluid balance may be helpful in some.

Other tubular functions such as acidification of the urine and resorption of filtered loads of protein and sodium may also be affected before changes in glomerular filtration rate. Those proximal tubular functions may be better preserved than distal tubular concentrating ability. Even in the absence of frank metabolic acidosis, unrecognized problems in acid–base balance may affect the growth and general health of some patients with valves.

Bladder Function

The congenital obstruction produced by posterior urethral valves often results in significant collagen deposition within the bladder (49). This, in addition to muscular hypertrophy, may lead to uninhibited contractions and noncompliance that can persist after relief of the obstruction. Other patients may exhibit myogenic failure. Typical urodynamic findings of posterior urethral valves in patients with persistent dysfunction are demonstrated in Fig. 50B.11 (8,18). These patterns are thought to persist in up to 25% of patients in spite of adequate relief of the obstruction. Boys with valves typically have very little sensation of fullness even at extreme pressures. This may be due to exposure of the bladder to such pressures all throughout development. Bladder emptying may play an important role in bladder function after valve ablation. Failure to empty well may expose the bladder and kidneys to consistently higher pressure and promote urinary tract infection.

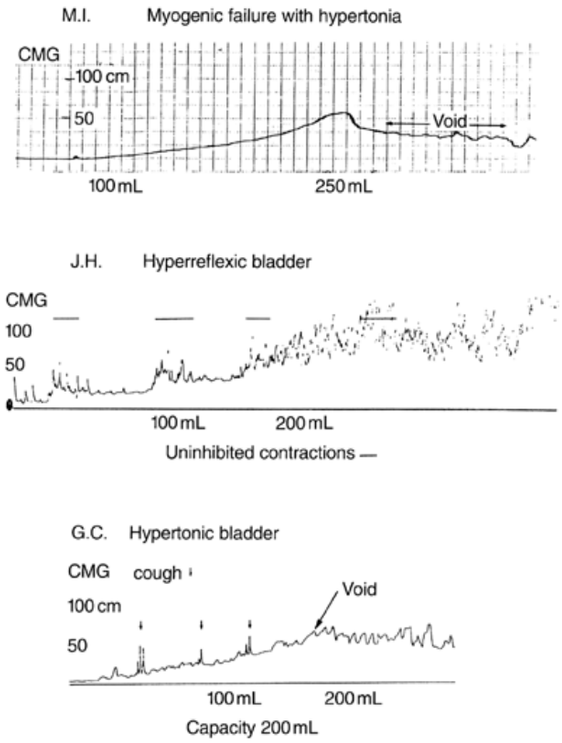

FIGURE 50B.11. Urodynamic tracings showing the three common types of detrusor dysfunction seen in posterior urethral valves. (From Peters CA, Bolkier M, Bauer SB, et al. The urodynamic consequences of posterior urethral valves. *J Urol* 1990;144:122, with permission.)

Debate has developed concerning the effect of bladder defunctionalization on ultimate bladder function. Leome and associates (104), followed by Tanagho (142) and Close and Mitchell (28), have suggested that the bladder must cycle with filling and emptying to develop normally. Others have noted that relief from pressure and obstruction, even with defunctionalization, can result in normal function. It is clear that bladder function can change over time in patients with valves. Before valve ablation, Holmdahl and colleagues (76) found small, hypercontractile bladders in all children. After valve ablation, the bladder capacity increased, although

some boys demonstrated uninhibited contractions and poor emptying.

Bladder dysfunction may cause urinary incontinence in boys after valve ablation but may have far worse ramifications. Increased intravesical pressure may contribute to vesicoureteral reflux, hydronephrosis, and even secondary renal deterioration (75). Parkhouse and colleagues (116) showed that adolescents who had incontinence in childhood had a more severe degree of renal insufficiency. Even though much of the incontinence in the group improved at puberty with growth of the prostate, the authors suggested that bladder dysfunction and increased intravesical pressure created an unfavorable environment for the kidneys.

Management of bladder dysfunction is based on urodynamic findings (95,96,100). Treatment consists of providing a low-pressure environment with adequate bladder emptying. Timed voiding with double voiding techniques may be sufficient to empty with intravesical pressures below a critical level. In those who do not respond to this, anticholinergic therapy or clean intermittent catheterization may be required. Because boys with valves have normal sensation, clean intermittent catheterization is often poorly tolerated. In the worst-case scenario, bladder augmentation may be necessary. This can be accomplished with many different substances, including small and large bowel, stomach, and urothelium with the use of dilated ureter (1,11,20,24,102).

VESICOURETERAL REFLUX

Vesicoureteral reflux is found in one-third to one-half of patients with posterior urethral valves. This usually is reflux secondary to increased intravesical pressure and loss of ureterovesical junction competence, but the study of Henneberry and Stephens (71) suggests that primary reflux may also be present in some. They demonstrated a significant incidence of lateral ectopia in their study of fetuses and newborn infants.

Because reflux is common in posterior urethral valves, it should not influence the overall management (90). At least one-third of the reflux resolves with treatment of the primary outlet obstruction. Surgical intervention is usually reserved for patients with breakthrough urinary infections or those with massive reflux that interferes with bladder function.

Whether reflux affects prognosis is controversial. Johnston and Kulatilake (91) in 1971 found that those patients with bilateral reflux at diagnosis had a mortality rate of 57%, those with unilateral reflux had a mortality rate of 17.4%, and those with no reflux had a mortality rate of 9.1%. Johnston (90) also reported a higher incidence of end-stage renal disease in patients with reflux. The etiology of this is unclear. Hulbert and Duckett (79), however, did not show a correlation between reflux and renal function in 120 patients followed for an average of 5 years. Williams (151) also published the same results as early as 1973.

Prenatal Diagnosis

Most boys with posterior urethral valves are now diagnosed antenatally because of the improved sensitivity and specificity of ultrasonography and its widespread use in pregnant women. Unfortunately, antenatal ultrasonography is usually not performed until 20 weeks of gestational age, which is too late to change the outcome of renal and pulmonary development for some patients (65,68).

Hutton and colleagues (82) reported 17 cases of antenatally detected valves at a mean of 18 weeks of gestation. The ultrasound appearance was characterized with respect to dilation, cystic change or echogenicity of the renal cortex, and the amount of amniotic fluid. With median follow-up of 5.7 years, 10 of the 17 boys had a poor outcome, with death in 4 and chronic renal failure in 6. Eight of nine boys with marked prenatal hydroureteronephrosis at an early gestational age did poorly, in contrast to only two of eight with milder upper tract changes. The authors concluded that the worrisome findings provided important information for parental counseling. Others have noted that early detection of severe upper tract changes secondary to posterior urethral valves does not change the outcome but does identify patients more at risk for renal failure (85).

Beyond the ultrasonic appearance of the kidneys and bladder *in utero,* the quality of the fetal urine, obtained by ultrasonically guided aspiration, may provide additional information about the risk of renal failure. The fetal kidney usually produces hypotonic urine with various parameters used to predict eventual renal function. Normal ranges of fetal urinary concentration of various urine markers and electrolytes have been proposed based on the gestational age of the fetus (Table 50B.1). However, there have been clear cases in which the eventual outcome for the patient did not match that predicted by antenatal determination of fetal urine quality (51). It has been suggested that serial urine measurements may be of greater benefit than a single evaluation alone (86). Furthermore, urinary β_2-microglobulin and *N*-acetyl-ß-D-glucosaminidase may be

helpful in identifying severe forms of obstruction, as may amino acid concentration in the urine (53,143).

Sodium	<100 mEq/L
Chloride	<90 mEq/L
Calcium	<2 mmol/L (8 mg/dL)
Phosphate	<2 mmol/L
Osmolality	<210 mosmol/kg
Protein	<20 mg/dL
β_2-Microglobulin	<2–4 mg/L

From Spitzer A. The current approach to the assessment of fetal renal function: fact or fiction? *Pediatr Nephrol* 1996;10:230, with permission.

TABLE 50B.1. NORMAL FETAL URINE VALUES

The ultimate goal in caring for any patient besides identifying a problem is to intervene when necessary and improve the ultimate outcome. Initially, therefore, there was enthusiasm for prenatal intervention for posterior urethral valves in hopes of improving ultimate renal and pulmonary function. The benefit of such intervention, even when effective from a mechanical standpoint, remains controversial. Effectiveness must be evaluated in terms of both pulmonary and renal function (103). Once the natural history of severe hydronephrosis and oligohydramnios is reasonably well defined and understood, it should be relatively easy to determine whether prenatal intervention in certain circumstances may benefit the fetus from a pulmonary standpoint (67). On the other hand, many variables affect the ultimate outcome for renal function in boys with posterior urethral valves, and not all can be determined antenatally. When so many variables potentially play a role in outcome, it is much more difficult to predict the natural history early in gestation. Even if antenatal intervention does not change the ultimate number of boys progressing to renal failure with posterior urethral valves, it will be difficult to determine whether it does or does not affect the timing of such progression. In any event, with appropriate criteria less than 1% of boys with antenatally detected hydronephrosis should undergo any consideration of antenatal intervention.

Freedman and colleagues (56) evaluated 55 consecutive patients who underwent prenatal intervention, including 13 patients with posterior urethral valves. Unfortunately, they concluded that prenatal intervention resulted in no difference in outcome from those detected postnatally. In a later report, however, Freedman and colleagues (57) noted that fetal intervention may help those fetuses with the most severe forms of obstructive uropathy generally associated with a fatal outcome. They suggested that intervention might allow some boys to progress along a course similar to less severe cases. Holmes and Baskin (77) reviewed the outcome of 33 fetuses undergoing antenatal intervention for valves over a 17-year period. All patients had favorable urinary parameters and a mean gestational age of 21.8 weeks at intervention. They found that intervention carried a rate of immediate fetal demise of 40%. They also concluded that intervention may not change the progression of renal function despite the finding of favorable urinary electrolytes. They therefore concluded that parental counseling should focus on the fact that intervention may assist in bringing the fetus to term and then surviving from a pulmonary standpoint but that the sequela of the valves may not be preventable. El-Ghoneimi and colleagues (52) also concluded that the ultimate outcome of children with valves from a renal standpoint has not been affected by prenatal diagnosis. The exact role of fetoscopy and valve ablation or vesicoamniotic shunting remains to be determined and probably will require a long and well-organized multicenter trial (122).

Multiple factors may influence the outcome of posterior urethral valves. Embryologic dysfunction associated with them may have a profound role in prognosis. Stephens' ureteral bud theory suggested that renal dysplasia in valves is not solely a function of increased pressure secondary to obstruction but also depends on the position of the ureteral bud. The lateral ectopia of the ureteral bud in valve patients led to renal dysplasia or hypoplasia much as it could in patients without a lower tract problem. Abnormalities in signaling and control between the ureteral bud and metanephric blastema may contribute to abnormal inducements that are just beginning to become understood. Other genetic determinants may influence such interactions and then affect the response of a given kidney to an insult such as obstruction (73,74,156).

Postnatal Evaluation

The typical radiographic evaluation of children with posterior urethral valves has evolved. Intravenous pyelography was the study of choice for the upper urinary system 20 years ago but has largely been replaced by ultrasonography and nuclear renography. Lower tract evaluation is done using voiding cystourethrography, which is diagnostic. Urodynamic evaluation of the bladder may ultimately be necessary to evaluate and treat persistent bladder dysfunction.

Ultrasound

Ultrasound was a significant advance in diagnosis. Not only does it tell us the degree of hydronephrosis, but it also can assist in predicting renal functional outcome through many other parameters. The determination of renal parenchymal thickness and renal size can be important. Renal echogenicity can predict the degree of dysplasia. However, the most important radiographic finding appears to be that of corticomedullary differentiation. Hulbert and colleagues (81) showed that patients with a lack of corticomedullary differentiation appear to have a higher percentage of renal insufficiency.

Ultrasound also has been used to evaluate the bladder in children with posterior urethral valves. Dilated ureters posterior to the bladder in addition to abnormal bladder thickness are highly suggestive of posterior urethral valves. There have been attempts to correlate bladder wall thickness ultrasonographically with a diagnosis of posterior urethral valves. This, however, remains somewhat problematic in that the state of bladder filling clearly influences the bladder wall thickness.

Renography

The MAG-3 Lasix renogram has become the standard for determining upper tract function and drainage. This has replaced the need for invasive upper tract urodynamics

studies (Whitaker test) in most children. Prognostically, serial studies not only assess degree of response to specific treatments, but also can predict further renal reserve and long-term outcome.

Voiding Cystourethrogram

The ultimate diagnosis of posterior urethral valves is made by a well-performed voiding cystourethrogram VCUG. This requires a voiding phase within the study. The hallmarks of posterior urethral valves include a dilated posterior urethra, elevated bladder neck, and trabeculated bladder. One may also see a filling defect at the prostatomembranous junction or an enlarged bladder. Vesicoureteral reflux is present in 50% of the patients. Findings such as these make endoscopy mandatory to complete diagnosis and allow for treatment.

MANAGEMENT

The vast majority of boys with posterior urethral valves are now diagnosed *in utero.* This affords initial management from a team approach including pediatric urologists, pediatric nephrologists, the maternal-fetal medicine physician, neonatologists, and pediatricians. Depending on the severity of the renal impairment and the gestational age at birth, different problems may arise.

The initial management after birth must include drainage of the bladder. This is usually done per urethra with a small, soft feeding tube. One must be sure that the catheter is in the bladder to achieve adequate drainage. At times, the catheter may coil in the dilated posterior urethra due to difficulty passing the elevated bladder neck. Urine may drain, despite inadequate bladder decompression. If necessary, radiographs should be obtained to ensure proper placement in the urinary bladder. In some rare cases, the urethra cannot be traversed and access to the bladder must to obtained suprapubically. Once bladder access is obtained, aggressive management of any fluid and electrolyte problems is required. Patients often have voluminous urine output secondary to loss of concentrating ability and may lose a significant amount of solute in the urine in the form of sodium and potassium (37). Prudent intravenous fluid management includes aggressive fluid and electrolyte replacement (43,44).

Children with valves may also have potentially severe acidosis depending, again, on the severity of the renal dysfunction. Careful assessment of urine and serum bicarbonate concentration may aid in adjusting intravenous fluid replacement and bicarbonate therapy in such patients (23).

The renal function, as measured by serum creatinine, should be monitored closely after bladder drainage. The measured creatinine in the first several days of life reflects that of the mother. Subsequently, the creatinine measures the clearance of the child. In the presence of an elevated serum creatinine, the time required to see a decrease may be highly variable and may depend on the gestational age at birth. Some authors have suggested that the creatinine level after approximately 5 days of drainage would be useful in determining appropriate intervention. Without a satisfactory decrease in creatinine, an upper tract diversion was often considered in the past. Gonzales (64) has reported that nadir creatinine of 1.8 mg/dL or greater after several days of transurethral drainage should prompt consideration of upper tract diversion. He considered patients with a creatinine level between 1.5 and 1.8 mg/dL to be an intermediate group in which endoscopic management or diversion might be appropriate. He reported that primary valve ablation should be performed in those patients whose creatinines fell to below 1.5 mg/dL. For patients without such a decrease, repeat ultrasounds may be useful to demonstrate decreased hydronephrosis and help avoid unnecessary upper tract diversion. Even with a persistently elevated serum creatinine, there has been a trend away from immediate upper tract diversion.

Transurethral Resection of Valves

Treatment of the valves has included open dissection by perineal urethrostomy, fluoroscopic rupture using a Whitaker hook, and antegrade passage of a balloon catheter (22,36,97,149). The primary treatment of choice is now direct endoscopic visualization and ablation (32) (Fig. 50B.12). Major improvements in technology have made transurethral valve ablation a viable option in virtually all cases. The availability of the 7-Fr scope with a working channel of 2 to 3 Fr allows access to the posterior urethra in most babies, even if premature. Improved fiberoptic lens

systems in such small scopes have made adequate visualization a reality. Proper ablation of valves should accomplish destruction of the valves while sparing the urethra from injury. Transurethral “resection” is clearly a misnomer because aggressive attempts at complete resection may lead to significant posterior urethral injury and resultant stricture (25,101). This complication produces a very significant reconstructive challenge.

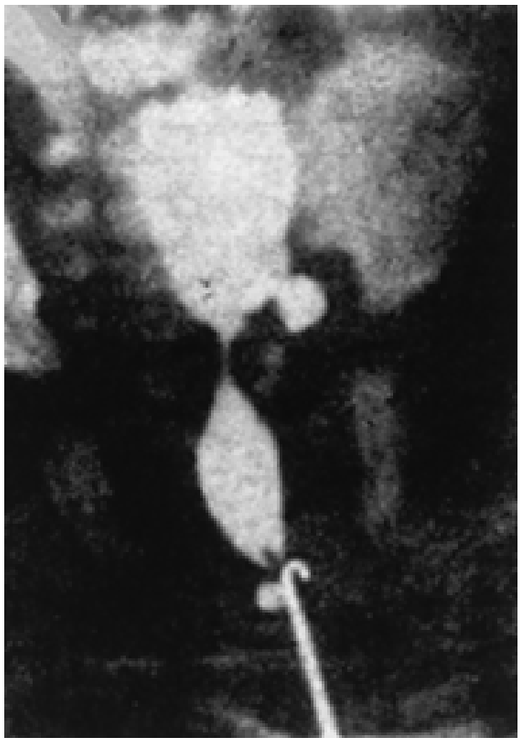

FIGURE 50B.12. Whitaker hook.

The goal of the transurethral technique is to ablate the valves so that they are nonobstructive. This can be accomplished in a retrograde fashion using small instruments and a Bugby electrode. Ablation is accomplished using cutting current and incisions at the 5, 7, and 12 o'clock positions. In older children, incision can be easily accomplished using a resectoscope and a wire hook electrode to engage and incise the valve (Fig. 50B.13).

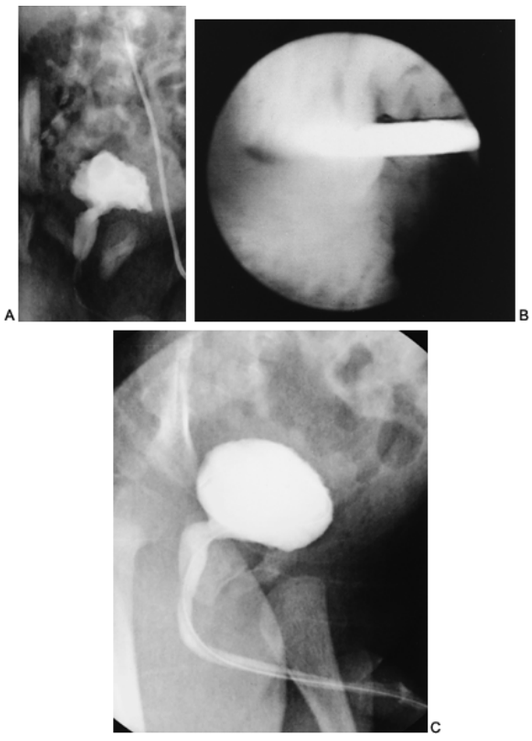

FIGURE 50B.13. A: Preoperative valves. **B:** Endoscopic view of valves. **C:** Postoperative valves.

Zaontz and Firlit (158) described an antegrade technique for ablation of valves. Access to the bladder is gained percutaneously, and a flexible cystoscope is passed through the bladder neck (Fig. 50B.14). The valves are ablated in a similar position using a Bugby electrode or the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (12,47,48). This approach offers the advantage of avoidance of instrumentation to the small male distal urethra, although reported strictures after neonatal valve ablation have been rare. It may allow endoscopic access to the valves of premature boys who previously might not have accepted available cystoscopes in a retrograde fashion.

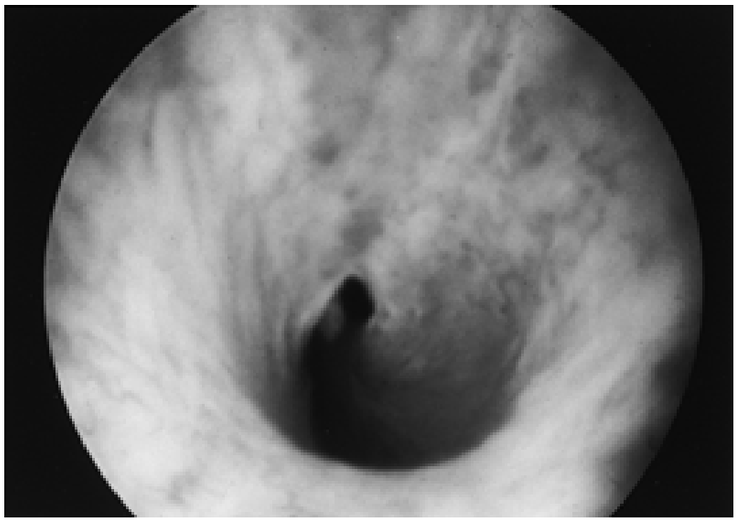

FIGURE 50B.14. Antegrade endoscopic view of posterior urethral valves.

Primary valve ablation reliably relieves the urethral obstruction and allows the bladder to cycle regularly (112). Some authors have suggested that such cycling is important to decrease collagen deposition and prevent noncompliance. When treated with primary valve ablation, many patients demonstrate a resolution of initial reflux, and most have remarkable improvement in upper tract hydronephrosis. Concern may remain for the adequacy of upper tract drainage in an occasional child with persistent hydronephrosis and renal insufficiency. In that setting, patience and close follow-up are necessary to gain confidence that the kidneys are recovering as much as possible and that upper tract diversion is not warranted.

Vesicostomy

In children whose valves cannot be primarily ablated, usually for technical reasons, vesicostomy remains a viable option of treatment. The functioning vesicostomy provides good drainage of the lower tract with a minimally invasive, easily reversible technique. Duckett (41,42) was an early proponent of vesicostomy, as were Walker and Padron (147). They noted that the cutaneous vesicostomy was safe and ensured adequate drainage, although their review did not show any overall improvement in renal function when compared with primary valve ablation.

We believe that vesicostomy is an excellent choice for drainage in select cases of posterior urethral valves. We have primarily used it in very premature infants in whom safe visualization or incision of the valves was not possible. Vesicostomy can be performed through a small, 2-cm transverse incision made below the umbilicus. After the anterior bladder is exposed, it should be mobilized to the urachus, which may be divided. Although the valve bladder is generally quite thick and less prone to prolapse, the vesicostomy should be performed posterior to the urachus to make sure that the posterior wall of the bladder is not redundant and prone to prolapse. When done in this fashion, the cystostomy into the thick valve bladder may be made large (24 Fr) to avoid stenosis. The bladder wall adjacent to the cystostomy is then attached with suture at the level of the fascia and skin. Importantly, a vesicostomy allows cycling of the bladder to take place at low pressures (94).

High Diversion

The decision to proceed with high diversion is difficult, as discussed previously. Several reports from Toronto have supported upper tract diversion to maximize renal function (26,99). Krueger and colleagues (99) compared two groups of children treated for valves with renal insufficiency. They thought that patients demonstrated improved renal function and better somatic growth when treated with upper tract diversion compared with those undergoing primary valve ablation. Their conclusions, however, have been challenged by several authors concerned about selection bias in that study. Duckett and Norris (45) and Reinberg and colleagues (124,125) in separate reports evaluated similar patients undergoing upper tract diversion and did not find a benefit in terms of renal function.

If high diversion was not without specific disadvantages, one could argue that the surgeon and patient risk little by proceeding with this to maximize renal function. However, such diversions make it cumbersome to keep the child dry as he grows, and it commits the child to major upper tract reconstructive procedures. Recent concerns have suggested that complete diversion of urine from the bladder may ultimately compromise bladder function. If upper tract diversion is to be done, we prefer a cutaneous pyelostomy when possible, although a proximal loop cutaneous ureterostomy may often be easier to get to the skin without tension. A small incision is made at the level of the twelfth rib. The retroperitoneum is entered, and the ureter is identified. Care is taken not to injure the ureteral blood supply during dissection. If a proximal loop of ureter is brought to the skin, the ureteral adventitia and longitudinal blood supply are swept away from the area of incision and preserved. Proximal diversion provides excellent drainage of the kidneys and relatively simple closure. We often perform a renal biopsy at the same setting for prognostic purposes.

Total Reconstruction

Hendren (69,70) demonstrated that total reconstruction of the urinary system in patients born with valves could be accomplished when hydronephrosis persisted after primary valve ablation. Total ureteral tapering and reimplantation was often necessary. Hendren thought that such reconstruction eliminated potential ureterovesical junction obstruction, decreased stasis, and allowed more effective peristalsis. All of this was done to improve drainage and renal function. Hendren clearly showed that such reconstruction could be done with good results. Better understanding of the natural history of hydronephrosis associated with posterior urethral valves has demonstrated that true, persistent ureterovesical junction obstruction is rare. As much as one-third of vesicoureteral reflux will resolve with ablation of the valves alone. When significant hydronephrosis or reflux persists, bladder function must be carefully evaluated and managed. Thus most early upper tract reconstruction can be avoided in patients doing well.

Prognosis

The infant mortality rate related to valves has fallen from the 50% reported by Johnston and Kulatilake (92) in 1972 to the 1% to 3% reported by Churchill and colleagues (26) in 1990. Better urologic care, aggressive management with fluid and electrolyte replacement, antibiotics, and dialysis or transplantation have allowed these children an opportunity for life. Unfortunately, the outcome for patients with valves in terms of renal failure has not changed despite antenatal diagnosis and good urologic care (17,116,144). The incidence of renal failure continues to be 25% to 40% among patients with severe posterior urethral valves. Because of better survival, many of those patients have become candidates for renal transplantation. Results of transplantation have improved over the past several decades as well, primarily due to improved immunosuppressive therapy (7,83). More urologic interest in bladder dysfunction among valve patients and better resultant care may avoid renal failure and the need for transplantation in an occasional patient. It may also lengthen the time until transplantation is necessary (114). Besides protecting the native kidneys, recognizing and treating bladder function may also improve graft survival with transplantation. Reports have shown that transplantation can be safely performed in patients after valve ablation, although they must be followed closely to ensure no deterioration in the function of the bladder or renograph (84,136,141).

Fertility

It has been noted that most patients with treated valves were fertile as adults (117,152). However, occasional patients experienced anejaculation or retrograde ejaculation. The etiology of the problems appears to be multifactorial and is potentially related to an abnormal posterior urethra, obstructed ejaculatory duct, changes in bladder neck dynamics, or complications of valve ablation.

Minimalist Posterior Urethral Valves

Posterior urethral valves, as much as any congenital anomaly, occur in a wide spectrum of severity. This discussion has primarily concentrated on severe valves because they are the most typical. However, patients may be found with minimal valves, various voiding complaints, and no upper tract changes (121). They typically manifest after toilet training with a wide variety of complaints ranging from urgency, frequency, and incontinence to hematuria and urinary tract infection. The diagnosis of such valves is made by voiding cystourethrography (Fig. 50B.15), and treatment remains transurethral ablation. Despite relief of the obstruction, they may require significant voiding modification in the form of timed and double voiding techniques. They also sometimes require anticholinergic medications to store urine normally. If voiding complaints continue well after relief of obstruction, urodynamics are necessary to elucidate the problem and affect treatment.

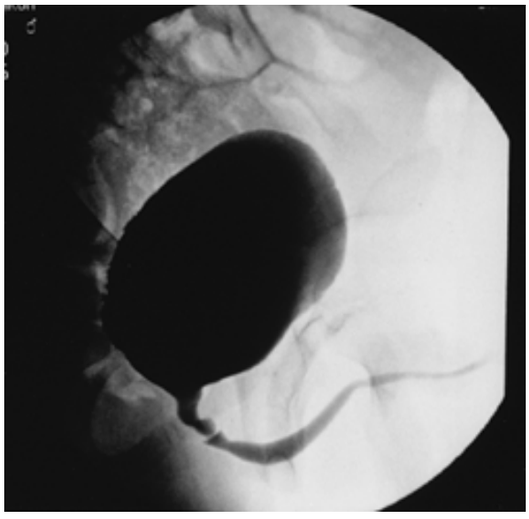

FIGURE 50B.15. VCUG of mini-valve.

ANTERIOR URETHRAL VALVES

Anterior urethral valves are a much less common cause of infravesical obstruction, with as much potential morbidity as posterior urethral valves. Because anterior urethral valves are occasionally found at the distal end of a diverticulum, it is unknown whether the anomaly developed primarily as a diverticulum with undermining of the distal urethra and secondary development of valvular obstruction or early

valvular obstruction that resulted in proximal maldevelopment of the urethra and spongiosum.

The embryologic origin of anterior urethral valves is somewhat controversial. It has been suggested that they may be the result of an aborted attempt of a urethral duplication, failure of alignment between the proximal and distal urethra resulting in a tissue remnant that may act as a valve, or congenital cystic dilation of periurethral glands resulting in a flaplike valve. These valves may be located anywhere in the anterior urethra. Forty percent have been found in the bulbous urethra, 30% at the penoscrotal junction, and the remaining 30% in the pendulous urethra. They have rarely been reported in the fossa navicularis (132).

Anterior urethral valves manifest with a wide spectrum of severity based on the degree of urethral dilation, presence of an associated diverticulum, and the grade of upper tract dilation. These patients commonly have dribbling of urination, difficulty in voiding, incontinence, poor urinary stream, and recurrent urinary tract infections. In the neonatal period, the obstruction may result in megacystis, bladder rupture, severe hydroureteronephrosis, azotemia, or urinary ascites (59). Older children may also have enuresis, postvoid dribbling, or failure to thrive.

VCUG is the diagnostic study of choice (Fig. 50B.16). Interestingly, the urethra often appears narrow distal to the valves and dilated proximally. The valve itself may be visualized as a linear defect along the ventral wall but also may only be noted as an abrupt change in the caliber of the urethra. Vesicoureteral reflux has been noted in approximately one-third of patients, and upper tract dilation noted in one-half.

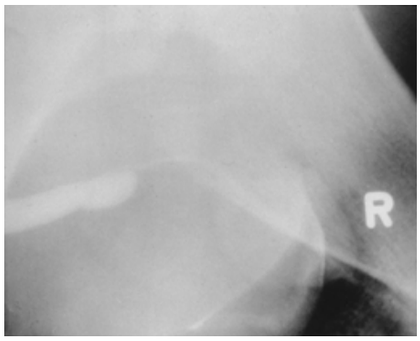

FIGURE 50B.16. VCUG of anterior urethral valves.

Endoscopically, the valve appears as a filmy, ventrally located cusp or flap of tissue (Fig. 50B.17). It occasionally has been described as an irislike membrane. One must examine the urethra carefully at the distal end of any urethral diverticulum because retrograde flow of irrigant may flatten the valve mechanism against the urethral wall. Suprapubic pressure with the bladder full and irrigation ports on the scope open may demonstrate the valve mechanism more readily. Furthermore, elevation of the valve with an endoscopic loop is invaluable in the identification of the lesion. Transurethral incision of the valve is effective for most patients, but one must be careful to aggressively incise to avoid any distal obstructing lip. Endoscopic treatment does leave the patient with a urethral diverticulum in most cases. An occasional patient with a huge diverticulum and a defect in the spongiosum may benefit from open repair, which allows reconstruction of the valve, diverticulum, and investing tissues (Fig. 50B.18). In a rare patient with severe renal disease associated with obstruction, a temporary cutaneous vesicostomy may be used to allow drainage and improvement in renal function (130).

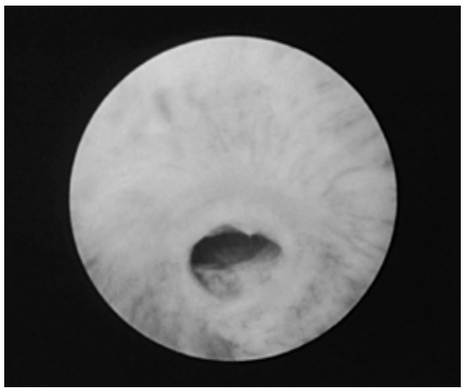

FIGURE 50B.17. Retrograde endoscopic view of anterior urethral valves.

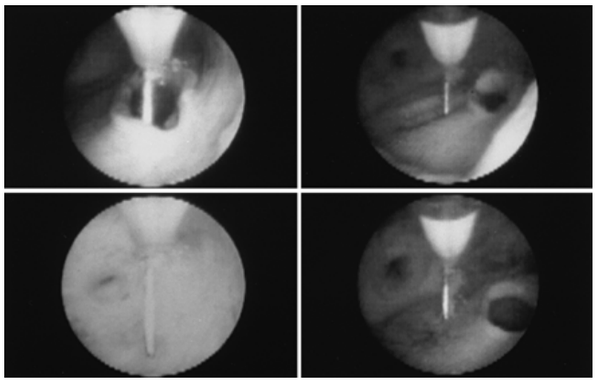

FIGURE 50B.18. Transurethral incision of anterior urethral valves.

URETHRAL ATRESIA AND AGENESIS

Urethral atresia and agenesis must be included in the differential diagnosis of renal anomalies and bilateral hydronephrosis diagnosed *in utero.* Unfortunately, unless there is some other egress for the urine to escape the bladder, such as a patent urachus or a urorectal communication, these lesions are not compatible with renal development. Management will depend on the specific anomaly and the amount of renal function salvaged by alternative urinary drainage.

URETHRAL STRICTURE

Urethral strictures in children are the result of three etiologic possibilities: congenital, infectious, or traumatic (iatrogenic or noniatrogenic).

Congenital

The question as to whether congenital strictures truly exist has been previously debated. Having cared for children who have had no previous trauma or instrumentation of the urethra and finding a stricture has convinced us that these do exist. However, the distinction between a congenital and a type 3 valve can be quite difficult, with the first being just distal to the veru and the latter found in the membranous urethra. The true incidence of congenital stricture is not known. However, if one defines a stricture as being congenital when there is no known trauma or instrumentation, Kaplan and Brock (93) found that 14% of the strictures they encountered in children fit this classification.

Infectious

Infectious etiology is a rare cause of strictures in children due to the generation time for strictures to develop, often being decades. Inflammatory etiology should be considered different than infectious, and indwelling catheters play a role in development.

Traumatic

A traumatic event is the single most important etiologic factor in the development of stricture in children. A straddle injury or iatrogenic trauma following endoscopy, traumatic urethral catheterization, and surgery accounts for most events leading to stricture. Previous series have shown posthypospadias surgery patients to represent the largest group of patients with iatrogenic stricture (93). Treatment for these is presented in Chapter 52B .

MEGALOURETHRA

Megalourethra is a rare congenital anomaly characterized by abnormal dilation of the pendulous urethra. It shares some of the characteristics of a urethral diverticulum but includes more extensive and uniform involvement of the urethra. The anomalies were originally described by Nesbitt (113) in 1955 and then classified by Dorairajan (38) in 1963. The classification of fusiforme and scaphoid types reflects the severity of the defect and the resultant effect on the corpus spongiosum and corpora cavernosum. The scaphoid form results from deficiency or absence of the ventral corpora spongiosum. A fusiforme megalourethra also affects the dorsal sponge and corpora cavernosa. More recently, Adamson and Burge (2) have described a third type with all corpora intact.

The cause of megalourethra remains somewhat controversial. Stephens and Fortune (139) postulated that a delay in cannulization of the distal epithelial core might lead to obstruction and proximal dilation. Others have suggested that embryologic arrest of the mesoderm investing the urethral folds influences the development of the corpora and erectile tissue (38).

Megalourethra is often associated not only with other urorectal anomalies such as imperforate anus, prune-belly

syndrome, and urethral valves, but also with varying degrees of uropathy (54,55,66,98,131,135). Diagnosis is often suspected on physical examination, particularly if the child is seen to void (Fig. 50B.19). The urethral meatus may be normally placed but patulous. The rare and more severe fusiforme type is often characterized by a soft, elongated phallus with palpably inadequate corpora. Ventral ballooning with voiding is typical of scaphoid megalourethra. Voiding cystourethrography and renal ultrasonography are performed to establish the diagnosis and evaluate the upper tracts (Fig. 50B.20).

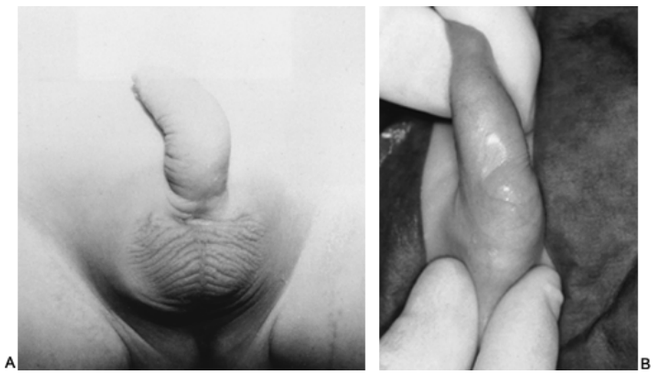

FIGURE 50B.19. Megalourethra suggested by physical examination.

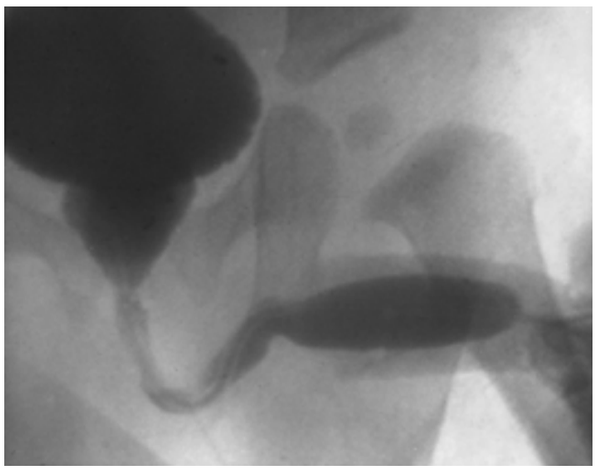

FIGURE 50B.20. VCUG of scaphoid megalourethra.

Treatment centers on reconstruction of the urethra and spongiosum using common principles of hypospadias repair. The scaphoid urethra can be opened longitudinally using the better dorsal and lateral tissue (Fig. 50B.21). The fusiforme variety presents a much more difficult challenge depending on the amount of corporal tissue present. Some may be impossible to completely repair from a functional standpoint and benefit from corporal reconstruction with placement of penile prostheses as adults. Uropathy remains a significant problem. Appel and colleagues (4) noted that 19 of 31 patients with scaphoid megalourethra ultimately developed azotemia or had died from renal failure, as did 7 of 10 with fusiforme megalourethra.

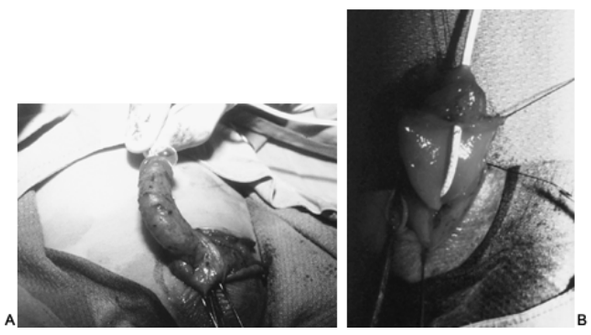

FIGURE 50B.21. Operative view of scaphoid megalourethra. **A:** Before opening urethra. **B:** With urethra laid open.

URETHRAL DUPLICATION

Another rare set of urethral anomalies is duplication. Johnson (86) suggested that faulty fusion of the genital ridge and urethral fold could result in two separate channels, and Lowsley (106) proposed persistence of the urogenital plate during infolding of the genital ridge as an explanation. Considering the many different anatomic variants, there is probably no common embryologic pathway to explain all findings of urethral duplication. Equally confusing have been classification schemes that have come forth for these anomalies. The wide variety of anatomic variations prohibits simple classification and easy division into specific categories (31,153). Simple, unique descriptions of each lesion as used by Effmann and

colleagues (46) based on the plane of duplication, the dominant urethra, and the position of the meatus are useful (Fig. 50B.22).

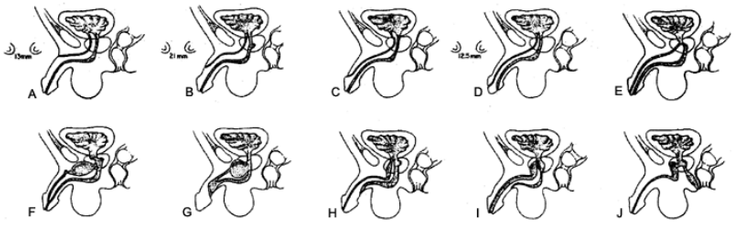

FIGURE 50B.22. A–J: Variations of presentation for urethral duplication in the sagittal plane. Note in each of these drawings that the ventrally positioned channel is depicted in the central region of the prostate, indicating that it is the more normal urethra. (From Colodny A. Urethral lesions in infants and children. In: Gillenwater JY, Grayhack JT, Howards SS, et al, eds. *Adult and pediatric urology,* ed 2. St. Louis: Mosby, 1991, with permission.)

Urethral duplication can occur with complete duplication of the phallus or urinary bladder as a more severe abnormality. Most duplications occur in the sagittal plane with a single phallus. When one is found above the other in this setting, the ventral one is virtually always the dominant urethra. Woodhouse and Williams (153) described sagittal duplication with the dominant, ventral urethra opening in an orthotopic position on the glans beneath a secondary epispadiac urethra. Sagittal duplication can also occur with the dominant urethra exiting in a hypospadiac position and the accessory urethra in the orthotopic position. Many of the nondominant dorsal urethras end blindly short of the bladder. If, however, they do reach the bladder, the child is often incontinent from the accessory channel. The dominant, ventral urethra typically has a normal path through the sphincter mechanisms and remains continent. In those cases associated with an epispadiac meatus, a widened symphysis

pubis may be found, suggesting a relationship to the exstrophy–epispadias complex (19,134).

In those patients with sagittal duplication and the dominant urethra in an abnormally ventral location, the anomaly can be complete or partial, in which case the urethra bifurcates distal to the bladder neck. The dominant, ventral meatus may be found anywhere along the penile shaft with the most severe position being that of a meatus located at the anterior anal verge (Fig. 50B.23). Despite that very abnormal location, the dominant urethra for urinary flow again is usually the ventral one, and the dorsal urethra is usually narrowed and inelastic (Fig. 50B.24).

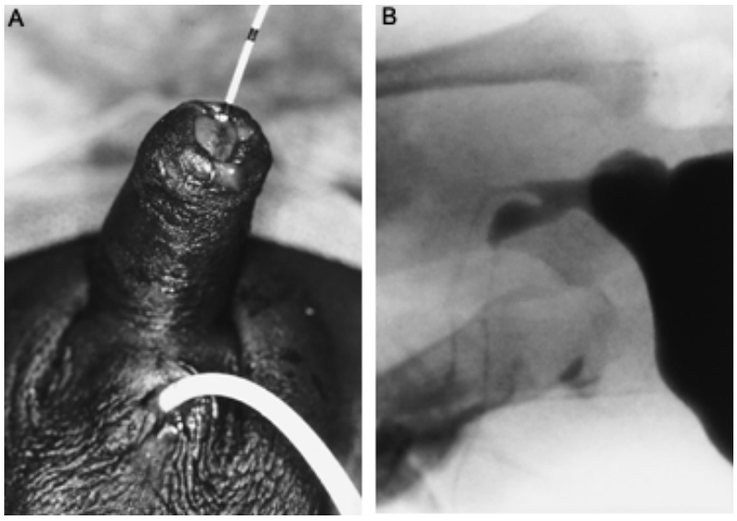

FIGURE 50B.23. Duplicated urethra. **B:** VCUG of complete duplication. (Courtesy of John Wiener, M.D., Duke University Medical Center.)

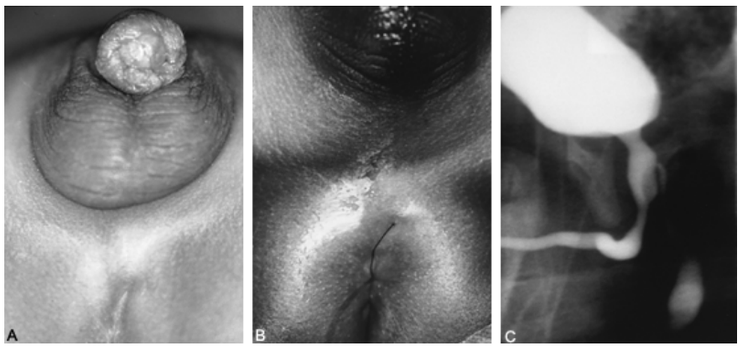

FIGURE 50B.24. A: Duplicated urethra. **B:** Anterior and margin. **C:** Urethrogram of duplicated urethra with unusual dominant dorsal urethra. (Courtesy of John Wiener, M.D., Duke University Medical Center.)

Management of the urethral duplication depends on the anatomy of each particular anomaly. The anatomy can usually be well defined on voiding cystourethrography, which allows preoperative planning for correction. Endoscopy

at the time of reconstruction may occasionally be necessary to completely understand the lesion. If the problem is noted because of minor splitting of the urinary stream during voiding, repair rarely may not be necessary (72). Such consideration is typically only appropriate for those patients with both meatuses immediately adjacent to each other, and even those patients may benefit from a simple meatoplasty to combine both openings as one. Complexity of the repair increases as the two openings diverge, especially if the dominant ventral meatus is very proximal. In that situation, the ventral perineal urethra usually must be mobilized away from the rectum to a more orthotopic position and the remainder of the urethra reconstructed with a variety of urethroplasty techniques. A complete prepuce is useful when present. Obviously, patients should not undergo neonatal circumcision if the anomaly is noted. Mucosal grafts may be necessary in some patients having undergone prior circumcision or surgery. They also may be necessary for some patients in whom the prepucial skin is not adequate in length. With the aggressive dissection needed for reconstruction of the ventral urethra, exposure for excision of the accessory, dorsal urethra is usually good. That structure may also be anastomosed to the ventral urethra proximally. Passerine-Glazel and colleagues (118) have described gradual serial dilation of the dorsal urethra to render it useful for voiding. We would prefer mobilization and reconstruction of the dominant urethra in most cases.

URETHRAL POLYPS

Urethral polyps are another unusual anomaly of the male urethra. They may be congenital in nature but have also been reported in adults, suggesting that they can be acquired or that they may slowly grow until large enough to cause symptoms (119) (Fig. 50B.25). Polyps most commonly arise from the verumontanum and are typically covered with transitional epithelium over a fibromuscular core. Arteaga and associates (5) in 1993 reported on 339 cases. The presenting symptoms for most patients included urinary retention, straining to void, urgency, stranguria, and hematuria (123). Voiding cystourethrography often shows a filling defect in the urethra that may vary in location (39). The diagnosis is then confirmed by cystoscopy, at which time treatment consists of transurethral excision (60).

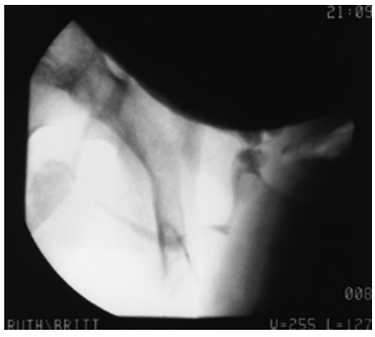

FIGURE 50B.25. Urethral polyp.

ABNORMALITIES OF COWPER'S GLANDS AND DUCTS

Cowper's glands are paired structures found along the posterolateral aspect of the proximal urethra. The main glands lie within the urogenital diaphragm, and accessory glands are located more distally along the bulbous urethra. The ducts from these paired organs travel medially and posteriorly from the gland to empty side-by-side in the bulbar urethra (Fig. 50B.26). Cysts, possibly developing due to obstruction of the orifices, may be seen as a filling defect along the floor of the bulbar urethra on voiding cystourethrography. These cysts were termed *syringoceles* by Maizels and colleagues (108) (Fig. 50B.27). Spontaneous rupture of these cysts may occur, resulting in a diverticular structure in that area or retrograde filling of a prominent duct. Many of the abnormalities of Cowper's glands and ducts may cause terminal hematuria, bloody spotting at the meatus, postvoid dribbling, or obstructive symptoms. Most Cowper's duct anomalies are discovered as minor findings on voiding cystourethrography done for urinary tract infection or other reasons and are probably asymptomatic.

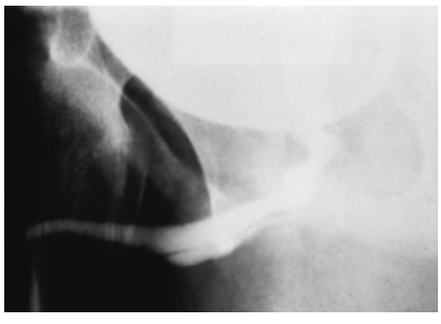

FIGURE 50B.26. VCUG of Cowper's duct.

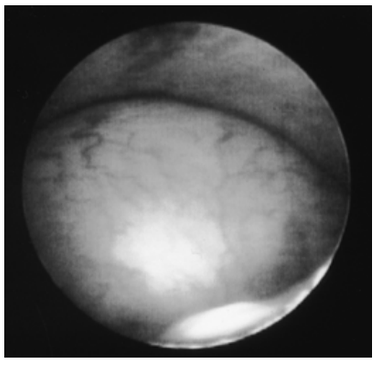

FIGURE 50B.27. Endoscopic view of Cowper's cyst.

Surgical treatment is reserved for those patients who are symptomatic. Transurethral unroofing of a cyst typically is adequate, although one should take care not to leave a distal obstructing lip, which may act as a valve. Open resection by a perineal approach has been occasionally performed for a massively enlarged cyst producing obstruction (15).

VALVE OF GUÉRIN (LACUNA MAGNA)

This very distal anomaly was first described by Guérin in 1864. It is a diverticulum of the dorsal urethra (lacuna magna) that is partially separated from the glanular urethra by a septum. Embryologically, it is thought to result from abnormal fusion of the very distal urethra formed from canalization of ectodermal ingrowth in the proximal urethra developing from urethral folds. Sommer and Stephens (138) discovered the anomaly in 10 of 20 routine postmortem examinations, suggesting that mild forms may be asymptomatic or a variant of normal. Symptomatic presentation is rare; Friedman and King (58) noted 10 symptomatic cases over a 7-year period. The most common presenting complaints in their experience were blood spotting in the underwear, hematospermia, and hematuria.

The diagnosis of such an anomaly is elusive unless one is looking carefully for it. The valve of Guérin may be noted on a VCUG if careful examination of the distal urethra is performed. The lacuna magna may mimic a small drop of contrast at the meatus (Fig. 50B.28). Even at endoscopy, the cystoscope will pass the lesion immediately with insertion without careful placement. Gentle probing of the dorsal aspect of the meatus may be useful in patients suspected of the anomaly. Once identified, the valve can be easily crushed and incised with the scissors.

FIGURE 50B.28. VCUG of a valve of Guérin. This appearance can be mimicked by a drop of contrast at the meatus.

MEATAL STENOSIS

Meatal stenosis is a common, usually acquired, abnormality of the male urethra. It is most often found in boys after newborn circumcision. Irritation of the meatus in the months or years following that procedure may eventually lead to narrowing of the meatus. The lesion is usually identified after toilet training when the urinary stream is easier to observe. The classic sign of meatal stenosis is a very narrow urinary stream that is upwardly deflected. In routine cases, not enough obstruction is created to cause renal or bladder effects or urinary tract infection. We have seen rare boys with meatal stenosis and a history of bloody spotting or intermittent dysuria who have responded well to meatotomy. Anecdotally, occasional boys have had resolution of enuresis with meatotomy as well.

One should be careful not to overdiagnose meatal stenosis based on the visual appearance of the meatus. Although appearing nearly pinpoint, the meatus may sometimes be very elastic at voiding. Meatal calibration or simple observation of voiding is typically diagnostic. By 18 years of age, 90% of boys have a meatal caliber of 12 Fr or larger. Treatment consists of a meatotomy. This historically required a brief anesthetic procedure. It is now well tolerated as an office procedure with the use of anesthetic creams. Acquired meatal stenosis after surgical reconstruction of the urethra, particularly following hypospadias repair, can result in much more significant obstruction and sequelae.

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51

TOOLS OF RECONSTRUCTION

Contents

51A RECONSTRUCTION OF THE URINARY TRACT: GENERAL PRINCIPLES

Michael E. Mitchell

Part of "51 - TOOLS OF RECONSTRUCTION "

M.E. Mitchell: Department of Urology, University of Washington; Division of Pediatric Urology, Children's Hospital and Regional Medical Center, Seattle, WA 98105.

The child with significant anatomic and/or functional abnormality of the urinary tract can present a major challenge. The spectrum of potential abnormalities can be broad and can encompass many anatomic and physiologic variations. Furthermore, it rapidly becomes obvious to one involved in treating such patients that not only does the understanding of these complex problems change with time but so do the available modalities for therapy. A century and a half ago, ureterosigmoidostomy was performed in a young boy with exstrophy, initiating the concept of a surgical approach to a problem that had been believed to be nonapproachable. Fifty years ago, urinary diversion was the most appropriate treatment for children with exstrophy, severe urethral valves, and myelodysplasia; however, it now is rarely used as a primary treatment for these conditions. The early part of the twentieth century ushered in more aggressive surgical approaches to a variety of urologic malformations in children. At that time, the primary therapy, urinary diversion, certainly salvaged renal function and the lives of many children. However, it was Hendren (16), among others, who initiated the next phase of treatment. He applied recently developed techniques of reimplantation of the ureter to prevent reflux (35), developed techniques for megaureter repair, and used newer endoscopic technology with fiberoptics primarily to destroy urethral valves (13,14). The result was what he termed *undiversion* (15). In fact, with his reconstruction of the urinary tract, he actually was correcting the primary problem such that the urinary diversion could be reversed and the previously nonfunctional urinary tract could function more appropriately. The net result of undiversion was that it became obvious that primary diversion could be and should be avoided. Care should focus on primary repair rather than diversion and undiversion. Hence, undiversion really paved the way for primary reconstruction. The real proof of the success of undiversion is that it rarely is necessary anymore. These facts lead us to the questions, where are we in this progression of understanding and technology, and what are some of the important lessons learned?

Lessons Learned

Patient Assessment

Although a certain patient may carry a well-recognized diagnosis (e.g., cloaca, cloacal exstrophy, exstrophy, epispadias, spina bifida, urethral valves, caudal regression, bilateral ectopia), each patient must be considered as unique and in the total context. Management and care must be tailored according to individual needs. How can the needs of a particular patient best be met to achieve an endpoint of “good health” and to maximize social acceptability? The following are the general goals of reconstruction:

- Protect renal function.
- Minimize infection.
- Maximize social acceptability (dependable urine and bowel control).

For some patients, normal voiding may be a real possibility. However, when not possible, intermittent catheterization may be the next best alternative and may result in a dry patient. However, this requires manual dexterity and commitment on the part of the patient and patient support systems. The limitations of the patient, family, and support systems must be clearly understood before reconstruction can be considered. For example, an orthotopic catheterizable stoma is ideal in the young female with good dexterity and mobility who is dedicated to making it work and is concerned about her body image. Unfortunately, the same form of continent diversion is a potential disaster in an obese, wheelchair-bound female patient with poor upper extremity dexterity. However, a catheterizable, continent channel constructed between the bladder and umbilicus may work ideally in such a patient. An extreme example is a teenager with myelodysplasia who refuses to actively participate in self-care. Urinary reconstruction that depends on frequent self-catheterization could result in significant risk of bladder rupture in such a patient. This patient may be best treated with pads or urinary diversion into an appliance.

A clear, individualized plan for reconstruction and care must be formulated to fit the particular clinical situation. Before any surgery, this plan is presented to the patient and family. All involved in the patient's care must make a clear commitment to the anticipated postreconstruction course of therapy. Without such a commitment, reconstruction should not be considered. The “technically best reconstruction in the world” is a failure if the patient and/or support systems cannot or will not comply with therapeutic plans.

The concept of support systems goes far beyond the immediate family. It includes school systems, local physicians, friends, institutional personnel, and the like. If a patient is either very young or incapable of self-care, a care support system must be in place to ensure maintenance of an adequate treatment plan. A complex patient with little or no dependable support system may be best treated with a passive form of therapy (i.e., diversion or pads) rather than risk loss of renal function or sepsis because someone “forgot” to catheterize or administer medications. As the surgeon, one should know the home environment of the patient considered for reconstruction. Unfortunately, this is all too often ignored in a busy clinical setting. A good surgeon knows and understands the surgery, a great surgeon also knows the patient.

Age and Development

The age of the patient can be a significant consideration. In very young children, major reconstruction as described by Hendren (15) may not always be appropriate. For example, it is now clear that it is not necessary to reconstruct dilated ureters in infants with valves or significant reflux. Many of these patients will improve significantly in the first year or two of life (4). Furthermore, megaureter repair in the very young child can result in obstruction (34). Similarly, ureteropelvic junction obstruction may improve with time in some patients (44). On the other hand, it progresses in some young patients. It may be impossible to perform intermittent catheterization frequently enough in the infant with myelodysplasia to protect the upper tracts, but in the older patient this is no problem. A primary difference between children and adults is that children, particularly the very young, are continually and rapidly changing. For example, it is well known that, in the urinary tract, the kidney does its major growth and maturational development in the first few years of life (see Chapter 47). It is becoming more apparent that the bladder also changes from its structure and physiology *in utero* to a completely different structure and physiology after potty training. Therefore strategy of treatment and follow-up must be adjusted to accommodate this potential change. This is true of both prereconstruction and postreconstruction patients. Stability in follow-up may be defined in terms of weeks and months, not years. The value of following the growth curves of these patients cannot be overemphasized. In many cases, a flattening in the patient's growth curve offers the first clue to difficulties in the young child. In fact, considering the many expensive tests used in the chronic care of children with significant urologic problems, the simple monitoring of height and weight often is the most useful in assessing the general status of the patient.

Children and young adults present an emotional and developmental “moving target” for the physician. Very young children heal faster than older children but may have a greater tendency to have urinary obstruction from edema. Therefore double-J stents may be useful in reimplantation of the ureter or pyeloplasty in neonates but may be used rarely in teenagers. It is possible to perform a pyeloplasty as a 24-hour admission in a 6-month-old, but not in a 10-year-old.

Emotional development and maturity of the patient significantly affect management planning. For example, it rarely is appropriate to anticipate that a 4-year-old child will actively participate in self-catheterization. However, most 8-year-old children will perform self-catheterization. Even so, there are many 8-year-old patients who can self-catheterize but who need to be continually reminded (this may go for teenagers as well), and there are some 8-year-old children who cannot catheterize themselves. Many young children and teenagers are capable of self-care but choose not to follow treatment plans. Caregivers often overlook this simple formulation in trying to understand why a patient is not doing as well as anticipated. Sometimes, what a patient says is happening is actually what the patient wants to be happening. Unfortunately, this may not be what is really

going on. A patient may inform a physician that all is going well, when actually this is not the case at all (this is why surgeons have difficulty getting accurate follow-up data from their patients).

Management of urinary and bowel incontinence seems to be particularly sensitive to these patient variables. It is a general rule of thumb that if a patient, regardless of chronologic age and maturity, does not care if he or she is wet (or soiled), treatment for incontinence will fail despite the wishes of family and physicians. Surgery for incontinence is based firmly on the maturity and commitment of the patient. This clearly changes with patient age, depending on school, cohort, and sibling pressures. Simply stated, the same procedure for incontinence may fail in a 6-year-old but be successful in an 8-year-old, with patient maturity being the main variable. Unfortunately, the failure at age 6 may jeopardize the treatment at age 8. Patient maturity and commitment go a long way toward securing a successful outcome in reconstruction surgery, particularly for urinary continence. These issues are as important as any preoperative study and can result in failure in the face of “perfect” surgery. Unfortunately, the assessment of maturity and commitment are difficult and presently not precise. Emotional testing instruments are available, but these are used in only the more complex and obvious situations (e.g., autism, developmental delay, severe illness) (24,40). Usually, however, the judgment on appropriate timing and type of procedure is left to the surgeon's assessment of the information available, such as direct observations in the preoperative period, interviews with parents and patients, and input from other professionals involved in the patient's care. The key questions to be answered are listed in Table 51A.1 .

Information	Key Questions to Be Answered
History	
Support systems	Are support systems in place? Are they committed to therapy as outlined?
Patient age and maturity	Will the patient be committed to and capable of following therapeutic plans?
Physical	
General growth and development	What is the general health of patient? Is there evidence of significant metabolic disease? What is the potential for change?
Neurologic and physical examination	Will patient be able to care for himself or herself? Can patient get to the toilet? Can patient do CIC?
	What are the specific needs of this patient?

CIC, clean intermittent catheterization.

TABLE 51A.1. ASSESSING THE CHILD FOR URINARY RECONSTRUCTION OR CONTINENCE SURGERY

History and physical examination of the patient should be thorough, with particular attention to findings that may have specific bearing on potential therapeutic options. Because of the broad spectrum of possible anatomic and physiologic abnormalities, only general concepts will be covered here. Broken down into the simplest terms, only a few questions need to be clearly answered.

1. What is the health of the patient and is there evidence of significant metabolic disease? What is the potential for change?

   Patient height, weight, vital signs, and general appearance often are the most direct method of answering this question. A history of polydipsia and polyuria may give early indication of significant renal impairment with concentrating defect. Polyuria complicates any reconstruction because the urine volume load must be accounted for in planning any continent reconstruction. This is particularly important in previously diverted patients who can produce large urine volumes. This can be overlooked because, usually, little attention is directed to urine volumes collected in external collection devices. Because children are in a constant state of change, correction of a pathology can have a major long-term positive effect; for example, when a chronic infection in the urinary tract is corrected. Another example would be urinary undiversion or reconstruction in a renal failure patient planned in preparation for renal transplant. Native renal nephrectomy may be considered if a significant renal concentrating defect would potentially contribute to patient dehydration after transplantation.

2. Will the patient be able to care for himself or herself? Can the patient get to the toilet? Can the patient possibly perform self-catheterization?

   Commitment to care has been mentioned previously; however, regardless of desire, realistic assessment of the patient's physical ability to perform self-care should be clearly and accurately assessed. It does not make sense to create a catheterizable stoma if the patient cannot perform self-catheterization and no support system is available to provide this aspect of care.

3. What are the specific needs of the patient?

   Every patient is different and unique, and the specific potential needs of the individual patient need to be clearly delineated. What is good for one patient may be totally inappropriate for the next. The caring physician must demonstrate diagnostic acumen to define these unique needs, and the flexibility and ingenuity to respond appropriately. These skills need to go far beyond the successful planning and execution of the surgical procedure.

   Broken down to the simplest denominator, a physician needs to know whether the patient has the mental capacity to comprehend, the physical ability to enact, and the will to carry out therapeutic plans.

STUDIES

The broad spectrum of potential pathologies makes required studies somewhat unique to the individual patient. In general, the studies required for urinary reconstruction need to define the anatomy and physiology of the entire genitourinary tract and other systems that may affect the success of the reconstruction. Most of these are outlined in Table 51A.2 and have been specifically mentioned elsewhere in this text.

Area of Interest	Useful Studies
1. Anatomy	PE, KUB, ultrasound with contrast (IVP, VCUG, retrograde, antegrade, fluoroscopy, CT), MRI, cystoscopy
2. Physiology	
a. Kidney	Chemistries (CBC, electrolytes, BUN, creatinine, calcium, phosphorus), DMSA, MAG-3 with furosemide, 24-hour urine for creatinine clearance and volume
b. Ureter, bladder, urethra	Contrast (antegrade perfusion study, IVP, urodynamics with fluoroscopy)
3. Other	
a. Pelvis	KUB, CT pelvis
b. Spine/neurology	Ultrasound (newborns), KUB, MRI
c. Gastrointestinal	Chemistries (vitamin B_{12}, folate, electrolytes), contrast (upper GI study)
d. Genital (internal)	Ultrasound, MRI, CT contrast (CT, genitogram), endoscopy

BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; DMSA, dimercaptosuccinic acid (scintigraphy); GI, gastrointestinal; IVP, intravenous pyelogram; KUB, abdominal radiograph; MAG-3, mercaptotriglycylglycine; MRI, magnetic resonance imaging; PE, physical examination; VCUG, voiding cystourethrogram.

TABLE 51A.2. STUDIES OFTEN REQUIRED FOR URINARY RECONSTRUCTION IN CHILDREN

Evaluation of the Anatomy of the Urinary Tract

The anatomy of the urinary tract can be assessed with a number of studies as outlined in Table 51A.2 . However, a detailed and accurate surgical history often provides more information than many expensive studies. Knowledge of what was previously done (surgeries and other therapies) and why may be critical to the ultimate success or failure of a planned complex procedure. Physical examination can be of great help as well. For example, observation of an abdominal mass may indicate ureteral or bladder outlet obstruction or possibly a problem with bowel elimination. Abdominal scars and stomas should correlate with the patient's history. Absence of abdominal muscles may indicate prune-belly syndrome and inherent problem with the structure of the ureters, bladder, and urethra. Imperforate anus may be associated with reflux and other urinary abnormalities. A single or absent perineal opening is consistent with a urogenital sinus or cloaca malformation and indicates a broad spectrum of potential malformation of the bladder, urethra, genitalia, rectum, and spine. Components of the vertebral, anal, cardiac, tracheal, esophageal, renal, and limb (VACTERL) association may implicate urinary abnormality. Epispadias may indicate significant bladder neck malfunction. Spinal malformation, sacral dimple, or hair patch may indicate potential for neurogenic bladder dysfunction.

Radiologic evaluation minimally includes a plain radiograph of the abdomen (KUB); renal; and bladder ultrasound and contrast studies to clearly define the entire urinary tract. For patients with previous surgery, diversion, infection history, or ureteral dilation, it often is helpful to study the ureters with fluoroscopy to define the exact anatomy of the ureters and the presence or absence of peristalsis. A voiding cystourethrogram (VCUG) will define the presence and grade of vesicoureteral reflux, reveal the nature of the bladder wall and bladder neck, and may help define the presence or absence of bladder outflow obstruction. In children, magnetic resonance imaging (MRI) or computed tomography (CT) rarely are necessary. However, they may be indicated in cases of poor renal function, question of calculus, or ureteral or renal ectopia.

Cystoscopy with anesthesia remains the gold standard for defining the anatomy of the pelvic structures that open to the perineum (16). Complex cases often require cystoscopy as an isolated diagnostic procedure before the definitive surgery. At the time of this initial diagnostic study, a suprapubic tube may be placed to facilitate urodynamic evaluation. It should never be presumed that radiology alone can totally define the anatomy despite the skill of the radiologist and the use of advanced technology.

Physiology of the upper and lower urinary tracts also should be evaluated carefully before reconstruction surgery. Kidney function is evaluated by standard chemistries. Debate exists in consideration of the timing of reconstruction or undiversion in the face of marginal renal function. It is now generally held that it is better to perform reconstruction before renal transplant to facilitate normalization of the urinary tract before transplantation and immunosuppression (11,26). Many children with obstructive uropathy (e.g., ureterocele, urethral valves, cloaca, ureteral ectopia) will have normal or only slightly elevated serum creatinine in the face of a significant concentrating defect. This may be suspected with slightly elevated serum blood urea nitrogen (BUN), resulting from dehydration. This is important to

realize before reconstruction, because the volume of urinary output in such patients can be quite prodigious and must be included in the calculations of functional bladder capacity. Twenty-four-hour urine collection for volume and clearance and urinary specific gravity will help define renal function and inability to concentrate urine.

The physiology of the ureters, bladder, and urethra can be defined with urodynamic evaluation. In the case of the ureters, antegrade perfusion with pressure monitoring (Whitaker test, or fixed pressure perfusion) and fluoroscopy can define peristaltic potential and possible obstruction (45,46,48). Mercaptotriglycylglycine (MAG-III) scan with furosemide (Lasix) washout also can be used. The specifics of these studies are covered elsewhere; however, observation of the presence or absence of ureteral peristalsis is crucial in planning ureteral repair. A peristaltic ureter usually can be tapered with realistic anticipation that it will ultimately function as a normal ureter. Conversely, an aperistaltic ureter usually indicates significant ureteral pathology that probably will *not* change with reconstruction; such a ureter must be considered to be a "lead pipe." It will function as a fixed tube only, with the energy for flow coming from the pressure differential of each end of the ureter (the kidney). Any distal ureteral resistance (i.e., reimplantation or poor bladder dynamics) will result in relative obstruction of the kidney. This is why reflux megaureters with history of infection and previous surgery (aperistaltic) seem to be more difficult to successfully reconstruct than obstructed megaureters (37).

The dynamic assessment of the lower urinary tract is the foundation of a successful reconstruction/undiversion. The problem is that the studies are difficult to perform in many patients because of patient factors (age and poor cooperation) and physiology (massive reflux or diverted urinary tract). The needs of each patient are determined by all information available; usually, the projected bladder capacity and need for construction of a catheterizable stoma are based on history as well as physical and urodynamic study. Hourly urine output is calculated based on the 24-hour collection. Functional bladder capacity can be estimated by assuming bladder emptying every 4 hours (catheterization more often than every 4 hours usually is inconvenient and not realistic). Therefore the approximate projected need for bladder volume is as follows:

24-hour urine volume ÷ 6 = Anticipated bladder capacity

For example, if a patient has a 24-hour urine volume of 2,400 mL, his or her 4-hour capacity is 400 mL. If the patient does not get up at night, he or she needs an 800-mL bladder to make it through. Furthermore, if from urodynamics, the bladder pressures are calculated to be more than 30 cm H_2O for a significant proportion of the time (based on anticipated urine volume), the patient is at risk to develop hydronephrosis (2,18).

As shown in the hypothetic study in Fig. 51A.1, if the calculated 4-hour volume is A, the patient has appropriate bladder volume and capacity, and reconstruction does not need to include bladder augmentation. However, with the same pressure–volume relationship, if the 4-hour urine volume is B, there may be inadequate volume/compliance to properly protect the upper tracts, particularly if the patient is not waking to empty the bladder at night. In such a patient, if reconstruction were anticipated without accommodation for this physiology, the upper tracts may be put at risk and urinary continence may be a problem.

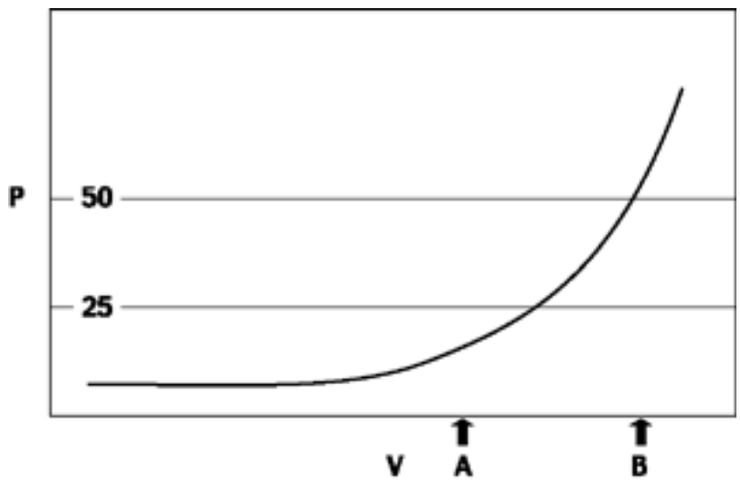

FIGURE 51A.1. Bladder pressure volume relationship. **A:** Average predicted 4-hour urine volume for patient A. **B:** Average predicted 4-hour urine volume for patient B. P, pressure; V, volume.

Other studies may relate to defining the anatomy and physiology of the pelvis, spine, gastrointestinal (GI) tract, and genital system, any or all of which could have direct or indirect impact on urinary reconstruction. However, because of the broad spectrum of pathology possible, the evaluation of a given patient must be individualized.

For patients with exstrophy complex, caudal regression, cloaca, and pelvic tumors, detailed evaluation of the pelvis may be necessary, including three-dimensional (3D) CT scan. The size of the pelvis may be relevant in considering physical space for a bladder or continent reservoir. This may be particularly important in the young patient after radiation therapy, or severe pelvic flattening in the patient with cloacal exstrophy. A wide symphyseal diastasis may indicate the need for pelvic osteotomy, particularly if reconstruction for continence is contemplated (5,23,27,33,39).

Many patients with significant urinary malformation also are at risk for spinal malformation. This is seen with ectopia of the kidneys, imperforate anus, cloacal malformations, and VACTERL complex (8,17,25,41,43). The spine can be evaluated with a variety of studies, including ultrasound in newborns, spine films, and MRI. MRI is useful in the evaluation of patients for cord tethering when clinical symptoms suggest this diagnosis.

Many urinary reconstructions require an intraabdominal approach and use of bowel; therefore assessment of the GI

tract is very important. Minimally, a KUB should be obtained with an abdominal ultrasound. Upper and lower GI series may be indicated, particularly in the patient with previous surgeries or history of intestinal malabsorption. A nutritional evaluation also may be considered in some patients, particularly if poor growth and development is observed, which may relate to chronic illness, renal or hepatic failure, chronic diarrhea, or ileostomy and short gut syndrome. This information may be critical in planning the surgical procedure and postoperative management of the patient. For example, small bowel resection may be contraindicated in a patient with cloacal exstrophy and an ileostomy, but gastrocystoplasty may be appropriate.

Evaluation of genital malformations beyond careful physical examination includes contrast studies of every available orifice (cystogram; vaginal and rectal study; or urogenital sinus study or cloacal study). MRI or CT can be used to augment the pelvic ultrasound to better define ureteral and müllerian duct structures. Endoscopy under anesthesia usually is the most dependable method for elucidating the potentially complex anatomy of some of these patients.

Preparation of the Patient and the Surgeon

With the current efforts to reduce hospitalization time, early hospitalization for bowel preparation and final assessment is a luxury that few medical systems can afford. This is unfortunate, because day-of-surgery admission for procedures that may take 12 to 14 hours sometimes is associated with increased risk from inadequate bowel preparation, superficial evaluation by anesthesia, and even inadequate information availability for the surgical team (patients forget to bring the outside studies). Therefore most institutions now will accept admission the day before a major procedure. However, in many cases, we see the patient the day before, in clinic, for reevaluation by the surgical team and anesthesiologist. Outpatient bowel preparations are inconsistent and seem to depend totally on patient and support systems. Patients in whom bowel preparation is critical should be admitted early. The type of bowel preparation is the surgeon's preference. The authors use a mechanical preparation only.

The Surgeon and the Operative Team

Other than the surgeon and his or her operative assistant(s), the team is completed by the following persons:

1. *Anesthesiologists* with extensive experience with children and prolonged operative procedures are the keystone to the operative team. Without excellence in anesthesia support, even the most skillful surgeon cannot and should not attempt a major urinary reconstruction in children.
2. A *scrub nurse* and a *circulator* who have extensive experience with pediatric urologic surgical techniques and procedures are important members of the team. To a large degree, the efficiency of the procedure resides with them. In a prolonged case, inexperience in this portion of the team can add hours to the operating time with needless frustration and tension. Ideally, the team should be composed of people with long-term commitment and extensive experience with these procedures.
3. A *hospital facility* that is equipped to handle complex surgeries and postoperative care and that is staffed with a full complement of pediatric specialties including pediatric neurosurgery, pediatric surgery, pediatric plastic surgery, pediatric orthopedic surgery, pediatric intensive care, infectious disease, pulmonology, gastroenterology, and rehabilitation medicine is necessary for a successful surgery.

The surgeon, who is in charge of this team, must approach challenging cases with as much information as possible (see previous discussion) and with a surgical plan that includes options for dealing with almost every anticipated complexity. The key is to always have an alternative plan—just in case. Still, the need for ingenuity and inventiveness at the time of the surgical procedure is always present.

COMPLEX RECONSTRUCTIONS

Urinary reconstructions, such as urinary undiversion, in the child can be complex in evaluation of the patient, in planning, and in execution (16). Each procedure is unique and depends on multiple variables, some of which are not very predictable (30,31 and 32,38). It sometimes is easier to consider the previously mentioned *clinical objectives:*

1. Protect renal function.
2. Minimize infection.
3. Maximize social acceptability.

With these in mind, the *surgical objectives* would be to achieve the following:

1. Unidirectional low-pressure flow of urine from the kidney to the bladder
2. A large, compliant bladder
3. Dependable urinary continence (Fig. 51A.2).

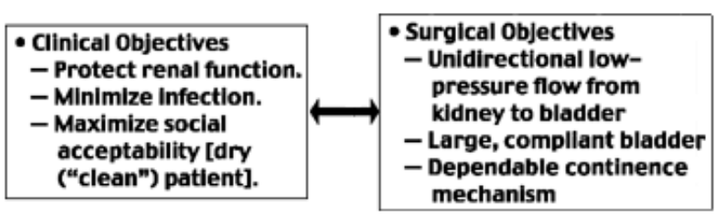

FIGURE 51A.2. Clinical and surgical objectives in urinary reconstruction in children.

Almost every urinary reconstruction can be broken down into multiple associated techniques that focus on achieving the aforementioned surgical objectives. The remainder of

this chapter is dedicated to a few of the currently used procedures and techniques believed to maximize potential for success in achieving these objectives. These certainly will change as the concepts and understanding of the physiology and pathophysiology of the developing urinary tract grows.

Unidirectional low-pressure flow from the kidney to the bladder is covered in the section on ureteral reimplantation, megaureter, and ureteroureterostomy. The urodynamic and radiologic evaluation also is covered elsewhere in this text. One important concept is that ureters can vary in potential for peristaltic function and potential for function. Certain ureters, classically those with associated urethral valves and/or reflux with recurrent infection, can have little potential for peristalsis. This seems to result from potentially irreversible change in the ureter with replacement of the ureteral muscularis with collagen. The net effect is that such a megaureter, when tapered and reimplanted, may become functionally obstructed regardless of the surgical procedure employed (7,21,22,28,37,42). Such ureters can be best considered “lead pipes”—conduits for urine whose flow depends on the pressure gradient. However, extensive tapering may improve the flow because wall tension for a given pressure is reduced so that minimal contraction potential is maximized (12). In the patient with prune-belly syndrome, the distal ureter can behave in such a manner while the proximal ureter functions more normally; therefore the tendency to remove as much of the distal ureter as possible. The appropriate timing for ureteral surgery to maximize the potential for healing and function is not known. However, it is the general impression of those with extensive experience in pediatric urinary reconstruction that the earlier the repair with restoration of “normal” physiology, the better the potential to achieve a normal ureter (9,13,47). Often, the repair includes correction of reflux and reduction of bladder pressure (29).

If construction of a large, compliant bladder is the cornerstone of urinary reconstruction, then clean intermittent catheterization (CIC) is the keystone. There are many procedures for the creation of a large, compliant bladder; however, as mentioned previously, the critical issue is not only the characteristics of the constructed bladder (reservoir) but the regularity and completeness of emptying. Unfortunately, this so often is limited by patient factors that are poorly understood before surgery, because the patient (and/or support systems) could not adequately comply with the plan of therapy (i.e., regular bladder emptying). It sometimes is better not to reconstruct, not to undivert, but rather to maintain some patients with passive modes of therapy (in pads or diversion), particularly if preoperative assessment raises questions about commitment or capability of the patient and support systems. In this author's opinion, this is the single, most critical issue of complex urinary reconstruction in children. Failures often come from nontechnical factors; unfortunately, the technical aspects tend to be discussed most often. Many options exist in bladder reconstruction. The current trend seems to be focused on early treatment, permitting the bladder to heal and function normally, thus avoiding the need for augmentation. This seems to be true in exstrophy, in patients with valves, and even in patients with congenital neurogenic bladder dysfunction (1,3,4,6,10,19,20,29,36,47,49). In fact, the need for augmentation may be interpreted, in the near future, as a failure in early treatment of the primary problem.

The cost of urinary continence can be high in terms of risk and heartache to the patient and family. It depends on multiple factors that ultimately determine a delicate balance between bladder function and urethral function (Fig. 51A.3). The surgical procedures described to increase urethral resistance to achieve continence (dryness) depend on the compliance and capacity of the bladder. However, the foundation of surgery for continence is CIC (Fig. 51A.3). Urinary continence with voiding to completion is certainly an objective of many reconstructions, but often is a difficult endpoint to achieve. In fact, many procedures for dryness totally depend on CIC, the Kropp procedure, the Mitrofanoff procedures, and almost all continent reservoirs, to mention a few. Furthermore, even if voiding is anticipated, as in a Young-Dees-Leadbetter procedure or with placement of an artificial sphincter, the potential for CIC still must be secure (i.e., with either a catheterizable urethra or stoma). CIC represents the single greatest contribution to urinary continence in children, not only as a primary therapy but also by facilitating potential for reconstruction in patients who previously could be treated safely only with pads or urinary diversion. Therefore the commitment to CIC by the patient and family/support system before surgery must be absolute. The only exception to this would be continent diversions based on the rectal sphincter

(i.e., ureterosigmoidostomy or the Ghoneim rectal bladder procedure).

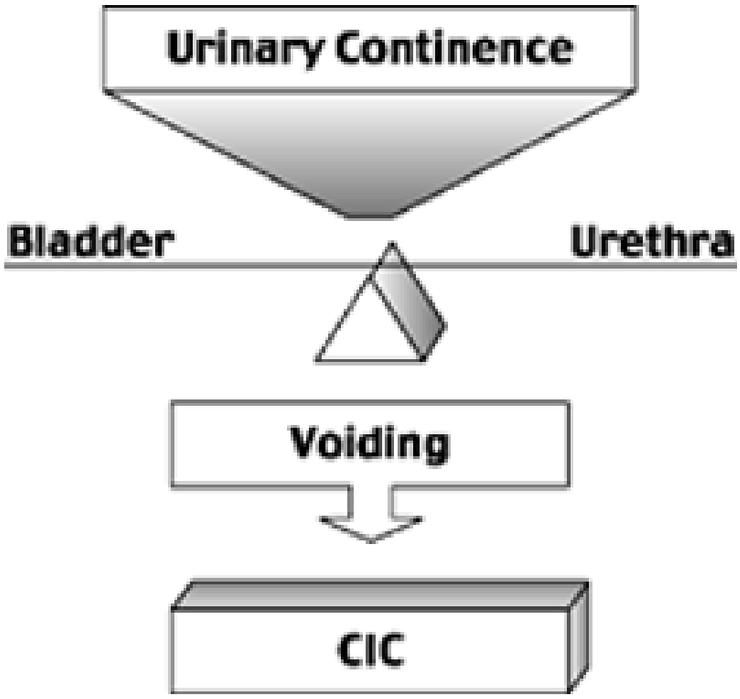

FIGURE 51A.3. Urinary continence, a delicate balance between bladder and urethral factors. Most reconstructions for continence in children are based on the potential need to use clean intermittent catheterization *(CIC).*

The potential for surgical complications from operations that involve a number of different procedures, such as ureteral reimplants with transureteroureterostomy (TUU), bladder augmentation, and bladder neck and Mitrofanoff procedures, increases with every additional procedure. Therefore the potential for complication is as shown in the following equation:

$0.90 \times 0.95 \times 0.85 \times 0.80 \times 0.85 \approx 0.49$

Even using favorable outcomes for each component, with each additional procedure the potential for complication is approximately 50%, which may be a somewhat pessimistic projection, but it does make the point that extreme care in planning and execution is necessary to achieve the anticipated results. During surgery, time should not be the critical factor. These procedures can be long and difficult and require complete concentration; therefore they should *not* be performed by a busy surgeon with a million places to go. The surgeon must be precise and meticulous. If there is any question about any aspect of a procedure during surgery, it should be *r*eperformed. An intraoperative assessment of, "that will probably be all right," often is condemnation for surgical complication or failure. Furthermore, if one is not confident in the way something looks during surgery, there is *no* confidence that the postoperative course will be smooth. Surgical exposure should be more than adequate; the flow of the operation must be orderly according to the preoperative plan. In contrast to the current trends to minimize surgery and surgical incisions, success in these cases often rests on doing more rather than less. Hendren, the father of undiversion and urinary reconstruction in children, maintains that, "The most common error in surgery is not doing enough, rather than doing too much." This author believes that this is a useful observation.

Complex urologic reconstructions such as undiversion of a previously diverted patient, repair of a cloaca, repair of a cloacal exstrophy, and primary and/or repeat repair of complex urologic malformations can be facilitated by keeping the following four stages of the procedure in mind:

1. Have a plan with multiple prioritized options.
2. Secure a wide exposure and keep all options open (do not throw anything away, do not cut any blood supply).
3. Define the anatomy completely before the repair is initiated.
4. Do a complete repair; cover all bases and satisfy all objectives.

The feeling at the conclusion of the procedure should be that this is absolutely the best job that could have been done.

In summary, complex urinary reconstruction in children is a challenge that encompasses a broad spectrum of procedures

and physiology. Every case is unique but usually can be broken down into component procedures that are well established. The patient evaluation, surgical plan, procedure, and follow-up flow naturally and are interdependent (Table 51A.3).

Phases of Urinary Reconstruction in Children	Key Questions
1. Patient evaluation History Physical Studies (e.g., radiograph, urodynamics)	1. What are the patient's special needs? Is clean intermittent catheterization (CIC) possible?
2. Surgical plan development Set goals and objectives Determine and prioritize options	2. What are the objectives? What is the surgical procedure?
3. The procedure Wide exposure, keep options open Define anatomy completely Repair completely, cover all bases	3. How can the potential for success be maximized?
4. Postoperative care Follow-up, anticipated Management of complications	4. Have goals and objectives been successfully achieved?

TABLE 51A.3. PHASES OF SUCCESSFUL URINARY RECONSTRUCTION IN CHILDREN

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51B VESICOURETERAL REFLUX SURGERY

Brent W. Snow

Patrick C. Cartwright

Part of "51 - TOOLS OF RECONSTRUCTION "

B.W. Snow: Division of Urology (Pediatric Urology), University of Utah Hospital/Primary Children's Medical Center, Salt Lake City, UT 84113.

P.C. Cartwright: Departments of Surgery and Pediatrics, University of Utah; Division of Pediatric Urology, Primary Children's Medical Center, Salt Lake City, UT 84113.

GENERAL CONSIDERATIONS

Indications for surgical correction of reflux may include (a) high-grade reflux unlikely to resolve; (b) persistent urinary infections despite prophylactic antibiotics; (c) poor compliance with prophylactic antibiotics; (d) reflux that persists in girls at puberty; (e) failure of kidney growth, presence of new kidney scars, or deterioration of renal function during observation; (f) parents highly unreliable to keep follow-up appointments; and (g) failure to thrive in young children with high-grade reflux. Indications for reimplantation are shown in Table 51B.1 .

MAJOR	MINOR
1. High-grade reflux	1. Reflux after puberty
2. Breakthrough infections	2. Failure to thrive in young child
3. Poor compliance with therapy	3. Unreliable parents
4. Poor renal growth or new scarring	

TABLE 51B.1. INDICATIONS FOR REIMPLANTATION

It probably is more accurate to say that the decision for surgery to correct reflux is based case by case and depends on multiple factors and considerations. Perhaps the most important preoperative consideration is whether reflux is primary or secondary. In the latter case, bladder dysfunction should be managed optimally before any surgical decisions are made (51). Furthermore, it is important that parents and patients are clear that correction of vesicoureteral reflux will not eliminate the potential for urinary tract infection, but that it will diminish the future risk of pyelonephritis. In the International Reflux Study, surgical patients experienced only half as many postoperative episodes of pyelonephritis as did the nonsurgical group (38). However, bacteriuria is relatively common, reported in up to 40% of postreimplant patients, most without pyelonephritis (64,66,68).

TECHNICAL CONSIDERATIONS

The literature regarding surgical correction of vesicoureteral reflux contains descriptions of a remarkable array of procedures. Generally, when a medical condition has many procedures described for its correction, it is because none of those procedures has a predictably successful outcome. However, in the case of ureteroneocystostomy most procedures share equally high success rates of greater than 95%.

In years past, cystoscopy was commonly performed before antireflux surgery to evaluate the bladder wall, ureteral orifice position, and submucosal ureteral tunnel length. Because the location and configuration of the orifice correlates closely with the radiographic grade of vesicoureteral reflux and measurement of tunnel length is poorly reproducible, cystoscopy before or at the time of antireflux

surgery seldom provides additional information regarding these variables.

Improvement in surgical technique, instrumentation, and magnification has lessened patient morbidity significantly. As always, good surgical exposure is key. Sponges packed in the bladder dome and retracted superiorly will flatten the posterior wall of the bladder, and vastly improve visualization of the trigone. A self-retaining ring retractor (Denis-Browne, Bookwalter) works nicely for this exposure. Many surgeons use surgical loupes to better visualize the ureter and to facilitate dissection. Delicate handling of the bladder and a “no touch” technique with the ureter have lessened the degree of postoperative ureteral edema, and thus shortened the hospital stay. The use of fine forceps (Gerald forceps) and fine-tipped scissors (tenotomy) are important.

A good understanding of the anatomy of the ureter in the pelvis is crucial in performing extravesical reimplantation. Many times, the ureter is not easily seen adjacent to the bladder and finding the ureter crossing posterior to the obliterated umbilical artery or anterior to the common iliac vessels facilitates surgical progress. It is important to recognize that the most common major complications after antireflux surgery are ureteral obstruction and persistent reflux. Keeping this in mind during the procedure helps the urologist create adequate submucosal tunnels and avoid obstructing sutures, ureteral devascularization, or acute ureteral angulation.

SURGICAL CORRECTION OF VESICOURETERAL REFLUX

Each of the techniques is predicated on creation of a flap valve mechanism at the distal ureterovesical junction. This generally takes the form of creating a submucosal tunnel buttressed beneath with detrusor muscle. A 5:1 ratio of ureteral tunnel length to ureteral diameter is the commonly quoted surgical goal, although documentation of this ratio in the literature is scant (55). The physics of a successful antireflux mechanism would require only that the pressure inside the distal ureter slightly exceed that of the bladder. This requires a servo-mechanism such that the intraluminal ureteral pressure is always slightly higher than that of the bladder and rapidly adjusts to bladder pressure. This requires elasticity of the ureteral wall and a luminal diameter that permits coaptation.

Procedures to correct reflux have been categorized in many ways. This section divides the repairs into intravesical, extravesical, combined, and endoscopic. The most common repairs and those that differ technically in a significant way are illustrated.

Intravesical Procedures

Politano-Leadbetter

One of the most commonly used reimplant techniques in the United States was described by Politano and Leadbetter in 1958 (57). Success rates of 98% to 99% are reported (12).

Technique

Once the bladder is open, the ureter is cannulated for ease of manipulation and a mucosal incision is made around the orifice (Fig. 51B.1). The ureter is dissected free proximally along Waldeyer's sheath away from its detrusor attachments. Once the ureter is free from the bladder, care is taken to sweep retroperitoneal tissue and peritoneum away from the posterior bladder wall so that a right-angle clamp can be passed into the retroperitoneal space from this original hiatus and directed to a more superior position where a new hiatus is to be created. The tip of the right angle is brought through muscle and mucosa at the intended site for the new hiatus, and a second right-angle clamp is then used to pass in the reverse direction. This allows the second clamp to grasp the traction stitch on the ureter and the ureter is thus drawn into the new hiatus. The original muscular hiatus is closed to reapproximate the floor of the bladder. A submucosal tunnel is created from the new hiatus toward the bladder neck so that the ureter can be reimplanted. Once the ureter has been passed through the submucosal tunnel to the proper position on the trigone, it is sutured in place with absorbable suture and the urothelium over the new and old hiatus are closed.

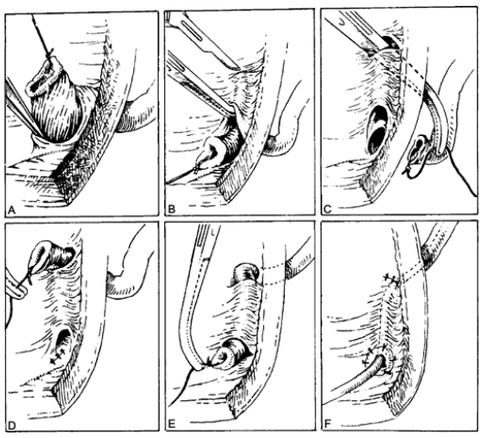

FIGURE 51B.1. Politano-Leadbetter. **A:** A traction stitch aids in dissection of the ureter to free it from bladder attachments. **B:** A new ureteral subepithelial tunnel is made with the right angle and a scalpel incision at the area of the new hiatus. **C:** The ureter is retrieved from its extravesical position. **D:** The ureter is drawn through the new hiatus in the bladder wall. **E:** The ureter is placed in its new subepithelial tunnel. **F:** Ureterovesical anastomosis is completed and the bladder epithelium repaired.

Concerns over the Leadbetter-Politano technique generally revolve around the formation of the new hiatus (15). The Leadbetter-Politano technique has a slightly higher risk of obstruction at the new hiatus as well as occasional problems resulting from inadvertent peritoneal penetration and injury to pelvic organs or intestine.

Glenn-Anderson

The Glenn-Anderson procedure remains one of the more common advancement procedures (procedures using the same ureteral hiatus) in the United States (30). Following modest ureteral mobilization (as per Leadbetter-Politano), a subepithelial tunnel is made from the hiatus down the trigone toward the bladder neck (Fig. 51B.2). The ureter is next passed through the subepithelial tunnel to the new

orifice site and matured. For widely spaced ureters on a large trigone, this procedure allows a great deal of promise because the ureter can be advanced significantly onto the trigone creating an adequate tunnel length. In some patients, the trigonal anatomy does not allow for enough advancement and enough new subepithelial tunnel to reliably prevent reflux. For patients with a smaller trigone, Allen (1) modified the technique by dividing detrusor lateral and superior to the original hiatus. This requires that detrusor be repaired after the ureter is "lateralized" to create a new hiatus. This allows the Glenn-Anderson procedure to be used in patients whose ureters do not otherwise allow a significant length of advancement toward the bladder neck from their original hiatus.

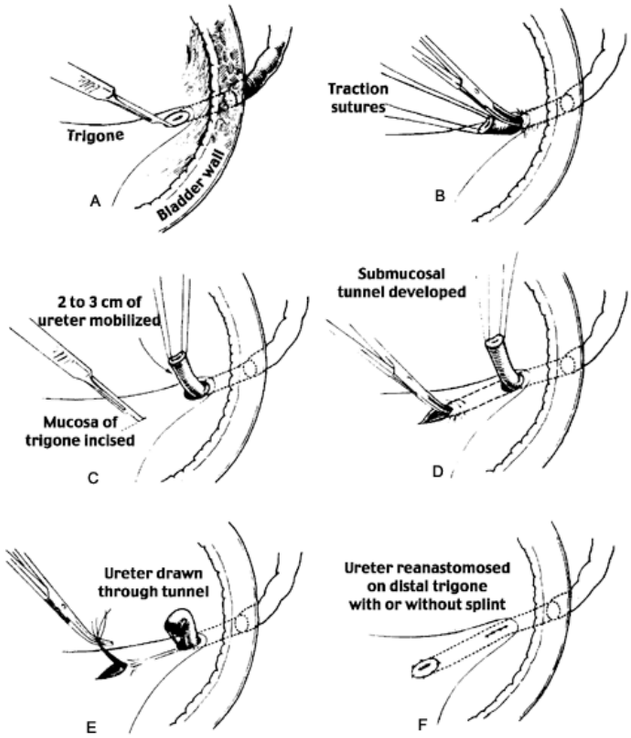

FIGURE 51B.2. Glenn-Anderson. **A:** Incision around the ureteral meatus. **B:** The ureter is freed from its bladder attachments. **C:** Bladder mucosa is incised. **D:** Submucosal tunnel is created. **E:** The ureter is placed in the submucosal tunnel. **F:** Vesicoureteral anastomosis is completed and the original site closed.

Cohen

Cohen (21) described a cross-trigonal reimplant that currently enjoys a great deal of popularity among pediatric urologists (40). A circular incision around the orifice is carried proximally allowing for 4 to 5 cm of ureteral mobilization (Fig. 51B.3). The detrusor hiatus is then partially closed inferiorly. Long subepithelial tunnels are made in a cross-trigonal fashion, placing one ureter cephalad to the other and allowing the ureteral orifice to be sutured in a position on the opposite side of the bladder from which it arises. This operation allows for significant lengthening of subepithelial tunnels without the need for a new hiatus. Therefore postoperative obstruction of the ureter has been reported less commonly with the Cohen technique than with other operations such as the Leadbetter-Politano, which uses a new hiatus. There has been significant concern that as these children grow, attempts at ureteral instrumentation for stones or other urologic disease might be thwarted by the unusual orifice position. However, techniques are available to facilitate instrumentation of the ureter in these patients.

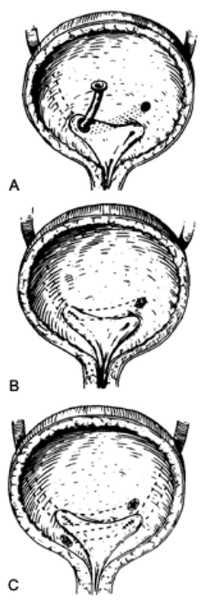

FIGURE 51B.3. Cohen. **A:** The right ureter is freed from its bladder attachments and mobilized with the future reimplant site noted by the *black dot*. **B:** The ureter is placed through the new subepithelial tunnel and anastomosed across the trigone on the opposite side of the bladder. **C:** Both ureters have been reimplanted across the trigone with the right ureter being cephalad to the left.

Hutch I

Hutch (36) contributed significantly to the early enthusiasm for reflux repair by describing a novel technique. This

involved splitting mucosa over the ureter, mobilizing the ureter to an intravesical position, and closing the detrusor and mucosa posterior to it. This left the orifice intact, moved the hiatus further laterally, and left a portion of the ureter exposed within the bladder. This procedure seldom is used at present because the intravesical ureteral length gained is not great, and lateral orifices remained in their original lateral position. In 1963, Hutch developed an advancement procedure that, since that time, has gone by the name of Hutch II (35). An incision around the ureteral orifice was made to include a mucosal flap extending toward the bladder neck. The ureter was mobilized modestly. The distal flap was excised, and the ureter was advanced toward the bladder neck into the flap defect. Again, the gain in submucosal tunnel length was modest. This operation, in part, paved the way for the more popular Glenn-Anderson procedure.

Bischoff

In 1957, Bischoff described a U-shaped incision wherein the curve of the U was created over the ureteral orifice and the arms of the U carried toward the bladder neck (11). The edges of the flap were mobilized and then sutured together to extend the ureteral tunnel toward the bladder neck over a ureteral stent. The ureter itself was not mobilized, and the new segment extending from the orifice was simply an epithelial tunnel. The procedure never gained popularity.

Witherington

Witherington described an operation using a mucosal flap based at the ureteral orifice (69). The mucosal flap was mobilized from over the ureteral tunnel and rotated down toward the bladder neck. This flap was anastomosed

to two parallel incision lines extending from the orifice toward the bladder neck. This procedure, again, created only an epithelial extension of the ureter, and because of the unusual mucosal flap creation and the minimal extension of the tunnel, it has not been used commonly.

Williams

Williams described a technique wherein a triangular incision distal to the orifice pointing toward the bladder neck was made (67). The ureter was elevated slightly and advanced into the apex of the triangle near the bladder neck. This procedure was not applied widely because it did not significantly mobilize the ureter and thus advancement was minimal.

Gil-Vernet

In 1984, Gil-Vernet touted a very simple technique for vesicoureteral reflux correction (29). This involved an incision made transversely across the interureteric ridge between the ureteral orifices (Fig. 51B.4). A suture was then placed just beneath the orifice and used to draw the ureteral orifices together in the midline. This operation showed initial success and has gained some popularity in Europe. The general feeling among pediatric urologists in the United States is that reflux resolution is not durable, and the technique is uncommonly used in this country.

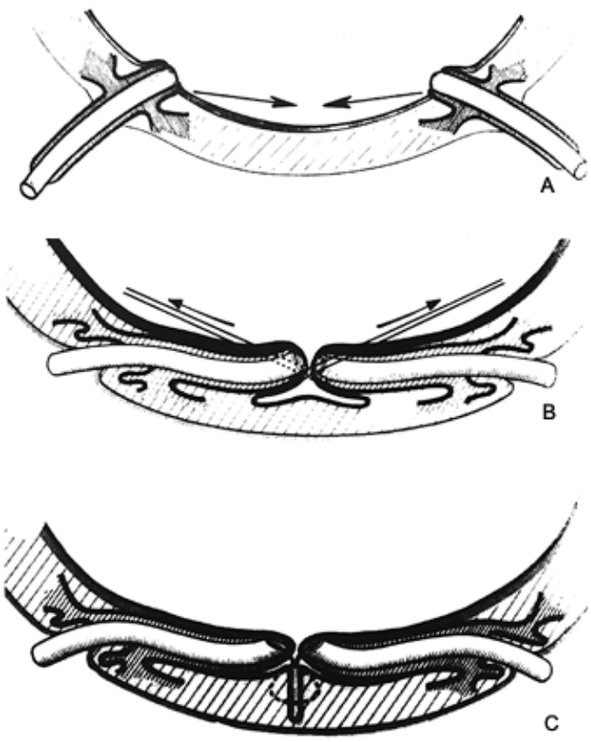

FIGURE 51B.4. Gil-Vernet. **A:** The *arrows* show how the ureters will be drawn together in the middle of the trigone. **B:** A suture is placed at the inferior edge of each ureter and drawn together. **C:** Suture being tied, inverting the trigone, and bringing the two ureteral orifices together near the midline.

Extravesical Procedures

Lich-Gregoir

This extravesical reimplant evolved at similar times in the United States (44) and in Europe (31). This simple technique has subsequently been used more commonly in Europe. It fell out of favor after a 1974 report by Hendren declaring a high reflux recurrence rate (33). As the detrusorrhaphy

procedure reintroduced the concept, enthusiasm for the Lich procedure was renewed because of its simplicity and diminished hospital stay.

Technique

This procedure is performed on the posterior lateral bladder wall where the ureter is found and dissected to the bladder hiatus (Fig. 51B.5). In a superior lateral direction from the hiatus, detrusor is divided with electrocautery and the fibers are separated down to the bladder epithelium creating a 3-cm-long epithelial bulge. The ureter is then laid into the trough upon the bladder epithelium, and detrusor muscle is closed over this to create backing for the ureteral tunnel. It is important that the tunnel be created in the same orientation that the ureter naturally courses. When the bladder is retracted, the tendency is to make the tunnel too medial, thereby giving the ureter an opportunity to be kinked. The authors use traction sutures to help flatten the posterior bladder wall and aid in the dissection. Judgment should be used about how cephalad to allow the hiatus to be on the posterior bladder wall with concern that bladder filling may induce ureteral angulation and obstruction.

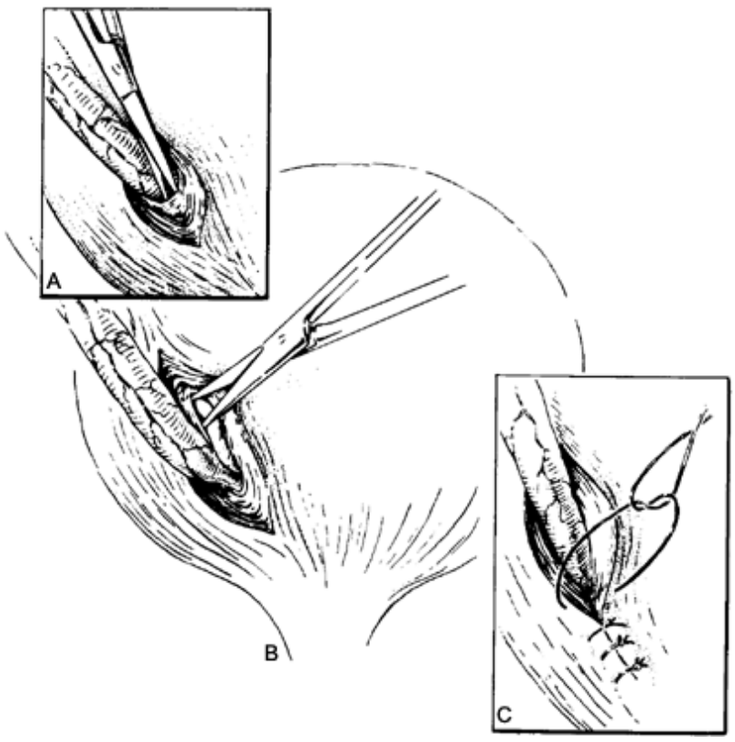

FIGURE 51B.5. Lich-Gregoir. **A:** Extravesical sharp dissection along the ureteral wall to the ureteral hiatus. **B:** The detrusor muscle is separated so that the epithelium can be easily seen. **C:** The detrusor muscle is sewn over the ureter so that the ureter lays against the epithelium and has more detrusor backing.

Detrusorrhaphy

In 1987, Zaontz and colleagues reported a modification of the Daines-Hodgson and Lich-Gregoir extravesical repairs (23,71). The ureter is located extravesically and followed to its insertion into the detrusor. A muscle incision is made around the ureteral insertion, extending 1 cm caudad and further cephalad on the detrusor, allowing muscle fibers to be separated and a bulge of the bladder epithelium to be seen (Fig. 51B.6 and Fig. 51B.7). The orifice is then advanced distally with two sutures placed from ureteral musculature to muscle edge at the distal extent of the detrusor incision; this improves the position of the orifice on the trigone. Once the ureter is advanced approximately 1 cm toward the bladder neck using this method, the ureter is placed within the muscular trough and muscle is closed over it up to a new hiatus. This portion is identical to a Lich-Gregoir repair. Initial success was reported in 93% of cases. Several reports have touted the quick return of bowel function, diminished pain, minimal bladder spasms, and shortened hospital stays using the detrusorrhaphy technique. There also have been reports of postoperative voiding dysfunction and urinary retention (9,45); some have suggested that this technique be limited to unilateral vesicoureteral reflux only caused by high rates of transient voiding dysfunction following bilateral procedures (25). Despite this issue, the procedure remains one of the more popular techniques used in the United States.

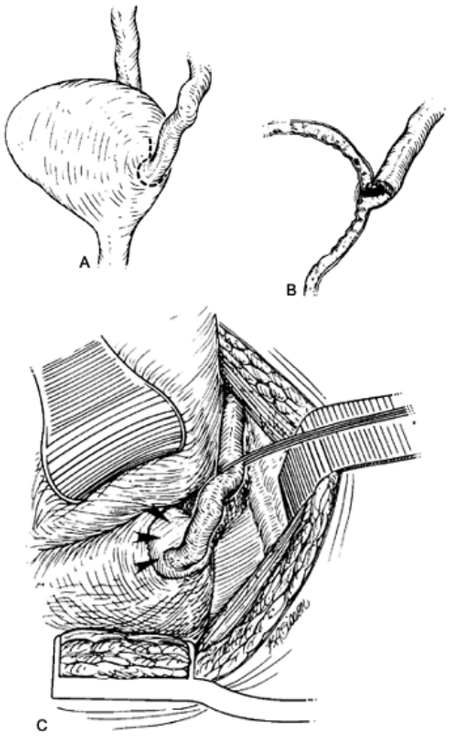

FIGURE 51B.6. Detrusorrhapy. **A, B:** An incision around the extravesical ureter with an extension cephalad on the bladder is made. **C:** The *arrowheads* depict the area around the extravesical ureter that has had the detrusor muscle separated away and the bladder epithelium bulging.

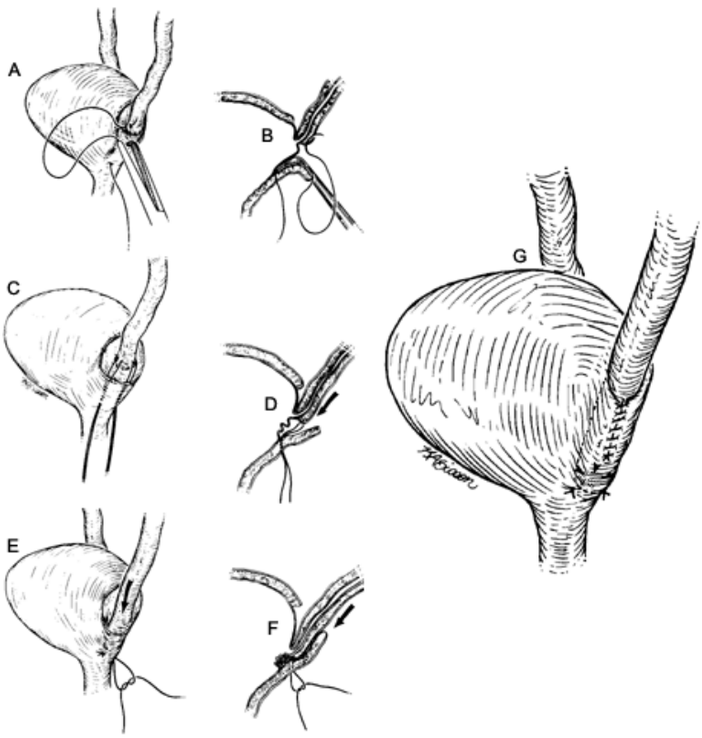

FIGURE 51B.7. Detrusorrhapy. **A:** Shows the suture from the ureter toward the bladder neck to advance the ureter toward the trigone. **B:** Is a cutaway side view of the same suture. **C:** Depicts both sutures in place ready to be tied, with **D** being the side view cutaway. **E:** Shows the one suture tied and the other suture being tied, advancing the ureter toward the trigone, with **F** showing the side view cutaway. **G:** Detrusor muscle being closed over the newly advanced ureter to complete the procedure.

Combined Procedure

Paquin

The Paquin technique combines an extravesical ureteral mobilization with an intravesical reimplant (56). Because of this combined approach, it is not used as often as an

exclusive intravesical or extravesical technique. It has been reported to be effective when used with a psoas hitch (49). Success rates have been reported as high as 96% (70).

Technique

The bladder is retracted medially, and the ureter is exposed extravesically, dissected to the bladder hiatus, ligated, and divided (Fig. 51B.8). The bladder is then opened, and a new hiatus superior to and lateral to the old one is chosen. A subepithelial tunnel is created in the direction of the trigone. The ureter is drawn through the subepithelial tunnel, spatulated, and sutured to the selected site on the trigone.

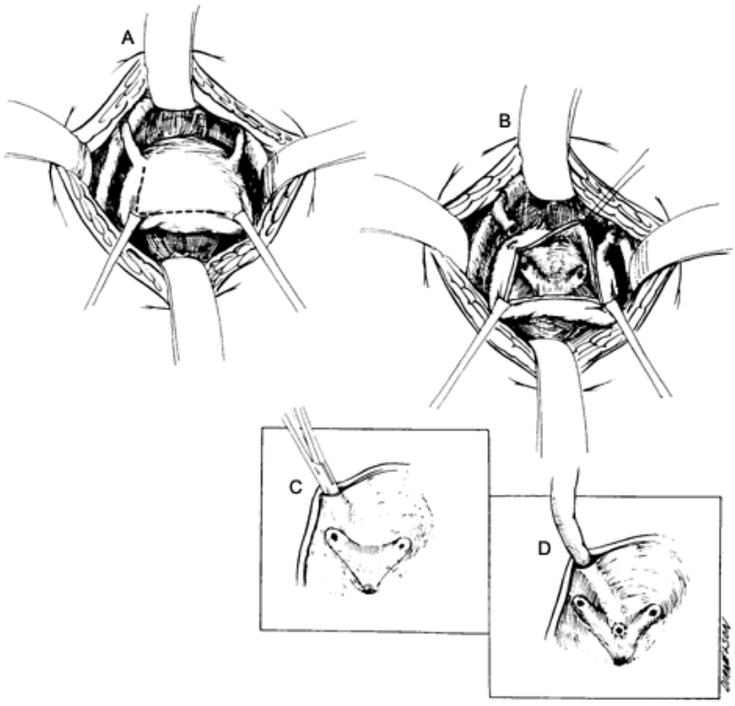

FIGURE 51B.8. Paquen. **A:** The bladder is opened with an L-shaped incision toward the ureter to be reimplanted. **B:** The ureter is divided from the bladder extravesically. **C:** A new subepithelial tunnel is made from a new hiatus toward the trigone. **D:** The ureter is passed through the subepithelial tunnel and reimplanted in the trigone and then the bladder is closed.

LAPAROSCOPIC AND ENDOSCOPIC URETERAL REIMPLANTATION

The past few years have seen a significant interest in developing laparoscopic techniques for achieving ureteral reimplantation. The initial efforts have involved an extravesical reimplant through a transperitoneal approach, essentially a modified Lich-Gregoir reimplant performed laparoscopically (4,5,61). After initial success in a porcine model, a few reports of clinical experience have emerged.

Ehrlich and associates issued an initial report on two patients with “successful outcome” and minimal perioperative discomfort (26). Janetschek and associates described their experience in six children, one of whom required postoperative ureteral stenting for 6 weeks owing to obstruction (37). Although they believed that the procedure was technically achievable, it proved quite complex and offered no significant recovery advantage to the patient. In a more recent and larger series, Larshmanan and colleagues have performed laparoscopic repair in 26 children (37 ureters) ages 4 to 13 years (42,43). The technique requires four ports and gains access to the bladder transperitoneally. Operative time, after an initial learning curve, is approximately 1.5 hours per ureter. With a minimal follow-up (3 months), only 1 of 37 ureters demonstrated vesicoureteral reflux.

Although Larshmanan and colleagues remain enthusiastic, many authors have concluded that the difficulty of the

technique puts laparoscopic extravesical reimplant in disfavor compared with open reimplant surgery. Difficult visualization in the deep retrovesical space along with an extended operative time have led to limited application of this approach to date.

TRANSVESICAL LAPAROSCOPIC URETERAL REIMPLANTATION

Shortly after the initial reports of extravesical reimplantation, experience with a combined transvesical and transurethral endoscopic approach to ureteral reimplantation was reported by two groups (16,54). The initial attempt by each group was to use the Gil-Vernet or trigonoplasty concept. The procedure has been termed *endoscopic trigonoplasty* or *percutaneous endoscopic trigonoplasty* (PET).

In this approach, the intravesical space is accessed via two laparoscopic ports placed suprapubically into the bladder. Using CO_2 insufflation of the bladder, a transverse dissection with an endoscopic scissor is carried out between the two ureteral orifices. Mucosa is dissected away from each side of the incision, exposing a muscular trough onto which the orifices may be advanced. Laparoscopic suturing allows a series of sutures to draw the orifices to the midline and thereby elongate the intravesical segment of the ureter (Fig. 51B.9).

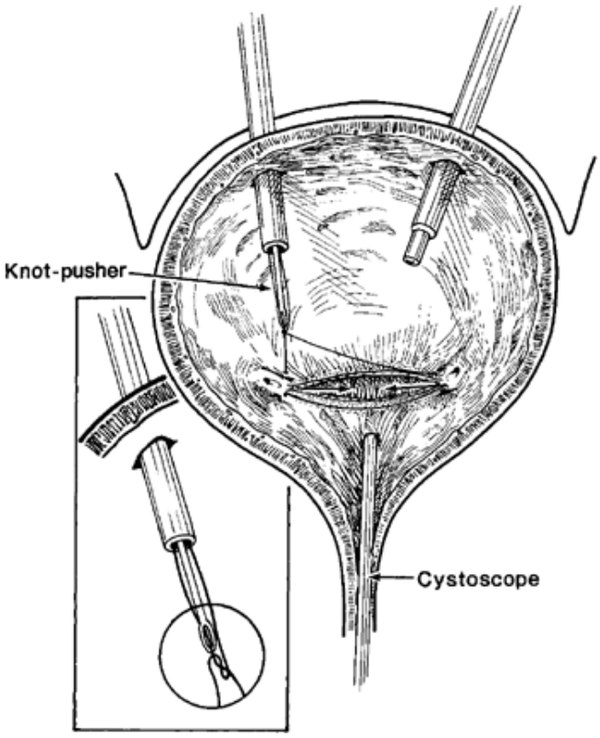

FIGURE 51B.9. Endoscopic trigonoplasty. The suture is tied in the midline drawing the orifices over the muscular trough.

In the most recent series from the two institutions pursuing this approach, success rates are only modest. Cartwright and Snow reported experience in 22 children undergoing percutaneous endoscopic trigonoplasty (16). Reflux was of moderate grade in most and high grade in a few. No ureteral obstruction was created with the procedure, but reflux resolved in only 20 of 32 (62.5%) ureters at a 6-month follow-up. Success was not related to patient age, side of reflux, initial reflux grade, operative sequence, or the presence of preoperative bladder instability. Okamura and associates recently reported a difference in outcomes in children versus adults (53). At 3 months, the resolution rate for adults and children were 96% and 70%, respectively. By 12 months of follow-up, this had decreased to 74% and 59%. As an extension of this technique, there has been a recent small report of seven children undergoing a limited cross-trigonal type of reimplantation following laparoscopic dissection of the ureter and repositioning intravesically (28). This resulted in long-term reflux resolution in 10 of 12 ureters.

Although interesting and technically challenging, these approaches do not seem to warrant clinical application at this point. New equipment and innovations may arise, which will improve the feasibility.

SUBURETERIC INJECTION FOR VESICOURETERAL REFLUX

In the search for a less invasive method to correct vesicoureteral reflux, the concept of subureteric injection was introduced. The basic premise is to supply a buttress beneath the ureteral orifice to compensate for the lack of usual muscular backing to the submucosal tunnel, and thereby cause ureteral mucosa to coapt during bladder filling and prevent reflux.

Matouschek introduced the idea in 1981 using polytetrafluoroethylene (Teflon) paste (47). The procedure was popularized and given the name STING procedure by O'Donnell and Puri shortly thereafter (52). Although the concept has good merit, there has been great discussion about what the ideal substance for injection might be. To date, there have been animal and clinical reports on many substances, both autologous and nonautologous, including the following: Teflon, polyvinyl alcohol, silicone particles (Deflux), bioglass, detachable membrane device, collagen, fat, bladder muscle cells, and chondrocytes (4,6,7,13,14,19,27,48,52,60,65).

The technique for subureteric injection is straightforward. The ureteral orifices are visualized through the cystoscope. A needle-tipped stent (18 to 25 gauge depending on the substance injected) is passed via the working channel and inserted beneath the bladder epithelium at the 6 o'clock position beginning 5 mm distal to the orifice. It is advanced beneath the orifice, and the substance is injected under direct visualization as the bulking material displaces the

lumen of the ureter anteriorly (Fig. 51B.10). This is continued until the orifice is pushed anteriorly and obtains an inverted crescent shape; the needle is left in place for 2 minutes so that extravasation upon withdrawal is minimized.

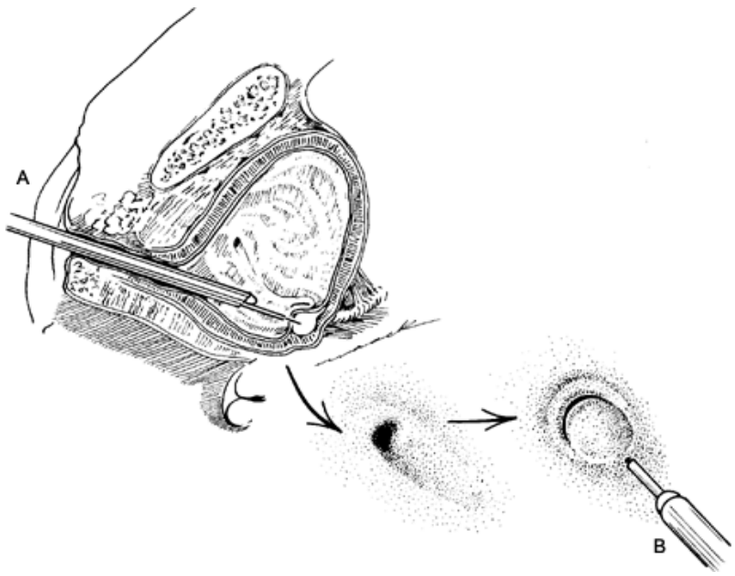

FIGURE 51B.10. Sting. Subureteric injection for reflux. **A:** Normal orifice. **B:** Orifice after subureteric becomes elevated and assumes an inverted crescent configuration.

The results of endoscopic treatment for vesicoureteral reflux are summarized in Table 51B.2 . In evaluating these data collectively, it is apparent that reasonable success can be obtained but that the rate of reflux cessation is routinely lower than for standard open reimplantation. In addition, some patients will require more than one injection to obtain the stated results and for all substances there is declining success as patients are followed longer postoperatively. The real attraction to this approach is minimal postoperative discomfort and feasibility to be completed as an outpatient procedure.

Study	Agent	Patient (*n*)	Ureters (*n*)	Success Rate (%) —1 Injection
Puri, Mercky	Teflon	4,234	6,316	75.9
Leonard, Frey, Frankenschmidt	Collagen	483	289	59.8
Sternberg, Lackgren	Deflux	75	101	68.0
Chanceller, Palona	Autologous fat	19	29	22.6
Diamond, Caldamone	Autologous chondrocytes	29	50	60.0

From Kershen RT, Atala A. New advances in injectable therapies for the treatment of incontinence and vesicoureteral reflux. *Urol Clin North Am* 1999;26(1):81, with permission.

TABLE 51B.2. OUTCOMES IN PATIENTS WITH SUBURETERIC INJECTION FOR REFLUX

Of the nonautologous materials, Teflon is by far the most commonly used (58,59). In addition to data on using Teflon in primary reflux, it has been reported as successful in approximately 90% of patients with persistent reflux after open reimplantation (41). Although its proponents quote a long track record of reasonable success with minimal morbidity, there has been concern about its safety, especially in children. Malizia and associates found, in experimental animals, both granuloma formation around Teflon particles and migration of the particles to lymph nodes, lung, and brain (46). Along with scattered clinical reports of particle migration, this has curtailed the use of the STING procedure

in the United States (20,24). The other substances each have drawbacks leading to limited clinical application. Bovine cross-linked collagen has been used with only modest success because of its tendency to break down and lose bulk over time.

Autologous substances may be the source for an eventual acceptable and durable agent due to lack of foreign body reaction and immunogenicity. Fat has proven to be a poor substance due to high bulk loss (18). Autologous collagen has been tried in experimental models and may experience less breakdown than bovine collagen does (17). Quite promising are both autologous bladder muscle cells and chondrocytes harvested and grown on alginate (3,4). Further clinical trials are underway with chondrocyte injection; as always, longer follow-up periods will be needed to see if cessation rates are acceptable. The attractiveness of simple subureteric injection is great enough that the search for an appropriate material, one that is safe, effective, and durable, will continue.

SURGICAL CORRECTION OF MEGAURETER

Regardless of the cause, surgical repair of a megaureter requires the use of one of three techniques: Starr plication, Kalicinski folding, or open tapering.

The most versatile of the techniques is open ureteral tapering, popularized by Hendren in 1969 (32). Careful inspection of the ureteral blood supply is made before deciding on which portion of the ureter to taper. Noncrushing ureteral clamps are placed around the ureter with the ureteral stent in the lumen of the portion to be preserved, and the excess megaureter wall is excised for 6 to 8 cm (Fig. 51B.11). The ureteral wall is then

reapproximated side to side with absorbable suture and reimplanted in a subepithelial tunnel by one of the standard methods.

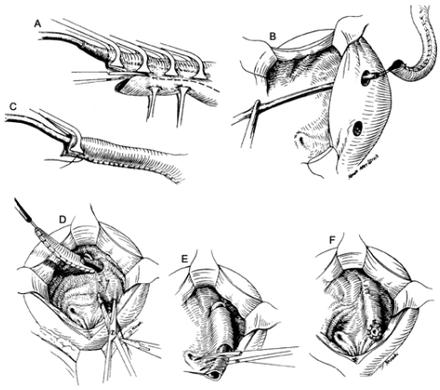

FIGURE 51B.11. Hendren. **A:** Shows megaureter clamps in place and the excessive megaureter tissue being excised. **B:** Shows closure of the megaureter over a ureteral stent. **C:** Extravesical view of the bladder showing the original hiatus and the new hiatus with the tapered megaureter being drawn into the bladder. **D:** A new subepithelial tunnel is made. **E:** The megaureter is drawn through the new tunnel to the trigone. **F:** The megaureter is sutured in place at the trigone with the bladder epithelium being repaired over the new hiatus.

Kalicinski and coauthors described a plication technique in which, over a ureteral stent, a running suture is placed parallel to the stent for the distal 6 to 8 cm (39) (Fig. 51B.12). This excludes a significant portion of the ureter from the urine-containing channel; this excluded portion is folded over the side of the remaining portion and is not excised. This technique is used for small to medium-sized megaureters. Subsequent studies have shown that the excluded ureter lumen obliterates and vascularity is preserved (8).

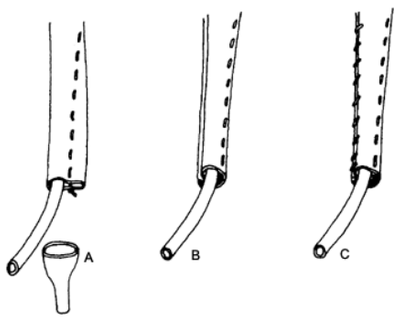

FIGURE 51B.12. Kalicinski. **A:** The distal narrow end of the megaureter is excised, and then a running suture parallel to the ureteral stent excludes a long triangle of the megaureter. **B, C:** The excluded portion of the megaureter is folded around the megaureter and tacked in place with absorbable suture narrowing the entire megaureter for reimplantation.

Starr described an alternative plication technique by placing ureteral sutures in a Lembert fashion along the distal 6 to 8 cm of the ureter, thus enfolding a segment of the ureteral wall over a ureteral stent (63) (Fig. 51B.13). A Starr plication is also chosen when the degree of megaureter is mild to moderate such that the bulk of the plicated ureter is not too great to put into a subepithelial tunnel. It enjoys the advantages of creating no open ureteral suture line and maintaining excellent ureteral blood supply.

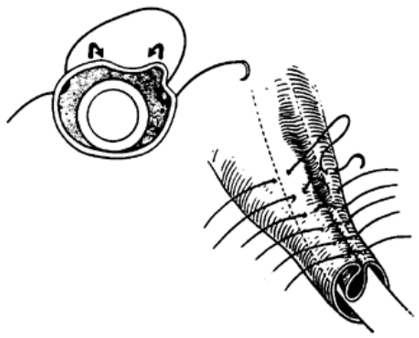

FIGURE 51B.13. Stan. Absorbable sutures are placed in a Lembert fashion to fold in the redundant megaureter making it snug around a ureteral stent.

Reimplantation after the ureter has been narrowed can be by any number of techniques, the most common are the Politano-Leadbetter with a new, more superior hiatus or a cross-trigonal technique (22). The entire tapering and reimplantation also may be accomplished extravesically. Psoas hitches have been employed commonly to lengthen and flatten the posterior bladder wall to allow a longer tunnel length for these more dilated ureters. Postoperative stenting is usually preferred in cases of tapering and in most cases of plication.

SPECIAL CIRCUMSTANCES

Ureteral Duplication

Ureteral duplication commonly is encountered with reflux. Conventional wisdom suggests that the ureters should be reimplanted together, as a common sheath, because distal ureteral blood supply often will be inseparable. Prior reports and personal experience suggest that such ureters may, in fact, be separable in certain cases, and the ureters may be managed individually. A challenging situation arises with duplicated ureters when one ureter is quite large and requires tapering. Tapering generally is carried out on the portion of the larger ureter opposite its attachment to the more normal one to avoid compromising the common blood supply. At other times, it may be best to resect much of the larger ureter, perform a ureteroureterostomy above the bladder, and reimplant the more normal ureter.

Neurogenic Bladders

Neurogenic bladders may function at higher elevated pressures and therefore are commonly associated with reflux that requires surgical repair. The detrusor may be thickened, making reimplantation difficult and not as successful as when performed in a normal bladder. It is crucial to optimize bladder storage parameters using medication, catheterization, or augmentation before or along with reimplantation; this will improve outcomes significantly.

Infants

In the past, surgical repair of reflux has been less successful in young infants when compared with older children. With the improvement of magnification and using loupe magnification and delicate tissue handling, success rates in young infants currently are likely equivalent to those in the older group. It is important to remember that a significant percentage of even high-grade reflux will resolve spontaneously as young infants move through their first year; thus, in most instances, observation is prudent (2,10). This is particularly pertinent in young boys who may initially have high voiding pressures that progressively decrease during the first year of life, making reimplantation unnecessary (62).

Complications

Ureteral obstruction is the most concerning complication after reimplant surgery. Although transient obstruction from edema is relatively common, persistent obstruction, thankfully, is quite unusual. Such obstruction occurs due to stenosis at the orifice, an ischemic distal segment, narrowing or angulation at the muscular hiatus, or kinking around a fibrous band in the retroperitoneum. It is appropriate to obtain ultrasound imaging after reimplant surgery to document that obstruction has not occurred. Imaging too quickly after reimplant surgery may be confusing because residual edema generally will cause modest dilation of the ureter and renal pelvis; imaging at 4 to 6 weeks minimizes this concern. When hydroureteronephrosis is discovered, the severity and clinical circumstances will guide treatment. If the obstruction is mild, observation with repeat imaging may be all that is necessary. If the patient has nausea and vomiting, poor appetite, or pain with worrisome dilation, a percutaneous nephrostomy tube may be needed. Cystoscopic stent insertion may be considered, but often is difficult early after surgery, particularly if cross-trigonal reimplants have been performed. If nephrostomy drainage and contrast imaging reveal continued obstruction, it may be prudent to place an indwelling stent in an antegrade fashion to remain in place for several weeks.

Persistent Reflux

Persistent reflux after reimplantation is a frustrating finding. Persistent reflux is more likely with higher initial grades of reflux. Some authors suggest that if the reflux is mild to moderate (grades I to III) before surgery, cystography after surgery is not required because of predictably high resolution rates. Cystography would only be used if these patients developed future urinary infections.

If cystography is performed and persistent reflux is found, observation on prophylactic antibiotics is almost always the first course of action. Careful voiding history should be obtained and voiding dysfunction should be eliminated, which is often a factor causing persistent reflux. Persistent reflux commonly resolves in the first 6 to 12 months after surgery. In the unusual patient requiring reoperation, standard open reimplant techniques can be performed with a high degree of success. Preoperative cystoscopy may be helpful to assess tunnel length and to evaluate for the possibility of a ureterovesical fistula (above orifice). Some have used the STING procedure in this circumstance, finding this to be a simple and relatively successful approach for persistent reflux.

Contralateral reflux occurs in 10% to 15% of patients who have undergone a unilateral reimplant. Again, the best course of action is observation (34). Almost all contralateral reflux is low grade and resolves within the first year after surgery (50). Prophylactic antibiotics may be necessary during this time. Again, voiding dysfunction should be suspected and treated if present.

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51C PYELOPLASTY, PYELOURETEROSTOMY, TRANSURETEROURETEROSTOMY, MEGAURETER, AND URETERAL RECONSTRUCTION

Michael C. Carr

Part of "51 - TOOLS OF RECONSTRUCTION "

M.C. Carr: Department of Urology, University of Pennsylvania; Children's Hospital of Philadelphia, Philadelphia, PA 19104-4399.

PYELOPLASTY

The approach to the repair of the ureteropelvic junction (UPJ) obstruction has evolved from a ureteral advancement procedure (Foley Y-V–plasty) to incising the ureter and allowing for secondary epithelialization (Davis intubated ureterotomy). In 1949, Anderson and Hynes (2) popularized a dismembered pyeloplasty technique in which the ureter is divided at the renal pelvis, spatulated, and reanastomosed to the opened renal pelvis. Historical approaches that were abandoned are now being revisited due to the popularity of endoscopic and laparoscopic techniques.

Foley Y-V–plasty

The Foley Y-V–plasty is best applied to reconstruction of the UPJ obstruction associated with high ureteral insertion (20). In many respects, it is limited; for example, it is rarely indicated in the patient with an obstructing lower-pole vessel. Furthermore, the technique also does not allow for surgical reduction of the dilated renal pelvis. Therefore use of the Foley Y-V–plasty and other flap techniques has, for the most part, been supplanted by the more versatile dismembered pyeloplasty.

In the approach for a Foley Y-V–plasty, the pelvis and proximal ureter are exposed in the retroperitoneum. A widely based triangular or V-shaped flap is marked on the renal pelvis (Fig. 51C.1). The base of the V is positioned on the dependent medial aspect of the renal pelvis while the apex is brought to the UPJ. The incision is made on the apex of the flap (i.e., the stem of the Y), and this is continued along the lateral aspect of the proximal ureter. The incision in the ureter should completely traverse the area of stenosis and extend well into normal-caliber proximal ureter. The pelvic flap and ureterotomy are then developed. A fine scalpel blade is used to make the initial pelvic incision. Potts or Metzenbaum scissors are used to complete the flap and ureterotomy incisions. An internal stent can be placed and the repair performed over it. The apex of the pelvic flap is first brought to the apex (inferior aspect) of ureterotomy using fine absorbable suture. The posterior walls are then approximated using interrupted or running suture technique. The repair is completed with anastomoses of the anterior walls. Many authors believe that it is preferable to use the interrupted suture technique because it decreases the potential for a purse-string effect on the suture line. An interrupted technique may also minimize ischemia compared with a running suture. However, with finer resorbable

sutures, a running vascular technique is faster and equally effective.

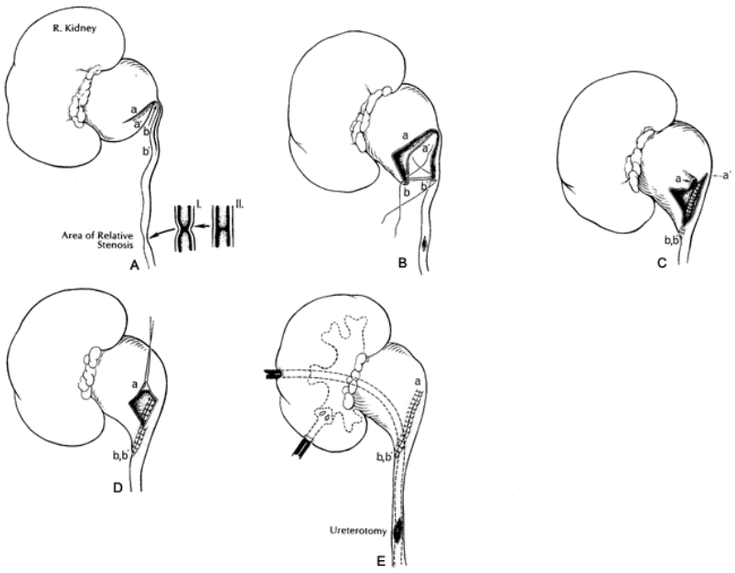

FIGURE 51C.1. Classic Foley Y-plasty. **A:** Anterior and posterior pelvic incisions should be the same length as the ureteral incision. **B:** The tip of the flap and the lower end of the ureterotomy should be approximated first. **C, D:** The closure is started at *(b,b')* and extended upward to *(a,a').* A dog-ear may form at point *a. I* and *II* illustrate the infrequent relative narrowing of the ureter, which is occasionally seen lower in the ureter. **E:** If there is a narrow segment, it can be treated by a ureterotomy or dilation. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH, et al, eds. *Campbell's urology,* ed 4. Philadelphia: WB Saunders, 1979, with permission.)

Intubated Ureterotomy

The Davis intubated ureterotomy, first described in 1943, is rarely used today as an open technique. This procedure, which depends on secondary epithelialization from the incised ureter, can be effective and should be reserved for the rare situation in which it appears to be needed. Its greatest use might be for correcting strictures in the lumbar ureter when the defect is too great to bring the kidney down or the distal ureter up for a primary anastomosis when insufficient upper ureter is present for a direct transureteroureterostomy.

The technical aspects of the intubated ureterotomy remain little changed from the thorough description of Smart (76). The strictured portion of the ureter should be adequately exposed with careful preservation of the ureteric blood supply. A ureterotomy is performed from at least 1 cm above the stricture to 1 cm below, in a meticulous fashion. Proximal diversion must be established with a well-located nephrostomy tube and a stent placed across the ureterotomy. It is critical that the stent not be so large as to

induce ischemia and possible stricture formation. Davis (13) recommends stenting for 4 to 6 weeks. A report by Ackerman and Frohmuller (1) achieved a 70% satisfactory result in 68 cases of ureteral intubation. Thus this technique does have sufficient success to maintain it in the reconstructive urologist's armamentarium.

Pelvic Flap Pyeloplasty

The Culp and DeWeerd (12) spiral flap is created from the renal pelvis, which is used to repair the defect at the UPJ (Fig. 51C.2). Such a flap is able to bridge the gap between the pelvis and healthy ureter over a distance of several centimeters. Scardino and Prince (70) described the use of a vertical flap that can be used in the situation of a dependent UPJ with a large, square-shaped extrarenal pelvis (Fig. 51C.3). The rare case of giant hydronephrosis that can be associated with a completely atretic ureter can be dealt with by reconstructing an entire ureter out of redundant pelvic tissue (39). This repair would seem to have a greater likelihood of success when compared with other autogenous pedicle graft repairs, such as full-thickness abdominal wall skin (38) or appendix (42,84).

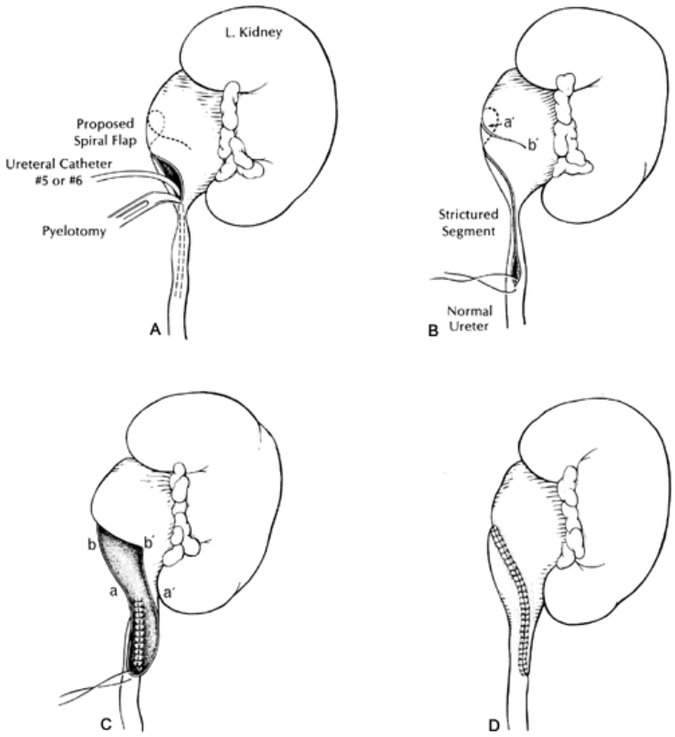

FIGURE 51C.2. Technique of Culp-DeWeerd spiral flap ureteropelvioplasty. **A:** If the ureteropelvic angle is oblique (greater than 90 degrees), a spiral flap will produce an acceptable ureteropelvic funnel. This method also produces a longer flap than the vertical flap operation. **B:** The pyelotomy should be planned and marked with sutures before opening the pelvis. A ratio of length to width of 2:1 or 3:1 should be planned. **C:** Suturing should start at the apex of the flap and the distal ureterostomy. **D:** The edges are closed with 4-0 or 5-0 absorbable sutures. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH, et al, eds. *Campbell's urology,* ed 4. Philadelphia: WB Saunders, 1979, with permission.)

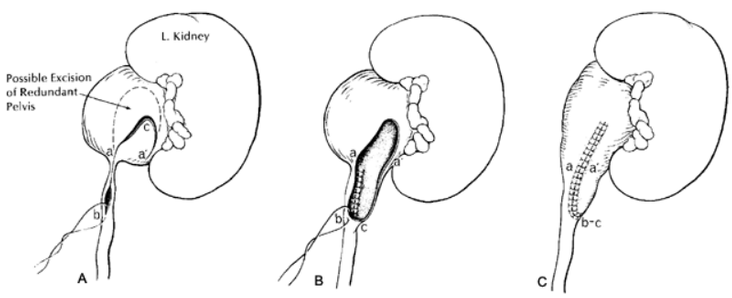

FIGURE 51C.3. Technique of Scardino-Prince vertical flap ureteropelvioplasty. **A:** This technique is best used when the ureteropelvic angle is approximately 90 degrees. The flap should have a 2:1 or 3:1 length-to-width ratio and be the same length as the ureterotomy. **B:** A pyelotomy is made in the lower pelvis and carried down the ureter. **C:** The flap is cut and redundant pelvic tissue excised with sharp plastic surgical scissors. The apex of the flap is sewn to the end of the ureterotomy incision. Absorbable sutures (4-0 or 5-0) are used, starting at the apex so that any dog-ears will be in the renal pelvis. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH, et al, eds. *Campbell's urology,* ed 4. Philadelphia: WB Saunders, 1979, with permission.)

Dismembered Pyeloplasty

Most urologists routinely use a dismembered pyeloplasty because this procedure is almost universally applicable for the repair of a primary UPJ obstruction. The technique may be used for a high or dependent insertion of the ureter on

the renal pelvis. It also facilitates reduction of a renal pelvis or straightening of a lengthy, tortuous proximal ureter. Furthermore, anterior or posterior transposition is easily accomplished in cases with aberrant lower-pole vessels. In contrast to a flap technique, the dismembered pyeloplasty allows complete excision of an anatomically or functionally abnormal UPJ. Dismembered pyeloplasty may be inappropriate in patients with a long segment of proximal ureteral obstruction or for patients in whom the UPJ is associated with a small intrarenal pelvis, which would be difficult to access.

With an open repair, the approach to the UPJ is retroperitoneal, using either an anterior abdominal approach with muscle-splitting technique (anterior) or a posterior lumbar approach (posterior lumbar). Exposure of the UPJ is generally obtained with initial identification of the proximal ureter in the retroperitoneum. The ureter is minimally dissected cephalad toward the renal pelvis. Care must be taken to preserve periureteral tissue for ureteral blood supply (Fig. 51C.4). Once the UPJ is identified and the pelvis dissected free of surrounding periureteral tissue, the medial aspect of the proximal ureter is marked with a fine suture placed below the level of the obstruction. This helps maintain proper orientation during repair and prevents twisting of the ureter, a known cause of operative failure, particularly when the repair is done from the posterior (kidney retracted medially and anteriorly). Similarly, the superior, lateral, and medial aspects of the dependent portion of the renal pelvis may be tagged with traction sutures. The UPJ is then transected and the proximal ureter spatulated on its lateral aspect well distal to the area of narrowing to the most dependent point of the anticipated anastomosis. The redundant portion of the renal pelvis is removed (amount depends on the degree of pelviectasis). One must beware of excessive excision in the patient with elongated calyces. The spatulated ureter is then brought along the medial aspect of the open renal pelvis. The anastomosis is initiated at the most dependent portion of the opened renal pelvis and at the most distal apex of the spatulated ureter. A 7-0 Maxon running suture is used to suture the spatulated ureter to the renal pelvis. The posterior suture is completed initially, followed by a second anterior suture. The technique is similar to that of a vascular anastomosis. It is sometimes helpful to leave a 5-Fr pediatric feeding tube in the ureter during the most distal portion of the anastomosis. This is removed before completion. A ureteral stent may be placed in very young patients or in complex cases. Usually, for straightforward pyeloplasty, tube drainage is not necessary. Most surgeons do leave a Penrose drain in the flank.

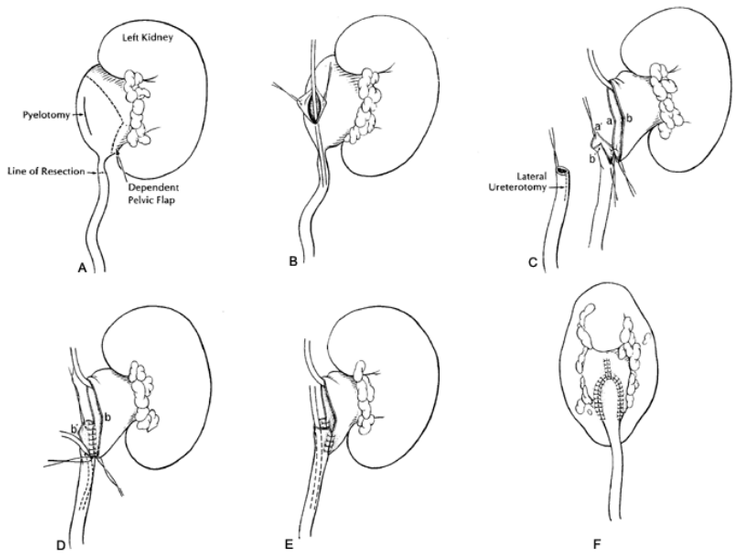

FIGURE 51C.4. Dismembered Foley Y-plasty operation. The obstructing segment is excised and a dependent funneling of the pelvis is achieved. **A:** The pyelotomy and ureterotomy incisions are planned and marked. **B:** The pyelotomy incision is started. **C:** The lateral ureterotomy is done and ureteral stent passed after excising the ureteral segment. **D:** Suturing with 4-0 or 5-0 absorbable sutures is started on the posterior surface at the apex. **E:** Traction sutures are used to approximate the edges. It is important not to crush the tissue with heavy forceps. The tip of the flap is sewn to the ureterotomy. It is important to start at the apex. **F:** The funnel is completed, and any redundant pelvis can be resected. The pelvis is reconstituted. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH, et al, eds. *Campbell's urology,* ed 4. Philadelphia: WB Saunders, 1979, with permission.)

Table 51C.1 outlines the success rate from a contemporary series of predominantly pediatric patients who underwent a dismembered pyeloplasty. Reported success rates range from 83% to 100% in these series. The authors report few complications. Prolonged drainage from the Penrose drain was noted in some instances, but this did tend to improve over time.

Author	Year	Patients/Kidneys	Success (%)
Poulsen, et al. (61a)	1987	35 adult and pediatric	100
O'Reilly (54)	1989	30	83–93
MacNeily, et al. (41)	1993	75	85
Shaul, et al. (74)	1994	32/33 (<2 mo old) 30/33 (>2 mo old)	97 91
Salem, et al. (68)	1995	100	98
McAleer and Kaplan (44)	1999	79	90
Houben, et al. (30)	2000	186/203	93

TABLE 51C.1. OPEN PYELOPLASTY

Endopyelotomy

The endoscopic approach to UPJ obstruction has been successful in both an antegrade and retrograde fashion. Balloon

dilation was attempted in 13 infants and children (median age of 16 months) (79). Following placement of a guidewire in a retrograde fashion along with dilation of the ureterovesical junction, a 3.8-Fr radial balloon dilator was used to dilate the UPJ, followed by stenting with a 4.8-Fr internal double pigtail catheter for 6 weeks. An overall success rate of 70% was achieved, but the follow-up was brief (3 to 6 months). A similar approach was used in several children using an Acucise device (Applied Medical, ureteral cutting balloon catheter, 5 Fr) (5). Postoperative stenting was required for 6 weeks, with a 100% success rate being achieved. In a much larger series of adult patients, Kim and colleagues (40) reported an overall success rate of 78%. However, two patients required angiographic studies and embolization of lower-pole branching arteries because they developed gross hematuria following Acucise endopyelotomy.

Antegrade endopyelotomy can be readily accomplished in both the adult and preadolescent or adolescent patient. Figenshau and Clayman (19) recommended this procedure for any patient with a reasonably functioning kidney (more than 25% on renal scan), mild to moderate hydronephrosis, and no evidence of a crossing vessel. Computed tomography (CT) or magnetic resonance imaging (MRI) can be used for preoperative assessment of a crossing vessel, or an endoluminal ultrasonography can be used before the procedure. Access to the kidney is usually achieved with the assistance of an interventional radiologist. A midpole posterior calyx provides good access to the UPJ. A percutaneous tract is established, which is dilated to 10 Fr (range of 10 to 18 Fr) if an Acucise balloon is used. An alternative is the use of a 2-Fr fine-tip right-angle electrosurgical probe. Direct visualization of the UPJ obstruction allows for use of a cold knife, electrocautery, and even contact laser fiber to achieve the endopyelotomy (64). Following fluoroscopic documentation of successful incision and/or dilation of the UPJ, a double-pigtail ureteral stent is placed under direct vision in the renal collecting system and fluoroscopically positioned into the bladder.

The issue at hand is whether the need for fluoroscopy with endourologic intervention along with two and sometimes three anesthetics for preoperative stent placement, endopyelotomy, and stent removal are justified when compared with the ease of an open pyeloplasty. Certainly, older pediatric patients may be managed with the less invasive procedures, with good overall results and improved postoperative convalescence.

Laparoscopic Pyeloplasty

The evolution of laparoscopic procedures includes the repair of the UPJ obstruction. Such a procedure is technically demanding because it requires the use of intracorporeal suturing (59). This technique has improved with the use of automatic laparoscopic suturing devices, which allow for much simpler placement of interrupted sutures. To date, most descriptions in the literature have included small series of patients (11,72). The initial descriptions of this technique included an intraabdominal approach with mobilization of the ascending or descending colon, depending on which kidney was affected. Tan described performing the procedure using a 7-mm umbilical trocar and two 6-mm instrument trocars (80). Gerota's fascia is opened with limited mobilization, and the UPJ obstruction is identified by tracing the dilated renal pelvis medially until the gonadal vessels are seen crossing the pelvis. Tan did not find it necessary to insert a ureteral catheter as a preoperative measure for identifying the UPJ. The pelvis is stabilized with a hitch stitch by passing a straight suture through the anterior abdominal wall, suturing the pelvis and passing the suture through the same entry point on the abdominal wall. External traction on the suture stabilizes the pelvis sufficiently to create the anastomosis. The pelvis is dismembered from the proximal ureter. The ureter is spatulated along its lateral margin using the renal pelvis to orient the ureter correctly. Anastomosis is begun by accurate placement of the suture at the apex of the spatulated ureter, taking care not to create a mucosal flap. The ureter is sutured to the most dependent part of the pyelotomy and the two dismembered ends reapproximated with an intracorporeal knot. The posterior anastomosis is completed with a continuous suture locked at the apex. The transanastomotic stent is placed by inserting a Teflon catheter into the anterior abdominal wall and steering it into the proximal ureter. A straight guidewire is passed through the catheter into the bladder. The catheter is withdrawn and a 3.8- or 5-Fr variable-length double-pigtail catheter is passed over this guidewire in an antegrade fashion into the bladder. The proximal end is placed in the renal pelvis. The anastomosis is then completed by closing the pyelotomy and anterior

layer with a second continuous suture. The hitch stitch is removed, the UPJ is allowed to drop back into the renal bed, and the proximal ureter and pelvis are inspected to ensure no kinking before the abdominal cavity is desufflated. The entire operation is completed within an average of 90 minutes (range of 70 to 160 minutes).

Table 51C.2 summarizes the published results of laparoscopic pyeloplasty. Even experienced laparoscopists can struggle with such a procedure, though. The patients tolerate surgery well, require reduced narcotics postoperatively, and are discharged home with shorter hospital stays than conventional open pyeloplasties.

TABLE 51C.2. LAPAROSCOPIC PYELOPLASTY

Author	Year	Patients/Kidneys	Primary/Secondary	Success (%)
Schuessler, et al. (72)	1993	5	5/0	100
Peters (59)	1995	1[a]	1	100
Moore, et al. (49)	1997	30	24/6	97
Tan (80)	1999	18[a]	16/2	87

[a]Pediatric.

PYELOURETEROSTOMY/URETEROURETEROSTOMY

Pyeloureterostomy or ipsilateral ureteroureterostomy can be used in duplex kidneys to treat upper-pole obstruction or reflux (usually to the lower pole). Significant difference in size does not seem to greatly affect the result. Huisman and colleagues report that significant luminal disparity at the time of ureteroureterostomy resulted in no adverse outcomes (33).

In complete ureteral duplication, the ureters may be treated as completely separate entities as long as care is taken to preserve the unique blood supply to each ureter. Often, when the ureteral orifices are close in the bladder, the distal portion of the duplex ureters will have a common blood supply and very tightly adherent sheath (common sheath). This is important to realize because separation of such ureters distally will result in ischemia of one or both ureters; therefore such ureters should be treated as a single unit. Proximal ureteroureterostomy or ureteropyelostomy and distal ureterectomy requires very careful dissection to preserve the blood supply of the ureter left in place. This is particularly true of the distal few centimeters of the ureter.

Surgical techniques for ureteroureterostomy and ureteropyelostomy are technically the same. Circumferential suture lines should be avoided; therefore the ureters are spatulated on opposite sides to elongate and oblique the suture line. Although, classically, interrupted 4-0 or 5-0 chromic sutures have been used, many surgeons are now running 6-0 or 7-0 monofilament resorbable sutures. The anastomosis should be absolutely watertight and leakage should *not* be expected. The key to a successful ureteroureterostomy is that it should be tension free, have good blood supply, be watertight, and have a stent going across the anastomosis.

A distal ureteroureterostomy is an excellent alternative for treating a *nondilated* ectopic ureter to an upper-pole segment. The upper-pole ureter is divided as distally as possible and sutured from end to side of the lower-pole ureter. Prestenting of the lower-pole ureter facilitates identification of this ureter and allows for placement of a stent across the anastomosis. The terminal portion of the ectopic ureter can either be left in place, dissected as far distally as possible or simply split widely, and its edges cautiously removed.

An alternative approach in the very young patient or a patient with significant function in the hydronephrotic upper-pole segment is to suture the upper-pole ureter (or pelvis) to the lower-pole pelvis (or ureter). This may be difficult in the patient with an intrarenal pelvis. In such a case, a proximal ureteroureterostomy may be considered. The approach would be like that for a dismembered pyeloplasty (anterior to the kidney but retroperitoneal), and the anastomosis should be free of tension. Table 51C.3 outlines the overall success rates for patients who have undergone either ureteroureterostomy or pyeloureterostomy.

Author	Year	*N*	Success (%)
Huisman, et al. (33)	1987	25	80[a]/85[b]
Smith, et al. (77)	1989	15	87
Shelfo, et al. (75)	1997	10	100[a]
Plaire, et al. (60)	1997	8	100
Bieri, et al. (4)	1998	22	91[b]

[a]Pyeloureterostomy. [b]Ureteroureterostomy.

TABLE 51C.3. URETEROURETEROSTOMY/PYELOURETEROSTOMY

What then is the risk of a distal ureteral stump causing a problem, and is there a certain anatomy that is more prone to developing an infection? This issue must be decided at the time of pyeloureterostomy or ureteroureterostomy. From the flank approach, the ureter can be dissected well down into the pelvis, particularly in the small child. A small inguinal incision can be made in an infant to remove the majority of the distal ureter, but a Pfannenstiel or Gibson incision may be needed in an older patient. In fact, 10% to 15% of patients can develop a urinary tract infection secondary to the ureteral stump being present (60). Those patients who develop a urinary tract infection were noted to either have reflux into the ectopic ureter preoperatively or developed reflux postoperatively. Thus reflux noted into the ectopic ureter necessitates ureteral stump removal at the time of the renal surgery.

The laparoscopic ureteroureterostomy or pyeloureterostomy has been hindered by intracorporal suturing. Experimental work has been performed using nonperforated titanium vascular closure staples to perform a ureteroureterostomy in a porcine model (43). Short-term histologic analysis shows that when a functionally patent anastomosis is achieved, the technique is fast and effective, without evidence of encrustation, stone formation, or intraluminal clips. Clinical application will undoubtedly be forthcoming.

Ureterocalicostomy

Neuwirt (52) is credited with the first description of the ureterocalicostomy, in which the ureter is sutured to the

renal capsule after successful anastomosis to a dependent calyx. This approach led to obstruction of the intrarenal ureteral segment because of fibrosis of the cortex. Jameson and colleagues (34) demonstrated that amputation of enough of the lower-pole cortex to permit the ureter to be safely joined to a tangential opening of the lower-pole calyx was required for success (Fig. 51C.5). Hawthorne and colleagues (24) emphasized this along with spatulation of the ureter to create a maximum diameter patent anastomosis. A stent and nephrostomy tube are usually used. Duckett performed the ureterocaliceal anastomosis over an 8-Fr feeding tube with running fine catgut. A nephrostomy tube (14-Fr Malecot) is also placed through the parenchyma into the renal pelvis or collecting system. Because the caliceal tissue may be inflamed, generous overlapping bites into the fornix and capsule may be of assistance in performing the anastomosis. An omental pedicle graft is brought through a posterior peritoneal window to wrap around the anastomosis. The nephrostomy is clamped, and the stent removed 2 to 3 weeks postoperatively. Such a repair for a previously failed pyeloplasty should be at least 2 months following the initial surgery to allow for resolution of the inflammatory process (15).

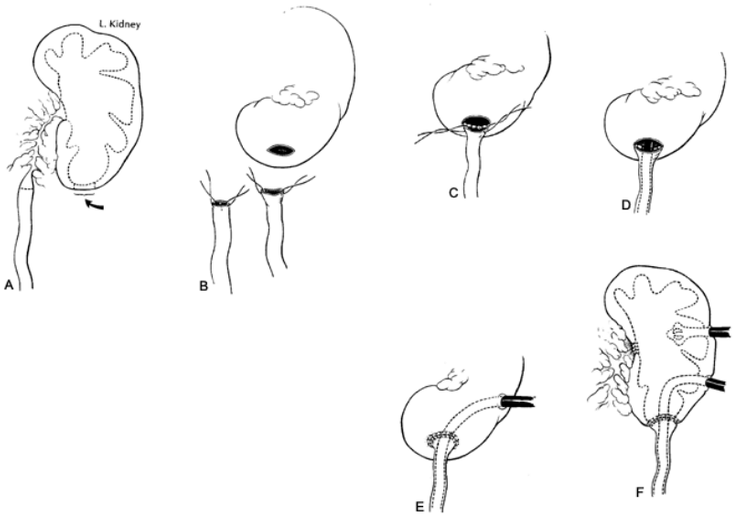

FIGURE 51C.5. Ureterocalyceal anastomosis for difficult situations in which anastomosis to the pelvis is impossible. **A:** The scar tissue is excised. The renal pelvis is closed after placing a stent and nephrostomy tubes. **B:** Ureterotomies are done after orientation sutures are placed in the ureter. The ureteral opening is enlarged, ready for the anastomosis. An elliptic segment of renal parenchyma is excised. The dimensions of the opening should be the same as those of the ureter to be anastomosed. **C:** Ureter is sutured to calyceal mucosa with interrupted 4-0 or 5-0 absorbable sutures. **D:** Ureteral stent is passed after posterior anastomosis is complete. **E:** Anastomosis is completed. **F:** Diagram of funneling. (Modified from Smart WR. Surgical correction of hydronephrosis. In: Harrison JH, et al, eds. *Campbell's urology,* ed 4. Philadelphia: WB Saunders, 1979, with permission.)

Although not as commonly used as some other techniques for dealing with a short ureter, the ureterocalicostomy can be particularly useful when the pelvis and upper ureter have been rendered unusable secondary to previous surgery or trauma (37). Table 51C.4 outlines several reported series of ureterocalicostomy and their overall success rate. Complications reported have included persistent obstruction of the ureter, renal artery thrombosis, anastomotic urinary leakage, and candidal perinephric abscess.

Author	Year	No. of Patients	Success (%)
Mesrobian and Kelalis (45)	1989	21	90
Ross, et al. (66)	1990	7	71
Selli, et al. (73)	1992	8	75
Rohrmann, et al. (65)	1997	3	100

TABLE 51C.4. URETEROCALICOSTOMY

TRANSURETEROURETEROSTOMY

One of the most useful techniques in urinary tract reconstruction is the transureteroureterostomy (TUU) (Fig. 51C.6). Following an initial description by Hodges and colleagues, the technique gained increasing popularity during the era of urinary undiversion (23,25,28). In both adults and pediatric series, reported success rates have exceeded 90%. This is been tempered by some reports of complications (16,69), but adherence to several principles ensures a uniformly favorable outcome. Wide exposure is essential and usually is achieved transabdominally. Adequate mobilization of the donor ureter is important so that a tension-free anastomosis can be accomplished. Wide

ureteral mobilization, including the gonadal vessels in some cases, permits the ureter to be brought to the opposite side without tension. If the ureter is too short to lie comfortably under the inferior mesenteric artery, the ureter should be placed above the vessel. The anastomosis should be placed on the medial wall of the recipient ureter. When possible, the recipient ureter should be left *in situ* without mobilization. This ensures a better blood supply to the area of anastomosis. Spatulation of the donor ureter should ensure a generous anastomosis with the recipient ureter. Size discrepancy between the ureters is not a problem. If the donor ureter is larger than the recipient ureter, it simply is cut at a right angle. The length of incision in the recipient ureter can be varied as needed. Drainage is particularly critical to prevent extravasation of urine and subsequent fibrosis with wound contracture around the TUU. Urine has a remarkable ability to induce the formation of fibrous tissue (55). Accordingly, ureteral wounds from which urine has been diverted have considerably less fibrosis surrounding them. A ureteral stent across the anastomosis is critical. As with any ureteral anastomosis, it should be watertight and well drained to prevent the potential for scar formation. Meticulous attention to technique clearly contributes to the achievement of this goal.

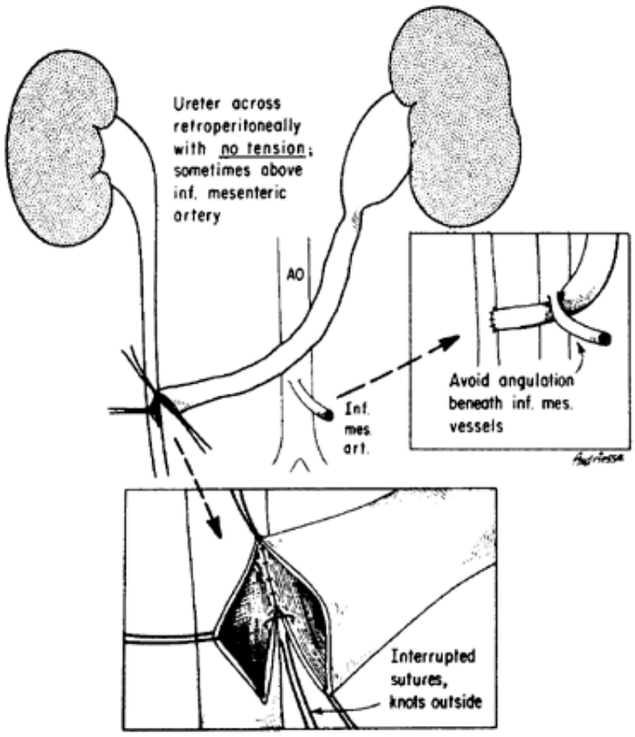

FIGURE 51C.6. Transureteroureterostomy. Meticulous attention to technical detail and avoidance of tension gives a high success rate. (From Hendren WH, Hensle TW. Transureteroureterostomy: experience with 75 cases. *J Urol* 1980;123:826, with permission.)

The usefulness of TUU is primarily in letting one good ureter serve as effective drainage for two renal units. On the other hand, both kidneys are now dependent on drainage from a single ureter. One good long reimplant with a TUU is usually better than two compromised reimplants. The psoas hitch contributes to success in this endeavor. In general, the better ureter with the least dilation is the preferred ureter in which to reimplant into the bladder. Used in this way, TUU can make a major contribution to successful nonrefluxing reconnection of the upper urinary tract to the bladder or urinary reservoir. Table 51C.5 outlines the results of both historical series and contemporary series in which a TUU was used. The overall success rate has been uniformly very good, with successful outcomes reflecting the diverse applications of the TUU (3,7,14). Patients included those with failed ureteroureterostomy, exstrophic bladder, spina bifida, noncontinent diversion, undiversion, and neuropathic bladder. Complications cited were rarely associated with the ureteral anastomosis but included anastomotic leakage, ischemic stenosis of the common ureteral trunk, and progressive deterioration of renal function in one kidney.

Author	Year	*N*	Success (%)
Hodges, et al. (28)	1980	100	94
Hendren and Hensle (25)	1980	75	96
Rushton, et al. (67)	1987	31	85
Villers, et al. (83)	1988	52	98
Campobasso, et al. (8)	1989	52	98
Rainwater, et al. (63)	1991	67	75
Mure, et al. (50)	2000	69	80[a]/ 96[b]

[a]Good results with no upper trace dilation.
[b]Without dilation.

TABLE 51C.5. TRANSURETEROURETEROSTOMY

Psoas Hitch and Boari Flap

A large and supple bladder can be used to make up for a deficient ureter. Even when the bladder is small and thick walled, it can often be gently stretched and surgically reshaped to permit a ureteral reimplant to be performed. In general, it is more satisfactory to use up bladder in achieving a nonrefluxing uroepithelial-to-uroepithelial anastomosis

than being concerned about the lack of bladder volume that can follow. Augmentation of the bladder effectively deals with the bladder problem, although it too has its own set of problems.

The mobilization of the portion of the bladder by suturing it upward against the psoas muscle above the iliac vessels was popularized in the late 1960s (62,81). This vesicopsoas hitch facilitates reimplantation of the short ureter and permits placement of at least the distal third of the ureter without difficulty (Fig. 51C.7).

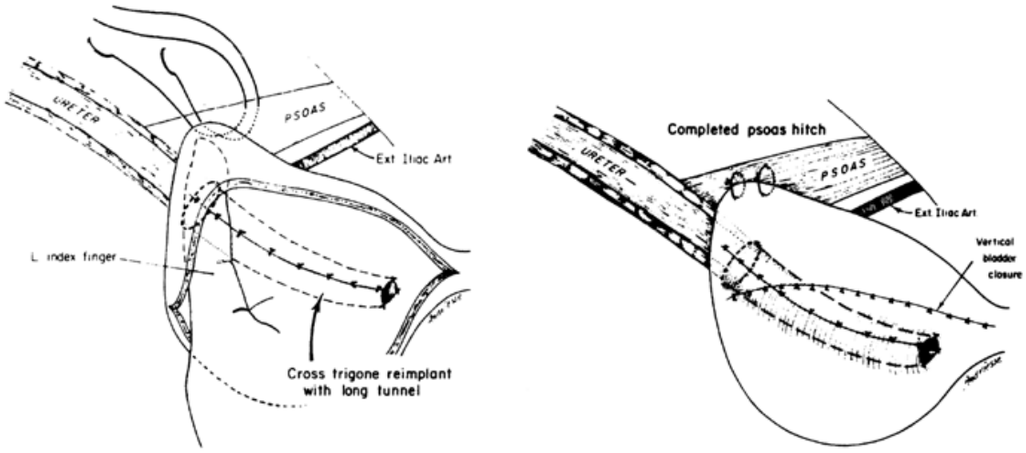

FIGURE 51C.7. Vesicopsoas hitch. Stretch of the bladder and fixation to psoas muscle permits a good reimplant of a short or dilated ureter. The Boari flap is an extension of this technique with a broad flap of detrusor hinged at the bladder dome. (From Hendren WH. Some alternatives to urinary diversion in children. *J Urol* 1978;119:653, with permission.)

The principles as espoused by Hendren (27) in performing such a procedure include opening the bladder on the side away from the proposed hitch to permit more bladder to the stretched up toward the psoas muscle. To facilitate a permanent fixation of the bladder to the muscle, fat is cleared off the psoas and bladder wall to ensure muscle-to-muscle apposition. Either absorbable suture or permanent suture is then placed through the bladder wall but not including the mucosa. It is generally easier to make the hiatus after seeing where the bladder will lie comfortably against the psoas and then creating the submucosal tunnel before fixing the bladder into position. The surgeon can hold the stretched bladder up against the psoas, relieving tension, while the assistant ties down the three to five sutures necessary to anchor the bladder. The sutures directed into the psoas muscle should avoid the genitofemoral nerve. The ureter is then drawn into the submucosal tunnel, taking care that there is no angulation or torsion at the hiatus. Stenting the ureter becomes the surgeon's preference at this point.

The Boari flap is an extension of the concept of the vesicopsoas hitch. Although originally performed successfully by Casati and Boari (10) in experimental dogs, the popularization of the use of a bladder flap for ureteral replacement is the work of Ockerblad (53). In this procedure, a bladder flap is formed from the front wall of the bladder with its hinge at the lateral dome of the bladder, permitting the flap to be rotated upward toward the kidney. By combining this flap with the vesicopsoas hitch, a nearly complete replacement of the ureter can be performed. Essential to the success of this flap is the preservation of a good blood supply to the bladder muscle that constitutes it. The base of the flap should be wider than the apex, and following the principles of plastic surgery, it is best to maintain a length-to-diameter ratio of not greater than 2:3 to 2:1. Boxer and colleagues (6) recommended a base with a width of at least 4 cm and apex of at least 3 cm. It is wise to fix the length of the muscular flap posteriorly against the muscle of the gutter to maintain its position. After the attachment of the ureter, it is tubularized as part of the bladder closure. An antirefluxing, submucosal course for the ureter in the upper portion of the flap can be created as recommended by Gil-Vernet (21).

MEGAURETER

The dilated ureter may contribute to urinary stasis and ineffective peristalsis, which can lead to ongoing damage to the kidney in the form of obstruction and recurrent urinary tract infections. Often diagnosed before birth, the newborn with a megaureter is placed on antibiotic prophylaxis. Voiding cystourethrography (VCUG) and diuretic renography determine the type of megaureter: refluxing, obstructed, both obstructed and refluxing, or neither with or without bladder outflow obstruction. Ureterostomy can stabilize the infected kidney and result in reduction of the ureteral ectasia and reduced ureteral scarring, even potentially making tapering

at subsequent reimplantation unnecessary (82). However, ureterostomy may also severely compromise the potential for future ureteral reconstruction.

Hendren's extensive experience with megaureters included performing an upper ureteral repair in nearly 50% of their patients during the 1960s, but only 14% in the 1990s (27a). Successful distal ureteral tapering and reimplantation led to a decrease in the diameter of proximal ureters the majority of the time. The technique of excisional tapering requires careful handling of the periureteral tissues, which provide blood supply to the ureters. The ureter is initially approached intravesically and then extravesically to straighten the ureter maximally. The redundant portion is excised, and formal tailoring performed. The lateral portion of the ureter is preserved and the redundant medial portion excised, with tubularization being performed over a 8- to 12-Fr catheter. The ureter must be gradually tapered to prevent an abrupt transition, which can lead to obstruction. The ureter is closed in a watertight fashion with a running, locking fine absorbable suture, followed by a second layer of absorbable suture. The distal aspect of the ureter is closed with interrupted suture to permit distal resection of the ureter. The ureter is then reimplanted using either a cross-trigonal or Politano-Leadbetter technique.

Carr and Hendren's overall success rate was greater in the obstructed megaureters as opposed to the refluxing megaureters (93% versus 83%). Presumably, this reflects the increased potential for scarring in the refluxing megaureter. The bladder's status also affected the outcome, with “normal” bladders providing for a greater success than those with a history of prior obstruction.

The excisional tapering repair was joined subsequently by two different infolding techniques: the Kalicinski and Starr procedures. These techniques decreased ureteral diameter by imbrication. The Kalicinski ureteral folding technique involves a running suture down the lateral aspect of the ureter to narrow the diameter (35). This free margin of the ureter is then folded back onto the ureter with interrupted sutures. Thus the diameter of the ureter is narrowed, but the bulkiness of the ureter remains. Ehrlich (17) reported an overall success rate of nearly 95% from megaureter surgery using his modification of the Kalicinski repair for megaureters. He simply folded the ureter under the narrowed lumen after placing horizontal mattress sutures to narrow the caliber of the ureter. Starr (78) described a double plication technique to accomplish a reduction in the caliber of the ureter, but this approach of double-folding may have a greater potential for obstruction to occur. Table 51C.6 lists the overall success rate for a number of contemporary series of megaureter repairs.

Author	Year	Technique	Megaureters	Type	Success (%)
Ehrlich (17)	1985	Folding	74	O, R	94.6
Peters, et al. (58)	1989	Variety	42	O	88
Hendren and Carr (27a)	1993	Tailoring	404	O, R	93/83
Mollard, et al. (47)	1993	Variety	39	O	92
Perovic (57)	1994	Extravesical (tunnel/psoas)	167	O, R	97
Kalicinski	1996	Folding	56	O	93
Vereecken and Proesmans (82)	1999	Variety	70	O	100

O, obstructed; R, refluxing.

TABLE 51C.6. MEGAURETERS

URETERAL RECONSTRUCTION

A number of surgical techniques for ureteral replacement have been described that may become of historical footnote, especially in an era in which tissue engineering holds great promise. The Davis intubated ureterotomy, first described in 1943, depends on secondary epithelialization from an incised ureter. It is no different than the endopyelotomy, in which prolonged stenting facilitates healing of this ureteral segment. An intact blood supply to the segment of the ureter is critical to facilitate appropriate healing. Whereas in the past a 70% satisfactory result was reported by Frohmuller, one wonders whether the use of small intestinal submucosa (SIS) may be beneficial in covering the intact mucosa of the incised ureter (1). Preservation of intact urothelium may be preferable to a small bowel pyelopyelostomy or segmental intestinal interposition (26).

The literature is replete with descriptions of free graft materials in experimental ureteral replacement, such as bladder mucosal graft (31,32), parietal peritoneum (18), and split-thickness skin graft (29). There are also descriptions of pedicle grafts using appendix (71), full-thickness abdominal wall skin to form a tube (38), and renal pelvis as a successful total ureteral replacement in association with giant hydronephrosis (39). Thus there may be a use for an occasional autogenous pedicle graft repair in clinical practice.

Goodwin and associates (22) popularized the *ileal ureter.* Hendren (26) reported further refinements in the technique. The review of the UCLA experience with children highlighted the importance of bladder emptying in situations of a refluxing ileal ureter (6). The ability of the ileum to resorb urea and electrolytes also can cause complications in patients with significant renal failure, particularly if compounded by poor drainage of the system. Hyperchloremic acidosis was not seen in the UCLA experience if the serum creatinine was less than 2 mg/dL before ileal ureter

construction. If intrahepatic disease limits urea metabolism, hyperammonemia can also be a problem. Middleton (46) demonstrated that the absorption of urinary solutes is directly proportional to the surface area of the ileum exposed and transit time. Ileal tapering reduces the surface area significantly, and this theoretically should be advantageous in the creation of ileal ureters in patients in renal failure. Furthermore, tapering of the lower ureters appears to be important in achieving an antirefluxing anastomosis of the ileal ureter to the bladder.

With the construction of a transversely tubularized bowel segment (TTBS) for use as a catheterizable channel, it seems only natural that this principle would be applied for ureteral replacement. Two case reports exist describing ureteral replacement using a reconstructed 2-cm segment of right colon (61) and transverse colon (36). The TTBS has advantages over ileum, tapered or not, for ureteral replacement. The segment used is much smaller, offering less surface to be exposed to urine. A double tube can replace extensive ureteral segments. Additional experience and long-term follow-up will be necessary to determine the ultimate utility of such a procedure, but this technique has rapidly gained favor for the reconstructive surgeon (48).

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51D AUGMENTATION CYSTOPLASTY

Michael E. Mitchell

J. Chadwick Plaire

Part of "51 - TOOLS OF RECONSTRUCTION "

M.E. Mitchell: Department of Urology, University of Washington; Division of Pediatric Urology, Children's Hospital and Regional Medical Center, Seattle, WA 98105.

J.C. Plaire: Children's Urology Associates, Las Vegas, NV 89109.

Augmentation cystoplasty is performed to increase bladder capacity and compliance. The primary use of augmentation cystoplasty in children is to protect renal function, to achieve urinary continence, and often, to facilitate urinary tract reconstruction. The most common problems associated with the need for bladder augmentation in children are neurogenic bladder dysfunction secondary to myelodysplasia, exstrophy of the bladder, and posterior urethral valves. However, many other conditions have resulted in the need for bladder augmentation (Table 51D.1).

Neurogenic Bladder
Myelodysplasia
Sacral agenesis
Caudal regression
Spinal tumors, vascular malformation
Myelitis
Idiopathic
Congenital
Exstrophy (cloacal, classic, epispadias)
Posterior urethral valves
Cloaca
Urogenital sinus
Bilateral single ectopic ureters
Infantile bladder syndrome
Ureterocele
Prune-belly syndrome
Other
Infection (tuberculosis, viral cystitis, bacterial cystitis)
Interstitial cystitis
Iatrogenic (multiple surgeries)
Chemotherapy
Radiation therapy
Tumor (rhabdomyosarcoma, neurofibromatosis)

TABLE 51D.1. CONDITIONS THAT MAY REQUIRE BLADDER AUGMENTATION

Only a small percentage of children undergoing augmentation cystoplasty can completely empty their bladder by voiding spontaneously. Therefore it was the success and widespread acceptance of clean intermittent catheterization in the mid-1970s that made augmentation cystoplasty and continent urinary diversion possible in children (34,35).

Intestinal segments commonly are used in augmentation cystoplasty. Ileum, sigmoid, and stomach all have been used, and studies show all these segments to be reliable (20,39,54). However, viable alternatives for bladder augmentation include the use of a dilated ureter (either naturally dilated or balloon dilated) and autoaugmentation. Autoaugmentation involves excision of the detrusor muscle from the dome of the bladder, allowing the epithelium to form a large diverticulum (6,10,11,14,45). Currently, tissue-engineered substrates such as small intestine submucosa (SIS) and synthetically engineered tissues are being investigated and may be commonly available in the future (24,31,33,44). At this time, gastrointestinal (GI) segments remain the gold standard for increasing bladder capacity and improving compliance. Even so, there are significant potential problems with using intestinal segments in the lower urinary tract. In children, some of these, such as the resorption of ammonium chloride with the use of large and small bowel, result in significant negative consequences such as chronic metabolic acidosis and associated growth retardation.

Therefore augmentation cystoplasty is offered only after medical intervention such as anticholinergic medicines and intermittent catheterization have failed to achieve dryness or to improve bladder compliance sufficiently. Almost all children who undergo augmentation cystoplasty will require intermittent catheterization. The commitment and capacity of both the child and the family to comply with catheterization must be assessed carefully. Any failure with catheterization could result in complication and potential harm to the patient. All potential complications should be discussed in detail with the family.

THE TECHNIQUE OF AUGMENTATION CYSTOPLASTY

General Principles

In augmentation cystoplasty, the two critical aspects of the surgery are the preparation of the bladder and the augmentation segment chosen.

Bladder

In augmentation cystoplasty, the bladder usually is addressed first. Most commonly, a midline incision is used to

expose the abdomen and pelvis. If possible, the peritoneum is not entered until the bladder has been prepared for augmentation. Therefore the peritoneum initially is dissected off of the dome and the posterior wall of the bladder. The bladder is then opened in the sagittal plane from the bladder neck anteriorly to the trigone posteriorly, thus forming a "clam-shell" configuration (Fig. 51D.1). This maneuver is extremely important because the bladder must be opened fully to prevent the augmentation segment from acting as a diverticulum with the formation of an "hour-glass" deformity. Supratrigonal cystectomy generally is not recommended because the augmentation segment is anastomosed to the wings of the bisected bladder. The native bladder wings can be used for implantation of a continent catheterizable channel (e.g., Mitrofanoff) or ureteral reimplantation. Concurrent procedures, such as ureteral reimplantation or bladder neck reconstruction, are performed before harvesting the augmentation segment. The exception is when concurrent placement of an artificial urinary sphincter (AUS) is performed. The AUS usually is placed after the augmentation cystoplasty is completed and the abdomen irrigated.

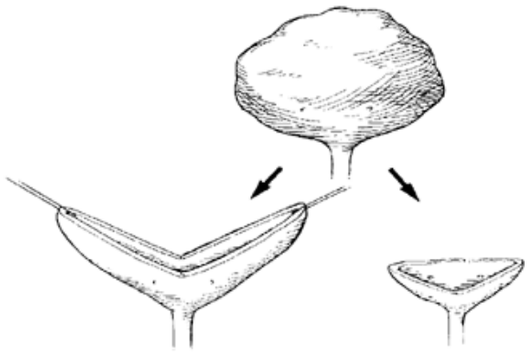

FIGURE 51D.1. The dysfunctional bladder is opened in the sagittal plane from the bladder neck to the trigone.

Augmentation Segment

The size and configuration of the augmentation segment probably are more important than the type of bowel used. To maximize the benefit of a given segment, it must be reconfigured ("detubularized") to maximize the added surface area to the bladder. The end-objective is a spherical bladder that, by geometry, maximizes the volume for a given bladder wall area (Fig. 51D.2). In addition, the spherical configuration also maximizes the radius of curvature, thereby increasing surface tension for a given bladder pressure, which tends to lead to further bladder expansion. This is the relationship of Laplace's law (T = kRP), where *T* is wall tension, *k* is a constant dependent on elasticity and wall characteristics, *R* is the radius of curvature, and *P* is the luminal pressure (Fig. 51D.3). Furthermore, by opening the tubular intestine on its antimesenteric border and reconfiguring the segment, the intrinsic innervation is disrupted and peristalsis is decreased significantly (22,29) (Table 51D.2). In general, the length of segment used depends on the radius of the bowel used; therefore a longer segment of small bowel usually is required. The length of segment used depends on the patient's age, available intestine, the size of the pelvis, and required bladder volume; usually this translates into a segment of 15 to 30 cm. If a segment of stomach is to be used as the augmentation segment, a wedge of at least one-third of the stomach is harvested (3). The gastric wedge requires no reconfiguring because it fits well onto the bivalved bladder (Fig. 51D.8). If the ureter is to be used as an augmentation segment, there must be significant dilation and it should likewise be detubularized before being anastomosed to the bladder (2) (Fig. 51D.9).

	Mean	Mean	Mean	Mean Value	First Contraction		Max. Contraction	
Cystoplasty	Age (yr)	F/U (mo)	Cap (mL)	At 300 mL cm H_2O	Mean Vol (mL)	Mean P cm H_2O	Mean Vol (mL)	Mean P cm H_2O
Tubular right colon	17.5	9.7	630	18.6	139	37	467	63
Detubularized right colon	28.5	5.1	641	9.4	329	24	596	42
Tubular ileum	66.8	7.0	311	36	110	60	218	81
Detubularized ileum	20.0	5.7	403	14.4	197	22	265	28

From Goldwasser B, et al. Cystometric properties of ileum and right colon after bladder augmentation, substitution or replacement. *J Urol* 1997; 138(2):1007, with permission.

TABLE 51D.2. EFFECT OF DETUBULARIZATION OF COLON AND ILEUM ON CYSTOPLASTY COMPLIANCE AND CONTRACTION

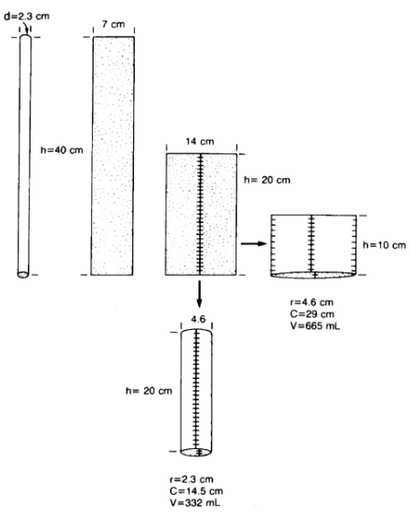

FIGURE 51D.2. Calculated capacity of 40-cm segment opened and folded twice is 665 mL. C, circumference; d, diameter; h, height; r, radius; V, volume. (From Hinman F Jr. Selection of intestinal segments for bladder substitution: physiological characteristics. *J Urol* 1988;139:521, with permission.)

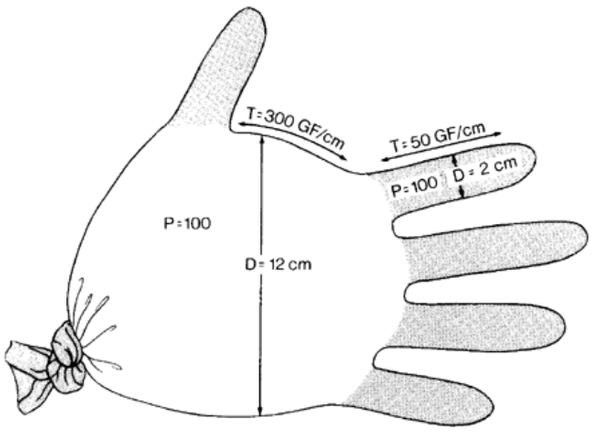

FIGURE 51D.3. Inflated surgeon's glove illustrates Laplace's relationship. Although pressure *(P)* is equal throughout, tension *(T)* is greater in proportion with greater diameter *(D).* (From Hinman F Jr. Selection of intestinal segments for bladder substitution: physical and physiological characteristics. *J Urol* 1988;139:522, with permission.)

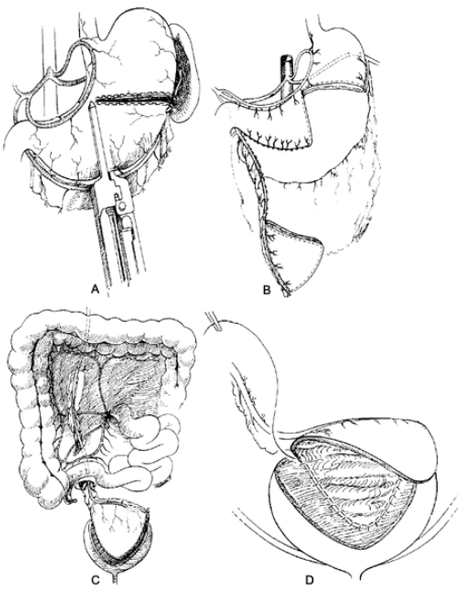

FIGURE 51D.8. A: A wedge from the body of the stomach is harvested with a stapling device. **B:** The gastric wedge usually is based on the blood supply from the right gastroepiploic vessel. **C:** The gastric wedge is brought through the transverse colon and small bowel mesentery to reach the bladder. **D:** The gastric wedge is sutured to the bladder in two layers.

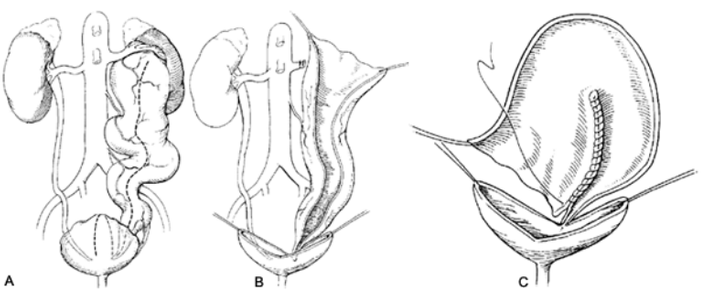

FIGURE 51D.9. A: A megaureter and poorly functioning kidney are required for ureterocystoplasty. **B:** After nephrectomy, the dilated ureter is detubularized, taking care to preserve the blood supply. **C:** The detubularized ureter is reconfigured before being anastomosed to the bladder.

The choice of augmentation segment needs to be tailored individually to each patient. For example, a patient with a short ileal mesentery may require use of the sigmoid to allow for a tension-free anastomosis. Patients with short gut, renal insufficiency, or a history of pelvic radiation may be better served with a gastrocystoplasty (3). Patients with myelomeningocele or imperforate anus theoretically could develop diarrhea if the ileocecal valve is taken from their GI tract (19,28). Other factors to consider include the need for ureteral reimplantation and the need for a continent catheterizable channel. In addition, if the child has a urinary

concentrating defect and makes large volumes of urine each day, then a larger segment may be required to provide sufficient capacity. Therefore it is important to consider each patient individually when selecting the appropriate augmentation segment (Table 51D.3).

Bowel Segment	Advantages	Disadvantages
Stomach	1. Previous radiation, short gut 2. Prevents systemic acidosis, salt retention 3. Facilitates tunnels for continence and antireflux 4. Reduces infection 5. May potentiate growth in children	1. Acid secretion salt loss, metabolic alkylosis 2. Hematuria-dysuria syndrome 3. More difficult to use
Jejunum	1. Few, not recommended	1. Salt and water loss, metabolic acidosis
Small Bowel	1. Availability 2. Good compliance 3. Less mucus	1. Metabolic acidosis salt resorption 2. Loss of resorption surface in GI tract (B_{12}, folate) 3. Sometimes difficult to work with (no tunnels)
Cecum	1. Availability 2. Good compliance 3. Potential for tunnels and use of IC valve	1. Metabolic acidosis, salt and water resorption 2. Loss of IC valve may cause diarrhea
Sigmoid	1. Most available 2. Good compliance 3. Potential for tunnels	1. Not available in some patients (radiation, constipation) 2. Metabolic acidosis, salt and water resorption 3. Possible increased potential for rupture

GI, gastrointestinal.

TABLE 51D.3. ADVANTAGES AND DISADVANTAGES OF SPECIFIC BOWEL SEGMENTS IN CHILDREN

Techniques of Augmentations

Ileocystoplasty

Use of ileum as an augmentation segment dates to the nineteenth century. As noted previously, the segment of ileum must be detubularized and reconfigured (Fig. 51D.4). A segment 15 to 30 cm in length with excellent blood supply is selected and folded back onto itself. This will permit assessment of the mesentery to ensure that the segment will reach into the pelvis without tension. Bowel clamps are used to prevent spillage of succus into the abdomen. An ileoileostomy is then performed superior to the isolated segment. The isolated segment is irrigated and opened on its antimesenteric border. The ileal segment is then folded into a U, S, or W shape, and the edges are sutured with a running absorbable suture. Once reconfigured, the reconfigured ileal cap is anastomosed to the bivalved bladder. It is easiest to start the anastomosis at the most posterior apex of the bivalved bladder. A suprapubic tube is brought out through the native bladder wall for drainage. Ileum does not allow for standard reimplantation of the ureters or the creation of a continent catheterizable channel (i.e., Mitrofanoff), but newer techniques such as the seromuscular trough, as described by Abol-Enein and Gonheim (1), do allow the use of ileum should these procedures be required (Fig. 51D.5). However, because of its muscle backing, native bladder (or a gastric flap) is still

the primary choice for ureteral reimplantation or construction of a Mitrofanoff valve.

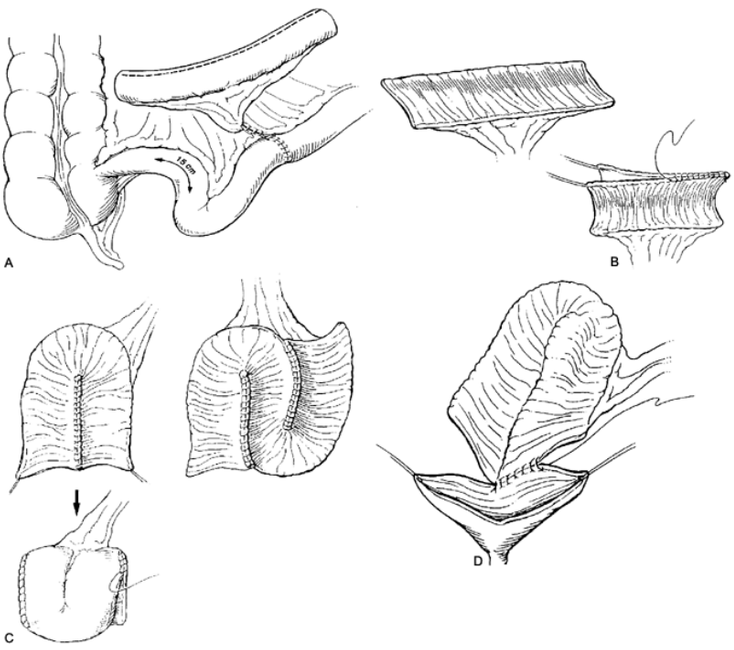

FIGURE 51D.4. A: A 15-cm segment of ileum proximal to the ileocecal valve is isolated and an ileoileostomy is performed. **B:** The isolated segment of ileum is opened along the antimesenteric border. The opened segment is then folded and the edges are sutured together. **C:** The opened segment is reconfigured to increase the surface volume. **D:** The reconfigured ileum is anastomosed to the opened bladder beginning at the posterior apex.

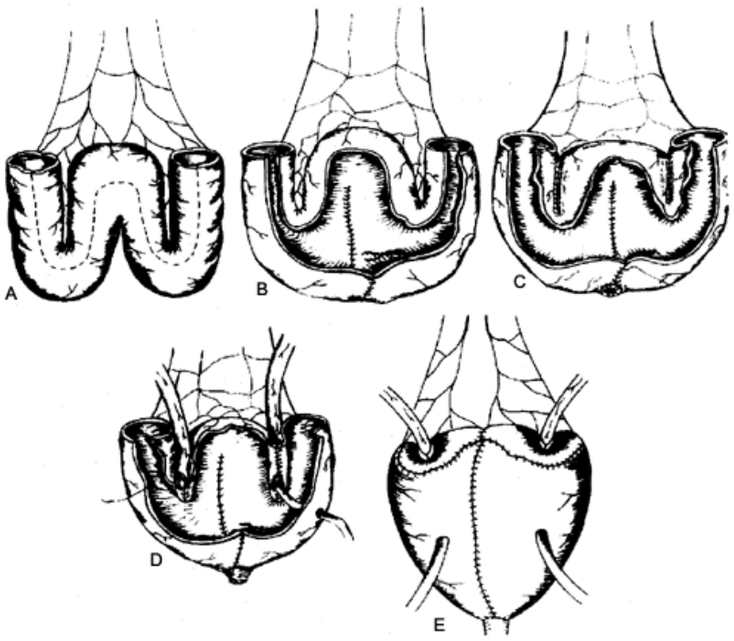

FIGURE 51D.5. A–E: The seromuscular trough formed by anastomosing the edges of the ileum together allows for nonrefluxing ureteral reimplantation into the ileum.

Sigmoid Cystoplasty

Sigmoid colon continues to be a commonly used segment in augmentation cystoplasty (21) (Fig. 51D.6). Native sigmoid produces strong unit contractions in its tubular form; therefore it must be opened and reconfigured. The proximity of the sigmoid colon to the bladder makes it a convenient choice, and mesenteric length is rarely a problem. A segment of sigmoid is isolated and divided along with the mesentery, preserving excellent blood supply. Colocolostomy usually is performed inferior to the isolated segment. Once the isolated segment is irrigated, it is opened along its antimesenteric border. The sigmoid can then be folded into a U shape and the edges anastomosed together before suturing to the bladder. In an alternative method described by Mitchell (40), the ends of the isolated sigmoid segment are closed and the opened antimesenteric edges are anastomosed to the bivalved bladder (Fig. 51D.7).

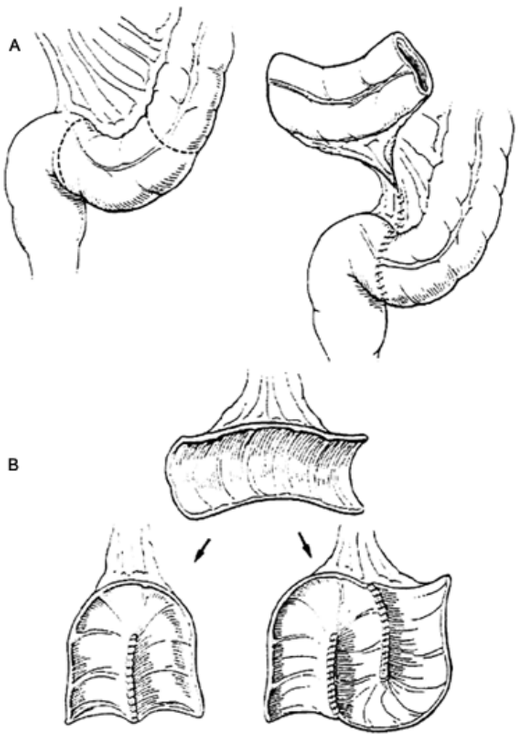

FIGURE 51D.6. A: A segment of the redundant sigmoid is resected and bowel continuity is reestablished. **B:** The isolated segment of sigmoid is opened on its antimesenteric border and then reconfigured before being anastomosed to the bladder.

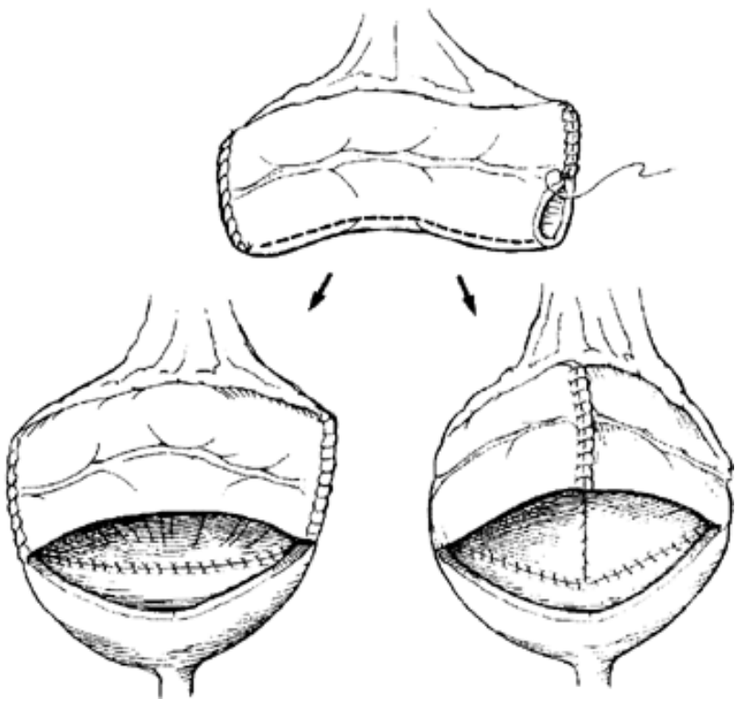

FIGURE 51D.7. The isolated segment of sigmoid is opened along the antimesenteric border. The two ends are then closed and the opened antimesenteric edges are sutured to the bladder.

Gastrocystoplasty

In 1988, Adams and colleagues (3) described the wedge gastrocystoplasty (Fig. 51D.8). This procedure requires an extended abdominal incision from the xiphoid process to the pubic symphysis. A gastric wedge from the midportion of the greater curvature of the stomach is harvested. The right gastroepiploic usually is more robust, but sometimes the segment can be based on the left gastroepiploic (common in the cloacal exstrophy patient). The wedge segment to be harvested includes both the anterior and posterior walls. The omentum is mobilized off of the transverse colon

and the stomach is grasped with Babcock clamps and brought into the surgical field. Generally, one-third of the stomach is harvested with the use of an intestinal stapling device. The short gastric branches off the proximal gastroepiploic vessel must be divided, leaving the short gastric branches to the augmentation segment intact. The stomach is closed in layers and a nasogastric tube is placed through the anastomosis. The isolated segment is then brought through both the transverse colon mesentery and the small bowel mesentery so that the pedicle is retroperitoneal. Next, the segment is anastomosed to the bivalved bladder. If a stapling device is used to harvest the stomach, the staple line must be excised before completing the anastomosis. The stomach wall provides an ideal backing for both ureteral reimplantation and the Mitrofanoff procedure.

Cecocystoplasty and Ileocecocystoplasty

The same principles used in other GI segments apply to the use of cecum and ileocecal segments. However, these segments usually are not used in patients with a neurogenic bladder secondary to spina bifida. These patients often rely on the ileocecal valve for fecal continence and may develop diarrhea postoperatively if the ileocecal valve is taken (19,28). However, the segments do provide teniae, which can be used as a flap-valve continence mechanism for reimplantation of ureters or a continent catheterizable channel.

Alternatives to Gastrointestinal Cystoplasty

Alternatives to intestinocystoplasty in children are given in Table 51D.4 .

Alternative	Advantages	Disadvantages
Ureter	1. Urinary epithelium, no mucus 2. Good compliance	1. Only applicable if the patient has a dilated ureter 2. Ureter may be scarred (reflux, infection)
Autoaugmentation (bladder myomectomy)	1. Urinary epithelium, no mucus 2. Relatively easy, no bowel resection	1. Inconsistent results can result in bladder scarring 2. Sometimes difficult (bladder scarring or diverticula)
Demucosalized intestinal flap on urothelium (colon, DAWG)	1. Urinary epithelium, decreased mucus 2. More physiologic	1. Difficult procedure 2. Inconsistent results
Bladder regeneration on substrate (SIS)	1. No bowel resection 2. Easily performed	1. Unproven in children 2. Dependent on native bladder potential for regeneration
Tissue engineering	1. Bladder regrowth in laboratory 2. Potentially unlimited capacity, no mucus	1. Unproven in children 2. Dependent on vascular and nerve ingrowth

DAWG, demucosalized augmentation with gastric segment.

TABLE 51D.4. ALTERNATIVES TO INTESTINOCYSTOPLASTY IN CHILDREN

Ureterocystoplasty

A massively dilated ureter and a nonfunctioning or poorly functioning kidney are the prerequisites to ureterocystoplasty (Fig. 51D.9). As with GI segments, the ureter is detubularized and folded into a U shape to increase the surface area and volume. The ureter may be opened all the way through the ureteral orifice, or a small nondetubularized distal segment may be left intact (2). The ureter then is anastomosed to the bivalved bladder in standard fashion. Great care must be taken to protect the blood supply to the ureter when performing the nephrectomy and mobilization of the ureter. The proximal ureteral blood supply comes from the aorta and is medial to the ureter, whereas the distal ureteral blood supply arises posterolateral. The major drawback to the use of ureter in augmentation cystoplasty is the paucity of patients who have both a megaureter and a nonfunctioning kidney. However, it has been shown in the animal model that it is possible to experimentally dilate a normal ureter and successfully use this for bladder augmentation (25).

Autoaugmentation

In autoaugmentation, the detrusor on the dome of the bladder is excised, leaving the mucosa intact and forming a diverticulum (Fig. 51D.10). The lateral edges of the bladder with intact detrusor can be sutured to the psoas muscle to prevent collapse of the diverticulum. The major drawback to autoaugmentation is limited increase in capacity and long-term scarring or fibrosis of the autoaugmentation segment. Some authors have combined autoaugmentation with demucosalized GI segments such as the stomach and the sigmoid colon (7,13,15,18). The long-term results of this type of augmentation are not consistent (9). Gonzalez and associates continue to use demucosalized sigmoid along with autoaugmentation in certain patients and reported a lower incidence of bladder calculi and mucus production (18).

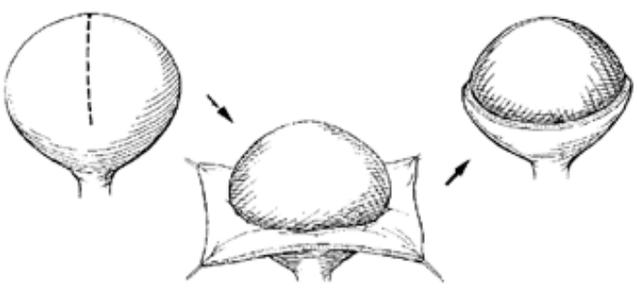

FIGURE 51D.10. In autoaugmentation, the detrusor is excised leaving the urothelium to act as a diverticulum.

CONTINENT URINARY RESERVOIRS

In children, a bladder that can be used in augmentation cystoplasty usually exists. However, if a suitable bladder template does not exist, then a heterotopic or orthotopic continent urinary reservoir may be constructed. Most of the experience with the various types of continent urinary reservoirs relates to the adult population following cystectomy.

However, at least two of these continent reservoirs were developed initially for pediatric patients. The Indiana pouch initially was used in patients with exstrophy who had previous cystectomy and the Kock pouch was developed by a pediatric surgeon to create a continent ileostomy. Examples of reservoirs now sometimes employed in the pediatric population include the Indiana pouch, Kock pouch, and gastric pouch (36,49,52). Obviously, many other continent reservoirs can be applied to children. The difficulty with the construction of a continent reservoir in children often is that a major limitation is that of limited useful intestine for construction of a urinary reservoir. For example, in the patient with cloacal exstrophy there is commonly an associated deficiency of large and small bowel such that stomach is the only reasonable tissue that can be used. This limitation is rarely present in the adult patient. The surgeon frequently must have imagination and individualize the reconstruction based on the patient's needs.

Indiana Pouch

The Indiana pouch is a continent urinary reservoir formed from an ileocecal segment of intestine (49) (Fig. 51D.11). Approximately 8 to 10 cm of terminal ileum, along with 20 cm of cecum and ascending colon, is harvested. Bowel continuity is reestablished. The colon segment is then split along its antimesenteric border up to the base of the cecum. The ureters are reimplanted into the tenia of the colon, thus creating a nonrefluxing anastomosis. The ileum is used as the efferent catheterizable channel. However, the ileum requires narrowing and this usually is done with a stapling device to ensure creation of a smooth, uniform caliber channel. The continence mechanism is based on the ileocecal valve, and continence is promoted by plication of the valve with Lembert sutures. The pouch is then closed by folding the distal colon down. The efferent limb is brought out as a stoma in the right lower quadrant. If the appendix is available, it can be used to construct the catheterizable channel (i.e., Penn pouch) and the terminal ileum can be used to augment the cecal reservoir.

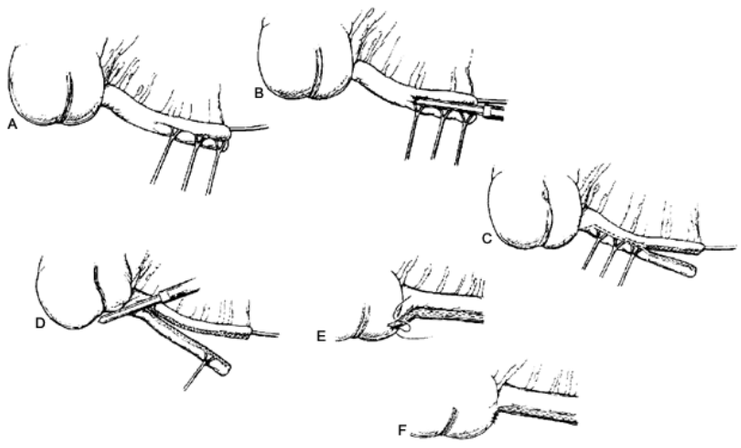

FIGURE 51D.11. The efferent continent catheterizable channel of the Indiana pouch is constructed from the distal ileal segment and ileocecal valve. The ileum is narrowed over a catheter with the use of a stapling device. Lembert sutures over the staples are used to plicate the ileocecal. **A–D:** Stapling technique. **E, F:** Placement of sutures at ileocecal valve.

Kock Pouch

The Kock pouch is a continent ileum-based reservoir originally introduced in 1982. The current Kock pouch has undergone numerous modifications by Skinner's group at the University of Southern California, thus decreasing the complication rate (52,53) (Fig. 51D.12). Continence and antireflux mechanisms of this pouch are based on creating nipple valves by intussuscepting the ileum at both ends of the isolated segment. The central segment, between the two

intussuscepted ends, is folded into a U and opened along the antimesenteric border. A spherical reservoir is then formed by folding the bowel segments appropriately. The afferent and efferent nipples are formed by intussuscepting a segment of ileum that has been stripped of a small segment of the mesentery. A stapling device is used to secure the nipple valves to the reservoir. Skinner and co-workers (52,53) also use mesh circumferentially around the intussuscepted segments outside the reservoir to provide additional support. The ureters can be sewn end-to-side into the afferent nipple and the efferent nipple is brought out to the skin as a continent catheterizable stoma.

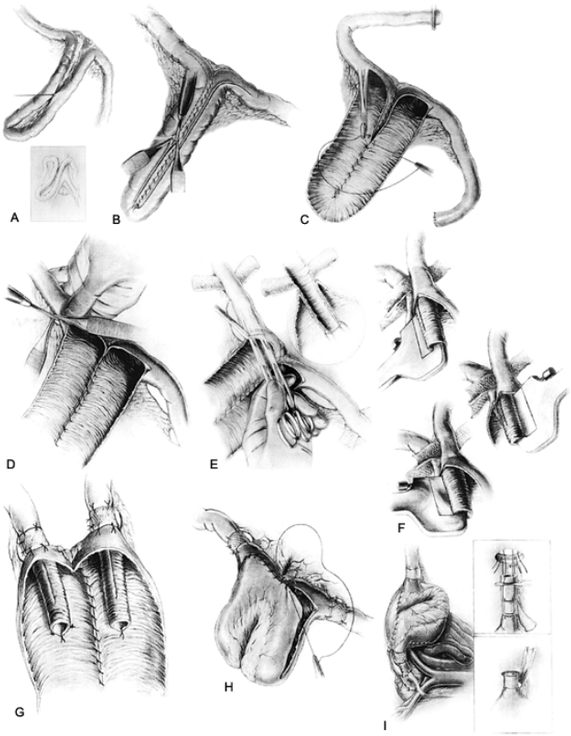

FIGURE 51D.12. A—I: Modifications of the Kock pouch done by Skinner's group at the University of Southern California. Their modifications have decreased the complication rate associated with this pouch.

The majority of the initial problems with this reservoir was the loss of the continence mechanism of the efferent nipple valve. The described modifications lowered the complication rate. In addition, bladder calculi have been known to form on the staple line.

Gastric Reservoir

A continent reservoir may be constructed using the wedge flap technique (36) (Fig. 51D.13). By harvesting a large wedge from the stomach, it may be made into a reservoir by suturing the apex to the urethra, or the wedge may be closed and used as a continent cutaneous reservoir. The muscle backing of the stomach allows for continent mechanisms and ureteral reimplantation to be based on the flap-valve principle. Alternatively, a strip of gastric tissue can be tubularized and nippled into the reservoir to provide a continent catheterizable channel. The problem with this reservoir is that it usually is difficult to resect enough stomach to create a large reservoir without compromising gastric capacity. It often is necessary to augment the gastric reservoir with a segment of bowel to increase capacity and reduce salt losses in the urine.

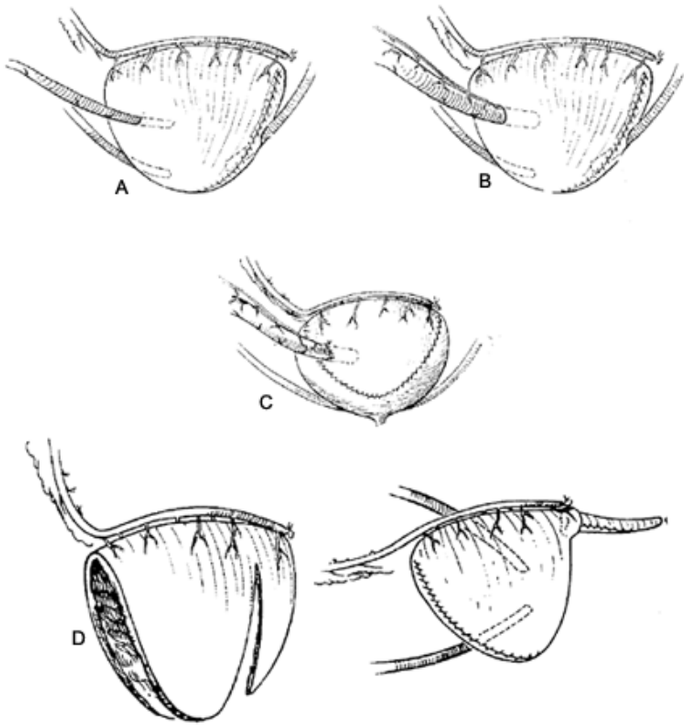

FIGURE 51D.13. A: The gastric wedge flap may be constructed into a continent urinary reservoir. **B:** The gastric muscle provides ideal backing for creation of continent catheterizable channels or ureteral reimplantation **(C). D:** A strip of the gastric wedge may be formed into a catheterizable channel. Continence may be obtained by creating a nipple valve.

Postoperative

Children remain on intravenous fluids, intravenous antibiotics, and nasogastric tube drainage until the return of bowel function. Suprapubic tubes are left to gravity drainage and are irrigated every 8 hours and as needed to promote continual drainage. H_2 blockers are used in patients after gastric augmentation who are on bladder drainage to prevent ulcer formation. The patient is discharged from the hospital with the suprapubic tube in place. Reservoir cycling is usually started at approximately 1 week postoperatively. The suprapubic tube is removed after 3 weeks. The family or child must demonstrate the ability to perform intermittent catheterization before removing the suprapubic tube.

COMPLICATIONS

Table 51D.5 presents metabolic consequences of bladder reconstruction with bowel.

Problem	Stomach	Ileum	Colon
Segment loss from GI tract	1. Early satiety 2. Decreased stomach-acid production 3. Increased gastrin production	1. Decreased absorption of B_{12}, folate, and iron 2. Short-gut syndrome	1. Diarrhea 2. Water loss
Acid–base balance	1. Alkalosis 2. Hematuria/dysuria	1. Chronic metabolic acidosis 2. Ammonium and chloride resorption	1. Acidosis 2. Bicarbonate loss 3. Ammonium chloride resorption
Salt balance	1. Sodium and potassium loss	1. Sodium and chloride resorption	1. Sodium and chloride resorption
Mucus	1. More soluble, less apparent	1. Problem with catheter obstruction, irrigation necessary	1. Problem with catheter obstruction, irrigation necessary
Stone formation	1. Rare problem (low pH)	1. Can be a major problem, irrigations recommended	1. Can be a major problem, irrigations recommended
Infection	1. Moderate	1. Common	1. Common
Tumor	1. None documented but too early to tell	1. Reported	1. Significant in ureterosigmoidostomy
Perforation	1. Reported with potential for ulcer formation in anuric or diverted patient	1. Reported, major problem because of potential for infection	1. Reported, major problem because of potential for infection

TABLE 51D.5. METABOLIC CONSEQUENCES OF BLADDER RECONSTRUCTION WITH BOWEL

Electrolyte Disturbances

Intestinal segments placed in the urinary tract retain their inherent properties of absorption and secretion of water and solutes. As such, different segments of the GI tract will produce different metabolic changes when placed in the urinary tract (37). Gastric segments continue to secrete hydrochloric acid with systemic bicarbonate release, which may result in hypochloremic metabolic alkalosis (3). Ileal and colonic segments absorb ammonia and chloride and secrete bicarbonate and sodium, which may lead to hyperchloremic metabolic acidosis (37). The severity of the metabolic disturbances depends on many factors such as the length of segment used, the amount of time urine is in contact with bowel mucosa, and the patient's metabolic reserve to compensate for electrolyte changes. Electrolyte changes usually are not significant in patients with normal renal function. However, patients who undergo augmentation cystoplasty with GI segments should be monitored periodically for electrolyte changes.

Megaloblastic Anemia

Vitamin B_{12} is absorbed in the distal ileum. Therefore if the distal ileum is removed from the GI tract, megaloblastic anemia may result secondary to B_{12} deficiency (8). B_{12} stores may last for up to 6 years and therefore this is a potentially late complication resulting from the use of distal ileum (38). One report documented B_{12} deficiency in 35% of patients 5 to 11 years after construction of a Kock pouch (4). This complication is prevented by sparing the distal 15 cm of ileum. However, if it is necessary to use the distal ileum in bladder reconstruction, long-term monitoring for megaloblastic anemia is necessary.

Mucous Production

GI segments used in urinary tract reconstruction continue to produce mucus. Mucous production is greatest from colonic segments, followed by ileal segments, with stomach producing the least (32). Mucous production may or may not be a problem for patients (17,27,47). Production of mucus usually increases at the time of a urinary tract infection. Increased mucus may slow or prohibit drainage from the reservoir through a small caliber catheter. Furthermore, mucous production has been implicated as a nidus for stone formation (42). To prevent complications, daily irrigation of mucus from the reservoir with normal saline is encouraged.

Tumor Formation

A long-term concern with placing GI segments in the urinary tract is tumor formation. It is well recognized that patients with ureterosigmoidostomies are at risk for the development of carcinoma and polyps at the ureterocolonic anastomosis (23,55). In the patients with ureterosigmoidostomies who developed tumors, the average time lapse before tumor detection was 26 years after ureterosigmoidostomy (23). In a meta-analysis review by Filmer and Spencer (16), 14 patients with augmentation cystoplasty were found to have developed carcinomas in the augmentation segment (8). Therefore long-term surveillance is important in children. Periodic cystoscopy is recommended 7 to 10 years after GI cystoplasty.

Reservoir Perforation

Delayed perforation of the reservoir is a well-recognized complication of augmentation cystoplasty and can be a catastrophic event (5,12,46,50,51). Several patients with GI continent urinary reservoirs or augmentations have decreased sensation and therefore delay in diagnosis is common. Symptoms may be abdominal discomfort, nausea, vomiting, abdominal distention, and peritonitis. An abdominal computed tomography (CT) scan with a contrast-filled bladder is probably the most accurate diagnostic tool. The exact etiology of delayed spontaneous perforation is unknown. It may be related to overdistention of the reservoir with areas of ischemia or unit contractions of the augmentation segment elevating the reservoir pressure. Therefore it is extremely important in children with high leak-point pressures to be compliant with catheterization schedules. Perforations have been seen in all GI segments. In the largest reported series, Indiana University reported a 8.3% incidence (22 of 264) in children with augmentations, with a slightly larger incidence in the sigmoid colon augmentations (48). Management of a child with a perforation usually includes surgical exploration with closure of the perforation and catheter drainage for several days.

Stone Formation

Most stones that form in GI urinary reservoirs are composed of struvite. Reservoir stones have been reported to form in all GI segments, but are extremely rare in gastric segments (26,30). Kronner and colleagues (30) at Indiana University found stones in 10% of their augmentation population. Likewise, Kaefer and associates (26) at Boston Children's Hospital found stones in 13% of their augmentation population. Stone formation is likely multifactorial in etiology, including the presence of urea-splitting bacteria, stasis of urine, mucus, and foreign bodies. Therefore preventive measures such as regular catheterization, irrigation of mucus, and antibiotic therapy for stone forming bacteriuria should be instituted.

Hematuria-dysuria Syndrome

Hematuria-dysuria syndrome is a complication that is unique to patients in whom gastric tissues are placed in the urinary tract. The syndrome originally was described by

Nguyen and coauthors (41) as any of the following symptoms in patients following gastrocystoplasty: bladder spasm; suprapubic, penile, or periurethral pain; coffee-brown or gross hematuria without infection; skin excoriation; and/or dysuria without infection (41). This syndrome is seen more commonly in patients who have intact urethral sensation and are incontinent. Hematuria-dysuria syndrome usually is intermittent in nature and rarely requires continuous therapy (43).

Urinary Tract Infections

Most of the GI urinary reservoirs are emptied by clean intermittent catheterization, and bacteriuria is common (17,20,27). Although most patients will have bacteriuria, a higher percentage of bacteriuria is reported with the use of bowel segments when compared with gastric segments. Asymptomatic bacteriuria is not treated routinely unless the organism is a urea-splitting organism. Symptoms and signs that may require antibiotic therapy include foul-smelling urine, fever, suprapubic discomfort, and urinalysis showing a white blood cell (WBC) count of greater than 50 WBCs per high-power field.

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51E THE BLADDER NECK AND CONTINENT CHANNELS

Beth Andersen

Richard W. Grady

Michael E. Mitchell

Part of "51 - TOOLS OF RECONSTRUCTION "

B. Andersen, R.W. Grady, and M.E. Mitchell: Department of Urology, The University of Washington Medical Center, Seattle, WA 98195; Section of Pediatric Urology, Children's Hospital & Regional Medical Center, Seattle, WA 98105.

THE MITROFANOFF PRINCIPLE AND CONSTRUCTION OF CONTINENT CATHETERIZABLE CHANNELS

Two decades ago, Paul Mitrofanoff (68) described a procedure using the appendix (or ureter) to construct a continent catheterizable channel to the bladder. This concept has come to be known as the *Mitrofanoff principle.* Although it was originally described for use in children with neurogenic bladders, it has become widely used for many different clinical situations. Channel continence is maintained by creating a flap valve by tunneling the channel into the bladder using techniques similar to ureteral reimplantation. Mitrofanoff initially described use of the appendix or ureter to construct a catheterizable channel combined with closure of the bladder neck. Since the introduction of “the concept,” other tubular structures have been used as the catheterizable channel and its application has been expanded to create a channel for catheterization into the intestine for antegrade enema instillation [antegrade continent enema (ACE) procedure] (59). Surgical experience with the Mitrofanoff principle has increased over the years with high patient satisfaction (38). It has become an extremely important adjunctive technique in pediatric urologic reconstruction.

Mitrofanoff Appendicovesicostomy

Surgical Technique

The patient is given an initial bowel preparation. We use a mechanical bowel preparation using polyethylene glycol–electrolyte solution. As described by Mitrofanoff in 1980, the appendix is mobilized, maintaining its vascular pedicle from the terminal branches of the ileocolic. The appendix is removed form the cecum (Fig. 51E.1A) and is reimplanted

into the bladder through a submucosal tunnel in the bladder wall (Fig. 51E.1B and Fig. 51E.1C). Either the anterior or posterior bladder wall can be used (43,86) as long as adequate tunnel length (four times the diameter of the tube) is maintained and the course of the channel is not angulated between the bladder mucosa and stoma (71,87,88). The appendix is best oriented in an antiperistaltic direction, but this is not always possible. A slowly absorbable suture is used to anchor the appendix into the bladder to prevent the appendix from slipping back out of the tunnel. The stoma is created by anastomosis of the opposite end of the appendix to the abdominal wall, either at the umbilicus or in a separate right lower quadrant site (11,23,68,71). It is important to meticulously maintain the appendix blood supply, to spatulate the anastomosis, and to insert a broad-based skin flap to prevent stomal stenosis (Fig. 51E.1D).

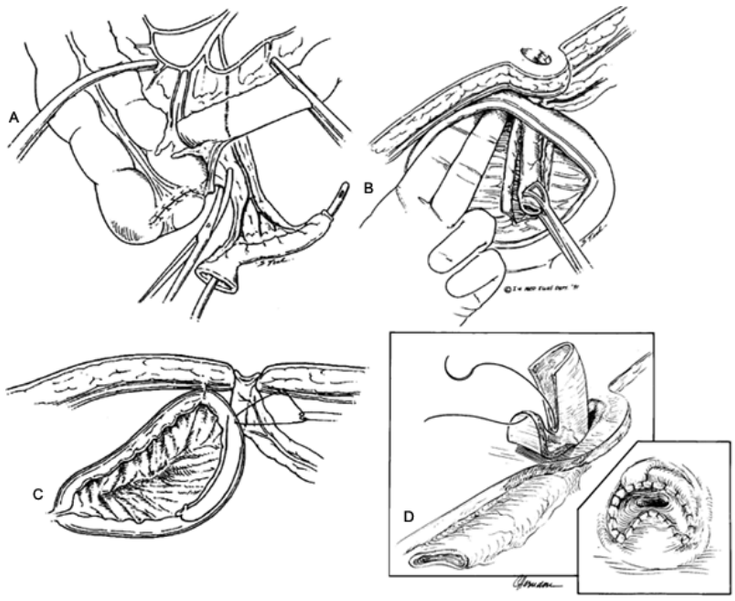

FIGURE 51E.1. Mitrofanoff construction. **A:** The appendix is divided from the cecum and is mobilized carefully, preserving the mesenteric blood supply. **B:** The mobilized appendix is tunneled submucosally into the posterior wall of the bladder. The bladder is secured to the posterior aspect of the abdominal wall to eliminate tension on the anastomosis and to ensure a straight path for catheterization. **C:** Lateral view of completed appendicovesicostomy demonstrating straight posterior submucosal tunnel. Note that the bladder is secured to the abdominal wall. **D:** The stoma is created using an inverted U or V umbilical skin flap, which is inset into the spatulated appendix to prevent stomal stenosis. The appendix mucosa is recessed into the umbilicus, minimizing visible scars and hiding the stoma site. (**A–C** from Keating MA, Rink RC, Adams MC, et al: Appendicovesicostomy: a useful adjunct to continent reconstruction of the bladder. *J Urol* 1993;149:1091, with permission.)

Surgical Results

Using the appendix for a catheterizable channel offers several advantages. The appendix provides a supple uniform channel intrinsically, which can usually be mobilized to reach the bladder and still have the stoma hidden within the umbilicus. The surgical results of appendicovesicostomy are good and predictably reproducible (9,23,36,42,43,86,87 and 88). There is an overall 86% to 98% surgical success rate (dry and catheterizing). To achieve urethral continence, it may be necessary to perform a concurrent bladder neck procedure and/or bladder augmentation if indicated by preoperative urodynamics. Important aspects to consider when creating a catheterizable channel are outlined in Table 51E.1 .

Aspect	Considerations
1. Preoperative bladder assessment	Should preoperative urodynamics be performed? Stomal continence depends on the presence of a sufficient capacity, compliant bladder, with adequate urethral resistance.
2. Bowel preparation	Use a mechanical bowel preparation (polyethylene glycol–electrolyte solution).
3. Appendix	Is there adequate appendix length, lumen, and blood supply? Can the appendix be placed in an antiperistaltic direction? If the appendix is absent or inadequate, consider creation of a transverse tubularized bowel segment channel from ileum or colon.
4. Location of tunnel	Is there adequate tunnel length on the anterior or posterior bladder wall?
5. Secure appendix in tunnel	Secure the appendix in long submucosal tunnel with slowly absorbing anchoring stitch and tacking sutures if necessary. Fix the bladder to the abdominal wall to support tunnel.
6. Ease of catheterization	Make sure path of catheter is direct and straight. Test ease of catheterization *before and after* closure.
7. Stoma	Use a skin flap and spatulated anastomosis (not circular stoma). Stoma is best situated in umbilicus if possible.

TABLE 51E.1. IMPORTANT ASPECTS OF CREATING A CATHETERIZABLE CHANNEL

Complications

The most common complication is stomal stenosis. Stomal stenosis occurs postoperatively in 7% to 24 % of patients. Reoperation rates have been reported in up to 7% to 26% of patients, mainly for correction of stomal stenosis, difficulty with catheterization, or revision of the flap valve continence mechanism (9,36,87). Stenosis of the stoma may be treated with initial dilation; however, formal surgical revision (V-Y–plasty) is often required to prevent recurrence. Parastomal infection and necrosis of the conduit are rare but can occur. Late complications of stone formation can also occur. Stones may develop in the bladder or reservoir as a result of inadequate drainage or mucus from the catheterizable channel and can be prevented by regular bladder irrigation. Risk of postoperative incontinence through the Mitrofanoff stoma can be reduced by forming an adequately long tunnel at least four times the diameter of the tube being implanted. To protect against loss of the valve mechanism and channel angulation, the bladder should be anchored to the abdominal wall to reduce tension on the tunnel anastomosis (Fig. 51E.1C). The relative length of the appendix can be increased with the use of a tubularized cecal cap (2,16,86) (Fig. 51E.2).

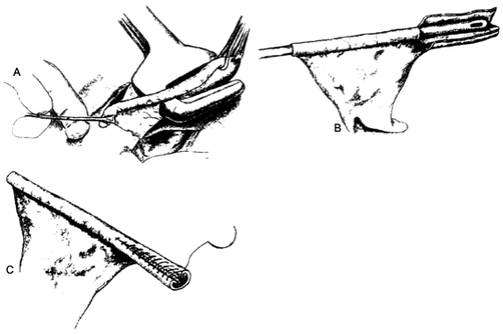

FIGURE 51E.2. Extended appendix with cecal cap. Stapled technique tubularizing contiguous cecum to increase the length of the catheterizable conduit. **A:** A window is made through the appendiceal mesentery. The base of the cecum is stapled, excluding a cecal segment adjacent to the proximal end of the appendix. **B:** The cecum is calibrated for tubularization in line with the appendiceal lumen. **C:** The adjacent cecum is tubularized in two layers over a catheter. [**A–C** from Cromie WJ, Barada JH, Weingarten JL. Cecal tubularization: lengthening technique for creation of catheterizable channel. *Urology* 1991:37(1):41, with permission.]

Alternative Options for Catheterizable Channel Construction

When the appendix is not available, there are other options. The ureter can be used (68,69). However, several disadvantages have been reported when the ureter is used for the channel. There are reports of increased discomfort with catheterization and a higher rate (22%) of stomal incontinence (69). Furthermore, when the ureter is used, the stoma can rarely be brought out through the umbilicus. However, the ureter can be used as a pedicle flap to construct an orthotopic catheterizable stoma in girls (41,67). There have been reports of use of the fallopian tube (92), vas deferens (23), and tubularized prepuce (47) to form catheterizable channels. However, these structures are less proven with long-term experience and therefore not recommended, except as a last resort. Tapered ileum can be used, but the mesentery is bulky, making the tunneling and stoma more difficult. More recently, techniques have been developed to create the channel by transverse tubularization of short segments of small or large intestine.

Transverse Tubularized Bowel Segments (Monti Procedure)

Wen-Horng Yang (94) first described the use of a transversely tubularized bowel segment to create a Mitrofanoff channel in 1993. Unfortunately, the novel catheterizable channel was not the focus of the paper, and the technique

did not become widely recognized until after Monti and colleagues published it in 1997 (66). Monti and associates (66) performed animal studies using the catheterizable channel, and later performed these techniques in humans. The beauty of the transverse tubularization technique is that the length of the tubularized channel is now a result of the diameter of the bowel segment used and that the mesentery becomes centralized (Fig. 51E.3). This allows the proximal and distal ends of the formed tube to be easily implanted into the bladder and external stoma without jeopardizing the blood supply. Also, the natural intestinal folds become oriented lengthwise in the channel, facilitating catheter passage. The procedure is versatile; short segments of small or large intestine from anywhere in the abdomen can be selected. Multiple channels can be constructed. Double-length channels can be constructed by attaching two channels in continuity (Fig. 51E.4). Use of transverse tubularized bowel segments has rapidly become popular as a second-line channel (after appendix) among pediatric urologic surgeons (9,12,30,31,34,85).

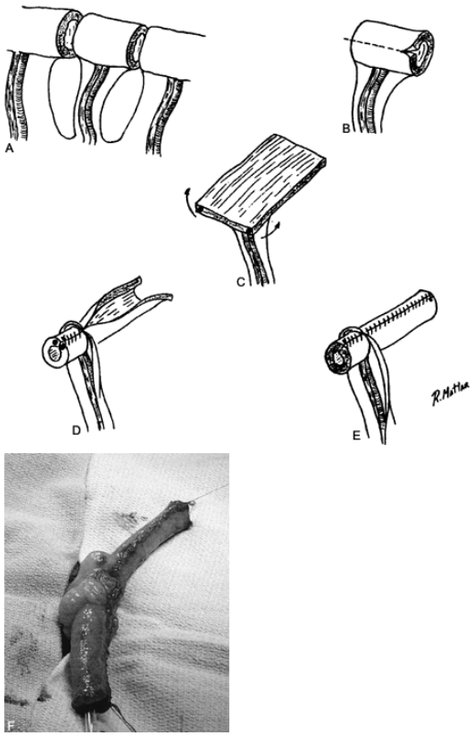

FIGURE 51E.3. Creation of a transverse ileal tube. **A:** A 2.5- to 3-cm intestinal segment is isolated. **B:** The intestinal segment is detubularized through a longitudinal incision made on one side at some distance from the mesentery. **C:** Isolated opened ileal segment, which is now a pedicle flap. **D:** The flap is transversely tubularized using a two-layer closure with absorbable suture. **E:** Completed transverse ileal channel. Note the mesenteric blood supply is now localized to one side of the channel. The side of the tube with the longer nonmesenteric length can be reimplanted. Note that if the initial longitudinal incision were placed directly antimesenteric, the blood supply would have a central location on the channel. **F:** Intraoperative photo of a completed transverse ileal channel. (**A–E** from Monti PR, DeCarvalho JR, Arap S. The Monti procedure: applications and complications. *Urology* 2000;55:617, with permission.)

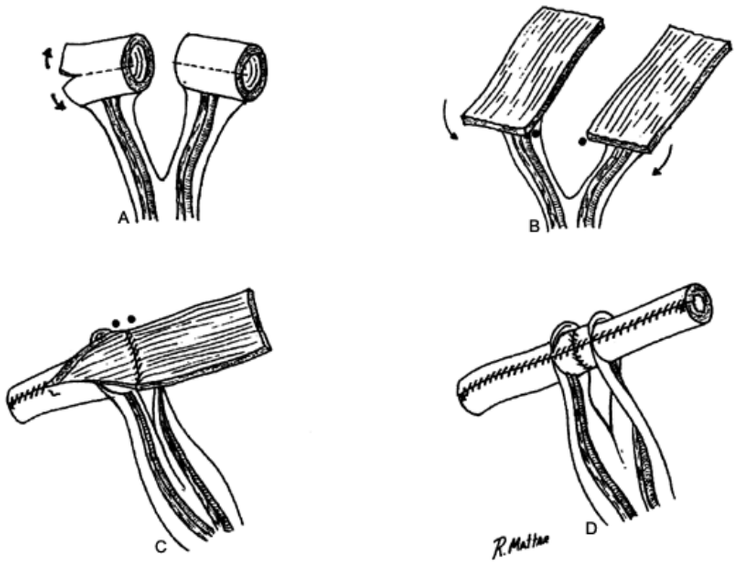

FIGURE 51E.4. Double-length transverse channel. **A:** Another useful technique is to create a double-length channel by selection of two adjacent short bowel segments that are sewn end-to-end to form a continuous channel. It is important to centralize the two mesenteric blood supplies using this technique by completing the transverse intestinal incisions as illustrated, close to the mesentery. **B:** The two adjacent flaps are rotated and joined end-to-end. (It is usually easier to join the two open segments before tubularization.) **C:** A long (double-length) tube is created by lengthwise tubularization. Note that formation of a colon transverse tubularized channel will already naturally be longer in length because the colon is a larger-diameter structure. **D:** Completed double-length channel. (From Monti PR, DeCarvalho JR, Arap S. The Monti procedure: applications and complications. *Urology* 2000;55:617, with permission.)

Surgical Technique

The bowel is cleansed preoperatively with a mechanical bowel preparation. A 2- to 3-cm segment of ileum is usually selected. (However, other segments of small or large intestine can be used.) Ileal anastomosis is performed. The bowel segment is isolated on its mesenteric vessels, and the antimesenteric end is split lengthwise (Fig. 51E.3). The intestine is then closed transversely over a 10- to 14-Fr catheter using a running or interrupted suture line. It is important to place interrupted sutures at either end of the closed channel to allow for subsequent spatulation. A two-layer closure (mucosal and serosal) is usually performed. If necessary, a longer catheterizable channel can be constructed by joining two adjacent intestinal segments together (Fig. 51E.4).

Surgical Results

A recent publication (65a) combined published results from all published series in which transversely tubularized bowel segments were used as continent channels. A total of 54 channels were included. The range of follow-up was from 6 to 14 months. Approximately 97% of the channels catheterized easily. The overall incidence of stomal stenosis was 6%. Continence rates were 91%. In comparison to appendicovesicostomy, the incidence of stomal stenosis was slightly lower and continence was the same. Although long-term results from transversely tubularized bowel segments are not yet available, the initial results are promising. The versatility and availability of using short intestinal segments for the Monti procedure make it an appealing technique.

Continent Vesicostomy

Surgical Technique

Continent vesicostomy formation was first described in the 1970s (77,78). Using Schneider's technique, a bladder tube is created from an anterior flap of full-thickness bladder measuring 9 cm in length and from 5 to 3 cm in width. The distal extent of the flap is tubularized, and the continence mechanism is created by intussusception of the channel within the bladder for a distance of at least 3 to 4 cm to form a valve mechanism (Fig. 51E.5). The distal end forms the stoma, which is brought out to the abdominal wall either at the umbilicus or at a separate lower abdominal wall stoma site. The technique is best suited for patients who have a large bladder capacity and nonthickened bladders. A modified technique to form a continent catheterizable bladder tube in children was described by Casale in 1995 (75a). This technique uses a bladder flap measuring 7 cm in length and 2 cm in width. The full-thickness

of the flap is tubularized distally. Proximally, the continence mechanism is formed using a submucosal tunnel. To create the proximal bladder tube and the submucosal tunnel, the proximal bladder incisions are extended for an additional 3 cm. The muscularis and mucosa of the bladder is tubularized proximally, and mucosal flaps are elevated bilaterally and joined to form a submucosal tunnel (9,42) (Fig. 51E.6). Continence and ease of catheterization of the vesicostomy are assessed after construction. The bladder is decompressed by catheter drainage during healing. A catheter is left within the vesicostomy channel for 3 weeks as it heals.

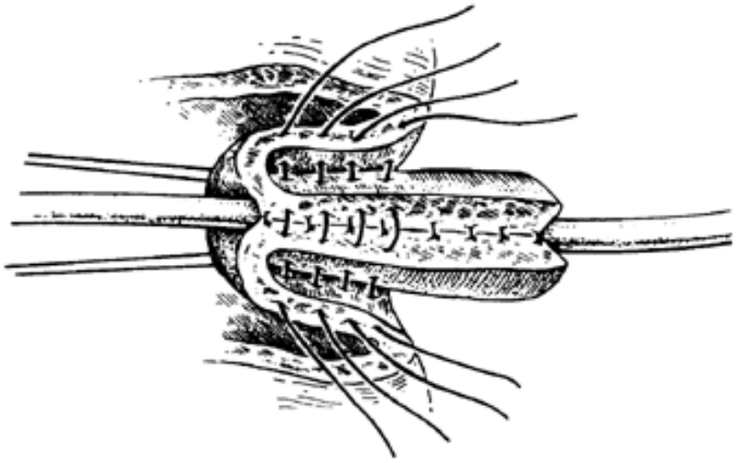

FIGURE 51E.5. Continent vesicostomy techniques. The anterior bladder flap has been intussuscepted to form a nipple valve mechanism for continence. (From Schneider KM, Reid RE, Fructman B, et al. The continent vesicostomy: clinical experiences in the adult. *J Urol* 1977;117:572, with permission.)

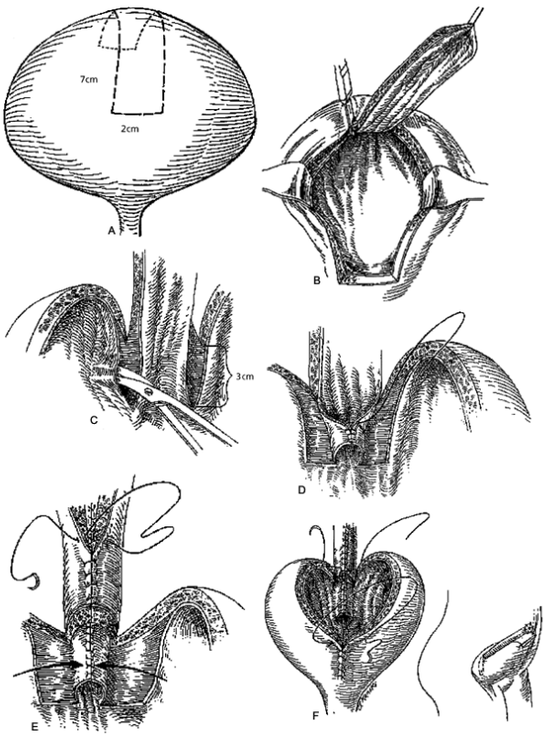

FIGURE 51E.6. Continent vesicostomy. **A:** A full-thickness anterior bladder flap is created measuring 2 cm in width and 7 cm in length. **B:** The bladder flap is rotated cephalad. **C:** The mucosal incisions are extended an additional 3 cm distally through the bladder mucosa at the base of the flap. The lateral adjacent mucosa is elevated in preparation for the submucosal tunnel. **D:** The mucosal and muscularis layers of the distal bladder incision are tubularized, with care to maintain the detrusor flap blood supply. **E:** A continuous tube is created by continuing tubularization of the full-thickness detrusor flap proximally. **F:** The adjacent mucosal flaps at the 3-cm extension of the tube are approximated to one another and closed, forming a submucosal tunnel. The tube is brought out to an abdominal wall stoma. (From Kaefer M, Retik AB. The Mitrofanoff principle in continent urinary reconstruction. *Urol Clin North Am* 1997;24(4):795, with permission.)

Surgical Results

In the largest published study of 17 adult patients who underwent continent vesicostomy using the intussuscepted valve technique (77,78), surgical success was reported in 13 (76%). Continent vesicostomy was not achieved in four patients, and two patients required a second procedure to repair the intussuscepted nipple valve mechanism (attributed to initial use of absorbable sutures). Cain and associates published results of 22 patients (median age of 10) who underwent continent vesicostomy using a modified Casale vesicostomy technique (9) (Fig. 51E.6). Complications occurred in 29% of patients in this series (6 of 21). All of these patients required surgical revision for difficulty with catheterization and stomal stenosis. The modified Casale vesicostomy technique has several advantages. It uses less bladder capacity (a smaller-dimension bladder flap is used), and it has better continence rates when compared with the nippled valve technique.

Antegrade Continence Enema

Surgical Technique

The Mitrofanoff continent catheterizable channel concept has also been applied to the colon to administer antegrade continence enemas (the ACE procedure). This technique was initially described (59) for patients with fecal incontinence refractory to conventional medical treatments. It is particularly well suited for patients who require regular high enema clean out. In the Malone ACE technique, the appendix is used to form a continent channel into the cecum. The initial reports describe reversing the direction of the appendix with tunneled reimplantation (Fig. 51E.7A and Fig. 51E.7B). However, more recent reports describe leaving the appendix *in situ,* with or without intussusception of the appendix into the base of the cecum, with similar continence results (56,89,91) (Fig. 51E.7C). Considerations important to success include patient and family motivation for fecal continence, thorough preoperative bowel preparation, and frequent catheterization postoperatively to prevent stomal stenosis. As with any reconstructive procedure, proper patient selection is critical.

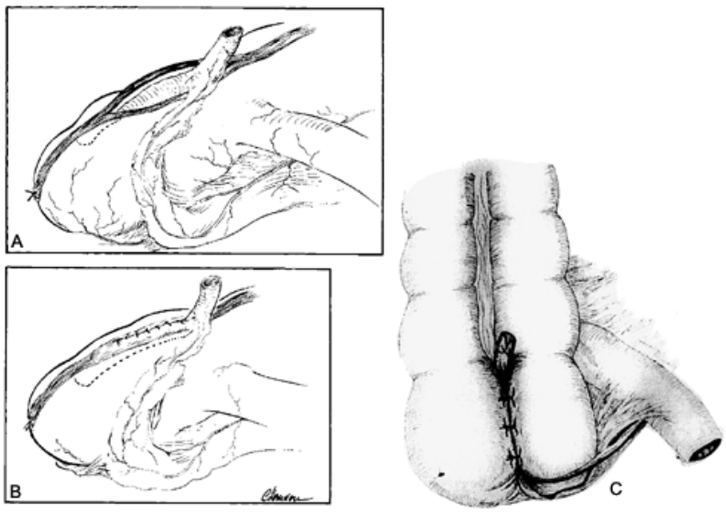

FIGURE 51E.7. Creation of an ACE channel. **A:** Reimplanted appendix ACE channel. The appendix is isolated in a similar fashion as when it is used for appendicovesicostomy. The direction of the appendix is reversed and it is tunneled into the cecum through a submucosal tunnel beneath the colonic taenia. **B:** Completed reimplant of the reversed appendix through a submucosal tunnel into the cecum. **C:** Creation of a channel using *in situ* appendix. The appendix can be imbricated into the cecum to promote continence. (**C** from Walsh RA, Waxman SW, Koyle MD. The Malone ACE procedure for fecal incontinence. *Infect Urol* 2000;July/Aug:102, with permission.)

ACE Irrigation

After ACE channel construction, the channel is intubated for 3 to 4 weeks. The indwelling catheter can be used to begin bowel irrigation when bowel function has returned in the postoperative period. Antegrade enema administration can usually be initiated through the indwelling catheter within the first week after surgery, depending on the extent of concurrent procedures. In this way, patients and their families can become comfortable with performing antegrade enemas before hospital discharge. After the indwelling catheter is removed, daily catheterizations are initiated. Even if daily antegrade enema administration is not necessary, the ACE channel should be catheterized every day to prevent stomal stenosis (35,91).

Several different solutions can be used for ACE irrigation. We prefer to start irrigation with a 1:1 mixture of glycerin and water, 10 to 20 mL of each. Glycerin is a hyperosmolar laxative that stimulates colon contraction. The volumes of glycerin and water can be adjusted for each patient to optimize timely stool evacuation (usually within 30 minutes) while minimizing abdominal cramping. This regimen has been used by others with good results (24). Other antegrade enema regimens include polyethylene glycol–electrolyte solutions, saline alone, docusate, or phosphate enemas followed by saline lavage (13,59). Unfortunately, hyperphosphatemia can result from colonic absorption of phosphate (15,61). To prevent the possible serious complication of phosphate toxicity (hyperphosphatemia, hypocalcemia, hypokalemia, metabolic acidosis, tetany, asystole, and even death), phosphate solutions are not recommended for antegrade enemas, especially in children. Other safer and effective regimens are available. Patient satisfaction with the ACE procedure improves with ongoing consultation with health care professionals familiar with ACE management to ensure an optimal antegrade enema regimen is established.

Malone ACE Complications

The largest reported series of Malone ACE procedures is from the United Kingdom (17). In this series of 300 Malone ACE procedures, the overall success rate was 79%. The main complication was stomal stenosis (30%). Other complications included stomal leakage (7%), adhesion obstruction (2%), gangrenous channel (2%), and phosphate toxicity resulting from retained phosphate enemas. Ultimately, larger, controlled, prospective studies are needed to provide more accurate information about the open ACE procedure as well as percutaneous and laparoscopic ACE techniques.

Alternatives to Use of the Appendix for ACE Construction

If the appendix is unavailable, channels can be created with cecal tubes or transverse tubularized bowel segments (17,91).

Percutaneous techniques can be used to secure access to the cecum. There is early experience with cecostomy button placement for antegrade enema administration (13,22,24,80). This technique uses a “button” device similar to those used for percutaneous gastrostomy. Long-term data on this technique are not yet available. A laparoscopic approach has also been advocated (56). In this technique, the appendix remains attached to the cecum. The appendix is mobilized, and the distal end is secured to the fascia and spatulated to a right lower quadrant stoma. The initial published series of patients who underwent laparoscopic ACE procedures showed complication rates were similar to those of open techniques (56). In 30 patients, stomal stenosis occurred in 8 (27%) and troublesome stomal leakage occurred in 2 (6.7%) (56).

Stoma Formation

Formation of the stoma site is an important aspect of catheterizable channel construction, both in terms of prevention of the most common complication (stomal stenosis) and for patient satisfaction. The initial stomas that brought a circumferential cuff of intestinal mucosa to the skin level were often complicated by stomal stenosis and stoma site irritation related to protrusion (35). These stomas were larger, and the cosmetic appearance was less pleasing. Currently, a V- or U-flap of skin is inset into the distal end of the spatulated catheterizable channel (Fig. 51E.8) (35,43,59). These techniques help prevent stomal stenosis and improve the cosmetic appearance. The umbilicus is used as the preferred stoma site for Mitrofanoff channels. There are several advantages to placement of the stoma at the umbilicus: (a) The cosmetic appearance can be excellent; (b) the central abdominal location facilitates easy catheterization while in a sitting position; and (c) the abdominal wall thickness at the umbilicus is thinnest, especially in older patients who have significant subcutaneous adipose elsewhere on their abdominal wall. A broad-based superior or inferior U- or V-flap technique is generally used to construct the umbilical stoma (Fig. 51E.1D and Fig. 51E.8). Given the typically already inverted characteristics of the umbilical skin, the effect is to create a completely hidden channel opening.

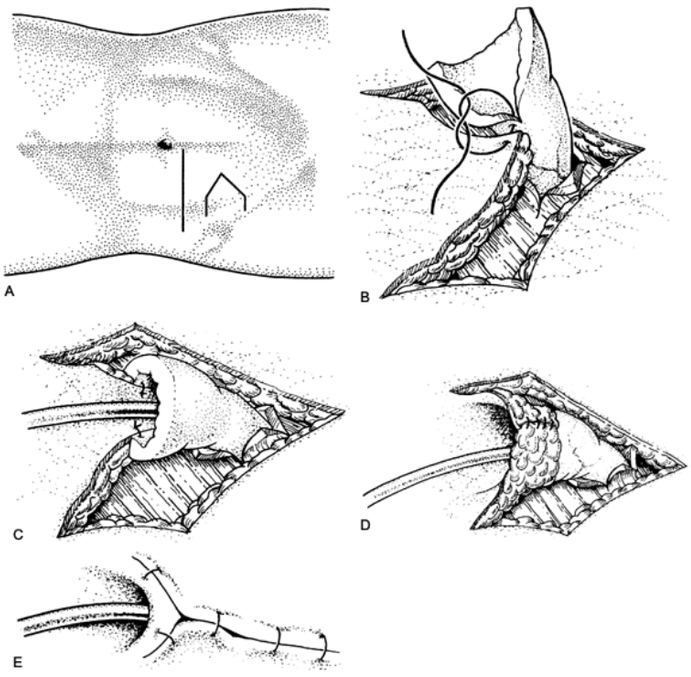

FIGURE 51E.8. Example of abdominal wall catheterizable stoma formation using a right lower quadrant cutaneous V-flap anastomosed to the spatulated appendix. **A:** A right lower quadrant broad-based V-flap is made as shown. **B:** The appendix or Monti catheterizable channel tube is spatulated and the skin flap anastomosis is performed. **C–E:** The skin flap is reconstructed forming a hidden channel stoma. (From Griffiths DM, Malone PS. The Malone antegrade continence enema. *J Pediatr Surg* 1995;30:69, with permission.)

Umbilicoplasty

If the patient does not have an umbilicus (as in cases of bladder or cloacal exstrophy), a neoumbilicus can be fashioned out of adjacent skin flaps. Our technique for umbilicoplasty is demonstrated in Fig. 51E.9 . The site for the umbilicus is chosen in the midline at the level of the iliac crests. The umbilicoplasty is generally part of concurrent intraabdominal procedures, and the initial midline abdominal incision is made keeping the umbilicoplasty in mind. The incision is carried to the left at the level of the selected site for the umbilicus, and a U-flap is fashioned from the midline skin. The U-flap is then advanced under the lower abdominal skin to create the central umbilical depression.

If a Mitrofanoff is being formed concurrently, the flap is anastomosed to the distal spatulated aspect of the channel using interrupted absorbable sutures (Fig. 51E.9). If there is no need for a concurrent midline incision at the level of the umbilicus, an “M incision” can be used to create skin flaps to anastomose to the catheterizable channel (Fig. 51E.10).

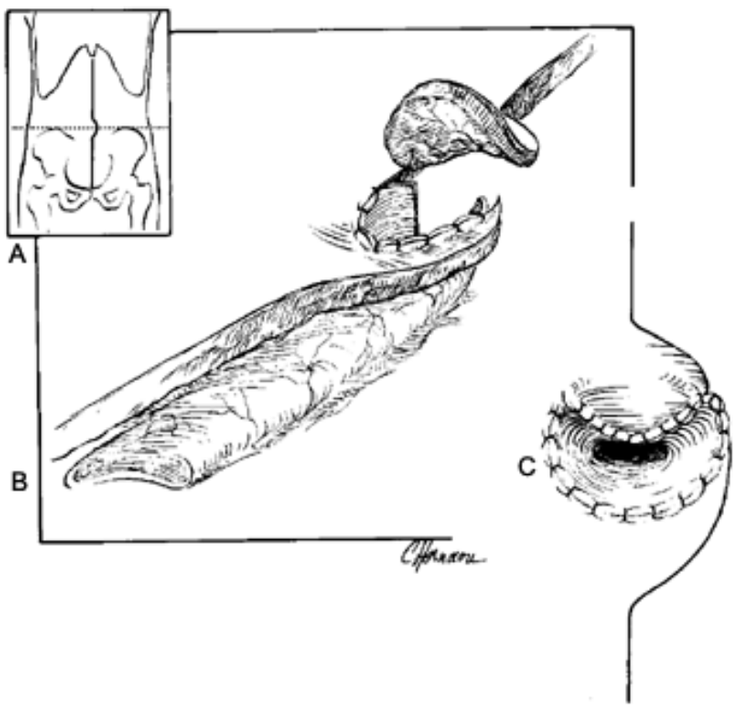

FIGURE 51E.9. Umbilicoplasty with concurrent midline incision. **A:** An initial midline incision is made, curved to the left at the level of the iliac crests. **B:** An adjacent U-flap is marked and inset into spatulated catheterizable channel. **C:** The left lateral aspect of the skin flap is advanced superiorly to create the completed stoma.

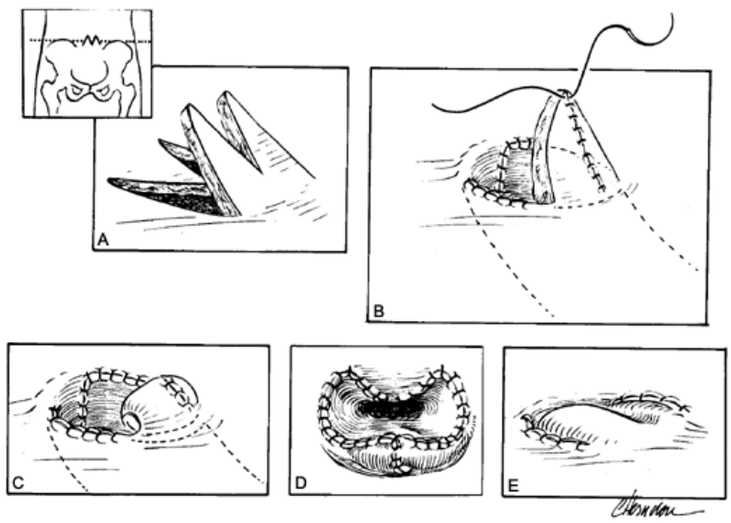

FIGURE 51E.10. Umbilicoplasty without concurrent midline incision. **A:** The “M-flap” incision is marked at the level of the iliac crests. **B:** The inner aspects of the inverted V-flaps are joined with absorbable interrupted sutures. **C:** The superior V-flap and the conjoined inferior skin flaps are anastomosed to the spatulated catheterizable channel. **D, E:** Superior and lateral views of the completed neoumblilicus and catheterizable stoma.

BLADDER NECK RECONSTRUCTION

Urinary continence requires coordination between the bladder and bladder outlet to maintain bladder outlet resistance at a higher pressure than intravesical pressure. Various factors affect this balance, including intrinsic urethral resistance, urinary sphincter function, pelvic floor support, and bladder volume/compliance. Therefore urinary incontinence may result when these mechanisms are abnormally developed or damaged as a result of previous surgery or trauma. When urinary incontinence results from low outlet resistance, operations to increase outlet resistance may be required. Patients with a variety of conditions (Table 51E.2) may require bladder neck operations when they fail conservative management to gain urinary continence.

Exstrophy–epispadias complex
Third stage of staged exstrophy repair (Jeffs approach)
Low outlet resistance following complete primary exstrophy repair (Mitchell approach)
Neurogenic bladder with low outlet resistance
Myelodysplasia
Sacral agenesis
Ureteral anomalies affecting continence
Bilateral ureteral ectopia
Erosive ectopic ureter
Scarring and fibrosis of bladder continence mechanisms producing low outlet resistance
Trauma
Previous surgery (e.g., urethral valves, cecoureterocele)

TABLE 51E.2. INDICATIONS

When considering bladder neck operations, the surgeon can choose between a number of operations (Table 51E.2). Each operation has unique advantages and disadvantages that must be considered in regard to the individual patient's specific needs (Table 51E.3 and Table 51E.4) and his or her underlying disease state. In general, these operations rely on urethral lengthening, urethral narrowing, urethral compression, and/or bladder neck suspension to create urinary continence (81). Some of these operations preserve patients' ability to void volitionally [i.e., Young-Dees-Leadbetter (YDL), artificial urinary sphincter (AUS)], but other operations do not (i.e., Kropp, Pippi-Salle).

Operation	Advantages	Disadvantages
Young-Dees-Leadbetter (or modifications)	Supports intrinsic sphincteric function; no foreign material	Potentially decreases bladder capacity to produce continence
Bladder neck sling	Technically easy, reversible	? Durability
Endoscopic injection therapy	Technically easy	? Durability; very inconsistent
Artificial urinary sphincter	Dependable, reversible	Limited durability of device; foreign body; expensive; dependent on patient dexterity and commitment
Bladder neck keeling		Limited applicability
Distal vaginal lengthening	Applicable to girls with a short urethra	Limited applicability

TABLE 51E.3. OPERATIONS THAT POTENTIALLY PRESERVE VOLITIONAL VOIDING

Operation	Advantages	Disadvantages
Kropp	Dependable dryness	Potential for bladder rupture, increased difficulty with catheterization, requires CIC
Pippi-Salle	Potential for "pop-off"	Requires CIC
Bladder neck closure	Dependable dryness	Mitrofanoff stoma required; CIC necessary; not easily reversible

CIC, continuous intermittent catheterization.

TABLE 51E.4. OPERATIONS THAT DO NOT PRESERVE VOLITIONAL VOIDING

Preoperative Evaluation

Before bladder neck surgery, absolute commitment of the patient and family to treatment plans must be appreciated. Regardless of the operation performed, patients must be willing and able to perform clean intermittent catheterization (CIC) after surgery. Patients who undergo a bladder neck reconstruction that does not preserve volitional voiding will always need to perform CIC to empty the bladder. Patients who undergo a bladder neck procedure that preserves volitional voiding may also need to perform CIC after surgery on a temporary or more permanent basis. At times, it can be difficult to predict whether there will be efficient bladder emptying postoperatively, even when the attempt is made to preserve volitional voiding.

Specific assessment of the lower urinary tract should include a urodynamic evaluation and cystoscopy, when indicated. A detailed history of the underlying disease state, including previous operations performed on the lower urinary tract, is also important because the blood supply to the lower urinary tract will likely be altered by these conditions.

Urodynamic Evaluation

Urodynamic evaluation is the cornerstone upon which lower urinary tract management is based. In particular, videourodynamic evaluation offers the best assessment of the lower urinary tract because fluoroscopic images are combined with simultaneous pressure monitoring. During urodynamic evaluation, the investigator should monitor detrusor compliance, the presence of uninhibited contractions, and leak-point pressure (LPP). Sensation with filling, functional bladder capacity, and ability to volitionally empty the bladder are also assessed during urodynamic evaluation. Simultaneous videoscopic monitoring allows evaluation of the bladder neck during filling and offers a sense of bladder shape and the presence of vesicoureteral reflux (VUR).

The urethra of some patients may be difficult to catheterize due to previous trauma or surgical procedures (e.g., exstrophy–epispadias). In these situations, we combine a cystourethroscopic examination with suprapubic placement of a urodynamic catheter to be used later for urodynamic evaluation. A “difficult urethra” strongly implies the need for construction of an alternative catheterization channel (Mitrofanoff) at the time of bladder neck reconstruction.

Cystoscopy

Following a careful history and physical examination, we perform cystourethroscopy for all patients who have a history of previous trauma or surgical procedures involving the lower urinary tract before proceeding to open reconstruction. Cystoscopy provides information regarding bladder capacity and the status of any previous repairs.

Indications for Urinary Outlet Procedures

The two most common conditions requiring urinary outlet procedures are neurogenic bladder with low outlet resistance and the exstrophy–epispadias complex. Important differences exist between these two conditions. Typically, patients with a neurogenic bladder cannot void volitionally, in contrast to patients with exstrophy–epispadias or low outlet

resistance due to prior trauma. Furthermore, patients with a neurogenic bladder can have learning disabilities, emotional impairment, and developmental delay that must be taken into account when considering reconstructive procedures that will require them to rely on CIC to effectively empty the bladder. Therefore specific factors must be considered for these patient populations.

Neurogenic Bladder with Low Outlet Resistance

Specific criteria for bladder neck reconstruction can be difficult to determine in this population. Most children with neurogenic bladder dysfunction who remain wet with intermittent catheterization and pharmacotherapy ultimately require surgery to become dry. In patients with myelodysplasia, McGuire and colleagues (62) found the fluoroscopic appearance of the bladder neck predicted continence, as evidenced by the fact that those with an open outlet invariably had leakage despite medical management. Similarly, those with an LPP of less than 55 cm H_2O are more prone to leakage secondary to stress incontinence when they transfer or ambulate (63). These urodynamic criteria help determine who is a potential candidate for a bladder neck operation. Patients with poor detrusor compliance or hyperreflexia refractory to medication will also need bladder augmentation to store urine at safe intravesical pressures.

Surgery for incontinence can be safely performed in young children with a neurogenic bladder. In fact, bladder neck reconstruction is technically easier in this age group because the bladder is still primarily an abdominal organ. Furthermore, there are psychologic benefits for the child to be continent before joining his or her peers in school (3). Therefore we offer surgery to families that have been compliant with intermittent catheterization and routine follow-up when the patient is 4 to 6 years old. However, if concerns exist about the family's or child's commitment to care and CIC, reconstruction should be deferred until these concerns have been adequately addressed. Otherwise, the surgeon risks a "pyhhric victory"—a victory in which the patient is now continent of urine but that damages the upper urinary tracts and puts his or her life at risk due to inattention to care (7).

Exstrophy–Epispadias Complex

Compared with those with a neurogenic bladder, patients with exstrophy have no bladder neck or anterior bladder wall but are more likely to be continent and able to void after bladder neck reconstruction. As a result, the urologist may consider bladder neck operations that preserve volitional voiding in this patient population. Results of a staged approach to reconstruction as championed by Robert Jeffs have become a popular form of management for bladder exstrophy (26,27). In this approach, the bladder is closed at birth and the epispadias and bladder neck are reconstructed later. Typically, adequate bladder capacity and interest to toilet train are confirmed before bladder neck reconstruction is performed. Gearhart and Jeffs (26) have recommended epispadias repair as a second stage because it produces resistance at the bladder neck, resulting in bladder cycling and increased bladder capacity. Bladder neck reconstruction usually follows as a third stage.

Urinary Outlet Procedures That Do Not Preserve Volitional Voiding

The two most commonly performed outlet operations in this category include the Kropp procedure and its modifications and the Pippi-Salle technique. These operations likely create continence by urethral lengthening and flap-valve compression. Kropp originally described his operation as creating a flap-valve mechanism similar to ureteral reimplantation in which bladder pressure closed the outlet. However, after surgery, these bladders often do not reach pressures comparable to those needed to compress the ureter. Instead, resistance is increased in part by mucosal coaptation within the tube as well as by compression from any rise in intravesical pressure. Kropp has demonstrated tube pressures average 25 cm H_2O at rest, rising to 60 cm H_2O at bladder capacity. The Pippi-Salle repair seems to function by a similar means (90).

Surgical Technique

Kropp Procedure

The Kropp operation begins with a midline retroperitoneal lower abdominal incision to expose the anterior bladder wall (Fig. 51E.11). Then, a 6 × 2 cm detrusor strip based upon the bladder neck is incised by electrocautery. The bladder neck remains attached to the remainder of the bladder. This rectangular strip is next tubularized over an 8-Fr (12- to 14-Fr in adolescents) retention catheter using two layers of absorbable suture. This detrusor tube is then tunneled under the urothelium along the base and posterior wall of the bladder. As a modification, the tunnel may be placed into a shallow trough on the bladder floor made by incising the mucosa longitudinally between the ureteral orifices rather than tunneling it under the urothelium. The meatus and midportion of the tube are sutured to underlying musculature, and the mucosal edges of the trough are sewn to either side of the tube to completely cover its suture line (84) (Fig. 51E.12). When augmentation is required, the bladder is left open and the peritoneum explored to select a bowel segment. In addition, we simultaneously create an appendicovesicostomy (Mitrofanoff principle) in essentially all cases of bladder reconstruction for neuropathic disorders.

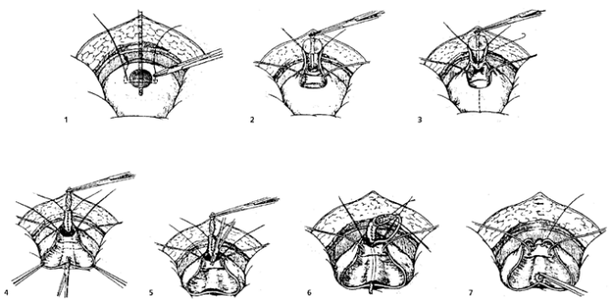

FIGURE 51E.11. Detrusor flap valve. A detrusor tube is created (anterior shown, posterior tube also possible) and tunneled submucosally in bladder to create a competent flap valve. (From Kropp KA, Angwafo FF. Urethral lengthening and reimplantation for neurogenic incontinence in children. *J Urol* 1986;135:534, with permission.)

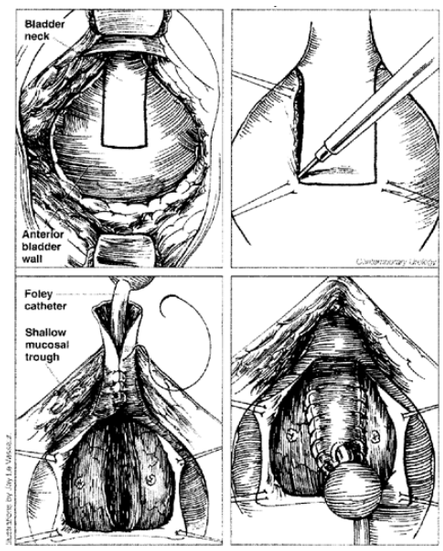

FIGURE 51E.12. Modified Kropp procedure. **Top left:** A rectangular strip is outlined on the anterior bladder wall based upon the bladder neck. **Top right:** The margins of the flap are incised. **Bottom left:** The flap is tubularized around an 8-Fr Foley catheter. **Bottom right:** The detrusor tube is laid into a shallow submucosal trough between the ureteral orifices.

The retention catheter and a suprapubic tube remain in place for 6 weeks. Then, the catheter is removed and the suprapubic (SP) tube occluded. This tube is subsequently removed once it is certain intermittent catheterization can easily be done per urethra or, preferentially, through the Mitrofanoff channel in patients with this means of access.

Pippi-Salle Operation

For the Pippi-Salle operation, a narrower and shorter rectangular flap 5 × 1.5 cm is mobilized, also based upon the bladder neck (Fig. 51E.13). Parallel longitudinal incisions of equal length are made 0.5 cm apart through the mucosa on the floor of the bladder between the ureteral orifices. These anterior and posterior strips are then sewn together in two layers over an 8-Fr catheter. To facilitate the repair, the ureters are usually reimplanted cephalad to the opening of the flap.

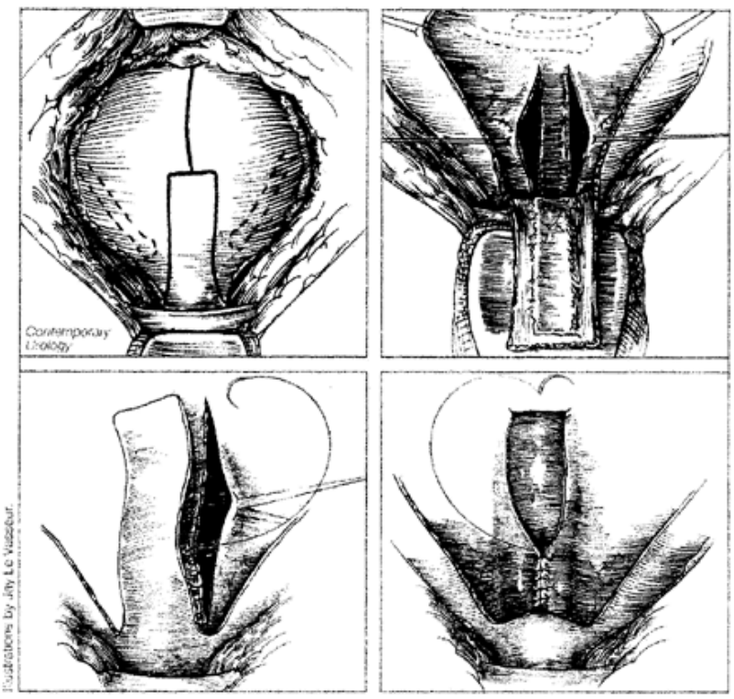

FIGURE 51E.13. Pippi-Salle procedure. **Top left:** A rectangular strip is outlined on the anterior bladder wall extending to the bladder neck. **Top right:** After the ureters are reimplanted cephalad, a rectangular flap is developed on the posterior bladder surface. **Bottom left:** The two flaps are sutured to create a tube lying on the bladder floor. **Bottom right:** The mucosa is closed over the detrusor tube.

Surgical Results

Kropp-type procedures have reported continence rates of 78% to 92% in both males and females (46,84). These results compare favorably to all other continence operations, including the Pippi-Salle, the AUSs, and bladder neck sling.

The main criticism of the repair has been difficulty with intermittent catheterization. Kropp reports 28% of his patients, both male and female, have had at least one episode of difficult catheterization, but only 14% had recurrent problems (90). Simultaneous construction of an accessory channel using the Mitrofanoff principle minimizes this complication.

LPPs following the Kropp procedure can be quite high. The original Kropp operation places most patients into complete urinary retention. This does increase the risk of bladder rupture in patients who have undergone bladder augmentation. The modified Kropp appears to create an outlet with a lower LPP so that patients are more likely to

leak if they delay catheterization. This difference likely relates to surgical technique. The Kropp procedure tunnels the detrusor tube, restoring the bladder neck to its original position while placing the whole tube intravesically. In contrast with the Kropp modification, the tube will not reach distally to the original bladder neck; therefore one-third to one-half the tube comes to lie extravesically. Apparently, this small difference makes the continence mechanism less efficient for urinary continence (84).

Both Kropp's and Pippi-Salle's original descriptions of their operations include bilateral ureteral reimplantation to move the ureters away from the site of outlet reconstruction (46,70). Ureteral reimplantation is typically performed for patients who have VUR on preoperative cystography. If ureteral reimplantation is not performed, approximately one-third of ureters will demonstrate VUR postoperatively. Fortunately, this new-onset VUR usually resolves spontaneously within 1 year (84).

Urinary Outlet Operations That Preserve Volitional Voiding

Young-Dees-Leadbetter–Type Bladder Neck Reconstruction

This operation represents an evolution of ideas that began early in the twentieth century and relies on urethral lengthening and narrowing to achieve urinary continence. In 1919, H.H. Young (94) described an operation to correct urinary incontinence by excising the posterior bladder neck and then narrowing the remaining tissue the bladder neck. In 1949, Dees (19) described a modification of this operation that removed more lateral tissue and lengthened the proximal urethra toward the trigone. Leadbetter (50) subsequently extended the degree or urethral lengthening and narrowing to such a degree that ureteral reimplantation was required to move the ureters out of the field of reconstruction. Others have modified this procedure further. Lepor and Jeffs (52) have described concomitant urethral suspension and intraoperative urodynamic evaluation to improve their results. They use a Marshall-Marchetti-Krantz procedure for urethral suspension and attempt to achieve a 3.5-cm continence length with a urethral closure pressure between 60 and 90 cm H_2O with bladder distention. Koff (44) described a further modification of this type of outlet reconstruction—the “cinch” procedure. This procedure involves wrapping the neourethra with a muscular flap and suspending it to the anterior abdominal wall. Jones and colleagues (39) also modified the Leadbetter procedure, called the *Mitchell repair.* In this procedure, the anterior urethra is incised transversely and the incision extended cephalad to narrow the bladder neck and lengthen the urethra.

Occasionally, trigonal tubularization must be combined with bladder augmentation; this type of bladder neck reconstruction decreases bladder capacity because bladder is used to create the continence mechanism (60). Various intestinal segments may also be used according to surgeon preference. The stomach offers the best potential to preserve spontaneous volitional voiding in this group, but it places these children at risk of hematuria-dysuria syndrome, which can be especially troubling in the face of persistent urinary incontinence (25). If augmentation is required, many surgeons will simultaneously perform an appendicovesicostomy for children who have difficult urethras to negotiate because of the possibility that they may require intermittent catheterization to empty the bladder after reconstruction.

Surgical Technique

Young-Dees-Leadbetter Procedure

Before performing the bladder neck reconstruction, ureteral reimplantation is usually required to move the ureteral orifices out of the field of reconstruction. To perform a YDL procedure (Fig. 51E.14), a strip of bladder mucosa (approximately 1 to 1.5 cm wide and 3 to 4 cm long) is mobilized and constructed into a tube over an 8- or 10-Fr urethral catheter using interrupted or running polyglycolic acid sutures (4-0 or 5-0). Use of an epinephrine-soaked sponge during this dissection may aid in hemostasis and visualization. Triangular flaps of demucosalized detrusor muscle are developed on either side of the mucosal tube and subsequently wrapped over the mucosal tube in a double-breasted technique using 3-0 polyglycolic acid sutures (27). This reinforces the neobladder, decreases the risk of fistula formation, and augments the outlet resistance (4).

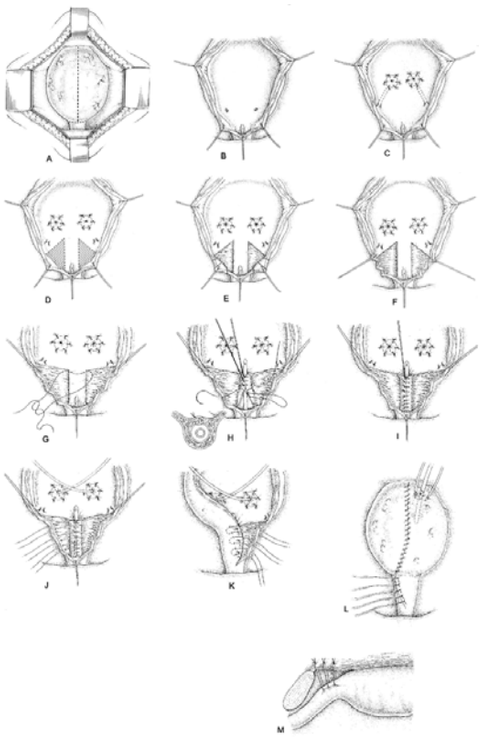

FIGURE 51E.14. Young-Dees-Leadbetter-Jeffs bladder neck reconstruction (BNR). **A:** After mobilization of the bladder neck and proximal urethra, a low transverse incision is extended vertically exposing the ureteral orifices and the entire trigone and proximal urethra. **B:** The bladder muscle lateral to the mucosal strip is denuded by sharp dissection. **C:** Ureteral reimplantation is performed using either a cross-trigonal technique or a cephalotrigonal technique to provide additional trigonal tissue for the repair. **D:** A strip of mucosa approximately 15 to 20 mm in width by 30 mm in length that extends from the midtrigone to the prostatic or posterior urethra is outlined. **E-F**: Multiple small incisions into the bladder muscle in the area of the denuded lateral triangles allow lengthening of the bladder neck area and allow the bladder to retract into a more cephalad position. **G-H:** The bladder neck is closed, beginning with a suture that incorporates detrusor muscle and urothelium. Each suture is placed on traction to draw up more of the strip to allow for easier subsequent placement of the more distal sutures. **I:** The completed mucosal layer of the repair. **J:** Ureteral stents, which will be left for 10 to 14 days, are placed and sutured. The first layer of the double-breasted bladder neck plasty is placed. **K:** The second layer of horizontal mattress sutures is placed. **L:** The bladder is closed after placement of a suprapubic catheter, which will remain in place for 3 weeks. **M:** The outer layer of the vest-over-pants repair is brought anteriorly as a Marshall-Marchetti-Krantz bladder neck suspension. (From Gearhart JP. Bladder neck reconstruction in the incontinent child. In: Frank J, Johnston, JH, eds. *Operative paediatric urology.* Edinburgh: Churchill Livingstone, 1990, with permission.)

Mitchell Repair

In a Mitchell repair (Fig. 51E.15), the anterior urethra should be incised *transversely* and the incision extended cephalad to narrow the bladder neck and lengthen the urethra. The incision is made full thickness. After cross-trigonal ureteral reimplantation, the urethral strip is tubularized in two layers over an 8- to 10-Fr urethral catheter, depending on the patient's age. The bladder may be closed in continuity with the urethral closure. This procedure effectively narrows and lengthens the urethra. Following the closure, dissection around the new bladder neck may be performed if a combined bladder neck wrap or sling is to be performed.

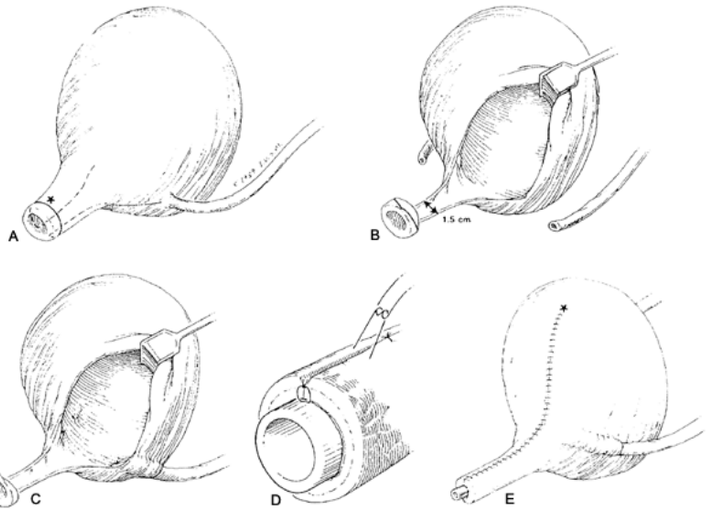

FIGURE 51E.15. Mitchell bladder neck plasty. **A:** A transverse incision is made distal to the original bladder neck area. Note the location of the asterisk relative to the incision. **B:** The incision is extended laterally, posteriorly, and then cephalad toward the ipsilateral ureteric orifice on each side. **C:** The ureters are dissected free from the bladder and reimplanted cephalad in the posterior bladder wall. **D:** The resultant posterior strip of bladder is tubularized in two layers. **E:** The bladder is closed longitudinally as an extension of the bladder neck closure. Note the site of the original bladder neck marked by the asterisk, which is now near the dome. (From Jones J, Mitchell M, Rink R. Improved results using a modification of the Young-Dees-Leadbetter bladder neck repair. *Br J Urol* 1993;71:555, with permission.)

Surgical Results

Bladder neck reconstruction in YDL procedures and its variants has yielded success rates of 30% to 80% or better for urinary continence in patients with bladder exstrophy (28,65). Many factors influence the outcome of surgery. For instance, an initial failed bladder closure or prior failed bladder neck reconstruction reduces the chance to achieve urinary continence later in these patients (28). Use of iliac osteotomies to provide a tension-free anastomosis and patient immobilization through the use of spica casting or Bryant's traction in the postoperative period increases the success of bladder closure and subsequent continence (29,55). Delayed bladder closure increases the likelihood of eventual bladder augmentation due to inadequate bladder capacity, which, in turn, reduces the chance for volitional voiding.

Woodhouse and Redgrave (93) have also reported that 8 of 13 patients with initially successful bladder closures and bladder neck reconstruction required further surgery in their second decade of life because of poorly compliant, low-capacity bladders that caused urinary incontinence.

ARTIFICIAL URINARY SPHINCTER

Indications

The pediatric patient with urinary incontinence secondary to intrinsic sphincter deficiency (ISD) presents a formidable challenge. Surgical options to achieve continence (versus dryness) in these children include procedures such as the YDL, urethral slings, periurethral injection of bulking agents, and the AUS. Of these various options, the AUS reliably allows the patient to spontaneously void postoperatively. From 25% to 30% of children with the AUSs in place have been reported to void spontaneously (32,53). Yet, unlike the other procedures to increase outlet resistance, the pressure exerted to compress the urethra or bladder neck is very dependable and determined by a pressure-regulating reservoir with different potential pressures (51 to 60, 61 to 70, 71 to 80, and 81 to 90 cm H_2O). Thus the AUS provides substantial and reliable outflow resistance for patients with urinary incontinence secondary to intrinsic sphincter deficiency and offers good potential for voiding.

The AUS is a mechanical device engineered to provide continence by circumferential compression of the bladder neck or bulbous urethra. In 1973, Scott and co-workers (79) were the first to report the use of the AUS for patients with incompetent urinary sphincters. The current model, the AS800, has been in use since 1983 and consists of three components: the pump, the reservoir, and the sphincter cuff, which are all interconnected by silicone tubing (Fig. 51E.16). To decrease the mechanical failure rate, several

modifications have been made to the original AUS. These include (a) treating the surface of the cuff with silicone, (b) narrowing the back cuff, (c) color-coding kink resistant tubing, and (d) making a seamless reservoir.

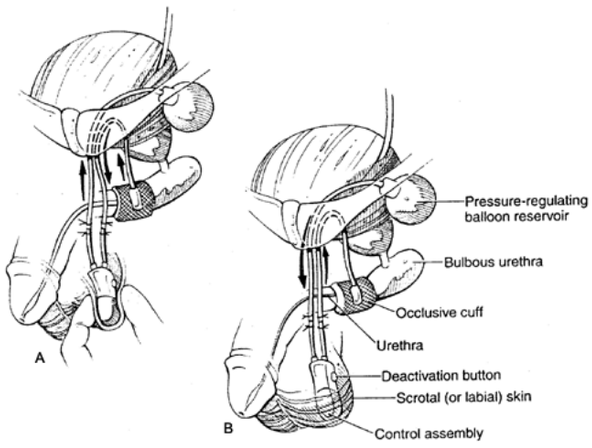

FIGURE 51E.16. Components and cycling of the AS800 AGUS. **A:** Squeezing of the scrotal/labial pump transfers fluid out of the compression cuff and into the reservoir initiating voiding. **B:** A delayed refill resistor slowly allows the cuff to refill automatically over 3 to 5 minutes.

The pump, placed in either the scrotum or labium majora, transfers fluid from an inflated cuff to the reservoir via a one-way valve. The pump has a refill-delay resistor that allows fluid to refill passively into the cuff after the bladder has been emptied. The pump also has a separate deactivation device with a poppet valve that allows the cuff to remain deflated if so desired. A modification of the pump for pediatric patients separates the deactivation device from the pump, thus allowing a smaller pump to be placed in the scrotum or labia of a small child.

The reservoir, placed either intraperitoneal or extraperitoneal, is an expandable silicone sphere and serves as the pressure regulator of the system. The fluid-filled reservoir transmits pressure to the sphincter cuff. The pressure exerted by the cuff is determined by the thickness of the reservoir wall. Currently, obtainable pressures are 51 to 60, 61 to 70, or 71 to 80 cm H_2O, depending on which reservoir is placed. The sphincter cuff (4 to 11 cm in length) is placed around the bladder neck or bulbous urethra and provides circumferential compression when filled with fluid. To empty the bladder, fluid must first be transferred from the cuff to the reservoir by sequential compression of the pump. The cuff then refills as fluid is passively transferred from the reservoir after 1 to 5 minutes.

Preoperative Assessment

The AUS is ideally suited for the patient who can void volitionally and who has a compliant but low-capacity bladder such that urinary outlet reconstruction would necessitate augmentation just to maintain capacity. Incontinent patients with adequate bladder capacity but ischemic or fibrotic tissue at the bladder neck may benefit from an AUS with sphincter placement at the bulbous urethra. However, the bulbous urethra can be used only in the postpubescent male. Children with a neurogenic bladder who can empty their bladders effectively with or without intermittent catheterization may also be good candidates for an AUS. Relative contraindications to AUS placement include patients who have chronic urinary tract infections because of the risk of infection of the AUS and patients with poor manual dexterity because they will not be able to manipulate the pump. Some investigators advise against using an AUS for patients who require CIC (54), but others do not see this as a contraindication (20). Because of the expectation of eventual revision and the dexterity required to use it, it is generally not the best option for younger patients.

Before implantation of the AUS in children, a complete medical history should detail the nature of incontinence, a summary of previous surgical procedures, expectations of the child and the family, the ability of the child or family to perform intermittent catheterization. Most importantly, the motivation and dedication of the child and family to the success of the procedure should be critically assessed. In general, the child should be at least 7 years of age and demonstrate excellent manual dexterity if he or she is going to be using the pump with commitment to using the device. The mental readiness of the child to accept responsibility is probably more important than age. It is also important that the family and child understand the mechanics of the device. Preoperative teaching of the child and the family before implantation of the AUS is critical to success. The family also must understand that the AUS is a mechanical device that will require revision in the future. Unfortunately, long-term effects of having a silicone device in the body are not known, but unlike with breast implants, difficulties have not been reported (76).

A critical component to the preoperative evaluation of a child anticipating a sphincter placement is videourodynamics. Important information to ascertain includes bladder capacity and compliance, the presence of uninhibited contractions, the presence of VUR, the appearance of the bladder neck, the LPP, the ability of the child to spontaneously void, and the postvoid residual. If the bladder neck is significantly incompetent or wide open, a balloon catheter is used to occlude the bladder neck to assess detrusor function. If decreased capacity, decreased compliance, or uninhibited contractions are detected with urodynamics, consideration should be given to a trial of anticholinergics before surgery. No improvement while taking anticholinergics may indicate the need for simultaneous augmentation at the time of AUS placement with minimal increased morbidity (64).

Operative Technique

At the time of AUS placement, the child should have sterile urine. A 24-hour course of intravenous antibiotics before the procedure may be considered, especially if the child performs CIC. Also, if a concomitant procedure is to be performed, such as a bladder augmentation or antegrade continence enema, a full mechanical and antibiotic bowel preparation should be performed.

Cystourethroscopy is performed before open bladder surgery and allows for a visual inspection of the urethra, the bladder neck, the ureteral orifices, and the bladder wall. High-grade reflux, bladder calculi, and ureteral ectopia close to or into the bladder neck are all relative contraindications to sphincter placement. In the male patient, a sponge is placed in the rectum to help prevent injury to the rectum during placement of the sphincter by facilitating identification of the anterior rectal wall. The vagina is irrigated with an antiseptic solution before surgery. A Foley catheter is placed after the surgical field has been prepared.

In children, the AUS is usually placed around the bladder neck. If concurrent bladder augmentation or a Mitrofanoff

procedure is to be performed, a midline incision provides appropriate exposure. Otherwise, a Pfannenstiel incision is indicated. When other procedures are planned, placement of the AUS is usually the final step in the surgery. If the bladder is opened for bladder augmentation, the plane between the bladder neck and vagina in the female and the bladder neck and rectum in the male is developed before completing the augmentation. The plane between the rectum or vagina and posterior bladder neck is more easily identified with the bladder open. If the bladder is not opened, traction on the Foley balloon aids in identifying the posterior and lateral aspects of the bladder neck. If there is any difficulty with development of this plane, the dome of the bladder should be opened to provide visual guidance.

Once the plane is developed around the bladder neck, the sizer is placed around the bladder neck. This sizer determines the appropriate size of the sphincter cuff to be used. The surgeon should place the sizer snugly, but not tightly. Usually, at the bladder neck in children, a cuff between 4 and 6.5 cm is used (Fig. 51E.17).

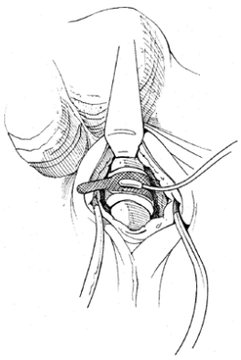

FIGURE 51E.17. The cuff tubing is passed through the hole in the cuff tab and then snapped into place.

The individual components of the AUS are then primed before being brought to the operative field. We prefer to use a 61- to 70-cm H_2O pressure-regulating balloon in children. The components are flushed with an isotonic contrast solution to remove all bubbles. Twenty-two milliliters of the contrast solution is placed in the reservoir, and the pump control is left full of fluid; the cuff is empty. The individual components are then brought to the surgical field. Antibiotic irrigant is liberally used in the wound throughout the surgery. The sphincter cuff is placed around the bladder neck and snapped to itself. The reservoir is then placed either intraperitoneal or in the preperitoneal space between the abdominal wall and peritoneum. The tubing from the reservoir and the tubing from the sphincter cuff are then brought through the rectus muscle on the side of the body that the pump will be placed. A plane is then developed above the rectus fascia down into the dependent portion of the scrotum or labia to place the pump.

After placement of the pump in the scrotum or labia, the tubes from the pump are connected with the tubing from the cuff and tubing from the reservoir. The tubing is color coded to ensure correct connections. We use the sutureless Quick Connect connectors to connect the tubing as provided by the manufacturer. It is important to not allow blood or debris to get into the system while making these connections. All connections are made above the level of the rectus fascia in the subcutaneous space.

In the older child with a fully developed scrotum or labia, we use the standard pump, which also contains the deactivation device. However, in the younger child without a fully developed scrotum or labia, we have used a modified pump. In this pediatric modification, the deactivation device is separate from the pump. This allows a smaller-sized component (pump without deactivation device) to be placed in the scrotum or labia. In this pediatric modification, the deactivation device is connected between the pump and the tubing from both the cuff and reservoir above the rectus fascia in the suprapubic space. The AUS is left deactivated with no fluid in the sphincter cuff for 6 weeks to allow healing.

Results and Complications

The results of the most recent large series of children with the AUS are characterized in Table 51E.5 .

Material	Advantages	Disadvantages
Rectus fascia	Autologous tissue	Morbidity of harvest
Fascia lata	Autologous tissue	Morbidity of harvest
Cadaveric fascia	No morbidity to harvest	? Risk for viral infections (prions)
Gracilis muscle	Well vascularized	Technically more difficult to harvest; bulky
Polypropylene	No morbidity to harvest	Foreign body; increased risk of erosion and infection
Silicon	No morbidity to harvest	Foreign body; increased risk of erosion and infection
Polytetrafluoroethylene (Gore-Tex)	No morbidity to harvest	Foreign body; increased risk for erosion and infection

TABLE 51E.5. BLADDER NECK SLING AND WRAP MATERIALS

Continence

Placement of an AUS is one of the most reliable means to increase bladder outlet resistance and provide continence in both adults and children. The reported continence rate for pediatric patients who have an AUS in place is between 71% and 100% (Table 51E.5).

Mechanical Failure and Revisions

One pitfall of the AUS is that it is a mechanical device; thus revisions will eventually be required. Fortunately, the improvements in design have significantly reduced the need for revisions. Simeoni and co-workers (82) found mechanical failures in 21 of 107 patients at follow-up. These failures included perforation or rupture of the cuff in two patients, perforation or rupture of the reservoir in three, perforation or rupture of the tubing in two, kinking of the tubing in

two, pump malfunction in six, fluid leakage in four, and organic material occluding the hydraulic system in two (82). Simmons and colleagues (83) described a mechanical failure rate of 1 per every 12.5 patient years in their 15-year follow-up of 134 patients. Similarly, Kryger and associates (48) reported 0.08 revisions per patient-year in patients who had the AS800 placed. Twelve of their revisions were for fluid leaks and six revisions were for component malfunction. In a meta-analysis of published studies in both adults and children, Hajivassiliou (37) reported a global revision rate of 32%.

Bladder Deterioration

After implantation of an AUS, some patients have demonstrated significant changes in detrusor function. Some of these patients have required subsequent augmentation to protect their renal function and to aid in achieving continence. In 1998, Kronner and colleagues (45) evaluated 38 children who underwent AUS alone. In follow-up, 15 of the 38 patients required subsequent augmentation cystoplasty at a mean of 49 months after initial AUS placement. They found no statistical significance in the preoperative bladder capacity or compliance when comparing those patients who eventually required augmentation with those patients who did not require augmentation (45). Therefore it is important to closely follow children in who an AUS is placed for subsequent change in bladder function. Proposed etiologies of deterioration in bladder function are unrecognized hyperreflexia or decreased compliance preoperatively, tethered chord, progression of myelomeningocele, or the bladder's response to outlet obstruction.

Erosion and Infection

Two potential complications of placing and artificial device into the body are erosion through adjacent tissues and infection. Gonzalez and co-workers (32) reported a 41% removal rate in follow-up, and all devices were removed secondary to either erosion or infection. Although not statistically significant, Gonzalez and associates (32) believed that risk factors for erosion in their patients included previous AUS erosion, previous bladder neck surgery, and a balloon pressure greater than 70 cm H_2O. No erosions were noted in patients with an AUS placed around a previously unoperated upon bladder neck. Therefore they have used the AUS as a first-line treatment for all patients with neurogenic sphincter incontinence (32). We, on the other hand, tend to use the AUS as a secondary procedure, unless the children void spontaneously before surgery.

BLADDER NECK SLINGS AND WRAPS

Sling operations are used to coapt the incompetent bladder neck. Typically, these are wrapped snugly around the bladder outlet. In that regard, they are similar to artificial sphincters. Sphincters, however, provide more effective closure, especially in boys, and have the advantage of reducing the closure pressure for voiding. Bladder neck wraps (and slings to some degree) should be considered to provide a fixed urethral closure. Complications of slings include erosion and difficult intermittent catheterization. Sling procedures also demonstrate less durability and seem to have less effectiveness in boys (49,72). We use them as an adjunct to other procedures.

Bladder neck wraps and slings may also be performed in conjunction with urethral lengthening (YDL) procedures. Series reporting on the use of bladder neck wraps alone suggest that this procedure does not consistently maintain long-term urinary continence, especially in male patients who constitute the gender majority in exstrophy (18,49). Bladder neck wrap and sling procedures have been performed with a variety of substances. These include autologous tissue–like rectus fascia, tensor fascia lata, and gracilis muscle and synthetic products such as silicon elastomers, Vicryl mesh, polytetrafluoroethylene membrane (Gore-Tex), and others. Fascia remains a popular choice for these procedures (6).

Surgical Technique

Bladder neck wrap and sling procedures may be performed transvaginally or transabdominally. The transvaginal approach is best suited for patients who do not require a concomitant transabdominal procedure and who are large enough to provide the surgeon with enough exposure to the anterior vaginal wall. As a result, transvaginal operations for urinary incontinence are rarely used for prepubertal girls.

With use of a transvaginal approach, the patient is first placed in the dorsolithotomy position. After sterile preparation and draping, a urethral catheter is placed to empty the bladder and assist in identifying the location of the urethra. The sling tissue to be used should be ready or harvested before beginning the vaginal dissection. An inverted U-flap or longitudinal incision is then made in the anterior vaginal wall to expose the underlying connective tissue. A low transverse abdominal incision is made. This incision is used to allow an endoscopic suture-passer such as the Stamey needle to transfer suture material from the vaginal incision to the abdominal incision. The bladder should be empty to reduce the chance of entering the bladder during suture passage. The sutures are attached to the sling material prior their passage to the anterior abdominal wall. The sutures can be tied to each other over the abdominal wall fascia or anchored to bone depending on surgeon preference (Fig. 51E.18).

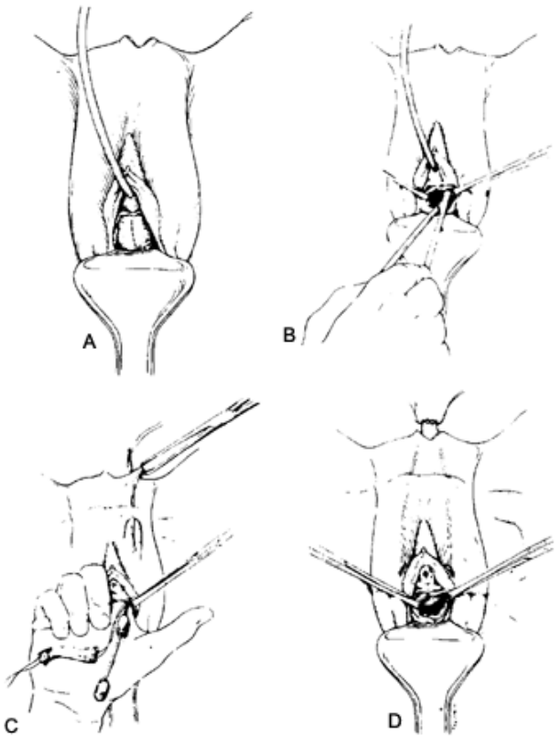

FIGURE 51E.18. A–D: McGuire's modified pubovaginal sling. A 1 × 3 cm rectus fascial strip is pulled up by techniques of a Stamey endoscopic suspension to add a compressive element. (From McGuire EJ, Wang C, Usitalo H, et al. Modified pubovaginal sling in girls with myelodysplasia. *J Urol* 1986;135:94, with permission.)

A transabdominal approach to bladder neck wraps and slings is most commonly used for children and male patients (Fig. 51E.19). It is often combined with other operations such as bladder augmentation. If this operation is performed alone, the surgeon may use a low transverse abdominal incision. Otherwise, it can be performed through a longitudinal

midline abdominal incision in combination with another operation.

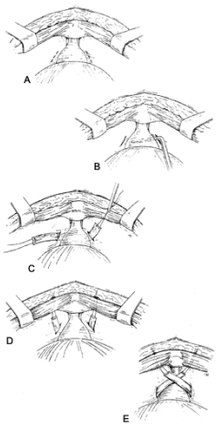

FIGURE 51E.19. A–E: Transabdominal approach for bladder neck wrap.

As in the case of AUS placement, safe circumnavigation of the bladder neck is the most technically difficult portion of this operation. Dissection around the bladder neck can prove technically challenging in these patients due to a patulous bladder neck, previous surgery in this area, and concomitant skeletal abnormalities in some of these patients. A prevesical and retrovesical approach may be necessary to accomplish this dissection without entering the bladder neck. The bladder may also be opened anteriorly to help identify the plane of dissection behind the bladder neck. If the urethra, vagina, or bladder neck are inadvertently entered during attempts to establish a plane of dissection around the bladder neck, the wrap or sling may still be performed if the opening is small, although healthy tissue should be brought between the bladder neck and sling tissue if possible. If the opening is large, the bladder neck procedure should be converted to another operation as appropriate. Bladder neck closure may be performed in this situation as well.

Once the bladder neck dissection has been preformed, the coapting tissue may be passed around the bladder neck. The number of times the tissue is passed around the bladder neck and the amount of tension placed on the wrap depend on surgeon preference and tissue availability. The bladder neck may be suspended from the inferior surface of the pubis symphysis following suture fixation of the fascial tissue to the bladder neck and to itself. Suprapubic urinary drainage following a bladder neck wrap or sling avoids pressure on the repair site. It also provides a mechanism for urinary drainage, if a trial of volitional voiding or CIC is unsuccessful in the initial postoperative period.

URETHRAL BULKING INJECTION

Politano and co-workers (73) introduced the concept of urethral bulking in 1974. At that time, they described the use of polytetrafluoroethylene (Teflon) paste to coapt the urethral wall by injecting it in a submucosal plane. Since then, various other agents have been proposed, including adipose, bovine collagen, carbon-coated beads (Durasphere), and silicon elastomers (Macroplastique) (74). Some investigators are also evaluating the use of myoblasts, chondrocytes, and other autologous agents (14). Each has advantages and disadvantages (Table 51E.6). None of these agents has demonstrated enough long-term success or dependability to replace other procedures. However, endoscopic injection of bulking agents is technically easy and offers minimal patient morbidity. It also preserves the ability of patients to void volitionally in many situations. Of note, before the use of bovine collagen for endoscopic bulking therapy, the patient must be tested for hypersensitivity to this agent. This is assessed by subdermal injection.

Agent	Advantages	Disadvantages
Polytetrafluoroethylene	Durable	Difficult to inject; tissue migration and granuloma formation (57,58)
Bovine collagen	Ease of injection (8)	Not durable (33); hypersensitivity reactions in some patients (1)
Autologous fat	Biocompatible	Not durable; morbid to harvest; difficult to inject (51)
Silicone elastomer (75)	Nonmigratory; durable	Long-term results?
Pyrolytic carbon–coated beads	Nonmigratory; durable	Long-term results?

TABLE 51E.6. PERIURETHRAL BULKING AGENTS

Injectable bulking agents may be used as *de novo* therapy or adjunctively after a bladder outlet operation. Currently, injectable therapy enjoys its broadest application for the treatment of intrinsic sphincter deficiency in women with stress urinary incontinence. Success rates vary widely. In general, success rates are highest immediately after therapy and deteriorate over time. Success rates also appear higher when injectable therapy is used as a first-line agent rather than as adjunctive therapy following bladder neck reconstruction (21).

At present, bovine collagen is the most popular injectable agent available. It is most commonly used for stress urinary incontinence in adult women. Several authors have used bovine collagen injections at the bladder neck to treat patients with stress incontinence after bladder neck reconstruction as well (5,10). Ben-Chaim and colleagues (5) reported an improvement in continence in 53% of patients after collagen therapy, although most required multiple injections.

In children, injectable bulking agents are more commonly used for adjunctive therapy for those patients who demonstrate slight urinary leakage due to stress incontinence after bladder neck reconstruction. These agents are rarely used for primary therapy in children with stress urinary incontinence.

Surgical Technique

Cystoscopic evaluation of the bladder and bladder neck is first performed. A large-bore needle (e.g., 17 gauge) is then inserted submucosally proximal to the bladder neck. The

needle is advanced in this plane, and the agent is injected (Fig. 51E.20). Proper needle placement is visually confirmed at this time by watching the submucosal tissue coapt as the agent is injected. The properties of the specific bulking agent and the plane of injection will dictate the ease of injection. Needle placement too deeply into the tissue will make injection difficult and will not result in tissue coaptation. Injections are typically performed at various locations in the urethra, such as the 3, 6, and 9 o'clock positions. The amount of agent injected depends on the particular bulking agent chosen, the ease of injection, and the ease of tissue coaptation.

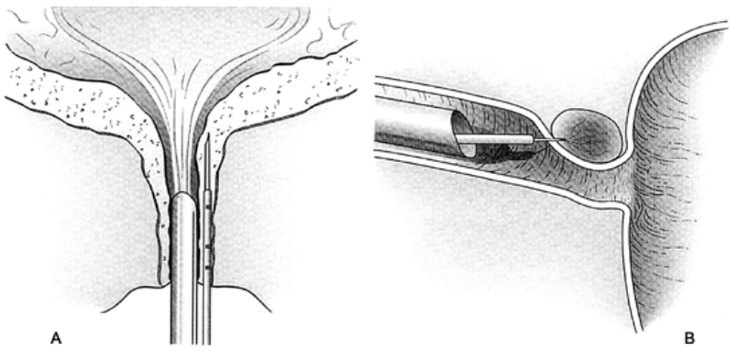

FIGURE 51E.20. A–B: Technique for periurethral injection.

BLADDER NECK CLOSURE

Bladder neck closure in conjunction with appendicovesicostomy is also an option in patients who have failed multiple attempts at bladder neck reconstruction. We reserve this as a final solution because it eliminates the chance to void per the urethra and commits the patient to intermittent catheterization. This procedure should not be taken lightly. It can be technically difficult to perform because it is often required in the patient who has had multiple previous surgeries and extensive scarring at the bladder neck. As with any closure, the dissection of the bladder neck should be complete enough to facilitate a two-layer closure. Both the bladder neck and urethra should be closed and healthy tissue placed between. Often, omentum can serve this purpose. Breakdown of a bladder neck closure can and does happen. This is very disappointing to both the patient and the surgeon.

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52
THE GENITALIA

Contents

52A GENITAL ANOMALIES

Terry W. Hensle

Part of "52 - THE GENITALIA "

T.W. Hensle: Department of Urology, Columbia University College of Physicians & Surgeons; Department of Pediatric Urology, Children's Hospital of New York, New York, NY 10032.

GENITAL ANOMALIES: MALE

In humans, the Y chromosome induces testis formation and thus male sexual development; in the absence of a Y chromosome, gonads differentiate into ovaries and female development ensues. Molecular genetic studies have identified the Y-located testis-determining gene SRY as well as autosomal and X-linked genes necessary for gonadal development (5,69,94).

Beginning at 8 weeks of gestation, genital development occurs in two distinct areas: internal duct structures and external genitalia (23). Development of internal duct structures in both male and female depends on the presence or absence of a fetal testis (Fig. 52A.1). In the presence of a fetal testis, there will be production of androgen (testosterone) as well as müllerian-inhibiting substance (MIS) (36). Secretion of fetal androgen by Leydig cells stimulates the Wolffian duct to differentiate into the vas deferens, seminal vesicle, and epididymis. At the same time, the Sertoli cells of the fetal testis secrete a nonsteroidal substance (MIS) that prevents development of müllerian duct structures into the fallopian tube, uterus, and upper third of the vagina. The development of the female internal duct system does not depend on hormonal induction and occurs normally in the absence of MIS, whereas the Wolffian duct structures will regress in the absence of high levels of fetal androgen (57).

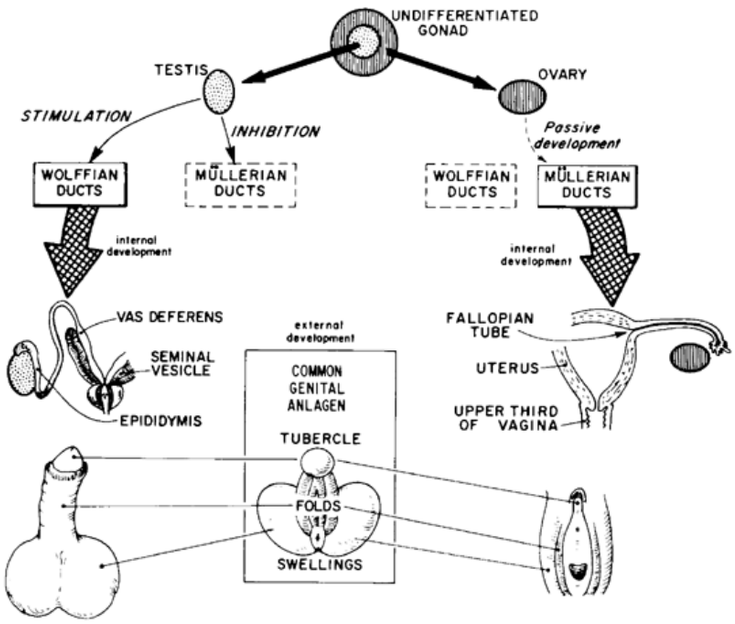

FIGURE 52A.1. Normal sexual development in the male and female. (Adapted from Federman DD. *Abnormal sexual development: a genetic and endocrine approach to differential diagnosis.* Philadelphia: WB Saunders, 1967, with permission.)

Differentiation of the external genitalia occurs somewhat later, probably between 12 and 16 weeks of gestation (Fig. 52A.1). The process in the male requires not only the fetal testis and adequate amounts of fetal androgen but also the ability of the target organ to respond to the circulating androgen. Testosterone exerts its effect on the target organ in several ways, the most important of which is the conversion of testosterone to dihydrotestosterone (DHT) under the enzymatic influence of 5α-reductase (11). This conversion takes place within the tissue of the common genital anlage, where DHT combines with a cytosol receptor that is

coded for by one or more X-linked genes (2,75). These androgen receptor complexes are then activated and moved to nuclear acceptors (3). Subsequently, DNA-dependent RNA polymerase activity increases, followed by enhanced production of protein. These serve as the initial steps for differentiation of the common genital anlage (50). Under the influence of DHT, the genital tubercle will differentiate into the glans penis, the genital folds become the shaft of the penis, and genital swellings become the scrotum. If there is a deficiency in production of fetal testosterone, failure of conversion of testosterone to DHT, or insensitivity in the target organ to DHT, the genital tubercle will passively develop into the clitoris, the genital folds will become labia minora, and the genital swellings will become labia majora (36,53).

The clinical and molecular spectrum of the androgen insensitivity syndromes (AIS) has been well defined over the past several years and offers one of the better examples of genetic interactions in the human sex determination pathway. This disorder is caused by mutations of the androgen receptor and is an X-linked recessive trait. Hiort and colleagues (49) studied 47 patients with AIS and characterized the underlying molecular abnormality in the androgen receptor gene. They noted that mutations in the androgen receptor gene may be present throughout the whole coding region, but provided evidence that several mutational hot spots exist. Bevan and associates (6) found milder mutations to be associated with milder clinical phenotypes. There also is clear evidence that phenotype does not solely depend on androgen receptor function. Nonetheless, some mutant receptors are able to respond to high dosages of androgens *in vitro,* suggesting that patients carrying these mutations may be candidates for androgen therapy (52).

There are significant numbers of patients with disorders of sexual differentiation in whom no mutation has yet been characterized. It is likely that further genes involved in sexual differentiation will be identified and shown to be the etiology of a number of these diseases (51,104).

Danso and Tobani (19) have used cytogenetic investigations in confusing states of intersexuality and disorders of sexual differentiation to make sex assignment slightly easier and more sensible. They suggest performing these studies in the very early stages of life. In all 87 patients studied, cytogenetic investigations helped to categorize the ambiguous genitalia patient accurately. They concluded that cytogenetic studies should be a prerequisite, are an advantage, and are imperative in patients with ambiguous genitalia.

In cases of genital anomalies, parents and sometimes patients themselves must be advised in a meaningful manner (96).

The anomalies of sexual development and their etiologies and management are discussed to provide the reader with a foundation when approaching these challenging and fascinating cases.

Penile Agenesis

Endocrine testicular function in patients with penile agenesis (Fig. 52A.2 and Fig. 52A.3) has been shown to be normal as judged by a normal response to gonadotropin stimulation (28,59,102). Recommended treatment should be early gender reassignment and gonadectomy. The urethra should be transposed anteriorly away from the anal verge, and the scrotal skin should be preserved to aid later vaginal construction. Recently, consideration has been given to penile reconstruction utilizing free flaps from the arm or leg to construct a phallus. This is very innovative and demanding surgery, with little long-term follow-up. With normal testes and receptor function, male imprinting may be significant, therefore providing possible justification for such efforts.

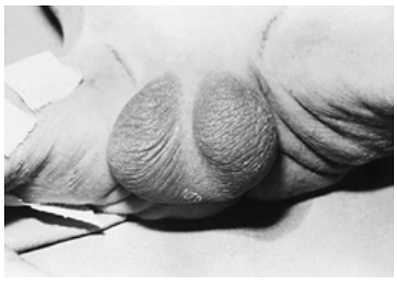

FIGURE 52A.2. Penile agenesis.

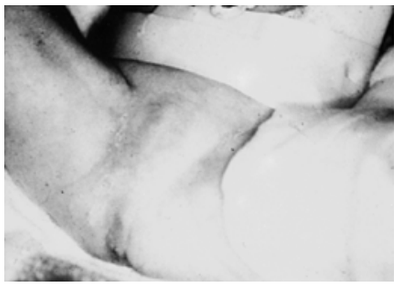

FIGURE 52A.3. Agenesis of the penis and scrotum.

Penile Duplication

Duplication of the penis is another rare anomaly, probably resulting from incomplete fusion of the genital tubercle. The anomaly appears in two basic forms, the first and more common being the bifid penis, which is often associated with the exstrophy-epispadias complex (Fig. 52A.4) and is present in almost every male with cloacal exstrophy. In these cases, the bifid penis consists of a single corporal body on each side associated with a hemiglans penis (55).

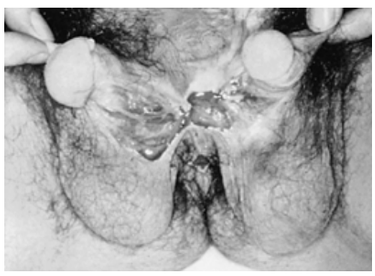

FIGURE 52A.4. Penile duplication in a patient with bladder exstrophy.

The other form of penile duplication is true diphallia. This is an extremely rare condition in which there is a duplication of all or part of the penis (91). The deformity exists in a spectrum that ranges from duplication of glans alone, arising from the single shaft (Fig. 52A.5), to complete duplication with two separate scrotums. With complete duplication, each penis has a complete urethra, which is associated with an independent bladder or at times with a bifid bladder. The urethral opening can be in the normal position or either hypospadiac or epispadiac. When bladder duplication is associated with penile duplication, both erection and urination can occur synchronously or asynchronously.

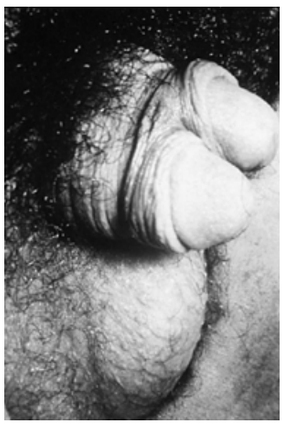

FIGURE 52A.5. Complete penile duplication.

Treatment of penile duplication varies depending on whether other congenital anomalies are present. If the bifid penis is associated with cloacal exstrophy, penile reconstruction may not be technically possible and gender reassignment is considered. One of the bifid phalluses can be removed, retaining the other to act as a clitoris. In true diphallia, the decision of which penis should be removed and which salvaged should be based on not only the physical appearance of both structures, but also on the size of the bladder associated with each segment, and the erectile function of each unit. Patients with true diphallia should also be thoroughly evaluated for other genitourinary or

gastrointestinal (GI) tract anomalies because the association of other anomalies with this defect is abnormally high.

Microphallus

Microphallus can best be defined as a normally formed penis (Fig. 52A.6) whose length is more than 2.5 standard deviations (SDs) below the norm for age (Table 52A.1) (25,95). In the neonatal period, the penis should measure at least 2 cm from pubis to tip when fully stretched (66). The term *microphallus* by definition excludes hypospadias and ambiguous genitalia.

Age	Mean ± SD cm	Mean −2.5 SD cm
Newborn, 30 wk	2.5 ± 0.4	1.5
Newborn, 34 wk	3.0 ± 0.4	2.0
Newborn, term	3.5 ± 0.4	2.4
0–5 mo	3.9 ± 0.8	1.9
6–12 mo	4.3 ± 0.8	2.3
1–2 yr	4.7 ± 0.8	2.6
2–3 yr	5.1 ± 0.9	2.9
3–4 yr	5.5 ± 0.9	3.3
4–5 yr	5.7 ± 0.9	3.5
5–6 yr	6.0 ± 0.9	3.8
6–7 yr	6.1 ± 0.9	3.9
7–8 yr	6.2 ± 1.0	3.7
8–9 yr	6.3 ± 1.0	3.8
9–10 yr	6.3 ± 1.0	3.8
10–11 yr	6.4 ± 1.1	3.7
Adult	13.3 ± 1.6	9.3

Adapted from Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. *J Pediatr* 1975;86:395, with permission.

TABLE 52A.1. STRETCHED PENILE LENGTH IN NORMAL MALES

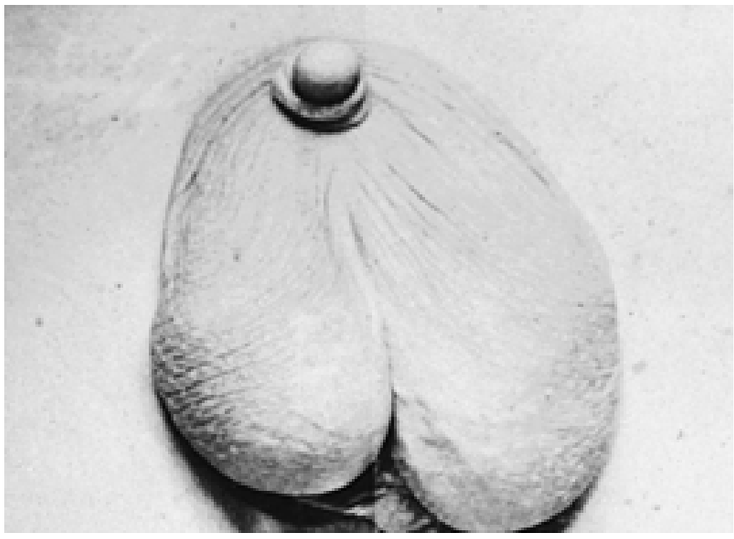

FIGURE 52A.6. True microphallus.

In general, the cause of microphallus can be thought of as either inadequate androgen stimulation of the target organ or an insensitivity of the target organ to available androgen. Inadequate amounts of androgen reaching the target organ can be on the basis of either poor Leydig's cell stimulation, thus suggesting a problem in the hypothalamic-pituitary axis, or a failure of the conversion of testosterone to DHT by 5α-reductase.

The nature of the defect can be determined by the individual's response to gonadotropin stimulation. In most infants with microphallus, the ability to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to gonadotropin-releasing hormone (GnRH) is present, and the testis is able to respond to LH by secreting testosterone. In addition, androgen-sensitive target organs such as the penis generally respond to testosterone administered locally or parenterally. Thus it seems that in most infants with microphallus, the hypothalamic–pituitary–end-organ axis distal to the hypothalamus is intact, implicating the hypothalamus as the site of the primary defect (66). Additional evidence for this is seen in several associated disorders, such as Kallmann's syndrome and Prader-Willi syndrome. Other endocrine disturbances, such as abnormal levels of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and growth hormone, can be seen frequently in patients with microphallus.

The treatment of microphallus should begin early (39). In rare individuals with identifiable AIS and associated microphallus, gonadectomy and gender conversion to female

is best done at an early stage. In most patients with true microphallus, male gender assessment can be maintained, and androgen stimulation should begin in the first year of life. Monthly injections of testosterone enanthate are given for 3 months in doses of 25 to 50 mg delivered parenterally (15). Application of 3% testosterone cream locally is also a reasonable way to deliver androgen; however, the absorption is variable, and the dose is not as easily controlled (60). In most instances of true microphallus, an increase of phallic growth of approximately 2 cm in the first year of treatment can be expected. When this early stimulation is stopped, the penis does not usually revert to its previous proportions. Multiple courses of androgen stimulation can be used, and if significant growth does not occur, gender conversion can be considered (77).

The long-term outlook for patients with true microphallus recently has been reviewed by Reilly and Woodhouse (89). In 12 postpubertal patients who had carried the diagnosis since childhood, they found the prospect for long-term sexual activity to be hopeful. Eleven of their patients experienced ejaculation, and nine were sexually active, all reporting vaginal penetration. All of the patients in their series had been stimulated with human chorionic gonadotropin, testosterone, or cortisone during childhood.

Penile Torsion

Rotational defects of the penis, or penile torsion (Fig. 52A.7), can occur in either a clockwise or counterclockwise position, with or without other associated defects such as hypospadias (83). The defect usually has more cosmetic than functional significance. Mild degrees of torsion are not associated with either erectile or voiding dysfunction, and the surgical correction of penile torsion usually is not indicated for children with a rotation of less than 90 degrees from the midline. Surgical correction of mild penile torsion usually involves nothing more than simply degloving the penis and reorienting the median raphe to its normal position (83).

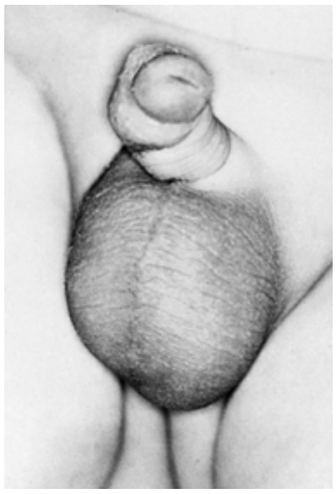

FIGURE 52A.7. Penile torsion. (Courtesy of A. Barry Belman, M.D.)

In cases of more significant penile torsion, there can be a defect in the position of the glans penis on the corporal bodies. In the treatment of patients with extreme torsion, the glans usually must be mobilized to some degree and rotated on the corpora to achieve derotation. This is a significant surgical undertaking and should not be considered in mild forms of penile torsion.

Lateral Curvature of the Penis

Lateral penile curvature rarely is recognized in infancy but certainly can be noted in early childhood and must be differentiated from chordee without hypospadias (Fig. 52A.8). Lateral curvature usually is caused by an overgrowth of one corporal body, or concomitant hypoplasia of the contralateral corpora (26). The defect can be associated with corporal injury, but in most instances, there is no history of trauma.

FIGURE 52A.8. Curvature of the penis secondary to unilateral corporal overgrowth. (Courtesy of John Duckett, M.D.)

Surgical correction of corporal discrepancies should be considered only when the discrepancy significantly interferes with erection. The procedure of choice in most instances was described by Nesbit and involves excising ellipses of the tunica albuginea from the dominant corpora in the area of maximum curvature to reduce the apparent defect (34). When corporal discrepancies are the

result of trauma, there is often a scar on the contralateral (shorter) corpora, which can be excised and grafted with either tunica vaginalis or some other form of genitourinary tissue.

Penile Lymphedema

Primary lymphedema (Fig. 52A.9) of the foreskin and penile shaft is a chronic condition seen in children with either abnormal penile lymphatics or a decreased number of lymph channels draining the foreskin (13). The condition occasionally is seen after circumcision; however, it also may be seen in uncircumcised newborn children as well as in adolescents. When it is seen in the uncircumcised newborn, elective circumcision should be avoided because this generally escalates the process of poor lymph drainage, making the situation worse.

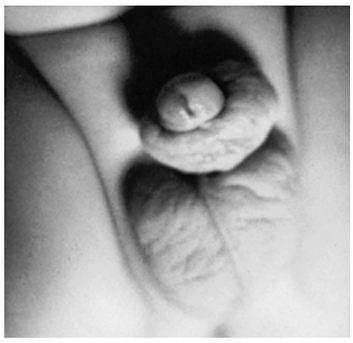

FIGURE 52A.9. Lymphedema of the foreskin following newborn circumcision.

In most instances, a reduction of the excess skin and subcutaneous tissue will give a reasonable cosmetic result. When the problem is extensive, the edema may involve the entire shaft and scrotum. Feins (24) has suggested extensive resection of the subcutaneous and lymphatic tissue to deal with the problem in its more severe form.

Penoscrotal Transposition

Complete transposition of the penis and scrotum (Fig. 52A.10) is a rare anomaly that often is associated with other congenital anomalies, many of which are incompatible with life. The embryologic defect is probably the abnormal positioning of the genital tubercle in relation to the genital swellings; this abnormality also has been referred to as a *prepenile scrotum* (17).

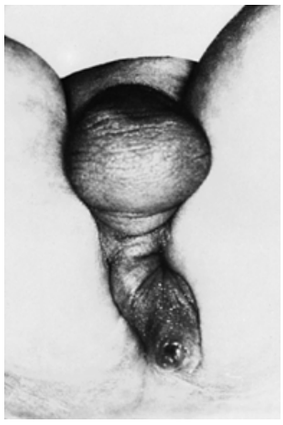

FIGURE 52A.10. Penoscrotal transposition. (Courtesy of A. Barry Belman, M.D.)

Scrotal transposition has been reported with both a normal penis and with bifid scrotum and various penile deformities. Surgical correction of the scrotal transposition is advocated for cosmetic and psychologic reasons, although urinary and erectile function are not always impeded by this anatomic inversion. There is at least one case report of a patient with complete penile-scrotal transposition who has produced four children (4). Surgical correction can be achieved either by completely dividing the scrotum and transposing the penis upward, or by tunneling the penis to a midline position.

Bifid Scrotum

Bifid scrotum usually is seen in conjunction with severe degrees of hypospadias such as penoscrotal or perineal hypospadias (Fig. 52A.11). It usually is associated with significant skin chordee, where the skin of the lateral surface of the penis is firmly attached to the midline between the two hemiscrotums. Surgical correction of the bifid scrotum involves release of skin anteriorly to be rotated down to the midline, with realignment of the two scrotal halves in the midline. The most severe form of bifid scrotum is scrotal transposition in which the scrotum appears to be transposed above the penis. This is not true penile-scrotal transposition as described earlier.

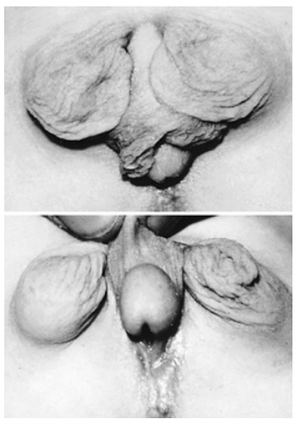

FIGURE 52A.11. Bifid scrotum in a patient with perineal hypospadias.

Scrotal Ectopia

Scrotal ectopia is a rare condition occasionally seen in boys with otherwise normal genitalia (64). The ectopic scrotum usually is found somewhere near the external inguinal ring but can be found anywhere along the inner thigh or buttocks (Fig. 52A.12). The testis on the side of the scrotal ectopia can be normal or dysplastic, and treatment should be based on the amount of ectopic scrotum present and the condition of the testes. If there is a significant amount of scrotum and reasonable testes, an attempt should be made to bring the testes down along with the ectopic scrotal tissue. If there is only a small, rudimentary amount of ectopic scrotal tissue or dysplastic testes, one or both should be removed.

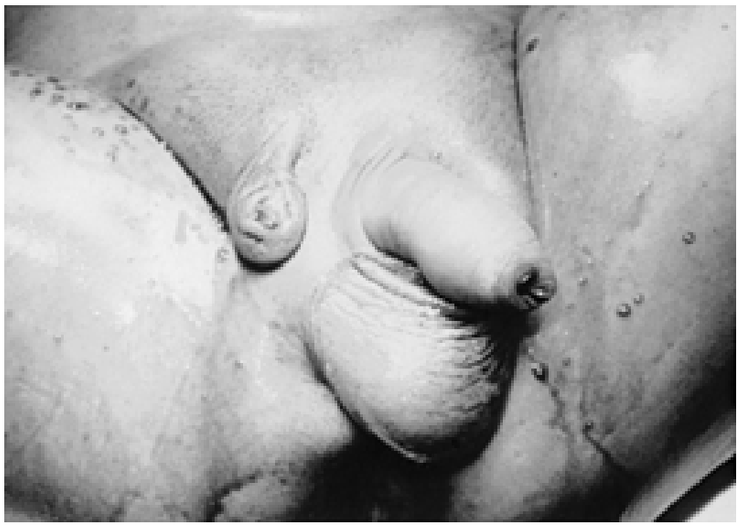

FIGURE 52A.12. Scrotal ectopia.

Scrotal Hypoplasia

Scrotal hypoplasia can be either unilateral or bilateral and usually is associated with the absence of a testis on one or both sides (Fig. 52A.13). If there is monorchia or anorchia, the scrotum is typically flat and nonrugated on the affected side. Usually, the placement of a testicular prosthesis along with the application of local testosterone cream will improve the cosmetic situation to a significant degree.

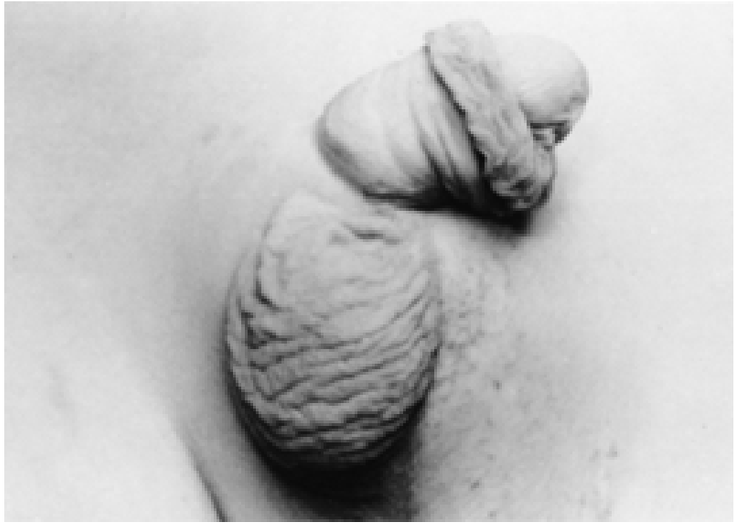

FIGURE 52A.13. Unilateral scrotal hypoplasia (left hemiscrotum is absent).

Scrotal Hemangioma

Hemangiomas of the scrotum are rare lesions first reported by Robert (90) in 1851. Hemangiomas are common and occur in 10% of all infants younger than 1 year of age. They may involve any area of the body and are not uncommon in the urogenital tract. However, hemangiomas of the external genitalia make up only 1% of all cutaneous hemangiomas and are more common in females than in males. Currently, fewer than 45 cases of scrotal hemangiomas are reported in the literature (86). Hemangiomas of the scrotum generally are seen in the first 20 years of life but may occur at any age; the youngest case reported is a 1-month-old infant. There are no reports of a complete involution of this lesion; rather, a progressive enlargement is commonly noted.

On physical examination, the scrotal hemangioma is a soft, spongy compressible mass that has a “bag of worms” sensation somewhat similar to a variocele of the cord. There is no pulsation or bruit associated with the mass. The overlying skin can have a normal color or a pinkish, bluish, or purplish tinge. Often, the skin is thinned in some areas due to the pressure of the tumor, and thickened in other regions (Fig. 52A.14). The testes, epididymides, and vas deferens are generally normal on palpation. The mass remains distended without visible decrease in size when the patient is supine with the scrotum elevated. The lesion occurs with equal frequency on the right and left sides, unlike a varicocele. Scrotal hemangioma can also occur bilaterally, and cases have been reported in association with bladder tumors and Klippel-Trenaunay syndrome (68).

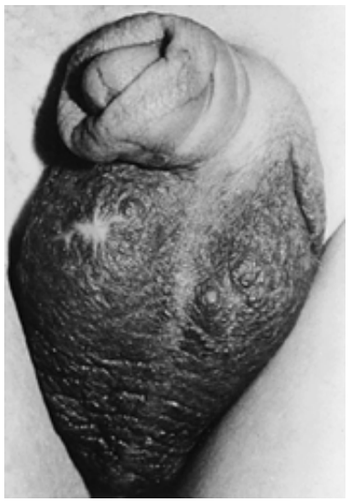

FIGURE 52A.14. Scrotal hemangioma.

The scrotal hemangioma usually is painless and nontender, although the mass can be associated with a feeling of heaviness and a dragging sensation. Angiography generally shows a capillary or venous (or both) hemangioma that may be supplied by a number of vessels, including the internal pudendal and the testicular artery among others. Microscopic examination reveals a benign unencapsulated lesion made up of a large number of cavernous vascular spaces supported by the subcutaneous tissue, with reduced cells and intraluminal thrombi present in the vascular spaces.

Complications of scrotal hemangioma include thrombosis, phlebitis, massive hemorrhage, and infertility. Eastridge and colleagues (22) reported that this lesion has no effect on potency or fertility. However, Gotoh and associates (32) reported a case of bilateral testicular damage, with absence of germinal cells in the seminiferous tubules and changes in the Sertoli cells, in a 16-year-old with a largely left-sided lesion. The authors postulated that the azoospermia was related to the high temperature of the hemangioma.

The treatment of choice is wide local excision of the tumor with the overlying skin, if possible. Other modalities that have been used include subcutaneous ligation, electrofulguration, intravenous (IV) prednisolone, solid carbon dioxide, and hemiscrotectomy and orchiectomy. Hemiscrotectomy and orchiectomy appear unnecessary because no testicular involvement or malignant changes within the lesion have been reported. Because of their natural involution, hemangiomas of other areas of the skin normally require no treatment (86).

Splenogonadal Fusion

Splenogonadal fusion is an unusual malformation consisting of an abnormal connection between the spleen and the gonad. The entity was first described in 1883 (8). Since then, 110 cases have been reported to date (37). Most of the cases present as a scrotal mass or scrotal tenderness (Fig. 52A.15). Some are discovered as an incidental finding at the time of herniorrhaphy or orchidopexy, and approximately 25% are found at autopsy. Four cases have been reported in females (40), and the abnormality has been seen from newborn to old age. Approximately half of the cases are reported in children, and only one case of splenogonadal fusion on the right side has been reported (84). The most common preoperative diagnosis is testicular neoplasm, which is reasonable because these splenic nodules are firm and do not transilluminate.

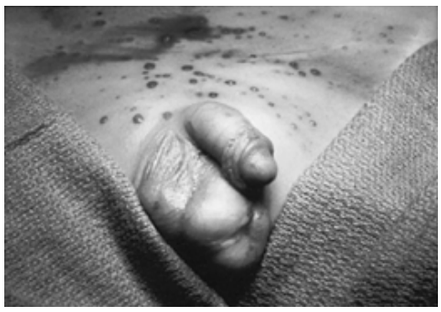

FIGURE 52A.15. Left hemiscrotal mass is consistent with splenogonadal fusion.

Two forms of the malformation have been presented clinically: continuous and discontinuous splenogonadal fusion (100). In continuous splenogonadal fusion, the main spleen remains connected to the left gonad by a strand of tissue. This cord may be completely splenic, fibrous, or beaded with multiple nodules of splenic tissue. With discontinuous

splenogonadal fusion, there is no connecting cord between the spleen proper and the left gonad. The ectopic splenic tissue is usually a distinct and encapsulated mass. Approximately 25% of the reported cases of continuous splenogonadal fusion will have other anomalies, including micrognathia, anal atresia, asymmetry of the skull, or abnormal fissures of the lung and liver. None of the reported cases of discontinuous splenogonadal fusion has demonstrated any other malformations.

The evaluation of splenogonadal fusion usually takes place in the operating room. In theory, a technetium-99 colloid liver spleen scan could easily identify splenic tissue in the scrotum (101); however, this usually is not done as a preoperative event. Scrotal ultrasound has not been helpful.

The treatment of splenogonadal fusion usually involves removal of both the testis and the adjoining mass (Fig. 52A.16). If one were able to make a diagnosis of ectopic splenic tissue before surgery, a simple excision of the splenic nodule would suffice in virtually all cases of discontinuous splenogonadal fusion. In cases of continuous splenogonadal fusion, exploratory laparotomy is usually necessary to properly identify any anatomy involved and to deal with the continuous cord that is usually present.

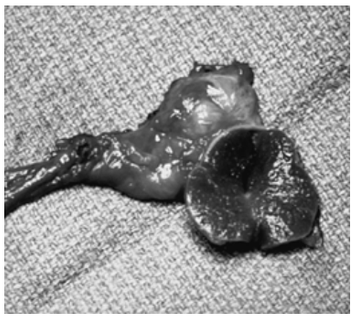

FIGURE 52A.16. Splenic tissue open adjacent to gonad.

GENITAL ANOMALIES: FEMALE

Embryology

The female reproductive system is derived primarily from the müllerian or paramesonephric ducts. In the absence of a fetal testis, there is no elaboration of androgen or MIS; therefore the Wolffian system regresses and the müllerian system is free to differentiate (10). Between the sixth and eighth weeks of gestation, the paired müllerian ducts develop lateral to the Wolffian ducts and then cross medially to fuse in the midline. The fused müllerian ducts then join the urogenital sinus at the müllerian tubercle and, by the tenth week of gestation, form a single tube called the *uterovaginal canal.* The lateral aspect of the müllerian ducts, which remains separate, will ultimately become the fallopian tubes, and the fused portion of the ducts, which thickens, will become the fundus, body, and cervix of the uterus.

The exact embryologic origin of the vagina is somewhat uncertain. Koff (61) suggested that the upper four-fifths of the vagina is formed from the müllerian duct and the lower fifth from the urogenital sinus. The major body of evidence supports the dual nature of the vagina, but the exact contribution from each source is still uncertain. At the twelfth week of gestation, vaginal development begins at the müllerian tubercle, where the uterovaginal canal joins the urogenital sinus. Bilateral endodermal invaginations called *sinovaginal bulbs* form in the area of the müllerian tubercle. As the bulbs grow, the müllerian tubercle regresses and the distance between the uterovaginal lumen and the urogenital sinus increases. The sinovaginal bulb completes its growth by the fifteenth or sixteenth week of gestation and is called the *primitive vaginal plate.* Canalization of this cord of cells beings at the urogenital sinus and progresses cephalad, so by the fifth month of embryonic growth, vaginal development is complete (Fig. 52A.17).

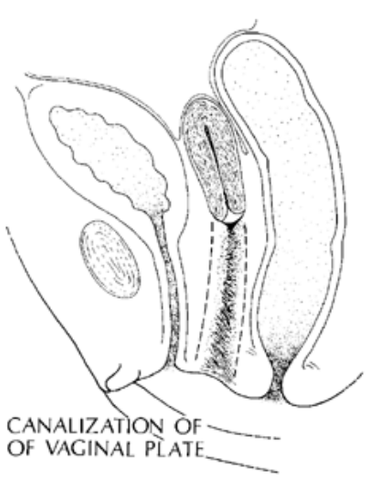

FIGURE 52A.17. Vaginal development.

Differentiation of the external genitalia of the female occurs between 12 and 16 weeks of gestation. In the absence of fetal androgen, particularly DHT, the common genital anlage develops passively into external genitalia of the female. The genital tubercle elongates slightly and becomes the clitoris, the urethral folds do not fuse and form labia minora, and the genital swellings form labia majora. The

urogenital groove remains open and forms the vestibule of the vagina (57).

Vaginal Agenesis (Mayer-Rokitansky-Kuster-Hauser Syndrome)

Complete absence or agenesis of the vagina probably results from a disorder of the ureterovaginal canal or the vaginal plate (Fig. 52A.18). Mayer (73) first reported vaginal agenesis in stillborn infants with multiple birth defects. Kuster (63) and Rokitansky (92) described the entity and recognized that there also was usually a rudimentary uterus with normal ovaries and normal external genitalia (Fig. 52A.19). Hauser and colleagues (41) reported the frequent association of renal and skeletal anomalies. Mayer-Rokitansky-Kuster-Hauser syndrome is a failure of müllerian duct fusion with resulting vaginal agenesis. The incidence of this syndrome has been reported to vary from 1 in 4,000 to 1 in 5,000 live female births (12). The ovaries and distal fallopian tubes arise from a distinct embryologic origin and are normal and functional. The patients are typically 46,XX females with normal secondary sex characteristics who most commonly have primary amenorrhea (93). The uterus in these patients may vary from normal to the more characteristic finding of a rudimentary bicornuate structure without a lumen. The association between congenital absence of the vagina and anomalies of the urogenital system is very common, with approximately one-third (34%) of these patients having renal abnormalities (27,35). The most common abnormality is agenesis of one kidney or ectopia of one or both kidneys. Fusion abnormalities such as horseshoe kidney and crossed renal ectopia also are very common.

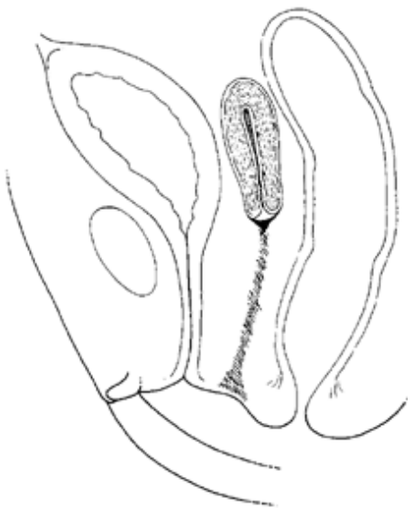

FIGURE 52A.18. Vaginal agenesis resulting from a failure of canalization of the vaginal plate.

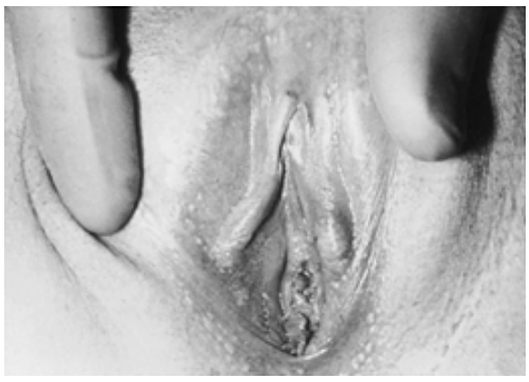

FIGURE 52A.19. External genitalia of a 13-year-old girl with vaginal agenesis.

Skeletal anomalies have been reported in 12% of these patients, which would make such anomalies approximately half as common as the renal anomalies seen (35). Two-thirds of the patients with skeletal anomalies have spine, limb, or rib anomalies. Six percent of the skeletal malformations were of the Klippel-Feil type, which reflects an aberration in cervical thoracic somite development (38). Duncan and associates (21) have recognized the frequency of these associated events and suggested that this combination of malformations be termed the *MURCS association,* an acronym for *mü* llerian duct aplasia, *r*enal aplasia, and *c*ervicothoracic somite association.

The diagnosis of vaginal agenesis is made most commonly at the time of puberty in association with amenorrhea. However, the diagnosis can also be made occasionally in the neonatal period, usually as the cause of a lower abdominal mass. In older patients, pelvic ultrasonography, computed tomography (CT) scanning, and laparoscopy are means of making an accurate diagnosis. Recently, magnetic resonance imaging (MRI) has emerged as a valuable modality in the evaluation and classification of developmental anomalies of the female genitourinary system (79,81). MRI should be analyzed in conjunction with other imaging modalities. Previous surgery makes MRI interpretation more difficult and therefore should be carried out before any surgical intervention, if possible. An accurate MRI examination may be extremely helpful before surgery, and it is essential for the radiologist to have knowledge of how such complex anomalies are managed and what pitfalls to avoid (65).

Treatment of vaginal agenesis is predicated on the anatomy present. If pain is present, radiographic imaging is necessary to define anatomy before surgery, which may be indicated to manage an obstructed uterine horn or subsequent endometriosis before the creation of a vagina. If there is a uterus and the vaginal remnant is too short to reach the

perineum, construction of a vagina that will communicate with the uterus should be undertaken before the onset of menses (18). This usually is accomplished using a free split-thickness skin graft as advocated by McIndoe (74), or an isolated intestinal segment (71). If only the distal portion of the vagina is absent, posterior and lateral skin flaps can be mobilized and rotated into the proximal portion of the vagina to provide an introitus; however, in most instances, this is difficult to accomplish and the long-term results vary. If no uterus is present, construction of a vagina should be undertaken just before the initiation of sexual activity. A split-thickness skin graft or an isolated intestinal segment is most often used for vaginal construction. Gosalbez and coauthors (31) reported the use of ureter for vaginal reconstruction. Hensle and Chang (47) recently reviewed the pertinent diagnostic and pretreatment considerations as well as the surgical options, in particular, bowel vaginoplasty, for these patients. An international collaborative study evaluated patients with congenital vaginal agenesis and reported an overall success rate of 68.2% for any primary surgical reconstruction (30).

Vaginal agenesis has been reported in association with a uterus and functional endometrium. These patients often have an obstructive lesion of the reproductive tract with a hematometrocolpos of the existing vagina. Treatment may involve the creation of a functional vagina that can drain the uterine cavity. Letterie (67) reported a case of a two-step approach to management of a patient with both cervical and vaginal agenesis. At the time of this publication, this patient was 2 years postoperative without complications and had regular monthly menses without dysmenorrhea or pelvic pain. However, cases of morbidity and mortality with attempted anastomotic procedures have been reported in the literature (16).

Congenital Vaginal Obstruction (Hydrocolpos and Hydrometrocolpos)

Congenital vaginal occlusions are probably the result of an incomplete canalization of the vagina that occurs during the fifth month of gestation. An imperforate hymen can result in gross distention of the vagina, which is termed *hydrocolpos,* or in distention of both the vagina and uterus, which is called *hydrometrocolpos.* Congenital vaginal obstruction most commonly is caused by a simple imperforate hymen (99) (Fig. 52A.20A), and less commonly by more proximal lesions such as a high transverse vaginal septum (9) (Fig. 52A.20B). A high transverse vaginal septum can also be associated with partial anterior vaginal agenesis, as well as with persistence of a common urogenital sinus.

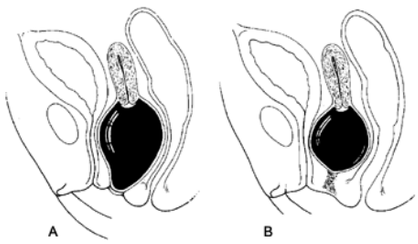

FIGURE 52A.20. Congenital vaginal obstruction. **A:** Imperforate hymen. **B:** High transverse septum.

The newborn with vaginal obstruction will have a lower abdominal mass and often urinary tract obstruction. The abdominal mass is the distended vagina, which results from excessive secretion of the cervical glands in response to maternal estrogen. Abdominal ultrasonography reveals a large midline sonolucent mass displacing the bladder forward and the rectum posteriorly. Percutaneous needle aspiration and injection of contrast material may aid in the diagnosis and can be performed either through the perineum or the anterior abdominal wall (Fig. 52A.21). If no abdominal mass is present at birth, the condition often is not detected until early adolescence, at which time symptoms may include amenorrhea, cyclic abdominal pain, and an abdominal mass secondary to hematocolpos (Fig. 52A.22).

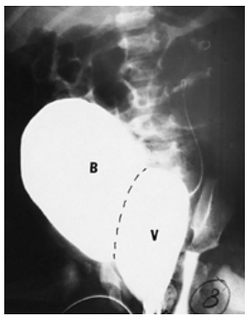

FIGURE 52A.21. Percutaneous injection of obstructed vagina *(V)* in newborn, with simultaneous cystogram *(B)* and retrograde catheterization of solitary left ureter and kidney.

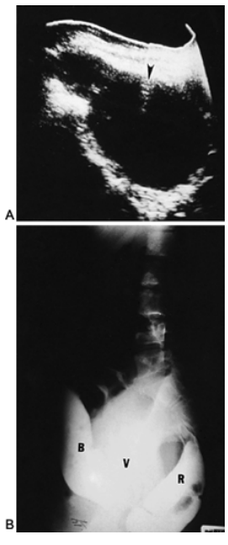

FIGURE 52A.22. A:13-year-old girl with sonolucent midline mass. Note cervical impression *(arrowhead)*. **B:** Lateral view of same patient with midline mass pushing bladder *(B)* forward and rectum *(R)* posteriorly. V, vagina.

The treatment of vaginal obstruction depends on the anatomy. An imperforate hymen in the newborn that bulges at the introitus can be incised easily without anesthesia. It is important to identify the anatomy at the time of the drainage procedure to be certain that there is neither a

common urogenital sinus nor other urinary anomaly associated with the lower vaginal obstruction. Obstruction resulting from a high transverse vaginal septum or a partial agenesis of the anterior portion of the vagina can be more difficult to correct. These children must be investigated thoroughly before treatment. The high transverse vaginal septum with or without a common urogenital sinus probably is best treated by draining the vagina anteriorly with a simultaneous perineal vaginal pull-through. However, if the rectum and anus are displaced anteriorly, it may be difficult to perform a definite vaginoplasty in the infant. In this situation, it may be more appropriate simply to drain the obstructed vagina through the common urogenital sinus and delay the vaginal reconstruction until a later date, when it can be done in conjunction with a posterior anoplasty.

Fusion and Duplication Anomalies

Disorders of embryogenesis that produce duplication anomalies of the vagina and uterus occur at approximately 9 weeks of gestation and involve progression of the uterovaginal septum (1). These anomalies, which are very common, can include two uteri and two cervices fused with a single vagina or two separate vaginas, and two uteri fused with a single cervix and a single vagina (20) (Fig. 52A.23).

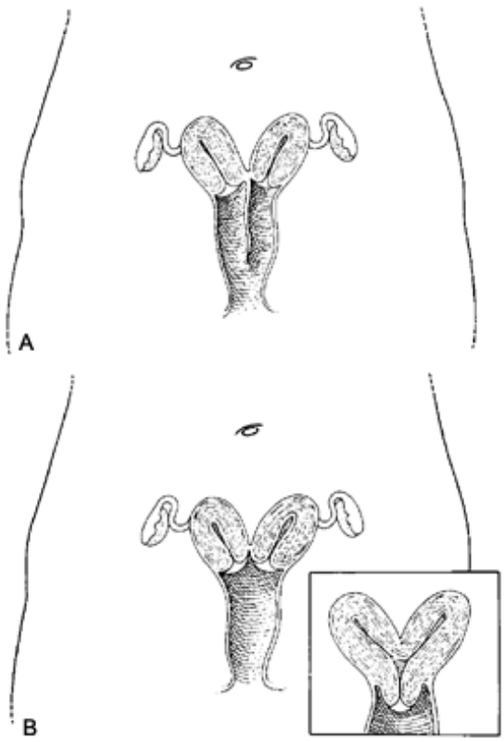

FIGURE 52A.23. A–B: Fusion anomalies of uterus and vagina.

If there is complete vaginal duplication, one vagina can be obstructed and the other patent so that the external genitalia will appear normal (9,99) (Fig. 52A.24). The diagnosis of uterus didelphys and a unilateral obstructed vagina should be entertained as part of the differential diagnosis in a newborn with a sonolucent abdominal mass. Classically, the mass will push the bladder forward and the normal vagina posteriorly (Fig. 52A.25). Vaginoscopy may reveal a bulging mass high in the vaginal sidewall. If technically possible, simple incision of the obstructing septum will provide adequate drainage; however, further division of the septum usually is necessary (14). At times, a formal laparotomy is required to provide adequate drainage and to confirm the diagnosis. Careful attention to the anatomy is essential to avoid an unnecessary ablative procedure. Simple

division of the vaginal septum is all that is warranted in most of these patients, because successful term pregnancies have been reported in both uterine horns, suggesting that fertility is not impaired.

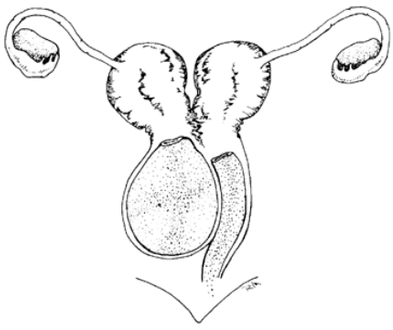

FIGURE 52A.24. Unilateral obstruction of duplex vagina in patient with uterus didelphys.

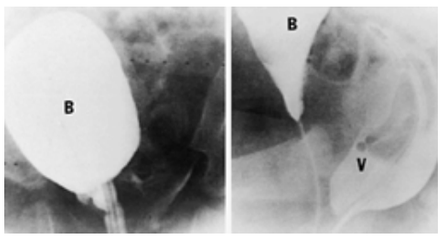

FIGURE 52A.25. Simultaneous cystogram and vaginogram in a patient with uterus didelphys and unilateral obstruction of a duplex vagina, showing separation of the bladder *(B)* and normal vagina *(V).*

This condition should also be considered in pubertal girls who, despite having menses, present with cyclic pelvic discomfort and a mass. By ultrasound, the mass will either be sonolucent or have some scattered internal echoes. A vaginogram will once again show the bladder and normal vagina pushed apart by the mass (Fig. 52A.26). Pelvic MRI will typically show a normal uterine horn above a dilated blood-filled vagina. The blood gives off a very bright signal on the T_1-weighted image (Fig. 52A.27). Treatment of pubertal girls is identical to that for younger patients and can most frequently be done vaginally.

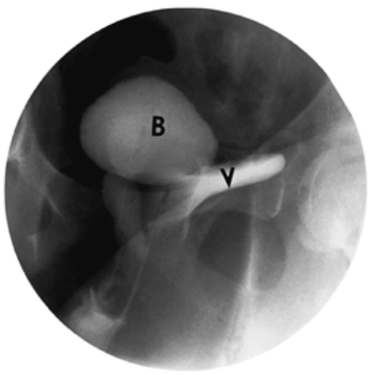

FIGURE 52A.26. Separation of the bladder *(B)* and normal vagina *(V)* by a distended obstructed hemivagina.

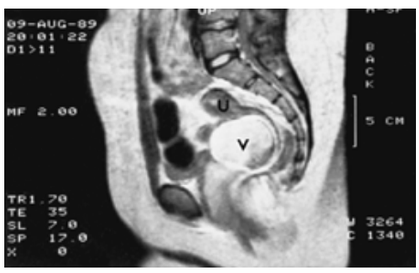

FIGURE 52A.27. Pelvic magnetic resonance image. U, uterus; V, vagina.

Urogenital Sinus Anomalies

Urogenital sinus is a common channel into which both the urinary and genital tracts open. There is a wide spectrum of urogenital anomalies caused by a lack of development of the urogenital sinus and its derivatives. The common urogenital sinus is a normal stage of embryonic development in both sexes. In the normal female, an arrest in development of the müllerian ducts at 9 weeks of gestation, after they have fused with the urogenital sinus, could be manifested as a urovaginal confluence or common urogenital sinus (Fig. 52A.28) (103). An arrest of vaginal differentiation at a slightly later date can lead to the varying degrees of the urogenital sinus

anomaly seen clinically (Fig. 52A.29). A long urogenital sinus with a short vagina and a high urethral opening will result if the defect occurs at an early stage. A short urogenital sinus with an almost normal vaginal vestibule and low urethral orifice will occur if the arrest is late in development (72). Early defects with a high insertion of the vagina and urethra into the urogenital sinus are also commonly associated with an anteriorly placed anus. This indicates that there is also poor formation of the urorectal septum in these patients.

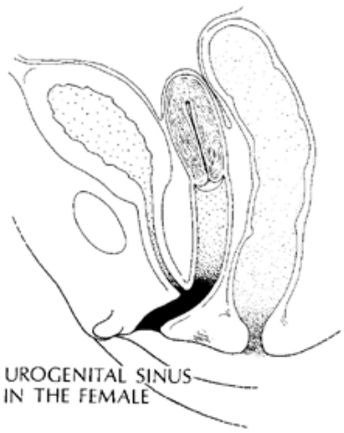

FIGURE 52A.28. Urogenital sinus anomaly.

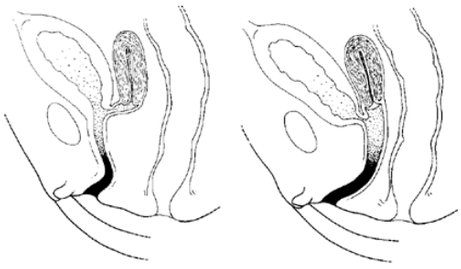

FIGURE 52A.29. Variations of the urogenital sinus anomaly.

The diagnostic approach to the urogenital sinus is based on adequately defining the anatomy present. Retrograde contrast material injection into the urogenital sinus will help delineate the length of the common channel and identify the anatomic relationship of the vagina and urethra (45) (Fig. 52A.30). Endoscopy of the urogenital sinus can provide important information about the length of the urethra, particularly in cases of high confluence of the vagina and the urethra. In such patients, catheterization of the urethra can be difficult, if not impossible.

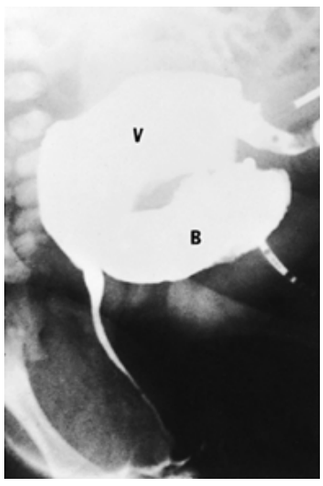

FIGURE 52A.30. Sinogram of urogenital sinus showing high confluence of bladder *(B)* and vagina *(V)* into a long urogenital sinus.

Once the anatomy of the defect has been clearly identified, the various treatment options can be considered. If the urogenital sinus is low, with a short common channel, a simple U-flap vaginoplasty will be effective (42). Unfortunately, the urogenital sinus often is associated with an anteriorly placed anus, which may require posterior relocation to accomplish a skin-flap vaginoplasty from the perineum (46). If the vagina enters the urogenital sinus too far proximally, a division of the vaginal moiety from the urogenital sinus will be necessary in conjunction with a pull-through vaginoplasty. In the most difficult form, there is a confluence of both the bladder and vagina high in the urogenital sinus. This defect requires not only a pull-through vaginoplasty but also often the creation of a neourethra from the anterior vaginal wall (44).

Cloacal Anomalies

The combination of a urogenital sinus and an anorectal anomaly usually is referred to as a *cloacal malformation* (33). In the early embryo, there is a cloacal stage during which there is confluence of the allantois (the early urinary and genital tract) and hindgut (97). At 4 to 6 weeks of gestation, the urorectal septum should descend and divide the allantois from the hindgut; however, if this separation does not take place, a common cloaca will result. A persistent cloaca is the conjunction of the urethra, vagina, and rectum into a single common channel. Expertise in management of this constellation

of structural abnormalities is critical to avoid catastrophic consequences.

These infants generally are born with abdominal distention and an abnormal perineum. There is usually no anus and a single perineal opening is usually found, although in some severe cases no perineal opening may be obvious. Frequently there is a hooded appearance to the phalluslike structure, which gives an initial masculinized gender appearance (Fig. 52A.31). Patients with cloacal disorders may initially be thought to represent intersex disorders. The bladder may enter the common urogenital sinus either just inside the perineal opening or very high. The insertion of the bladder may be associated with a relatively normal length of urethra or may occur very close to the bladder neck. The entrance of the rectum into the cloaca can similarly be either high or low, near the perineum (54) (Fig. 52A.32). Vaginal abnormalities are common in patients with a cloacal anomaly, and vaginal duplication is the most common of the abnormalities seen. There also may be significant obstruction at the perineum in these patients, causing both hydrocolpos and obstructive uropathy (Fig. 52A.33).

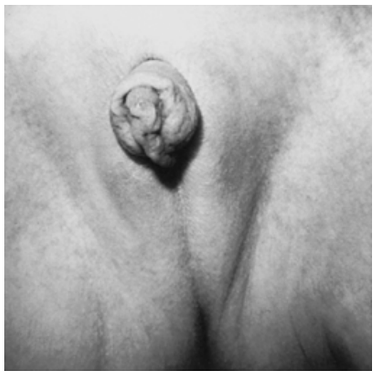

FIGURE 52A.31. Perineum of a patient with a cloacal anomaly.

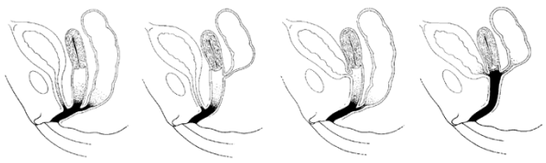

FIGURE 52A.32. Various forms of the cloacal anomaly.

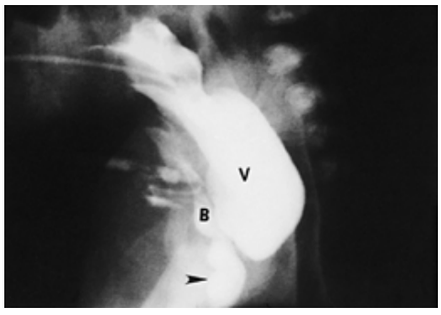

FIGURE 52A.33. Antegrade study of the bladder *(B)* and vagina *(V)* in a patient with a cloacal anomaly, demonstrating a dilated urogenital sinus *(arrowhead)* and relative obstruction at the perineal outlet.

The diagnosis of a cloacal anomaly is confirmed by retrograde contrast studies through the single perineal opening. There is often a confluence of the genitourinary and the GI systems. However, often, all of the components of the anomaly will not fill on a retrograde study; thus it is not until an open procedure is performed that the exact anatomy can be defined.

Treatment of the various forms of cloacal anomalies is complex and presents one of the more difficult problems for pediatric surgeons and pediatric urologists. The first principle of treatment is to completely identify the anatomy involved (58). Reconstruction must be individualized based on the defined anatomy. Clearly, the GI tract must be dealt with initially, and if the opening of the rectum into the urogenital sinus is low, a simple cutback anoplasty in the perineum may be possible (43). More frequently, however, a supralevator opening is present, and a primary colostomy is necessary, followed by a later pull-through procedure. If there is no significant urinary obstruction, specific treatment may not be necessary in the immediate perinatal period. If urinary obstruction exists, a simple cutback of the urogenital sinus may afford adequate egress of urine to relieve obstruction. However, in the young patient with a cloaca and high imperforate anus, there often will be a high confluence (urethra, vaginas, and rectal fistula). In such cases, the patient usually will void into the cloaca and drain poorly, hence these children will have dilated müllerian structures and hydronephrosis. Clean intermittent catheterization of the cloaca usually will provide temporary resolution of the vaginal distention and bladder outflow obstruction, and the patient can be stabilized for months until definitive repair is planned. The obstruction of the distal cloaca is curious and often behaves like a voiding dyssynergia.

Stricture or narrowness of the distal cloaca is rarely the actual cause of the obstruction. Simple calibration and dilation will not resolve urinary retention in a cloaca patient.

Complete reconstruction of a cloacal anomaly is technically easier in later infancy and should be delayed until after 1 year of age, if possible (85). If feasible, reconstruction should be performed in one stage. Hendren (46) has stressed the importance of repairing the imperforate anus at the time of vaginal reconstruction. When a cutback anoplasty or pull-through is performed, it is important to be certain that the anus is placed far enough posteriorly to allow enough perineum for an adequate vaginal introitus and urethra. Once detachment of the rectum has been accomplished, the operative approach to the anterior portion of the cloacal anomaly is similar to that of a straightforward urogenital sinus (42). Pena (82) has achieved favorable results using a posterior sagittal anorectovaginoplasty. A percentage of patients will require laparotomy if the vagina or rectum does not easily reach the perineum without tension.

Masses of the Introitus

A mass at the introitus between the labia is often a diagnostic dilemma. The differential diagnosis includes prolapse of the urethra, prolapsed ectopic ureterocele, or prolapsed rhabdomyosarcoma. It is important to recognize each of these entities and to understand the diagnostic criteria for each.

Prolapse of the urethra (Fig. 52A.34) occurs almost exclusively in African American girls between the ages of 3 and 9 years. The child often has blood spotting on the underwear and a necrotic mass at the introitus, which represents a prolapsed and infarcted portion of the anterior urethra (80). The etiology of this lesion is unclear, although the histology closely resembles the capillary hemangioma pattern of a urethral caruncle in an adult. An accurate diagnosis depends on recognition of the entity. No diagnostic studies are needed, and the treatment usually involves simple excision of the prolapsed segment with suturing of the normal urethra to the meatus (87). Complications are virtually nonexistent except mild degrees of meatal stenosis following excision of the prolapsed segment and primary repair.

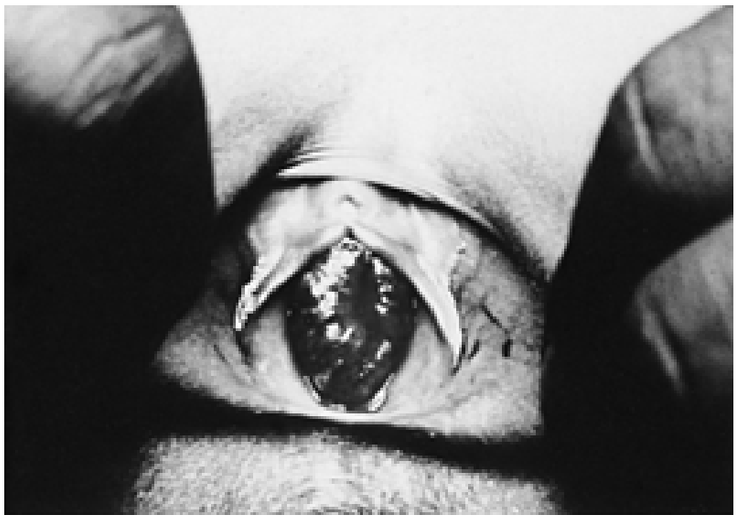

FIGURE 52A.34. Prolapsed urethra in a 9-year-old African American girl.

A prolapsed ectopic ureterocele can present as an intralabial introital mass (70) (Fig. 52A.35). This is usually a

smooth white or slightly edematous lesion that extrudes from the urethral meatus. The urethral meatus usually can be seen above the lesion. The diagnosis often can be made on IV urography, which will demonstrate a lower pole collecting system, which is pushed laterally and inferiorly (drooping lily sign) with displacement of the ureter away from the midline on the affected side, and a filling defect in the bladder (Fig. 52A.36) (78). Direct injection of the prolapsed segment is possible and may demonstrate the anatomy involved; however, this often is difficult to do, especially in newborns.

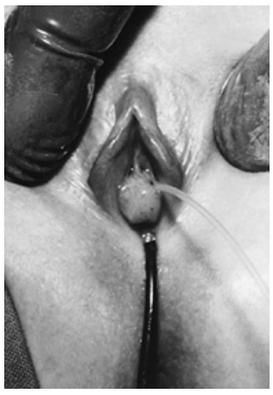

FIGURE 52A.35. Prolapsed ureterocele in a 3-year-old girl.

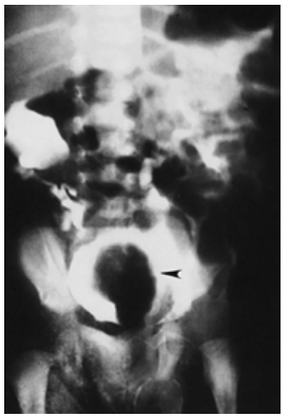

FIGURE 52A.36. Intravenous urogram in a patient with an ectopic ureterocele, demonstrating a right lower pole collecting system being pushed laterally and inferiorly (drooping lily sign) along with a filling defect in the bladder *(arrowhead).*

Sarcoma botryoides, or rhabdomyosarcoma of the bladder or vagina, is the most common malignancy of the lower genitourinary system seen in infancy (48). It commonly presents with blood spotting on the underwear, and the lesion appears as a lobulated, grapelike mass. The diagnosis can be made by direct biopsy, but the extent of the lesion is best determined by pelvic ultrasonography and CT scan (76) (Fig. 52A.37).

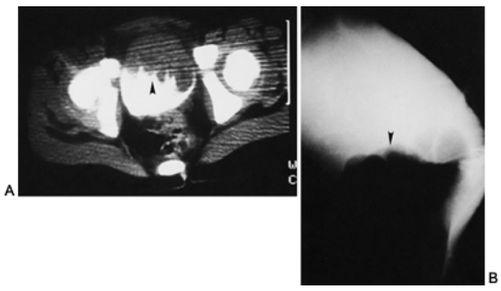

FIGURE 52A.37. Computed tomogrpahy scan **(A)** and cystourethrogram **(B)** in a patient with a bladder rhabdomyosarcoma, demonstrating a filling defect in the anterior portion of the bladder *(arrowheads).*

Other lesions that can appear as intralabial masses include a low simple imperforate hymen, which can present as a bulging intralabial mass in newborn girls (88) (Fig. 52A.38). This is often simply an imperforate hymen with some degree of hydrocolpos resulting from maternal estrogen stimulation. These lesions are easily recognized and need incision and drainage; rarely do they require further therapy.

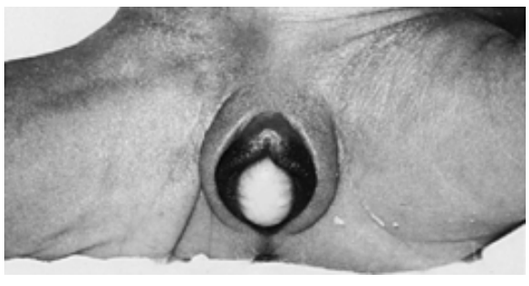

FIGURE 52A.38. Bulging hymen in a newborn girl.

Paraurethral cysts (7) also present as interlabial masses in female infants. They tend to displace the urethral meatus to one side, and a normal urethra and vaginal introitus usually can be identified (Fig. 52A.39). These cysts seem to be

embryologic remnants of Skene's glands or Gartner's duct. Most of these cysts will rupture spontaneously, but they may have to be incised and drained.

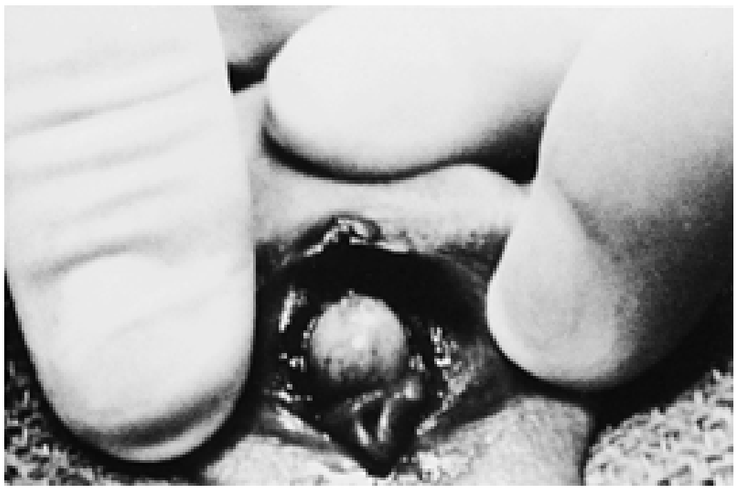

FIGURE 52A.39. Paraurethral cyst in a 1-year-old girl.

Cystic lesions of the meatus also can occur in males (Fig. 52A.40). Parameatal urethral cysts were first reported in the English literature in 1956 (98), and scattered reports have appeared since. Most recently, 41 cases were reviewed from Japan (62), and in that review, although the patients ranged in age from 9 months to 43 years, almost 50% presented at younger than 15 years of age. The mass was totally asymptomatic in 75% of the cases, and dysuria was the presentation in the other 25%.

FIGURE 52A.40. Parameatal cyst in a 3-year-old boy.

Although the etiology of these cysts is unclear, we believe that they are most likely related to some obstruction of one of the paired parameatal glands (29). Histologic features include a cyst wall lining that can vary from columnar to transitional to cuboidal epithelial. The most common lining is columnar. Treatment of these parameatal urethral cysts usually consists of simple unroofing. In a minute number of patients, the cyst may recur, and in this situation, total excision of the lining is required.

Conclusion

There is a vast spectrum of symptoms and presentations of female genital anomalies. A careful history and physical examination enhanced with reliable imaging modalities are of utmost importance. A detailed assessment of genetic, gonadal, and phenotypic status is essential. The experienced multispecialty team with an accurate diagnosis and appropriate treatment plan offers the best chance of achieving optimal psychosocial, sexual, and reproductive function.

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52B HYPOSPADIAS

Warren Snodgrass

Laurence S. Baskin

Michael E. Mitchell

Part of "52 - THE GENITALIA "

W. Snodgrass: Department of Urology, University of Texas Southwestern Medical Center at Dallas, Children's Medical Center, Dallas, TX 79410.

L.S. Baskin: Department of Urology, University of California–San Francisco, San Francisco, CA 94143.

M.E. Mitchell: Department of Urology, University of Washington; Division of Pediatric Urology, Children's Hospital and Regional Medical Center, Seattle, WA 98105.

Hypospadias is a common congenital anomaly of the penis in which the urethra opens proximal to its normal position at the tip of the glans. The term has been credited to Galenus and is derived from the Greek words *hypo*, meaning "under," and *spadon,* indicating a "rent" (20). Extending distally from the hypospadiac meatus is a strip of epithelium overlying connective tissues, the remnant of the unformed urethra, which in the past decade has been commonly referred to as the "urethral plate." In addition, the penis with hypospadias typically has an incompletely formed prepuce and may exhibit ventral curvature. Therefore correction of the anomaly includes penile straightening, urethroplasty, glansplasty, and circumcision, with the ultimate goal a functionally and cosmetically normal penis.

Using modern surgical techniques, this ideal can often be realized, usually in a single outpatient procedure. It has not always been so. Carl Beck (20) reviewed the state of the art in 1917 when operations were done in two or more stages and concluded, "It is not absolutely necessary to obtain a

cosmetic result with smooth surfaces and a urethra in the center of the glans." Although he wrote just 30 years after the modern era of hypospadias surgery began, Beck (20) already found that "the surgeon has to choose from a chaos of methods to find the proper one for his case, and without experience he often chooses the wrong method with subsequent failure." Since Beck's time, operative techniques have continued to proliferate as the field of hypospadias surgery has grown to include not only proximal anomalies that were the original focus of intervention, but also the less severe distal lesions, which are more common. Furthermore, as late as 1981, Mills and colleagues (90) still questioned the need for a meatus at the tip of the glans, having observed that "if the anatomically normal phallus is the goal of the surgeon and family, then they must be aware of the attendant risks of the techniques that accomplish this goal."

Previous editions of this textbook were published in 1987, 1991, and 1996, and in each the chapter on hypospadias was written by the late John Duckett. In describing this discipline he coined the term *hypospadiology,* and it is no exaggeration to say that Duckett was one of history's greatest hypospadiologists. His MAGPI procedure revolutionized the repair of distal hypospadias and, together with the onlay and tubularized preputial flaps he popularized, made it possible to correct almost any hypospadias anomaly by one of Duckett's methods. Furthermore, he challenged the longstanding view that penile curvature indicates a fibrotic urethral plate, thereby paving the way for greater reliance on surgical techniques that use these tissues.

Yet the field continues to evolve, and procedures that once were standard have fewer proponents today. Instead, new understanding of both penile curvature and the nature of the urethral plate creates new options for repair that bring hypospadias surgery nearer its goal. Consequently, this chapter emphasizes these techniques and presents an updated algorithm for hypospadias repair.

EMBRYOLOGY

The external genitalia of the developing fetus are initially indifferent, capable of developing either the male or female phenotype (Fig. 52B.1). This anlage first appears as the genital tubercle during the sixth week of gestation. Subsequently, endodermal cells from the cloaca extend along the ventral midline surface of the tubercle to form the embryologic urethral plate. Then proliferation of mesoderm on either side of the plate creates urethral folds while the superficial layer of cells within the plate dies, the end result being the urethral groove.

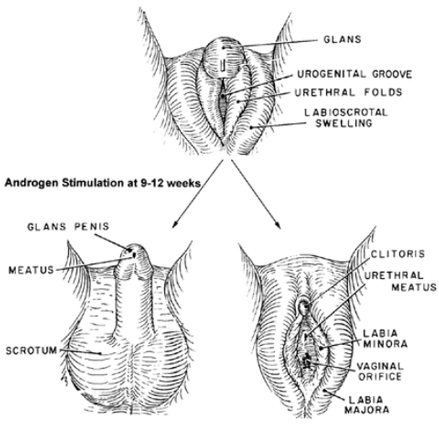

FIGURE 52B.1. Embryology of the external genitalia. The indifferent anlage are programmed to develop the female phenotype unless androgen stimulation occurs between the ninth and twelfth weeks of gestation.

The primordia of the external genitalia inherently feminize unless appropriate androgenic stimulation occurs between the ninth and twelfth weeks of gestation, when fetal Leydig cells within the testes begin producing testosterone. The microsomal enzyme 5α-reductase type 2 in genital tissues converts testosterone to dihydrotestosterone, which interacts with the androgen receptor and results in synthesis of proteins with androgenic effects.

This hormone stimulation causes the tubercle to elongate, prompts fusion of the urethral folds, and tubularizes the urethral groove beginning proximally and continuing to the level of the glans (Fig. 52B.2). The mechanism of glanular formation has been disputed. Prior investigations concluded that its development involved both fusion of glans folds proximally and ectodermal ingrowth distally (9,61,110,133). However, immunohistologic studies by one of us (LSB) suggest instead that the entire male urethra, including the glanular portion, forms by tubularization of the endodermally derived urethral plate from fusion of urethral and glanular folds. The stratified squamous epithelium of the distal glanular urethra arises from cell differentiation rather than ectodermal ingrowth (84).

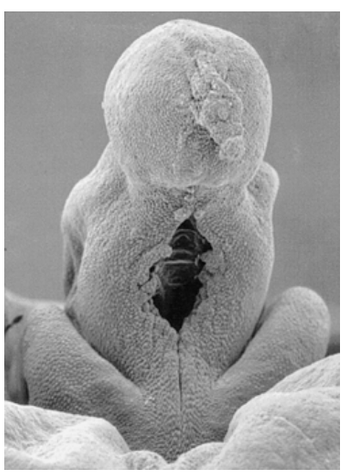

FIGURE 52B.2. Fusion of the urethral folds. A key step in penile development is fusion of the urethral folds, which tubularizes the urethral groove. In females, the urethral folds become labia minora.

Mesenchyme within the urethral folds then differentiates into corpus spongiosum and ultimately fuses with the glans as urethral formation is completed. The corpora cavernosa and preputial skin have different rates of growth on their dorsal and ventral aspects during penile development. Consequently, the fetal penis typically exhibits ventral angulation (61,79) (Fig. 52B.3). Furthermore, the ectodermal tissues of the prepuce on the dorsal surface proliferate at a faster rate than does the mesoderm forming the corpora cavernosa. As a result, folds of skin extend over the glans dorsally, traveling obliquely on either side back to the urethral opening ventrally. As tubularization of the urethra proceeds distally, these ventral preputial

extensions fuse in the midline, terminating in the frenulum (73).

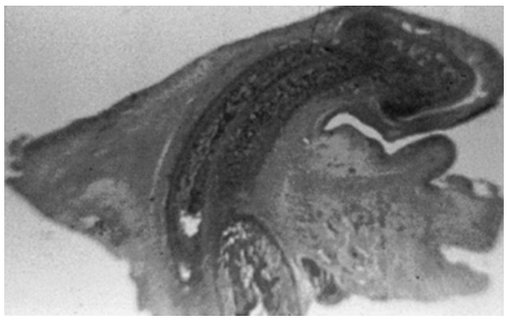

FIGURE 52B.3. Curvature of a normal penis at 22 weeks of gestation. (From Kaplan GW, Lamm DL. Embryogenesis of chordee. *J Urol* 1975;114:769, with permission.)

Sensation of the penile shaft, glans, and anterior urethra is primarily derived from the dorsal penile nerve, with the frenulum also receiving innervation from the perineal nerve (134). Branches of the dorsal nerve extend longitudinally along the surface of the tunica albuginea enclosing the corpora cavernosa, from the 1 to 5 o'clock and 11 to 7 o'clock positions, before terminating in the glans. According to the anatomic studies of Baskin and colleagues (17), no nerve fibers are found at the 12 o'clock location in either normal or hypospadias penises (Fig. 52B.4).

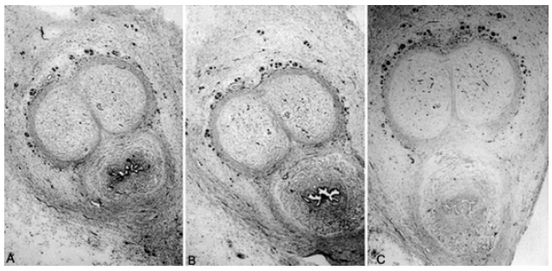

FIGURE 52B.4. Normal human fetal penis, 25 weeks. **A-C:** Transverse sections distal to proximal immunostained with neuromarker 5-100 (25×). Note localization of 5-100 nerve marker in brown completely surrounding the cavernous bodies up to the junction with the urethral spongiosum along the penile shaft except at the 12 o'clock position.

Hypospadias results from an arrest of urethral formation. Based on the sequence of steps in normal penile development, typical findings of the anomaly can therefore be predicted. The urethral opening is found anywhere along the ventral midline from the perineum to the glans depending on the time at which fusion of the urethral folds ceased. The strip of epithelium clinically referred to as the urethral plate extends from the opening distally to the tip of the glans where the meatus would normally be located. This plate exhibits a spectrum from a flat surface to a deep cleft, presumably reflecting the extent of development of the urethral groove.

In the hypospadias penis, the ventral glans does not fuse in the midline, but instead consists of two “wings,” one on each side of the urethral plate. Similarly, corpus spongiosum usually does not cover the ventral aspect of the most distally formed urethra, but rather diverges laterally to join the glans wings. Accordingly, shaft skin often adheres directly to the distal urethra. Furthermore, in most cases there is only a dorsal hood of prepuce, development having stopped before its ventral aspect and frenulum could form. Finally, the penis may demonstrate persistent ventral angulation, which has been commonly referred to as “chordee.”

CLASSIFICATION

The severity of hypospadias is generally determined by the position of the urethral meatus and the extent of ventral penile angulation. However, the location of the urethral opening may be misleading. For example, a subcoronal meatus can be the terminus of a penile urethra lacking corpus spongiosum envelopment, which therefore consists only of a thin epithelial tube extending from the midshaft or penoscrotal junction (Fig. 52B.5). Similarly, correction of penile angulation may relocate the meatus to a more proximal location. Consequently, preoperative assessment not uncommonly underestimates the true severity of the lesion.

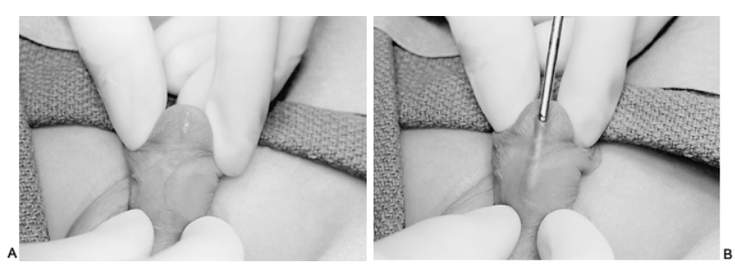

FIGURE 52B.5. A: Proximal glanular hypospadias. **B:** Sound demonstrates the distal aspect of the urethra to be a thin tube, lacking normal investment by the corpus spongiosum.

Historically, hypospadias has been classified in three degrees. *First-degree hypospadias* refers to a glanular meatus. Openings on the penile shaft are termed *second-degree hypospadias,* and penoscrotal to perineal anomalies are *third-degree hypospadias.* The urologic literature identifies glanular, subcoronal, distal shaft, midshaft, penoscrotal, scrotal, and perineal hypospadias, although, again, the shortcomings of any preoperative classification must be recognized.

Most boys with hypospadias have a subcoronal or proximal glanular meatus. This finding is predicted by the fact the last step of urethral formation occurs in this region. Overall, approximately 80% of hypospadiac meatuses are located on the proximal glans or distal shaft, 15% are midshaft to penoscrotal, and the remainder are scrotal to perineal.

One subgroup of distal hypospadias that warrants special mention is the megameatus intact prepuce (MIP) variant (44). Boys with this lesion have an enlarged, “blunderbuss” urethral opening concealed by a completely formed prepuce (Fig. 52B.6). Consequently, the anomaly is often not detected before circumcision and is sometimes misconstrued as a surgical injury. According to Duckett and Baskin (46), 6% of distal hypospadias consists of this variant, which they state is not associated with chordee. However, we have found typical ventral penile angulation in some cases.

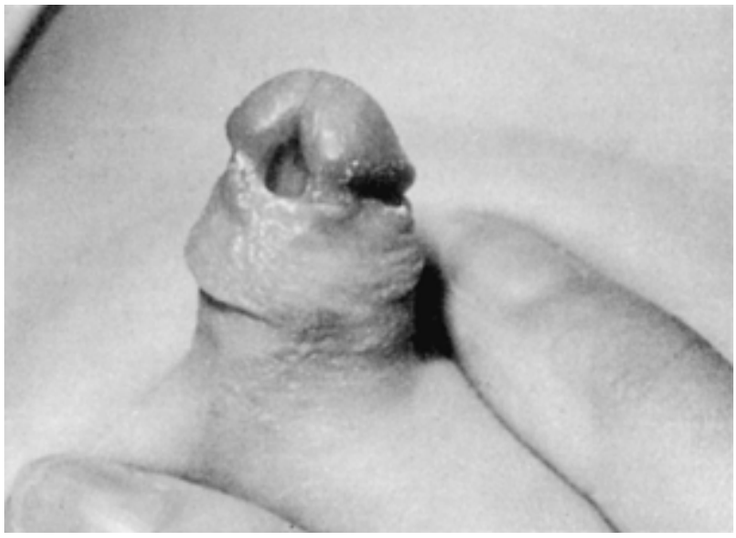

FIGURE 52B.6. Megameatus intact prepuce hypospadias variant. Newborn circumcision was performed before the anomaly was recognized.

INCIDENCE

Hypospadias is a common congenital anomaly. In fact, a study of the 18 leading major birth defects in the United States (which notably did not include cryptorchidism) reported that hypospadias was the most common anomaly among whites, second most common among African Americans, and fourth most common among Hispanics (28). In the late 1960s, birth registries in the United States reported its occurrence in 16 per 10,000 live births, from which it has been calculated the defect is found in 1 of 300 boys. This figure corresponds to the results of nineteenth-century surveys (20). However, birth defect monitoring programs subsequently recorded a rising incidence of hypospadias during the 1970s and 1980s in seven European countries. Analysis of recent U.S. data also shows an apparent doubling in the rate of hypospadias between 1968 and 1993 (99). Although it is possible that increased reporting of minor glanular lesions accounts for some of this trend, it is noteworthy that the incidence of penile shaft and more proximal defects rose threefold to fivefold during this time interval.

Although the overall incidence of hypospadias is between 0.3% and 0.6%, there is a significantly greater risk of the anomaly once it has occurred within a family. Bauer and colleagues (19) studied family pedigrees in 307 hypospadiac boys and found that 21% had another family member with the condition. Fathers reported having hypospadias in 7% of cases. The likelihood that a second child would be born with hypospadias was 12%, increasing to 21% if the father was affected. The authors cautioned, however, that their population was skewed toward more severe hypospadias and that the degree influenced their findings. For example, no boy with a coronal defect had a brother with hypospadias, whereas of those with penoscrotal defects, 18% had an affected sibling.

Further evidence of genetic risk factors underlying hypospadias comes from the Birth Defects Monitoring Program referenced previously (28). In their study of congenital malformation distributions among racial and ethnic groups, the comparable rates of hypospadias per 10,000 live births were 33 in whites, 25 in African Americans, and 15 in Hispanics.

ETIOLOGY

Although it is a common birth defect, the cause of hypospadias remains obscure. Observations regarding racial and familial incidences suggest genetic factors inherited in a multifactorial fashion. However, most boys diagnosed with the anomaly do not have a known family history of hypospadias. Furthermore, whether a given case appears to be sporadic or inherited, the presumption has long been that hypospadias results from an endocrinopathy with incomplete masculinization. As mentioned previously, the external genitalia are initially indifferent, and in the absence of androgenic stimuli develop the female phenotype. Therefore disorders of testosterone synthesis, 5α-reduction to dihydrotestosterone, or the structure or function of the androgen receptor, as well as errors in postreceptor activity or the timing of androgen stimulation, all theoretically could result in hypospadias. In that regard, hypospadias may occupy one end of a spectrum, which, at the opposite extreme, includes intersexuality.

Disordered testosterone production is implicated as a cause of hypospadias by the findings of several investigations. For example, elevated basal levels of luteinizing hormone (LH) (94) and blunted testosterone response to luteinizing hormone–releasing hormone (LH-RH) or human chorionic gonadotropin (hCG) stimulation (6,94,114) have been reported, especially in boys with proximal lesions. Similarly Gearhart and colleagues (56) found elevated basal LH levels in 16 adult men with hypospadias. Taken together, these studies may indicate Leydig cell unresponsiveness to stimulation or defective testosterone synthesis. Further evidence of the latter was recently reported by

Aaronson and El-Sherbiny (1). They found that 66% of boys with midshaft to coronal, and 40% with penoscrotal, lesions had significantly elevated levels of testosterone precursors.

Assuming normal hormone production, hypospadias could also result from deficient 5α-reductase type 2 conversion of testosterone to dihydrotestosterone. Neither Allen and Griffin (6) nor Gearhart and colleagues (55) found impaired 5α-reductase activity in their evaluations of prepubertal boys with hypospadias, although the total number of patients studied was small. Recently, DNA sequence analysis in a larger series indicated that 8% of boys had mutations in the genes coding for 5α-reductase type 2 production (115). The authors concluded such mutations could diminish enzyme efficiency, thereby reducing tissue levels of dihydrotestosterone required for normal penile development.

Studies to determine the role of the androgen receptor in hypospadias originally characterized the receptor according to its physicochemical properties, most notably androgen binding. Based on tissue cultures of genital skin, these investigations reported conflicting results, some indicating decreased receptor levels while others yielded normal findings (132). In recent years, molecular biology techniques have improved detection and characterization of the receptor. Point mutations have subsequently been described in association with perineal hypospadias (7,18,67,129). Sutherland and colleagues (129) evaluated 40 boys with penile hypospadias, finding a mutation of the androgen receptor in only one, who had a distal shaft lesion. One difficulty in determining etiologies for hypospadias is that most studies have applied specific tests to groups of patients rather than using an array of tests to establish diagnoses in individual patients (4). Nevertheless, the findings of multiple defects in the processes of masculinization support the conclusion of Allen and Griffin (6) that hypospadias most likely is the nonspecific result of a variety of endocrinopathies.

Increasingly, researchers are examining the role of cellular signals other than testosterone and dihydrotestosterone in normal phallic development and hypospadias. For example, embryogenesis of the urogenital system depends on epithelial-mesenchymal interactions, and it has been hypothesized that aberrant signaling between epithelium and mesenchyme could result in hypospadias (84). In addition, defects in homeobox (Hox) genes might also adversely influence penile development. Hox genes regulate transcription and play an essential role in directing embryogenesis, with Hox A and D clusters expressed in regionalized domains along the axis of the urogenital tract. Transgenetic mice with loss of function in single Hox A or D genes exhibit homeobox transformations and impaired genitourinary morphogenesis (22,39,72,102). Human males with hand-foot-genital syndrome, an autosomal-dominant disorder characterized by a mutation in Hox A13, exhibit hypospadias (40,53,92). Furthermore, embryonic expression of certain Hox genes is regulated by hormonal influences as, for example, estrogen and the synthetic estrogen diethylstilbestrol (DES) inhibit Hox A9, Hox A10, Hox A11, and Hox A13 genes in mice (85).

Another problem is recognized from investigations of possible links between environmental agents and hypospadias. The apparent upward trend of hypospadias reported during the past two decades has raised concerns of increased in utero exposure to progesterones, estrogens, or other antiandrogens. However, despite the increased incidence of the anomaly, epidemiologic studies require evaluation of such large populations of mothers and offspring to reach statistical significance as to be unfeasible (2). Available clinical reports have mixed findings. In one study of 130 boys with hypospadias, 11 mothers gave a history of having ingested progestins, alone or in combination with estrogen, in early pregnancy (2). Offspring of mothers treated with DES have also been noted to have a greater likelihood of hypospadias by some investigators (59,66), but not by others (41). Oral contraceptives, particularly if continued in early pregnancy when the penis is developing, could theoretically cause hypospadias, but case control studies (78) and a meta-analysis of relevant articles (103) have failed to establish any significant association. One recent report found a fivefold increased incidence of hypospadias in boys conceived by *in vitro* fertilization, which might indicate disturbance of the maternal-fetal endocrine milieu by the progesterone therapy that accompanies assisted reproductive technology (86,116). Pesticides, fungicides, and industrial pollutants, which inhibit function of the androgen receptor, have been identified as possible contributors to disordered male sexual development (80).

ASSOCIATED ANOMALIES

Cryptorchidism

Because both hypospadias and cryptorchidism may result from androgen deficiencies, it is not surprising the two conditions may coexist. Studies indicate that approximately 8% of boys with hypospadias also have an undescended testicle. Furthermore, the incidence varies according to the severity of hypospadias, with 5% of distal versus up to 32% of proximal lesions associated with cryptorchidism (27,81).

Prostatic Utricle

This vestigial structure has a mixed origin, arising from the mullerian ducts and urogenital sinus. Enlargement of the utricle has been noted in boys with hypospadias, possibly indicating delayed or inadequate secretion of müllerian inhibiting factor or incomplete masculinization of the urogenital sinus (38). Although an enlarged utricle is sometimes found in distal hypospadias, both the incidence and size increase with increasing severity of hypospadias, occurring

in approximately 11% of penoscrotal to perineal cases (38,74,113). Enlarged utricles can result in urinary tract infection, but more commonly cause difficulty with catheterization during hypospadias repair.

Intersexuality

Although hypospadias and intersex disorders may occupy different points along a spectrum, the boy with an isolated urethral opening on the shaft of a normal-size phallus rarely has a dilemma of gender identity. The likelihood of intersexuality increases, however, with a meatus positioned in the scrotum or perineum. Similarly, hypospadias associated with cryptorchidism may indicate an intersex disorder, and if the undescended testis is nonpalpable the risk of intersexuality approaches 50% (77). Possible intersex disorders associated with hypospadias phenotype are listed in Table 52B.1 .

Adrenogenital syndrome: A newborn with hypospadias and bilaterally nonpalpable testes must be evaluated for female pseudohermaphroditism.
Mixed gonadal dysgenesis: These patients have unilateral cryptorchidism, representing the dysgenetic streak gonad, and often have a small phallus.
Male pseudohermaphroditism: This diagnosis is usually considered in newborns with scrotal or perineal hypospadias with palpable gonads, or after the adrenogenital syndrome has been ruled out in those with nonpalpable gonads.
True hermaphroditism: Asymmetric gonadal descent and hypospadias sometimes indicate this intersex state.

TABLE 52B.1. INTERSEX DISORDERS ASSOCIATED WITH HYPOSPADIAS

Malformation Syndromes

Hypospadias, often associated with cryptorchidism, occurs in a number of recognized syndromes (13,76). Among these are the Opitz and the Smith-Lemli-Opitz. Hypertelorism and hypospadias are the key features in males with Opitz syndrome, which includes both X-linked and autosomal-dominant forms with similar clinical manifestations. Other findings include mild to moderate mental retardation and swallowing problems resulting in aspiration.

The Smith-Lemli-Opitz syndrome is the first described with multiple congenital anomalies attributed to a single metabolic defect (95). This autosomal-recessive condition occurs in 1:20,000 births, ranking it third in prevalence among whites, behind cystic fibrosis and phenylketonuria. Affected individuals have impaired cholesterol synthesis because of a deficiency of 7-dehydrocholesterol reductase, resulting in mental retardation, facial deformities, syndactyly, and genital anomalies. The spectrum of external genital findings in males ranges from a female phenotype to hypospadias with cryptorchidism.

PRESENTATION AND EVALUATION

Hypospadias is usually recognized during initial physical examination of the newborn. Typically, the abnormal prepuce calls attention to the anomaly and then further evaluation often finds the penile raphe displaced from the midline and the glans tilted downward. The meatus may appear pinhole in size but is not usually obstructive. Ventral curvature of the penile shaft may be noted during erection.

These characteristics, the dorsal hood, altered glans morphology, and penile curvature, also can now be identified prenatally by fetal ultrasonography. Observation of micturition from a ventrally displaced meatus confirms the diagnosis. Initial reports described penoscrotal hypospadias detected between 29 and 34 weeks in association with multiple congenital anomalies (119). More recently, isolated glanular hypospadias has been diagnosed as early as 20 weeks (35).

Although some boys with hypospadias have demonstrable endocrinopathies, intersex evaluations are generally limited to those with scrotal or perineal urethral openings and patients with both hypospadias and cryptorchidism (64,118). In these situations, physical examination and the karyotype guide subsequent evaluation and therapy.

Before 1975, it was routine for boys with hypospadias to undergo intravenous pyelography and voiding cystourethrography. However, given the fact even severe hypospadias is an arrest in development beyond the eighth week of gestation after the ureteral bud has joined the metanephros, the likelihood of detecting upper urinary tract anomalies is small, with clinically significant lesions found in less than 5% (27,112,113). Today, with prenatal ultrasonography done routinely, the yield from screening predictably would be even less. Therefore radiologic studies are obtained only in those few boys with hypospadias who also develop urinary tract infection or whose anomaly is part of a malformation syndrome.

Because proximal hypospadias interferes with both normal voiding and procreation, the need for reconstruction is not questioned. However, parents not infrequently ask whether a subcoronal or proximal glanular defect justifies an operation. The authors are not aware of any study addressing the psychologic impact of such anomalies if left untreated. Fichtner and colleagues (51) implied that they were of little significance based on the response by 10 of 16 men in Germany with distal hypospadias who stated that they and their partners were unaware of any genital deformity. However, these patients lived in a country where circumcision is rarely done, so a partially formed prepuce may have seemed more normal than it might have appeared to men in the United States.

Because the abnormal foreskin often calls attention to hypospadias, it may be reasonable to recommend its removal. In addition, many boys with distal lesions have a transverse web of tissue just distal to the meatus, which may deflect the urinary stream. Furthermore, approximately

10% of these patients have ventral penile curvature. Given the ability of modern operations to create a functionally and cosmetically normal penis, it makes little sense to perform circumcision without simultaneous urethroplasty.

Based on a variety of psychologic, anesthetic, and surgical considerations, the recommended age for hypospadias repair is between 6 and 18 months (8,29). However, the healthy term boy with an adequately sized phallus can safely undergo this procedure as day surgery as early as 3 months of age. Preterm infants initially have a higher risk for postanesthetic apnea, but elective day surgery can probably be accomplished by 5 months of age (30).

Pretreatment with androgen stimulation is sometimes considered, especially in boys with a small phallus and proximal hypospadias. Testosterone cream or injection and hCG injections have been used, but the parenteral route is more reliable. Proponents report that therapy increases penile size, making it possible to harvest longer preputial flaps (54,82), and even decreases severity of hypospadias by moving the meatus distally (82). Others have not found testosterone stimulation beneficial (46). Gearhart and Jeffs (54) recommend that 2 mg/kg of testosterone enanthate be given intramuscularly (IM) 5 and 2 weeks preoperatively, but there are no uniform dosing guidelines, and androgen therapy for microphallus typically involves higher doses, 25 to 50 mg IM once a month for 3 months.

SURGICAL REPAIR

The goal of hypospadias surgery is to create a penis with both normal function and appearance. Because the anomaly includes a wide spectrum of severity, ranging from the glanular to perineal meatus in a penis that may be straight or significantly curved, it is not surprising that well over 200 operative techniques and variations have been described. The fact that the origins of nearly all of these procedures can be traced to the late 1800s, when surgical repair began in earnest, attests to the difficulty of achieving a functional neourethra in a straight penis that appears to have only been circumcised.

In the past decade, new concepts regarding the etiologies of penile curvature and the best means to correct it have gained acceptance. As a result, the urethral plate is now more commonly preserved and incorporated into the urethroplasty. Together these developments have brought hypospadias surgery nearer its ultimate functional and cosmetic goals. The following section presents a brief overview of the history of hypospadiology to explain the evolution of its modern principles.

HISTORICAL BACKGROUND

In 1869, Karl Thiersch first tubularized skin flaps to repair epispadias. Theophile Anger adopted his technique for hypospadias and in 1874 reported successful repair of a penoscrotal lesion, inaugurating the modern era of hypospadias surgery. Soon thereafter, the French surgeons Duplay, Nové-Josserand, and Ombrédanne each described methods that became the foundation on which the work of subsequent generations of hypospadiologists has been based (Fig. 52B.7). Of the three, Duplay's contributions have arguably been the most enduring, earning him the title “father of hypospadias surgery” (12).

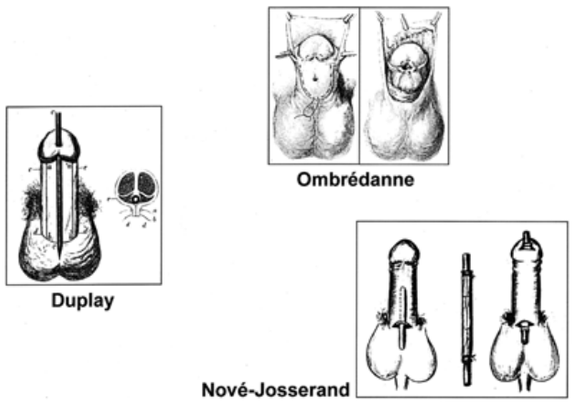

FIGURE 52B.7. The French schools of urethroplasty. Duplay's first method of constructing the neourethra by tubularizing ventral shaft skin. The inset depicts his second method in which a buried dorsal strip of skin was expected to epithelialize ventrally around a catheter. Ombrédanne's flap was centered on the meatus and drawn closed by a single purse-string suture into a pouchlike urethra. Nové-Josserand placed tubularized skin grafts subcutaneously using trocars.

The early pioneers generally limited intervention to boys with proximal defects and significant curvature, meaning the repair of hypospadias began with the most difficult cases. These operations were usually done in multiple stages as recommended by Duplay. First, the penis was straightened. Then the neourethra was fashioned and in the final stage joined to the native urethra. Although today most repairs are accomplished in a single operation, this sequence of steps is still followed. Any penile curvature must first be corrected, because the means used for straightening determines the options available for urethroplasty.

Chordee

Ambroise Pare may have been the first to describe chordee in the medical literature. Writing in the 1500s, he observed that the “bridle” or “ligament” of the penis was occasionally too short, resulting in downward curvature, and he advised that it be cut to achieve straightening. Two hundred years later, Pierre Dionis agreed that transverse incision of a short bridle would remedy penile bending (108). In 1842, Mettauer (89) found that multiple subcutaneous incisions were needed to divide the “contracted structures,” which impaired normal erections. Bouisson further elaborated on this theme, describing in 1861 excision of a “fibrous band” through a transverse incision closed vertically (69). Duplay adopted Bouisson's technique in the first stage of his operation (Fig. 52B.8), and then Edmunds (48) modified it somewhat by formally resecting the “shrunken” urethral groove from the tip of the glans back to the meatus.

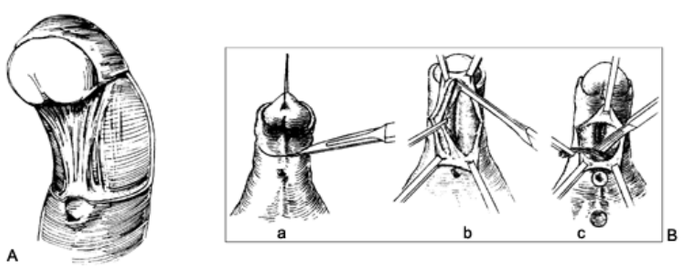

FIGURE 52B.8. A: Traditional concept of chordee tissues representing fibrous remnants of dartos fascia, Buck's fascia, and corpus spongiosum extending in a fan shape from the meatus to the glans. (From Hinman F Jr. *Atlas of pediatric urologic surgery.* Philadelphia: Saunders, 1994:554, with permission.) **B:** Duplay's method to straighten the penis. A transverse skin incision was made across the urethral plate *(a),* fibrous subcutaneous tissues were excised *(b),* and then the skin was closed vertically *(c).*

Over time, these descriptions of “bridles,” “contracted structures,” and “fibrous bands” were replaced with scientific terms such as “dysgenetic mesenchyme” and “dysplastic corpus spongiosum.” Gradually, the notion became firmly entrenched that the urethral remnant distal to the hypospadiac meatus consisted of epithelium covering dense fibrous tissues of abortive spongiosum (31). Meanwhile, surgical excision of these tissues also became more extensive. For example, in 1955 Byars (25) warned that abnormal fibrous elements had to be removed from the entire ventral half of the penile circumference down to the corpora cavernosa and into the intercorporeal septum.

Devine and Horton wrote extensively on chordee in the 1960s and 1970s, emphasizing the additional contribution of dysgenetic dartos and Buck's fasciae to penile curvature. Like Byars, they believed meticulous dissection to remove all

fibrous tissues should leave the corpora cavernosal surface “clean and glistening” (36). Even into the mid-1980s it was the practice of many surgeons to approach proximal hypospadias repairs via a subcoronal circumferential incision with removal of the urethral groove down to the meatus. After Duckett popularized the term *urethral plate,* some have argued that the plate either is comprised of fibrous tissues or it tethers the corpora cavernosa by fibrous attachments to produce penile curvature (16).

However, alternative views regarding the causes of penile bending are also found sporadically in literature dating to the 1800s. For example, although he used Bouisson's method to straighten the penis, van Hook (71) wrote in 1898, “It must not be forgotten that the downward curvature of the penis is largely due to lack of development of the corpora cavernosa.” But not until 1952 was there a serious challenge to the prevailing opinion that chordee results from fibrous spongiosum. Smith and Blackfield (117) argued that they were able to reliably correct bending without resecting any “phantom” midline bowstring by simply releasing ventral skin attachments distal to the meatus. Then Allen and Spence (5) found that a circumferential skin incision proximal to the meatus was also effective, enabling the penis to be straightened without disturbing the meatus in distal hypospadias. Critics described this approach as a “glorified circumcision.”

Artificial erection is required both to accurately diagnose and assess the degree of penile curvature and to demonstrate success of corrective measures. Therefore it is important to emphasize all these concepts developed before Gittes and McLaughlin (60) described corpora cavernosa injection in 1974. Until that time, intraoperative evaluation was largely based on visual inspection and palpation of the ventrum with countertraction on the glans.

Nesbit (93) reported dorsal plication in 1965, presenting three cases of chordee without hypospadias. None had a fibrous bowstring, but instead were each thought to have “rare” corpora cavernosal asymmetry. Although today this means of straightening is commonly called *Nesbit plication,* the technique had already been described by Syng Physick in 1844 (96). But it was Duckett who popularized this approach, insisting that corpora cavernosal disproportion was the most likely cause of persistent bending after the penis was degloved, when he realized that transection of the urethral plate under these circumstances did *not* achieve straightening (15,70). Through the combined force of this observation backed by his strong personality, Duckett was able to convince many hypospadiologists to stop excising the plate and rely instead on dorsal plication.

Urethroplasty

Neourethras were first constructed from local skin flaps. Applying Thiersch's operation to hypospadias, Duplay made parallel longitudinal incisions from the meatus extending distally and rolled the skin into a tube, covering this neourethra with lateral skin flaps. His approach had the disadvantage of overlapping suture lines and often required a relaxing incision through the dorsal shaft skin for sufficient mobility to close skin flaps ventrally. Several years later, Duplay reported a second means of repair. By cutting a narrower skin strip for the neourethra, he found it easier to close the ventral shaft without a relaxing maneuver. However, it was no longer possible to roll a tube, so Duplay simply left a catheter lying on this now buried strip of skin, convinced that epithelialization during healing would complete the neourethra (12). Predictably, both of Duplay's operations commonly resulted in fistulae and eventually fell into disuse until Browne (23) briefly resurrected his second method. Nevertheless, today the name Thiersch-Duplay is evoked when local skin is tubularized.

It was the apparent need for additional tissues to form the neourethra or resurface the ventral penis that gave rise to literally hundreds of operations (Fig. 52B.9). Many surgeons used the adjacent scrotum, with Cecil (26) ultimately refining the technique by creating the urethra from penile skin while using scrotum for ventral shaft covering. This kept hair out of the neourethra, but it meant that hairy skin extended to the corona.

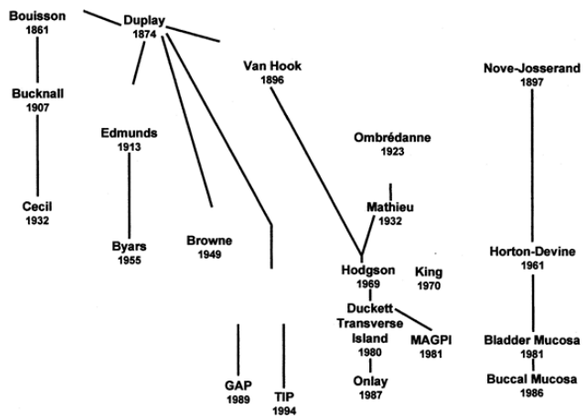

FIGURE 52B.9. Abbreviated genealogy of hypospadias repairs.

Meanwhile, in 1896 van Hook may have been the first to tubularize a pedicle flap of preputial skin (71). Shortly thereafter, Edmunds (48) introduced splitting the prepuce and transposing it ventrally for later tubularization. Byars (25) added a slight modification, and today the term *Byars' flaps* describes the first of a two-stage repair.

Another school of urethroplasty began with Ombrédanne's report of a U-shaped flap, centered on the meatus, which was drawn into a pouchlike neourethra by a single purse-string suture (12). Mathieu (88) added some refinements, replacing the purse-string closure with parallel suture lines. This “flip-flap” repair subsequently became one of the most widely used operations for distal hypospadias.

Hodgson (68) combined elements of the flip-flap and preputial pedicle flap in his various repairs. Furthermore, he supported Devine and Horton's enthusiasm for one-stage repairs, which gradually replaced multistaged operations in the 1960s. Asopa and colleagues (10) and Duckett (42) further modified these techniques to describe tubularized preputial flaps and, later, the onlay flap (50).

The third school of urethroplasty is credited to Nové-Josserand. Before the late 1800s, trocars had been used to tunnel under the skin and through the glans to create a neourethra. Nové-Josserand placed tubularized skin grafts subcutaneously by this means. Subsequently, homografts of veins and appendix were all tried without much success, primarily because of strictures (12). The preputial grafts described by Devine and Horton and the more recent use of bladder and buccal mucosa all derive from Nové-Josserand's earlier efforts.

One innovation without obvious connection to these French surgeons was the meatoplasty and glansplasty, or MAGPI. Introduced by Duckett in 1981, the operation was primarily intended for the subcoronal meatus (43). Previously such distal hypospadias usually had not been repaired because it rarely caused voiding or procreational difficulties, but this relatively simple procedure with few complications offered the means to improve the appearance of the glans. Soon other techniques to repair more severe hypospadias came under increasing scrutiny, as the standard for measuring success was raised to include not only functional outcomes, but also the cosmetic results.

By the late 1980s, the hypospadiologist could rely on the MAGPI, flip-flap, or onlay and tubularized preputial flap to correct most abnormalities (21). However, one problem with flip-flaps and onlays was the rounded, horizontally oriented meatus that often resulted. Both Johanson and Avellán (75) and Rich and colleagues (107) recognized that urethral plate configuration actually determined the cosmetic outcome, because a flat plate yielded a horizontal meatus while a deeply grooved one produced a more normal, vertically orientated meatus. Consequently, Rich and colleagues (107) described “hinging” the flat plate by incising it distally to improve meatal cosmesis. A few months later, Snodgrass (121) extended this midline incision through the entire urethral plate and realized that the plate could then be tubularized without adding skin flaps.

NEW CONCEPTS

From these trials and errors, four concepts emerged in the 1990s that have revolutionized hypospadias repair. The first is designation of the tissues distal to the hypospadiac meatus as the urethral plate, implying that it is a unique structure. Although the term was coined in reference to epispadias (104), Duckett popularized its use in hypospadias. Previously no distinction had been made between the urethral plate and glans. Instead, the glans was described as being flat or grooved when this appearance actually referred to characteristics of the plate. The developmental arrest that results in hypospadias leaves the ventral glans open with its wings fused to the lateral edges of the urethral plate.

The second concept is that the urethral plate is rarely the cause of penile bending. It is important to emphasize that there have been very few reports concerning histology of the

hypospadiac penis, and the authors are aware of only one that purported to demonstrate fibrous tissue comprising an inelastic band stretching under the surface epithelium from the meatus to the glans (98). Conversely, Avellán and Knutsson (11) did not find histologic evidence of a fibrous band within the tissues of the urethral plate in patients with hypospadias and ventral penile curvature. We have also obtained biopsies of the urethral plate, as well as the corpus spongiosum, dartos, and Buck's fasciae in a small number of boys with hypospadias and penile curvature, and have yet to encounter fibrous or dysplastic tissues (127).

A limited number of autopsy studies also challenge the fibrous bowstring theory of chordee. For example, Marshall and colleagues (87) examined one newborn with penoscrotal hypospadias and found no fibrotic tissues within the urethral plate and no abnormal fibrotic attachments of the plate to the underlying corpora cavernosa. Similarly, the fetal specimens evaluated by Kaplan and Lamm (79) demonstrated ventral curvature without fibrous tissues or bands. Their report corroborated the earlier studies of Glenister (61), suggesting that the penis is normally curved during development and may remain so if development is arrested. It is an interesting historical observation that the French word *chordee,* meaning “cord” or “band,” apparently did not come into popular use until the 1950s. Now perhaps it, like the older terms *bridles* and *ligaments,* should be retired.

Third, incorporation of the urethral plate into the neourethra may reduce surgical complications. Hollowell and colleagues (70), Mollard and Castagnola (91), and Wiener and colleagues (132) all reported advantages to onlay versus tubularized preputial island flaps. In these series, reliance on an intact urethral plate as scaffolding to support the neourethra was cited as a benefit of the onlay approach.

The fourth concept is that the urethral plate can be primarily tubularized without additional skin flaps after a dorsal midline relaxing incision is made. This observation was first reported in 1994 in a small series of boys with distal hypospadias (121). Multicenter experiences with the technique for both distal (122) and proximal (123) hypospadias confirmed the findings and led to widespread use of the principle.

DECISION MAKING IN HYPOSPADIAS SURGERY

In the past, the choice of operation was determined by specific meatal and glanular (actually urethral plate) configuration encountered. For example, the MAGPI was best limited to the small, pliable subcoronal or glanular meatus with a flat ventral glans. So-called meatal variants (58) were better managed by other techniques, such as the glans approximation procedure (135) and pyramid repairs (44) for a patulous meatus with a deep glanular groove, or flip-flap and onlay flaps when the glans was flat.

Now it is commonly held that *every* primary operation for hypospadias begin with preservation of the urethral plate. Decision making as to method of repair occurs after degloving the penis and correction of the chordee.

CORRECTION OF PENILE CURVATURE

No study has assessed curvature by artificial erection before degloving the penis, so the relative contribution of ventral shaft skin to penile bending is difficult to determine. However, several features of the skin in hypospadiac penises are obvious. First, there are often relative deficiencies not only of the ventral prepuce but also of the ventral shaft skin. In addition, coverage proximal to the meatus may be quite thin due to deficiencies in the dartos and corpus spongiosum normally interposed between skin and urethra. Furthermore, the median raphe is typically displaced laterally, sometimes in association with torsion of the penis. That these skin anomalies may twist or bend the penis is apparent, and without doubt the ventral glans tilt observed with most hypospadias is usually due to skin tethering, because it resolves when these attachments are released.

A circumscribing incision is made subcoronally and 2 mm proximal to the meatus to begin distal hypospadias repair. If the skin overlaying the distal urethra is thin, however, a U-shaped incision is extended back to healthy skin. Similarly, a U-shaped incision is made along the lateral borders of the urethral plate to the meatus for proximal hypospadias. The penis is then degloved to the scrotal junction in the plane between dartos and Buck's fasciae, and artificial erection subsequently is done in every case, because even a coronal meatus is sometimes associated with penile bending.

In a series of boys with penile hypospadias treated with onlay flaps, 27% still had curvature requiring intervention after the penis was degloved (15). Similarly, the tubularized, incised plate multicenter studies combined found 24% of patients with bending when the skin was released (unpublished data). As expected embryologically, significant curvature is more likely as the severity of the hypospadias increases. Baskin and colleagues (15) attributed this bending to corpora cavernosal disproportion, and in both their and the multicenter reports, dorsal plication was done to achieve straightening.

An algorithm to correct penile curvature is depicted in Fig. 52B.10 . When the degree of bending is mild, dorsal plication will reliably straighten the penis (Fig. 52B.11). However, curvature greater than 30 degrees has traditionally next led to transection of the urethral plate, even though this step alone often is not sufficient to accomplish straightening. Because it is preferable to retain the plate, when possible, the authors now follow the suggestion of Mollard and Castagnola (91) and first mobilize the plate from the meatus to the corona, dissecting immediately along the corpora cavernosal surface (Fig. 52B.12). In limited experience, this maneuver has not completely corrected bending,

but in some cases has improved it such that dorsal plication was then feasible to achieve straightening without having to transect the plate.

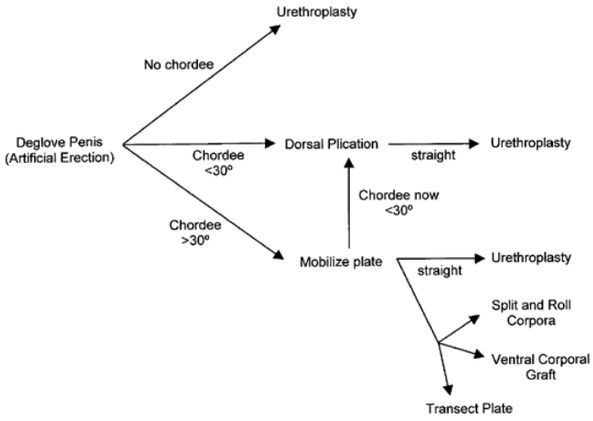

FIGURE 52B.10. Algorithm for penile straightening. After the skin is degloved, most boys with hypospadias have either a straight phallus or mild ventral curvature readily corrected by dorsal plication.

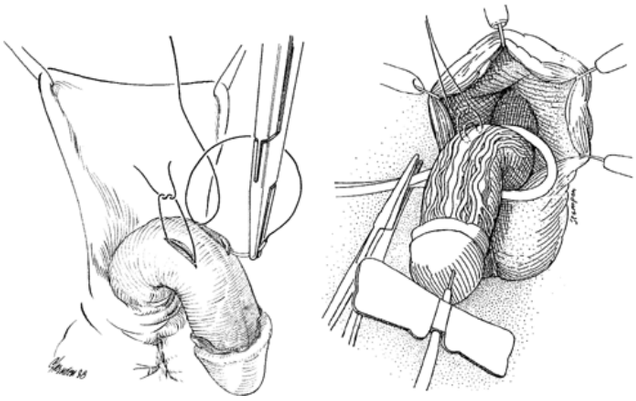

FIGURE 52B.11. Dorsal plication for penile straightening. Parallel incisions are made superficially into the tunica albuginea of the corpora cavernosa adjacent to the neurovascular bundles opposite the point of greatest curvature. It is not necessary to remove an ellipse of tunica or to expose spongy tissues. The 6-0 Prolene sutures are placed as shown, burying the knot. Alternatively, because their studies found no sensory nerves at the 12 o'clock position, Baskin and colleagues (17) recommend dorsal plication in the midline.

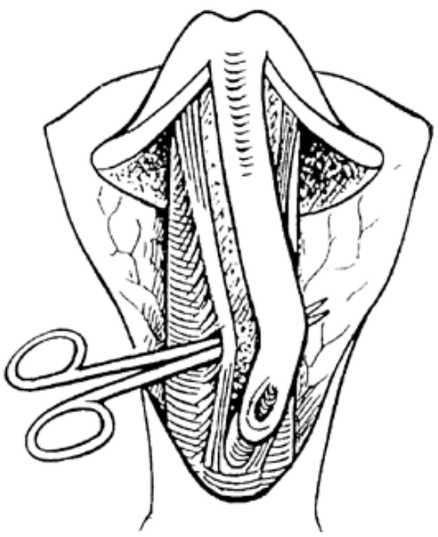

FIGURE 52B.12. Mobilization of the urethral plate from the underlying corpora cavernosa may assist in penile straightening. [From Mollard P, Castagnola C. Hypospadias: the release of chordee without driving the urethral plate and onlay island flap (92 cases). *J Urol* 1994;152:1238, with permission.]

Despite these measures, there remain occasional instances in which penile straightening requires transection of the urethral plate. After transection, bending sometimes resolves or improves to an extent that dorsal plication is then successful. In other patients, however, there is still too much curvature, or the penis is intrinsically so short, that plication may not be adequate or advisable. In these circumstances, ventral grafting to lengthen the corpora cavernosa has been done using dermal (37) or tunica vaginalis (100) grafts. Others dissect ventrally into the intercorporeal septum to separate the corpora cavernosa and then rotate the corpora laterally to straighten the penis (32,34,83). Perovic and colleagues (101) recommend complete penile disassembly when there is severe curvature.

TUBULARIZED, INCISED PLATE URETHROPLASTY

In most hypospadias repairs, penile straightening is achieved without transecting the urethral plate (Fig. 52B.13). Next, 1:100,000 epinephrine is infiltrated into the ventral glans along the visible junction to the plate. Then the plate is separated from the glans wings by parallel longitudinal incisions and the wings are mobilized laterally for subsequent

tension-free closure. With the occasional exception of the deeply grooved urethral plate, most often the plate at this stage is too narrow to be tubularized.

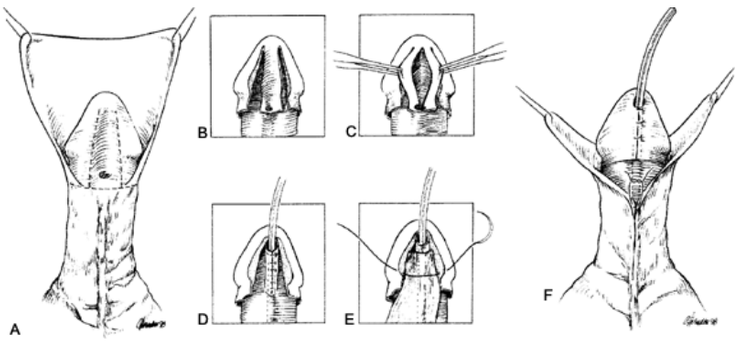

FIGURE 52B.13. Tubularized, incised plate hypospadias repair. **A:** *Horizontal dotted line* indicating circumscribing incision approximately 2 mm proximal to the meatus. *Vertical dotted lines* indicate the junction of the urethral plate to the glans wings. **B:** Urethral plate is separated from the glans wings, which are then mobilized laterally. **C:** The key step of the operation is a deep, midline incision into the urethral plate extending from within the meatus to its distal margin, but not continuing into the glans apex. **D:** The plate is tubularized over a small stent leaving a generous, oval meatus. **E:** The neourethra is covered by a dartos flap, and then glansplasty begins at the coronal margin. **F:** Glans wings, mucosal collar, and ventral shaft skin are closed. (From Snodgrass W. Tubulanized incised plate hypospadias repair: indications, technique, and complications. *Urology* 1999;54:6, with permission.)

The key step in the operation is a midline relaxing incision made from within the meatus to the distal extent of the plate. This incision carries through the epithelial surface of the plate deeply into underlying connective tissues down to the corpora cavernosa. With the surgeon and assistant maintaining countertraction using fine forceps, division of the plate is observed to widen it significantly, and continues until no additional mobility is gained. It is recommended that tenotomy scissors, rather than a knife, be used so as to gain sufficient depth without injury to the corpora cavernosa.

Plate configuration determines the depth of the relaxing incision (Fig. 52B.14). When the urethral plate is flat, the incision will be made deeper than when it is already naturally grooved. Regardless, plate incision should consistently serve to broaden the plate tissue to the extent that the neourethra will exceed 12 Fr (Fig. 52B.15). If bleeding occurs, 1:1,000 epinephrine is dripped onto the site and then pressure is held for several minutes. A tourniquet can also be applied at the base of the penis, but it is advisable not

to use electrocautery either to incise the plate or control bleeding.

FIGURE 52B.14. The depth of the midline urethral plate incision is determined by the extent of its natural groove. The relatively flatter plate on the far right requires a deeper incision than the more deeply grooved plate in the middle figure.

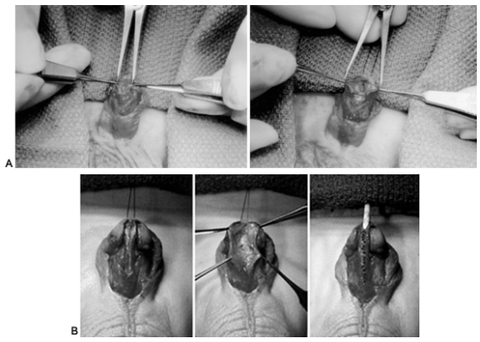

FIGURE 52B.15. Results of urethral plate incision. **A:** Before incision, the plate in this case measured 6 mm in width. After the dorsal relaxing incision, the plate measured 15 mm in width, ensuring a final neourethra greater than 12 Fr. **B:** Midline incision markedly widens the urethral plate in a case of proximal shaft hypospadias.

Before tubularization, a 6-Fr stent is passed into the bladder for postoperative urinary drainage. Closure of the urethral plate always begins at the midglans level, with no more than one, or rarely two, stitches placed further distally. To avoid stenosis, the neomeatus should have a generous oval opening. The plate can be tubularized using a running subepithelial 7-0 chromic catgut suture.

The entire neourethra is covered with a thin dartos pedicle mobilized from the dorsal prepuce and shaft skin. This provides a very important second layer of tissue over the neourethra closure line. Next, the glans wings are closed in the midline using a subepithelial 6-0 suture of the cornea, followed by a 6-0 chromic catgut vertical mattress to approximate the glans surface. One or two additional stitches are placed further distally, again with care to avoid constricting the neomeatus. Simple stitches of 7-0 chromic catgut between glans and meatus at the 4 and 8 o'clock positions may improve the cosmetic results of the meatus.

The mucosal collar is approximated in the midline and the shaft skin is refashioned to simulate the median raphe (120). In obese boys, the skin should be anchored to the base of the penis using absorbable sutures to minimize its distal migration (i.e., formation of a “buried penis”). Subcuticular stitches are advised along all skin edges to avoid suture tracks (126). A Tegaderm dressing is applied at the conclusion of the procedure (Fig. 52B.16), and the child discharged home. The stent drips urine into diapers for 5 to 7 days.

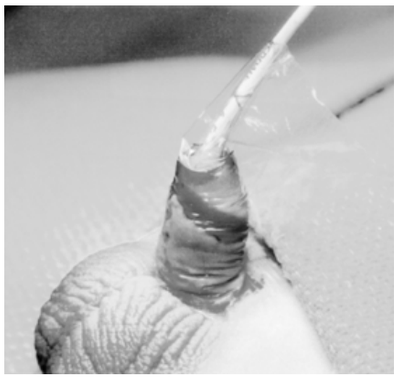

FIGURE 52B.16. Postoperative dressing preferred by the author.

OUTCOMES OF TUBULARIZED, INCISED PLATE URETHROPLASTY

Tubularized, incised plate (TIP) hypospadias repair produces a functional neourethra greater than 10 Fr ending in a vertical, slitlike meatus (Fig. 52B.17). The effectiveness of this repair is thought to relate to the use of healthy urethral plate tissue, which has good potential to regenerate midline epithelium, thus expanding urethral tissue without skin flaps or grafts. After surgery, most boys appear to have only been circumcised. The results to this point have been durable, with low incidence of meatal stenosis, neourethral stricture, and diverticulum formation (124). However, relative to other repairs, follow-up is short. The most frequent complication has been that of fistula formation, which occurs in approximately 2% of the total cases reported to date (125). However, the likelihood of fistulae is minimized by covering the neourethra with a dartos flap (52,121).

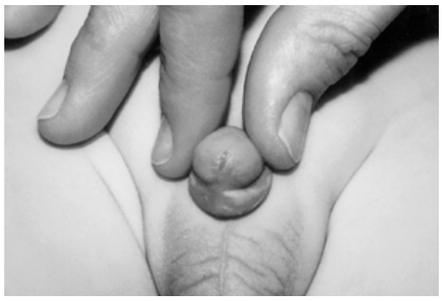

FIGURE 52B.17. Postoperative appearance following tubularized, incised plate (TIP) repair.

A significant advantage of hypospadias repair using the TIP urethroplasty is that it can be used to correct essentially all distal and many proximal anomalies. The glans approximation procedure (GAP) and pyramid repair also involve tubularization of the urethral plate. However, the GAP was designed only for cases with a patulous meatus and a deeply grooved plate and has the disadvantage of overlapping suture lines between the urethroplasty and glans closure. Similarly, the pyramid was only described for use in megameatus repair. By definition, boys with this variant have a generous, in fact sometimes too wide, urethral plate, but in some the plate lies flat in a horizontal plane such that midline incision helps recess the neourethra deeper into the glans. Consequently, repair of these specific anomalies follows essentially the same steps described previously.

Both the TIP and MAGPI can be used to correct proximal glanular hypospadias. Both procedures have low

complication rates, and the MAGPI has the advantage of being a stentless repair. Drawbacks of MAGPI include its potential distortion of the glans and meatal regression. Unless the meatus is pinhole in size and freely mobile, it will not advance distally. The dorsal sutures may act less to move the urethra than to pull the glans apex proximally, resulting in a flattened rather than conical glans. Early postoperative results of MAGPI may not be durable. Whereas Park and colleagues (97) reported no meatal regression at 3-year follow-up, Hastie and colleagues (65) found partial regression in 26 of 28 cases with similar long-term evaluation.

At the time the MAGPI was introduced, it was unparalleled in its ability to achieve excellent cosmetic results in the repair of distal hypospadias. The TIP repair currently seems to accomplish the same goal without glans distortion and with little risk of meatal regression. Similarly, the TIP concept can be applied to cases that previously would have required either flip-flap or onlay flap techniques to create the neourethra, without many of the difficulties experienced with these repairs. The resulting meatus is usually slitlike and vertically oriented on the glans.

OTHER REPAIRS

The two contraindications to TIP urethroplasty are (a) severe curvature requiring transection of the urethral plate and (b) a plate that appears thin or is insufficiently widened after dorsal incision. Options for repair in these circumstances are found in the algorithm in Fig. 52B.18 .

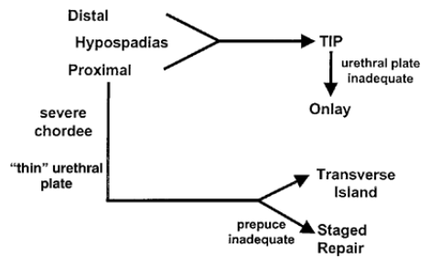

FIGURE 52B.18. Algorithm for primary hypospadias repair. TIP, tubularized, incised plate.

Onlay Flaps

Rarely, the lateral margins of the urethral plate may appear thin due to deficiency of its connective tissues. In this situation (which the authors have encountered in approximately 1% of cases), all unhealthy tissues must be excised. An onlay flap is generally necessary to complete the urethroplasty (Fig. 52B.19). However, the preputial flap should be a minimal width to avoid a diverticulum.

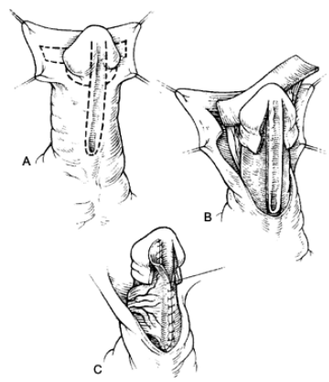

FIGURE 52B.19. Onlay preputial flap. **A, B:** A rectangular flap of appropriate length and a width of approximately 8 to 10 mm is cut from the inner prepuce, maintaining its blood supply. **C:** The flap is rotated ventrally and sutured to the urethral plate. The pedicle of the flap is used to cover the neourethral suture lines.

Tubularized Preputial Flap

Two options remain for urethroplasty when severe penile curvature leads to transection of the urethral plate. One is to complete the repair in one stage using a tubularized preputial flap (Fig. 52B.20). A rectangular flap of sufficient length and a width of approximately 14 mm is developed from the inner prepuce, tubularized, and then rotated ventrally maintaining its blood supply. Although the tubularized preputial flap offers the advantage of a one-stage repair, in some series it has been associated with complication rates of 38% to 50%, including fistulae, meatal stenosis, strictures, and diverticula (49,132).

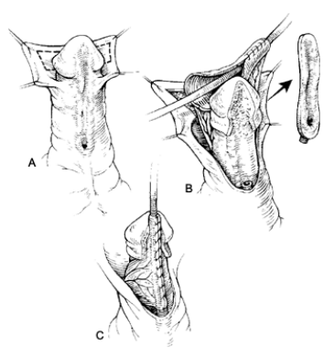

FIGURE 52B.20. Tubularized preputial flap. **A:** A rectangular flap of appropriate length approximately 14 mm wide can be harvested from the inner prepuce. **B:** Following resection of the urethral plate, the flap is mobilized and then tubularized over a stent. **C:** The neourethra is rotated ventrally, placing the suture line against the corpora cavernosa.

Two-stage Repair

When the proximal urethral plate must be transected. it may be preferable to stage the urethroplasty (Fig. 52B.21). The dorsal prepuce is split to the level of the corona and the resultant flaps are advanced ventrally to provide adequate

skin for later tubularization. In the past, the distal urethral plate was also excised and the prepuce advanced into the space between the glans wings. However, the prepuce may be rotated to the subcoronal level *without* disturbing the distal plate.

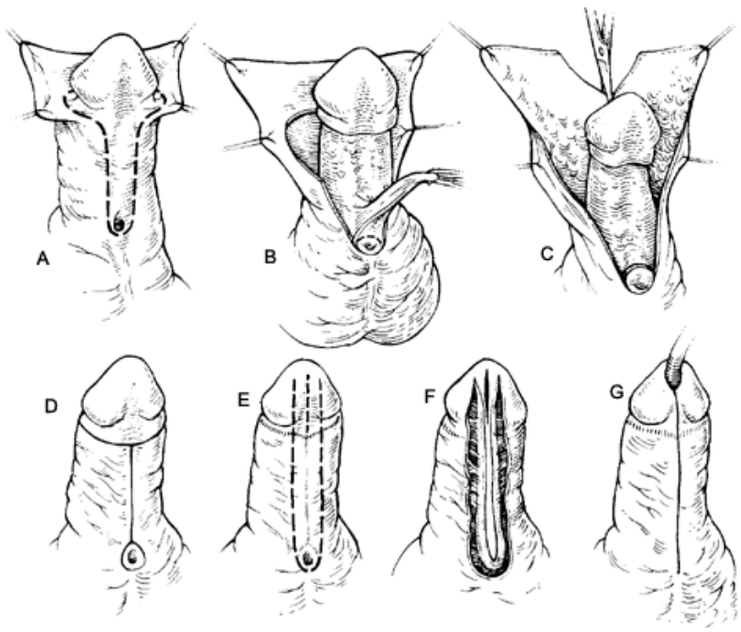

FIGURE 52B.21. Two-stage hypospadias repair. **A:** The initial U-shaped skin incision preserves the urethral plate. **B:** Removal of the shaft portion of the urethral plate is sometimes needed for penile straightening. **C:** Prepuce is incised dorsally to rotate skin to the ventrum. **D:** The first stage is completed using subcuticular stitches. **E:** Lines of incision for the second stage. The glanular incisions are the same as those used in distal TIP urethroplasty, with the outer incisions separating the glans wings from the urethral plate while the midline relaxing incision widens the plate. **F:** The incisions are completed and the neourethra will next be tubularized over a stent. **G:** The completed repair.

The second stage is done 6 months later. Parallel longitudinal incisions 12 to 14 mm apart outline the flap on the penile shaft and continue distally onto the glans wings at their junction with the urethral plate. Then the plate is incised in the midline, and the entire strip of plate and skin is tubularized into the neourethra.

Although the trend since the early 1980s has been toward one-stage repairs using tubularized preputial flaps, there has been a resurgence of support for a two-stage repair for boys with proximal hypospadias and severe penile curvature. This approach permits careful correction of the chordee and maximizes the potential for viable ventral flaps. Reports have emphasized that this approach may yield fewer complications and better cosmetic results than a one-stage approach in this setting (63,105).

COMPLICATIONS

Several general precautions may diminish the risk for complications following hypospadias repair. With reconstruction now recommended in the first few months of life, use of delicate instruments, fine suture materials, and optical magnification

is essential. Careful attention to the blood supply of flaps and meticulous wound hemostasis are of obvious importance. Given the choice of vascularized flaps versus free grafts, most surgeons today prefer vascularized tissues. Creating a neourethra of appropriate size that is neither too small nor too large and then interposing a barrier layer between it and the skin will also reduce the likelihood of subsequent problems.

Urethrocutaneous Fistula

Urethrocutaneous fistula is the most common complication of hypospadias repair. Although most are isolated findings, a fistula sometimes indicates meatal stenosis, distal urethral stricture, or the presence of a diverticulum. Historically, fistulae have occurred in up to 50% of patients, but reports of the operations described in this chapter document much lower rates. As discussed previously, fistulae have been noted in 2% of TIP urethroplasties. Onlay and tubularized preputial flaps develop this complication in 6% to 17% of cases (15,57,131), and modern two-stage repairs have a 5% or less incidence of fistulae (63,105).

Meatal Stenosis

Inadequate blood supply to the meatus or iatrogenic constriction of the opening during repair can result in meatal stenosis. Regardless of the operative procedure, at its conclusion the meatus should have a generous oval configuration. In the TIP repair, incising dorsally beyond the plate into the glans apex, suturing the neourethra too far distally, or constricting the meatus during glans closure can all lead to stenosis. Occasionally, the meatus appears small in an asymptomatic patient after surgery, but in our experience, a 10-Fr sound has always passed easily, and routine calibration is not necessary. Meatal stenosis occurs in less than 5% of boys undergoing modern repairs.

Urethral Stricture

A stricture of the neourethra usually indicates a region with poor vascularity (assuming the original diameter was adequate). The proximal anastomosis of tubularized preputial flaps is also an area more prone to strictures (62). Therefore an advantage of both onlay flaps and the two-stage approach is avoidance of such a circumferential anastomosis. However, given the large number of hypospadias operations and the few patients reported with strictures, it appears that this is currently not a complication of major significance (47,111). Neourethral stricture seems to be uncommon following TIP repair. In their study of onlay and tubularized preputial flaps, Wiener and colleagues (131) had a combined 6% rate of strictures and did not find a significant difference in risk between the two types of repair.

Diverticula

Diverticula typically cause visible ballooning of the reconstructed urethra during voiding and postvoid dribbling. They develop secondary to distal obstruction, from creation of too large a neourethra, or as a result of turbulent urinary flow (3). One case has been reported in association with meatal stenosis after TIP repair (123), but otherwise this is an unlikely complication of that procedure because skin flaps are not used. When preputial skin is required, onlay flaps develop diverticulum less often than do tubularized ones, the latter having a reported incidence of approximately 10% (3,131). This finding is cited as an advantage of securing onlay flaps to the stable urethral plate. Greenfield and colleagues (63) noted a 21% incidence of diverticula in their two-stage repairs and concluded that these resulted from turbulent flow proximal to the comparatively fixed glanular urethra. When skin flaps are needed, it is important to avoid the temptation of creating a larger than normal neourethra.

Recurrent Penile Curvature

Artificial erection should detect penile curvature at the time of repair and then document its correction. Although the etiology of bending and the best means to achieve straightening remain sources of debate, there have been very few reports of recurrent curvature after hypospadias surgery in childhood. Vandersteen and Husmann (130) evaluated 22 men with recurrent curvature more than 10 years after proximal hypospadias repair, all of whom had undergone artificial erection followed by corporoplasty using either dorsal plication or ventral tunica vaginalis patch grafts. Failures of both plications and grafts were noted, but definitive risk factors could not be identified in this small series.

Other Complications

Several other complications occasionally occur following hypospadias repair. Dehiscence may be the result of several factors, including infection, poor vascularity, or tension on the repair. Use of small stents for urinary drainage may reduce pressure on suture lines that can develop from postoperative swelling. Stents size 6 Fr are preferred for repairs in children because they provide adequate urinary drainage with minimal risk.

Suture tracks are a theoretic risk whenever stitches penetrate the skin. We have found these to occur on the ventral penile shaft despite use of 6-0 chromic catgut for wound closure. They may not be apparent until more than 1 year postoperatively, presumably because of the time needed for such small sinuses to fill with keratin (126). Following application of eutectic mixture of local anesthetics (EMLA) cream, these can be opened with a sharp-pointed scissors in

the office, but most likely would have been avoided in the first place by subcuticular wound closures.

Scars on the dorsum of the penis and glans should not result from the procedures described in this chapter. A deformed, scarred glans is particularly distressing and often cannot be improved, which emphasizes need for delicate handling of these important tissues. Similarly, we routinely attempt to create a median raphe ventrally as preputial flaps are rotated, avoiding “bear hug” flap closures that once were popular and still are occasionally depicted in textbooks. A functional penis with unsightly scars can, at best, be considered only a partial success of hypospadias repair.

REOPERATION

Reoperative surgery after hypospadias repair ranges from closure of simple fistulae to extensive reconstruction of the entire neourethra. Every boy with a complication should be carefully evaluated to detect other associated problems, because reoperations must be designed to address all comorbid conditions. In addition to office examination, reports of previous operations should be reviewed. In general, reoperations are delayed at least 6 months following the last repair to allow complete healing. Then, at the time of surgery, urethroscopy is done to directly visualize the urethra, facilitating diagnosis of fistulae, strictures, and diverticula. Distending the urethra with methylene blue is also useful to detect small fistulae that might otherwise be overlooked.

The principles of fistula repair include excision of all unhealthy tissues, watertight urethral closure, and interposition of a barrier layer between the urethra and skin (Fig. 52B.22). Small fistulae on the penile shaft can be circumferentially excised down to the urethra with a full-thickness skin flap then advanced to cover the repair. These minor procedures do not require postoperative urinary diversion. However, subcoronal and glanular fistulae require more extensive dissection. The distal urethra is opened from the meatus to the fistula and separated from the glans. After unhealthy tissues are excised, the hypospadias repair is essentially redone, tubularizing the urethra, covering it with dartos tissues from the penile shaft, and then reapproximating the glans wings. Therefore a stent is left indwelling for 5 to 7 days.

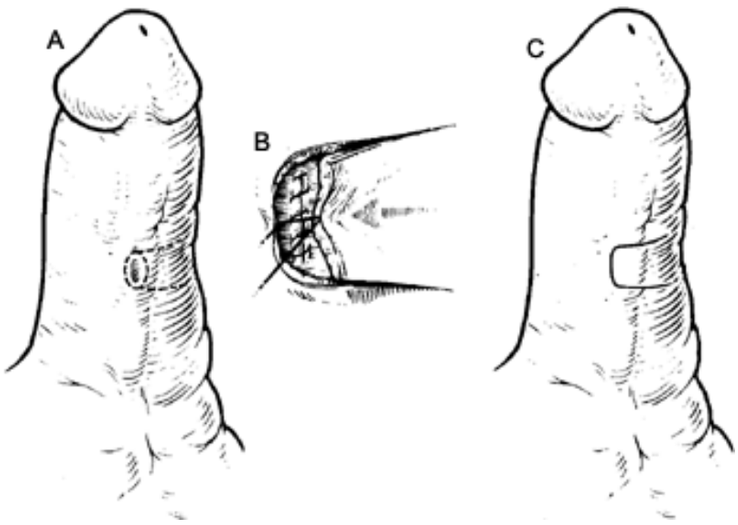

FIGURE 52B.22. Fistula repair. **A:** Proposed lines of incision around the fistula extend laterally to create a skin flap. **B:** After excision of the fistula tract, the urethra is closed and the flap advanced to accomplish wound closure without overlapping suture lines. **C:** The repair is completed using subcuticular stitches.

Short neourethral strictures may respond to a single dilation under anesthesia (14,111), especially if the lesion is detected within the first few postoperative months (111). Alternatively, direct-vision internal urethrotomy may also be considered in this situation. Unfortunately, initial improvement may not prove durable; Duel and colleagues (47) reported long-term success by these methods in only 20% of patients. Because neourethral strictures and meatal stenoses may indicate regions of compromised vascularity, healthy tissues must be incorporated into their repair. This is best accomplished using flip-flaps or onlay flaps derived from local tissues.

Diverticulum repair involves excision of redundant tissues followed by closure of the urethra to an appropriate diameter. Overlapping suture lines are avoided either through use of a degloving skin incision or by interposing dartos tissues. An indwelling stent is used for postoperative urinary diversion.

After a failed hypospadias repair, there is often insufficient penile skin to reconstruct the urethra. One option is incision and tubularization of the urethral plate, which generally remains supple despite the glans approximation procedure, flip-flaps, or onlay flaps (106,109,122). TIP urethroplasty has also been used after MAGPI and even following dehiscence of a prior TIP repair (125). However, reconstruction must be based on healthy tissues; therefore a reoperative urethroplasty cannot depend on incision of an obviously scarred plate. Similarly, should it be apparent from previous operative records or the visual appearance of tissues that the urethral plate has been excised and replaced, for example by tubularized prepuce, a relaxing incision probably cannot be done with the expectation of satisfactory healing.

When neither the TIP method nor vascularized penile flaps are feasible, buccal mucosa grafts are used, preferentially as an onlay rather than tubularized urethroplasty. The technique has been well described (24,33,45) and consists of first preparing the recipient bed of the penis. All scarred tissues are excised, and artificial erection is performed to be certain there is no residual curvature. The proposed graft is then outlined on the inner cheek, avoiding encroachment on either Stenson's duct or the vermilion border (Fig. 52B.23). Buccal mucosa grafts tend not to shrink. The edges of the proposed graft are infiltrated with 1:100,000

epinephrine for hemostasis, and then the graft is harvested by sharp dissection superficial to the buccinator muscle. The wound is sutured using 4-0 chromic catgut.

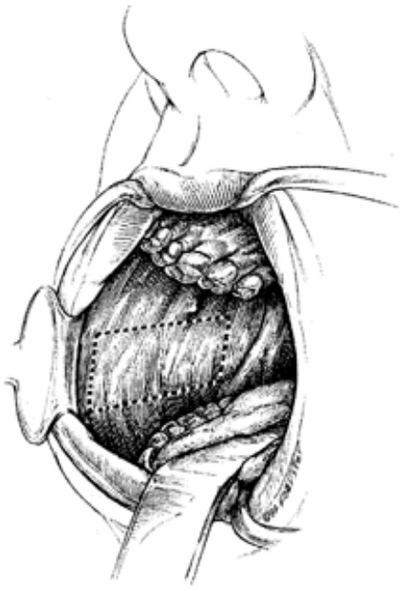

FIGURE 52B.23. Buccal mucosa graft. *Dotted line* indicates region for graft harvest avoiding Stenson's duct and the vermilion border.

All fat and muscle remaining on the graft is excised, and then it is sewn onto the dorsal urethra as an onlay patch. When necessary, tube grafts can be constructed by tubularizing a single wide graft or by combining two narrower strips.

Several considerations may influence the likelihood of graft take. First, it is important to cover grafts with well-vascularized tissues. The vascularity of ventral shaft skin and dartos is unreliable in extensive reoperations, so tunica vaginalis pedicles are used (128). We prefer to obtain these through a small scrotal incision that allows the pedicle to be generously mobilized proximally from the spermatic cord, minimizing the risk of penile tethering when it is tunneled to the surgical site. Second, histology of buccal grafts demonstrates greater intrinsic vascularity than seen with other tissues (45), yet the graft still must survive the initial period of imbibition and revascularization. Consequently, it is also important to immobilize the wound for at least 5 days and to minimize patient activity during this crucial phase of recovery. Urethral stents are used for urinary diversion for 14 days.

CONCLUSIONS AND FUTURE DIRECTIONS

TIP urethroplasty is applicable to nearly all distal and many proximal hypospadias anomalies, and it may also be useful in reoperations. The rare case with a urethral plate that is inadequate for incision and tubularization can readily be converted to another operative technique. The main limitation is severe penile curvature, which occurs in a minority of cases, usually with penoscrotal or more proximal defects. But if curvature limits options for urethroplasty, desire to preserve the urethral plate drives reconsideration of the means used to straighten the penis. For example, influenced by Mollard and Castagnola (91), we have elevated the plate from the corpora cavernosa to assist in penile straightening and then incised and tubularized it. Whether such maneuvers are advisable remains to be seen.

Despite more than 100 years of operative intervention for penile curvature, the cause of “chordee” and therefore the best means to correct it remain sources of controversy. As previously mentioned, we are accumulating specimens of the urethral plate, corpus spongiosum, and dartos and Buck's fasciae from boys with hypospadias, and our preliminary data challenge the concept of fibrous dysplasia of these tissues. This finding might be predicted from the normal development of the urethral folds, which, in the absence of androgen stimulation, differentiate into connective tissues within the labia minora. The practical importance of such observations is further evidence that there are rarely fibrous bands to excise in order to straighten the penis.

The algorithm proposed in this chapter for urethroplasty offers the hypospadiologist an orderly decision-making process using repairs with good functional and cosmetic outcomes and low complication rates. There are additional techniques not included in this review that some use with good results. Any operation that consistently yields good functional and cosmetic results can be a useful part of the surgeon's armamentarium. But if the choices for urethroplasty have recently been simplified, the standard for measuring success has also been raised. Furthermore, there are subtle nuances of technique applied by knowledgeable surgeons according to specific anatomic findings of individual cases, which defy description in a general chapter. Consequently, the occasional operator might best continue to avoid hypospadias repair, leaving it instead within the domain of the experienced hypospadiologist.

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52C INTERSEX

Douglas A. Husmann

Part of "52 - THE GENITALIA "

D.A. Husmann: Department of Urology, Mayo Clinic, Rochester, MN 55905.

Prevailing psychologic theories state that three factors determine how a person will interact with society: sexual identity, personal goals, and lifestyle. Intersex disorders, or the simultaneous expression of female and male characteristics within the same individual, may lead to the patient's inability to define either psychologically or physically his or her sexual identity. The disorientation that results from an ambiguous sexual identity can lead to significant mental confusion, psychologic trauma, and the patient's dissatisfaction with his or her role in society. To successfully understand and manage the patient with an intersex disorder, the physician must be cognizant of the difference between the terms gender role and gender identity. *Gender role* is a person's sex as assigned by the physician, family, and society in general. G *ender identification* is a person's self-assigned sex. In individuals with intersex disorders, the pediatric urologist classically has been cast as the individual to reconstruct the dysfunctional anatomy to match the assigned gender role. Over the past decade, it has become apparent that the assigned gender role of some individuals with intersex disorders eventually will not match their gender identity. This chapter is written with the purpose of helping the physician better understand the relationship between sexual development, sexual identification, and intersex disorders.

SEXUAL DEVELOPMENT

Sexual differentiation follows the classic sequence of chromosomal sex determining the development of the fetal gonad, with the endocrine function of the gonad eventually establishing the sexual phenotype. Each step in the development of the sexual phenotype depends on the appropriate timing and function of the preceding event.

Chromosomal Sex

It is well established that the sexual phenotype of humans is determined by a chromosomal difference between the sexes,

with females having two X chromosomes and males having one X and one Y chromosome. Two broad categories of sex ambiguity exist. First, if the genotype and the gonadal sex match but are incongruous with the phenotype, clinical evaluations usually reveal defects in either the synthesis of or lack of the end-organ response to sex steroids. Second, if the chromosomal sex is disparate from the gonadal sex, the etiology of the sexual ambiguity is usually a genetic abnormality. Most of the strides made in understanding how genes determine gonadal differentiation have come from the investigations of these latter individuals.

Genes Determining Development of the Bipotential Gonad

The gonad is believed to be bipotential, capable of forming into either a testis or an ovary until the sixth week of gestation. The initial formation of the bipotential gonad requires the function of at least three different genes: Wilms' tumor gene (WT-1), Fushi-Tarazu factor–1 (Ftz-F1), and LIM-1 (Fig. 52C.1) (123,208,213).

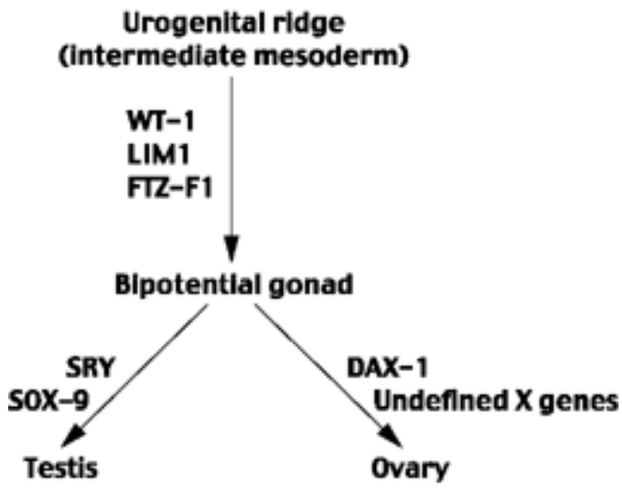

FIGURE 52C.1. Genes involved in gonadal development and gonadal differentiation.

Wilms' Tumor Gene (WT-1)

The best-characterized transcriptional regulatory factor known to be necessary for the development of the bipotential gonad is the Wilms' tumor suppressor gene (WT-1) located at the 11p13 locus. The WT-1 gene is variably expressed during different time points of embryogenesis in various organs. Its expression is mandatory for the development of both the kidney and the gonad. The development of the kidney and the testis arise from two diverse embryonic progenitor tissues: the kidney arises from the ureteral bud and the metanephric blastema, and the testicle and epididymis arise from the primordial germ cells, the germinal epithelium, and the mesonephric duct. The WT-1 gene plays an integral role in the interaction between the various tissue components in organogenesis. In renal development, WT-1 is first manifested in the metanephric blastema and is mandatory for the induction of the ureteral bud from the mesonephric duct. Delayed or diminished WT-1 function early in the development of the kidney is alleged to be responsible for the development of ureteral bud abnormalities or renal agenesis. Later in renal development, activation of the WT-1 gene again appears to be necessary to organize the renal tubules. It is hypothesized that alterations in the function of the WT-1 gene at the latter point of organogenesis will lead to renal dysplasia or renal dysmorphism or induce abnormal mesenchymal epithelial interactions that will result in the production of a Wilms' tumor.

Within the testicle, WT-1 is first expressed within the germinal epithelium and is believed to coordinate the interaction between the germ cells, germinal epithelium, and mesonephric ducts. The absence of WT-1 function early in testicular development is believed to result in testicular agenesis. Disruption of WT-1 function later in organogenesis leads to the development of streak gonads and/or dysgerminomas.

In essence, abnormal WT-1 expression can affect the normal developmental process of the kidney and testicle along with the tumorigenic potential of the organs. In the clinical arena, WT-1 abnormalities have been found to be associated with sporadic cases of Wilms' tumor, WAGR syndrome (Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation) and Deny-Drash syndrome (congenital nephrotic syndrome, Wilms' tumor, and mixed gonadal dysgenesis) (38,111,123,124,147).

Location Chromosome 11p12-13

Location chromosome 11p12-13 (LIM-1) is a transcriptional regulator factor that serves as an intermediary messenger between the developing germinal epithelium and the mesonephric ducts during the organization of the gonad and between the collecting ducts and the renal tubules in the kidney. Homozygous deletions in mammals have been found to result in both renal and gonadal agenesis (123,181).

Fushi-Tarzu Factor –1 and the Regulation of Steroidogenic Factor–1

The main purpose of the Fushi-Tarzu factor–1 (Ftz-F1) gene in gonadal differentiation is to regulate the nuclear hormone receptor called steroidogenic factor–1 (SF-1). A functional SF-1 gene is necessary for the production of müllerian inhibitory factor (MIF) and several of the enzymes used in producing steroid hormones. Ftz-F1 is originally expressed in the urogenital ridge during gonadal development. As gonadal organogenesis continues Ftz-F1 ceases to be expressed within the developing ovary but continues to be expressed within the Sertoli cells of the developing testicle. FTZ-F1 upregulates the production of SF-1 within the Sertoli cells and is responsible for the transcription of the antimüllerian hormone gene, and subsequently, the production of MIF. Latter in embryogenesis,

FTZ-F1 or SF-1 genes become expressed within both the ovary and testis. Inappropriate function of these genes at this time results in the inability of the gonad to maintain gonadal integrity and failure of the gonad to produce the appropriate steroid hormones necessary for sexual differentiation. It is currently hypothesized that a delayed or diminished FTZ-F1 or SF-1 secretion early in organogenesis results in complete gonadal agenesis with the persistence of the müllerian ductal systems. Inadequate secretion of the two transcriptional factors following gonadal development results in the inability of the individual to maintain the gonadal tissue, eventually resulting in the development of streak gonads and inadequate sexual differentiation (123,128,183,208,213).

Genes Affecting Testicular and Ovarian Differentiation

Once the bipotential gonad is formed, the next pivotal occurrence in sexual determination is the presence or absence of a gene located on the short arm of the Y chromosome, termed the *sex-determining region* (SRY). It is the activity of SRY and its interplay with SOX-9 and DAX-1 that determines if the fetus will develop either a testis or an ovary.

Sex-Determining Region of the Y Chromosome—SRY (Testicular Determination)

In the developing fetus, SRY production originates not from the germ cells but rather from the somatic cells of the urogenital ridge. This finding is consistent with the hypothesis that the germ cells are originally bipotential, the sex-specific gonad being determined by the secretion of SRY from the somatic cell lines. Clinically, three important observations have documented that SRY determines whether or not a testicle is formed: (a) The microinjection of the SRY gene into an XX fertilized ovum results in offspring with testes and male external genitalia, (b) 15% to 20% of human XY females have mutations in the SRY gene, and (b) the majority of XX males are found to carry the SRY gene (32,109,123,200).

SOX-9 (Testicular Determination)

The existence of another testicular determining gene in addition to SRY was identified because of the association of congenital skeletal malformations with 46,XY sex reversal. In this syndrome, known as campomelic dysplasia, 46,XY sex reversal is present in three-fourths of the affected males. Genetic evaluations of the sex-reversed males revealed a functional SRY. In an effort to explain how a 46,XY female could develop in the presence of a functional SRY, extensive genetic analyses were performed. The investigations revealed that the affected males have a translocation abnormality involving the SOX-9 gene located on the long arm of chromosome 17 (autosomal sex reversal).

SOX-9 is originally expressed within the urogenital ridge in both sexes before the appearance of SRY. SRY expression upregulates SOX-9 in the male. However, if no SRY is expressed (i.e., a female), SOX-9 is downregulated. It is currently believed that SOX-9 activation plays an integral role in the development of the epididymis and the interaction between the epididymis and the testis. Inadequate or delayed SOX-9 function is alleged to result in testicular dysgenesis. In addition to its role in testicular development, this gene also has been found to play a function in cartilage formation; hence, its diminished or abnormal function results in both skeletal abnormalities (campomelic dysplasia) and 46,XY sex reversal (105,190,205,221).

DAX-1 (Ovarian Determination)

According to classic Jostarian teaching, removal of the testes from a male fetus results in the development of female external and internal genitalia, that is, female phenotype by default. This concept, although true for the phenotypic expression of the individual, is not true for development of the gonads. Indeed, it is currently known that active genetic regulation of at least one gene is required for the development of a fully functional ovary. This finding arose from the investigations of 46,XY females with intact SRY locations. Chromosomal analysis of these patients revealed that duplications of the short (p21) arm of the X chromosome could overwhelm SRY function, resulting in a female gonadal determination and phenotype. The finding that duplicated Xp21 regions resulted in XY sex reversal gave rise to the concept that ovarian development was directly related to the number of copies of this gene, that is, dosage-sensitive sex reversal. Through careful investigation, the short arm of the X chromosome, a gene known as *DAX-1,* was eventually isolated and found to be responsible for ovarian determination. Examinations of the developing gonads reveal that DAX-1 is originally present in the bipotential urogenital ridge and gonads. The products of SRY and DAX-1 competitively compete for a regulatory protein known as the *steroidogenic acute regulatory protein* (StAR), with SRY having a higher affinity for the promoter. (The StAR protein facilitates the movement of cholesterol into the mitochondria for its conversion to pregnenolone—the first step in steroidogenesis.) In the normal male, individual SRY production overpowers the one functional DAX-1 gene, stimulates StAR activity, and subsequently results in testicular organogenesis and increased testosterone production. If two functional DAX-1 genes are present, DAX-1–induced proteins result in StAR downregulation, inhibition of testicular development, and ovarian organogenesis, that is, dosage-sensitive sex reversal (14,19,20,101,141,123,193,195).

Although the DAX-1 gene appears to play the key role in ovarian determination, other downstream X-linked genes appear to be required for complete ovarian development. This discovery arose from investigations of patients with only one functional DAX-1 gene, such as 46,XY males who

are missing a functional SRY locus and patients with Turner's syndrome (45,X). The default gonadal pathway within these individuals is for testicular regression (unsuppressed solitary DAX-1 function) and ovary formation. Investigations of embryos with these deformities reveal that they originally form ovarian tissue; however, complete ovarian formation does not occur and a streak gonad eventually develops. These findings strongly suggest that other still-to-be-identified genes located on the X chromosome are necessary for complete ovarian development (22,42,123,214).

Hormonal Secretion and the Establishment of Sexual Phenotype

The sexual phenotype is chiefly determined by the appropriate hormonal function of the testis (Fig. 52C.2) (101).

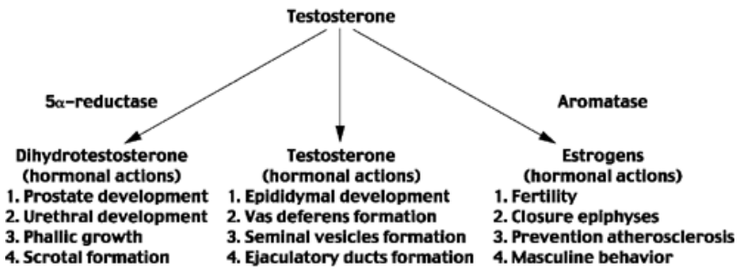

FIGURE 52C.2. Physiologic activities of testosterone in the male. Proper hormonal function determines the sexual phenotype and plays a large role in gender identity.

Müllerian Inhibitory Factor

Sertoli cells secrete MIF in a sexually dimorphic pattern beginning in the seventh week of gestation until puberty. In infants and prepubertal boys, MIF is a highly specific marker of testicular tissue. With puberty, secretion of this hormone by the testis decreases and ovarian production increases, eventually resulting in MIF values that overlap between the two sexes. In males, MIF's downregulation chiefly occurs as a result of androgen secretion. Without appropriate androgen function (e.g., in defects of androgen synthesis or action), postpubertal MIF levels may be elevated persistently because of the increased stimulation of the testicle (Sertoli cells) by elevated levels of gonadotropins [follicle-stimulating hormone (FSH)].

During normal physiologic development, MIF becomes bound to the MIF receptor present on the mesenchymal cells that surround the müllerian ducts. It is believed that MIF causes dissolution of the müllerian ducts by inhibiting the action of various growth factors. The production of MIF and the subsequent activation of its receptor are responsible for the regression of the uterus, fallopian tubes, and upper one-third to two-thirds of the vagina. MIF's secretion and subsequent action is the first hormonal event to occur in the development of the male phenotype. Following its normal activity, the only vestigial müllerian remnants left behind in the male are the appendix testis and the prostatic utricle. The appropriate timing of MIF secretion is critical because the müllerian ducts lose their ability to respond to MIF by the end of the eighth week of gestation.

MIF predominantly acts as a paracrine hormone, that is, a hormone that binds to nearby cells to affect their function. In patients with asymmetric gonadal differentiation (i.e., mixed gonadal dysgenesis) in whom a streak gonad is present on one side or in individuals who have an element of testicular dysgenesis present, the reduced volume of Sertoli cells results in diminished local levels of MIF. Clinically, this becomes manifest with the development of unilateral salpinx or hemiuterus. In essence, the degree of müllerian ductal persistence in intersexual disorders is directly related to the Sertoli cell volume of the ipsilateral testicle and the functional local levels of MIF (23,97,99,114,169,170).

Virilization of the Genital Tract

Virilization of the male fetus results from the activity of testosterone or its 5 α-reduced metabolite dihydrotestosterone. Under most circumstances, testosterone diffuses into the cell via an activity gradient. Inside the cell, it may be bound directly to the androgen receptor reduced by 5α-reductase to the more potent male hormone, dihydrotestosterone, or aromatized to the female hormone, estradiol (Fig. 52C.2).

For a target organ to be virilized, testosterone or dihydrotestosterone must bind to the androgen receptor. Both steroids bind to the same androgen receptor protein; the chief difference between the two is that the receptor's affinity for dihydrotestosterone is four to five times higher than that of testosterone. During embryogenesis, the enzyme 5α-reductase is known to be absent from the proximal wolffian ductal tissues. It is therefore believed that the direct diffusion of testosterone down the lumen of the wolffian ducts is responsible for the stabilization of the epididymis, vas deferens, seminal vesicles, ampullae of the vas deferens, and the ejaculatory ducts. Because of the low levels of testosterone secreted by the fetal testis and its weak affinity for the androgen receptor, testosterone cannot directly

virilize the prostatic and penile urethra, prostate, penis, and scrotum. Formation of these latter masculine structures requires the beneficial support of the 5α-reductase enzyme and its more potent metabolite dihydrotestosterone. As can be determined from this discussion, absence of appropriate androgen receptor function results in resolution of the wolffian ducts and feminization of the external genitalia. In turn, absence of 5α-reductase enzyme results in normal formation of the epididymis, vas deferens, seminal vesicles, and ejaculatory ducts; however, feminization of the external genitalia will be present (57,93,120,136,199,207,217).

Initial Testosterone Secretion: Gestational Weeks 7 to 12

The production of testosterone by the Leydig cells in the seventh to twelfth week of gestation is responsible for the masculinization of the penis. Whether a gonadotropin is responsible for this initial testosterone surge is controversial. For certain, we can state that an elevation in fetal luteinizing hormone (LH) is not the cause for testosterone secretion during this time because fetal LH is not produced until the twelfth gestational week. It is currently debatable whether the placental secretion of human chorionic gonadotropin (hCG) or the autonomous secretion of testosterone by the Leydig cell is responsible for the initial androgen surge. This argument is primarily centered upon whether or not the hCG and LH receptors, necessary prerequisites for gonadotrophic hormones to activate the testis, are absent from the fetal testis during this time interval. This controversy is still unanswered, with some laboratories demonstrating the presence of the gonadotropin receptors in the testis during this time, while others contest their findings.

Whether or not gonadotropins are responsible for this surge is important in understanding the pathophysiology of penile malformations. If gonadotropins do not play a major role in the production of the initial testosterone surge, the etiology of hypospadias and other penile malformations is due to either the delayed autonomous secretion of androgens by the Leydig cells and/or end-organ insensitivity. If, however, placental gonadotropins play a major role in the initial surge of testosterone, either gonadotropin malfunction (inadequate secretion of placental hCG), malfunction of the Leydig cell, or end-organ insensitivity may be responsible for these congenital abnormalities (3,31,34,39,90,119,171,194,220).

Testosterone Secretion After Gestational Week 12 and During the Neonatal Time Period

The fetal hypothalamic and pituitary gland initiate their function during the twelfth week of gestation, reaching neonatal peak values in the twenty-second week. Ironically, fetal serum testosterone reaches its peak in the fourteenth week of gestation and subsequently decreases in concentration. This reduction in fetal testosterone levels occurs despite the presence of an elevated fetal LH. The decline in testosterone is believed to be due to the direct suppressive effects of maternal prolactin and estradiol on testicular steroidogenesis. Between the eighteenth week of gestation and birth, no significant differences in serum testosterone levels are found between the male and female fetus. Fetal LH secretions also will be inhibited by elevated maternal estradiol and will nadir during the thirtieth week of gestation.

In the male infant, a vigorous rise in neonatal testosterone secretion occurs within the first 48 hours after birth. This brief postpartal surge in testosterone secretion is due to the loss of the direct inhibitory control of the maternal estrogen and prolactin on the Leydig cells of the testes; it is not correlated with an increased output of fetal LH. As the maternal estrogens and prolactin continue to decrease in the neonate's serum during the first postnatal week, a surge in LH secretion subsequently occurs. This postpartal LH surge is due to the removal of negative inhibitory effects of maternal estradiol and prolactin on the hypothalamus. The hypothalamus, freed from the effects of the negative feedback, increases the release of hypothalamic gonadotropin-releasing hormone (GnRH). Eventually, this translates into an increase in pituitary secretion of LH and an increase in the testicle's production of testosterone. Neonatal testosterone values usually peak during the second to third month of life. By the sixth month of life, testosterone will fall to sexually indifferent levels, where it will remain until puberty (39,44,90,102,103,142,219).

Feminization of the Genital Tract

According to classic Jostarin teaching, feminization of the internal müllerian ducts and external genitalia is an autonomous process. The evidence for this comes from Jost's classic experiments with gonadectomized male and female fetuses developing entirely along female phenotypes. Although this finding suggests that the female phenotype forms by default, it should be remembered that the female embryo is bathed in a “sea” of female hormones throughout embryogenesis. Unlike aberrant androgen receptor function, defects in the physiologic function of the estrogen receptor until recently were believed to be incompatible with life. Over the past decade, several cases of partial estrogen resistance or aromatase deficiency have been documented to exist. These defects result in normal external male or female phenotypes; however, infertility of both sexes, an increased incidence of coronary atherosclerosis, and increased height are evident among the affected individuals. Although it was once believed that testosterone was responsible for closure of the epiphyses and cessation of skeletal growth, evaluation of patients with estrogen receptor defects have revealed that estrogen both initiates and completes skeletal maturation.

Testosterone acts to close the epiphysis only via its aromatization to estradiol (84,101,110,188,191,197).

Androgen Imprinting

The physiologic purposes of the fetal and neonatal androgen surges are not fully understood. However, experimental studies have discovered that both fetal and neonatal testosterone may act to permanently imprint how an androgen- sensitive organ will respond to testosterone at puberty. In essence, lack of fetal or neonatal androgens at key points during embryogenesis results in a diminished capacity of the androgen-dependent organ to respond to testosterone at adulthood. At this time, fetal and neonatal androgen imprinting is believed to have two major effects: one central activity, related to masculine behaviors and one peripheral activity, related to how androgen-sensitive organs such as the prostate and seminal vesicles will grow in response to androgens in adulthood (13,55,90,148,158,163,203).

INTERSEX AND SEXUALITY

An infant who is born with ambiguous genitalia prompts two major concerns: Which gender role should be assigned? Will the patient's gender identity at maturation match the gender assignment? To assign a gender role, the physician must understand how an infant's gender identity is derived. To provide a basis for this knowledge, we review the impact of steroid hormones, genetic determination, and societal or familial nurturing on the establishment of gender identity.

Sexually Dimorphic Brain Structures

Critical to the understanding of sexuality and brain function is the knowledge that significant sexual differences in brain formation exist between the sexes. These sexually dimorphic areas—the preoptic area, the nucleus of the stria terminalis, the medial nucleus of the amygdala, parts of the cerebral cortex, the corpus callosum, and the main fiber tract connecting the cerebral hemispheres—have increased levels of androgen and estrogen receptors. During embryologic development, these regions possess several specific regulatory mechanisms unique to them. Specifically, the androgen receptor protein is generally considered as an autoregulatory receptor. Studies in the brain, however, have revealed that androgens can upregulate the production of the androgen receptor in the sexually dimorphic areas of the brain in both males and females. Upregulation of the androgen receptor in the developing brain results in a masculine brain configuration. In essence, the presence of androgens, not genetic makeup, appears to have a major impact on brain development in sexually dimorphic areas (71,85,86 and 87,126,132,135,175).

Imprinting of the Brain by Steroid Hormones: Effects on Brain Development and Sexuality

The current concept regarding imprinting the brain by steroid hormones is based on the perception that the human brain is bipotential with regard to sex. Brain development in the male or female direction is determined by the influence of the steroid sex hormones. The basic concept of this hypothesis is that the patient's genetic code determines whether or not testes or ovaries will develop. After gonadal determination occurs, it is the hormonal products of the gonads that establish both the sexual differentiation of the genitalia and the brain. In this theory, the same prenatal and neonatal testosterone surges that cause development of the internal masculine ducts and development of the external genitalia also impose masculinity on the brain. The masculine brain develops under direct hormonal influence, whereas the feminine brain forms in default—similar to the Jostarian theory for development of the müllerian ducts and external female genitalia.

Steroidal hormones have two major effects on the brain and behavior: activational and organizational. Activational influences typically occur in mature animals. They are transient and depend on the rise and fall of hormonal levels. A classic example of this is the waxing and waning of sexual interest in females during different phases of their menstrual cycle. The organizational ability of steroids on brain development is critical to the understanding of gender identification and intersexual disorders. Experimental studies have documented that alterations in the levels of fetal steroid hormones can sexually reverse the dimorphic areas of the brain, change the secretion patterns of gonadotropins, and permanently affect the adult's reproductive and nonreproductive behavior (e.g., aggression, ability to interpret geometric designs). It is noteworthy that the fetal hormonal influence on the organization of sexual behavior is not an all-or-none phenomenon. Male and female characteristics exist on a continuum, with the amount, duration, and timing of fetal and neonatal hormone exposure determining their position on the continuum (86,101,157).

Estrogen Hypothesis (Masculinization of Brain by the Aromatization of Testosterone to Estrogen)

Numerous laboratory studies have found that treatment of female fetal and or neonatal laboratory animals with high levels of estrogens enhances masculine behaviors and impairs feminine responses. Similarly, treatment of male rodents with aromatase inhibitors results in increased feminine traits. Although on the surface, the idea of estrogens enhancing masculine traits appears to be paradoxical, we now know that in the fetal central nervous system, testosterone serves as the primary source for estrogen. Within the

developing fetus, estrogens are tightly bound by α-fetoprotein, making this steroid hormone relatively unavailable to the developing brain. α-Fetoprotein, the chief serum protein in the fetus has less of an affinity for testosterone, allowing free testosterone to readily enter into the cerebrospinal fluid (CSF). Once in the brain, testosterone has two major effects: (a) inducing production of its own receptor in the sexually dimorphic areas of the brain and (b) activating the androgen receptor, which upregulates the production of brain aromatase. Upregulation of brain aromatase in the sexually dimorphic areas of the brain results in the increased production of estradiol within these regions. The increased levels of estradiol are then responsible for developing the anatomic differences in the sexually dimorphic areas of the brain and establishing masculine traits.

It is interesting to note that in testicular feminized animals, testosterone freely enters into the CSF, but because of faulty androgen receptors, no induction of brain aromatase occurs. Failure of the activated androgen receptor to induce brain aromatase results in feminization of the brain. In partial androgen insensitivity syndromes, the development of masculinity is variable, depending on the activity of the androgen receptor (86,126,132,135,175).

Critical Time Periods for Sexual Organization of the Brain by Steroid Hormones

The ability of steroid hormones to affect the organization of the brain appears to have a significant timing variability among different species. The capability of steroids to organize the brain has been found to occur within three different time periods, depending on the species studied. The brains of most species of monkeys and guinea pigs were affected during the prenatal period only. Rats and mice brains were affected during the prenatal, perinatal, and immediate postnatal periods, and hamsters and songbirds brains were affected in the postnatal period only. The ability of steroid hormones to organize the brain in humans is currently unknown. Two major hypotheses exist; the first states that the critical time period for sexual organization in the human occurs only prenatally during gestational weeks 8 to 24. The alternative hypothesis is that both a prenatal and postnatal steroid organizational affect occurs simultaneously, with the peaks of fetal and neonatal androgen secretion, that is, gestational weeks 8 to 24 and postpartum during the first 6 months of life. This latter hypothesis is based on experimental findings in the rhesus macaque monkeys. Within this species, early exposure of female fetuses to androgens resulted in abnormal-appearing external genitalia and more masculine behavior, whereas exposure to androgens later in development or in the early neonatal time span resulted in normal-appearing external genitalia but variable degrees of masculine behavior. Using this hypothesis, various scenarios have been developed in which the timing of hormonal manipulations can produce masculine traits, feminine traits, bisexuality, or asexuality (40,66,67,69,70,117,156).

Steroid Hormones Organizational Effects on Gonadotropin Release

Exposure of the developing brain to steroid hormones determines the pattern of gonadotropin release established at puberty. Specifically, male and female mammals differ in their patterns of gonadotropin release. In females, gonadotropins are released in a cyclic fashion, producing the fluctuations of ovarian hormones associated with the menstrual cycle. In males, gonadotropin release is secreted in a more constant fashion, with some diurnal variation. This results in the production of high, fairly constant levels of testosterone in adulthood. In experiments carried out in rodents (species in which perinatal organization of the brain occurs), the ability to obtain either a cyclic or tonic secretion pattern of gonadotropins appears to be regulated by the levels of testosterone secreted during perinatal life. Inadequate testosterone secretion in male rat pups in the perinatal time span results in the cyclic secretion of gonadotropins in adulthood, with affected adult males being able to support implanted ovaries. Similarly, treatment of female rat pups with testosterone shortly after birth prevents the cyclic release of gonadotropins (66,86).

Effects of Prenatal, Perinatal, and Postnatal Steroids on Reproductive Behavior

In rodents, testicular hormones have a dramatic influence on the development of reproductive behavior in the male and female. When testosterone is administered to female rodent pups (remember rodents are perinatal in brain organization), their reproductive behavior is permanently altered. For example, if the androgenized female pups are given estrogens and progesterones as an adult, they will not demonstrate routine female sexual behavior, that is, lordosis (a posture characterized by an arched back showing receptivity to a male); rather, the androgenized females will demonstrate masculine behavior by mounting receptive females. Similarly in nonandrogenized male pups given androgens as an adult, they will not demonstrate routine male sexual behavior; that is, they will not mount sexually receptive females; rather, the nonandrogenized males will show lordosis and be receptive to males. In keeping with the concept that estrogen secretion plays little if any role in sexuality, female rat pups oophorectomized at birth and given activating doses of estradiol and progesterone as adults, will act as females. If given testosterone, they are no more likely than any normal female to show male behavioral patterns. However, there is some controversy regarding whether the neonatal ovarian secretions enhance the quality of feminine behavior. In any event, it appears as if testosterone,

not estrogens, predominantly determine sexual behavior (69,70).

Although the behavior of animals in response to prenatal, perinatal, and neonatal steroids may be studied in a regulated fashion and conclusions derived from these investigations, it is far more difficult to evaluate the organizational effects of prenatal and postnatal steroids on sexual behavior in humans. This area of clinical investigation is fraught with hazards regarding interpretation of the data. Investigators often have preconceived concepts, the number of cases are small, and the hormonal defect present may be individualistic. Conclusions from human studies should therefore be interpreted with great caution until numerous studies from various authors can confirm similar findings.

When sexual behavior in intersex disorders is evaluated, two specific sexual traits are usually measured: (a) gender identity, the sense the person has of being either male or female and (b) sexual orientation. When the data regarding intersex are interpreted, it is important to note that abnormalities in gender identity normally occur in approximately 1 in 30,000 men and 1 in 100,000 women. The incidence of homosexuality in both males and females without an associated intersex disorder appears to be approximately 5% (8,96).

Information regarding the ability of prenatal and neonatal hormones to influence sexual orientation in the human has largely come from the studies of patients virilized secondary to congenital adrenal hyperplasia and from diethylstilbestrol (DES)-exposed female fetuses. Regarding the ability of excess androgens to affect sexual orientation in women with congenital adrenal hyperplasia, the data are controversial. Two studies, one from the United States and another from Germany, found that these women were more likely to have bisexual or homosexual interests (47,48,145). In contrast, another key study demonstrated that both homosexual and heterosexual interests were reduced in women with congenital adrenal hyperplasia compared to normal controls (224). Interpretation of these papers and the data regarding sexual orientation of women virilized by congenital adrenal hyperplasia is extremely difficult. The success and type of the genital reconstruction procedures were not taken into consideration. (Could the success of the surgical procedures affect sexual orientation?) In addition, the adequacy of hormonal control of the patient often is not stated. Because sexual interest requires appropriate hormonal activation, it is possible that either inadequately suppressed or oversuppressed adrenal function in patients with congenital adrenal hyperplasia could have resulted in alterations in sexual interest.

In an effort to clarify this issue, sexual orientation studies of DES-exposed women have been performed. It is noteworthy that high levels of DES in rodents and rhesus monkeys does not affect the development of the female external genitalia, but they do masculinize the brain (69,70). Evaluation of DES-exposed women regarding their sexual orientation has confirmed an increase in bisexual and homosexual activity, while physical examinations have revealed normal external female genitalia. The findings that DES-treated females have a higher incidence of homosexuality rules out the possibility that abnormalities of the female sexual organs discouraged heterosexual interests and significantly strengthens the conclusions that hormones influence the brain mechanisms involved with sexual orientation (86,138,140).

Scientific evidence also indicates that hormones contribute to the development of gender identity. This concept is predominately supported by data from three different sources: (a) women with virilizing congenital adrenal hyperplasia, (b) males with 5α-reductase deficiency who were raised as females, and (c) male infants raised as females following neonatal penile ablation. In all three scenarios, the fetuses were exposed to high levels of androgens and their brains should subsequently have been masculinized. When evaluating women with virilizing congenital adrenal hyperplasia, most of the patients have a female gender identity; however, the incidence of gender dysmorphia—the patient choosing to switch from a female to a male gender identity—is significantly higher than normal (138,224,225).

Lending further support to the argument that hormones may establish gender identity is the information regarding 5α-reductase patients. Individuals with this enzymatic deficiency are born with a diminutive phallic structure associated with severe penoscrotal hypospadias and bilateral cryptorchidism. However, the brain should be masculinized because testosterone metabolized to estradiol by the enzyme aromatase is responsible for masculinization of the brain. If the neonate is incompletely evaluated at birth, the appearance of the external genitalia is feminine and the infant may be assigned to a female sex and raised as a girl. At puberty, the external genitalia virilize, and in many cases, the patients will preferentially switch to the male gender identity (95). In final support of this hypothesis are the reports of two different infants who had their penis ablated during a circumcision, one at 2 months of age the other at 7 months of age. Both were reassigned to the female gender and surgically repaired to have female-appearing genitalia. The child who had his penis ablated at 2 months of age is currently 26 years old and has accepted a female gender identity. This patient is predominantly sexually attracted to females but has been sexually active with both men and women. She has characterized her own sexual identity as bisexual. With maturation, the patient whose penis was ablated at 7 months of age became unhappy with his female role and underwent phallic construction at 25 years of age. He is now living as a male (26,46,225).

Regarding the ability of steroids to affect the sexual behavior of humans, we would caution the reader that the degree of virilization of the external genitalia at birth does not necessarily correlate with the sexual behavioral outcome and gender identity. Genital formation occurs between

gestational weeks 8 and 12 and is the result of the combined influence of testosterone secretion, 5α-reductase activity, functional androgen receptor, and end-organ responsiveness. In contrast, sexual behavioral outcomes are based on the combination of testosterone secretion, a functional androgen receptor, and brain aromatase activity during gestational weeks 8 to 24, with possible fine tuning of sexual behavior modified by the postpartal androgen surge during the first 6 months of life. Clinical confirmation that external genital size and development are not correlated to sexual behavior can be found in the fact that most genetic females with virilization due to congenital adrenal hyperplasia are assigned to the female gender and reared as girls. When these individuals are evaluated in adulthood, most are pleased with their sexual assignments. Corroborating the fact that genital size and development at birth cannot predict the adult's sexual behavior may be found in genetic males with 5α-reductase deficiency. Individuals with this disorder have hypospadiac micropenis at birth. Even if raised as girls, almost all invariably adopt a male gender role in adulthood as their phallic structure grows in response to testosterone (86,95,225).

Genetic Determination of Sexual Behavior

“We used to think our fate was in our stars. Now we know, in large part our fate is in our genes” (209). The power of new scientific technologies has revolutionized the biologic underpinning of many human traits. Geneticists using linkage studies have reported the location of many genes that can be correlated to human behavior. Locations of genes related to psychiatric illnesses, alcoholism, aggression, and sexual orientation have been published. Indeed, in 1991 Drs. Bailey and Pillard reported on the finding that a substantial genetic component to homosexuality exists. Bolstering this concept was the finding by Dr. Simon LeVay, who noted a relationship between brain structure and homosexuality. Indeed, implicit in these researchers' writings is the argument that homosexuality should be accepted because if an individual's sexual behavior is genetically based, then men or women have little choice over their sexual orientation, a concept called genetic fatalism. Genetic fatalism is the perception that if a behavior is in our biologic codes, it is fixed and unchangeable. This hypothesis is unnerving to some geneticists and physicians because of its similarity to the “eugenics theory” indorsed by the Frankfort Institute of Hereditary and Biology in the 1920s and 1930s. Specifically, at that time, researchers in the United States and Western Europe had discovered that the intelligence quotient (IQ) scores of African Americans and eastern Europeans were lower than standard norms. They subsequently failed to assess the social or educational environment as possible causes for the inferior scores. Instead, they leapt to the conclusion that African Americans and Eastern Europeans were biologically inferior. The Ku Klux Klan and the Nazis used this “scientific finding” as a reason for the persecutions of African Americans in the southern United States and for the termination of the Jews and Eastern Europeans during World War II. Several scientists currently fear that finding a genetic basis for sexual behavior would not lead to an increased acceptance of homosexuality, but rather to the development of a method that could identify and purify the gene pool to prevent its sexual degradation (6,9,10 and 11,72,78,118).

At this time, it is unknown how much of the sexual behavior of an intersex patient could be determined by direct genetic influence. It is hoped that with completion of the human genome project that scientists could establish normal genetic standards for gender identity. If this could be done, comparisons of the genetic code of intersex patients to normal standards for individuals who have accepted a male or female gender could aid the physician in determining sexual assignment. Unfortunately, use of genetic technologies for this purpose strikes at the very heart of scientific fears.

Familial and Societal Impact on Sexuality (the Nurturing Hypothesis)

Psychiatrists have argued for decades whether nature (biologic factors) or nurturing (social factors) will eventually determine an infant's sexuality. How the family and society influence the sexuality of the intersex patient is difficult, if not impossible, to measure. The nurturing hypothesis states that the sexual identity of an individual is largely determined by the parental interpretation of the genitalia's appearance. The parental perception of the child's sexual gender affects how he or she is dressed, hairstyles, and physical activities. Psychosexual development and the establishment of gender identity are therefore based on social contact. Imitation of same-sex specific activities combined by differential reinforcement by the child's parents, siblings, and peers establishes the individual's gender identity. According to this hypothesis, social imprinting overrules the genetic determinants and the fetal/neonatal hormonal milieu the infant was exposed to. At this time, several scientific reports disprove this theory. Although there is little doubt that nurturing plays a role in sexual determination, it is too simplistic to believe that nurturing alone establishes an individual's sexual identity (26,46,52,139,143).

INTERSEXUAL DISORDERS

Evaluation of the Intersex Child

History and Physical Examination

Clinical evaluation of the infant with an intersex disorder begins with a carefully taken historical evaluation. Particular attention is given regarding maternal medications used just before or during pregnancy. A family history should be

obtained with direct inquiry regarding the possible presence of genital defects or infertility in the father, siblings, or other close male relatives.

Physical examination should include observation of the skin for abnormal skin pigmentation. In infants with congenital adrenal hyperplasia, excess adrenocorticotropic hormone (ACTH) secretion may result in increased skin pigmentation of the aureole and external genitalia. Palpation of the abdomen for masses and evaluation of the infant for an imperforate anus or cloacal abnormality are necessary. Indeed, in our experience, approximately 25% of cloacal abnormalities were originally misdiagnosed as an intersex disorder (4). The appearance of the external genitalia should be recorded and, if the parents allow, photographed. Care should be given to note the size and shape of the phallus. A well-developed phallus suggests the presence of circulating high levels of androgens, associated with a functional androgen receptor and 5α-reductase enzyme. The position of the urethral meatus should be recorded. The symmetry of scrotal development is evaluated. Asymmetric scrotal development suggests the presence of functioning testicular tissue on the well-developed side. Palpation for the presence of gonadal tissue is imperative for the initial differential diagnosis. I would caution the reader that appearance of the external genitalia may vary widely in patients with the same condition; therefore, the definitive diagnosis should not be made on physical appearance alone.

Buccal Smear

A buccal smear for the presence of a Barr body (inactive second X chromosome) or fluorescein *in situ* hybridization stains for the presence of a Y chromosome may be performed. We have found these tests to be quick and insightful in the evaluation of infants with suspected congenital adrenal hyperplasia. It is, however, our opinion that the limited results of these tests are insufficient for the complete genetic evaluation of the neonate with an intersex disorder, and in all circumstances, a full karyotype evaluation is necessary.

Karyotype

A karyotype may be available within 24 to 72 hours, depending on the facility. The result of this genetic evaluation along with the physical examination classically is used to classify intersex disorders into its categories (Fig. 52C.3) (5).

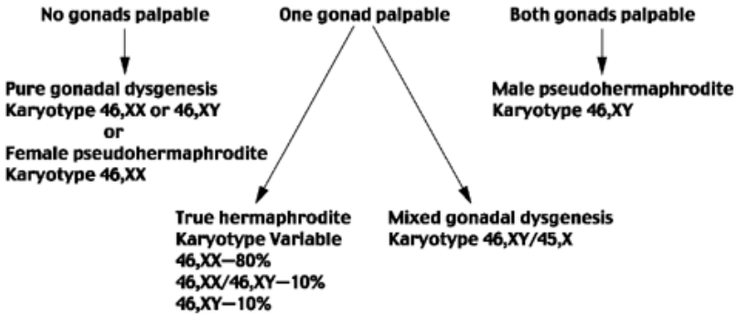

FIGURE 52C.3. Schematic for the initial workup of the infant with an intersex disorder. Schematic for rapid evaluation of an infant with an intersex disorder.

Metabolic Studies

Infants should be evaluated for hypoglycemia, hyponatremia, hyperkalemia, and metabolic acidosis, chemical imbalances that can develop with untreated congenital adrenal hyperplasia. A rapid assay for 17α-hydroxyprogesterone should be performed to rule out 21-hydroxylase deficiency. In addition, a timed urine collection for elevated titers of 17-ketosteroids and pregnanetriol is obtained for completeness. Serum samples from both the infant and the mother for testosterone levels are acquired. The maternal testosterone levels are obtained to rule out exogenous maternal steroid ingestion or the presence of a functional maternal adrenal or ovarian tumor as the cause for virilization of a female infant. The infant's serum testosterone level is evaluated to ascertain testicular function. Male neonatal testosterone levels are rapidly fluctuating during the first 6 months of life; we therefore measure testosterone levels at the time of the initial evaluation and again at 2, 4, and 6 months of age (39,44,90,102,103,142,219).

In 46,XY males with bilateral impalpable gonads, determination of müllerian inhibitory substance (MIS) has been touted to aid in determining if functional testicular tissue is present. Specifically, serum MIS values that are normal (greater than 5 ng/mL) are indicative of testicular function. Low or undetectable levels of MIS suggest either anorchia or

the presence of dysgenetic gonads. Unfortunately, low or undetectable levels of MIS alone are not conclusive enough to diagnose anorchia. In these situations, the physician must proceed with either surgical exploration or laparoscopy to confirm the absence of a dysgenetic testis. Because of the continued need to confirm anorchia by surgical means, measurement of MIS values in our experience does not significantly help the diagnostic investigations of the intersex patient (75,98,115).

Human Chorionic Gonadotropin and Pituitary Functional Evaluations

Some experts believe that hCG stimulation tests and pituitary functional investigations are helpful in infants with nonpalpable gonads who fail to demonstrate the appropriate neonatal rise in testosterone. We do not routinely use these evaluations because of two major concerns: (a) A positive test response only determines the presence of functional testicular tissue and does not adequately define the intersex condition, and (b) a negative response to the initial hCG stimulation test is associated with a 15% false-negative rate; that is, although functioning testicular tissue is present, there is little to no increase in testosterone in response to hCG. (Note: Serum testosterone should rise tenfold in response to the hCG stimulation test. Absence of a tenfold rise is indicative of either absent testes or substrate depletion in the chronically understimulated hypogonadotrophic male.)

Although we do not routinely use the hCG stimulation tests to aid in the diagnosis of the intersex child, we do use an hCG trial to confirm the absence of testicular tissue in true hermaphrodites being raised as females. In this circumstance, we perform the test approximately 1 month after all functional testicular tissue has presumably been removed. To perform the hCG stimulation test, baseline FSH, LH, MIS (helps rule out the presence of functioning testicular tissue), and serum testosterone levels are obtained before hCG stimulation. A dose of hCG is administered at 100 IU/kg (maximum of 1,500 units hCG) every 48 hours for three doses, administered over 3 days (i.e., Monday, Wednesday, and Friday). A serum testosterone is again obtained 12 hours after the third injection. The presence of functioning testicular tissue is documented if there is a tenfold rise in testosterone over the baseline value. If a tenfold rise is absent, a chronic hCG stimulation test may be performed at the physician's discretion. Performance of a chronic hCG trial takes 6 weeks to perform, but it significantly enhances the ability of this test to determine the presence of functional testicular tissue. A chronic trial of hCG is administered at a similar dosage as noted before but is given every fifth day for 6 weeks. A repeat serum testosterone level is taken at the end of the sixth week. A serum testosterone value of less than 200 ng/dL is indicative of the absence of testicular tissue (75,90,98,115,121,172).

Radiographic Studies

The mainstay radiographic studies obtained in evaluating the neonate with intersex disorders are the abdominal and pelvic ultrasound, genitogram, and on occasion, the pelvic magnetic resonance image (MRI). Abdominal and pelvic ultrasonography usually demonstrate müllerian structures lying behind the bladder in most cases of female pseudohermaphroditism, true hermaphrodites, and mixed gonadal dysgenesis. The ultrasound also may be used to assess for the location of the gonads. Unfortunately, in our experience, the ability of ultrasound to detect the presence or location of the gonads has been highly variable. The genitogram, a simultaneous voiding cystourethrogram and vaginogram, is extremely useful in determining the presence of a vagina, the vaginal size and configuration, and the level at which the vagina opens into the urogenital sinus. It is also helpful in confirming the ultrasound findings of a uterus by identifying the presence of a cervical impression within the vaginal vault. On occasion, we have found a pelvic MRI study to be of significant help when we have discordant findings between the ultrasound and genitogram evaluations.

Vaginoscopy and Cystoscopy

Examination of the urogenital sinus is imperative before surgical reconstruction. It allows physicians to confirm the location of the vaginal opening and the presence or absence of a cervix. We often use these procedures to place glide wires and, subsequently, Foley catheters into the vaginal vault and the bladder. Placement of catheters into these structures facilitates their proper identification during the subsequent surgical dissection.

Gonadal Biopsy, Laparoscopy, and Exploratory Laparotomy

The intersexual abnormalities of congenital adrenal hyperplasia and some forms of androgen insensitivity are made by metabolic evaluations; all other intersex disorders require a gonadal biopsy and histologic evaluation of the gonadal tissue for appropriate diagnosis. Palpable gonads may be exposed for biopsy by an inguinal incision, whereas impalpable gonads are approached by either a low Pfannenstiel incision or laparoscopy. In either case, the gonad must be fully exposed. When mobilizing the gonad, the physician must pay attention to the adjacent tissues for either wolffian or müllerian ductal structures. Bilobar or elongated gonads are consistent with either a true hermaphrodite or dysgenetic gonads. If the gonad is bilobar, biopsies must be taken from each lobe. If the gonad is ovoid and homogenous, it is

recommended that the gonad is deeply bivalved, and biopsies should contain both peripheral and central gonadal tissue. This is imperative because ovarian and testicular tissues may overlie one another, causing superficial biopsies to miss the underlying component. Frozen sections of the tissue are evaluated. If dysgenetic tissue is present, we prefer to remove the gonad at this time. If frozen sections reveal both ovarian and testicular tissue, we usually remove the gonadal tissue that is inconsistent with the assignment of the sex of rearing at this setting (1).

CLASSIFICATION OF INTERSEX DISORDERS

Female Pseudohermaphrodites

Female pseudohermaphrodites are characterized by a 46,XX genotype, nonpalpable gonads, (i.e., normal ovaries), and a variable degree of virilization of the external genitalia. Congenital adrenal hyperplasia is the cause of female pseudohermaphroditism in more than 95% of the cases; the remaining virilized female infants are usually due to excess maternal androgens. Two different enzymatic deficiencies are predominantly responsible for the virilizing sexual ambiguity of congenital adrenal hyperplasia, 21-hydroxylase deficiency and 11ß-hydroxylase deficiency. Both are inherited recessive disorders, and genetic counseling of affected families should be obtained (113,212).

Virilizing Congenital Adrenal Hyperplasia: 21-Hydroxylase Deficiency

More than 90% of the cases of congenital adrenal hyperplasia result from 21-hydroxylase deficiency. The enzyme 21-hydroxylase catalyzes the conversion of progesterone and 17α-hydroxyprogesterone to deoxycorticosterone (DOC) and deoxycortisol, respectively (Fig. 52C.4). Enzymatic blockade results in a reduced output of cortisol. Because cortisol negatively feeds back to the pituitary to stop ACTH secretion, loss of cortisol production results in increased ACTH production. In turn, the increased ACTH production drives the adrenal to attempt to make more cortisol. This eventually causes the increase in the concentration of the metabolites above the enzymatic block, particularly, 17-hydroxyprogesterone and 17-hydoxypregnenolone. These latter substances are metabolized to androgens and result in the virilization of the fetus.

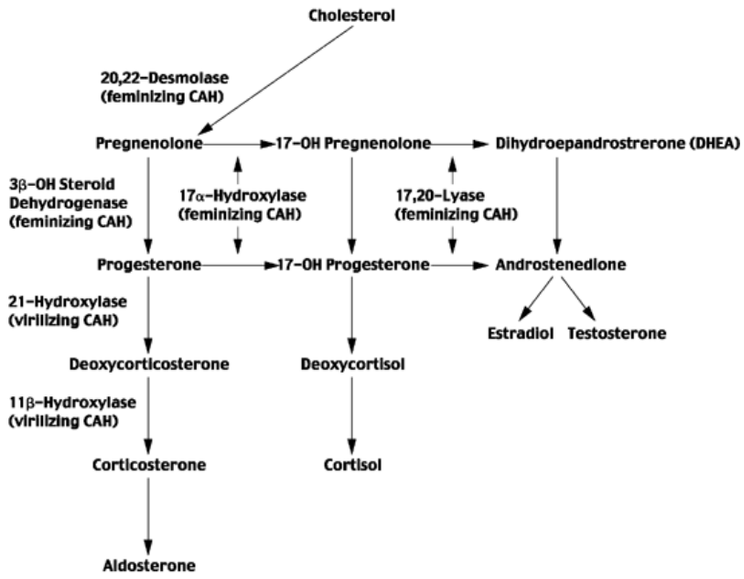

FIGURE 52C.4. Pathway for cortisol synthesis: defects in steroid biosynthesis associated with intersex disorders. Both feminizing (defects in the enzymes: 20,22-desmolase, 3b-OH steroid dehydrogenase, 17a-hydroxlyase and 17,20-lyase) and masculinizing forms of congenital adrenal hyperplasia (defects in the enzymes: 21-hydroxylase and 11b-hydroxlyase) are known to exist.

This hereditary disorder is due to a mutation on the short arm of chromosome 6 that encodes for the 21-hydroxylase enzyme. Three forms of 21-hydroxylase deficiency exist: classic, simple virilizing, and nonclassic disorders. The three disorders are due to variable activity levels of the gene. The classic disorder is defined by the combination of salt wasting and virilization, the simple virilizing disorder is manifested by virilization and no salt wasting, and the nonclassic disorder has normal genital differentiation but becomes manifest by postpubertal virilization. The nonclassic 21-hydroxylase deficiency has a rather high incidence of occurrence with approximately 1% of the population manifesting this genetic abnormality (15,113,218).

The diagnosis of 21-hydroxylase deficiency is suspected in a masculinized infant without palpable gonads. In general, the salt-wasting forms of this disorder are manifested by the most severe virilization of the external genitalia. Pelvic ultrasound documents the presence of a uterus. Chromosomal analysis reveals a 46,XX karyotype. Metabolic evaluations reveal significantly elevated levels of 17-hydroxyprogesterone and adrenal androgens (androstenedione). If assessed, 24-hour urine values for 17-ketosteroids and pregnanetriol are elevated (Fig. 52C.4).

If this disorder goes unrecognized, approximately three-fifths of the affected infants will develop vomiting dehydration, hyperkalemia, and circulatory collapse due to the reduction of aldosterone production within the first 2 weeks of life. In children with the salt-wasting form of this disorder, plasma renin levels are significantly elevated. Measuring the plasma renin to urinary aldosterone ratios is therefore frequently used to monitor adequacy of medical therapy. Elevated ratios are indicative of salt loss and poor medical control. If 21-hydroxylase deficiency is left undiagnosed or is poorly treated, the infants grow rapidly, developing a muscular build with precocious growth of pubic hair and increasing phallic enlargement. Bone age becomes advanced and the epiphyses fuse early. Menstruation and breast development are inhibited (113,122,161,218).

Although the diagnosis is almost invariably made on metabolic evaluation and confirmed by karyotype and radiologic findings, if laparoscopy or surgical exploration is performed, it reveals the presence of only müllerian structures. The wolffian ductal structures having already regressed by the time the adrenal androgens reach high concentrations (113,218).

Virilizing Congenital Adrenal Hyperplasia: 11ß-Hydroxylase Deficiency

Abnormalities in 11ß-hydroxylase activity occur as a result of genetic mutations located on the long arm of chromosome 8. Deficiency in this enzyme accounts for approximately 9% of the individuals with congenital adrenal hyperplasia. Loss of this enzyme's activity results in the accumulation of both 17- hydroxyprogesterone and the salt-retaining metabolites DOC and 11-deoxycortisol. Unlike 21-hydroxylase deficiency, for which the onset of hypovolemic shock is a significant risk, infants affected with 11ß-hydroxylase deficiency are often hypertensive because of mineralocorticoid excess. Hypokalemia, however, may be of significant concern because of the increased mineralocorticoid secretion with resultant potassium wasting. The genital ambiguity of the affected infant is highly variable, depending on the activity of the enzyme. Clinically, poor to no correlation can be found between the degree of virilization, the extent of the patient's hypertension, and hypokalemia. Diagnosis of this enzymatic defect is confirmed by finding high levels of 17-hydroxyprogesterone, DOC, and 11-deoxycortisol (Fig. 52C.4). Plasma renin levels are usually very low because of the excess secretion of mineralocorticoids (113,211,212).

Congenital Adrenal Hyperplasia: Prenatal Diagnosis and Maternal Treatment

In families with a history of congenital adrenal hyperplasia, prenatal therapy with dexamethasone, initiated before the tenth week of gestation, can significantly reduce the risk of female virilization. Ideally, once pregnancy has been confirmed in a family with a positive history of congenital adrenal hyperplasia, the mother is started on dexamethasone 20 µmg/kg given twice daily beginning at the fifth week of gestation. Confirmation that the genetic abnormality for congenital adrenal hyperplasia is present may be performed by two different methods. At 9 to 11 weeks of gestation, chorionic villus samples can be obtained for both karyotype analysis and for the presence of the CYP 21 gene, the gene responsible for the most common type of congenital adrenal hyperplasia, 21-hydroxylase deficiency. An alternative to chorionic villus sampling is to wait to 15 to 18 weeks of gestation and analyze the amniotic fluid for the karyotype, CYP 21 expression and 17-hydroxyprogesterone levels. The latter evaluation is useful for the other forms of congenital adrenal hyperplasia. If the fetus is found to be either a male or if no evidence of congenital adrenal hyperplasia is present, the dexamethasone is discontinued (137,180).

Congenital Adrenal Hyperplasia: Postnatal Treatment

Medical therapy involves treatment with hydrocortisone. This medication replaces the corticosteroid deficiency and prevents overstimulation of the adrenal glands by ACTH. In patients with salt-wasting disorders or in individuals who are found to have elevated renin levels, mineralocorticoid therapy with 9α-fluorohydrocortisone (Florinef) is done to prevent salt wasting and/or hypokalemia. Efficacy of pharmacologic therapy is ascertained by intermittent measurements of serum 17-hyroxyprogesterone, serum renin-to-urinary aldosterone ratios, and serum testosterone. Gender

assignment should always be female. Most physicians advocate early feminizing surgery, including clitoroplasty, feminizing genitoplasty, and vaginoplasty (15,122).

Maternal Medications and Tumors: Effects on Fetal Phenotype

Progesterone is used to prevent abortions in the first trimester of pregnancy, especially following *in vitro* fertilization. Progesterone can effect the developing fetus in various ways. In high concentrations in the female fetus, it can act as a weak androgen by binding to the androgen receptor. In the male infant, it can impair androgen activity by directly interfering with the synthesis of testosterone by the testis, cross-regulate (downregulate) the androgen receptor and competitively inhibit testosterone activity by acting as a substrate for 5α-reductase. In essence, progesterone can virilize a female infant and feminize a male. In the female infant with virilization or the male infant with hypospadias and cryptorchidism, a careful maternal history for the use of progesterone should be ascertained to rule out this cause as a possible etiology for the abnormal phenotype (27,151,159,184).

Maternal tumors, especially luteomas of the ovary, have been associated with virilization of the female fetus. To rule out excess production of androgen by the mother, we obtain a maternal blood sample at the time we evaluate the neonate with an intersex disorder. If a diagnosis of female pseudohermaphroditism is made, we analyze the maternal blood sample for the presence of androgens (129,204).

Male Pseudohermaphrodites

This category of intersex abnormalities is characterized by a 46,XY genotype, normal testes (bilaterally palpable gonads), with either partial or complete failure of the external genitalia to masculinize. The presence of müllerian ductal structures is variable, depending on the cause of the disorder. Male pseudohermaphroditism may occur as a result of a defect in any of the three events required for virilization: androgen synthesis, androgen action, or müllerian ductal regression.

Defects in Androgen Synthesis via the Adrenal Glands and Testicles

Feminizing Congenital Adrenal Hyperplasias: 3ß-Hydroxylase Deficiency, 17α-Hydroxylase/17,20-Lyase Deficiency, and 20,22-Desmolase

Deficiency in any one of the steroidogenic enzymes—3ß-hydroxylase, 17α-hydroxylase/17,20-lyase and 20,22-desmolase—results in the insufficient secretion of both adrenal and gonadal steroids. These disorders occur rarely and frequently are fatal. Because of the locations of the enzymatic blockade, the male infant cannot form the more potent androgens, androstenedione and testosterone (Fig. 52C.4). Affected males have either proximal hypospadias (usually perineal in location, with or without associated cryptorchidism) or complete failure to virilize. Females may exhibit mild clitoromegaly. Females are always assigned to the female gender. Male gender assignment is usually based on the ability of the phallus to enlarge in response to androgens (1,25,149,185,222).

Deficient Androgen Synthesis via the Testis

17ß-Hydroxysteroid Dehydrogenase Deficiency

The enzyme 17ß-hydroxysteroid dehydrogenase is mainly limited to the testis. It serves to catalyze the conversion of androstenedione to the more potent androgen testosterone. Defects in this enzyme are inherited in an autosomal-recessive pattern and are usually seen in Arabs from the Gaza strip. Males with 17ß-hydroxysteroid dehydrogenase (17ß-HSD) deficiency, also known as *17-ketosteroid deficiency,* have a feminine external genitalia associated with a mild to moderate degree of clitoral hypertrophy. The urethra and a blind ending vaginal pouch have separate ostium. Wolffian ductal derivatives are present suggesting that androstenedione is a potent enough androgen to stabilize these structures. The testes may be located anywhere from an intraabdominal position to the labial folds. Diagnosis is made at puberty, when penile growth and the development of male secondary sexual characteristics occur. The virilization that develops at puberty is due to increased levels of serum androstenedione with the conversion of the androstenedione to testosterone by nonmutant 17α-HSD isoenzymes in nontesticular locations. This virilization also is aided by the pubertal increase in activity of 5α-reductase enzymes. Gynecomastia may simultaneously occur within affected individuals at puberty as a result of the peripheral conversion of high levels of androstenedione to estradiol by aromatase. Gender conversion at puberty from the female sex of rearing to a male gender identity is the norm. It is noteworthy that some subjects have undergone clitoroplasty, gonadectomy, and vaginoplasty to the female gender in infancy. Unfortunately, no long-term results regarding their long-term gender identity have been forthcoming. Diagnosis is based on an increased level of serum androstenedione to testosterone in postpubertal patients and or an increase in this ratio following hCG stimulation in prepubertal patients. If identified in the neonate or prepubertal infant, testosterone therapy to enlarge phallic size, reconstruction of the hypospadias, and assignment of the infant to the male sex of rearing is recommended (15,74,94,177).

Leydig Cell Agenesis

Leydig cell agenesis, a rare disorder, is characterized by a male genotype, female levels of testosterone, no response of

the testes to hCG stimulation, and the absence of Leydig cells on testicular biopsy. The clinical appearance of affected individuals is usually that of a feminine external genitalia with mild clitoromegaly with the urethra and a short blind ending vaginal pouch having two separate ostium. On rare occasions, genital ambiguity or micropenis is noted suggesting that Leydig cells once had been present but subsequently disappeared. Testicular position varies from intraabdominal to intralabial in location. Wolffian ductal structures are present and müllerian ductal structures are absent. Most patients present with the complaint of primary amenorrhea in the late teenage years. Diagnosis is made by the combination of karyotype evaluation, endocrine analysis, and testicular biopsy. Patients invariably gender identify as female. Female sex of rearing, orchiectomy, vaginoplasty, and estrogen replacement therapy are standard (142).

Defects in Androgen Action

Complete Androgen Insensitivity

Complete androgen insensitivity (CAIS), also known as *testicular feminization syndrome,* arises either *de novo* in the infant or is inherited in an X-linked recessive pattern. A female phenotype, a male karyotype, and bilateral testes characterize this disorder. The phenotype of individuals with CAIS is so classically feminine that affected individuals are not usually diagnosed at birth. Characteristically, the clinical diagnosis occurs by the finding of a testis within an inguinal hernia, (approximately 2% of all prepubertal females undergoing hernia repair have this disorder) or by the evaluation of amenorrhea at puberty. Physical findings in affected individuals reveal a normal to small clitoris, associated with normal labia and a short, blind-ending vagina. Because various different mutations that may or may not involve the androgen receptor are responsible for this clinical disorder, müllerian and wolffian ductal structures may or may not be present. When completely evaluated, approximately one-third of the affected individuals have either vestigial wolffian or müllerian ductal structures present. Breast development is normal because of the conversion of high plasma testosterone levels to estradiol by the aromatase enzyme. The development of pubic and axillary hair requires androgen activity; subsequently; hair development within these regions is sparse to nonexistent. Testes may be located in the labial, inguinal, or intraabdominal positions. The incidence of malignant tumors developing within the testicles, if left *in situ* after puberty, has been reported to range as high as 10%. Although seminomas predominate as the most common type of tumor within CAIS patients, other nonseminomatous germ cell tumors also have been reported. No prepubertal cases of testicular malignancy in CAIS are known to exist.

The diagnosis of CAIS is based on clinical and family history, endocrinologic evaluation, and characterization of the patient's androgen receptor. In the prepubertal infant with a female phenotype and testis tissue, endocrinologic studies are not very useful and usually reveal normal prepubertal levels of LH, FSH, and testosterone. In this situation, the major concern is misdiagnosing a patient with a 5α-reductase deficiency (male sex of rearing) as having CAIS (female sex of rearing). If the diagnosis is in doubt in the prepubertal patient, genetic sequencing of the patient's 5α-reductase and androgen receptor genes are of significant benefit. Endocrinologic assessment of the untreated postpubertal patient with CAIS classically reveals elevated LH, testosterone, and estradiol levels.

Patients with CAIS characterize their sexual identity as female, apparently because masculinization of the brain requires a functional androgen receptor to upregulate the brain aromatase enzyme. CAIS patients should therefore be raised as female. Gonadectomy is indicated to prevent the development of testicular neoplasia. In the prepubertal patient, we prefer to remove the gonads when the diagnosis is made and initiate estradiol therapy at puberty. This alleviates the concern that the patient could be lost to follow-up and a testicular malignancy could develop before removal of the gonads. Alternatively, one could leave the gonads in place to allow breast development to occur spontaneously with removal of the gonads in the immediate postpuberty time span. In either situation, long-term hormonal therapy is necessary. On occasion, patients may suffer from dyspareunia because of a foreshortened vaginal vault. If this occurs, either an augmentation vaginoplasty using bowel, split-thickness skin grafts (McIndoe procedure), or sequential vaginal dilation may be necessary to enlarge the vagina (1,15,30,59,83,86,88,126,132,135,146,162,175,178).

Partial Androgen Insensitivity

Partial androgen insensitivity presents as a variety of clinical syndromes: Reifenstein, Lub, Gilbert-Dreyfus, and Rosewater. It usually is due to a single base pair mutation in the androgen receptor gene that may arise *de novo* or be inherited as an X-linked or autosomal-recessive trait. Ironically, although the same genetic defect may be present within a family, the phenotypic expression within each affected individual may vary greatly. Indeed, in some families with the same identical gene defect, the phenotypic variability has ranged from complete failure of the fetus to virilize to various degrees of hypospadias. Because of the unpredictability of phenotypic expression with the same point mutation, prenatal and neonatal counseling of affected families is extremely difficult. The clinical spectrum of partial androgen insensitivity can run from mild virilization (mild clitoromegaly, separate urethral and vaginal openings with partial labial fusion) to normal male genitalia, with affected males exhibiting only infertility and gynecomastia at adulthood.

Management of the patient with partial androgen insensitivity syndrome should be tailored to the individual.

Because of the wide variability in phenotypic expression, the sex of rearing is frequently chosen based on the individual's ability to respond to testosterone. We usually recommend a trial of testosterone ethanate in a dose of 2 mg/kg given intramuscularly. The response of the penis to testosterone is evaluated in 3 weeks. If an inadequate growth response is noted, we double the dose of testosterone and reassess in another 3 weeks. If no response is noted to the second dose of testosterone, consideration for gender conversion may be given. In some families, siblings with identical point mutations have been raised successfully as females (failure to virilize, i.e., no phallic growth with testosterone) and other siblings with the identical point mutations have been raised successfully as males (virilized with testosterone). Although a trial of neonatal testosterone injections is still the most common method to determine the sex of rearing in these cases, a few words of caution should be given. In the infant with partial androgen insensitivity, whether phallic growth response to testosterone is durable is controversial; some authors report favorable long-term response, whereas others have not. Further complicating this issue is that some affected individuals with perineal hypospadias and micropenis who were raised as males have not successfully identified to the male gender in adulthood. Hypothetically, the inability of the affected individual to gender identify with males could reflect the fact that partial androgen insensitivity resulted in both the failure of androgens to imprint the brain and in inadequate virilization of the external genitalia (15,19,54,68,73,90,91,116,144,160,168,189,210,216).

5α-Reductase Type 2 Deficiency

5α-Reductase is the enzyme responsible for catalyzing the conversion of testosterone to its fourfold to fivefold more potent metabolite, dihydrotestosterone. Two forms of 5α-reductase exist in humans: type 1 predominates in skin and nongenital tissues, and type 2 predominates in the sexual organs. The type 2 enzyme is responsible for masculinization of the external genitalia and prostate. Defective action of the type 2 enzyme is inherited as an autosomal-recessive disorder and results in a syndrome called pseudovaginal perineal hypospadias. At this time, more than 35 different mutations in the type 2 gene have been identified. The percentage of residual enzyme activity of the mutant gene results in the variations of phenotypic male expression found in this disorder. Classically, affected males have a small penis with severe hypospadias, variable degrees of scrotal development, a urogenital sinus, and separate openings for the urethra and a small, blind-ending vaginal pouch. Testes are usually inguinal or labial in location. In untreated patients, marked virilization occurs at puberty. Postpubertal virilization occurs because of the increasing levels of testosterone and conversion of the elevated testosterone levels to dihydrotestosterone by the nonmutant type 1 gene. Masculinization of the brain appears to be intact with individuals who were misdiagnosed at birth and raised as girls, subsequently changing the gender identity from females to males at puberty. Diagnosis is based on metabolic evaluation with the finding of a high serum testosterone to dihydrotestosterone ratio (normal 14 ± 5 to 1) combined with an abnormal genetic sequencing of the 5α-reductase type 2 gene. Recommended treatment is with genital reconstruction as a male. It should be noted that most of these patients have small phallic structures as an adult despite prepubertal androgen therapy. Despite documentation that some affected individuals can produce sperm, no cases of fertility have ever been reported. The risk of testicular neoplasia within this patient population does not appear to be increased (93,95,160,207,215,217).

Persistent Müllerian Duct Syndrome

In the absence of MIF, müllerian ducts develop to form the uterus, salpinx, and upper one-third to two-thirds of the vagina. Persistent müllerian duct syndrome is usually diagnosed at the time of laparoscopy/orchiopexy for either unilateral or bilateral cryptorchidism. The cryptorchid testicle is typically associated with an inguinal hernia, with the uterus or fallopian tubes found within the hernia sac; consequently, the other clinical name for this syndrome is hernia uterine inguinalis. Besides the presence of hernia uterine inguinale, transverse testicular ectopia is another commonly encountered entity with this disorder. Indeed, when transverse testicular ectopy is found on physical examination, strong consideration for the possible diagnosis of persistent müllerian duct syndrome should be given. Appropriate screening examinations, with a pelvic ultrasound and serum MIF levels, subsequently should be obtained.

In the persistent müllerian duct syndrome, testosterone secretion and response of the gonads to gonadotropins (hCG stimulation test) is within normal limits. This syndrome is therefore never found to be associated with hypospadias. Consequently, the constellation of persistent müllerian ducts and associated hypospadias should rule out this clinical etiology and considerations for another diagnosis should be made.

If the patient with persistent müllerian duct syndrome is seen before puberty, the serum measurement of müllerian inhibitory factor is a useful screening test to define the existing congenital abnormality. In approximately half of these patients, MIF is low or undetectable (MIF negative). These patients usually are found to have a mutation in the MIF gene and subsequently cannot secrete MIF. Analyses of these patients have found that the MIF gene is located on chromosome 19, and defects are inherited in an autosomally recessive pattern. In the remaining patients, serum MIF levels are normal or high (MIF positive), and these patients usually have mutations in their MIF receptor. Chromosomal analysis of these patients reveals a defect in the MIF receptor genes located on chromosome 12. This defect is also inherited in an autosomal-recessive pattern. Identification

of one patient with either disorder should prompt screening of other male siblings with a physical examination. Those with cryptorchidism should undergo further workup with a screening pelvic ultrasound to rule out the presence of this syndrome. The likelihood of coexisting male siblings with this disorder is approximately 25% (33,92,125,170).

Orchiopexy in children with persistent müllerian duct syndrome is no small feat and is usually encountered when a surgeon least expects it. Indeed, the surgeon is usually unaware of the diagnosis until the gonad is found attached to a fallopian tube at the time of surgical exploration. When this phenomenon is encountered in the operating room, a blood sample should be obtained for both karyotype analysis and serum MIF levels. The gonad should be biopsied and replaced along with the herniated müllerian ducts into the pelvis and the hernia closed. Full evaluation of the patient for an intersex disorder subsequently should be performed.

Despite normal testosterone secretion in these patients, the spermatogenic function of patients with persistent müllerian ductal syndrome usually is impaired, with infertility being a frequent occurrence. Whether the infertility is due to primary gonadal dysfunction or is a consequence of testicular undescent is controversial. Because fertility occasionally has been reported within affected individuals, every attempt should be made to place the testicles down into the scrotum. After a 46,XY karyotype and a normal testicular histology are confirmed, a second operative procedure is performed. Experience dictates that if the testicle was palpable before the first operation, then the gonadal vessels are usually long enough to allow for a successful orchiopexy using standard techniques. If, however, the testicle was impalpable, the testicle may be unable to reach the pelvis because of either a shortened gonadal artery or, in most circumstances, entanglement of the vas deferens with the uterus and tubes. If the gonadal vessels are limiting the dissection, a Fowler-Stephens orchiopexy, ligating the gonadal vessels and leaving the fallopian tubes and vasal structures intact, is performed. Hypothetically, it is tempting to excise the persistent müllerian structures, because leaving the müllerian structures *in situ* could predispose to endometrial malignancies, hematuria, and voiding dysfunction. Surprisingly, long-term follow-up of patients with müllerian structures left *in situ* reveals these complications to be extremely rare.

If the uterus and fallopian tubes are limiting the dissection, the fimbriae and distal fallopian tube are left intact and severed from the proximal tube. Note the distal fallopian tube intricately shares blood supply with the gonadal vessels. Injury to the gonadal vessels is common if complete salpingectomy is performed. Unfortunately, in most cases, this maneuver is still not enough to allow the gonad to reach the scrotum. Excision of the uterine fundus is then necessary. During this dissection, the surgeon must be aware that an extreme risk of vasal injury exists. Strong consideration should be given to performing a partial hysterectomy, leaving the myometrium behind where it is attached to the vas.

At this time, the true risk of malignancy in testes associated with persistent müllerian duct syndrome is unknown, with reported ranges varying from 2% to 15%. Because of the unknown risk of neoplasia within these gonads, we believe that any testicle that cannot be lowered into a palpable position should be excised (51,56,104,125,173,201).

True Hermaphrodites

True hermaphroditism is characterized by the presence of both ovaries and testicles. The karyotype and the appearance of the external genitalia vary widely, ranging from an apparent normal male to an apparent normal female with mild clitoral hypertrophy. Most affected patients (approximately 60%) tend to be masculinized with a well-developed phallus with perineal hypospadias and a single urogenital sinus opening. The labial scrotal folds show asymmetry, with one side, usually the right, being well developed with a palpable gonad; a poorly formed contralateral hemiscrotum without a palpable gonad usually is noted. Most cases arise from a sporadic mutation; however, an autosomal-recessive inheritance pattern also is know to exist. The genotypic findings of true hermaphroditism vary depending on the race evaluated. Currently, more than 70% of the recorded cases have a karyotype of 46,XX and have been reported in African Americans. Twenty percent of the cases occur in Caucasians, with the most common karyotype finding being a mosaic configuration of either 46,XX/46,XY or 47,XXX/46,XY. Ten percent of the cases arise in people of Asian inheritance; the most common genotype abnormality found within this racial group is 46,XY. Although one would assume that XX/XY mosaicisms, and SRY mutations and or translocations would be the cause of true hermaphroditism, less than 40% of the total cases are found to have these genetic abnormalities. The finding that approximately 60% of true hermaphrodites lack an SRY gene suggests that other non-SRY locations play a role in the development of the testes in this intersex abnormality.

True hermaphroditism is characterized by the presence of both ovarian and testicular tissue. The most common gonadal composition found is the ovotestis/ovary (35%), bilateral ovotestis (25%), ovary and testis (25%), and ovotestis/testis (15%). The testis is much more likely to be present on the right side. The ability to palpate the gonad is directly related to the extent of testicular tissue present within the gonad. Although ovotestes are usually bilobar in configuration, one lobe being testicular the other ovarian, up to 20% may occur in an oval configuration with one cell type or the other confined to the deep hilar region of the gonad. To rule out the presence of an ovotestis, the bilobar gonad should have each lobe biopsied and the ovoid gonad

should be bivalved and deep biopsies taken. The internal ductal structures are usually appropriate for the type of gonad found—wolffian structures for testes and müllerian structures for ovaries. Indeed, approximately 80% of true hermaphrodites have a rudimentary or fully formed uterus present. In ovotestis, fallopian tubes are predominant, although both ductal structures may be seen. The ovarian histology and function is normal and several pregnancies have been confirmed in true hermaphrodites that were raised as females. In contrast, the testicular tissue is found to have spermatogonia in infancy and early childhood, but the testis almost invariably undergoes fibrosis with maturation. Fertility in true hermaphrodites raised as males is rare.

The diagnosis of true hermaphroditism is usually suggested by either the genotype (mosaic XX/XY) or the findings of müllerian structures in a predominantly virilized neonate. Confirmation of the diagnosis is found by gonadal biopsy combined with laparotomy or laparoscopy. Gonadectomy of the tissue not consistent with sex of rearing should be performed as a neonate. In patients raised as females, remnant testicular tissue left behind will cause virilization at puberty. Verification that all testicular tissue was removed may be ascertained by monitoring serum testosterone after hCG stimulation or by the measurement of MIF secretion. At this time, approximately one-third of true hermaphrodites are raised as males because of extensive virilization of the fetus, an abnormal or absent uterus, or familial desires. If raised as a male, the hypospadias is repaired and all testicular tissue is lowered into the scrotum. Testicular tumors, gonadoblastomas, dysgerminomas, and germ cell tumors will develop in approximately 1% of the patients. In children raised as males, testosterone supplementation at puberty or early adulthood is usually required because of progressive testicular fibrosis. If the infant is raised as a female, clitoroplasty and vaginoplasty are performed. Hormonal supplementation in true hermaphrodites raised as a female is rarely necessary (7,15,24,43,75,76,98,115,206).

True Hermaphroditism and Its Relationship to 46,XX Sex Reversal

Estimated to be present in 1 in 20,000 to 1 in 30,000 men, 46,XX sex reversal is a fairly common abnormality. Of these patients, 90% have a normal-appearing male phenotype and are diagnosed because of complaints of infertility, gynecomastia, or failure of fetal genotype to match the neonatal phenotype. Ten percent of the patients will have hypospadias, micropenis, or genital ambiguity. Translocation of the SRY gene is found in one-third of the cases. The remaining two-thirds are believed to be due to either loss of the testis inhibiting gene (DAX-1) or a gain in the function of a non-SRY testes-determining gene. Several cases of both true hermaphroditism and XX sex reversal have been found to exist within the same family, causing scientists to hypothesize that these disorders are a spectrum of one single genetic defect that could produce either disease. Affected males are shorter than normal because a Y-linked growth gene is absent. Serum testosterone and the response of the testis to hCG are normal during puberty and early adulthood, but they become abnormal with time because of progressive maturational-induced testicular fibrosis. No increase in the risk of testicular malignancy is associated with this disorder. Prepubertal diagnosis is made when genital ambiguity is associated with a 46,XX karyotype. Laboratory studies reveal a neonatal elevation in serum testosterone. Stimulation tests with hCG reveal an appropriate rise in testosterone values. Gonadal exploration and biopsy reveal normal testes. Affected patients should be raised as a male. Testosterone replacement therapy is necessary in adulthood because of progressive fibrotic replacement of the testis (15,108,112,165,167).

Conditions Associated with Dysgenetic Gonads

Gonadal dysgenesis is a spectrum of disorders ranging from complete to partial gonadal dysgenesis. The current clinical and genetic data suggest that these various syndromes are different phenotypic manifestations of a common disease process. Karyotypes may vary from normal 46,XX and 46,XY to a variety of mosaic defects.

Complete Gonadal Dysgenesis

XX Gonadal Dysgenesis or Pure Gonadal Dysgenesis

Patients with XX gonadal dysgenesis classically are diagnosed following a workup of delayed puberty/primary amenorrhea. Affected individuals have a female phenotype, the absence of Turner's stigmata, a 46,XX karyotype, the presence of müllerian ductal structures, and bilateral streak gonads. The condition arises as either a spontaneous mutation or is inherited in an autosomal-recessive manner. Genetic mutations known to cause this disorder include partial deletions of the X chromosome, isolated mutations in the WT-1 gene, and mutations in the FSH receptor. Unlike the patients with 46,XY gonadal dysgenesis, risk for gonadal tumor formation is not increased. Treatment is with hormonal replacement (131,187).

Turner's Syndrome

Turner's syndrome occurs in 1 of every 2,000 female births. This syndrome is characterized by the findings of complete or mosaic X monosomy (45,X or 45,X/46,XX), along with one or more of the characteristic Turner's stigmata of web neck, congenital lymphedema, shield chest, aortic valvular defects, coarctation of the aorta, horseshoe kidney, impaired somatic growth, and absent puberty. “Anti-Turner stigmata genes” are located on the short arm of the Y chromosome and the long arm of the X chromosome. The homologous

genes located on the X chromosome are not subject to X-inactivation. The presence of two active anti-Turner's genes prevents the development of Turner stigmata. In Turner's syndrome in which one X is missing, the haploinsufficiency of the anti-Turner gene results in the expression of Turner stigmata. Pathologic studies of infants with Turner's genotype reveal that ovaries differentiate within the fetus but degenerate to streak gonads with maturation. Pregnancy has been reported in rare individuals with Turner's syndrome because of failure of the ovaries to completely regress. The streak gonads are not at risk for malignant degeneration and are subsequently left *in situ.* Growth hormone therapy is initiated in early childhood, with estrogen therapy begun at late adolescence (187,196,223).

XY Gonadal Dysgenesis (Swyer Syndrome) and Male Turner's Syndrome

Infants with 46,XY gonadal dysgenesis (Swyer syndrome) are characterized by the absence of testicular development despite the presence of the Y chromosome. This intersex disorder is typified by a high risk of the gonads developing a testicular malignancy, up to 60% occurrence, if the patient is not diagnosed until early adulthood. A variety of testicular tumors have been reported, the most common of which is gonadoblastoma; however, dysgerminomas, seminomas, and nonseminomatous germ cell tumors have been reported to occur in approximately 15% of these patients. Classically, gonadoblastomas or dysgerminomas are found in the neonate or infant, whereas the more malignant germ cells are seen in late adolescence to adulthood. Only 20% of patients with 46,XY gonadal dysgenesis have an identifiable genetic mutation. These are usually found to be either a mutation in the SRY gene, a Y chromosomal deletions/translocation, or a mutation in the autosomal genes WT-1 or SOX-9. Occasionally, patients with this disorder have the clinical features of Turner's syndrome, resulting in a clinical entity known as the male Turner's syndrome. This latter disorder is due to a deletion of the short arm of the Y chromosome that encompasses both the SRY region and the anti-Turner gene. Classically, the infant with 46,XY gonadal dysgenesis has a female phenotype. Patients come to clinical attention because either the phenotypic expression of the infant does not match the fetal genotype, a hormonally functioning tumor causes precocious puberty (either estrogen or testosterone secreting gonadal tumors), or there are complaints of delayed onset of puberty/primary amenorrhea. Müllerian ductal structures usually are present (failure of MIF secretion), and wolffian ductal structures are vestigial to absent (lack of testosterone secretion). Endocrine studies reveal female levels of testosterone and no response to hCG. LH and FSH levels are elevated. Karyotype analysis reveals a 46,XY configuration. Surgical exploration reveals streak gonads, a uterus, and fallopian tubes. Because of the high risk of malignancy, gonadectomy should be carried out at the time of diagnosis. Patients should be raised as females and estrogen replacement therapy begun at puberty (60,79,134,179,186,202).

Partial Gonadal Dysgenesis: Mixed Gonadal Dysgenesis

Mixed gonadal dysgenesis bridges the gap between Turner's syndrome (45,X/46,XX and bilateral streak gonads) and testicular dysgenesis (46,XY with bilateral partial testicular dysgenesis). Affected patients usually have a mosaic karyotype of 45,X/46,XY, with one streak gonad and one testicle. Patients with this disorder typically present in one of two fashions: (a) the most common is the infant referred for evaluation with ambiguous external genitalia and one palpable gonad, and (b) the other classic presentation is a prenatal consultation for a mosaic genotype found on amniocentesis or chorionic villus sampling. It is interesting for the physician to note that in the latter circumstance, almost 90% of the infants with a 45,X/46,XY genotype found on fetal evaluation will be born with normal male external genitalia (35,174,176,198). When faced with a prenatal consultation for fetal mosaicism with 45,X/46,XY karyotype, several key points need to be remembered: (a) A normal masculine phenotype will be present in 90% of the affected males. (b) Close follow-up of these individuals has failed to reveal an increased incidence for gonadal malignancy; however, this may just be due to inadequate length of follow-up. (c) As maturation develops the patient is at risk for the development of progressive gonadal dysgenesis, decreased fertility, and low testosterone levels. (d) The most worrisome finding is that approximately 20% of the infants with this genotypic abnormality have either mental retardation or autism (35,192,198).

In individuals with mixed gonadal dysgenesis presenting with ambiguous genitalia, the phenotype usually reveals a penoscrotal or more proximal hypospadias, associated with small phallic size, one palpable gonad, and asymmetric labial scrotal folds with a palpable gonad located either inguinally or within the scrotal fold on the more developed side. Endocrinologic workup reveals elevated levels of testosterone in the newborn. A prompt response to hCG stimulation will be found. MIS expression is variable, but in our experience, it is usually in normal male range.

On surgical exploration, patients are found to have a unilateral salpinx and a rudimentary unicornuate uterus associated with the nonpalpable streak gonad. In addition, as many as one-third of the patients are found to have coexisting rudimentary mesonephric ductal structures, a finding suggesting that at one time testosterone secretion may have been present from the streak gonad. On the contralateral side with the palpable gonad, gonadal biopsy usually reveals either a normal or partially dysgenetic testis. Persistent müllerian structures or partial absence of the mesonephric ducts frequently is associated with the testicle.

This latter finding suggests that abnormal hormonal function of the testis is present. The risk of gonadoblastoma development in the dysgenetic testis or streak is estimated to be 15% to 30%, respectively (179,202). Because of the increased risk of malignancy, all streak gonads or partially dysgenetic testes are removed. The risk of tumors developing in a fully descended testis with a normal histology on biopsy is low but above normal. It is noteworthy that even in the neonatal testis with a normal histology, long-term follow-up will show development of poor Leydig cell function and poor to absent spermatogenesis. Almost invariably, infants with mixed gonadal dysgenesis who are raised as males will have infertility and require the need for supplemental testosterone in adulthood (45,164,198).

In a well-virilized male with the gonad descended into the scrotum, it is our preference to raise these individuals as males. Laparotomy is performed to remove the streak gonad, fallopian tube, and rudimentary uterus in infancy. Gonadal biopsy of the descended gonad is performed to confirm the presence of a normal testis. If the testis is normal, we leave the testis *in situ.* If the testis is partially dysgenetic, we remove the gonad and opt for placement of a testicular prosthesis at a latter point. Reconstruction of the phallus is performed between 8 and 12 months of age. Long-term follow-up of these individuals is mandatory to both assess for the eventual hormonal functional capability of the testis at puberty and to instruct the patient in the importance of self-testicular examination (45,164,198).

In undervirilized patients, rearing as a female is preferred due to the increased risk of gonadal malignancies and the chance of fertility being almost nonexistent. We will usually perform a laparotomy and biopsy both gonads in infancy. If histologic confirmation of a streak gonad and a dysgenetic testis are noted, simultaneous bilateral gonadectomy and feminizing genitoplasty are performed. Hormonal replacement therapy with estrogen will be necessary in late adolescence (28,82,198).

Mixed Gonadal Dysgenesis: Deny-Drash Syndrome

The classic triad of Wilms' tumor, ambiguous genitalia, and progressive glomerulopathy is found in approximately 5% of patients with mixed gonadal dysgenesis and is known as *Deny-Drash syndrome.* Classically, this syndrome is revealed by the presence of hypertension and nephrotic syndrome in an infant with a history of ambiguous genitalia. Renal biopsy usually reveals diffuse mesangial sclerosis. Wilms' tumor development often occurs within the first 2 years of life and is more often bilateral. Genetic evaluations reveal a mutation in the WT-1 gene, with inappropriate activity of the WT-1 gene eventually leading to both renal and gonadal maldevelopment (45,50,124,130).

Partial Gonadal Dysgenesis: Testicular Dysgenesis

Testicular dysgenesis, also known as *dysgenetic male pseudohermaphroditism,* is characterized by ambiguous genitalia that may range from a female phenotype with mild clitoral hypertrophy to a male with hypospadias and bilateral cryptorchidism. The genotype is 46,XY without mosaicism. The testes are partially dysgenetic, resulting in inadequate secretion of MIS and testosterone. Invariably, both müllerian and wolffian ductal structures are present. This disorder can be differentiated from true hermaphroditism by gonadal biopsy. In testicular dysgenesis, gonadal histology reveals disordered seminiferous tubules, a paucity of Leydig cells, and excess stromal tissue. No ovarian tissue is identified. Malignant transformation of the testis into gonadoblastoma or dysgerminoma may occur in up to 30% of individuals if the gonads are left *in situ.* Endocrine testing in the neonate usually reveals testosterone levels to be in the female to low male levels. A blunted response of testosterone to hCG stimulation usually is seen. MIF levels usually are in the female range. Sex of rearing is decided by the degree of virilization present. Irrespective of the sex of rearing, the dysgenetic gonads should be removed as a neonate. If raised as a male, phallic reconstruction is carried out between 9 and 12 months of age. If raised as a female, feminizing genitoplasty and vaginoplasty are performed simultaneously with gonadectomy. Hormonal replacement is initiated in late adolescence (29,100,106).

SURGICAL MANAGEMENT OF INTERSEX

Gender Assignment

The gender assignment of the infant is performed in consultation with pediatric urology, endocrinology, genetics, child psychology, and the informed consent of the parents. Each case should be evaluated individually, and the gender assignment decided on by the infant's degree of virilization, gonadal function, the predicted efficacy of hormonal therapy, and the natural history of the primary intersex abnormality. We believe that early and long-term counseling of the patient and the patient's family with a group of physicians that both the parents and patient may bond with is critical for a successful long-term outcome (2,46,63,64 and 65,133,143,145).

Clitoroplasty

Phallic reduction to form a clitoris is usually performed in the neonatal time period. To initiate this procedure, the adherent prepuce is freed from the glans and a stay suture is placed through it. Depending on the physician preference, a transverse circumcising incision is made either completely

around or three-fourths of the way around the phallus, preserving a 5-mm mucosal collar. (Note: Some surgeons prefer to preserve the ventral cutaneous aspect of the clitoral shaft, similar to preserving the urethral plate in hypospadias. Personally, I find this interferes with the visualization for resection of the subtunical erectile tissue and prefer the complete circumcising incision.) The corpora then are mobilized to their bifurcation, proximal to the pubic bone. Two lateral coporotomies are performed, and the erectile tissue is removed as far proximally and distally as possible. Removal of the cavernosal spongy tissue with preservation of the tunical component allows the physician to preserve innervation to the glans. If bleeding arises from the central corporal arteries, it can be controlled by electrocoagulation or suture ligatures. The glans may be large in caliber and a wedge resection is frequently necessary to achieve a normal clitoral diameter. Because the dorsum of the glans has the most innervation, a wedge resection is taken from the ventral aspect and the glans is reapproximated. Following its reduction, the dorsal portion of the clitoris is secured to the ventral perichondrium of the pubic bone with two subcutaneous sutures, and the ventral portion of the clitoris is secured with two subcutaneous sutures to the residual corporal bodies. As these sutures are tied, the excess empty corporal tunics will accordion upon themselves below the pubic bone. The dorsal phallic skin is cut in the midline in the manner of Byar's flaps. Care is taken not to extend this cut too far dorsally. The slight excess of dorsal phallic skin will serve as a clitoral hood. Extending the incisions on either side of the ventral midline skin carries out a vulvoplasty. These incisions are made caudally in a horseshoe configuration. This allows a ventral U-shaped flap to exist that may be used to simultaneously perform a flap vaginoplasty if necessary (see the following section). The redundant phallic skin is subsequently brought down to form labia minora (Fig. 52C.5) (16,17,18,82,107,166).

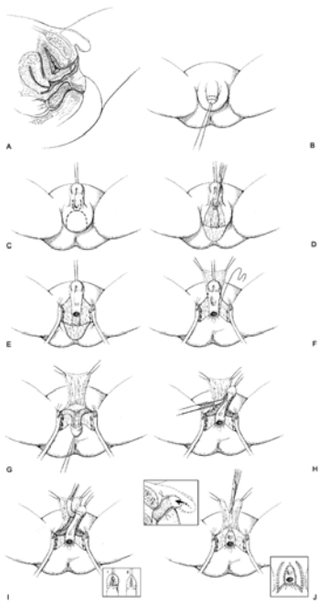

FIGURE 52C.5. Simultaneous clitoroplasty and U-shaped flap vaginoplasty for a low-lying vaginal confluence and an enlarged glans. **A:** Cross section of low-lying vaginal confluence. **B:** Stay suture placed in glans with skin marked for eventual circumcising incision. **C:** Markings for perineal U-shaped flap and preservation of urethral groove. **D:** Incision of urogenital sinus to expose urethral and vaginal openings. **E:** Visualization of urethral and vaginal ostium. **F:** Approximation of U-shaped flap to vaginal vault and extension of ventral urethral incisions into a circumscribing incision to expose corpora. **G:** Dorsal exposure of corpora down to corporal bifurcation. **H:** Incision on lateral aspects of corpora to "shell out" spongy tissue. **I:** Removal of spongy tissue. Alternative incisional markings noted on ventral urethral groove to enhance visibility for corporal dissection. *Inset* reveals ventral glandular wedge removed to reduce size of glans. **J:** Fixation of glans to ventral pubic periosteum and residual corporal bodies. Completion of vulvoplasty.

Low Vaginoplasty

A U-shaped flap or "cut back" vaginoplasty is frequently performed simultaneously with the clitoroplasty for a low-lying vaginal confluence. Before the vaginoplasty, simultaneous cystoscopy and vaginoscopy are performed to assess the position of the vagina with the perineal skin. If this examination confirms a low-lying vagina (i.e., distal to the external sphincter), we place a catheter into the bladder to aid in identification of the urethra and proceed with the operation. A U-shaped flap is dissected free from the urogenital sinus with a combination of sharp and blunt dissection. If this procedure is performed in an adolescent or adult, infiltration of the incision with 1% lidocaine with epinephrine aids the dissection and hemostasis. It is often easier to define the plane between the U-shaped flap and the urogenital sinus on the lateral aspect of the dissection and work medially. Mobilization of the urogenital sinus is performed as far proximally as the surgeon can visualize. Care must be taken not to injure the rectum that lies immediately posterior to the vaginal vault. After adequate mobilization of the vagina, the UG sinus is cut in the ventral midline position. The midline incision into the UG sinus/vagina is then approximated to the apex of the U-shaped flap. Labia minora and majora are created with the dorsal phallic skin as previously described (Fig. 52C.5) (82,150,157).

Midvaginoplasty

If the cystoscopy and vaginoscopy suggest a mid to high vaginal confluence (i.e., at or slightly above the external sphincter), we usually perform the clitoroplasty alone in infancy with plans for vaginal reconstruction deferred until the patient is 2 to 3 years of age. When ready for reconstruction, cystoscopy and vaginoscopy are again performed. In these circumstances, we prefer to place two catheters, one into the bladder and the other into the vagina. Incisions are made to remobilize the labia minora. A U-shaped incision is then made in the perineum and a circumferential incision around the common urogenital sinus is performed. Stay sutures are placed into the UG sinus, and the entire sinus is mobilized. As the urethra is mobilized from the pubis, some dense avascular attachments are usually noted that will need to be sharply divided. By a combination of blunt and sharp dissection, a total of 3 to 4 cm of urogenital sinus can be mobilized easily. Similar to the U-shaped cut back procedure, care should be taken when mobilizing the vaginal vault posteriorly not to injure the rectum. Once the vaginal Foley balloon is easily palpable, a ventral midline incision into the urogenital sinus and vagina is made. The deepest cut into the UG sinus/vagina is then approximated to the apex of the U-shaped flap. The labia minora subsequently are reapproximated (Fig. 52C.6) (127,155).

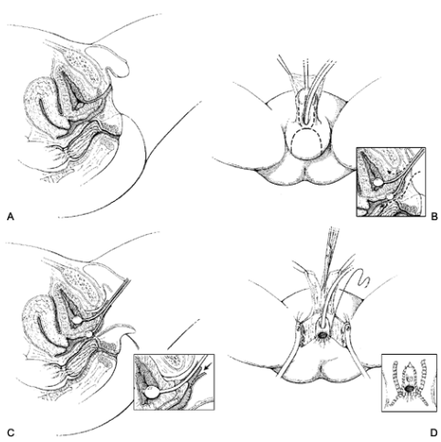

FIGURE 52C.6. Complete urogenital sinus mobilization for a mid-lying vaginal confluence. **A:** Cross section of mid-lying vaginal confluence. **B:** Catheters placed into bladder and vagina, with skin markings for U-shaped perineal incision and circumferential incision around the common urogenital sinus opening. Cross-sectional diagram demonstrating pathway for urogenital sinus mobilization. **C:** Urogenital sinus mobilized for 3 to 4 cm. Ventral incision into urogenital sinus, exposing urethral and vaginal ostium. **D:** Approximation of perineal U-shaped flap to vaginal ostium and completion of labioplasty.

High Vaginoplasty

In patients with adrenal genital syndrome and full phallic masculinization, repair of the vagina can be extremely complex. These patients usually have a long narrow UG sinus, with the vaginal vault opening just below the bladder neck. Although we have repaired these individuals in infancy or early childhood using either the Passerini-Glazel maneuver (creation of vagina via inverted penile skin) or buttock skin flaps, the long-term follow-up of our patients has revealed profound vaginal stenosis to develop at or following puberty. This experience has significantly tempered our enthusiasm for repair of the high urogenital sinus vaginal confluence in infancy and early childhood. At present, in the patients with full masculinization and adrenal genital syndrome, we perform the feminizing genitoplasty

and defer the vaginoplasty until after puberty, usually when the patient is older than 13 years of age. It is noteworthy that in some of these patients, intermittent catheterization of the urogenital sinus may be necessary to prevent recurrent episodes of pyovaginitis before repair. Reconstruction is initiated by placement of a 200-mL tissue expander with a remote access port into both labia. Care is taken to position the expander flat to prevent buckling or displacement during expansion. Three weeks after its placement, expansion is initiated with normal saline. The volume of saline used is determined by the patient's tolerance to the injection. Our goal is for a volume of approximately 100 to 150 mL per expander, with a total volume of 200 to 300 mL. While expansion is occurring, we have the patient limit their physical activity and keep the labial region and inner thighs well lubricated with A and D ointment to prevent the development of skin abrasions. At the time of vaginal reconstruction, cystoscopy and vaginoscopy and placement of catheters over glide wires into the bladder and vagina are the initial steps. Two labial flaps approximately 6 cm in width and 8 to 10 cm in length are raised by incising the expanded labia. Care is taken to verify that the labial margins may be reapproximated without tension and that the integrity of a 2- to 3-cm perineal based vascular pedicle is maintained. The implants are removed preserving the newly developed vascularized sheath around the expander.

A U-shaped perineal incision is made, along with a circumferential incision around the UG sinus. Circumferential dissection of the UG sinus is performed until the balloons within the bladder and vagina can be palpated. If one can easily palpate the separation between both balloons per the perineal incision, the vagina can be dissected free from the common urogenital sinus/urethra. The connection of the urethra to the vagina subsequently is closed in layers to prevent fistula formation. The vagina is further mobilized with a combination of sharp and blunt dissection. When mobilization is complete the vagina is incised at 6 o'clock to prevent a circutarial scar. The labial flaps are rotated medially,

attaching their base to the U-shaped perineal flap, then to the contralateral labial-based flap and eventually attaching the flaps circumferentially to the proximal vagina. A “dog ear” may be present on the medial aspect of the perineal-based labial flap. The epithelium from this dog ear may be removed safely; however, care should be taken to preserve the underlying subcutaneous tissue and the labial skin reapproximated. In our experience, this approach usually can be successfully used to repair the *de novo* high vaginal take off from the urogenital sinus without resultant vaginal strictures developing (Fig. 52C.7). In the patient with a history of surgical failures, separation of the strictured vagina from the urethra may be extremely difficult, if not impossible. In this situation, a Pfannenstiel

incision is made, and the posterior aspect of the bladder is mobilized free from the uterus and vagina. Mobilization of the vagina from the bladder and rectum is performed. In most cases, the combination of vaginal mobilization from the abdominal position along with the perineal flaps developed by the tissue expander is adequate to construct the vagina. Unfortunately we have had patients where the proximal vagina still did not reach the perineal-based flaps. In these circumstances, we have had to resort to interposing a segment of sigmoid colon between the vagina and the labial flaps to prevent recurrent vaginal stenosis (12,21,37,49,58,59,80,82,153,154).

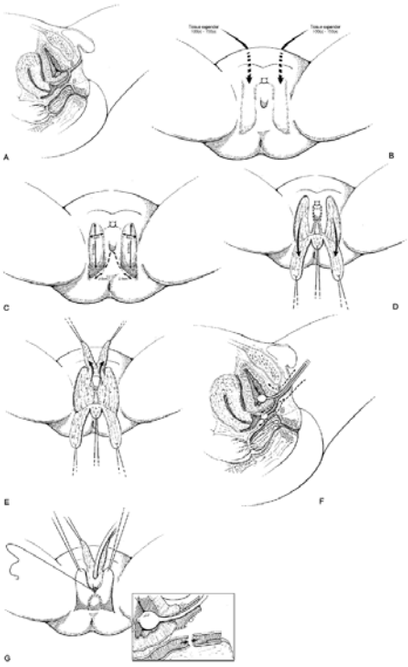

FIGURE 52C.7. Combination of complete urogenital sinus mobilization and labial flap vaginoplasty using tissue expanders for a high-lying vaginal confluence. **A:** Cross section of high-lying vaginal confluence. **B:** Placement of bilateral labial tissue 150-mL capacity expanders. **C:** Outline of labial flaps, base of 2- to 3-cm flap is maintained, flap heights of 8 to 10 cm and 6 cm in width usually can be obtained. Care is taken to verify that the residual labial margins can be reapproximated without undue stress. A U-shaped perineal incision is again made. **D:** Circumscribing incision around urogenital sinus. **E:** Mobilization of medial residual labial tissue for eventual labial reconstruction along with mobilization of labial flaps and U-shaped perineal flap for formal vaginoplasty. **F:** Lateral view of mobilization of urogenital sinus with transection of vagina from urethra. **G:** Formation of distal vagina via combination of perineal-based U-shaped flap and labial tissue. Lateral view demonstrating closed urethral vaginal confluence and anastomosis of proximal vaginal to labial flaps.

Vaginal Agenesis

In children with complete vaginal agenesis, the vagina may be formed with gradual vaginal dilation, skin graft techniques (i.e., a McIndoe procedure) with labial tissue expanders or with bowel vaginoplasty. In our experience, sequential vaginal dilation and skin graft techniques have not been successful in the prepubertal patient because of the need to pursue vigorous self-dilation to maintain vaginal patency. Labial tissue expanders are extremely useful, but to date, these have only been applied to the postpubertal patient. If construction is to be performed in infancy or early childhood, we believe that bowel vaginoplasty, especially using the sigmoid colon, has the best long-term result. In postpubertal patients, the combination of perineal tissue expanders and sigmoid vaginoplasty can produce both an excellent cosmetic appearance and functional vagina (Fig. 52C.8) (15,30,37,41,58,59,81,89,182).

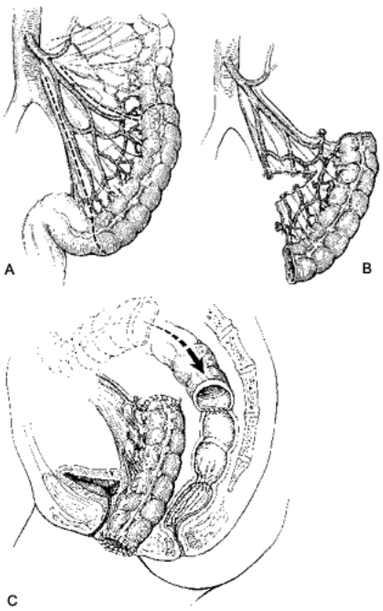

FIGURE 52C.8. Sigmoid vaginoplasty for vaginal agenesis. **A:** A 15- to 20-cm segment of sigmoid colon is chosen for vaginoplasty. **B:** Mobilization of mesentery with preservation of collateral vessels close to colonic wall. **C:** Fixation of colon to perineum and reanastomosis of descending to residual sigmoid colon.

Construction of Male Genitalia

Assignment of the intersex patient to the male gender requires the ability to construct cosmetically acceptable male

external genitalia. If the testes have been removed because of the risk of malignant transformation, scrotoplasty and placement of testicular prosthesis will be required. Phallic reconstruction is a major task. Various techniques have been used, including tubed abdominal flaps with cartilaginous stiffeners or penile prosthesis, rectus abdominis myocutaneous flaps, and more recently, innervated vascularized free graft forearm skin flaps. When using free graft forearm flaps, the radial artery and vein may be anastomosed to either the inferior epigastric artery and vein or, alternatively, to the internal pudendal artery and vein. The lateral cutaneous nerve of the forearm is anastomosed to the pudendal nerve. Although good results have been reported, our own experience with this procedure has been fraught with complications, predominantly urethrocutaneous fistula, poor neural sensation, and erosions of the penile prosthesis. At this time, the surgical results using this technique are still in doubt. Indeed, even if this procedure can be performed successfully, the microsurgical techniques applied are technically difficult and should not be attempted until late adolescence or early adulthood. It is currently unknown what the delay in phallic reconstruction into adulthood will have on psychologic development of the infant/child who will undergo this procedure (36,53,61,62,77,152).

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53

PEDIATRIC ANDROLOGY

Stanley J. Kogan

Faruk Hadziselimovic

Stuart S. Howards

Dale Huff

Howard M. Snyder III

S.J. Kogan: Department of Urology, Weil Medical College of the Cornell University School of Medicine, New York, NY 10021; New York Medical College, Valhalla, NY 10595; Attending Pediatric Urologist, New York Hospital, New York, NY 10021; Westchester Medical Center, Valhalla, NY 10595.

F. Hadziselimovic: Departments of Urology and Physiology, University of Virginia Hospital, Charlottesville, VA 22908.

S.S. Howards: Privat Dozent, University of Basle, Switzerland. Director, Kinder Toges Klinik, Liestal, Switzerland.

D. Huff: Senior Pathologist, Department of Pathology, Children's Hospital of Philadelphia, Philadelphia, PA 19104.

H.M. Snyder, III: Department of Surgery, University of Pennsylvania School of Medicine; Division of Pediatric Urology, Children's Hospital of Philadelphia, Philadelphia, PA 19104.

Contents

THE EMBRYOLOGY AND ENDOCRINOLOGY OF EPIDIDYMAL-TESTICULAR DEVELOPMENT AND DESCENT IN HUMANS

Part of "53 - PEDIATRIC ANDROLOGY "

Since John Hunter's original description, there have been ongoing attempts to establish definitively the mechanisms involved with testicular descent. Many theories have been postulated, beyond the scope of detailed discussion here. These theories include the role of the gubernaculum and epididymis; the changes resulting from the androgen environmental milieu, either directly or indirectly mediated through the spinal nucleus of the genitofemoral nerve innervating the gubernaculum; the role of estrogens and müllerian-inhibiting substance (MIS); and the effects of abdominal pressure and differential body growth on the descending testis. Cryptorchidism is a heterogenous disorder

with a variety of causes. Furthermore, knowledge of the normal embryology is essential to understand the changes involved with abnormal testicular descent (Fig. 53.1).

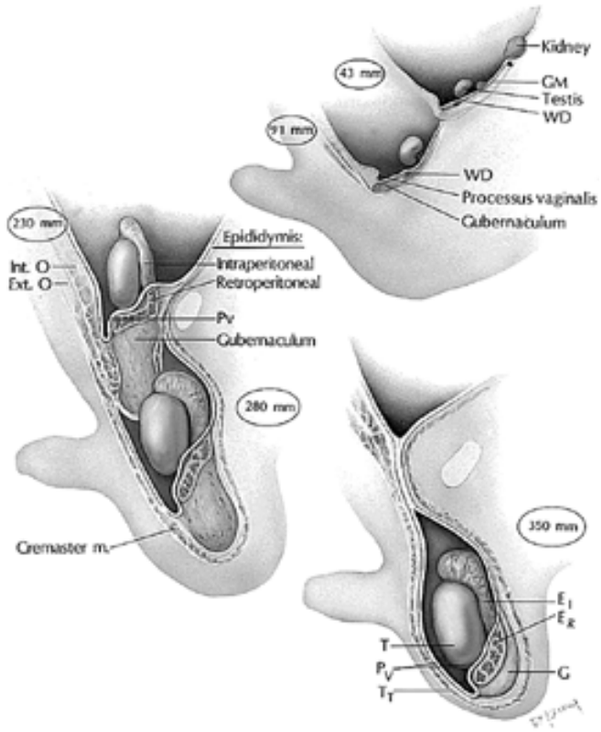

FIGURE 53.1. Testicular descent in humans. The wolffian duct *(WD)* differentiates into the epididymis, which is clearly recognizable at a 230-mm crown-rump length. The gubernaculum never herniates through the abdominal wall. El, intraperitoneal section of epididymis; ER, extraperitoneal section of epididymis; Ext. 0, external oblique; GM, gubernaculum; Int. 0, internal oblique abdominal muscle; Pv, processus vaginalis; T, testis; TT, tunica dartos.

The Bipotential Period

The Fourth Postfertilization Week: Mesonephric Body, Mesonephric Duct, and Attachment of the Future Tail of the Epididymis to the Embyronic Inguinal Region

Sexual differentiation begins as part of blastogenesis during the fourth postovulatory week. Blastogenesis is the process by which the blueprint of the basic body plan is laid down in successive craniocaudal waves of differentiation, growth, degeneration, resorption, and remodeling (207). This process is under the control of homeobox genes.

The onset of sexual differentiation is marked by the appearance of the paired mesonephric bodies and mesonephric ducts—the embryonic precursors of the gonads and male ductal system, respectively. By postfertilization day 22, the mesonephric bodies begin to differentiate from within the nephrogenic cord of the intermediate mesoderm in the cervical region. Their caudal growth and differentiation proceed with that of the somites and follow the dorsal caudal curve of the embryo. By day 28, their distal ends reach the midlumbar region in the caudal curl of the embryo simultaneously with the appearance of the midlumbar somites (64,242,261). By day 24, the mesonephric ducts appear at the posterolateral borders of the mesonephric bodies in the cervical region in direct contact with the ectodermal ring of the surface ectoderm (128,210). The mesonephric ducts remain in contact with the ectodermal ring during their caudal growth, which is more rapid than that of the mesonephric bodies and somites. By day 26, the mesonephric ducts have grown around the distal ends of the mesonephric bodies in contact with the ectodermal ring of the future embryonic inguinal region and genital swellings and have turned medially, losing contact with the surface ectoderm, to reach the lateral walls of the cloaca to which they fuse (208,209,211).

That segment of the mesonephric duct that curves around the distal end of the mesonephric body is referred to as the *first curve* of the duct (64,242). It will become the tail of the epididymis and remains attached to the anterior wall of the caudal curl in the future inguinal region of the embryo. At this point, the gubernaculum and inguinal canal will develop in the next 2 weeks (6). The segment of the mesonephric duct cranial to the first curve will become the head and body of the epididymis. The segment distal to the first curve will become the vas deferens. The mesonephric bodies will degenerate and be replaced by the bipotential gonads.

By the end of the fourth week, the blueprint for gonadal and gubernacular development is complete. The embryonic anlage and relationships necessary for epididymal-testicular descent are in place. An intimate ectodermal-mesodermal association between the ectodermal ring and the future tail of the epididymis in the inguinal area and genital swelling is present (210). The observation that the future tail of the epididymis and the future lower pole of the testis are attached to the future internal inguinal ring in the anterior abdominal wall provides extremely strong evidence against the theory of transabdominal testicular descent at a later developmental period in humans (64,211,284).

The Fifth Through Seventh Postfertilization Weeks: Development of the Gonad, Gubernaculum, Abdominal Wall, and Paramesonephric Duct

Proliferation and migration of primordial germ cells from the yolk sac into the ventromedial surface of the mesonephric bodies begins in the fourth week. These processes accelerate during the fifth and sixth weeks, forming the bipotential gonad. The enlarging gonad replaces the regressing mesonephric body by the end of the sixth week (128,211,279).

Undifferentiated lateral plate mesoderm grows between

the mesonephric duct and the surface ectoderm in a craniocaudal direction during the fourth week. During the fifth and sixth weeks, the abdominal muscles, the cremaster muscle, and aponeuroses gradually differentiate within this mesenchyme. At the same time, the gubernaculum appears as a column of mesenchyme within the developing abdominal wall at the point of attachment of the first curve of the mesonephric duct to the anterior wall of the caudal curl referred to earlier. The gubernaculum protrudes into the abdomen, and its tip is attached to the first curve of the mesonephric duct (i.e., the future tail of the epididymis). A wisp of mesenchyme, the scrotal ligament, extends from the distal end of the gubernaculum to the dermis of the genital swelling. The gonadal ligament attaches the lower pole of the gonad to the first curve of the epididymis at the site of the gubernacular attachment. The muscles of the abdominal wall and the gubernaculum differentiate simultaneously. The muscles and aponeuroses develop around the gubernaculum, forming the inguinal canal and the internal and external rings. These structures are recognized histologically by the end of the seventh week and continue to mature for the next few weeks (6,64,170).

During the sixth week, the paramesonephric duct differentiates along the lateral border of the mesonephric duct. It crosses medially ventral to the first curve of the mesonephric duct and comes to lie medial to the mesonephric duct in the pelvis. At their point of crossing at the first curve of the mesonephric duct, both ducts are attached to the gubernaculum below and to the gonadal ligament above (64,128,211).

By the end of the seventh postfertilization week, the bipotential organogenesis of the gonad, mesonephric duct, abdominal wall, and gubernaculum is complete. Development of the paramesonephric duct has begun but will not be complete until the end of the eighth week. The anatomy is identical in male and female embryos. The first curve of the mesonephric duct and the developing paramesonephric duct are attached to the lower pole of the gonad by the gonadal ligament above and below to the gubernaculum in the internal ring. The gubernaculum fills the inguinal canal. Its caudal extension, the scrotal ligament, fuses with the dermis of the labial-scrotal fold. The presence of the lower pole of the gonad and the future tail of the epididymis at the internal ring even before the seventh week excludes transabdominal descent in humans (64,211). The embryo is ready for male sexual differentiation.

Male Sexual Differentiation

The Seventh and Eighth Postfertilization Weeks: Testicular Differentiation

Continued development of the structures necessary for epididymal-testicular descent depends on testicular differentiation, which begins during the end of the sixth week under the influence of the testicular-determining factor or the sex-determining region on the Y chromosome. The bipotential gonad is remodeled into an oval, smooth-surfaced testis covered by a tunica albuginea. Testicular cords containing Sertoli cells appear, and primordial germ cells migrate into the cords and differentiate into gonocytes. Rising levels of human chorionic gonadotropins (hCG) stimulate the differentiation and maturation of fetal Leydig cells. Histologic testicular differentiation is complete by the end of the eighth week, and testicular endocrinologic function begins with production of MIS by Sertoli cells and testosterone by fetal Leydig cells (128,211,266).

The Ninth Through Twelfth Postfertilization Weeks: Masculinization of the Gonadal Ducts and External Genitalia and the Appearance of the Processus Vaginalis

Testicular production of MIS and testosterone causes masculinization of the gonadal ducts and external genitalia. Rising local levels of MIS in the ninth week initiate regression of the paramesonephric duct. Resorption begins at the point where the paramesonephric duct crosses ventral to the first curve of the mesonephric duct and proceeds in cranial and caudal directions (128). With the disappearance of the paramesonephric duct in the tenth week, the anatomic attachment of the junction of the lower pole of the testis, first curve of the mesonephric duct, and the gubernaculum to the upper midline of the pelvis is lost. Simultaneously, local testosterone stimulates differentiation of the mesonephric duct into the male ductal system. The first curve of the mesonephric duct becomes the tail of the epididymis. The segment of the duct cranial to the first curve becomes the head and body of the epididymis. The segment distal to the first curve becomes the vas deferens. Fusion of the testicular and epididymal ducts does not occur until midpregnancy, and epididymal maturation continues throughout fetal life (101). Systemic testosterone induces masculinization of the external genitalia, which is completed by the end of the twelfth postfertilization week (128,254). The processus vaginalis appears as a dimplelike invagination of peritoneum into the inguinal canal ventromedial to the gubernaculum (101). At the end of the twelfth postfertilization week, the lower pole of the testis and the tail of the epididymis are attached to the bipotential gubernaculum and lie in the internal ring. Before inguinal-scrotal descent can occur, the gubernaculum must be masculinized.

The Thirteenth Through Twentieth Postfertilization Weeks: Maturation of Gonocytes and Gubernacular Swelling

During the thirteenth week, the level of hCG, the number of fetal Leydig cells, and the level of testosterone are at their highest levels noted during fetal life. The high level of testosterone stimulates gonocytes to begin differentiation into fetal spermatogonia (62). The gubernaculum, which

has been a thin cord, begins to swell by accumulation of water and hyaluronic acid and attains a diameter equal to that of the testis (6,101,121,170). The control mechanisms of gubernacular swelling are not well described. The details of the changing histology of the gubernaculum with increasing gestational age are not documented. By 19 weeks postfertilization age (21 menstrual weeks), the stage is set for inguinal-scrotal descent.

The Twenty-first Through the Fortieth Menstrual Week: Final Masculinization of the Caudal End of the Fetus and Inguinal-scrotal Descent

Final masculinization of the caudal end of the fetus is part of inguinal-scrotal descent and includes scrotal enlargement, growth of the three layers of the abdominal wall (including the cremaster muscle) and the processus vaginalis into the scrotum, and elongation of the spermatic vessels and vas deferens. Following or simultaneous with these events, the testicular-epididymal-gubernacular unit descends rapidly from the internal ring through the inguinal canal and into the scrotum (6,101). Autopsy and prenatal ultrasound studies of the timing of descent show remarkably similar results. Descent is complete in a few fetuses by 21 weeks; in 30% by 25 weeks; in 75% by 28 weeks; in 95% by 32 weeks; and in 98% to 99% by 40 weeks (3,109). Some consider failure of descent by 28 weeks to be abnormal. Failure of descent by 40 weeks can reasonably be considered as abnormal even if descent occurs during the first year of life. Failure of epididymal-testicular descent is a congenital malformation, and its causes are prenatal in origin.

The mechanical forces responsible for descent are poorly understood. Gubernacular motility, gubernacular contraction, gubernacular resorption, cremaster contraction, epididymal development and contraction, increased intraabdominal pressure, and normal skeletal muscle function have all been implicated. Normal development of all the embryologic structures described earlier, including masculinization of the caudal end of the embryo, is a prerequisite for descent. The endocrinologic and molecular control mechanisms responsible for the development of those embryologic structures and for the initiation and completion of descent are also poorly understood. Androgens, calcitonin gene–related peptide mediated through the genitofemoral nerve and nucleus, MIS, and Hox genes have all been implicated as molecular controls for descent. Hypoplasia of germ cells noted in undescended testes from the last trimester of pregnancy (47) supports the view that androgens play an important role in the control of descent. This supports the rationale for the hormonal treatment to induce descent (as discussed later). The theories concerning the mechanical forces and control mechanisms involved stimulate controversy and are the subjects of numerous reviews (101,108,121). Much of the data is derived from animal models and may not apply to humans. More anatomic, endocrinologic, and molecular data in humans are needed to fully understand the complex process of inguinal-scrotal descent of the testicular-epididymal-gubernacular unit.

Endocrinology and Histology of Germ Cell Development

The development of testicular histology and endocrine function begins during the seventh postfertilization week, continues into adulthood, and is characterized by five brief dramatic spurts of activity, or steps in maturation, separated by longer intervening periods of less dramatic activity. The five steps in maturation occur in the seventh postfertilization week, the thirteenth postfertilization week, the second postnatal month, and the fifth postnatal year, and then at puberty. The two prenatal landmarks are intimately related to the embryologic steps described previously; refer to the preceding sections for references. Each landmark is a major step in germ cell maturation. The first is initiated by testicular determining factor or the sex-determining region of the Y chromosome. Each of the remaining steps are initiated by a preceding surge in the level of gonadotropin, number and maturation of Leydig cells, and level of testosterone. Each step is accompanied by a step in maturation of Sertoli cells.

The maturation of germ cells is depicted in Fig. 53.2 . The histologic and hormonal features of the steps in maturation

are shown in Fig. 53.3 . The total germ cell count (the number of all germ cells of all subtypes) is an important indicator of the health of the testis and is often expressed as the number of germ cells per tubule. Figure 53.4 shows the normal number of germ cells per tubule by postnatal age. The differential count tabulates the number of each subtype individually.

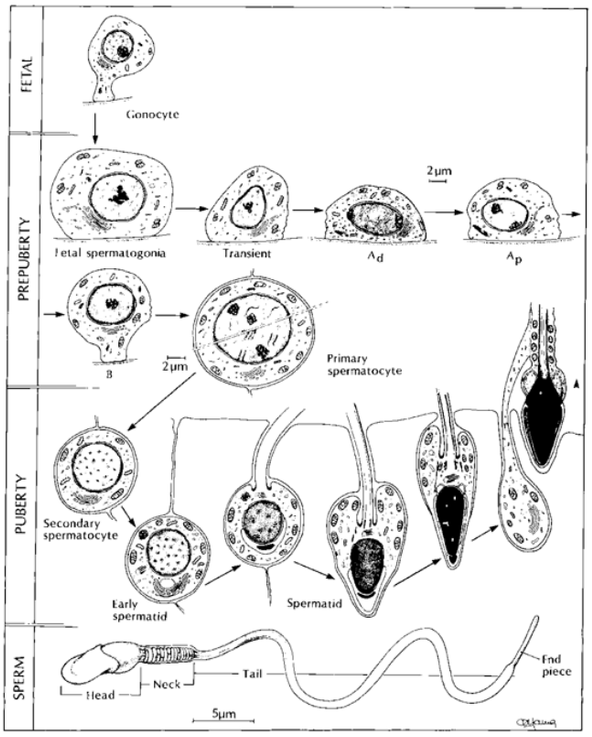

FIGURE 53.2. Development and differentiation of germ cells from fetal life until puberty.

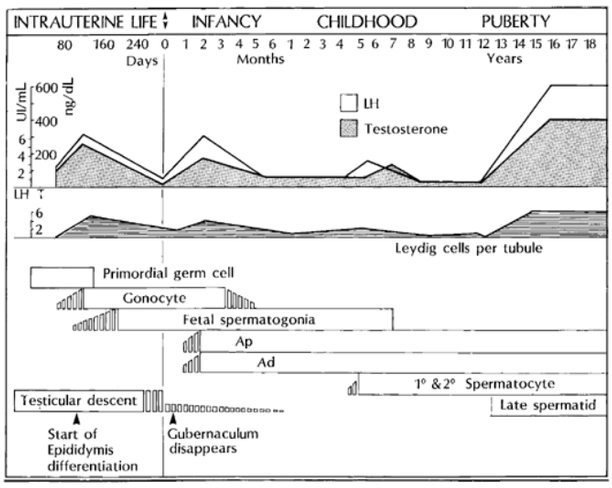

FIGURE 53.3. Testicular development. Luteinizing hormone *(LH)* and testosterone in relation to age. The five steps in maturation can be recognized at less than 60 postfertilization days, 990 postfertilization days, 2 months postnatal age, 5 years, and 12 years, respectively.

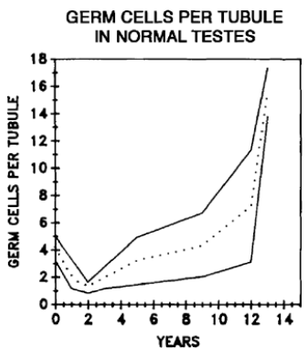

FIGURE 53.4. Germ cells per tubule in normal testes. (*Dotted line* is mean, ±1 SD.)

First Step in Maturation, Seventh Postfertilization Week: Development and Expansion of the Fetal Stem Cell Pool (Gonocytes)

During the differentiation of the bipotential gonad into the testis, under the control of the sex-determining region of the Y chromosome, primordial germ cells enter the emerging testicular cords and differentiate into gonocytes. The gonocytes constitute the fetal stem cell pool of germ cells. They lie in the centers of the testicular cords. hCG stimulates fetal Leydig cell development, proliferation, and testosterone secretion. Gonocyte proliferation expands the fetal stem cell pool. Simultaneously, fetal Sertoli cells differentiate and secrete MIS. Masculinization of the mesonephric duct, paramesonephric duct, and external genitalia begins.

Second Step in Maturation, Thirteenth Postfertilization Week: Gonocytes Begin Maturation into Fetal Spermatogonia

The level of hCG, number of fetal Leydig cells, and the level of testosterone reach their peaks. Gonocytes, the fetal stem cell pool, begin to migrate to the basement membranes of the seminiferous tubules and differentiate into fetal spermatogonia. As stem cells, the gonocytes simultaneously replenish their own numbers. Masculinization of the external genitalia and resorption of the paramesonephric duct are complete by 13 weeks. Masculinization of the mesonephric duct into epididymis continues. Masculinization, or "swelling," of the gubernaculum begins. The differentiation of fetal spermatogonia continues throughout fetal life.

Third Step, Second Postnatal Month: Disappearance of the Fetal Stem Cell Pool (Gonocytes), Development of the Adult Stem Cell Pool (Adult Dark Spermatogonia), and Reduction in Numbers of Germ Cells

At 2 months postnatal age, the seminiferous tubules contain numerous germ cells. Approximately 50% of the germ cells are gonocytes; the rest are fetal spermatogonia (89). At this time, a surge in levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) stimulates proliferation of fetal Leydig cells. The activated fetal Leydig cells produce a surge in the level of testosterone, which then triggers the transformation of gonocytes (70,71,278). Only a minority of gonocytes differentiate into adult dark spermatogonia; the majority undergo apoptosis and disappear. As a result of this change, gonocytes constituting the fetal stem cell pool are replaced by adult dark spermatogonia, constituting the adult stem cell pool (41). The total number of germ cells falls because of the death of most gonocytes. The transformation and disappearance of gonocytes is normally complete by 6 months of age. Then the level of gonadotropins falls. Fetal Leydig cells regress into inactive juvenile Leydig cells. The level of testosterone falls. The adult stem cell pool expands while some adult dark spermatogonia mature into adult pale spermatogonia. Fetal spermatogonia begin to disappear. Fetal Sertoli cells mature into type Sa Sertoli cells.

The histology of the testis is fundamentally changed (Fig. 53.5). Before the event, histologic sections show large numbers of activated fetal Leydig cells and seminiferous tubules filled with large numbers of germ cells with many gonocytes and no adult dark spermatogonia (94,99). After the event, only a few small juvenile Leydig cells remain; the seminiferous tubules contain only a few germ cells with no gonocytes and increasing numbers of adult dark spermatogonia (89,118). This transformation of the fetal stem cell pool into the adult stem cell pool is a prerequisite for future maturation of the testis.

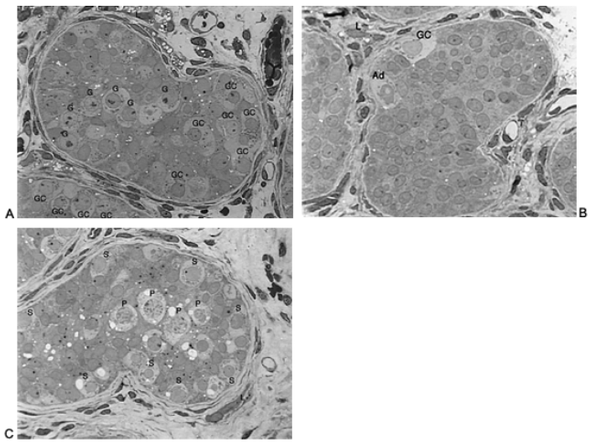

FIGURE 53.5. Normal testicular histology. **A:** Before maturation of gonocytes into adult dark spermatogonia at 2 months of age. Large fetal Leydig cells *(L);* tubule filled with numerous germ cells *(GC),* including gonocytes *(G);* no adult dark spermatogonia. **B:** After maturation of gonocytes at 1 year age. Small juvenile Leydig cells *(L);* tubule with few germ cells *(GC),* including adult dark spermatogonia *(Ad);* no gonocytes. **C:** After onset of meiosis at age 5 years. Large juvenile Leydig cells *(L);* tubule containing spermatogonia *(Sp);* and primary spermatocytes *(P)* in the center of the tubule.

Fourth Step, The Fifth Postnatal Year: Onset of Meiosis

At 5 years of age, simultaneous transient peaks are seen in urinary LH (268), number and size of juvenile Leydig cells, and level of testosterone. The increased testosterone stimulates an increase in the number of total germ cells and of adult dark spermatogonia and triggers the maturation of the mitotic adult spermatogonia into primary spermatocytes, which are germ cells in the prophase of the first meiotic division. Sa Sertoli cells mature into Sb Sertoli cells (101). The onset of meiosis at age 5 years, a process of fundamental importance, is often overlooked.

The concept that the prepubertal testis is quiescent is erroneous. The adult stem cell pool is established at 2 months of age, and meiosis is initiated at 5 years of age. Final germ cell maturation at puberty depends on completion of these two prepubertal developmental landmarks.

Fifth Step, Puberty: Complete Spermiogenesis

The pubertal surge in LH and FSH stimulates the inactive juvenile Leydig cells to proliferate and mature into adult Leydig cells. Activated adult Leydig cells produce the massive pubertal surge in testosterone, which triggers rapid proliferation of germ cells; final maturation to secondary spermatocytes, early spermatids, late spermatids, and sperm; and final maturation of Sertoli cells from Sb to Sc forms. Complete spermiogenesis is seen in most boys by the age of 13 to 15 years. These maturational steps demonstrate the principle that rising levels of gonadotropins stimulate proliferation and maturation of Leydig cells, rising testosterone levels, and proliferation and maturation of germ cells and Sertoli cells.

CONGENITAL AND ACQUIRED SCROTAL ABNORMALITIES

Part of "53 - PEDIATRIC ANDROLOGY "

Congenital Developmental Anomalies

The paired genital swellings on each side of the genital tubercle give rise to the future scrotum, which is initially filled with a compact undifferentiated mesenchymal ground substance before the testis descends. Congenital scrotal anomalies occur when normal posterocaudal migration of the paired labioscrotal folds is impaired. This occurs in intersex conditions, severe hypospadias, cloacal exstrophy, and tail anomalies of the embryo, and sometimes occur as an isolated defect. These instances suggest that both hormonal and mechanical influences may affect scrotal development.

Scrotal Hypoplasia

Scrotal hypoplasia is sometimes seen in association with cryptorchidism or absent testes. The scrotal skin is often

completely flattened and quantitatively deficient. Prominence of the surrounding pubic and perineal skin may suggest a greater overall size to the scrotum, although the consistency and appearance of this skin is different. Scrotal hypoplasia makes orchiopexy or testicular prosthesis placement more difficult. Testes placed dependently at orchiopexy in a hypoplastic scrotum may appear to be in a nondependent position, although over a few years of follow-up, the scrotum seems to grow and accommodate the testes. Prostheses sometimes remain high and appear asymmetric when placed in a hypoplastic scrotum, even when the patient is followed through puberty, resulting in an unsatisfactory cosmetic appearance. Pretreatment with testosterone has been suggested to enlarge the hypoplastic scrotum in anorchid boys (143).

Scrotal Ectopia

Scrotal ectopic may occur on the inner thigh, on the perineum, or in the pubic region lateral to the penis. This condition is most commonly seen in males with cloacal exstrophy with diphallus (Fig. 53.6) as well as in myelodysplastic boys. Mininberg and Richman (194) encountered it in “syndromes,” and Lamm and Kaplan (162) encountered it in otherwise normal children. The testis normally lies within the ectopic scrotum, although it sometimes may be hypoplastic. Treatment usually consists of excision when the ectopic scrotum is distant.

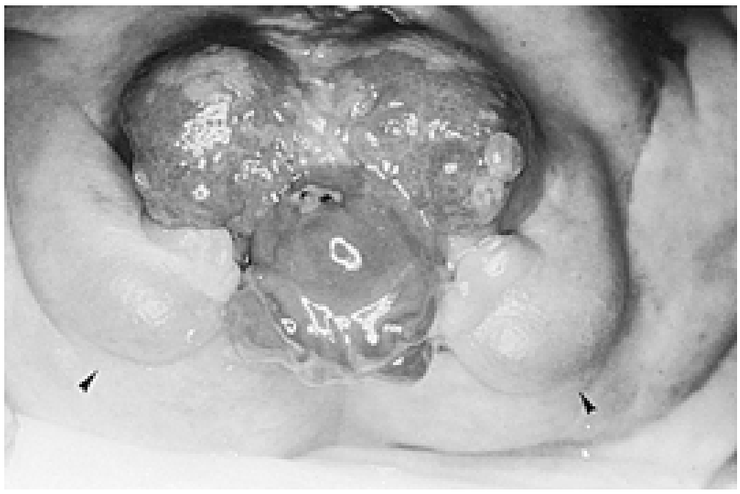

FIGURE 53.6. Scrotal ectopia *(arrowheads)* in 46,XY male with cloacal exstrophy.

Bifid Scrotum and Penoscrotal Transposition

Bifid scrotum and varying degrees of penoscrotal transposition occur most often associated with severe hypospadias, intersex conditions, and caudal regression syndrome, and rarely occur as an isolated finding (193) (Fig. 53.7). Failure of fusion or caudal migration results in separation of the two hemiscrotal compartments in the former instance and envelopment of the penis in the latter. Bifid scrotum is usually corrected naturally as part of a hypospadias repair or feminizing genital reconstruction in intersex. Minor degrees of penoscrotal transposition can be left untreated, although more severe degrees should be corrected with an M- to Y-type of scrotal recession. Techniques for simultaneous correction of chordee, hypospadias, and coexisting penoscrotal transposition have been described (58).

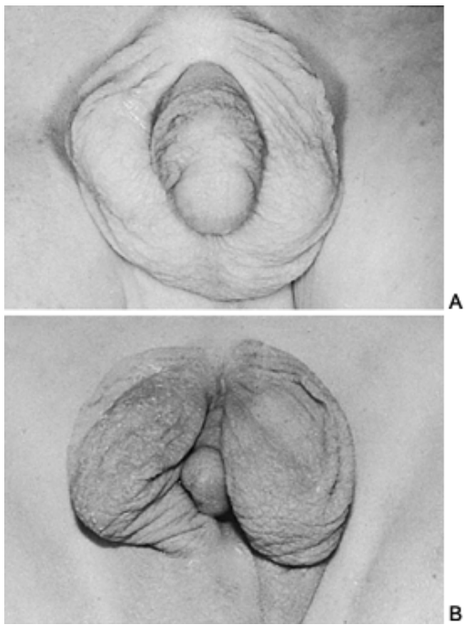

FIGURE 53.7. Penoscrotal transportation. **A:** Incomplete. **B:** Complete.

Scrotal Wall Swellings

Scrotal swellings may result from conditions involving either the scrotal wall or the intrascrotal contents. Scrotal wall swellings occur less often than swellings of the intrascrotal contents but may be painful and may simulate the latter. In some cases, the differential diagnosis may be made only by surgical exploration.

Acute Idiopathic Scrotal Wall Edema

Acute idiopathic scrotal wall edema is an uncommonly encountered scrotal swelling involving one or both hemiscrotal compartments. The overlying skin may be thickened, edematous, and discolored, with a peculiar violaceous hue (61,134). In some instances, the swelling and erythema may extend onto the abdominal wall or into the perineum. The underlying testis, epididymis, and cord usually are easily palpated, are always nontender, and are not swollen, allowing differentiation from more serious acute intrascrotal conditions. An inflammatory cause has been suggested (e.g., secondary to insect bite or contact), but documentation of these suggested causes is lacking. The actual cause is unknown. Treatment with antibiotics, antihistamines, and corticosteroids has been advocated, but it appears that this condition resolves spontaneously without treatment and without sequelae. Its importance lies in its distinction from the more serious acute intrascrotal catastrophic conditions that it may simulate.

Acute Vasculitis

Acute vasculitis of the scrotal wall from Henoch-Schönlein purpura (HSP) is uncommon but also simulates an intrascrotal catastrophe. Both the scrotal wall and the testis are involved in up to 15% of patients, and genital findings may precede the onset of the characteristic rash elsewhere (138,212). The scrotum is purpuric and erythematous and is usually tender and swollen, often making examination difficult. The testis, when involved, is often exquisitely tender, is swollen, and may completely mimic the findings seen in spermatic cord torsion. Unfortunately, to further complicate matters, spermatic cord torsion has been reported to occur in HSP (177). A high index of suspicion is needed in making this diagnosis. Adjunctive diagnostic aids, especially isotope scrotal scanning, should be used to ensure the integrity of the testis when the diagnosis is not clear (257). This condition resolves with resolution of the generalized condition without genital sequelae.

Spontaneous Gangrene

Spontaneous gangrene of the scrotal wall is a rare but serious cause of scrotal wall swelling in childhood. Swelling, edema, and then frank necrosis progressing to gangrene may occur, resulting in fever and toxemia. Most cases have occurred in neonates and have been associated with an identifiable portal of entry, such as after circumcision (227,282). Treatment consists of intense antibiotic therapy, wet soaks, and sometimes incision or debridement.

Cutaneous Cysts and Tumors

Cutaneous cysts and tumors of the scrotal wall are uncommon in childhood. Sebaceous and epidermoid inclusion cysts are usually easy to identify from their intracutaneous position, completely separate from the underlying intrascrotal contents. Dermoid cysts occur in the scrotum along the midline raphe, similar to their midline position elsewhere in the body, and sometimes are difficult to distinguish from the intrascrotal structures because of their deeper position. Scrotal sonography aids in this diagnosis; operative excision is indicated for confirmation of diagnosis.

Swellings of the Intrascrotal Contents

Swellings of the intrascrotal contents are a commonly encountered problem in pediatric urologic practice and sometimes present a difficult differential diagnostic challenge. Acute swellings resulting from spermatic cord torsion or incarcerated hernia represent surgical emergencies and must be acted on expeditiously, whereas other swellings, such as reducible hernia, hydrocele, and varicocele represent entities in which proper diagnosis is important for appropriate elective treatment. Optimal treatment depends on an exact diagnosis and a clear understanding of the nature of the underlying problem.

Hernias and Hydroceles

Hernias and hydroceles result from failure of fusion and obliteration of the processus vaginalis (Fig. 53.8). When the entire processus vaginalis remains patent, as is commonly encountered in infants, a knuckle of bowel may protrude into the lumen of the hernia sac and may incarcerate or strangulate, the latter presenting as an acute painful erythematous scrotal swelling, inguinal swelling, or both. If the distal processus vaginalis is obliterated but the neck remains open, a groin mass rather than a scrotal mass will be encountered. For example, chronic incarceration of omentum may present as a nontender, nonreducible groin swelling, with the testis palpable separately below. A more common occurrence, however, is an intermittently palpable nontender groin swelling representing intermittent prolapse of bowel or omentum into a hernia sac, with spontaneous reduction. Sometimes, in these instances, the hernia may never be observed by the examining physician, and one must rely only on a good history from the parent to diagnose this condition.

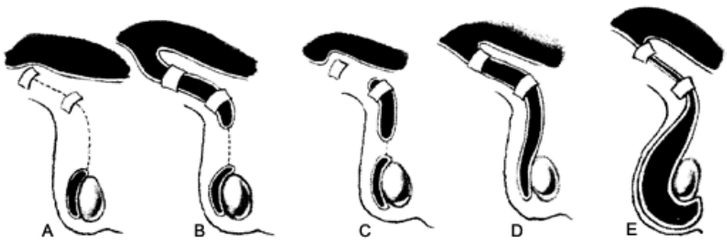

FIGURE 53.8. Diagrammatic representation of persisting patent processus vaginalis. **A:** Normal obliteration of patient processus. **B:** Patent processus proximally with inguinal bulge; processus obliterated distally. **C:** Closure proximal and distal with loculated hydrocele of cord. **D:** Complete patency with hernia sac extending into scrotum. **E:** Partial proximal closure, resulting in scrotal hydrocele and proximal patent processus. (From Lewis JE Jr: *Atlas of infant surgery.* St. Louis: Mosby, 1967, with permission.)

Strangulated hernias require immediate surgical exploration to prevent necrosis of the hernia sac contents. Infants with incarcerated inguinal hernias may be more prone testicular strangulation resulting from the increased pressure on their spermatic cord with resultant testicular atrophy (198,222). Children with incarcerated hernias should be admitted for observation, sedated, and placed in Trendelenburg position with subsequent attempts at manual reduction. Usually, these maneuvers result in successful reduction, but elective hernia repair should be done within a short period thereafter because reincarceration commonly occurs. Children with asymptomatic reducible inguinal hernias should undergo repair within a reasonable period after diagnosis to minimize the risk of incarceration or strangulation. The latter occurs commonly in infants, and surgical repair of inguinal hernias should not be deferred because of the patient's age.

Controversy exists regarding the necessity for exploration of the contralateral inguinal canal. In general, it is believed that closure of the processus vaginalis occurs in most infants during the first several months of age and that a persisting patent processus clinically evident thereafter should be surgically repaired. These figures have led some to believe that routine contralateral inguinal exploration is not advisable, a view based also on the added anesthesia time required for both repairs and the small but definite incidence of testis atrophy, vas injury, and secondary fixation of the testis in an extrascrotal position after inguinal hernia surgery (104). On

the other hand, hernias *do occur* in boys who have undergone previous contralateral inguinal hernia repair. A contralateral patent processus vaginalis was found in 59% of boys up to age 16 years who underwent bilateral exploration for a unilateral clinically apparent hernia (195). These figures are somewhat age dependent, with a greater frequency of clinical hernias present in younger boys, especially those younger than 6 months. McGregor and colleagues (186) reevaluated 130 patients over a postoperative follow-up period averaging 20 years and found that 29% eventually developed a contralateral inguinal hernia after previous unilateral repair. The chance of contralateral occurrence was found to depend on which side had originally been repaired. If the left side had been repaired formerly, there was a 41% chance of a subsequent right-sided hernia requiring surgical correction; if the right side was repaired first, there was only 14% chance of a hernia subsequently occurring on the left. Furthermore, nearly half of the subsequent contralateral hernias occurred within 1 year of the original repair. Despite these observations, they believed that routine contralateral groin exploration was unwarranted because, statistically, two explorations yielding negative findings would be required for every right-sided exploration yielding positive findings, and six left-sided explorations yielding negative findings would be done—an unacceptably high figure in their view (186). However, current opinions diverge somewhat from their conclusions. In a survey of 48 experienced pediatric surgeons, 80% routinely explored the contralateral groin in boys and 90% in females (231). In general, most surgeons dealing with pediatric hernias believe that the contralateral groin exploration can be done safely and expeditiously (i.e., in the hands of a competent pediatric surgeon); both sides should be explored in cases in which only one hernia is clinically evident in boys younger than age 2 years.

More recently, this approach has been refined further using minimally invasive techniques. Intraoperative inguinoscopic evaluation of the contralateral internal inguinal ring (through the opened hernia sac) has been advocated. A 90-degree viewing lens facilitates this diagnostic maneuver. If the internal ring is dilated, contralateral inguinal exploration is performed. A simpler alternative is to simply perform a pneumoperitoneum by placing a small catheter into the peritoneal cavity through the opened hernia sac, producing temporary inflation pressures to 15 cm H_2O. Crepitus or a visible bulge in the contralateral asymptomatic groin is a positive indication for exploration. Although individual preference dictates which of these maneuvers is undertaken, most pediatric urologists currently use some form of evaluation of the contralateral asymptomatic groin.

Hydroceles

Hydroceles represent persistence of the processus vaginalis along its course with partial or complete fusion of the processus proximally. In children, virtually all hydroceles are communicating (i.e., a narrow persistent processus vaginalis that allows the hydrocele periodically to fill with fluid), resulting in intermittent enlargement (Fig. 53.8). Hence, a history of a childhood scrotal swelling that intermittently enlarges in the absence of a clinical hernia confirms the presence of a patent processus vaginalis. Therefore a related pediatric urologic caveat is that boys with hydroceles should always be explored through an inguinal incision rather than through the scrotum to allow for ligation of the coexisting processus vaginalis.

Most infants with a scrotal swelling caused by a hydrocele undergo spontaneous closure of the processus vaginalis with subsequent resolution of the hydrocele. Therefore surgical repair is usually reserved for persistent swellings beyond age 2 years because after this age, spontaneous closure of the persisting processus vaginalis occurs far less frequently. Size of the scrotal swelling should not influence a decision regarding early surgical correction because many of these swellings can be quite large yet will still resolve spontaneously. Observation of a clinical hernia, however, is an indication for prompt surgical repair, as is the rare occurrence of significant hydrocele enlargement.

Occasionally, an isolated scrotal hydrocele may be encountered in the absence of a proximal patent processus vaginalis. The cause of this may not be obvious but sometimes is the presenting sign of a serious underlying condition (e.g., a testicular tumor or chronic epididymitis). In these instances, proximal exploration through an inguinal incision still should be used rather than a scrotal or inguinoscrotal approach, as is commonly used in adults. This proximal approach allows for diagnosis and ligation of an occult patent processus vaginalis and for proximal spermatic cord occlusion if an unsuspected tumor becomes evident.

A loculated hydrocele (hydrocele of the cord) may occur anywhere along the spermatic cord, presenting as a firm groin swelling that is sometimes difficult to distinguish from an incarcerated inguinal hernia or paratesticular rhabdomyosarcoma of the cord. Transillumination of the mass and sonography may aid in this distinction and many swellings in this location usually require surgical exploration for confirmation of diagnosis and treatment.

Antenatal or Postnatal Peritonitis

Antenatal or postnatal peritonitis may present with scrotal findings. An *in utero* intestinal perforation may heal, but spillage of intraabdominal meconium may track down a patent processus vaginalis into the scrotum, causing an inflammatory mass. As an example, the case shown in Fig. 53.9 is a healthy term boy who presented with bilateral scrotal hydroceles at birth. As the hydroceles regressed over the first several weeks, a few hard nodular masses were palpated, related to the right testis and epididymis, raising the concern of an intrascrotal tumor. Scrotal sonography

demonstrated several echogenic foci in both hemiscrotums, suggesting multiple areas of calcification. A plain film subsequently revealed multiple calcified areas in the scrotum and inguinal canal characteristic of meconium peritonitis (259). Similarly, acute appendiceal perforation in boys can track down a patent processus vaginalis and present as an acutely inflamed scrotum with minimal or no intraabdominal or inguinal signs. If pus is encountered in an exploration of an acutely inflamed scrotum, appendicitis with perforation should be considered. Similarly, idiopathic fat necrosis within the scrotum may mimic this condition (57).

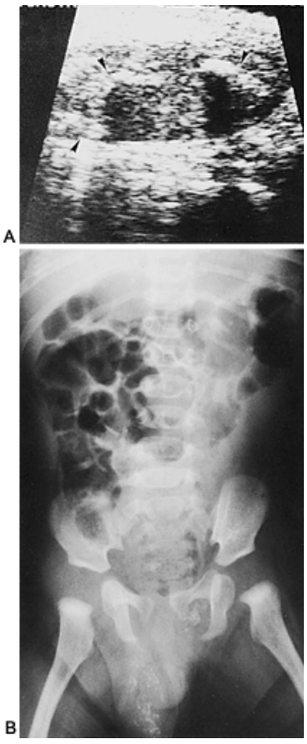

FIGURE 53.9. Meconium peritonitis and scrotal mass in a 4-month-old boy. **A:** Longitudinal sonogram of right hemiscrotum demonstrating multiple extratesticular echogenic foci *(arrows)* surrounding testis, suggesting calcification. **B:** Plain film indicating multiple calcified areas in scrotum and left inguinal canal along the processus vaginalis.

Orchitis

Orchitis as an isolated finding in boys is uncommon and usually results from a concomitant viral infection or as a reactive change to an adjacent epididymitis. The testis is acutely swollen and exquisitely painful, may be surrounded by a reactive hydrocele, and may mimic other acute intrascrotal processes completely. Testicular inflammatory swelling in mumps usually occurs in postpubertal boys and rarely occurs under age 10 years. Estimates of the frequency of mumps orchitis in the literature range from 3% to 100%, but in one carefully analyzed study, the frequency was 30%. One-third of those having orchitis developed subsequent atrophy (12). The risk of infertility is increased in this group, and there is a questionably increased risk of malignancy developing in these atrophic testes. The treatment is usually supportive, with analgesics, scrotal elevation, and ice packs used in the acute phase.

Epididymitis

Epididymitis is a more common cause of scrotal swelling in childhood than is usually believed. Gierup and colleagues (78) collected 48 cases over a 25-year period; more recently, Gislason and colleagues (84) reviewed an additional 25 childhood cases seen over 5 years. Most pediatric urologic referral practices encounter children with epididymitis regularly because this condition occurs more commonly in boys who have urinary infections, who have structural lesions of the urinary tract, or who undergo reconstructive surgery and have indwelling urethral catheters. When the findings from four series of acute scrotal swellings in boys were collated, epididymitis was noted as the underlying cause in 8% to 41% (23,133,166,197). The peak incidence is usually in adolescence.

Epididymitis may result from an acute urinary tract infection with retrograde spread of infection along the vas deferens. The common embryologic derivation of the ureter, vas deferens, seminal vesicle, and epididymis should be remembered, and in some boys, structural abnormalities of the termination of these organs in the trigone and posterior urethra may be present, predisposing them to retrograde vasitis and epididymitis (Fig. 53.10). Indwelling urethral catheters may sometimes precipitate an attack of acute epididymitis in boys with these structural abnormalities without previous urologic symptoms (Fig. 53.11). In older boys, epididymitis is a cause of acute, painful scrotal swellings, often in the absence of demonstrable bacterial infection. Numerous studies, including culture of direct epididymal aspirations, have generally failed to demonstrate organisms in these instances. In such cases, viral and atypical bacterial infections have been postulated as the cause.

Uncommonly, epididymitis may be associated with an unusual organism (e.g., *Salmonella, Haemophilus*) in the absence of demonstrable urinary tract infection. In these circumstances, direct hematogenous seeding may be the cause. Purulent epididymitis or chronic epididymitis may occur, requiring surgical exploration for diagnosis or drainage of the epididymal abscess.

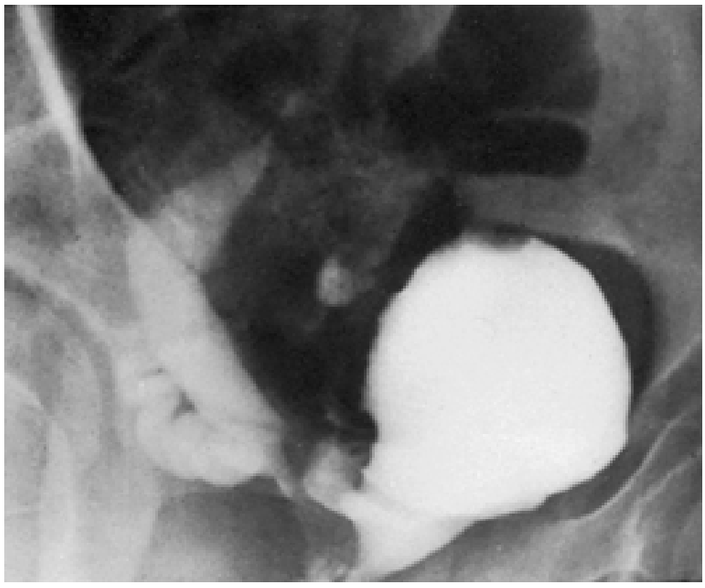

FIGURE 53.10. Persistent mesonephric duct in a 6-year-old boy with anorectal anomaly and rectourethral fistula. The voiding cystourethrogram demonstrates reflux into a markedly dilated convoluted vas deferens and ureter.

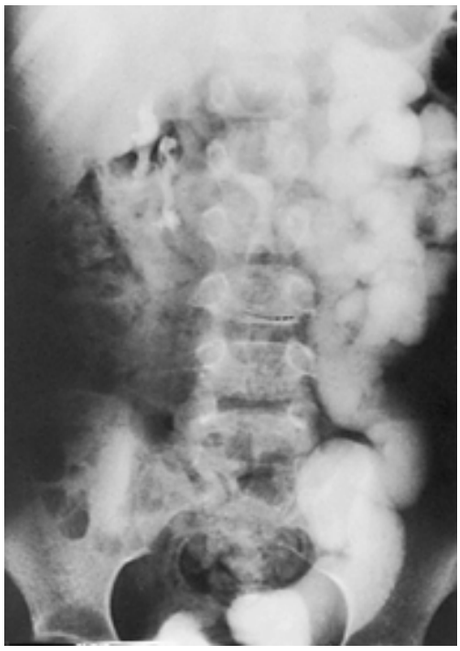

FIGURE 53.11. Left epididymitis in a 4-year-old boy who was previously asymptomatic with an indwelling urethral catheter after open-heart surgery. The intravenous pyelogram reveals previously unsuspected horseshoe kidney, gross left hydroureteronephrosis. A Y ureter was found draining the right side and isthmus.

These findings raise the issue of whether radiologic urinary tract screening to detect underlying structural abnormalities is indicated in boys who have epididymitis diagnosed at any age. Some have indicated that infants with epididymitis have an increased likelihood of having underlying structural genitourinary abnormalities and recommend that complete urologic investigations be performed (243,272). Others who have reviewed this problem in older children suggest that underlying structural problems are uncommon in this population (84). A selective approach to this problem should be practiced. Boys with epididymitis associated with an acute urinary infection are evaluated with a sonogram and voiding cystourethrogram, just as any other boy with an acute urinary infection. Preadolescent boys with epididymitis having sterile urine have a sonogram and voiding cystourethrogram done as well, although the number of abnormalities found in this group is smaller than in the former. Adolescent boys with epididymitis undergo screening sonography of the kidneys and pelvis to ensure normalcy of the upper urinary tract and to ensure that a rarely encountered wolffian or müllerian duct remnant is not present. Circumcision status seems to play a role: Epididymitis occurs three times as often in uncircumcised boys, regardless of age (15).

The diagnosis of epididymitis is made by direct physical examination; the epididymidis is usually found to be enlarged, firm, and exquisitely tender, usually with a normal adjacent testis. In some instances, the intrascrotal contents are obscured by a surrounding hydrocele, making the diagnosis difficult. Prehn's sign (relief of pain with elevation of the involved testis) in our experience has not proved to be a reliable diagnostic aid in children because of inaccuracies observed with this maneuver and the small size of the pediatric scrotum that naturally draws up the testis. Associated fever, leukocytosis, pyuria, and bacteriuria occur more commonly with epididymitis, helping distinguish epididymitis from other causes of acute scrotal swelling. However, these findings should be considered as supportive findings to the general clinical history and examination, rather than as absolute indicators that epididymitis is present. Two studies indicate that although 46% of their patients with epididymitis had pyuria, between 27% and 40% of the patients with spermatic cord torsion also had pyuria (2,256). Scrotal sonography, isotope scrotal scanning, or both may aid in the difficult case (see later discussion). Treatment with appropriate antibiotics should be provided based on urine culture and sensitivities, as well as scrotal elevation and restrained physical activity until the acute phase subsides. Worsening swelling and symptoms should raise the issue of a misdiagnosis, such as a missed spermatic cord torsion, and appropriate reevaluation or surgical exploration may then be indicated.

Varicoceles

The incidence of varicoceles in boys has been reported to range from 9.0% to 25.8%. A summation of the larger series in the world literature shows a mean of 16.2% in 21,878 boys of ages 10 through 25. Testicular damage related to an ipsilateral varicocele has been debated for years, but current thought focuses on the alterations in blood flow to both testes noted when a unilateral varicocele is present. Free communication is noted between the arteries at the testicular level, as well as between the veins of the pampiniform plexus (Fig. 53.12). As venous blood flows up the spermatic cord, adjacent arterial blood is normally cooled from 37 degrees to 33 degrees by a countercurrent heat-exchange process (265). When a varicocele forms, the countercurrent heat exchange process is disrupted, and because pelvic venous crossover anastomoses are present, the arterial and testicular temperatures in both testes remain elevated even though the varicocele is unilateral. Intratesticular hormone production and spermatogenesis is disrupted as a result.

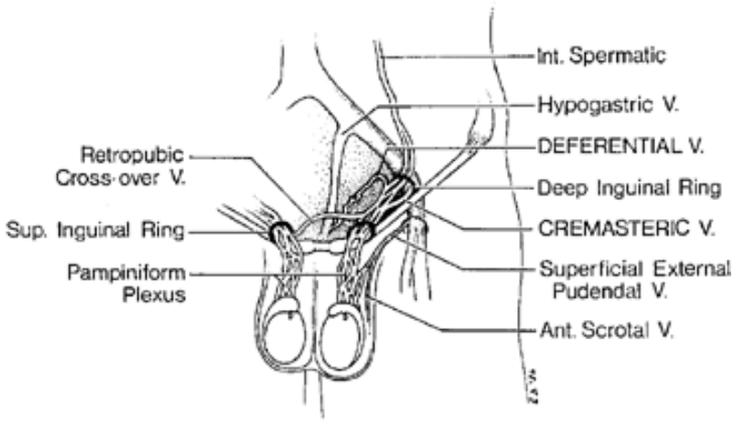

FIGURE 53.12. Venous drainage of the testes. (From Levitt SB, Gill B, et al. Routine intraoperative venography in the treatment of pediatric varicocele. *J Urol* 1987;137:716, with permission.)

In 1982, Lyon and co-workers (180) reported that the majority of boys with left varicoceles had small left testes. Pozza and colleagues (219) found that 74% of 35 boys younger than 16 years of age with varicoceles had atrophy of the testis and 90% had abnormal testis biopsies. On the other hand, Wyllie (283) found that in 50 normal boys without varicoceles between the ages 10 and 13, there was no significant difference in testis size. Sayfan and colleagues (233) found that young asymptomatic men with varicoceles had significantly lower testis volume (21.5 mL) and total sperm counts (71 million) than normal controls (30.0 mL; 186 million) and that their testis volume was similar to that for infertile men (21.3 mL; 35 million). Kass and Belman (135) found that of 20 boys who had varicocele repair, 16 were noted to experience an increase in the relative size of the left testis as compared with the right after the repair. Hosli (112) reported on 20 young men ages 20 to 29 who had had varicoceles repaired at ages 9 to 17. The two testes were equal in size, and the semen quality was better than in an untreated control group. Okuyama and co-workers (205) studied 40 boys with varicoceles, 24 of whom were treated surgically and 16 of whom refused operation. Testis size improved significantly in the treated boys and deteriorated in the controls. Semen quality was much better in the patients who had surgery. Laven and colleagues (165) did a randomized study of 88 adolescent males with varicoceles, of whom 33 were observed and 34 were treated. They also studied 21 controls. All patients were followed for a year. The right and left testis volume was smaller in the boys with varicoceles than in the controls. After treatment, both left and right testes caught up with the controls, whereas the testes of the untreated group remained smaller than those of the controls. Similar effects were seen on semen quality. These data strongly suggest that varicoceles can injure the testes in some adolescent boys; in addition, these data are substantiated further by the abnormal results of gonadotropin-releasing hormone (GnRH) infusion tests seen in some boys with varicoceles.

Spermatic Cord Torsion

Scrotal swellings secondary to spermatic cord torsion (Fig. 53.13) represent one of the most serious emergencies encountered in pediatric urology in terms of both the need for urgent management and the potential for long-term potential serious sequelae. Urgent accurate diagnosis is needed, followed by surgical exploration and detorsion of the testis. Time is a critical factor because testis survival relates directly to the duration of torsion (4,9,33,56,74).

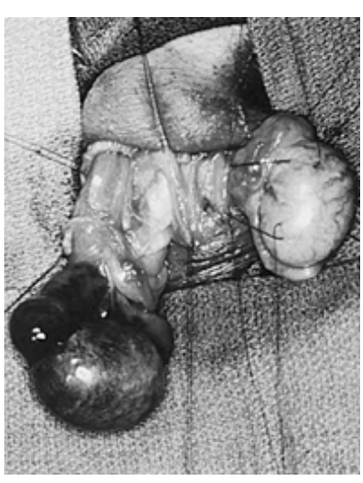

FIGURE 53.13. Right spermatic cord torsion in a 12-year-old boy.

The frequency of spermatic cord torsion has been estimated at 1 in 4,000 males younger than age 25 years, making it relatively common (274). This figure probably underestimates the true frequency because many episodes of missed torsion exist, as well as being misdiagnosed with other conditions. Furthermore, evidence now shows that many, if not most, cases of absent testes result from previous spermatic cord torsion (148). Although it has been stated that two-thirds of cases of spermatic cord torsion occur in boys between ages 12 and 18 years (274), torsion may occur at any age and has clearly been identified and reported antenatally, neonatally, throughout childhood, and in adulthood (127,137,271). An anatomic abnormality in which the peritoneal investiture of the testis inserts high on the spermatic cord rather than on the lower pole allows for poor testicular fixation and extreme testicular mobility (the bell-clapper deformity), predisposing to twisting (Fig. 53.14). Most instances of torsion occur intravaginally (i.e., within this sac); however, in the neonate, extravaginal torsion (i.e., a true twist of the entire spermatic cord and testis) is more common. Because this abnormality of the tunica vaginalis is believed to frequently exist bilaterally and because cases of sequential torsion on the opposite side have followed previous unilateral torsion in cases where the uninvolved side was not suture-fixed in place, bilateral suture fixation of the tests is mandatory in any case of unilateral torsion (14,105).

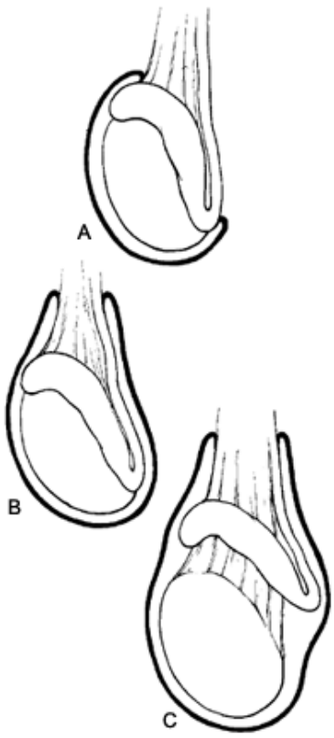

FIGURE 53.14. Diagrammatic representation of the anatomy of spermatic cord torsion. **A:** Normal anatomy. Tunica vaginalis does not envelop the epididymis. **B:** Bell-clapper deformity. Tunica vaginalis extends high on the spermatic cord, enveloping the epididymis and allowing the testis to twist within. **C:** Testis suspended from the epididymis, allowing twist to occur between the testis and epididymis.

Just how long can the testis in torsion survive without undergoing irreversible atrophy? Several experimental preparations examining the effects of complete torsion of rat and dog testes reveal that the “safe” period for recovery of germinal and tubular epithelium may be somewhere between 4 and 6 hours, although severe, irreversible abnormalities may be seen after even 1 hour (49,166,251,253,264). One classic article indicated that 17 of 19 boys had their testis saved when operated on within 24 hours of symptom onset, whereas in none of 31 boys operated on after that time was testis salvage feasible. In several additional reviews, maximum survival (70% to 90%) was noted in patients operated on within 12 hours of symptom onset. Survival decreased significantly during the next 12 hours but was still possible. After 24 hours of torsion in humans, testicular infarction is the rule. The degree of torsion influences survival because not all torsion results in complete ischemia; 720 degrees of torsion experimentally have been shown to be necessary for complete, irreversible cessation of blood flow (49,264). Furthermore, in humans, spontaneous incomplete or complete detorsion is not uncommon, explaining the occasional occurrence of testicular salvage after prolonged periods. Nevertheless, these data serve to illustrate graphically the effect of delayed diagnosis on testicular survival.

If time is so critical, why has therapy been delayed so often? Failure to suspect torsion as the underlying cause of the acute scrotal inflammation is the most common reason. Also, a lack of uniformity of symptoms and physical findings often suggests alternative diagnoses and has led to a variety of descriptive titles of literature dealing with this subject (166,273). The classic description of torsion includes a sudden onset of hemiscrotal pain, followed by swelling, acute nausea, and vomiting in the absence of fever and urinary symptoms. However, a painless swollen testis, which may occur in up to 10% of torsions (most often in newborns), can occur, causing delay in diagnosis (133). Failure to understand that torsion is the leading cause of acute scrotal inflammation in childhood, not epididymitis, can cause diagnostic delay and testicular wastage. An additional cause for delay in therapy sometimes results from the blind faith of treating physicians in the newer diagnostic modalities available to distinguish the various cases of scrotal inflammation. Conflict between clinical impressions and diagnostic testing has led to delay in exploration in some and even missed torsion in others. Further discussion of this

aspect of management follows in the subsequent section on differential diagnosis of scrotal swellings.

Although the recognition of spermatic cord torsion may be somewhat complicated, management is completely straightforward and not controversial. Surgical exploration should be performed immediately. However, manual derotation as a temporizing maneuver may be attempted after administration of intravenous morphine (0.1 mg/kg of body weight) (17,73). It has been suggested that the anterior portion of each testis torts toward the midline; hence, it should be rotated outward to achieve detorsion (255), although not all agree and attempts can be made in each direction. Successful detorsion is usually associated with marked pain relief immediately and may be documented with Doppler examination. Surgical fixation with nonabsorbable sutures should follow within 24 hours to prevent retorsion, which commonly occurs. Cases have been reported in which retorsion has occurred when the previous suture fixation was done with absorbable sutures (157,187,267). Simultaneous fixation of the opposite, uninvolved testis is also mandatory because contralateral sequential torsion has been reported in more than 40% of cases in which the uninvolved testis was not fixed at the time of torsion (158,250).

Neonatal Torsion

Neonatal torsion represents a unique and distinct situation. The finding of a painless, discolored, hemiscrotal swelling in the neonate is indicative of spermatic cord torsion and should in no circumstances be considered a diagnostic problem. Unfortunately, bilateral synchronous and asynchronous cases may occur. The duration of torsion is difficult to determine in many of these circumstances, and in some instances, torsion may have occurred before birth. A review of this subject covered approximately 120 previously reported cases in the literature through 1983 (244). Attitudes concerning management of this condition were polled among the members of the Society for Pediatric Urology. Most believed that the diagnosis of this condition was self-evident and that exploration was indicated; however, the testicular salvage rate was disappointing. Further controversy over the frequency of contralateral torsion in these instances and the need to suture-fix the contralateral testis existed because most of these torsions occur extravaginally. This controversy led some to adopt a less aggressive attitude toward emergent exploration.

With increased recognition of this problem, antenatal torsion is similarly being diagnosed with increased frequency. Reports of calcified testes and hypoplastic testes at birth, as well as the report of a “free-floating necrotic intraabdominal testis” found at exploration of a newborn presenting with an acute abdomen and an ipsilateral empty scrotum (196), illustrate the spectrum of presentations of this condition. Further investigations indicate that many instances of unilateral absent testes result from antenatal torsion (114,152). Unfortunately, testicular salvage after antenatal spermatic cord torsion has not been reported and is unlikely.

The fate of the torted and contralateral untorted testes after correction of spermatic cord torsion has received considerable attention. Salvage rates of “viable” testes have varied, but some series reported atrophy in one-third to two-thirds of these testes. A correlation between duration of torsion and subsequent atrophy exists (158,182). These data suggest that in some instances, surgeons are preserving poorly viable testes that should have been removed. Furthermore, the incidence of morbidity (e.g., prolonged high fever, scrotal abscess, drainage of necrotic tubules through the scrotal incision) is high, approaching 20% in some series (274).

Some additional information suggests that the testis undergoing torsion can adversely affect the contralateral testis by a presumed immunologic process. Various adult rat experimental preparations, beyond the scope of full discussion here, have demonstrated contralateral histologic abnormalities in unilateral torsion (49,152,199) (Fig. 53.15). Raised antibody titers have been detected in rats and mice in some instances (106,152,258) but were not detected in rabbits (35). Diminished fertility was noted after mating in these circumstances (49,191,199). Orchiectomy (49), splenectomy and azathioprine administration (199), and corticosteroid administration (152) have attenuated these adverse findings, further suggesting that an immunologic process is operative. Data suggest that the prepubertal rat testis subjected to torsion does not result in these abnormalities (152,200). Human clinical correlates of these experimental findings exist. Eighteen patients who had prolonged prepubertal spermatic cord torsion who underwent detorsion with replacement of the testis in the scrotum were reviewed 7 to 23 years later. Of the five married men, all were fathers. Of the 13 unmarried men, only 3 had abnormal semen analyses. None showed any abnormal sperm autoantibodies. In another study, though, only 9 of 23 adults who had previous spermatic cord torsion had normal semen in their ejaculate (11,178). Some of these patients had elevated FSH levels, indicating abnormal testicular function. These studies demonstrate that the contralateral testis may be affected adversely by the torted testis and that orchiectomy should be done if a prolonged period has elapsed because the onset of symptoms or if a rapid return of blood flow is not seen after detorsion. Leaving a marginal testis in place probably causes more potential harm than benefit.

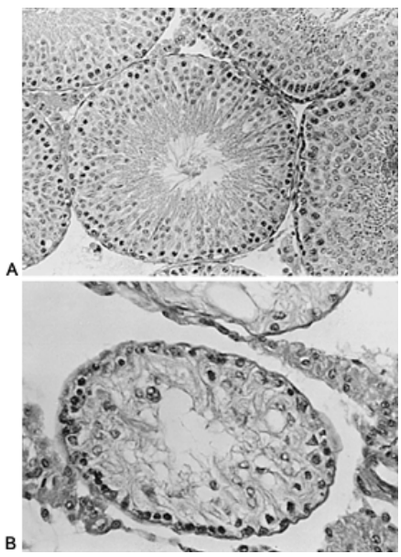

FIGURE 53.15. Histologic findings in the contralateral testis of adult rats (age 53 days) 30 days after undergoing chronic unilateral testicular torsion. **A:** Control contralateral testis with normal tubular diameter and spermatogenesis. **B:** Contralateral testis has absent spermatogenesis and reduced tubular diameter. (From Kogan SJ, Owens G, Tarter T, et al. Mechanisms of injury in unilateral testis torsion. *Eur Urol* 1986;12:184, with permission.)

Torsion of the Testicular Appendages

Torsion of the testicular appendages occurs frequently and may totally mimic the inflammatory findings of spermatic cord torsion. When an inflammatory, painful hydrocele occurs, obscuring the testis completely and precluding adequate examination, concern must be exercised to exclude

spermatic cord torsion. Testicular appendages tend to twist when they are long and pedunculated. Venous engorgement occurs, followed by arterial occlusion and then appendiceal infarction. In some instances, the appendage may become strikingly enlarged, sometimes as large the testis (Fig. 53.16). When the appendage in torsion is easily seen and palpated through the scrotal skin (blue-dot sign) and the underlying testis feels normal, spermatic cord torsion may be excluded with complete confidence despite the surrounding inflammation.

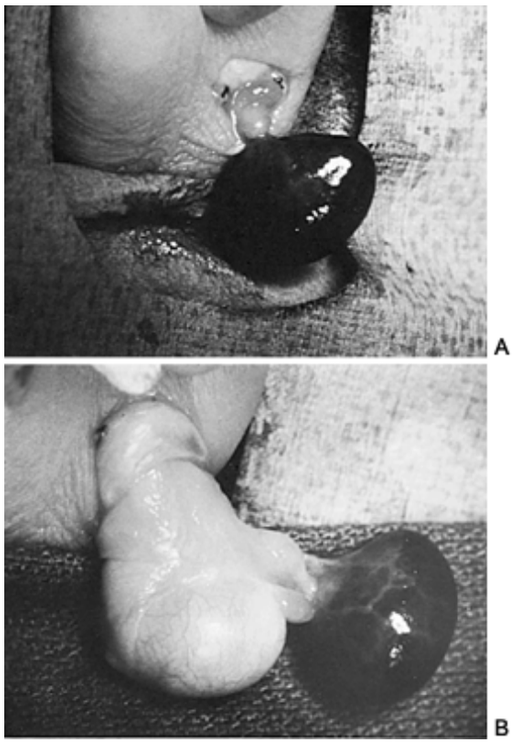

FIGURE 53.16. Torsion of the testicular appendage in an 8-year-old boy presenting with 6 hours of acute scrotal pain and inflammation. A large, infarcted intrascrotal mass protrudes **(A),** followed by the testis **(B).** In this unusual case, the infarcted appendix testis is as large as the testis.

Testicular appendages exist at both the superior and inferior testicular poles (Fig. 53.17), and any may undergo torsion. Clinically, the appendix testis is the most commonly encountered appendage, occurring in 92% of one autopsy series, and also is the most common appendage undergoing torsion (230,249). Embryologically, this appendage represents the remnant of the cranial part of the müllerian duct. The appendix epididymis represents a remnant of the cranial end of the wolffian duct, as do the paradidymis and vas aberrans.

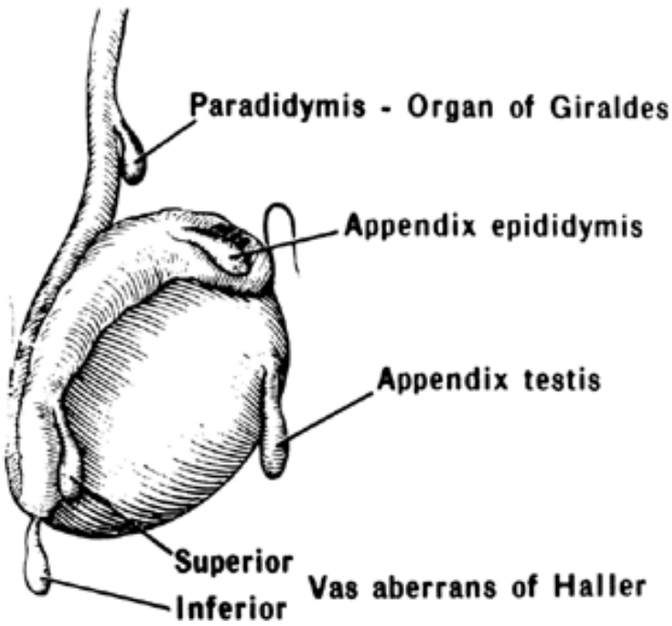

FIGURE 53.17. Anatomic distribution of the testicular appendages. (From Rolnick D, Kawanoul S, Szanto P, et al. Anatomical incidence of testicular appendages. *J Urol* 1968;100:755, with permission.)

Although many surgeons advocate emergent exploration of all cases of acute scrotal inflammation, those boys having testicular appendiceal torsion may be spared this inconvenience providing the diagnosis is made with accuracy (e.g., by clearly palpating a normal testis or finding a blue-dot sign). Virtually all cases of testicular appendiceal torsion resolve spontaneously, often with autoinfarction of the appendix. Supportive analgesics are offered and a follow-up reexamination is important to document resolution of the swelling. The rare instance in which pain is persistent or recurrent after a previous bout has resolved may be dealt with by an ambulatory surgical excision. Although asynchronous contralateral appendiceal torsion occurs, it is uncommon and most surgeons do not elect to remove both appendages when operating for this condition.

Testicular and Paratesticular Tumors

Testicular and paratesticular spermatic cord tumors are an important but uncommon cause of scrotal swellings in children. They may present insidiously and may not be apparent at an initial examination done for nonspecific scrotal pain. Alternatively, a tumor may be obscured by a hydrocele of recent onset, making palpation of the tumor mass impossible. Testicular tumors also may have an inflammatory presentation, with chronic erythema and thickening of the overlying skin and underlying swelling. More often, they initially present as a bland, firm, nontender asymptomatic scrotal mass.

Differential Diagnosis of Scrotal Swellings

The differential diagnosis of these scrotal swellings requires a thorough working knowledge of the underlying conditions as well as an attempt to characterize the swelling at hand. Evaluation of physical characteristics such as consistency, nodularity, and ability to transilluminate the swelling are helpful in arriving at correct diagnosis. Accurate localization of the swelling to an intratesticular or paratesticular position and determination of reducibility of the mass similarly help characterize the swelling. The key factor in these instances of scrotal swelling is to determine whether the underlying testis is palpably normal because testicular swelling usually indicates serious disease. Useful differential diagnostic points are listed in Table 53.1 .

	Spermatic Cord Torsion	Epididymoorchitis	Appendiceal Torsion
Age	First year and adolescence	Adolescence and after	9–12 yr
Symptoms and signs			
Pain	Acute, severe onset	Gradual localization to upper or posterior of testis	Usually gradual
	Frequent antecedent similar pains	Uncommon	Occasional
	Localized to testis and radiates to groin and lower abdomen	Usually localized to epididymis and testis, sometimes to groin	Localized to appendix or general scrotal region
Fever	Rare	Common	Rare
Vomiting	Frequent	Rare	Rare
Dysuria	Rare	Common	Rare
Physical examination	Testis may be high-riding, swollen, exquisitely tender	Testis and epididymis are firm, tender, swollen	Testis usually normal; firm mass may be seen and felt at upper pole; distinct from epididymis
Laboratory examination			
Pyuria, urinary infection	Rare	Common	Rare
Blood flow (Doppler, isotope scrotal scan)	Diminished	Increased	Normal or increased

TABLE 53.1. DIFFERENTIAL DIAGNOSIS OF ACUTE SCROTAL SWELLING IN CHILDHOOD

Chronic persisting scrotal swellings that cannot be accurately diagnosed clinically should be explored surgically because serious disease often underlies in these circumstances. When one is dealing with acute swellings, it is helpful to characterize the swelling as being either *ischemic* or *inflammatory* in nature. This principle has also formed the basis for noninvasive adjunctive diagnostic tests developed to diagnose these swellings nonoperatively. Radionuclide scrotal scanning with technetium-99m pertechnetate, first introduced in 1973, has gained wide acceptance in this context. Imaging of the scrotum after injection of this agent allows for rapid distinction between inflammatory conditions with an increase in vascularity and ischemic conditions such as torsion, where a cold “hole” in the isotope distribution is noted (Fig. 53.18). The Doppler ultrasonic stethoscope was introduced shortly thereafter based on the same principle. With this instrument in the emergency room, the

examiner could make a rapid distinction between torsion (ischemic) and other inflammatory conditions resulting in an increased blood flow. The latter procedure would seem to represent the ideal way to diagnose torsion were it not for a significant incidence of both false-positive and false-negative results (202,216). A chronically torsive testis often develops a surrounding hyperemic shell of vessels from the spermatic cord, causing a Doppler reading of intact flow. Technique seems to affect the results, and proper probe position and compression of the spermatic cord above (funicular compression test) are important to prevent confusing pulsations from inflamed overlying scrotal skin from blood flow through the spermatic vessels (107). Formal Doppler ultrasound examination of the acutely inflamed scrotum is more accurate, although still harboring a definite potential for error. A recent review using color Doppler ultrasound in this context in expert hands achieved a 90% sensitivity and 99% specificity in diagnosis (8). The authors indicate appropriately that the ideal use of this test is to add an adjunctive objective measure to the clinical evaluation where an equivocal or low suspicion of torsion is present.

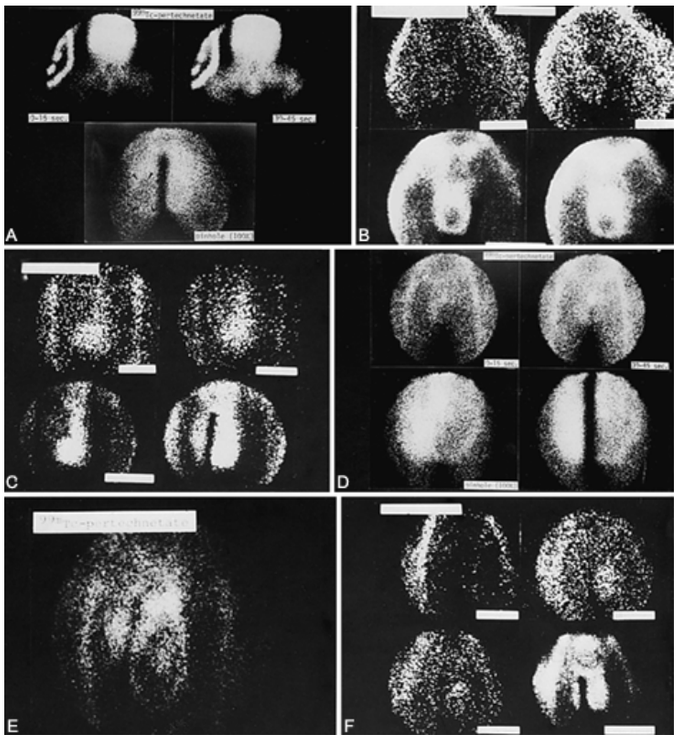

FIGURE 53.18. Radionuclide scrotal scanning. **A:** Acute (right) torsion. Cold central photopenic area is evident *(arrowheads)*. **B:** Chronic (right) torsion. Central defect is evident with hyperemic surrounding shell of vessels. **C:** Epididymitis (left). Diffusely increased flow on dynamic and static images. **D:** Torsion of (right) testicular appendage. Dynamic imaging may show normal or increased flow; static imaging shows increased flow. **E;** Hernia hydrocele may simulate cold, central defect seen in torsion. **F:** Scrotal abscess may simulate inflammatory changes of epididymitis or sometimes the cold central defect seen in torsion. (**A** and **D** courtesy of Drs. K.J. Chun and D.M. Milstein.)

Radioisotope scrotal scanning has proved highly accurate in trained hands; however, this examination is not readily available in all clinical settings and requires skill in interpretation. Proper imaging of the intrascrotal contents is critical; in particular, a pinhole converging collimator should be used to obtain sharp, enlarged images. A review of 464 cases of acute scrotal inflammation indicated that in only 4% was an incorrect diagnosis reached (107). False-positive isotope scans, in which torsion is incorrectly believed to be present, may result from overlying hernias or hydroceles and sometimes are seen with epididymitis. False-negative scans may result from abscess formation, from late torsion with surrounding hyperemia, or from recent detorsion-retorsion (Fig. 53.18). Two reviews contrasted the diagnostic accuracy of isotope scanning and Doppler flowmetry (85,229). In the first, the scan findings were correct in 100% of cases, whereas the Doppler findings were indeterminate in 30% of 20 patients explored for torsion (229). In the second, 7 of 32 consecutive patients with an acute scrotum had spermatic cord torsion (85). Five of seven had the diagnosis confirmed by both modalities; six of seven Doppler studies were consistent with torsion, and five of seven isotope scans were positive. These authors concluded that neither examination was accurate enough to be used individually.

A longstanding personal experience with radioisotope scrotal imaging demonstrated the accuracy of scrotal imaging in correctly diagnosing testicular torsion and the correct scan parameters for predicting that torsion was not present. In a review of 19 patients originally and in numerous other instances surgical exploration or long-term clinical follow-up has demonstrated a 100% scan accuracy in predicting patients with nontorsion. No patient was subsequently found to have torsion or to show evidence of testicular atrophy. In this manner, the scrotal scan was found to be extremely helpful in complementing the clinical impression and in minimizing explorations in all but clear-cut necessary cases. By contrast, in 45 patients suspected of having torsion who were operated on immediately, 40 had torsion at surgical exploration, giving a clinical diagnostic accuracy of 88%. We believed that the 5 patients who underwent an “unnecessary” surgical exploration did not justify routine use of scrotal scanning in this group to confirm an already obvious diagnosis (150,151). This experience has been formulated into an approach that can be used in managing boys with acute scrotal inflammation (Fig. 53.19). Those boys whose clinical history and examination strongly indicate spermatic cord torsion undergo surgical exploration without any delay for adjunctive diagnostic testing. For those boys with equivocal findings, a radionuclide scrotal scan is expeditiously obtained. If the scan findings indicate a photopenic central defect compatible with torsion, the patient undergoes immediate surgical exploration because experience indicates that this finding seldom occurs in other conditions. Different findings (e.g., hyperemia, normal flow) when correlated with the clinical history allow for a more conservative observation approach to be used with a high degree of certainty that spermatic cord torsion is not present. Furthermore, delay from diagnostic testing of strongly suspected cases of torsion is eliminated by this approach. As stated previously, a similar approach can be used based on emergency use of Doppler ultrasound; however, this study is more operator dependent and subject to both false-positive and false-negative misinterpretations.

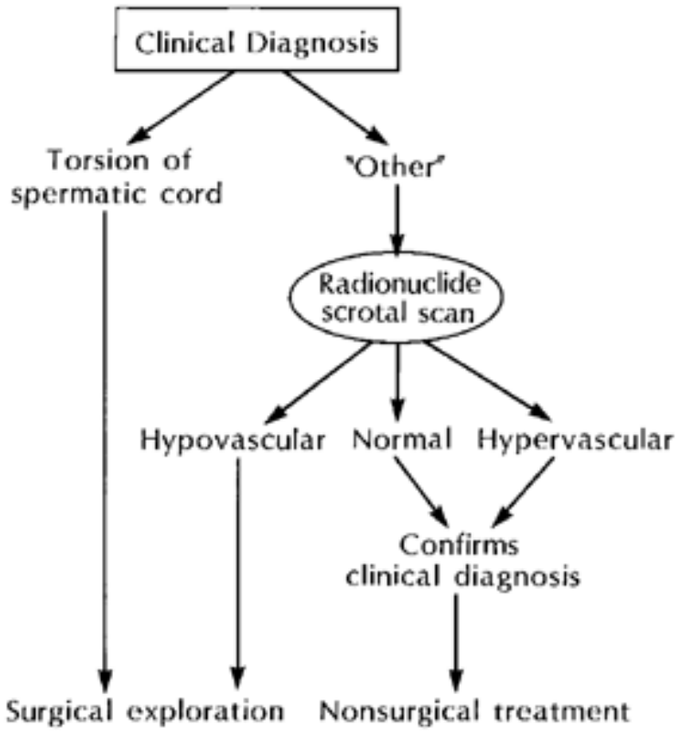

FIGURE 53.19. Clinical management of the acutely inflamed scrotum in childhood.

CONGENITAL ABNORMALITIES OF THE VAS DEFERENS AND EPIDIDYMIS

Part of "53 - PEDIATRIC ANDROLOGY "

Once considered a rarity, congenital abnormalities of the epididymis and vas deferens are now recognized with frequency, especially in situations in which the testes are abnormal, such as infertility and cryptorchidism. Scorer and Farrington (238) and Marshall and Shermeta (184) devised classifications of these abnormalities, which have been further revised and addended by Kroovand and Perlmutter (159), creating a comprehensive working classification of mesonephric duct abnormalities (Table 53.2). In this section, abnormalities solely of the vas deferens and epididymis are discussed.

I. Agenesis of all mesonephric duct derivatives

II. Epididymis
  A. Agenesis of epididymis
  B. Failure of urogenital union: agenesis or loss of continuity
    1. Nonunion between the head of epididymis and testis
      a. Gross
      b. Microscopic
    2. Agenesis or atresia of the midepididymis
    3. Agenesis or atresia of the tail of epididymis
  C. Elongated or looped epididymis
  D. Epididymal cyst, with or without loss of continuity

III. Vas deferens
  A. Agenesis of vas deferens
    1. Complete
    2. Segmental
  B. Persistent mesonephric duct: ureter entering vas deferens

IV. Seminal vesicle
  A. Agenesis of seminal vesicle
  B. Seminal vesicle cyst
  C. Ureter entering seminal vesicle

V. Ejaculatory duct
  A. Agenesis of ejaculatory duct

TABLE 53.2. CONGENITAL ANOMALIES OF THE MESONEPHRIC DUCTS IN THE MALE

Congenital Unilateral Absence or Atresia of the Vas Deferens

Congenital unilateral absence or atresia of the vas deferens occurs in approximately 0.5% to 1% of the general population (36,192,238). The latter has been encountered in 1% of boys undergoing herniorrhaphy (178) and in 20% of

boys with congenital rubella undergoing orchiopexy (221). Bilateral absence has been estimated with a frequency of 1% to 10% in azoospermatic men (122,204). Azoospermia occurs with regularity in boys with cystic fibrosis and may be accompanied by rudimentary development of the entire mesonephric ductal system (36,111). In general, absence of the vas is associated with epididymal abnormalities (192). With bilateral absence, the body and tail of the epididymis are usually also absent; the globus major is usually intact (238). An absent vas deferens should also raise the suspicion of a possible upper urinary tract abnormality because the ureter and vas deferens are both derived from the mesonephric duct (59). Ipsilateral renal agenesis occurs more commonly in these instances and may be identified by sonography in these boys. A persistent common mesonephric duct occurs when the terminal excretory duct fails to separate into the ureter and vas deferens, resulting in a persistent common single orifice located somewhere between the trigone and the verumontanum. This is associated with recurrent urinary tract infections and epididymitis and may be diagnosed by voiding cystourethrography (188) (Fig. 53.10). The ipsilateral seminal vesicle is often cystic, and the ipsilateral kidney is often dysplastic, suggesting total dysplasia of the mesonephric duct and metanephros in these instances (226,237).

Congenital Abnormalities of the Epididymis

Congenital abnormalities of the epididymis are varied, ranging from total absence to segmental atresias to gross structural abnormalities of the intact organ. Most abnormalities of the epididymis have been identified in patients with obstructive azoospermia and cryptorchidism. The latter has now been extensively studied in children, and numerous references confirm a spectrum of epididymal abnormalities in association with this condition. Epididymal abnormalities occur in approximately 33% to 50% of cryptorchid boys (184,238) and are especially associated with testes in an intracanalicular or intraabdominal position. The most common abnormality is an extended epididymis (Fig. 53.20) (159). In some instances, the looped epididymal tail may be markedly elongated, extending down the entire inguinal canal into the scrotum. In these circumstances, the epididymis may be mistaken for a blind- ending spermatic cord or an atrophic testis and may be inadvertently injured or excised, leaving an undiagnosed cryptorchid testis intraabdominally (Fig. 53.21) (155). Varying degrees of separation of the epididymis from the cryptorchid testis are also common, with the epididymis suspended on a mesentery (Fig. 53.22). Some of these abnormalities may have functional significance because they may result in occult microscopic ductal obstruction or may affect sperm capacitation.

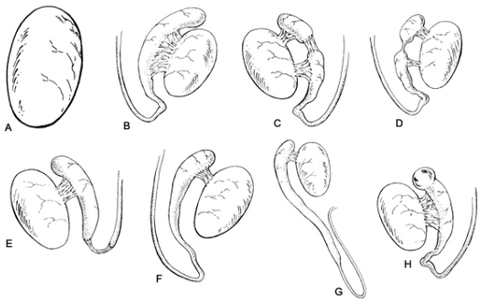

FIGURE 53.20. Congenital structural abnormalities of the epididymitis and vas deferens. **A:** Agenesis of all mesonephric duct derivatives. **B:** Nonunion between the globus major of the epididymis and the testis. **C:** Agenesis at the midepididymis. **D:** Atresia at the midepididymis. **E:** Agenesis or atresia at the tail of the epididymis. **F:** Extended or looped epididymis and vas deferens. **G:** Extended or looped epididymis and vas deferens, a more severe abnormality. **H:** Epididymal cyst of globus major. (From Kroovand RL, Perlmutter AD. Congenital anomalies of the vas deferens and epididymis. In: Kogan SJ, Hafez ESE, eds. *Pediatric andrology.* Boston: Martinus Nijhoff, 1981:173, with permission.)

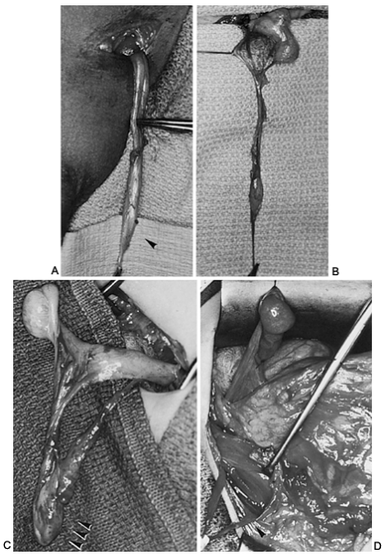

FIGURE 53.21. Epididymal structural abnormalities mistaken for blind-ending spermatic cord. **A:** Long-looped vas deferens with nubbin at end *(arrowhead).* The testis lies within the internal ring. **B:** Similar example with long-looped vas deferens and nubbin at end, extending down inguinal canal. The testis was intraabdominal. **C:** Older child with structure mimicking atrophic testis with collapsed surrounding tunica vaginalis at end *(arrowheads)* that had exited through the external inguinal ring. **D:** Blind-ending gubernacular-like structure *(arrowhead)* passing down through inguinal canal. The testis lies above within the abdomen. (From Kogan SJ. Cryptorchidism. In: Kelalis PP, King LR, Belman AB, eds. *Clinical pediatric urology,* 2nd ed. Philadelphia: WB Saunders, 1985, with permission.)

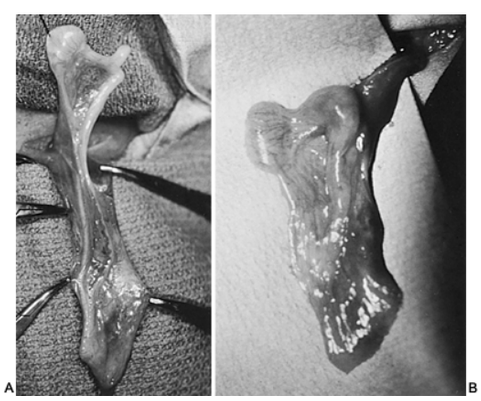

FIGURE 53.22. Examples of partial epididymal detachment in cryptorchid testes. **A:** Detachment of the body and tail with long-looped vas deferens. **B:** Virtually complete epididymal detachment with flimsy attachment at epididymal head by a few tubules.

CONGENITAL AND ACQUIRED DISORDERS OF THE TESTES

Part of "53 - PEDIATRIC ANDROLOGY "

Congenital disorders of the testes in childhood are one of the most common problems dealt with in pediatric urologic

practice. In this section, they are arbitrarily classified into disorders of number, size, and location.

Unilateral Congenital Absence of the Testes

Unilateral congenital absence of the testes occurs uncommonly, with an estimated frequency of 4.0% in cryptorchid males. Unilateral congenital absence (monorchia) occurs more commonly (1:25) than bilateral absence or anorchidism (1:20,000) (175). Absence of the testis may occur from either agenesis (i.e., total development failure of the gonadal ridge) or early deterioration of the testis at some time after initial formation (i.e., by torsion). Because normal fetal testis function is responsible for ipsilateral regression of the müllerian duct and stimulation of the ipsilateral mesonephric duct, examination of these structures gives inferential information about abnormal development of the ipsilateral testis. When the testis is found to be absent at surgical exploration, several distinct developmental findings may be encountered: a blind ending tuft of spermatic vessels, blind ending ductal structures (epididymis, vas, or both), blind ending spermatic cord (vas and vessels), or absence of all structures. In a review of 65 cases of surgically diagnosed monorchia, a blind ending spermatic cord was the most commonly encountered pattern, occurring in 69% of patients (Table 53.3). Absence of all structures, possibly indicating testicular agenesis, was extremely uncommon (14%), and müllerian remnant structures were not seen at surgery (148). Because the testis is necessary to induce ipsilateral formation of the wolffian (mesonephric) duct and cause regression of the müllerian duct, these surgical findings suggest that the testis formed initially but deteriorated subsequently (i.e., after the fourteenth week, when vas formation is completed). Furthermore, in 20% of patients, microscopic examination of a nubbin of tissue at the end of the excised spermatic cord revealed hemosiderin, calcification, or hyalinized tissue compatible with old testicular

infarction, suggesting that an *in utero* vascular accident had occurred (i.e., secondary to testicular torsion) (Fig. 53.23). These findings suggest that *in utero* testicular torsion may be the cause of most cases of congenitally "absent" testes and that most cases of testicular absence result from degeneration of a previously formed testis rather than primary agenesis (118).

Findings	Number	Percentage
Minispermatic vessels	47	72
Wolffian structures	54	83
Vessels and wolffian structures	45	69
Vessels and vas	20	31
Vessels, vas, and epididymis	12	18
Vessels, vas, epididymis, and terminal nubbin of tissue	13	20
Vas only	9	14
Vessels only	2	3
Absence of vessels and wolffian structures	9	14
TOTAL	65	100

TABLE 53.3. FINDINGS IN 65 PATIENTS WITH UNILATERAL ABSENT TESTES

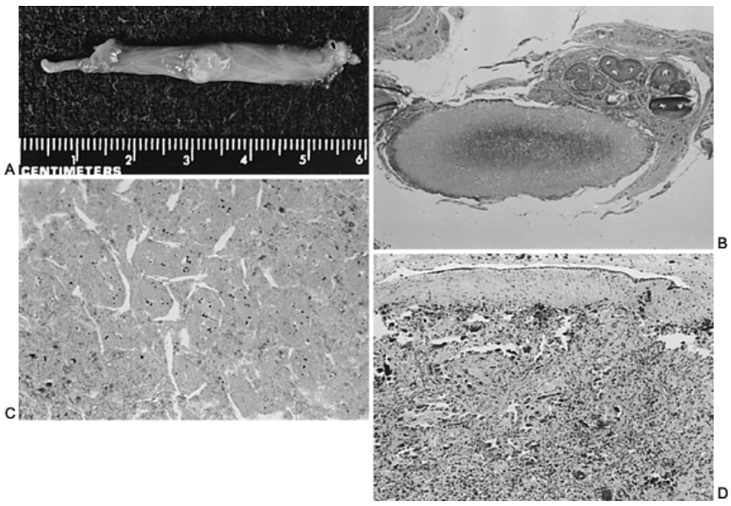

FIGURE 53.23. Gross and microscopic findings in congenitally absent testes. **A:** Surgical specimen of scrotal nubbin *(arrowhead)* in 3-month-old infant with impalpable testis. **B:** Microscopic view (reduced magnification from ×20) demonstrating necrotic debris with partial calcification in the center with adjacent epididymis. **C:** Higher-power view shows calcification and ghosts of remaining tubules (reduced magnification ×300). **D:** Infarcted testis parenchyma with focal calcification and hemosiderin. Tunica is present along with serosal surface superiorly (reduced magnification ×125). (From Kogan SJ, Gill B, Bennett B, et al. Human monorchidism: a clinicopathological study of unilateral absent testes in 65 boys. *J Urol* 1986;135:758, with permission.)

Bilateral Congenital Absence of the Testes

Similar findings are encountered in bilateral congenital anorchia, where vasa are usually found at surgical exploration (173). In this syndrome, absent testes are encountered in an otherwise normal 46,XY phenotypical male. Because testis formation is necessary *in utero* to stimulate external genital development, these findings imply that the testes deteriorated at some point in time after completion of masculinization (i.e., after the twelfth to fourteenth week). This syndrome has therefore been appropriately called the *vanishing testis* or *testicular regression syndrome* (1). Gonadotropin levels in anorchic boys are usually elevated, even early in life (Table 53.4). Even at birth, FSH levels may be elevated, as seen in boys with bilateral neonatal torsion (153)

and boys with congenital bilateral anorchia; however, LH levels may not elevate until puberty. Testosterone levels in anorchic boys do not rise in response to hCG stimulation; whereas most boys with testes present usually respond to hCG stimulation. When anorchidism is suspected, measurement of basal FSH and LH levels and the response of testosterone secretion to hCG stimulation have predicted the absence of functioning testicular tissue (5,173). When there is a failure to respond to hCG and an elevated FSH (and LH) level, bilateral congenital anorchia may be diagnosed and surgical exploration for confirmation of diagnosis is not necessary. In these instances, rather than performing an extensive exploratory laparotomy, testicular prostheses are placed through an inguinal incision. When both components of this test are not fulfilled, however (i.e., when a testosterone response to hCG occurs or when gonadotropin levels are not elevated even though a testosterone response does not occur), a thorough search must be made because a testis (at least one) lies within.

			hCG Stimulation Testosterone	
Age (yr)	LH (ng/mL)	FSH (ng/mL)	Before	After
4	21	318	25	24
5	29	330	31	32
5	29	320	43	41
5.5	61	475	40	40
6	24	308	23	21
7	25	321	25	25
7	27	328	42	44
9	80	900	36	40
10	37	370	44	43
12	180	2,100	62	65

FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

TABLE 53.4. ENDOCRINE STUDIES IN 10 ANORCHIC BOYS

Confusion regarding the interpretation and diagnostic accuracy of this test has arisen (154). Three cases with apparently false and misleading evaluations in which testes were found at surgical exploration have been published (10). In these instances, however, careful analysis reveals that both components of the strictly defined criteria of a negative test were not fulfilled. The editorial comment after publication also suggested that gonadotropin levels in bilateral anorchics may fall into the normal range between ages 4 and 8 years, resulting from relative pituitary-hypothalamic inactivity at this age. Although the latter information was extrapolated from anorchic 45,XO females who demonstrated this phenomenon and no similar data from anorchic boys were

presented, the implication was made that normal gonadotropin levels might occur in the absence of testes. A subsequent review of gonadotropin levels in 30 congenitally anorchic males revealed that one prepubertal patient had normal gonadotropin levels, although the remainder all had elevated levels, indicating that normal levels in prepubertal boys cannot exclude the diagnosis of anorchia. One of two pubertal patients with elevated levels had hypoplastic testes present, indicating the gonadotropin levels alone cannot diagnose anorchia in the postpubertal male (124). Similarly hCG testing alone will not distinguish between anorchia and bilateral impalpable cryptorchidism because a lack of hCG-induced response may occur in hypogonadotropic hypogonadal patients with testes present. Therefore caution must be exercised in analyzing data from postpubertal patients because secondary gonadal failure from damaged testes may be present, resulting (rarely) in elevated gonadotropin levels and failure of response to hCG. In summary, the endocrine diagnosis of bilateral anorchia rests only on demonstration of raised gonadotropin levels and a negative testosterone response to hCG. In other circumstances, a testis may be present (Table 53.5).

	FSH, LH	Testosterone After hCG
Testes Absent		
Bilateral congenital anorchia	↑	0
Possible in prepubertal bilateral congenital anorchia (i.e., ages 3–9 yr) LHRH→	Normal ↑	0 0
Testes Present		
Bilateral impalpable cryptorchidism	Normal	↑
Possible in hypogonadotropic hypogonadism	Low	0
Prolonged hCG →	—	↑
Possible in postpubertal bilateral hypoplastic/damaged testes present	↑	0

FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone.
From Kogan SJ. Work-up and management of the bilateral, non-palpable testis. In: Gonzales ET Jr, Roth DR, (eds.). *Common problems in pediatric urology.* Chicago: Year Book, 1991:302.

TABLE 53.5. FINDINGS IN DIAGNOSTIC HORMONAL TESTING FOR BILATERAL CONGENITAL ANORCHIA

Hormonal testing is not sufficiently accurate to predict unilateral testicular absence. Measurement of FSH and LH levels in 44 patients with monorchia revealed that mean levels were slightly higher than published control values, although too much variation in individual levels existed to make isolated measurements a clinically useful test. Peak-stimulated FSH and LH levels after GnRH stimulation in boys with unilateral impalpable testes who were subsequently found to have a testis present at surgical exploration were contrasted with those in boys having unilateral absent testes subsequently documented surgically. The results in both groups were indistinguishable, making it an insufficiently accurate clinical discriminatory test (Fig. 53.24) (148,213a).

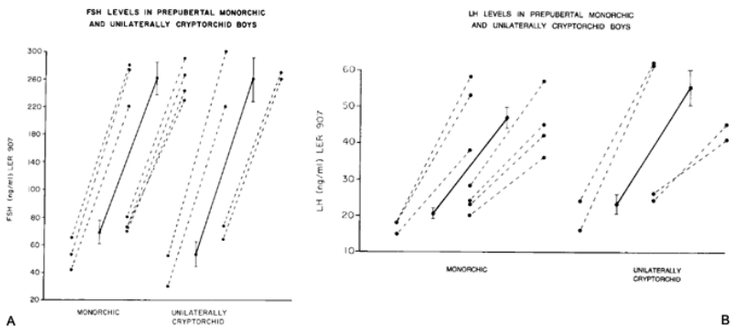

FIGURE 53.24. Follicle-stimulating hormone *(FSH)* **(A)** and luteinizing hormone *(LH)* **(B)** levels in prepubertal monorchic and unilaterally cryptorchid boys, both with clinically impalpable testes, after gonadotropin-releasing hormone (GnRH) stimulation. *Solid lines* represent mean values; *dotted lines* represent individual values. (From Palmer LS, Gill B, Kogan SJ. Endocrine analysis of childhood monorchism. *J Urol* 1997;158:594.)

Polyorchidism

Polyorchidism is a rare abnormality that probably results from division of the gonadal ridge early in development, as evidenced by the fact that both testes usually have a common proximal blood supply. Occasionally, a common vas deferens is present, although usually the epididymis and vas deferens are separate (189). In a review of 53 cases, Plender and colleagues (218) found that in 15% of patients, at least one of the ipsilateral testes was cryptorchid. Therefore, in most instances, the supernumerary testis is descended and discovered as an asymptomatic swelling in the scrotum. The usual indication for surgical exploration is for confirmation of diagnosis. Instances of torsion and malignancy also have been reported.

Abnormalities of Testicular Size

Abnormalities of testicular size are uncommon at birth. Newborn boys normally have testes measuring about 1 mL. The testes enlarge somewhat during the first few months of life, probably secondary to the postnatal testosterone surge

that occurs at 2 months of age, and then decline slightly in size remaining about 1 to 2 mL until puberty onset (34). Both hypoplastic and enlarged testes uncommonly occur at birth, the former usually the result of partial or complete antenatal torsion and the latter as a finding when the contralateral testis is hypoplastic (117). Testicular enlargement is the earliest sign of pubertal onset in boys, and successive pubertal stages are marked by progressive further testicular enlargement. Abnormalities of testicular size may be noted in both prepubertal and pubertal boys. Measurements of the testes may be accurately done with an orchidometer (Fig. 53.25), with the measured volume compared with published measurements in normal boys at varying ages (235).

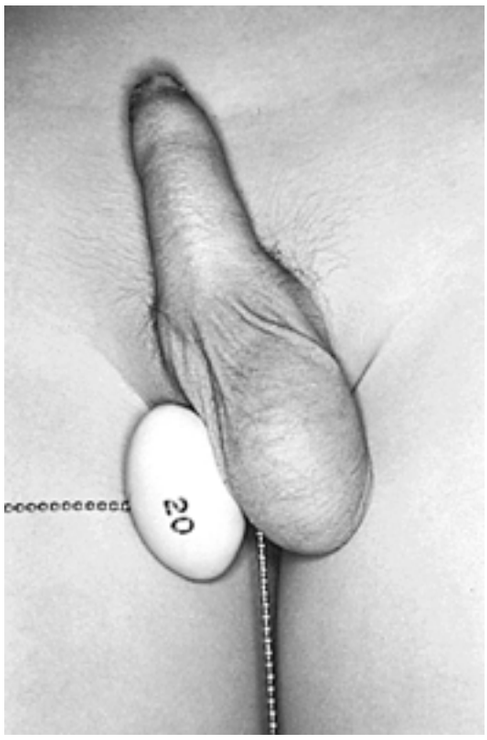

FIGURE 53.25. Compensatory hypertrophy of the descended testis of a 12-year-old boy with unilaterally absent contralateral testis. A testis of 20 mL represents the ninety-ninth percentile. At age 13 years 2 months, the testis had grown to 50 mL. (From Kogan SJ. Fertility in cryptorchidism. In: Hadziselimovic F, ed. *Cryptorchidism: management and implications.* New York: Springer-Verlag, 1983:71, with permission.)

Microorchidism

Microorchidism may be congenital or may be associated with various syndromes. Najaar and colleagues (201) described a syndrome of bilateral hypoplastic rudimentary testes and micropenis in siblings in whom the testes were markedly diminished in size and hormonally deficient. The testes are noted to be smaller than expected in Klinefelter's syndrome, even prepubertally (28), and in abnormalities of the hypothalamic-pituitary-gonadal axis (hypogonadotropic hypogonadism). Failure of growth may also result in microorchidism, as is often seen in boys with cryptorchidism and with varicoceles. Smaller-than-normal testes were seen in 19% of cryptorchid boys at stage P2 puberty, 28.6% at stages P3 and P4, and 38% at stage P5 (54). Abnormally small ipsilateral testes have been described in 33% to 50% of

boys with varicoceles, with this finding occurring more commonly after puberty and in association with large varicoceles (136,156,180). Testicular atrophy also may cause small testes, such as atrophy secondary to previous hernia repair with partial vascular compromise to the testis or testicular torsion. The latter may be a common cause of “idiopathic” testis hypoplasia (148).

Macroorchidism

Unilateral macroorchidism usually results secondarily from a disorder of the contralateral testis, that is, from atrophy or absence, secondary to congenital monorchia or previous torsion (117,148), or from cryptorchidism. Unilateral compensatory hypertrophy was found in 12% of boys with undescended or absent contralateral testes and was associated with FSH hypersecretion. Adult follow-up of seven men revealed oligospermia, suggesting that the hypertrophied testis was abnormal as well (163). Bilateral testis enlargement is sometimes associated with various syndromes. Precocious puberty (i.e., resulting from an intracranial mass) may cause premature skeletal growth and secondary sexual development and testicular enlargement commensurate with the patient's pubertal stage. Hypothyroidism uncommonly causes precocious puberty and bilateral testicular enlargement. Boys with mental retardation have an increased frequency of bilateral macroorchidism. Some have a rare chromosomal disorder in which a small, almost detached portion of the long arm of the X chromosome is seen (fragile-X syndrome) (263). Measurement of testis size in mentally retarded males has been suggested as a simple screening test for this condition. Occasionally, a patient is encountered with unilateral or bilateral macroorchidism in the absence of an identifiable cause (“idiopathic”) (24,168). Gonadotropin measurements and a thorough thyroid evaluation should be done, as well as scrotal sonography, to exclude a subtle intrascrotal neoplastic process. If these are normal, there is usually no indication for scrotal exploration or biopsy.

Adult-onset or acquired congenital adrenal hyperplasia is another rare cause of unilateral testicular enlargement (39). More commonly, in children, this condition results in bilateral testicular enlargement, usually with testicular nodularity resulting from islands of benign hyperplastic adrenal tissue within the testis (141,203). The latter conditions are sometimes difficult to distinguish from testicular Leydig cell tumors, which may have similar clinical and endocrinologic manifestations (269). Serotal sonography is useful in diagnosing these conditions and in evaluating potential neoplastic causes of unilateral and bilateral testicular enlargement.

Cystic Testicular Dysplasia

Cystic dysplasia is an uncommon cause for painless testicular enlargement in childhood but one that is now recognized with increased frequency. Failure of fusion between the efferent ducts and the rete testis and the epididymal ducts, which results from abnormal mesonephric duct connection with the testis, is the presumed cause. The frequent finding of ipsilateral renal agenesis, dysplasia, duplex kidneys, and seminal vesicle cysts supports this theory. This testis is enlarged, with a sonographic finding of multiple tiny punctate cystic lesions compressing the normal adjacent parenchyma. Providing the diagnosis is established with certainty, observation or subtotal or complete orchiectomy is indicated and treatment must be individualized (171).

Abnormal Descent of the Testes: Cryptorchidism

Incidence

Available data suggest that the incidence of cryptorchidism in premature boys is 9.2% to 30.0%, whereas the incidence of cryptorchidism in term boys is 3.4% to 5.8%. Kleinteich and colleagues (144) have combined several previous studies and found that after 1 year, 1.82% of 88,526 patients had undescended testes. The percentage remained the same until puberty. Scorer and Farrington (238), however, found that at the end of 12 months, 28 of 3,612 babies (0.8%) still had cryptorchidism, and the incidence remained the same up to puberty. These findings underline that after the first year spontaneous descent is unlikely to occur.

Locations

Abnormal descent causes the testis to occupy an ectopic or truly undescended position outside the scrotum. Ectopic testes descend normally through the external inguinal ring but are misdirected in the subsequent descent to an extrascrotal position. Fibrous obstruction of the scrotal inlet and abnormalities of the gubernacula have been described in association with this condition. The most common site of ectopia is the superficial inguinal pouch between the external oblique aponeurosis and the subcutaneous tissue. Perineal, prepenile, transverse scrotal, femoral, and abdominal positions are other less common sites of ectopia. By contrast, true cryptorchid testes are arrested in their normal line of descent and may occupy an intraabdominal, intracanalicular, or suprascrotal position. Whereas the latter testes may be responsive to hormonal treatment, the former (ectopic) testes are mechanically fixed in place, therefore requiring operative treatment (Fig. 53.26).

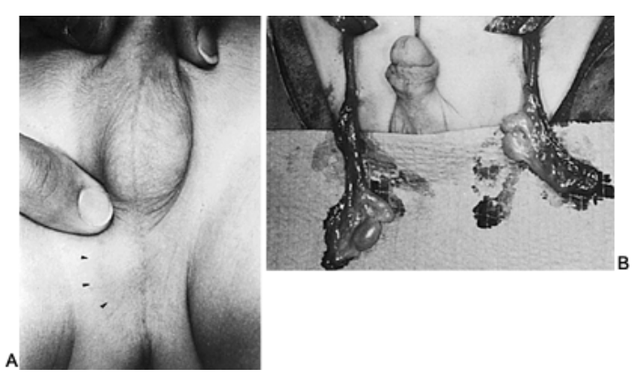

FIGURE 53.26. A 3-year-old boy with (right) perineal ectopic undescended testis and (left) inguinal cryptorchid testis. **A:** Gross examination reveals perineal bulge *(arrowheads)*. **B:** Surgical exposure demonstrates differences in spermatic cord length and in testis size.

Cryptorchidism, or incomplete testicular descent, can be described as unilateral or bilateral, and the position of the testis as abdominal, inguinal, prescrotal, or gliding. The gliding testis is not a retractile testis but rather one that upon being manipulated to the upper portion of the scrotum immediately retracts. However, these testes have the same histology as the cryptorchid testes arrested in their true line of descent, in contrast to true ectopic testes, which have a

normal histology. Therefore the term *ectopic testis* should be used only for those testes that descend normally through the external inguinal ring but are misdirected in their subsequent descent to perineal, prepenile, transverse scrotal, femoral, or umbilical positions.

One-third of boys with true cryptorchidism have bilateral cryptorchid testes; two-thirds are unilateral. The right side seems to be affected more often than the left side (70% versus 30%). Abdominal cryptorchidism has been found in 8% of patients, inguinal cryptorchidism in 72%, and prescrotal cryptorchidism in 20%. In 2.6% (156 of 6,127) of patients, testicular aplasia or anorchia has been observed (144).

Histology and Endocrine Pathology

Reduced number of germ cells is the most clinically significant histopathologic feature of the cryptorchid testis (96). In some hands, the degree of germ cell reduction is prepubertal biopsies is used to predict future fertility and to select patients for hormonal treatment to stimulate germ cell maturation and proliferation. The reduction in number of germ cells becomes apparent during the second year of postnatal life and persists thereafter. Several large series show a remarkably similar reduction in numbers of germ cells expressed as the number of germ cells per tubule (Fig. 53.27 and Fig. 53.28) (234). The origins of this germ cell depletion lie in impaired function of the hypothalamic-pituitary-gonadal axis and resultant failure to establish an adequate adult stem cell pool (adult dark spermatogonia) during the second month of postnatal life, failure to initiate meiosis during the fifth year, and failure to establish complete spermiogenesis at puberty. Intrauterine germ cell hypoplasia extends the endocrinopathy back into the prenatal period. These endocrine abnormalities are the rationale for the hormonal treatment of the reduced numbers of germ cells characteristic of the cryptorchid testis (97,103).

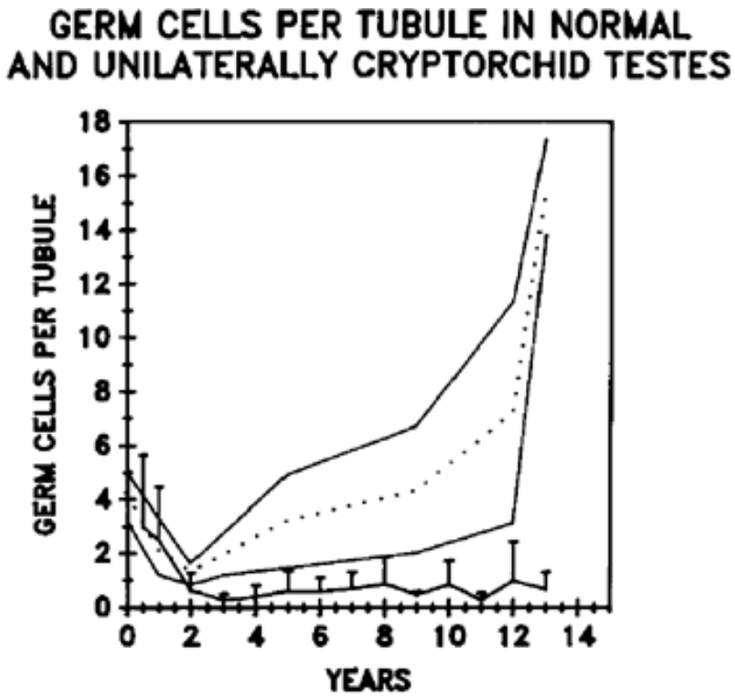

FIGURE 53.27. Germ cell counts in unilateral undescended testis (bottom line) compared with normals. (*Dotted line* = mean ± 1 SD.)

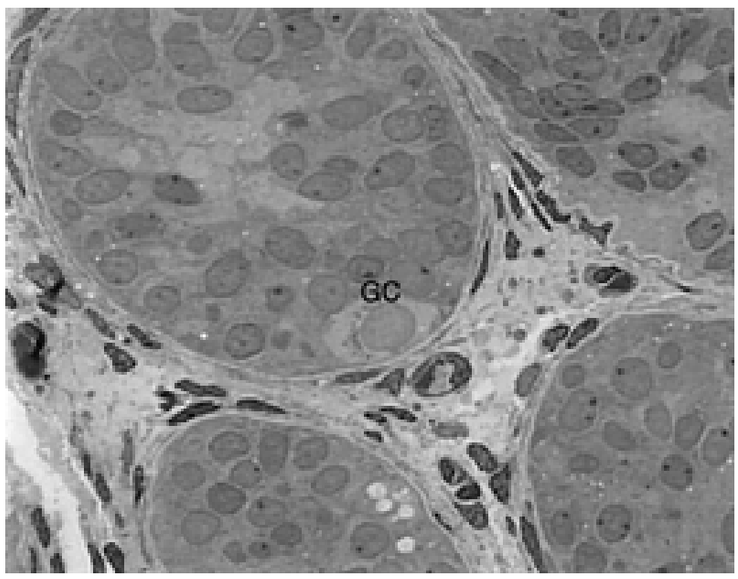

FIGURE 53.28. Histopathology of undescended testis. Absence of juvenile Leydig cells. Tubule with rare germ cells *(GC)* and absence of adult spermatogonia and primary spermatocytes. (Semithin section, toluidine blue; 600× magnification.)

Intrauterine Abnormalities

Little is known regarding possible abnormalities of the first two steps in maturation. Germ cell hypoplasia in 23% of cryptorchid testes in the third trimester of pregnancy is the earliest histologic abnormality described (47), suggesting an intrauterine abnormality in the endocrine control of Leydig cell proliferation and reduced testosterone secretion (92). Confirmation of these findings would add to the existing evidence that reduced levels of testosterone may contribute

to failure of testicular descent in addition to failure of proliferation and maturation of germ cells.

Abnormalities of the Third Step in Maturation, Second Postnatal Month: Failure to Develop an Adequate Adult Stem Cell Pool

Transformation of the fetal stem cell pool (gonocytes) into the adult stem cell pool (adult dark spermatogonia) normally seen in the second postnatal month is defective and delayed in cryptorchid boys. The LH and FSH surge does not normally occur (76). Fetal Leydig cells remain hypoplastic and unstimulated (89,93,115,118). The normal testosterone surge does not develop (7,75,88). Therefore gonocytes neither mature into adult dark spermatogonia nor disappear through apoptosis; rather, they persist through the first year of life. This causes the characteristic cryptorchid testis pathology during the first year: increased numbers of total germ cells, increased numbers of gonocytes, absence of adult dark spermatogonia, and hypoplasia of Leydig cells (115,116). When the abortive transfer occurs at around 12 months, many fewer gonocytes than normal mature into adult dark spermatogonia while many more than normal undergo apoptosis and disappear. This causes the characteristic appearance of the cryptorchid testis after the first year of life: reduced numbers of all germ cells and a disproportionately severely reduced number of adult dark spermatogonia. Failure to develop a normal adult stem cell pool (adult dark spermatogonia) during the first year causes the continued reduction in germ cell counts which persists thereafter.

Abnormalities of the Fourth Step, Fifth Postnatal Year: Failure to Initiate Meiosis

The peaks in numbers of juvenile Leydig cells, adult dark spermatogonia, and total germ cells that normally appear at 5 years of age fail to appear in cryptorchid testes. Primary spermatocytes, which normally appear at this time, fail to appear (115,116,118). Failure to establish meiosis during this maturational step contributes to the continued low numbers of germ cells in the cryptorchid testis.

Abnormalities of the Fifth Step, Puberty: Failure to Obtain Complete Spermatogenesis

The response of the cryptorchid testis to pubertal gonadotropin stimulation varies. In some, the response is so weak that proliferation of the adult stem cell pool (adult dark spermatogonia), meiosis, and spermiogenesis fail to occur. In others, a partial response leads to transient abortive meiosis and spermiogenesis. During early puberty, many cryptorchid testes have a severely reduced number or complete absence of germ cells. Rarely, a cryptorchid testis may show focal spermiogenesis only to the spermatid stage, and the spermatids show severe morphologic abnormalities. The histopathology becomes more severe with age so that by early adulthood all untreated cryptorchid testes completely lack germ cells.

The failure to establish a normal adult stem cell pool during the first year of life, the reduced numbers of germ cells, and the failure of spermiogenesis during puberty cause the subfertility of cryptorchidism. A direct correlation exists between the number of germ cells in prepubertal cryptorchid testis biopsies and the quality of spermiograms in late adolescence and early adulthood, with boys who have the most severe reduction in germ cell numbers having the poorest spermiograms and greatest risk for subfertility (47,98).

Histology in Relation to Position of the Testis

The number of tubules with germ cells and the number of the spermatogonia per tubule change considerably with the position of the testicles. The higher the testis location, the worse its histology (101,238). By the onset of puberty, more than 90% of all intraabdominally located testes completely lose their germ cells, whereas in inguinal and prescrotal testes, a total absence of the germ cells was noted in 41% and 20% (101).

Histology of the Contralateral Descended Testis in Unilateral Cryptorchidism

Unilateral cryptorchidism is a bilateral disease. The contralateral descended testis in unilateral cryptorchidism is abnormal, demonstrating similar abnormalities to those in the cryptorchid testis, but to a lesser degree (Fig. 53.29) (115,116). The contralateral descended testis affects fertility. A nearly normal contralateral descended testis may provide adequate fertility even in a patient with a severely abnormal cryptorchid testis. A contralateral descended testis with an inadequate adult stem cell pool, failure of meiosis, inadequate numbers of germ cells, and failure of spermiogenesis

will ensure subfertility in a patient with a severely involved cryptorchid testis.

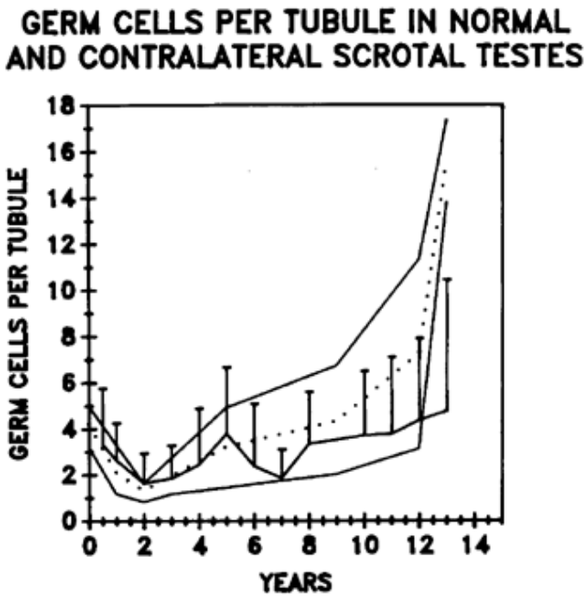

FIGURE 53.29. Germ cell counts in contralateral descended testes (line with spikes) in unilateral cryptorchidism compared with normals. (*Dotted line* = mean ±1 SD.)

Biochemical Evidence for Hormonal Involvement

A normal increase in plasma testosterone in the early postnatal period does not occur in most boys with undescended testes (75). Furthermore, an impaired LH and FSH response to GnRH has been observed in boys with cryptorchidism (29). Finally, impaired testicular testosterone response to hCG has also been noted in cryptorchid boys (69). This deficiency of LH and consequently of testosterone secretion disappears after puberty (29). Some of the patients with the most pronounced hypogonadotrophic hypogonadism in prepuberty develop hypergonadotropic hypogonadism after puberty (90).

Diagnosis

Examination Technique

Every general pediatric examination in boys should include examination of the testicular position. The room and the examiner's hands have to be warm, the boy being examined should be given time to relax, and the examination should not be hurried. If cryptorchidism is suspected, the patient should be examined in the cross-legged position. Once the patient is sitting comfortably in this position, most retractile testes descend spontaneously without being manipulated by the examiner. The gonad may be manipulated gently into the scrotum with the thumb and forefinger. Another helpful approach, particularly in older boys, is application of pressure on the femoral artery in the groin. If the testis is retractile, it should immediately descend and remain in the scrotum for a while. Testicular volume can be established by estimating the length and short diameter of the testis or by measuring the testis with an orchidometer. Testes that do descend into the upper portion of the scrotum but immediately upon release return to the prescrotal position are gliding testes and need to be treated.

High scrotal testes have an increased tendency to glide, and the scrotum may be less developed on the affected side. The management of these high scrotal testes is difficult. Most have normal histology, but in a small proportion, considerable damage to the gonad develops with time. Therefore a careful annual check of the development and position of these gonads is recommended. If any doubt concerning lack of proper growth and position arises, hormonal treatment should be started, particularly if the testis becomes a gliding one.

Diagnostic Tests

Ultrasound has been frequently used in the diagnosis of impalpable testes; however, clinical experience indicates a very high rate of misdiagnosis. In many instances, the testis will be reported as absent but is easily palpable in the groin or scrotum at clinical examination. Because ultrasound demonstration of a testis demands that a surgical procedure follow anyway and because of the high false-negative rate (testis present despite negative ultrasound) and need for surgery to follow, ultrasound diagnosis is unuseful in most instances (113).

Computed tomography (CT) scanning has been reported as being more accurate, but its radiation burden to the small child is significant and it still falls short of the essentially 100% accuracy needed in these instances. Similarly, magnetic resonance imaging (MRI) evaluation is involved, cumbersome, and expensive and can be justified only in select cases (e.g., extremely obese individuals in whom the surgical morbidity may be outweighed by the potential information gained). These experiences have led to our abandoning routine radiologic evaluations for impalpable testes, because they are not sufficiently accurate and are not cost-justifiable. Instead, we practice selective diagnostic laparoscopy in certain instances.

Laparoscopy

The use of laparoscopy for the diagnosis of impalpable testes was first suggested by Cortesi and co-workers (48) as an outgrowth of cystoscopy. In recent years, the explosive growth of laparoscopic surgery has led to its enthusiastic application to patients with impalpable cryptorchidism. In approximately 20% of cryptorchid boys, the testis is impalpable; in approximately one-fourth to one-third of boys, these the testes will be found to be intraabdominal. Here, one would hope laparoscopy would have its greatest utility.

In a survey of the American Academy of Pediatrics, Urology Section, covering 5,428 cases, 75% of the members used laparoscopy for evaluating impalpable testes. The minor complication rate was about 4%, and a significant complication (bleeding; bowel, bladder, or vascular injury; or omental herniation) occurred in about 1% (217). With refinements in technique, added experience, and further miniaturization of instruments, even the neonate can now safely undergo laparoscopy.

The real issue then is whether *routine* use of laparoscopy for diagnosing impalpable testes is justified or whether *selective* use is more rational. Opinions vary widely, but the data indicate that routine use for diagnosis alone is not warranted unless laparoscopic surgical treatment is to follow as well. Proponents of the "routine" view claim that the procedure adds little time and helps them decide better incision placement and plan the surgery better. Advocates of the "selective" viewpoint indicate that laparoscopy is not cost-effective or patient-friendly because many "unnecessary" laparoscopies are done (i.e., routine inguinal exploration would have provided the same information in virtually all instances).

Diagnostic laparoscopy is most useful when it obviates the need for further surgery. In Fig. 53.30, summarizing the locations of 432 impalpable testes, it appears to be helpful in only 10% (the intraabdominal vanishing testis group and absent vas and vessels group). Exploration was required in all abdominal and inguinal testes to perform orchidopexy and to confirm the diagnosis in the inguinal vanishing testis group. However, additional consideration must apply, incorporating the benefits for those who alter their incision locations when an abdominal testis is present and for those performing laparoscopic orchidopexy, which is a logical treatment following laparoscopic diagnosis and which would benefit an additional 27% (intraabdominal testis group). Other similar analyses echoes these findings (42).

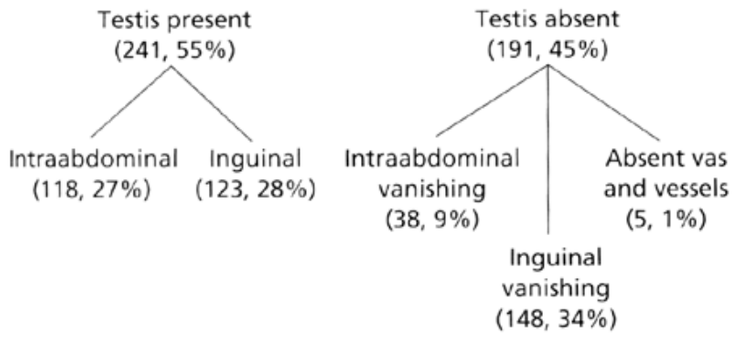

FIGURE 53.30. Laparoscopic findings in 432 impalpable testes: a collation of five series.

Our experience indicates that exploration through a standard inguinal incision, with intraperitoneal extension, when necessary, demonstrates all of the needed information in most instances. In younger boys who have a hint of atrophic testicular tissue in the scrotum and who demonstrate contralateral testicular hypertrophy, laparoscopy is superfluous. In older obese boys with normal scrotal development, laparoscopy is also usually unnecessary because the testes are present, although impalpable. We believe that laparoscopy is useful in reoperative cases in which an incomplete exploration has preceded (failure to visualize spermatic vessels or explore intraperitoneally). Therefore the decision for laparoscopy rests on the personal experience of the operator: whether a standard inguinal incision is used routinely, whether a testicular prosthesis will be inserted (requiring a suprascrotal incision anyway), and whether laparoscopic orchidopexy will be undertaken. Therefore surgeon's bias plays a significant role.

Treatment

Indications

Once cryptorchidism is diagnosed, early treatment (age 8 to 12 months) should be initiated. The main indications for early treatment are the increased infertility risk in both unilateral and bilateral cryptorchid patients, increased malignancy risk, and increased risk testicular torsion. Treatment of the often-associated inguinal hernia is an additional benefit. Prevention of the psychologic problems because of an empty scrotal sac plays a lesser but still important role. Early hormonal treatment and early surgical treatment have not been shown to engender any increased risk.

Fertility Outcome

In 1960, Charny (37) stated:

> Testicular biopsy in a large number of testes brought into the scrotum by a variety of techniques failed to reveal a single instance of normal spermatogenesis. The prevailing methods of treatment of cryptorchidism are not satisfactory and the operative techniques as practiced by most surgeons yield better cosmetic than functional results. If the surgical technique cannot be improved sufficiently, boys with asymptomatic cryptorchidism without clinically recognized hernia should be spared the hazard and inconvenience of orchiopexy.

Identical observations were promulgated by Mack and colleagues (181), Canlorbe (30), and Sizonenko and co-workers (246). Patients completely lacking germ cells will, in all probability, develop sterility, and even a successful prepubertal orchiopexy cannot significantly improve the number of germ cells in their gonads or their fertility. These observations have been confirmed in prospective studies that reaffirmed the poor fertility prognosis for either unilaterally or bilaterally cryptorchid patients lacking germ cells who underwent orchiopexy during the prepubertal period (90). As a consequence of undescended testes, some investigators find infertility rates as high as 32% in unilateral cryptorchid patients and 59% in bilateral cryptorchid patients (100,146). By adulthood, previously cryptorchid testes have only 10% of the germ cells found in the normal

population despite prepubertal orchiopexy (144). Although some improvement in the germ cell content of cryptorchid testes that were successfully operated on was achieved, biopsy results showed that not a single testis out of 235 (79 unilateral cryptorchid testes, 78 bilateral cryptorchid testes, and 78 contralateral descended testes) that was intrascrotal 1 or several years after surgery achieved the normal level of germ cells (144).

During the last 20 years, early orchiopexy (by 1 year of age) has become the standard of treatment for boys with cryptorchidism (240). Published studies and general experience indicate that with appropriate training, orchidopexy can be performed as safely and efficiently in these earlier years as in the older child. By performing early orchidopexy, it is hoped that the progressive histologic deterioration noted in cryptorchid boys will be arrested and that early scrotal testis placement ultimate fertility will be preserved.

Cryptorchid Testis and Malignant Changes

One indication for correction of cryptorchidism is the recognized increased risk of neoplasia. It is difficult to determine the true incidence of cancer in cryptorchid patients because the data are not precise and calculations are often based on statistical assumptions; accordingly, statistics vary. There is evidence that the risk of testicular cancer is increasing in the United States and in Denmark. The current lifetime risk for all American males is approximately 0.2%, or 1:500 (285). The combined risk for all cryptorchid males, irrespective of the location of the testes, has been calculated at 20 to 46 times greater than for patients with normally located testes (38). Other epidemiologic studies suggest that the lifetime risk is only about ten times that of men with descended testes (63,236). In a case-control study of 108 cases of testicular cancer in men younger than age 30 years, cryptorchidism was a major risk factor, with a relative risk (RR) equal to 9.0 (53). A reasonable summary of these data, which can be given to parents, is that men with descended testes have a 1 in 500 lifetime risk of developing testicular cancer, whereas men with cryptorchid testes have a 1 in 50 incidence. The multiple factors that affect germ cell development may result in various degrees of atrophy and tubular dysgenesis, which may later result in malignant changes (50).

There are reasonably strong data indicating that the abdominal cryptorchid testis has a significantly higher risk of developing cancer than the inguinal cryptorchid testis; therefore these patients require increased lifelong surveillance. Abdominal undescended testes showed a fourfold increased risk over inguinal undescended testes in one series (50). In about 10% of individuals with unilateral cryptorchidism and cancer, the tumor develops in the contralateral testis, suggesting a possible genetic predisposition. Similarly, there is an increased frequency of carcinoma *in situ* in the cryptorchid and contralateral descended testis (248). These findings were found in less than 1% in prepubertal and adolescent biopsies of cryptorchid testes (91); however, in one study, 8% of men had a previous orchidopexy (247). When a unilaterally cryptorchid testis is the site of a testicular cancer or carcinoma *in situ,* biopsy of the contralateral descended testis may be indicated.

The issue of the malignant potential should be discussed with the patient's parents. If he is prepubertal, the parents should be informed that orchidopexy will not reduce the risk of cancer; that the risk, although low, is higher than in a descended testis; that orchidopexy will allow for early diagnosis if a malignancy develops; and furthermore, that such tumors have an extremely high cure rate. If the patient is postpubertal, a careful discussion of the risks and the benefits of orchiectomy versus orchidopexy should be presented so that the family may make an informed decision.

Hormonal Treatment

Hormonal therapy has been used for two purposes: (a) induction of testicular descent and (b) stimulation of germ cell maturation and proliferation to improve fertility in those boys at greatest risk for subfertility (less than 0.2 germ cells per tubule). Testicular descent and germ cell maturation and proliferation are thought to be androgen dependent. hCG treatment was the only treatment used for testicular descent until approximately 1975. Bergada (16) reported the largest series of hCG-treated boys. He obtained a success rate of 40% in boys with bilateral cryptorchidism and 33% in those with unilateral cryptorchidism. Experience indicates that the success rate is higher in older children, which argues against its use because current practice is to treat cryptorchid boys by 12 months of age. Furthermore, if retractile testes are carefully excluded from the groups undergoing treatment, data indicate that the overall success rate is low. In addition, a 20% subsequent retraction rate in “successfully” treated boys has been reported.

Treatment with GnRH nasal spray was introduced in Europe in 1975 for treating testicular descent, with variable success rates (13% to 78%) reported. The drug was never released in the United States for this purpose. European investigators then began treating cryptorchid boys with GnRH nasal spray (Kryptokur) in combination with hCG (87). Boys with retractile testes were excluded. The success rates for induction of descent were measured in a meta-analysis of 33 trials, 11 of which were randomized, published between 1958 and 1990. The success rates were 12% for Kryptokur versus 5% for a placebo. The success rates in all randomized trials were 21% for GnRH, 19% for hCG, and 45% for placebo (223).

The Basel treatment protocol combines Kryptokur 1.2 mg per day for 28 days, followed by hCG 1,500 IU per week for 3 weeks. The success rate reported for permanent testicular descent 4 years after completion of treatment was 65%. Nearly identical results (67%) were reported by Waldschmidt and colleagues (270) after a follow-up of 5 years. The effectiveness of a low-dose LH-releasing hormone

(LHRH) analog (Buserelin) was evaluated in a double-blind, placebo-controlled study. Matched patients were assigned randomly to receive Buserelin, placebo, or surgery. Buserelin (20 μmg) was administered daily in a nasal spray, and some patients were treated subsequently with hCG. Twenty-eight percent of the Buserelin-treated cryptorchid testes descended, contrasting with none in the placebo group. hCG influenced descent in both groups but was more efficacious when administered after treating with Buserelin. Boys treated with Buserelin had the highest number and the best maturation of germ cells; hCG did not further affect germ cell maturation. The results of these treatments were better the lower the position of the testis and the younger the patient before treatment. Those who responded to hCG treatment had better spermiograms than those who had surgery alone or received no treatment (91).

These results indicated the beneficial effect of Buserelin on the germ cells. Therefore one rational approach for treatment of cryptorchidism is to initiate treatment with GnRH (Kryptokur) followed by hCG. This can be expected to induce complete permanent descent in 20% to 65% of patients, depending on the pretreatment position of the testis. No further treatment is needed in this group other than routine follow-up. The remaining nonresponders undergo orchidopexy and testicular biopsy. If fewer than 0.2 germ cells per tubule are found, the outlook for fertility is poor, and patients are treated with Buserelin nasal spray (10 μmg by nasal spray every other day for 6 months after orchidopexy) to stimulate germ cell maturation and proliferation and thereby improve the outlook for future fertility. This approach forms the basis for contemporary medical treatment of boys at high risk for subsequent subfertility (fewer than 0.2 germ cells per tubule at biopsy), as practiced in some countries, but this approach is not an option presently in the United States, where Kryptokur and Buserelin are not available for these treatments (20,91).

Temporary penile enlargement has been reported with hCG use but not as a side effect of GnRH treatment. Occasionally, testicular pain may be encountered as well during treatment. If this occurs, treatment should be terminated and orchidopexy performed to minimize the possibility of testicular torsion (102).

Recent reports of increased germ cell apoptosis in patients treated with hCG but not with primary surgery have led some to conclude that hormonal treatment may injure the testis and impair fertility. These findings were not confirmed in our studies, in which apoptosis of Sa Sertoli cells during hormonal treatment were noted; however, these cells usually undergo increased apoptosis during testicular maturation (95). Others have found that a higher number of spermatogonia per tubule were present in biopsies of 1- to 3-year-old cryptorchid boys undergoing surgery alone versus those pretreated unsuccessfully with hCG or GnRH, concluding that hormonal treatment may be deleterious in this age group (46). Alternatively, hormonal treatment in this context may be selecting out treatment failures whose biopsies may be expected to demonstrate poorer histopathology.

SURGICAL ASPECTS OF PEDIATRIC ANDROLOGY

Part of "53 - PEDIATRIC ANDROLOGY "

Surgical Aspects of the Testicular Vasculature

Studies investigating the significance of the vascular supply of the human testis have been limited. Studies of testicular blood supply in the fetus with cryptorchidism, in patients with varicoceles, and in patients with cryptorchidism offer interesting and contrasting insights into clinical significance.

The normal adult descended testis is supplied by three arteries: the internal spermatic artery, derived from the aorta; the vasal artery, derived from the inferior vesical artery; and the cremasteric artery, derived from the inferior epigastric artery. Dissections in fetuses between 13 and 33 weeks of gestation demonstrated that all testes had an intact internal spermatic artery and vasal artery, and about three-fourths had all three arteries present, whether they were in an abdominal undescended position or were descended. Fetal testes with only two arteries present were always within the abdomen (232). Another study done in cadavers of all ages, including 11 children, demonstrated that the vasal and internal spermatic arteries were equal in size and that large-caliber anastomoses between the internal spermatic and vasal arteries were present in 87% of specimens (167). The testicular veins follow similar patterns, intercommunicating within the pampiniform plexus at the testicular level. Intraoperative venographic studies performed at the time of varicocelectomy have defined well the characteristic venographic patterns of the testis (Fig. 53.12), and experimental venographic studies have indicated that the main collateral drainage from the descended testis (i.e., after ligation of the internal spermatic vein) is through the cremasteric veins, not the vasal veins (132).

However, some have questioned whether the vasculature in cryptorchid patients corresponds to the normal descended testis. High ligation of the internal spermatic artery and vein (i.e., at the time of radical nephrectomy for Wilms' tumor) is not associated with atrophy of the descended testis. Similarly, high ligation of the internal spermatic artery and vein at the suprainguinal ring level at the time of varicocelectomy (Palomo procedure) does not generally result in testicular atrophy. In cryptorchid boys having a long-looped vas, major intercommunications between the internal spermatic artery and vasal collaterals are present, allowing for reasonably safe high or low vessel ligation in most instances (140,145). In the true abdominal testis without a long-looped vas, internal spermatic artery ligation may be less reliable, explaining the divergent

results that have been reported when this procedure is applied without making this distinction. In this circumstance, the main collateral arterial supply may be from the vasal artery because the cremasteric arterial collaterals may be developed only in the normally descended testes (26). If these collaterals are underdeveloped, microvascular orchidopexy, staged internal spermatic vessel transection orchidopexy, or staged orchidopexy may be considered. Previous inguinal surgery also may alter the normal venous and lymphatic drainage.

Studies of the intratesticular arteries demonstrate also that the main artery lies posteriorly underneath the epididymis, then coursing anteriorly in a very superficial position before branching and penetrating deeply. The superficial location, especially at the lower pole, makes it vulnerable to damage from traction sutures (i.e., during orchidopexy), so awareness of the course of the artery and individual visualization in each case is important (125). This and the previous information regarding the arterial and venous supply of normal and descended testes is of practical importance in performing (individualized) testicular surgery.

Surgical Inguinal Anatomy

A knowledge of the anatomy of the inguinal canal helps keep the surgeon out of trouble. A better understanding of the retroperitoneal fascial anatomy permits an improved understanding of the anatomic basis for orchidopexy and herniorrhaphy (120). The essential concept is that the retroperitoneal fascia outside the peritoneum is a continuous layer acting as a “felt” in which the spermatic vessels and vas, as well as the ureter, are imbedded and bound (Fig. 53.31A). This fascia, also known as the *endoabdominal fascia,* has a number of areas of condensation. In the floor of the inguinal canal, it is condensed as transversalis fascia. It is then reflected in a thinner form as the internal spermatic fascia enveloping the vas, vessels, and processus vaginalis within the inguinal canal. This layer is just inside the

cremaster muscle, which is an extension of the internal oblique muscle.

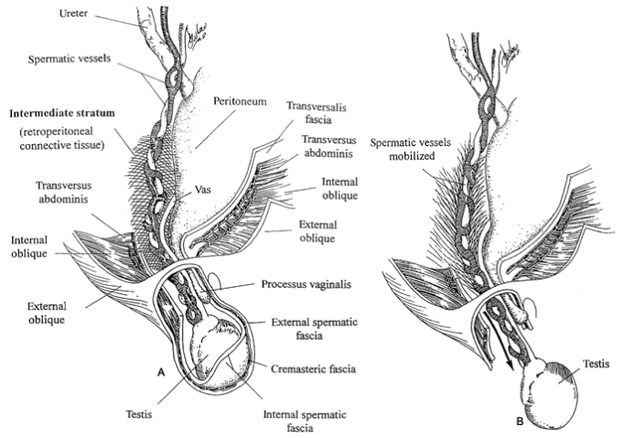

FIGURE 53.31. A: Surgical anatomy of the inguinal canal. The spermatic vessels and vas are imbedded and bound in the retroperitoneal fascia outside the peritoneum. **B:** An undescended testis must be freed by freeing the vas and vessels from the retroperitoneal endoabdominal fascia. This permits even intraabdominal testes to be placed within the scrotum.

When the testis stops short of a normal descended position, the vas and vessels are enveloped in the retroperitoneal endoabdominal fascia. Freeing these structures from their fascial attachments permits even intraabdominal testes to be placed within the scrotum (Fig. 53.31B). The vas and vessels are rarely so short as to make scrotal placement of the testis impossible (142). Laparoscopic orchidopexy permits high retroperitoneal mobilization of the spermatic vessels and emphasizes this point (131).

Within the inguinal canal, the first anatomic consideration is to divide the cremaster muscle to gain access to the spermatic cord and the internal inguinal ring. Dissection within the internal ring will achieve almost all the mobilization required for a successful orchidopexy. The internal spermatic fascia must be divided to permit access to the processus vaginalis, which is separated in the inguinal canal from the vas and vessels. As the dissection proceeds through the internal ring, the vas and vessels are elevated out of the posterior enveloping portion of the endoabdominal fascia as they move forward with the peritoneum. This step has been referred to by varying terms such as *division of the lateral spermatic fascia* or *division of the bands of Denis Browne.* To complete the mobilizations of the vas and vessels from the enveloping endoabdominal fascia, or conceptually, the retroperitoneal feltlike layer in which they become embedded when descent stopped, the spermatic vessels and vas are dissected posteriorly from the undersurface of the peritoneum. As the delicate fibers are teased away from the vas and vessels, adequate mobilization to permit the testis to reach the scrotum is almost always achieved. Rarely today is division of the inguinal canal floor required. The old concept of collapsing triangles to create a straighter course for the spermatic vessels into the scrotum (Prentiss maneuver) appears much less important than the concept of adequate retroperitoneal mobilization of the spermatic vessels. These findings are reemphasized in observing that the most common cause for inadequate testis placement identified during reoperative orchidopexy is the failure to perform an adequate high retroperitoneal dissection (183). In doing this, however, it is important to prevent dissection too closely to both the vas and vessels because this will result in unsatisfactory outcomes.

Surgical Incisions

The incisions used for surgery on the testis, scrotum, and cord structures are similar and hence are discussed here in common.

Standard Inguinal Incision

The standard inguinal incision is used for entry into the inguinal canal to perform hernia repair, orchiopexy, or varicocelectomy, as well as for delivery of the testis from the scrotum to perform hydrocelectomy or radical orchiectomy for tumor. This incision is best placed transversely in the lower abdominal skin crease, where it usually results in an indefinable linear scar. Oblique incisions paralleling the inguinal canal should be avoided because they do not follow Langer's lines and often result in broad unsightly scars. The argument that oblique incisions can be used to extend the surgical dissection higher, as in treating high undescended testes, is not founded. In children, the same exposure can usually be obtained by using a transverse incision of adequate length or even placed higher above the inguinal skin crease. This same incision may be placed slightly lower to obtain delivery of the testis and spermatic cord for subinguinal microscopic varicocelectomy.

Following the skin incision, Scarpa's fascia is divided and the external oblique aponeurosis is exposed and opened parallel to the inguinal ligament. Care must be taken to avoid transection of the underlying ilioinguinal nerve, which often hugs the underside of the external oblique fascia, especially in older children. At this point, herniorrhaphy, orchiopexy, or varicocelectomy may be accomplished, as detailed in the following sections. Closure of the external oblique and the subcutaneous tissue and skin is done with an absorbable suture of appropriate size. Bilateral inguinal incisions may be used for simultaneous repair of bilateral defects. In general, these incisions are extremely well tolerated in children and heal without difficulty.

Suprainguinal Retroperitoneal Muscle-splitting Incisions

Suprainguinal retroperitoneal muscle-splitting incisions have been described mostly for “high ligation” of the internal spermatic vein for varicocelectomy. Some advocate this approach directly above the internal inguinal ring at a level above the divergence of the vas deferens because the internal spermatic vein is more likely to be single at this level (214). A transverse skin incision is made and then retracted superiorly, and the external oblique aponeurosis is incised, followed by splitting of the underlying muscles to gain entry to the retroperitoneal space. Alternatively, a true lower quadrant or flank incision (123) may be made to approach the internal spermatic vein higher in the retroperitoneum. In these approaches, care must be taken to identify and protect the adjacent ureter. These muscle-splitting incisions are closed thereafter in layers with absorbable sutures, resulting in a very strong closure.

Lower Abdominal Incisions for Simultaneous Exposure of Both Testes

Various lower abdominal incisions for simultaneous exposure of both testes have been described and are used primarily for orchiopexy when both testes are high or impalpable,

when simultaneous separate inguinal incisions may not give adequate exposure for safe dissection. Flynn and King (68) recommended a midline transperitoneal approach for dissection of the intraabdominal testis, followed by creation of a new inguinal ring just lateral to the pubic tubercle so that the spermatic cord might assume the most direct route into the scrotum (Fig. 53.32). This incision may also be used to approach the testis preperitoneally by dissection along the rectus sheath laterally until the retroperitoneum is entered and then mobilizing the testis and cord at that level (22,119,176). In some instances, especially when an extensive exposure of bilateral intraabdominal testes is necessary, both lower rectus muscles may be totally transected, resulting in wide preperitoneal or intraperitoneal exposure. The latter is the ideal incision to use in boys with prune-belly syndrome who are undergoing orchiopexy because their lower abdominal muscles are already attenuated.

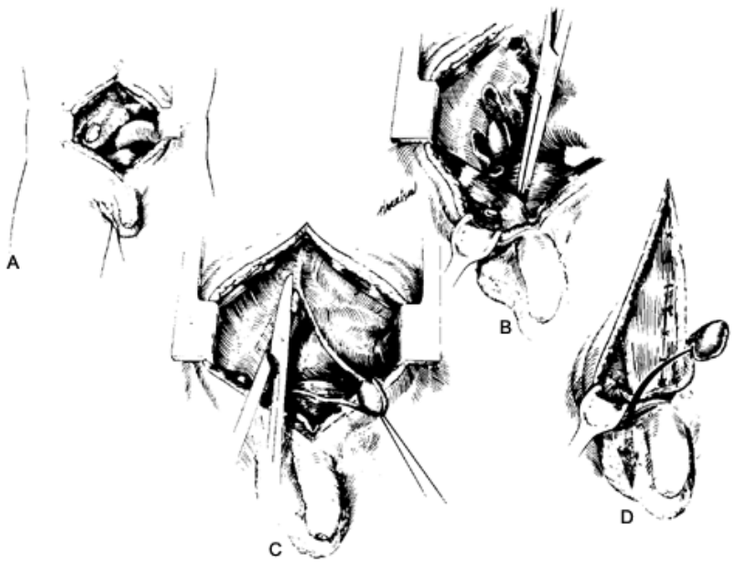

FIGURE 53.32. Technique of transabdominal orchiopexy. **A:** Intraabdominal view showing testis intraperitoneally at pelvic brim. **B:** Testicular mobilization from posterior peritoneum and restraining bands. **C:** New external ring created at the level of lateral rectus muscle border and superior pubic ramus. **D:** Testis brought through the opening and placed within the scrotum. (From Kogan SJ. Cryptorchidism. In: Kelalis PP, King LR, Belman AB, eds. *Clinical pediatric urology,* 2nd ed. Philadelphia: WB Saunders 1985, with permission.)

Minimally Invasive Access

Laparoscopy has added a new dimension for accessing the testis and spermatic cord. Improvements in technique, miniaturization of instruments, and added experience have facilitated laparoscopic access to these structures as an alternative approach to standard open surgery. Laparoscopic access is best suited for treating the intraabdominal undescended testes. However, this approach can be used for either transperitoneal or preperitoneal varicocele repair as well. The major benefit of laparoscopic minimal access approach is the wide operative field accessed through the minimal abdominal incision. The techniques of trocar placement are described subsequently under treatment of each individual condition.

Incisions into the Scrotum

Incisions into the scrotum are made to allow direct access to the testis and paratesticular structures. In children, the most common indications are for exploration of suspected testicular torsion or torsion of a testicular appendage. Although individual transverse scrotal incisions may be made for direct access to each hemiscrotal compartment, a vertical midline raphe incision is preferred because it is simpler and more cosmetic. The midline raphe is incised, with care taken to avoid carrying the incision onto the base of the penis. Following dissection deeper between the hemiscrotal compartments, a separate incision is made into each, through which each testis is delivered separately. Following

biopsy or detorsion and suture fixation, the separate incisions are each closed with interrupted absorbable sutures. The midline raphe incision is then closed separately in one layer with interrupted absorbable sutures. It is important to reemphasize that, in children, scrotal incisions are not used to perform testicular biopsies when solid tumors are suspected. Furthermore, in children, hydrocelectomy is usually performed through an inguinal incision because of the high likelihood of a patent processus vaginalis. Scrotal incisions are also made to fix the testis in place as part of an orchiopexy procedure. Previously described practices of testicular fixation to the contralateral thigh by direct suture or by rubber band traction are not advised because a high frequency of testicular atrophy results in these instances. Fixation of the testis into the contralateral hemiscrotal compartment across the midline septum has been described (206) and continues to have its advocates. However, the most popular method of fixation is the subcutaneous pouch method, with fixation of the testis beneath the skin and above the dartos muscle (164). Following adequate mobilization of the spermatic cord and testis, a short transverse ipsilateral scrotal incision is made through the skin. A plane is developed with a hemostat between the skin and the underlying dartos, creating a pocket to accommodate the testis and epididymis. An incision of sufficient size to pull the testis within is then made in the underlying dartos with the aid of a previously placed traction suture. The testis is positioned in the pouch, and the traction suture is passed through the dependent scrotal skin and then tied to itself or fastened to a button or gauze pledget. Some prefer to suture the testis directly to the dartos internally rather than using a transscrotal suture. Thereafter, the scrotal incision is closed with interrupted fine chromic sutures in one layer.

Specific Situations

Hernias and Hydrocele Surgery

The scrotum is always prepped and draped into the operative field. This permits access to the scrotum during the operative procedure, which is often necessary. The skin incision is usually just a little longer than the length of the inguinal canal and is placed directly over it. The medial end of the incision may be easily determined by feeling the position of the cord structures as they exit the external ring immediately lateral to the pubic tubercle. Blunt and sharp dissection is carried down to the fascia of the external oblique, which is cleared at the pubic tubercle to expose the cord structures as they exit the external ring. This step ensures that the incision made in the external oblique fascia will be properly positioned over the canal. If the external ring is not identified, it is easy to inadvertently place the fascial incision too high or medial, causing the cord structures to be missed. The external oblique fascia is opened through the external ring. By doing this, the delivery of an associated hydrocele is much facilitated. The cremaster muscle is mobilized off the undersurface of the external oblique and the transversalis muscles. This permits the cord structures to be raised. By teasing the cremaster fibers off the cord at the internal ring, a small retractor may be inserted later to expose the peritoneum, ensuring a high ligation of the processus vaginalis at its junction with the peritoneum. The next step is to open the internal spermatic fascia by superficially elevating the tissues over the vas and vessels to prevent injury to these underlying structures. Once the internal spermatic fascia is opened, the processus vaginalis can be separated. It is always wise to check that the vas and vessels are reidentified separate from the processus and that there is nothing in the processus before dividing it. The processus is then divided between hemostats and dissected up to the internal ring, where it is twisted and doubly ligated at its junction with the peritoneum. If the surgeon has trouble identifying the processus vaginalis, a simple solution is to place a small retractor through the internal ring; then, with gentle traction on the cord structures, the peritoneum can be readily identified. This permits a proximal to distal dissection to identify the processus or confirm its nonpatency.

The surgeon now must deal with the collection of fluid within the tunica vaginalis in a communicating hydrocele. The testis is delivered through gentle traction on the distal end of the processus and the cord structures. The plane of dissection is kept immediately adjacent to the tunica vaginalis, which makes this procedure avascular. If there has been fluid collection in the tunica vaginalis, as is seen in a communicating hydrocele, the tunica vaginalis will be thicker than in an uncomplicated hernia. Here, the risk of a persisting hydrocele increases if the tunica vaginalis is not widely opened and securely maintained open. For this reason, the tunica vaginalis is then turned back behind the cord structures with a single stitch in a bottle technique. Usually, there is no need to excise any of the tunica vaginalis unless it is very bulky and thickened. With an inguinal hernia, the tunica vaginalis is often much flimsier, and a wide opening often is adequate to ensure the edges do not recoapt, permitting the formation of a reactive hydrocele postoperatively. After this step, gentle traction on the scrotum will use the gubernaculum and its attachment to the testis to reinvert the testis within the tunica vaginalis and then return the testis to a dependent scrotal position. This should be confirmed by careful palpation of the testis in the scrotum before inguinal closure is begun. If any question exists, the testis should be redelivered inguinally and, if necessary, the gubernaculum divided and the testis sufficiently mobilized to be placed into a subdartos pouch. There is no substitute for a secure scrotal positioning of the testis in the first instance in groin surgery carried out in children. Reconstruction of the inguinal canal is accomplished by reapproximation of the external oblique fascia;

however, a good check of the transversalis fascia constituting the floor of the inguinal canal at the internal ring is important. If the ring is excessively large, one or two stitches to close the transversalis fascia at this level may prevent a later direct hernia, although this is indeed a rare complication of groin surgery in children.

Scrotal Exploration for Acute Torsion of the Spermatic Cord or Testicular Appendages

Scrotal exploration for acute torsion of the spermatic cord or testicular appendages is accomplished through two separate transverse hemiscrotal incisions or a single midline raphe incision. The successive scrotal layers are incised, and the testis is delivered. Intravaginal torsion may not be evident until the tunica vaginalis is opened (Fig. 53.33). Detorsion and application of warm saline soaks is accomplished, during which time the contralateral testis is delivered. The tunica vaginalis is opened, and suture fixation of the testis is done in at least two places between the testis capsule and the dartos of the scrotum. A nonabsorbable suture must be used because both experimental and clinical evidence indicates that torsion may recur after previous suture fixation with absorbable suture material. Thereafter, the torsive testis is reassessed, and a decision is made regarding orchiectomy versus preservation and suture fixation. Removal of questionably viable testes should be considered in light of current information suggesting that the contralateral testis may be adversely affected by a retained damaged testis in some instances. When appendiceal torsion is encountered, the appendix is ligated or fulgurated carefully and excised. Contralateral appendiceal excision and suture fixation of the testis are not usually done.

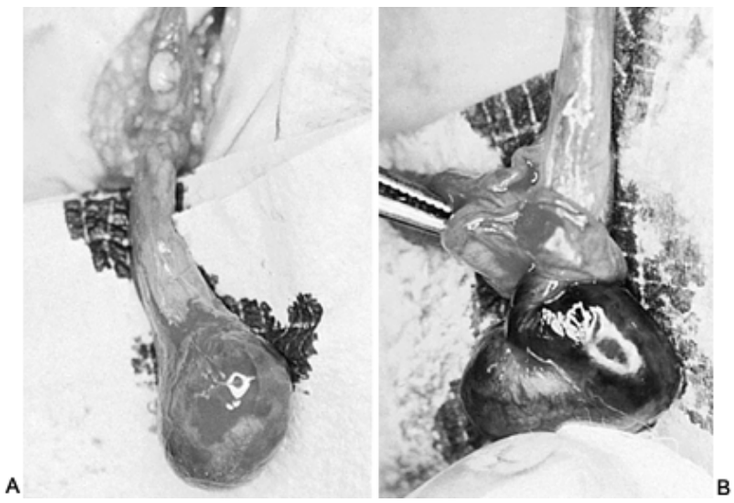

FIGURE 53.33. Acute spermatic cord torsion in a 3-year-old boy. **A:** Inflamed testis is delivered, but twist is not evident. **B:** Incision of surrounding tunica vaginalis reveals intravaginal torsion.

Varicocelectomy

Multiple techniques for treating pediatric varicoceles have been described; however, some (e.g., retrograde femoral vein catheterization with embolization or sclerotherapy) are not widely used. Those used frequently by pediatric urologists are high retroperitoneal ligation and laparoscopic or microsurgical varicocelectomy. A proximal inguinal approach may be associated with increased risk of varicocele recurrence (81).

Open transinguinal repair consists of opening the inguinal canal in standard fashion, mobilizing the entire spermatic cord over a Penrose drain, and then carefully identifying and ligating the offending varicosities, which at this inguinal level are usually multiple. Positioning the patient in a reverse Trendelenburg position and using optical loupe magnification aids in identifying the dilated veins. The artery is identified and preserved. In some instances, when arterial identification is difficult, warm saline or papaverine drip directly on the vessels is helpful. Care must be taken to avoid the ilioinguinal nerve and the vas deferens and its vessels. Use of intraoperative venography may aid in avoiding unrecognized “bypass collaterals,” which will result in a persistent varicocele (81,172).

Open high retroperitoneal exposure offers advantages over the transinguinal route. The incompetent internal spermatic vein is more often single, and the exposure is above the vas deferens and its accompanying vessels, thereby avoiding them completely. A transverse abdominal incision is made one to two fingerbreadths medial to the anterior superior iliac spine and the same distance above the estimated position of the internal inguinal ring. A muscle-splitting technique is used to enter the retroperitoneum. Reverse Trendelenburg position and a slight contralateral tilt of the abdomen on the operating table aid in exposure, which is obtained with appropriate-size right-angle retractors retracting the muscles. The internal spermatic vessels are identified on the posterior aspect of the peritoneum and are looped with a Penrose drain or holding sutures. This exposure may prove difficult in the obese adolescent; traction on the ipsilateral testicle often will aid in identifying the elusive vessels in this circumstance. At this level, the vas and its surrounding vessels are well inferior. Ligation is performed in the manner described previously and is complemented by using internal spermatic venography.

Transperitoneal laparoscopic varicocelectomy has been adopted preferentially by some pediatric urologists. The advantages provided by this minimally invasive surgical route are obvious: rapid patient recovery and mobilization, minimal morbidity and pain, and rapid return to all normal activities. Additional benefits are that a direct, magnified visualization of the internal spermatic vessels and collaterals high above the vas deferens and surrounding vessels occurs. This approach is especially useful in the rare circumstance when bilateral varicoceles are present. Disadvantages of this approach are the longer operative time, increased cost, and potential for injury of abdominal viscera and vessels resulting from trocar insertion and/or dissection. As with other aspects of laparoscopic surgery, evolutions in technique and instrumentation have occurred. Miniaturization of laparoscopic ports and instrumentation has lessened morbidity without compromising surgical technique and safety. Improved camera optics have significantly facilitated surgical visualization.

For transperitoneal laparoscopic repair, an incision is made at the umbilicus and deepened down to the infraumbilical midline fascia, which is incised. A vertical incision on the inferior crest of the umbilicus is made when the umbilicus is deep, and a curvilinear incision following the crest when it is flat. Pneumoperitoneum is produced either by Veress needle insertion while elevating the umbilicus and abdominal wall with towel clips, when checking the needle position with the open saline drop and direct injection techniques, or by continuing the dissection into the peritoneum with port insertion under direct vision. A 5-mm video port is then established. Pneumoperitoneum is established using a maximum pressure of 12 cm H_2O. A second 5-mm port is placed in the midline just over the pubis under direct vision, a position that ultimately will be hidden in the pubic hairline. A third 3-mm port is placed midway between the other ports in the midline or midway between the umbilicus and the anterior superior iliac spine, superior to the internal inguinal ring. The bowels are retracted with steep Trendelenburg's position and tilting the table slightly to the right. The posterior peritoneum is incised over the internal spermatic vessels using a T incision, and the spermatic veins are mobilized. A 5-mm clip applier is passed through the lowest port, and the veins are elevated, clipped, and divided. Some surgeons will clip the entire arterial and venous pedicle without attempting to isolate the artery, simplifying the procedure considerably. After reducing the pneumoperitoneum pressure and ensuring that the operative field is dry, the surgeon removes the trocars under direct vision. Fascial closure is made for the umbilical and lowest incisions; the 3-mm port requires skin closure only, along with the others.

Preperitoneal laparoscopic repair avoids injury to intraabdominal structures because the internal spermatic vessels are isolated extraperitoneally. Following infraumbilical incision in the manner described earlier, a subcutaneous plane is developed over the left anterior rectus sheath, which is then incised for a short distance to the left of the midline. The left rectus muscle is retracted laterally, and a peanut dissector is passed posterior to the left rectus muscle to the level of the pubis, establishing a pathway for the 10-mm preperitoneal balloon dissector, which is then inserted and manually inflated. The preperitoneal space is developed under direct vision using a 0-degree viewing lens. The balloon dissector is deflated and removed, and a Hassan 10-mm port is placed and pneumopreperitoneum at 12 cm H_2O pressure is established. Two additional ports are placed under direct vision in the midline, as described for the transperitoneal approach. The internal spermatic vessels are identified, aided by traction on the testicle, which is draped into the sterile operative field. The vessels are grasped and elevated well above the vas deferens and its vessels, which can be seen coursing medially; varicocelectomy proceeds as described for the transperitoneal laparoscopic repair. Using this technique eliminates the risks of bowel injury and postoperative hernias because the peritoneum is not opened and the testicular artery can be identified and preserved in most cases.

As with other surgeries, opinions vary greatly regarding the benefits of each approach for varicocelectomy. A recent extensive multicenter report of 195 children undergoing laparoscopic varicocelectomy indicated the overall benefits (e.g., comparable operating time to open surgery, comparable low recurrence rate, minimally invasive surgery, precision of operative procedure) outweighed the disadvantages of this approach (e.g., recurrent hydroceles, potential for increased expense) (60). Recent publications for (169) and against (66,169) microsurgical varicocelectomy also support this approach.

Cryptorchidism

Although there have been many refinements in the incisions and operations used for orchiopexy, successful surgical placement of the testis within the scrotum continues to depend on the surgical principles first enunciated by Bevan (18) in 1899, namely adequate mobilization of the testis and spermatic vessels, repair of the associated hernia, and adequate fixation of the testis within the scrotum. The choice of surgical procedure to achieve these goals is determined to a great extent by the location of the testis; therefore the procedures for palpable and impalpable undescended testes are considered here separately.

Palpable Undescended Testes

Palpable undescended testes are usually located within the superficial ectopic space or within or emerging from the inguinal canal; therefore they are best approached through the standard inguinal incision (Fig. 53.34A). The distal attachments to the scrotum are divided sharply, observing carefully to avoid a long-looped vas that sometimes extends distally beyond the testis. Occasionally, these attachments may be ectopic (i.e., extending toward the thigh or pubis). The testis and cord are then sharply dissected up to and into the internal inguinal ring (Fig. 53.34B). No attempt is made to dissect within the cord substance because it does not result in any significant cord lengthening and actually may endanger the spermatic artery. In some instances, as when the undescended testis is quite distal or lies in a superficial ectopic position, no additional dissection is needed; adequate spermatic cord length exists for satisfactory scrotal placement of the testis. Further dissection is necessary in some cases, especially along the lateral attachments of the spermatic cord (lateral spermatic fascia). Anatomic dissections have demonstrated that this extracanalicular dissection can provide up to three-fourths of the entire potential length obtainable during orchiopexy, with only one-fourth from the intracanalicular dissection (220). The internal inguinal ring may be opened with the cautery to allow higher dissection within the ring if additional length is needed. This dissection is essentially the mobilization of the spermatic vessels and the vas out of the enveloping endoabdominal fascia. In most cases, extending this mobilization allows sufficient lengthening of the spermatic vessels and vas deferens to be achieved so that even intraabdominal testes can be placed into the scrotum. The hernia sac, which is virtually always present with a true undescended testis and often present with an ectopic testis, is sharply dissected proximally off the cord, divided, twisted, doubly ligated at the internal ring with an absorbable suture, and then dropped back into a retroperitoneal position (Fig. 53.34C and Fig. 53.34D). Occasionally, this dissection of the hernia sac may be difficult, resulting in a proximal peritoneal tear extending within the internal ring. In such circumstances, the ring must be opened, as described previously, to obtain better visualization and a sound peritoneal closure. A pathway is made into the scrotum with the dissecting finger to ensure that there are no obstructing bands of tissue remaining. Scrotal fixation of the testis is done by the method described previously, and the groin incision is closed (Fig. 53.34E and Fig. 53.34F).

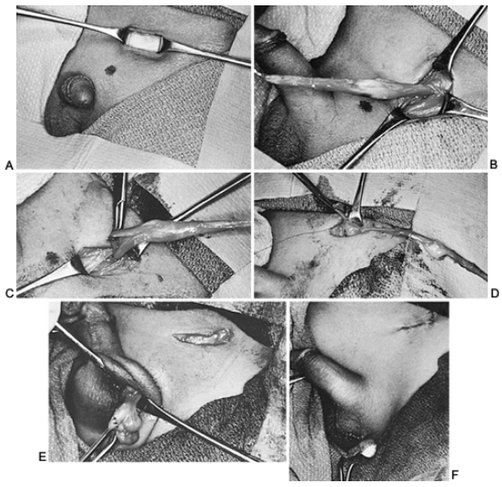

FIGURE 53.34. A–F: Technique of orchiopexy for palpable undescended testes (see text for description). (From Kogan SJ. Cryptorchidism. In: Kelalis PP, King LR, Belman AB, eds. *Clinical pediatric urology,* 2nd ed. Philadelphia: WB Saunders, 1985, with permission.)

The important elements, then, in obtaining adequate spermatic cord length for orchiopexy are mobilization up into the internal inguinal ring, division of the hernia sac, dissection of the cord off the posterior peritoneum, and division of the enveloping fascia for an adequate distance. It is often surprising how high the spermatic cord can be dissected through the standard inguinal incision, and the dissection may be carried almost up to the lower pole of the kidney in young children when necessary. The limiting factor in these instances is not the skin incision but rather the internal inguinal ring, which should be opened generously to give adequate exposure. When these maneuvers still do not achieve adequate spermatic cord length for successful scrotal placement of the testis, the floor of the internal ring may be taken down, dividing the internal epigastric vessels and transversalis fascia to create a mild increase in spermatic cord length. The floor of the inguinal canal is then closed over the cord, superimposing the internal and external inguinal rings. Skeletization of the vas deferens to achieve additional cord length should not be attempted because the vas deferens is seldom short enough to be an impediment to successful orchiopexy and because of the inherent dangers to the vas deferens occurring by this manipulation (241).

A recent series of boys with palpable undescended testes undergoing orchidopexy by accessing the testis thorough a single high scrotal incision calls attention to the experience that, in many instances, the cryptorchid testis and hernia sac can be safely treated in this manner. The short inguinal canal and reasonable testis mobility in many allows for tension-free testis placement in the scrotum and a high ligation of the hernia sac, saving an additional inguinal incision. Although this approach was used in this series also for treating previously operated upon cryptorchid testes (i.e., those resulting from previous hernia repair or failed orchidopexy), caution must be advised in this setting because the possibility of vas or vessel injury is definitely increased (32).

Impalpable Testes

In the patient with a unilateral impalpable undescended testis, we have been disinclined to use laparoscopy primarily because of our facility in resolving the findings through a standard inguinal incision. In most cases in which the testis is absent, we have found that the vas and vessels ended distal to the internal ring (262). With aggressive mobilization of the spermatic vessels by a transperitoneal approach done through the same inguinal incision, we have been able to place almost all intraabdominal testes into the scrotum in a

primary operation. When there are bilateral impalpable testes, however, the situation is different. Here, there appears to be a much stronger rationale for the use of initial laparoscopy because it does indeed let one plan an appropriate strategic approach. We do not believe that the decision concerning the placement of incisions is very critical, because we have consistently been able to deal with all types of undescended testes through a standard inguinal incision with at most a minor lateral extension. This permits the internal ring to be opened, providing excellent exposure for even an extensive mobilization of the spermatic pedicle.

If at laparoscopy two intraabdominal testes within 2.5 cm of the internal ring are located, these should be able to be mobilized to place them in the scrotum without division of the spermatic artery (217). This can be accomplished by laparoscopic orchiopexy (131) or by open surgery. In the older boy, a laparoscopic orchiopexy may produce less discomfort than one carried out with two inguinal incisions.

In the small boy, however, recovery is so rapid as to make this consideration a minor one. If at laparoscopy two very high intraabdominal testes are located, this could perhaps be the most justifiable case for the use of primary laparoscopic approach to orchiopexy. A primary clipping of the spermatic artery will cause the vasal artery to hypertrophy and make a subsequent staged orchiopexy more successful (21,27). The experimental work by Pascual and colleagues (215) provides a good physiologic rationale for this approach. A secondary laparoscopic orchiopexy in this staged fashion has been shown to be highly successful. In the boy who is found at laparoscopy to have only one intraabdominal testis, our approach is to be very conservative concerning the possible loss of that testis, because hormonal replacement is not trouble free. Laparoscopic or microvascular orchidopexy offer the safest approaches in this circumstance.

Unilateral Impalpable Testes

Unilateral impalpable testes are explored through a standard inguinal incision, with lateral extension if necessary, although some prefer an initial higher transverse incision in the lower abdominal quadrant. If the testis or a small tongue of protruding peritoneum is not encountered within the inguinal canal, the internal inguinal ring is immediately opened, as previously described. This tongue of peritoneum often is the harbinger of an intraabdominal testis within, and further mobilization of this protrusion often results in prolapse of the testis out of its intraabdominal position. When the testis is still not evident, no further dissection is done through the internal ring because the vas associated with an intraabdominal testis often runs close by the internal ring and the vas or the vasal artery may be injured by retroperitoneal dissection. Instead, the peritoneum knuckle that presents at the internal ring is opened; this transperitoneal exposure permits rapid identification of an intraabdominal testis. Although the testis is a retroperitoneal organ, it is often more easily visualized intraperitoneally, just as the ovary is visualized suspended on its mesentery intraperitoneally in the female. Once identified, a suture is taken through the capsule of the testis, and gentle traction is applied to assess the spermatic cord length so that the appropriate method of orchiopexy may then be chosen.

Bilateral Impalpable Testes

When bilateral impalpable testes are present, they can be approached through any one of the previously described transverse lower abdominal skin crease incisions. Because the protruding peritoneal processus or the testis itself is often encountered within the inguinal canal, both canals are opened initially. When no structures are evident, the skin and subcutaneous fascia are dissected superiorly off the rectus fascia, and a midline vertical incision is made, followed by preperitoneal or transperitoneal exposure. Because direct visualization of the proximal spermatic vessels is helpful in these instances, a transperitoneal exposure is preferred. In the course of exploring for an impalpable testis, it may become evident that the testis is not present. Various anatomic patterns may be found, indicating that monorchia exists (Table 53.3). If structures resembling a blind-ending spermatic cord, vas deferens, or vessels alone are found within the inguinal canal at the onset of exploration, they are traced within the internal ring to the point of divergence of the vas deferens and accompanying vessels to ensure that the miniature vessels visualized are, in fact, the spermatic vessels and are not cremasteric, vasal, or otherwise. This is an extremely important surgical point because blind-ending spermatic vessels are the *sine qua non* of testicular absence, and there are no recorded cases in which these vessels were present and a testis was found elsewhere (174). Therefore identification of the spermatic vessels coursing up the posterior retroperitoneum signals the end of the exploration; it is unnecessary to carry the exploration further, provided accurate identification of spermatic vessels is made. If a vas deferens alone is encountered, exploration is carried further as previously indicated because a wide separation of the vas deferens and the testis is possible with the testis lying higher within the abdomen (Fig. 53.35). Similarly, initial apparent absence of all structures demands that the exploration proceed further.

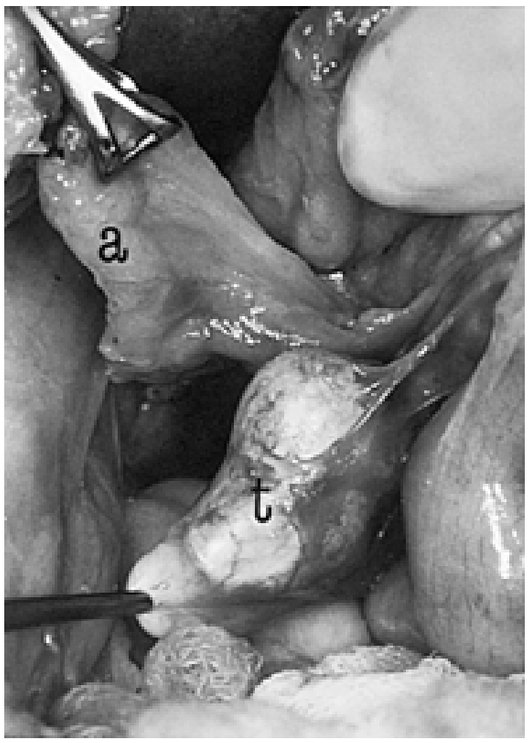

FIGURE 53.35. Testis *(t)* located immediately adherent to mesentery of appendix *(a)* medial to cecum. Rudimentary epididymis was present; vas deferens was absent. (From Wu RHK, Kogan SJ, Levitt SB. Testicular failure in an adolescent with a mesoappendicular testis. *Urology* 1966;27:434.)

An additional reason for accurately identifying the spermatic vessels within the internal inguinal ring is the

common misleading appearance of these higher located undescended testes. Jones (130) has clearly stated this problem best:

> It should be mentioned that at operation, even when it appears that an atrophic testis had been located, a thorough exploration in the region of the internal ring is still necessary for the macroscopic findings are sometimes bizarre and misleading. Segments of the vas may be absent; a structure resembling the spermatic cord may lay a false scent into the scrotum while the testis lies in the abdomen. Conversely it is sometimes helpful to invaginate the scrotum into the inguinal incision to inspect the contents before proceeding to further exploration.

The surgical implications of this problem are very clear. Structures within the inguinal canal consisting of a looped epididymis or vas deferens may resemble a blind-ending spermatic cord or atrophic testis and may be mistakenly excised. An absent testis may be misdiagnosed, where the testis may actually lie above within the abdomen (184). Occult undescended testes have been discovered above the internal inguinal ring at reexploration after the initial exploration failed to accurately define these structures within the inguinal canal or to include an intraperitoneal exploration (147).

Following completion of this extensive exploration when the testis is identified gentle stretch with a traction suture will allow assessment of spermatic vessel length. If this assessment indicates that adequate length may be achieved by a standard high dissection of the spermatic cord, this approach should be pursued as the most favorable choice. Many surgeons do not appreciate that a conventional high dissection of the spermatic cord will allow for successful orchiopexy of most intraabdominal testes (Fig. 53.36).

If the initial assessment reveals that the vessels are too short, precluding satisfactory scrotal placement by this means, a primary orchiopexy by transection of the testicular vessels, with or without microvascular anastomosis, or a staged orchiopexy will be required.

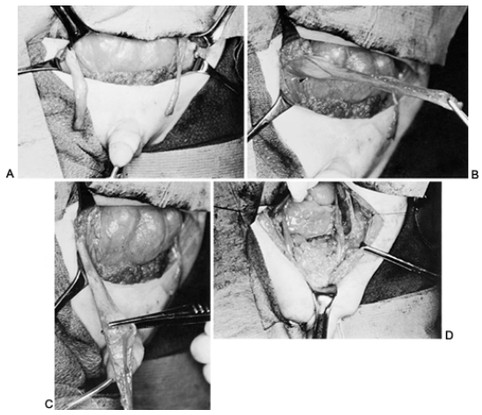

FIGURE 53.36. Technique of orchiopexy of impalpable intraabdominal testes by high retroperitoneal dissection. Excellent exposure is provided by complete rectus muscle transection. **A:** Processus vaginalis extending down inguinal canal often indicates higher intraabdominal testis. **B:** Testis extruded from its intraabdominal position into processus. **C:** High retroperitoneal dissection allows for adequate spermatic cord length for testis to reach scrotum. **D:** Direct course of each spermatic cord into scrotum following scrotal fixation.

Orchiopexy by Spermatic Vessel Transection

Bevan (19) originally described orchiopexy by spermatic vessel transection in 1903; however, because of poor results, it rapidly fell out of favor until Fowler and Stephens (72) in 1959 better characterized the vascular anatomy of these high-undescended testes using intraoperative angiography to demonstrate vascular anastomoses between the vasal and spermatic arteries. They recommended temporarily occluding the internal spermatic vessels to test the capability of this collateral blood supply (Fowler-Stephens test). Using these principles, they achieved successful scrotal placement of the testis in 8 of 12 patients. Brendler and Wulfson (25) further refined this procedure by indicating that the spermatic vessels should be ligated high away from the testis, avoiding dissection within the cord itself achieving scrotal placement in all five of their patients. Clatworthy and colleagues (40) reported on the results of 32 testicular vessel transections, which were divided into those done as a “premeditated” procedure and those done as a “salvage” operation following unsuccessful extensive previous cord mobilization. In the former group, 18 of 21 operations were successful; in the latter, only 6 of 11 did not undergo atrophy, leading to the recommendation that the epigastric vessels and floor of the inguinal canal be left intact and that mobilization of the posterior wall of the hernia sac off the spermatic cord be avoided. Johnston (129), in discussing orchiopexy of the intraabdominal testis in prune-belly syndrome, further refined this procedure by indicating that a broad strip of medially based peritoneum along the vas deferens should be left intact, along with its extensive collateral blood supply (Fig. 53.37). Additional series incorporating these important modifications of the original operation have proved even more successful (149). Gibbons and colleagues (77) reported success in 22 of 27 patients with intraabdominal testes, with most failures encountered initially when the vessel transection followed extensive spermatic cord mobilization. These authors retrospectively analyzed the possible pitfalls in performing this procedure as (a) failing to leave the wide, medially based peritoneal strip attached to the vas deferens; (b) doing the procedure as a salvage operation; (c) ligating the internal spermatic vessels too close to the testis; and (d) directly injuring the vasal artery in the course of mobilization.

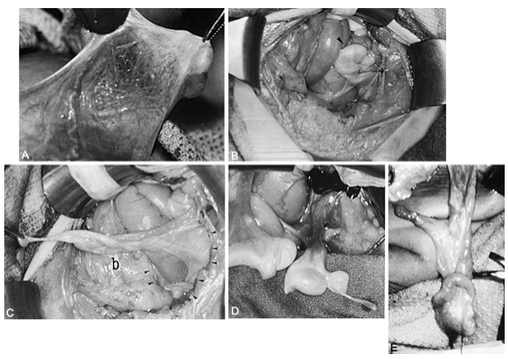

FIGURE 53.37. Technique of orchiopexy of intraabdominal testis by testicular vessel transection technique. **A:** Close-up showing collateral vascularity in the peritoneal strip between the spermatic and vasal vessels. **B:** Transabdominal exposure demonstrating high intraabdominal tests *(arrowhead).* Bladder is at inferior margin of figure. **C:** Left intraabdominal testis, spermatic vessels, and medially based peritoneal strip *(arrowheads)* along the vas deferens. b, bladder. **D:** Nontraumatic bulldog clamp applied high on spermatic vessels. **E:** Testis brought down on collateral blood supply within medially based peritoneal strip along vas deferens. (**A** from Kogan SJ. Cryptorchidism. In: Kelalis PP, King L R, Belman AB, eds. *Clinical pediatric urology,* 2nd ed. Philadelphia: WB Saunders, 1985:864, with permission.)

In a more recent review of orchidopexy by this technique, King (140) obtained success in 23 of 24 patients. He used an approach that preserves the medial strip of peritoneum along the vas deferens and its blood supply. Koff and Sethi (145) modified the traditional approach by indicating the testicular artery could be safely ligated low, adjacent to the testis, as long as the vasal collaterals were avoided. Woodard and Trulock (281) have listed the conditions that preclude doing an orchiopexy by testicular vessel transection as (a) the presence of a short, limiting vas deferens; (b) a hypoplastic testis with an uncertain blood supply; (c) segmental vas atresia; and (d) a detached epididymis.

Ransley and co-workers (224) described a variation of this operation in which the internal spermatic vessels are first ligated without mobilization at an initial stage. Several months later, the vessels are divided, and orchiopexy is completed as described previously. This approach allows for enhanced collateral vessel development and may be more reliable, especially in very small patients. Woodard and Parrott (280) have also indicated that orchiopexy of the intraabdominal testes found in patients with prune-belly syndrome may often be done in the neonatal period by mobilization of the intact spermatic pedicle without the need for division of the spermatic vessels.

Microvascular Orchiopexy

Microvascular orchiopexy has given an added dimension to the treatment of intraabdominal testes. The reestablishment of an intact blood supply to the testis by anastomosing the internal spermatic artery to the inferior epigastric artery would seem to offer additional safety beyond reliance on the collateral blood supply accompanying the vas deferens. The microsurgical equipment needed includes a good operating microscope with a foot control for focus, zoom, and positioning. Microvascular clamps, microscissors, a microneedle-holder, and 10-0 nylon sutures with fine microneedles are also required. The donor vessels are usually the inferior epigastric artery and vein. Topical agents such as lidocaine and papaverine may be applied to the vessels, and systemic anticoagulation may be used. For microsurgical orchiopexy, the initial exposure and procedure are the same as for testicular vessel transection; however, in this case, the internal spermatic vessels are dissected up toward their juncture with the aorta or vena cava before ligation. This procedure is especially important in younger children because these vessels are extremely small. The medial peritoneal pedicle along the vas deferens is developed. The inferior epigastric vessels are exposed by incising the floor of the inguinal canal, with dissection superiorly under the rectus muscle to achieve an adequate length for anastomosis. The vessels are dissected out at 5 to 10× magnification and are kept moist with warmed saline. Branches are coagulated 2 mm away from the donor vessel. It is important to have 1 to 3 cm of the vessel dissected free of the surrounding tissue. The next step is to remove the perivascular connective tissue. Arterial spasm can be relieved by 1% lidocaine irrigation. Once isolated, the clamp approximator is applied to the vessels, leaving adequate room for suturing. The clamp must be placed so that it can be flipped over without

difficulty. The artery is transected, and the adventitia is pulled over the lumen at several points, after which it is pulled forward and cut flush with the lumen and removed. The lumen is then irrigated with heparinized saline to remove clots and debris and then is stretched with a small jeweler's forceps. The clamp is adjusted to leave an appropriate distance between the two vessel ends so that suturing can be done without tension.

Several techniques of vessel anastomosis are satisfactory. The sutures should be symmetric full-thickness bites. A jeweler's forceps in the lumen guides the suture. Gentle traction is placed on the first suture while the next is placed 180 degrees apart. After the guide sutures are placed, the anterior wall between them is sutured and the vessel flipped to proceed with the posterior wall. After the anastomosis is completed, it is wrapped in clear plastic or a silicone cuff. The distal clamp is removed first to watch for backflow; then the proximal clamp is removed. If the anastomosis is patent, expansile pulsations and wriggling distal to the anastomosis are evident. If there is a discrepancy in vessel size, a smaller vessel can be transected in an oblique fashion to make the lumens more proportional (Fig. 53.38). The vein is done thereafter in a similar manner. Fixation of the testis in the scrotum should be done within a dartos pouch and the addition of two permanent sutures between the scrotal septum and the tunica albuginea of the testis. Closure of the abdomen is performed as previously described.

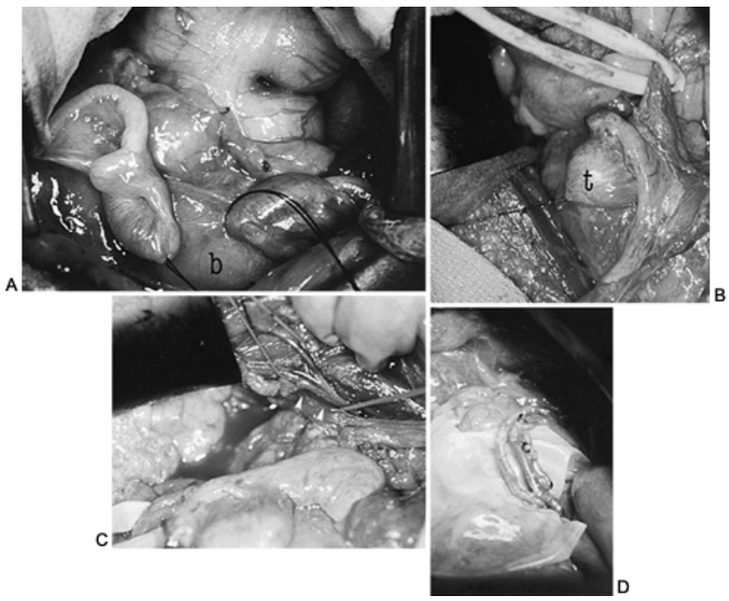

FIGURE 53.38. Technique of orchiopexy of intraabdominal testis by microvascular reanastomosis. **A:** Bilateral intraabdominal testes found adjacent to bladder *(b)*. **B:** Spermatic vessels (Penrose drain), testis with traction suture *(t),* processus mobilized from within inguinal canal *(lower right).* **C:** Inferior epigastric artery and vein *(arrowheads)* mobilized from under rectus muscle. **D:** Microvascular anastomosis of testicular artery and vein to epigastric vessels. Testis is already positioned inferiorly.

The results of microvascular orchidopexy have been reported, ranging from 55% to 100% successful scrotal testis placement of these abdominal tests without atrophy (26). In a recent review assessing the published results of orchidopexy for the abdominal testis, an overall success rate of

80% for microvascular repair is cited, contrasting favorable with other techniques (55). As with other orchidopexy techniques, however, each has its advocates and detractors. Only someone skilled in the method should undertake microvascular orchidopexy because the procedure is technically demanding. The microscope is seldom available “routinely” for impalpable cases especially when unilateral, and a separate readmission is often necessary after initial laparoscopic diagnosis. Absolute indications for a microvascular procedure include solitary abdominal testis and contralateral atrophy following previous orchidopexy. This procedure should be reserved for the truly high testis not amenable to extended high mobilization.

Staged Orchiopexy

When neither of the previous procedures is possible or appropriate, a staged orchiopexy may be performed. With improved awareness of the surgical anatomy of cryptorchid testes and expanded surgical techniques (e.g., laparoscopic mobilization), the need for staged orchidopexy has diminished dramatically. Previous estimates describing the need

for this operation have ranged form 0.6% (86) to 21.5% (43,67); this discrepancy probably represents the percentage of very high testes present in these series. Two series of staged orchiopexies have indicated a success rate between 82% and 90%, testifying to the efficacy of this approach (139,286). Following maximal mobilization of the cord and testis, the testis is sutured to its most dependent position obtainable without tension, such as the pubic tubercle, inguinal ligament, or scrotum, with a nonabsorbable suture, left long for subsequent identification. The second-stage exploration is done after an interval of at least 1 year. Considerable scarring may be present, and these reoperations are difficult procedures, with a definite risk of vas and vessel injury. The testis and spermatic cord must again be mobilized completely at the second stage, with the expectation that the time interval has allowed for additional lengthening of the spermatic cord that will result in successful scrotal testicular placement. In a careful, critical review, Redman (228) suggested that staged orchiopexies represent instances of less-than-complete initial explorations, with a more extensive secondary procedure needed thereafter. He further questioned the concept that further spermatic and cord lengthening occurs after the first procedure. Experience with a select limited number of patients in whom both the initial and second stages were personally performed suggests that this phenomenon of cord lengthening does occur; however, because scrotal testicular placement was successful in all following the second stage. With the more extensive dissection that accompanies contemporary orchiopexy techniques as well as selective use of more specialized techniques for intraabdominal testes, staged orchiopexies are undertaken far less frequently than were done in the past.

Laparoscopic Orchidopexy

This procedure is an inevitable extension of the increased use of diagnostic laparoscopy. After visualization of an abdominal testicle, two additional trocars are placed lateral to the rectus muscle, either one or both on the contralateral side. A subjective assessment of the spermatic vessel length is then undertaken: If traction on the testis indicates that it will reach over to the contralateral internal inguinal ring, it suggests that the spermatic vessels are long enough that single-stage orchidopexy may be successful. The distal extension of the processus vaginalis is then freed from the inguinal canal, taking care to identify and protect the long-looped vas that is often present. The peritoneal lining lateral to the testis and spermatic vessels is dissected after making an L-shaped incision over the internal ring, extending the longer limb proximally along the vessels. A higher dissection may be accomplished if necessary by incising the peritoneum lateral to the adjacent colon and reflecting it medially. Extreme care is used in protecting the medially based pedicle of peritoneum along the vas deferens and the bladder. When adequate mobilization is achieved, a new course is made into the scrotum immediately lateral to the pubic tubercle. A variety of techniques may be used, including tunneling a grasper retrograde into the scrotum then passage of an additional trocar into the abdomen, grasping, and pulling the testis into the scrotum; or using graduated Teflon dilators retrograde in a similar fashion; or using a radially dilating trocar to enlarge the new passage. The testis is then fixed in the manner described before, and the trocar incisions are closed with absorbable sutures if they are greater than 3 mm in size.

If the testis is found initially to be too high for primary laparoscopic orchidopexy, a staged interruption of the vessels should be undertaken before any extensive mobilization is undertaken. This may be done with laparoscopic clips or by laser coagulation, which is used to prevent thermal injury to adjacent structures. After a minimal interval of 4 months, during which time the collateral blood supply along the vas deferens is established, laparoscopic access is reestablished and orchidopexy is accomplished as described earlier. This staged approach offers increased safety and success when higher testes are present than a single-stage laparoscopic approach.

Initial reports indicate as good, if not better, overall success rates using these techniques as those reported with open surgical orchidopexy. A trend toward overuse of the two-stage technique and increased orchiectomy rate by surgeons performing laparoscopic orchidopexy has been described (65).

Reoperative Orchidopexy

A reoperative orchidopexy may be required after previous inguinal hernia repair in which the testis becomes scarred to a position above the scrotum or alternatively following a failed attempt at primary orchidopexy. Experience with these problems has led to the evolution of a technique that seems especially suited to the anatomic challenges presented by a reoperative orchidopexy (31). After closure of the external oblique fascia at the initial surgery, the anterior surface of the cord often is densely scarred to its undersurface, resulting from the inherent inflammation associated with suture placement and perhaps the usual lack of fat within the inguinal canal. The posterior surface of the spermatic cord generally is less adherent to the floor of the canal and the transversalis fascia, making this a safer point for reoperation.

The previous inguinal incision is reopened and dissection is carried within the subcutaneous fat till a position distal to the testis is reached. The testis is elevated, and the adherent scar is carefully teased off the testis, cleaning toward the testis to avoid excessive traction on the spermatic cord. Once the testis is elevated, the course of the spermatic cord distal to the pubic tubercle can be appreciated. An en bloc

dissection toward the pubic tubercle is undertaken staying some distance from the cord. The pubic tubercle is a useful landmark because it marks the point of insertion of the floor of the inguinal canal (the transversalis fascia) to the bony pelvis. At this point, a plane of dissection is established posterior to the spermatic cord because this plane is less adherent than the anterior plane (Fig. 53.39A). If dense scarring is present posteriorly, the transversalis fascia is freed en bloc with the cord. Although this is rarely necessary, reconstruction of this area in children is easily carried out.

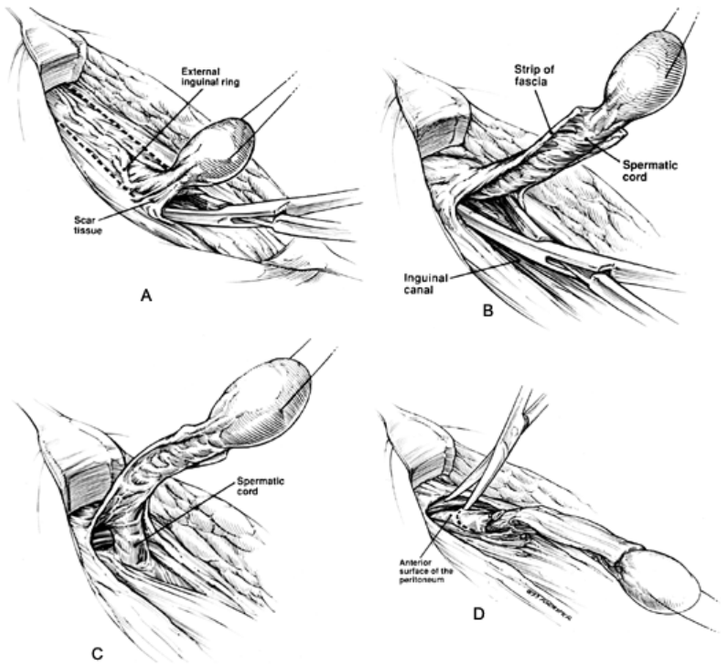

FIGURE 53.39. A: Initial dissection elevates the testes, and scar tissue is divided, staying away from the cord structures. A posterior plane of dissection is established at the pubic tubercle (insertion of the transversalis fascia—the floor of the inguinal canal). *Dotted lines* mark incisions in external oblique fascia. **B:** A strip of external oblique fascia is mobilized with the underlying adherent spermatic cord. **C:** When the external oblique muscle is visualized beyond the spermatic cord, the external oblique fascial strip can be divided without risk to the cord. **D:** When the peritoneum is opened above the site of the previus ligation of the processus vaginalis, unoperated tissue is reached and the operation may proceed as a routine orchidopexy.

As the posterior plane is developed, a strip of the external oblique fascia adherent to the underlying spermatic cord is defined by making parallel incisions in the external oblique fascia and raising this strip with the underlying cord (Fig. 53.39B). This dissection continues until the musculature of the internal oblique lateral to the internal ring is visualized (Fig. 53.39C).

At this level, the strip of fascia is freed, allowing visualization of the peritoneum through the internal inguinal ring (Fig. 53.39D). The peritoneum is opened above the site of its previous closure where adhesions to the underlying vas and vessels are usually present, allowing rapid and accurate identity of the course of the vas and vessels. Dissection from above completes any posterior dissection that is incomplete from below, allowing the cord to be mobilized into the area of the retroperitoneum that has not previously been approached. A Deaver retractor underneath the peritoneum permits it to be lifted forward so that the spermatic vessels can be mobilized completely from the enveloping endoabdominal fascia, as has been described in the previous segment dealing with anatomy.

This en bloc mobilization of the testis and then spermatic cord with its overlying fascia is the essential step in avoiding reoperative injury to the vas and vessels. It is often surprising to see how much distal testis placement can be achieved once the dissection proceeds into virginal territory in the retroperitoneum. In the initial report of this experience in 1993, a good result was achieved in 24 of 25 patients (31). By adhering to this approach, continued experience suggests that at least a 90% success rate is achievable in these difficult cases.

Role of Testicular Biopsy

It is well recognized that testicular biopsy is an invaluable tool at all ages for assessing the nature and degree of damage to the testis. Testicular biopsy might be used in pediatric urology at the time of orchidopexy to assess the fertility potential of the cryptorchid and contralateral testis, at the time of varicocele repair, during scrotal fixation for torsion to determine ipsilateral testis viability and contralateral testis damage, in the diagnostic assessment of unexplained intratesticular masses, and in the evaluation of the contralateral testis when a testis tumor is present.

Opinions vary regarding the desirability of performing testicular biopsy at the time of orchidopexy. Studies indicate that prepubertal testis biopsy correlates directly with later semen density (47,102). Data also indicate that testis biopsy at the time of prepubertal orchidopexy can define a subgroup of patients who can be expected to be infertile and whom may benefit from adjunctive hormonal treatment, making this a worthwhile pursuit when additional medical treatment is offered. Biopsy of boys with bilateral cryptorchidism is essential because they are at highest risk for infertility. An additional group of unilaterally cryptorchid boys with severe germ cell depletion in the cryptorchid testis would benefit as well because germ cell counts in the contralateral descended testis correlate well with counts in the cryptorchid mate (115).

Testis biopsy should be performed in the least-vascular-appearing part of the testis. Studies suggest that the anterosuperior portion in general is best, but each testis should be assessed individually, visualizing the superficial vascular distribution. A sharp capsular incision with a short beveled cut into the underlying parenchyma allows the protruding tubules to be excised with a microscissors. The capsule is closed with fine (6-0) absorbable sutures. Persisting oozing is controlled by pressure; thermal cauterization is avoided. Immediate fixation is done to prevent desiccation of the tiny specimen. When biopsy is performed in this manner, testis damage is not evident subsequently. Theoretical risks of inducing serum or seminal antibodies have not been substantiated (45).

A small number of boys initially treated for cryptorchidism, varicocele, monorchidism, testicular neoplasm, or testis loss from inflammation or trauma will ultimately suffer a second sequential condition of a similar nature affecting the ipsilateral or contralateral testis, which may potentially affect later fertility. Testicular biopsies play an important role in evaluating some of these patients because their antifertility effect in some instances may be additive. In a personal series of 29 patients of this nature seen over a 3-year period, 33% of patients had abnormal numbers of germ cells in both testes, some with severe reductions. These data indicate that an aggressive approach to diagnosis is important when sequential conditions exist, including testicular biopsy, because the ultimate fertility effect is unpredictable in any individual instance and timely interventional treatment may be important.

Insertion of a Testicular Prosthesis

The preceding descriptions indicate that a plethora of surgical approaches exist to successfully treat the intraabdominal undescended testis. Orchiectomy of the undescended testis is not indicated in the prepubescent child except when there is a major separation of the testis and its ductal structures. In postpubertal boys, the abdominal testis often is atrophied, is devoid of germ cells, and harbors an increased chance of malignant degeneration. Orchiectomy is often the procedure of choice in these circumstances, even though successful orchiopexy may be technically feasible (185). In these circumstances, insertion of a testicular prosthesis is indicated. Other boys born without functioning testes and those with atrophy or loss from trauma, cancer, torsion, or previous inguinal surgery are similar candidates. Although few studies exist documenting the psychologic efficacy and importance of prosthesis placement (13), it is our strong impression that prosthesis placement is important in the monorchic or orchiectomized boy.

Controversy existed regarding the safety of the silicone components of testicular prostheses resulting from the medicolegal issues that surrounded implanted silicone breast prostheses. Whereas most pediatric urologists have not encountered long-term problems with silicone-filled testicular prostheses, their safety had not been studied thoroughly. In 1995, saline-filled silicone shell prostheses were introduced,

and implantation at selected centers was undertaken under a U.S. Food and Drug Administration–mandated prospective study protocol. As part of a greater group including adult patients, 73 pediatric patients underwent implantation. Approximately 84% were missing their testicles at the onset; about 25% of the total had both testes missing (bilateral anorchia). This study was discontinued because of the lack of serious adverse events and general good results. The data and results for the pediatric patients have been recently reported (213). Presently, both a saline-filled testicular prosthesis (Mentor Corporation) and a semisolid silicone carving block device (Silimed Corporation) are available for pediatric and adult implantation.

In general, the largest prosthesis that does not look unsightly is implanted. Many patients do not indicate a desire for replacement with a larger prosthesis after puberty because the dependency of the existing one often lends a normal cosmetic appearance. Testicular prostheses should not be implanted through a scrotal incision, especially through the prepubertal thin scrotum, because the chance of spontaneous extrusion is significantly increased. The scrotum is dilated with the aid of the dissecting finger, a moist gauze sponge, or both. The scrotum is inverted, and an absorbable suture is passed through the prosthesis suture tab and then carefully through the dartos, with precautions taken that the suture does not penetrate the overlying scrotal skin. If the latter occurs, the suture should be removed and placed again. After the prosthesis is positioned dependently, the neck of the scrotum is closed with two or three absorbable sutures to prevent spontaneous or traumatic upward migration. The wound is irrigated with an antibiotic solution, and a broad-spectrum antibiotic is prescribed for 72 hours. With use of these techniques, no patient has experienced a scrotal infection following prosthesis placement or has had prosthesis extrusion or displacement, including a few who previously had infected or extruded prostheses elsewhere and who were subsequently reoperated on after appropriate interval treatment.

Surgical Complications After Orchiopexy

Surgical complications after orchidopexy (e.g., atrophy, inadequate scrotal location, ductal system injury) have been analyzed in a number of reports (51,179,183,190). Orchiopexy was possible in almost 90% of 207 patients having either palpable or impalpable undescended testes, with 187 patients (also almost 90%) achieving a satisfactory scrotal position. In 6 of these patients undergoing orchiopexy, the testis was in a high scrotal position and was retracted into an inguinal position, and in 13 (7%) postoperative atrophy occurred. In this series of 233 patients, 12 underwent orchiectomy rather than orchiopexy because of dysplastic or primary atrophic appearances. No intraoperative complications were noted (179). In another series of 492 patients, results were graded as “good,” “fair,” or “poor” according to the testis size, position, consistency, and mobility. Only 60% of testes had a good result, with 22% characterized as poor. Of the overall group, 16% were clearly atrophic (51). Of course, postoperative atrophy in undescended testes must be related to the preoperative size of the testis because some undescended testes are small to begin with; hence, it is likely that some of the “atrophic” testes in this series do not represent surgically induced atrophy. A brighter outlook regarding atrophy is seen in Mengel and Hecker's (190) series, in which a 2% atrophy rate was encountered. Surgical complications occur more frequently with impalpable undescended testes and are cited as high as 20% to 50% in the older literature (174). With the techniques currently available, however, significantly reduced complication rates are encountered.

Maizels and co-workers (183) examined the reasons for inadequate testis position following orchiopexy in a series of 350 boys, finding a 10% frequency of failure of the initial surgical procedure. Retroperitoneal dissection adequately corrected the initial failure in 58%, whereas local inguinal dissection was adequate in 37%. They concluded that incomplete initial dissection appeared to be the cause of inadequate position after orchiopexy and that aggressive high surgical dissection should prevent inadequate scrotal testicular placement in most instances. Docimo (55) also published a meta-analysis of the results of surgical therapy for cryptorchidism, noting that after 1985, results of surgery stratified by initial position of the testis considerably improved. The results for testes located around the pubic tubercle are now reported to be between 95% and 100% achieving a scrotal position. By contrast, the abdominal testes achieved a 77% success rate. More recently, incorporation of the principles of extended retroperitoneal mobilization as described previously resulted in a 90% success rate for abdominal testes (142). In Docimo's review, there was a statistically significant difference based on age at orchidopexy, with children older than 6 years of age demonstrating a 10% worsened result. This might reflect the greater difficulty of achieving a satisfactory retroperitoneal mobilization in the older child. Present experience suggests that laparoscopic high mobilization of the spermatic vessels will achieve comparable success rates to those results seen in younger boys (131).

Figures regarding intraoperative injury to the vas deferens are difficult to come by. Mengel and Hecker (190) cite a 1% to 2% frequency in their series. Vas deferens injury during orchiopexy is completely preventable, and even these figures should be considered excessive.

Surgical Complications from Hernia/Hydrocele Repair

Postsurgical complications of spermatic cord surgery consist mainly of injury to the vas deferens and spermatic artery and retraction of the testis. Care must be taken in dissecting the

hernia sac off the cord, ensuring that undue traction or pressure is not put on the spermatic vessels. When the internal inguinal ring is narrowed to prevent herniation as part of the repair, an adequate lumen must still be left to allow the spermatic cord to pass without compression. Extreme care must be used to ensure that the testis occupies a dependent scrotal position after hernia repair because secondarily undescended testes can occur with the testis fixing to the overlying scar. In these circumstances, secondary changes in the testis may occur similar to those occurring in truly cryptorchid testes as a result of the continued extrascrotal position (100). Similar perils may be encountered during the hydrocelectomy, especially when the hydrocele is chronic and thick walled. In these circumstances, it is better to lay open the hydrocele and suture-evert the sac behind the spermatic cord and testis rather than to excise the sac and risk accidental incision/excision of a meandering hidden vas deferens. Occasionally, pathologic examination of an excised hernia or hydrocele sac will indicate that a segment of vas deferens is inadvertently included. In one study of pediatric hernia sacs, 6% of specimens included a vas or vaslike structure; however, analysis suggested that many represented wolffian remnants and not the vas deferens (80). Another report (260) in which bilateral vas integrity was confirmed at reexploration after the excised hernia sacs from bilateral inguinal hernia repair contained “vasae” also indicates that these structures may be misinterpreted easily and that diligence during surgery is essential as well as in review of the subsequent pathology.

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54
PEDIATRIC UROLOGIC ONCOLOGY

Michael L. Ritchey

M.L. Ritchey: Division of Urology, University of Texas–Houston Medical School, Houston, TX 77030.

Contents

WILMS' TUMOR

Part of "54 - PEDIATRIC UROLOGIC ONCOLOGY "

Nephroblastoma, or Wilms' tumor, is an embryonal tumor that develops from remnants of immature kidney. Renal childhood tumors were described more than 150 years ago, but it was surgeon Max Wilms who proposed that all the various elements of the tumor were derived from the same cell (193). It is the most common primary malignant renal tumor of childhood and typically affects children younger than 6 years of age. At the beginning of the twentieth century, most children with Wilms' tumor died of their disease. Over the past decades, the survival of children with Wilms' tumor has improved rapidly.

Current treatment emphasis is on reducing the morbidity of treatment for low-risk patients, reserving more intensive treatment for selected high-risk patients in whom survival remains poor. This chapter reviews recent advances in the understanding of the biology and pathology of Wilms' tumor. The current management of children with all stages of nephroblastoma is discussed in detail.

Epidemiology

The annual incidence of Wilms' tumor is 10 cases per million children younger than 15 years of age or about 450 to 500 new cases annually in the United States (31). This tumor represents 5% to 6% of childhood cancers in the United States and is the most common malignant renal tumor of childhood. Nephroblastoma is a disease of young children, with a peak incidence of 36.5 months for males and 42.5 months for females with unilateral tumors. The disease occurs nearly equally in girls and boys worldwide, but the frequency is slightly higher among girls in the United States (32). Evidence of a consistent association of Wilms' tumor with any parental environmental exposure has not been provided.

Associated Syndromes

An increased incidence of Wilms' tumor has been noted in several recognizable syndromes (Table 54.1) (40,130).

These may be divided into those characterized by overgrowth and those lacking overgrowth. Syndromes with overgrowth features include hemihypertrophy, which may occur alone or as part of the Beckwith-Wiedemann syndrome (BWS). BWS is a rare disorder consisting of developmental anomalies characterized by excess growth at the cellular, organ, (macroglossia, nephromegaly, hepatomegaly) or body segment (hemihypertrophy) levels (6,191). Although most cases of BWS are sporadic, up to 15% exhibit heritable characteristics with apparent autosomal- dominant inheritance. The incidence of tumor development in BWS is 10% to 20% including Wilms' tumor, adrenocortical neoplasms, and hepatoblastoma. The risk of Wilms' tumor development in patients with hemihypertrophy and BWS is estimated to be approximately 4% to 10% (14,55). Children with BWS found to have nephromegaly (kidneys greater than or equal to the ninety-fifth percentile of age-adjusted renal length) are at the greatest risk for the development of Wilms' tumor (56). Other overgrowth syndromes, Perlman, Soto's, and the Simpson-Golabi-Behmel syndromes, also are associated with the development of Wilms' tumor (136,147).

Anomaly	Rate (per 1,000)
Aniridia	7.6
Beckwith-Wiedemann syndrome	8.4
Hemihypertrophy	33.8
Genitourinary anomalies	
?Hypospadias	13.4
?Cryptorchidism	37.3
?Hypospadias and cryptorchidism	12.0

TABLE 54.1. INCIDENCE OF CONGENITAL ANOMALIES IN PATIENTS WITH WILMS' TUMOR REPORTED TO THE NATIONAL WILMS' TUMOR STUDY GROUP

With or without the stigmata of BWS, 3% of patients who develop Wilms' tumor also may be affected by hemihypertrophy (31). The risk of Wilms' tumor development in patients with hemihypertrophy is estimated to be on the order of 3% to 5% (180). Isolated involvement of the leg is the most common manifestation in these patients (80) and may not become clinically apparent until after the diagnosis of Wilms' tumor. Hemihypertrophy may be ipsilateral or contralateral to the tumor. The mean age at diagnosis of Wilms' tumor in patients with BWS and hemihypertrophy is similar to that of the general Wilms' tumor population (31).

Genitourinary anomalies (renal fusion anomalies, cryptorchidism, hypospadias) are present in 4.5% of patients with Wilms' tumor (31). Because many of these disorders are common in children, prospective evaluation for the development of Wilms' tumor is not carried out in most children with genital anomalies. One specific association of male pseudohermaphroditism, renal mesangial sclerosis and nephroblastoma is the Denys-Drash syndrome (DDS) (63). One should have a high index of suspicion for the development of these conditions in patients with male pseudohermaphroditism (181). Although XY individuals have been reported most often, the DDS has been reported in genotypic/phenotypic females as well as in cases of gonadal dysgenesis. This syndrome is associated with mutations of the 11p13 Wilms' tumor gene (45).

The incidence of aniridia in Wilms' tumor patients is 1.1%. Aniridia and Wilms' tumor are most commonly associated in patients with the Wilms' tumor, aniridia, genital anomalies, and mental retardation (WAGR) syndrome (40). Most affected individuals have a constitutional deletion on chromosome 11 and the incidence of Wilms' tumor formation is 42% (97).

An association between Wilms' tumor and horseshoe kidney has been noted. A review of National Wilms' Tumor Study Group (NWTSG) patients found that patients with a horseshoe kidney have a sevenfold increased risk of developing a Wilms' tumor (129,137).

Periodic imaging with renal ultrasound has been recommended in children with hemihypertrophy, BWS, and aniridia. Review of most studies suggests 3 to 4 months is the appropriate screening interval resulting in lower-stage tumors at diagnosis (39,80). There were not enough patients in these retrospective reviews to determine whether early detection had an impact on patient survival. Two recent reports have called attention to the increased incidence of nonmalignant renal lesions in children with BWS (27,39). Nonmalignant lesions included medullary renal cysts in 13% of patients, hydronephrosis in 12%, and nephrolithiasis in 4%. In two patients, nephrectomy was performed for benign disease due to false-positive screening (39).

Genetics

The role of genetic alterations in Wilms' tumor development has been studied extensively. Nephroblastoma was once thought to have a substantial heritable fraction because of the frequency of bilaterality and association with congenital anomalies and specific syndromes. The diagnosis of Wilms' tumor is generally at an earlier age in patients with congenital anomalies and also in children with bilateral tumors (31). It was thought that these children had a germline mutation that predisposed to both the development of multiple tumors and an earlier age of onset than the general population, as had been noted for children with retinoblastoma (111).

Analysis of these differences between groups of Wilms' tumor patients led to the two-event theory for Wilms' tumor formation, which predicts that two genetic events are rate limiting for tumor formation (111). Individuals with a genetic predisposition carry an initial lesion in their germline.

Because all body cells have already been affected by the first event, only one new event in any one cell is required for tumor development. These patients would be expected to have an earlier age of onset and have a greater incidence of multiple tumors. By contrast, in individuals who are not genetically predisposed (sporadic cases), two relatively rare independent events are required in the same cell. Subsequent genetic studies in several tumors have confirmed the Knudson model (47). The clearest example of tumorigenesis following the inactivation of both copies of a single tumor suppressor gene is the development of retinoblastoma following the inactivation of the retinoblastoma gene RB1. However, it is now recognized that the heritable fraction of Wilms' tumor is small (less than 1%) (78). This falls far short of the 30% incidence predicted by the Knudson-Strong model. Unlike the genetic mechanism leading to the development of retinoblastoma, which only requires the inactivation of one single gene, the biologic pathways leading to the development of Wilms' tumor are complex and likely involve several genetic loci (48).

Several chromosomal regions have been associated with Wilms' tumor, including chromosome 11p13, which harbors the Wilms' tumor suppressor gene WT-1; chromosome 11p15, which includes the putative Wilms' tumor gene WT-2; chromosome 16q; chromosome 1p; and chromosome 17p (49). The first two loci have been implicated in the actual development of Wilms' tumor.

The first recognized cytogenetically visible chromosomal abnormality in Wilms' tumor was in patients with the WAGR syndrome (155). These children were shown to have heterozygous germline deletions at band p13 of chromosome 11. With use of cloning techniques, the Wilms' tumor suppressor gene WT-1 was identified (24,37). The genetic consequences of WT-1 inactivation appear to be restricted to organs that normally express this tumor suppressor gene. WT-1 is expressed transiently in the developing kidney and also in specific cells of the gonads. The characterization of WT-1 has not only provided insight into the mechanisms underlying the development of Wilms' tumor, but also in those involved in genitourinary development (46,151).

A recent report reviewed the incidence of constitutional WT-1 mutations in 201 patients with Wilms' tumor (59). Of these, eight were identified as carriers of mutations in the WT-1 gene. Patients with genitourinary anomalies had an increased risk for carrying a WT-1 mutation. Of 28 boys with Wilms' tumor with cryptorchidism, 7 had WT-1 mutations. No increased risk was observed for patients with nephrogenic rests, bilateral tumors, a history of secondary cancers, or family history of Wilms' tumor. This suggests a constitutional WT-1 mutation encodes truncated WT-1 proteins predisposed to the development of cryptorchidism, hypospadias, and Wilms' tumor. Four of the seven patients with WT-1 mutation and undescended testis also had hypospadias. Germline mutations in WT-1 gene are found most consistently in patients with DDS (44,145). More than 90% of DDS patients investigated to date harbored germline WT-1 mutations. It is postulated that the mutation in DDS patients results in an abnormally expressed protein, which alters regulation of transcription and urogenital development. Of interest, the affected gonads and kidneys in patients with DDS are heterozygous for germline mutations, implying that the WT-1 mutation acts dominantly with respect to genitourinary abnormalities (101).

Deletions and mutations of 11p13 have been shown to occur in tumor DNA from sporadic Wilms' tumors, as well as in the germline of patients with a genetic predisposition to cancer. Approximately 50% of tumors show loss of heterozygosity (LOH) for DNA markers on 11p13 (102,113), implying that these tumors had only one copy of the 11p gene suggesting that the two genetic events in the two-hit mutation occurred at the same locus. Tumor formation occurred after inactivation of one allele of an 11p13 gene and the subsequent mutation or loss of the homologous allele.

A second Wilms' tumor locus, WT-2, has been identified on the short arm of chromosome 11, 11p15.5 (154). This locus has been linked to the BWS with the finding of 11p15 triplication in some BWS patients and the mapping of familial BWS to 11p15 (114). Whether the BWS gene and WT-2 are one and the same gene or two distinct but closely linked genes, still needs to be elucidated. Many types of tumors show LOH in the 11p15 region (102), and the WT-2 gene may be important in the development of many different tumor types.

Other molecular genetic abnormalities have been found, including LOH for the long arm of chromosome 16q, which has been noted in approximately 20% of tumors (127). Similarly, loss of the short arm of chromosome 1p has been found in approximately 10% of cases. These genes are suspected to play a role in tumor progression rather than initiation of tumors. Studies are under way to assess the correlation between the different genetic abnormalities with histopathologic features and staging to determine whether molecular genetic studies are an additional indicator of clinical behavior and outcome.

Clinical Presentation

The typical presentation of a child with Wilms' tumor is that of an abdominal mass (Fig. 54.1). The tumor is palpable on physical examination in more than 90% of children. The tumor is generally quite large relative to the size of the child and not always confined to one side of the abdomen. The outline of a Wilms' tumor on examination is smooth and spherical. Other signs and symptoms at diagnosis are abdominal pain, gross hematuria, and fever. Hematuria occurs in one-fourth of children at diagnosis. Several tumors have been discovered during exploration for presumed appendicitis. Rupture of the tumor with hemorrhage

into the free peritoneal cavity can result in the presentation of an acute abdomen.

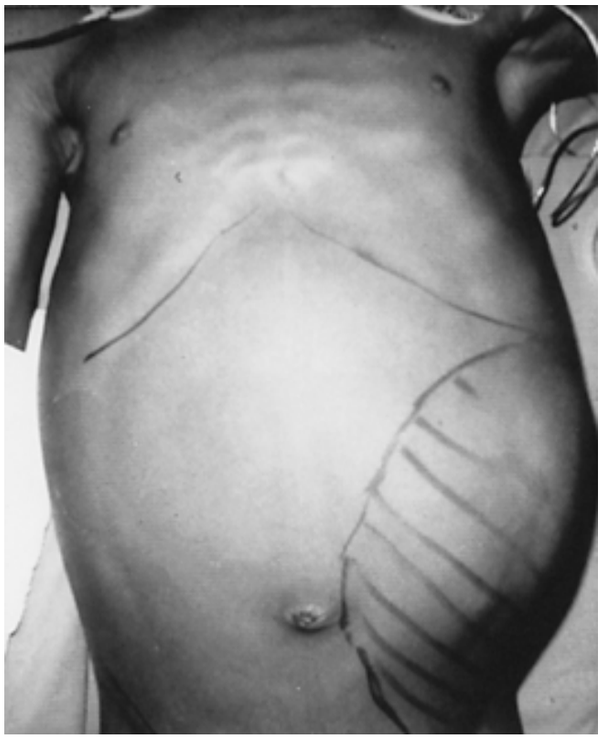

FIGURE 54.1. Typical large bulging abdominal mass in a child with nephroblastoma.

Additional symptoms may result from compression or invasion of adjacent structures. The propensity of Wilms' tumor to grow into the renal vein and inferior vena cava can produce atypical presentations. Varicocele, hepatomegaly due to hepatic vein obstruction, ascites, and congestive heart failure were found in less than 10% of patients with intracaval or atrial tumor extension in NWTS-3 (156). Occasionally, children with Wilms' tumor present with symptoms suggesting the production of bioactive substances by the tumor (46). Hypertension is present in 25% of cases and has been attributed to elevated plasma renin levels (185). During the physical examination, it is important to note signs of associated Wilms' tumor syndromes such as aniridia, hemihypertrophy, and genitourinary anomalies.

Preoperative Evaluation

Emergent operation is not necessary unless there is evidence of active bleeding or tumor rupture. Laboratory evaluation should include a complete peripheral blood count, platelet count, renal function tests, liver function tests, serum calcium, and urinalysis. Elevation of serum calcium can occur in children with congenital mesoblastic nephroma and rhabdoid tumor of the kidney (RTK). Acquired von Willebrand's disease has been found in 8% of newly diagnosed Wilms' tumor patients (45).

Imaging—Abdomen

Preoperative imaging studies are ordered with the intent of obtaining the correct diagnosis before surgical exploration, but an equally important goal is to establish that the contralateral kidney is functioning before performing a nephrectomy. Few distinguishing radiographic features allow a precise preoperative diagnosis of the histology of a renal mass. However, defining the exact histology is probably not as important as establishing that a solid renal tumor is present, which will help the surgeon plan for a major cancer operation. The preoperative diagnosis was incorrect in 2.5% of NWTS-3 patients (the child had Wilms' tumor but there was an erroneous diagnosis before surgical exploration), and the majority of these patients did not have any preoperative imaging studies performed (158). This group of patients was found to have an increased incidence of surgical complications, which underscores the importance of the imaging evaluation.

Advances in imaging have resulted in ultrasound and/or computed tomography (CT) supplanting the intravenous pyelogram (IVP). Classically, the IVP reveals distortion of the renal contour with splaying of the collecting system. Ultrasonography is performed routinely in most children with abdominal masses and can distinguish between solid and cystic lesions. Ultrasound can generally identify the kidneys and determine whether the mass is of renal origin. Another important role of imaging is to exclude intracaval tumor extension, which occurs in 4% of Wilms' tumor patients (Fig. 54.2) (156). Magnetic resonance imaging (MRI) is the study of choice if extension of tumor into the inferior vena cava (IVC) cannot be excluded by ultrasound (189).

If vascular invasion is not present, cystoscopy with retrograde pyelography is warranted to exclude ureteral extension in children with a nonfunctioning kidney, particularly if hematuria is present. Recognition of ureteral invasion before nephrectomy will facilitate a complete en bloc resection.

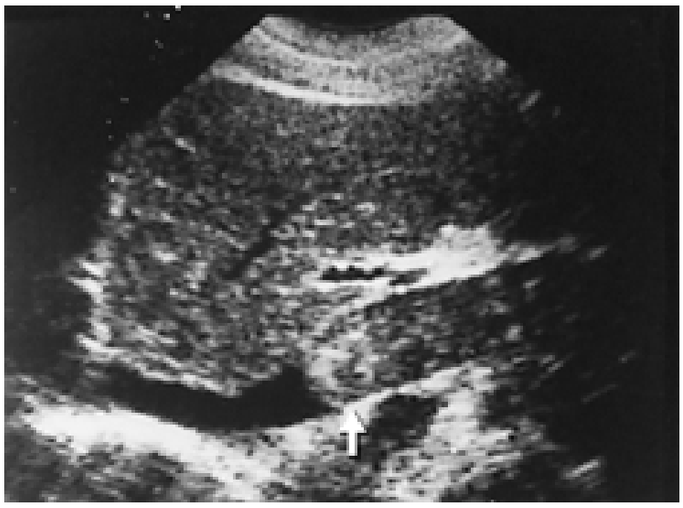

FIGURE 54.2. Ultrasound that depicts intracaval thrombus *(arrow).*

CT and MRI can further define the extent of the lesion (Fig. 54.3), but many childhood renal tumors have similar appearances (35,71,190). The role of CT and MRI in staging of the renal tumor continues to be defined (41,54,61). Accurate staging of children with Wilms' tumors is essential to define tumor extent before initiating treatment because outcome is highly correlated with stage (53). However, these data are derived most accurately from the findings at surgery as confirmed by pathologic examination. The local tumor burden (regional lymph node involvement, residual disease, diffuse tumor spillage) determines whether the child receives abdominal irradiation and also the intensity of the chemotherapy regimen.

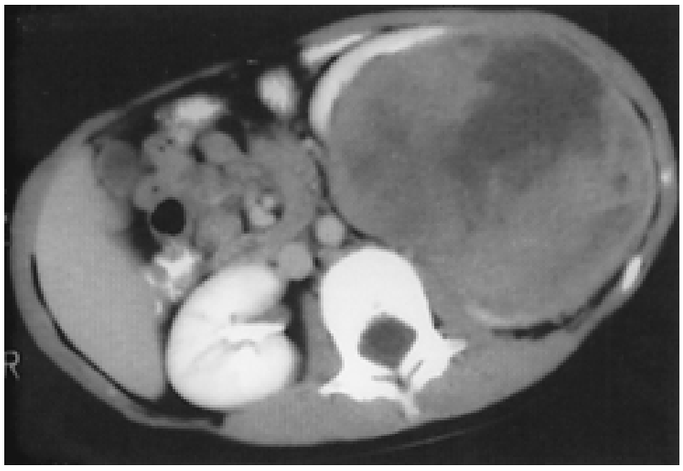

FIGURE 54.3. Computed tomography scan of a large left Wilms' tumor with a small rim of functioning renal parenchyma.

Preoperative CT can reveal evidence of regional adenopathy and suggest extrarenal tumor extension into the perirenal fat and into adjacent structures. However, prospective correlation with pathologic findings to validate the utility of CT staging has not been done. Most children identified as having possible invasion of the liver on CT are found at the time of surgical exploration to have hepatic compression, rather than hepatic invasion (138). Enlarged retroperitoneal benign lymph nodes are common in children, which can create significant diagnostic error. Correlation between pathologic findings and lymph node evaluation at surgical exploration in Wilms' tumor patients have found false-positive and false-negative error rates of 18% and 31%, respectively (142). It should not be expected that current imaging modalities will have greater accuracy. A recent report using positron emission tomography with the glucose analog 2-deoxy-2-fluoro-D-glucose does show promise in imaging of renal tumors (173). This technique can provide anatomic imaging of both the primary tumor and metastatic disease, but at present, experience in childhood malignancies is limited.

Assessment of the contralateral kidney in Wilms' tumor patients is necessary to exclude bilateral disease. Both CT and MRI are more accurate than ultrasound in identifying small lesions (nephrogenic rests or Wilms' tumor) in the opposite kidney, but a review of children with synchronous bilateral Wilms' tumor enrolled in NWTS-4 found that 7% of bilateral lesions were missed by preoperative imaging (163).

Imaging—Metastatic Disease

Plain chest radiographs should be obtained to determine whether pulmonary metastases are present. Most centers obtain CT of the chest in the initial evaluation of children with Wilms' tumor. Additional imaging studies are recommended to detect the presence of metastases in selected renal tumors with unfavorable histology (54). Clear cell sarcoma of the kidney (CCSK) and renal cell carcinoma (RCC) have a propensity to metastasize to the skeleton. Skeletal surveys and bone scans are both recommended after the histologic diagnosis is confirmed. RTK and CCSK are associated with brain metastases and MRI of the brain should be obtained in the early postoperative period.

Additional imaging studies are helpful under specific conditions. A radionuclide bone scan and x-ray skeletal survey are obtained postoperatively on all children with CCSK to exclude skeletal metastases (54). Cranial CT or MRI is performed on all children with CCSK or with RTK because both are associated with intracranial metastases (188).

Differential Diagnosis

Nephroblastoma accounts for more than 90% of renal tumors in children. Distinguishing radiographic features that will allow a precise preoperative diagnosis of the histology of a renal mass are few. Other clinical parameters will aid the clinician in narrowing the diagnostic possibilities in a child with a renal mass. The development of a renal tumor in a child known to have aniridia, hemihypertrophy, or other syndromes associated with an increased incidence of nephroblastoma safely can be assumed to be a Wilms' tumor. Bilateral or multicentric tumors are more typical of Wilms' tumor, but renal lymphoma can present in this fashion. Congenital mesoblastic nephroma (CMN) is the most likely diagnosis in a neonate with a renal mass. However, favorable histology Wilms' tumor and RTK also can present in the first few months of life. RTK and CCSK tumors should be considered in patients that present with brain or skeletal metastases. RCC is more common in the second decade of life (35).

Pathology

The gross appearance of Wilms' tumor is that of a spherical mass (Fig. 54.4) with a light gray or tan color on cross section. Wilms' tumor usually compresses the adjacent normal renal parenchyma forming a pseudocapsule composed of compressed, atrophic renal tissues. Most tumors are soft and friable with necrotic or hemorrhagic areas frequently noted. Wilms' tumor is characterized by tremendous histologic diversity. The classic triphasic pattern includes varying proportion of three cell types: blastemal, stromal, and epithelial. The proportion of each of these components varies, with some consisting of only biphasic or even monomorphous patterns (170). Wilms' tumors with predominantly epithelial differentiation have a low degree of aggressiveness, and most are stage I tumors (15). However, these tumors may be more resistant to therapy if they present as advanced stage disease. Blastemal predominant tumors are highly aggressive but very responsive to chemotherapy. In addition to expressing a variety of cell types found in a normal developing kidney, Wilms' tumor often contains tissues such as skeletal muscle, cartilage, and squamous epithelium. These heterotopic cell types likely reflect the primitive developmental potentials of metanephric blastema that are not expressed in normal nephrogenesis. Most Wilms' tumors are unicentric, but 7% are multicentric unilateral tumors. Extrarenal locations are rare and are thought to arise from displaced metanephric elements or mesonephric remnants.

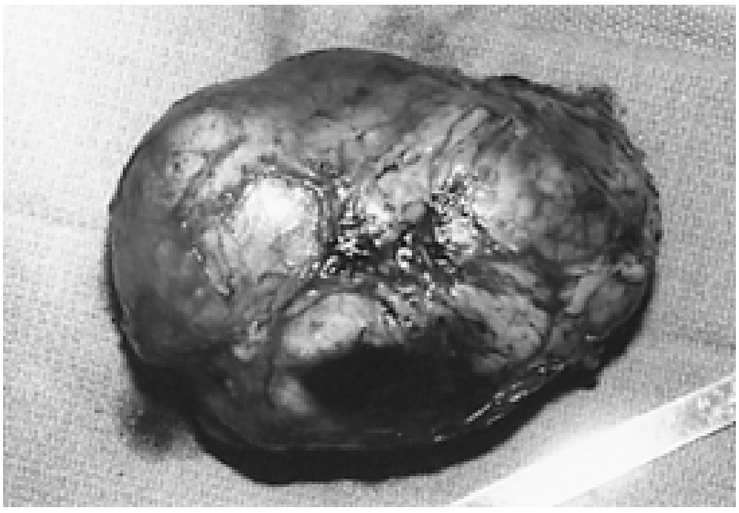

FIGURE 54.4. Gross specimen of a Wilms' tumor.

Analysis of early NWTSG patients identified a group of tumors with “unfavorable” histologic features (7) that were responsible for 50% of tumor deaths, but account for only 10% of patients (29). These characteristics included tumors of extreme nuclear atypia (anaplasia), and monomorphic sarcomatous appearing tumors. These latter tumors have been reclassified as the RTK and CCSK and are now considered to be distinct entities from Wilms' tumor (see the following discussion). These unfavorable features occurred in approximately 10% of patients, but accounted for almost half of the tumor deaths in early NWTSG studies (29).

The cytopathologic features of anaplasia are threefold or greater nuclear enlargement, hyperchromasia of enlarged nuclei, and increased mitotic figures. Anaplasia is associated with resistance to chemotherapy. This is evidenced by the similar incidence of anaplasia (5%) in the NWTSG and International Society of Paediatric Oncology (SIOP) studies (186). It is rare in the first 2 years of life, but the incidence increases to 13% in children age 5 years or older (23). Anaplastic features can occur focally, requiring thorough sampling of the primary tumor to avoid missing this poor prognostic feature (7). The definition of focal anaplasia is based on a topographic principle and requires that the anaplastic nuclear changes be confined to a specified region of the primary tumor and absent from the surrounding portions of the lesion (68). Diffuse anaplasia is diagnosed when anaplasia is present in more than one portion of the tumor or if it is found in any extrarenal or metastatic site. When the anaplastic component is completely removed, stage I, the outcome is generally excellent (194). This confirms the observation that anaplasia is more a marker of chemoresistance than inherent aggressiveness of the tumor. When anaplastic changes are not present, the tumor is referred to as being of favorable histology (FH) because of the generally good outcome for these patients (7).

Alterations of the p53 tumor suppressor gene and its encoded protein have been reported in anaplastic tumors (5). It has been suggested that the p53 tumor suppressor gene might underlie the development of a histopathologic variant of Wilms' tumor with poor prognosis. Another study however, identified a p53 mutation in a Wilms' tumor with favorable histology, the most common histologic variant and carrying an excellent prognosis (126). In this latter study, p53 mutations were found in tumors from patients with advanced disease, suggesting that p53 mutations are associated with advanced stage disease in Wilms' tumor, rather than with histologic features.

Precursor Lesions of Wilms' Tumor

Nephrogenic rests (NRs) are defined as foci of abnormally persistent nephrogenic cells that can form a Wilms' tumor (10). They have been found in 1% of kidneys in infants on postmortem examination (17) and in 30% to 40% of kidneys removed for Wilms' tumor (13). Two distinct categories of NRs have been identified, perilobar nephrogenic rest (PLNR) and intralobar nephrogenic rest (ILNR). This classification is based on the position of these lesions within the renal lobe. The developing renal lobe matures in a centrifugal fashion with each generation of nephrons added sequentially to the periphery. PLNR are found in the periphery while ILNR can be found anywhere within the renal lobe (Fig. 54.5). It is inferred that ILNR situated deep in the renal lobe reflect an earlier developmental event. The

presence of multiple or diffuse NRs will lead to the diagnosis of nephroblastomatosis.

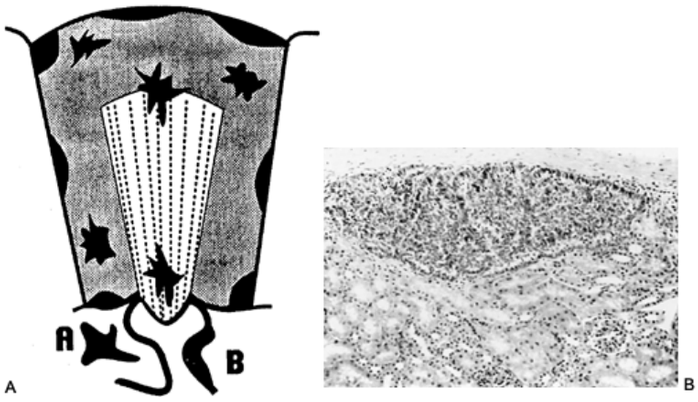

FIGURE 54.5. A: Illustration of renal lobe showing characteristic locations of intralobar nephrogenic rest (dark gray) and perilobar nephrogenic rest (black). (From Beckwith JB. Precursor lesions of Wilms' tumor: clinical and biological implications. *Med Pediatr Oncol* 1993;21:158, with permission.) **B:** Perilobar nephrogenic rest composed of blastemal cells just beneath the renal capsule (hematoxylin and eosin, 40× magnification).

ILNR and PLNR differ in several epidemiologic characteristics, summarized in Table 54.2 . The age at diagnosis is lower for Wilms' tumor arising in association with ILNR, and children with WAGR and Drash syndromes are more likely to have ILNR. In contrast, PLNR is of higher prevalence in hemihypertrophy and in BWS. Both types of NRs are associated with bilateral Wilms' tumor in which the incidence of NRs is much higher than seen in unilateral Wilms' tumor. Multiple rests in one kidney usually implies that NRs are present in the other kidney. Children younger than 12 months diagnosed with Wilms' tumor who also have NRs have a significantly increased risk of developing contralateral disease (49). An increased risk of metachronous Wilms' tumor was found in patients with BWS, hemihypertrophy, and aniridia. These patients need regular imaging surveillance to detect contralateral recurrence (Table 54.3). Because metachronous Wilms' tumor does occur in patients previously treated with conventional chemotherapeutic regimens, NRs cannot always be eradicated.

TABLE 54.2. APPROXIMATE PREVALENCE OF NEPHROGENIC RESTS

Patient Population	PLNR (%)	ILNR (%)
Infant autopsies	1	0.01
Renal dysplasia	3.5	Unknown
Unilateral Wilms' tumor	25	15
Synchronous bilateral Wilms' tumor	74–79	34–41
Metachronous bilateral Wilms' tumor	42	63–75
Beckwith-Wiedemann, hemihypertrophy	70–77	47–56
Aniridia	12–20	84–100
Drash syndrome	11	78

ILNR, intralobar nephrogenic rest; PLNR, perilobar nephrogenic rest. Adapted from Beckwith JB. Precursor lesions of Wilms' tumor: clinical and biological implications. *Med Pediatr Oncol* 1993;21:158, with permission.

TABLE 54.3. RECOMMENDED FOLLOW-UP IMAGING STUDIES FOR CHILDREN WITH RENAL NEOPLASMS OF PROVEN HISTOLOGY AND FREE OF METASTASES AT DIAGNOSIS

Tumor Type	Study	Schedule Following Therapy
Favorable histology Wilms' tumor; Stage I anaplastic Wilms' tumor	Chest films	6 wk and 3 mo postop; then q3mo × 5, q6mo × 3, yearly × 2
Irradiated patients only	Irradiated bony structures[a]	Yearly to full growth, then q5yr indefinitely[b]
Without NRs, stages I and II	Abdominal ultrasound	Yearly × 3
Without NRs, stage III	Abdominal ultrasound	As for chest films
With NRs, any stage[c]	Abdominal ultrasound	q3mo × 10, q6mo × 5, yearly × 5
Stages II and III anaplastic	Chest films Abdominal ultrasound	As for favorable histology q3mo × 4; q6mo × 4
Renal cell carcinoma	Chest films Skeletal survey and bone scan	As for favorable histology As for CCSK
Clear cell sarcoma of the kidney (CCSK)	Brain MRI and/or opacified CT Skeletal survey and bone scan Chest films	When CCSK is established, then q6mo × 10 As for favorable histology
Rhabdoid tumor	Brain MRI and/or opacified CT Chest films	As for CCSK As for favorable histology
Mesoblastic nephroma[d]	Abdominal ultrasound	q3mo × 6

[a]To include any irradiated osseous structures.
[b]To detect second neoplasms, benign (osteochondromas) or malignant.
[c]The panelists at the first International Conference on Molecular and Clinical Genetics of Childhood Renal Tumors, Albuquerque, New Mexico, May 1992 recommended a variation: q3mo for 5 yr or until age 7, whichever comes first.
[d]Data from the files of Dr. J.B. Beckwith reveal that 20 of 293 mesoblastic nephroma (MN) patients (7%) relapsed or had metastases at diagnosis; 4 of the 20 in the lungs, 1 of the 4 at diagnosis. All but 1 of the 19 relapses occurred within 1 year. Chest films for MN patients may be elected on a schedule such as q3mo × 4, q6mo × 2.
CT, computed tomography; MRI, magnetic resonance imaging.
Modified from D'Angio GJ, Rosenberg H, Sharples K, et al. Position paper: Imaging methods for primary renal tumors of childhood: Cost versus benefits. *Med Pediatr Oncol* 1993;21:205, with permission.

NRs have a varied life and most do not form Wilms' tumor. A rest can undergo maturation, sclerosis, involution, and complete disappearance. NRs display a spectrum of appearances. Hyperplastic NRs can produce a renal mass that can be mistaken for a small Wilms' tumor. Incisional biopsy of a hyperplastic rest is of little value in distinguishing this lesion from a Wilms' tumor. The biopsy should include the interface of the rest with the normal renal parenchyma. Wilms' tumor generally compresses the normal kidney with a pseudocapsule at their interface (16). Neoplastic induction of cells of an NR will produce Wilms' tumor and possibly other benign or malignant renal neoplasms. Given that the incidence of NRs is much greater than that of Wilms' tumor, it is not surprising that regression of the rests is common. Sclerosing ILNR can be indistinguishable from focal renal dysplasia (13). NRs also have been found in 4% of multicystic dysplastic kidneys (139), but only 1 in 2,000 are expected to develop a Wilms' tumor (12).

Prognostic Factors

Chromosomal Abnormalities

Because most patients with FH Wilms' tumor have excellent survival rates, it becomes increasingly difficult to find

any particular histologic feature of a given tumor that will predict the risk of relapse. The current focus of the NWTS-5 study of Wilms' tumor is to evaluate potential biologic factors that may predict tumor behavior. A tumor bank maintains specimens from all patients entered on the study. This has provided a valuable resource for molecular biology investigators. An intense research effort is under way to identify other biologic markers that could further stratify FH Wilms' tumor patients into low- and high-risk groups for relapse. Such a marker would allow a further reduction in treatment intensity for a large number of patients.

LOH for a portion of chromosome 16q has been noted in 20% of Wilms' tumor patients (127). This was not found to be a germline mutation, which suggests that this region may play a role in tumor progression rather than tumor initiation. A prospective study of 232 patients registered on the NWTSG found LOH for 16q in 17% of the tumors (91). Patients with tumor-specific LOH for chromosome 16q had a statistically significantly poorer 2-year relapse-free and overall survival than for those patients without LOH for chromosome 16q. This difference in outcome persisted after adjustment for histology and stage. If this information is confirmed in a larger prospective study, molecular markers may serve to further stratify Wilms' tumor patients for treatment. Patients identified with unfavorable molecular findings could be selected for alternative forms of therapy.

Dome and others (62) investigated telomerase levels in patients with Wilms' tumor. Telomerase is a reverse transcriptase that maintains chromosome ends, compensating for the loss of DNA that occurs in replication. High telomerase activity has been found to be an unfavorable prognostic feature for several types of cancers. In a case-cohort study of 78 patients with FH Wilms' tumor, telomerase enzyme activity; expression of human telomerase (hTR), the RNA component of telomerase; and mRNA expression of high telomerase reverse transcriptase (hTERT), the gene that encodes the catalytic component of the enzyme, were measured. All had detectable expression of hTR and 97% had detectable hTERT transcript. The hTERT mRNA levels correlated with the risk of recurrence even after adjustment for tumor stage. A larger study is under way to determine whether this is an independent prognostic indicator.

Cytokines

The growth of solid tumors is critically dependent on the induction of angiogenic cytokines identified to play a role in tumor induction of neovascularity. Vascular endocrine

growth factor (VEGF) is an angiogenic cytokine detected with increased frequency and quantity in experimental and clinical specimens of Wilms' tumor (108,109). VEGF was found in 10 of 12 clinical Wilms' tumor specimens tested. In experimental animals, lung metastases were far more likely to occur in animals with VEGF-positive tumors. The potential of anti-VEGF therapy to suppress tumor growth also has been assessed (168). Tumors were induced in kidneys of nude mice by the injection of tumor cells. After 1 week, anti-VEGF antibody was given intraperitoneally. This resulted in a greater than 95% reduction in tumor weight and abolished lung metastases. Once therapy was stopped, tumor growth rebounded. This therapy is now entering clinical phase II trials to assess its efficacy in humans.

DNA Content

Measurement of DNA content can be used to estimate the proliferative rate of populations of cells comprising solid malignancies. Flow cytometry has been performed on Wilms' tumor specimens to try and identify aggressive populations of tumor cells that may predict which low-stage tumors are at risk for metastatic disease (152). However, the results from smaller institutional studies have been inconclusive. The predictive value of DNA content is being examined in the NWTS-5 cohort. Similarly, nuclear morphometric techniques have been evaluated in Wilms' tumor to predict clinical outcome (143). A recent study of 218 patients found that nuclear morphometry was unable to predict disease-free survival (33).

Tumor Markers

The criteria for an ideal tumor marker are that the substance can be readily assayed, the assay must be sensitive and the marker must be specific for the tumor type, levels must return to normal following treatment, and subsequent elevation must correlate with evidence of tumor recurrence. Several biologic markers for Wilms' tumor under investigation include serum renin, neuron-specific enolase, hyaluronic acid, hyaluronidase, and hyaluronic acid stimulating activity (46). The latter markers are of particular interest in that hyaluronic acid metabolism may be associated with tumorigenesis and angiogenesis. Elevated levels of hyaluronic acid and hyaluronic acid-stimulating activity have been reported in both urine and serum of Wilms' tumor patients (124). Following surgical removal of the tumor, the levels returned to normal. Patients with persistent disease or relapse had significantly higher levels 1 to 6 months after surgery. Elevated urine levels of basic fibroblast growth factor have been found in Wilms' tumor patients (125). Stage III, IV patients had significantly higher preoperative levels when compared with stage I, II patients. Patients with relapse or persistent disease had significantly elevated late postoperative levels when compared with disease-free patients and controls. More studies are needed to define the clinical role of these two markers in patients with Wilms' tumor.

Elevated plasma renin levels have been reported in Wilms' tumor patients, and following treatment, plasma renin levels are reduced (185). There has been no clear correlation with systemic blood pressure, which has been attributed to the elevation of an inactive precursor of rennin—prorenin—rather than active renin. Elevated plasma renin levels also have been noted with relapse of Wilms' tumor (46). In all cases, the renin level had decreased after initial tumor excision and then subsequently became elevated.

Staging and Patterns of Spread

The most important determinants of outcome in children with Wilms' tumor are the histopathology and tumor stage. Accurate staging of Wilms' tumor allows treatment results to be evaluated and enables universal comparisons of outcomes. In North America, the most widely used staging system is the one developed by the NWTSG (Table 54.4) and is based primarily on the surgical and histopathologic findings. For NWTS-4, the distribution by stage for randomized patients was stage I—41.8%, stage II—27.5%, stage III—21.5%, and stage IV—9.3% (86). Patients with anaplastic tumors are twice as likely to present with stage IV disease than those with favorable histology tumors (83).

Stage	Characteristics
I	Tumor limited to the kidney and completely excised. The renal capsule is intact and the tumor was not ruptured before removal. There is no residual tumor.
II	Tumor extends through the perirenal capsule, but is completely excised. Local spillage of tumor may be confined to the flank, or the tumor may have been biopsied. Extrarenal vessels may contain tumor thrombus or be infiltrated by tumor.
III	Residual nonhematogenous tumor confined to the abdomen: lymph node involvement, diffuse peritoneal spillage, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed.
IV	Hematogenous metastases to lung, liver, bone, brain, and so on.
V	Bilateral renal involvement at diagnosis.

TABLE 54.4. STAGING SYSTEM OF THE NATIONAL WILMS' TUMOR STUDY

Examination for extension through the capsule, residual disease, vascular involvement and lymph node involvement is essential to properly assess the extent of the tumor. Stage I tumors are limited to the kidney and completely resected. However, evidence for tumor extension can be subtle. The first signs of spread outside the kidney are in the renal sinus

and lymphatic vessels. Penetration through the renal capsule is the next most common site of extrarenal spread. Tumors that penetrate the renal capsule are considered stage II lesions. Clear demonstration of tumor cells in the perirenal fat is required to document capsular penetration. Tumor extension into the renal sinus is now considered stage II (187) disease. This was identified as one of several variables predictive of tumor relapse in favorable histology stage I tumors in NWTS-3 patients (187). These 'microsubstaging' variables are invasion of the tumor capsule, presence of an inflammatory pseudocapsule, renal sinus invasion, and tumor in the intrarenal vessels.

Surgical Management

Surgical excision is the initial treatment for most children with Wilms' tumor. The surgeon has an important responsibility to perform safe and complete removal of the Wilms' tumor. Shamberger and co-workers confirmed the important role of the surgeon in removing the tumor without rupture or spill (277). Tumor spillage, unfavorable histology, and stage III disease (diffuse tumor spill, incomplete tumor removal) were all found to be predictors of local abdominal relapse. The absence of any lymph node sampling also was associated with an increased risk of

abdominal recurrence presumably because of incomplete staging. The 2-year survival after abdominal recurrence was 43% emphasizing the importance of the surgeon in performing careful and complete tumor resection.

Complete tumor resection improves patient survival. Another important surgical objective is determining tumor extent. The surgeon's responsibility is not only to remove the primary tumor intact, but also to assess the tumor spread precisely. Accurate staging is essential for the subsequent determination of the need for radiation therapy and the administration of the appropriate chemotherapy regimen.

Technique

The transperitoneal approach to the tumor is recommended. The flank approach should not be used because adequate staging cannot be performed and the contralateral kidney cannot be examined. Once the peritoneal cavity is entered, thorough exploration of the abdominal cavity is carried out. One should assess the liver, regional lymph nodes in the periaortic area, and look for other evidence of tumor spread. The presence or absence of lymph node metastases is of major importance in determining treatment and relapse-free survival (142,171). Thus selective sampling of suspicious nodes is necessary for accurate staging. There is no evidence that extensive lymph node removal alters the outcome in patients with Wilms' tumor, and thus formal retroperitoneal lymph node dissection (RPLND) is not recommended.

Exploration of the contralateral kidney should be performed before nephrectomy. The colon is reflected and Gerota's fascia opened so that the kidney can be palpated and visually inspected on all surfaces for evidence of a synchronous bilateral tumor or evidence of NRs. These may not be identified on preoperative imaging studies, especially if they are small and/or flat. Any abnormalities of the opposite kidney should be biopsied. The presence of bilateral Wilms' tumor alters the surgical approach significantly (see the following discussion); thus the status of the contralateral kidney must be determined *before* nephrectomy.

After the contralateral exploration is completed, radical nephrectomy is performed. The colon is mobilized off the tumor and reflected medially preserving the colonic blood supply. Gentle handling of the tumor throughout the procedure is mandatory to avoid tumor spillage because these patients have a sixfold increase in local abdominal relapse (171). Although early ligation of the renal vein does not appear to have an appreciable effect on survival, separate ligation is performed before mobilization of the tumor, but only if exposure is adequate. Palpation of the renal vein and inferior vena cava should be performed to exclude intravascular tumor extension before vessel ligation. Wilms' tumor extends into the inferior vena cava in approximately 6% of cases and may be clinically asymptomatic in more than 50% (156).

Another important aspect of surgery for Wilms' tumor is to minimize surgical related morbidity. NWTS-4 patients undergoing primary nephrectomy had an 11% incidence of surgical complications (166). The most common complications were hemorrhage and small bowel obstruction. SIOP investigators have reported a lower rate of complications when nephrectomy is performed after preoperative chemotherapy (73). Complications were reported in 8% of patients, but this included tumor ruptures. Excluding these patients decreased the incidence of surgical complications to 5.7%.

National Wilms' Tumor Study Group Trials

Since the inception of the NWTSG, many significant advancements have been made in the understanding and treatment of nephroblastoma. The first two NWTSG studies, NWTS-1 (1969–1973) and NWTS-2 (1974–1978), showed that postoperative local irradiation was unnecessary for group I patients (51,52). The combination of vincristine (VCR) and dactinomycin (AMD) was noted to be more effective than the use of either drug alone, and the addition of doxorubicin (DOX) improved survival for higher-stage patients. Other important findings of the early clinical trials included identification of unfavorable histologic features and other prognostic factors that allowed refinement of the staging system, stratifying patients into high- and low-risk treatment groups. Patients with positive lymph nodes and diffuse tumor spill were found to be at increased risk of abdominal relapse and therefore considered stage III and given whole abdominal irradiation. These findings were incorporated into the design of subsequent NWTSG studies to try and decrease the intensity of therapy for the majority of low-risk patients.

In NWTS-3 (1979–1986), patients with stage I, FH Wilms' tumor were treated successfully with either a 10- or 18-week regimen of VCR and AMD (53). This considerably decreased the amount of chemotherapy administered and the total duration of treatment. The 4-year relapse-free survival was 89%, and the overall survival was 95.6%. Stage II FH patients treated with AMD and VCR without postoperative radiation therapy (XRT) had an equivalent survival, with a 4-year overall survival of 91.1% for patients that received the same treatment plus DOX with or without XRT. This demonstrated that the cardiotoxic drug DOX is not necessary for the successful treatment of this group of patients. XRT could now be omitted for the majority of children with Wilms' tumor. For stage III FH patients, the dosage of abdominal irradiation was reduced to 10.8 Gy. This was shown to be as effective as 20 Gy in preventing abdominal relapse if DOX was added to VCR and AMD. The 4-year relapse-free survival for stage III patients was 82% in NWTS-3, and the 4-year overall survival was 90.9%. Patients with stage IV FH tumors received abdominal (local) irradiation based on the local tumor stage. In addition, they all received 12 Gy to both lungs. In combination with VCR, AMD, and DOX, the 4-year relapse-free survival was 79%, and the overall survival was 80.9%. No statistically significant improvement in survival was noted when cyclophosphamide was added to the three-drug regimen.

The NWTS-4 study was completed in 1994. This study compared the efficacy and toxicity of a single-dose schedule (pulse-intensive) compared with divided-dose treatment regimens of AMD and DOX. The pulse-intensive regimens achieved equivalent survival while decreasing the cost of therapy through modification of the schedule of drug administration (86). In addition, treatment durations of approximately 6 and 15 months were compared in patients with stages II to IV/FH tumors (87). Treatment with a 6-month duration of chemotherapy was as effective as 15 months. Overall, the 4-year survival for patients with FH Wilms' tumor (all stages) now exceeds 90%.

Children with anaplastic Wilms' tumors were randomized in NWTS-3 and NWTS-4 to receive either VCR, AMD, and DOX or those three drugs with the addition of cyclophosphamide. The results were analyzed after the tumors were reclassified using the criteria of Faria and Beckwith (68). There was no difference in outcome between the regimens for children with focal anaplasia who had a prognosis similar to that for favorable histology patients (84). For stage II to IV diffuse anaplasia, the addition of cyclophosphamide to the three-drug regimen improved the 4-year relapse-free survival (27.2% versus 54.8%).

Treatment recommendations of the current intergroup study, NWTS-5 opened in 1995, are outlined in Table 54.5 . This is a single-arm therapeutic trial without any randomization for therapy. Prospective collection of information regarding biologic features of the tumors is under way. A collection of banked tumor specimens is available to evaluate new prognostic factors that may be identified in the future. This study will attempt to verify the preliminary findings that LOH for chromosomes 16q and 1p are useful in identifying patients who are at increased risk for relapse (91). If molecular genetic markers are predictive of clinical behavior, they may be used in subsequent clinical trials to further stratify patients for therapy.

TABLE 54.5. TREATMENT PROTOCOL FOR NATIONAL WILMS' TUMOR STUDY-5

Stage/Histology	Radiotherapy	Chemotherapy
Stage I, II FH	None	EE-4A—pulse-intensive AMD plus VCR (18 wk)
Stage I anaplasia		
Stage III, IV FH	1,080 cGy[a]	DD-4A—pulse-intensive AMD, VCR, and DOX (24 wk)
Stage II–IV focal anaplasia		
Stage II–IV diffuse anaplasia	Yes[b]	Regimen I: AMD, VCR, DOX, CPM, and etoposide
Stage I–IV CCSK		
Stage I–IV rhabdoid tumor of the kidney	Yes[b]	Regimen RTK: carboplatin, etoposide, and CPM

[a]Stage IV FH patients are given radiation based on the local tumor stage.
[b]Radiation therapy is given to all CCSK and RTK patients. Consult protocol for specific treatment.
AMD, dactinomycin; CCSK, clear cell sarcoma of the kidney; CP, cyclophosphamide; DOX, doxorubicin; FH, favorable histology; RTK, rhabdoid tumor of the kidney; VCR, vincristine.

Treatment for patients with stage I or II FH, and stage I anaplastic Wilms' tumor is a pulse intensive regimen of VCR and AMD for 18 weeks. Patients with stage III FH and stage II to III focal anaplasia are treated with AMD, VCR, and DOX and 10.8 Gy abdominal irradiation. Patients with stage IV FH tumors receive abdominal irradiation based on the local tumor stage and 12 Gy to both lungs. Finally, children with stage II to IV diffuse anaplasia are treated on NWTS-5 with a new chemotherapeutic regimen combining VCR, DOX, cyclophosphamide, and etoposide in an attempt to further improve the survival of this high-risk

group. All these patients will receive irradiation to the tumor bed.

A select group of patients younger than 2 years of age with stage I FH tumors weighing less than 550 g were selected for management with surgery alone in NWTS (85). This was based on preliminary observation of favorable outcomes on small numbers of such patients when postoperative adjuvant therapy had been omitted (117). A review of NWTSG patients had found excellent outcomes for such patients, albeit with postoperative chemotherapy (81). This portion of the study was suspended when the number of tumor relapses exceeded the limit allowed by the design of the study. The design of the study was that the trial would be stopped when a 2-year relapse-free survival below 95% could be excluded. It was recommended that all children with stage I tumors receive AMD and VCR. The 2-year survival rate is 100% with a median follow-up of 1.61 years (88). Extended follow-up of this cohort of patients continues. Observation of untreated children may yield interesting information on the role of chemotherapy in decreasing the incidence of contralateral relapse in patients with NRs (89).

Preoperative Therapy

SIOP Trials

The clinical protocols conducted by SIOP for treatment of Wilms' tumor have included preoperative therapy since the early 1970s. This approach usually results in tumor shrinkage (Fig. 54.6), reducing the risk of intraoperative rupture or spill (119,120). It also is postulated that the neoadjuvant therapy will treat micrometastases, leading to a more favorable stage distribution at the time of surgery. A greater number of patients have “postchemotherapy stage I” tumors. This was thought to be a significant advantage in terms of decreasing morbidity of treatment, particularly the late effects of radiotherapy. When SIOP and NWTSG began their prospective studies, all children with Wilms' tumor received postoperative radiation therapy.

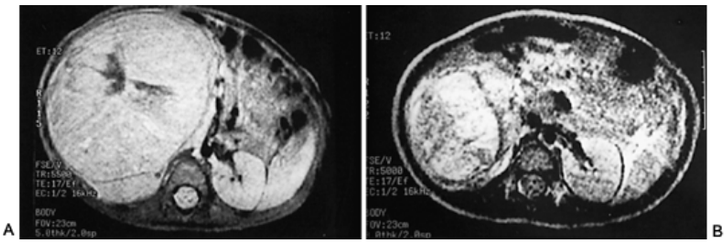

FIGURE 54.6. A: Magnetic resonance imaging scan of a large inoperable Wilms' tumor. **B:** After 6 weeks of chemotherapy, the same tumor has decreased in size dramatically.

The first two SIOP studies answered questions with regard to the use of prenephrectomy XRT (119). The third SIOP study, SIOP-5, showed that 4 weeks of AMD and VCR was as effective as prenephrectomy XRT in avoiding surgical tumor rupture and increasing the proportion of patients with low stage disease (120). SIOP-6, the fourth SIOP study on Wilms' tumor, demonstrated that patients with postnephrectomy stage I disease can safely be treated with 18 weeks of AMD and VCR (183). Those with stage II lymph node–negative disease; however, were shown to require more intensive postnephrectomy chemotherapy, including the use of an anthracycline (183). Finally, SIOP-6 confirmed the need for a three-drug chemotherapy regimen following nephrectomy for those with more advanced stage disease (i.e., stage II lymph node positive and stage III). The fifth SIOP Wilms' tumor trial, SIOP-9, found no significant additional tumor shrinkage benefit after 4 weeks of preoperative AMD and VCR (184). The latest SIOP study on Wilms' tumor, SIOP 93-01, aims to determine whether postoperative therapy can be omitted in selected stage I patients (21) and whether survival can be improved in certain high-risk patients with the use of etoposide, ifosfamide, and carboplatin.

The staging information obtained following prenephrectomy chemotherapy does not reflect the original tumor stage and may inadequately define the risk of intraabdominal recurrence. This was demonstrated by the increased frequency of intraabdominal recurrence in unirradiated “postchemotherapy stage II” tumors (classified following 4 weeks of prenephrectomy chemotherapy) without positive lymph nodes (SIOP staging criteria) (183). As a result, these patients are now given an anthracycline as part of the chemotherapy regimen (82). The added chemotherapy

could increase the incidence of late complications (see the following discussion). Both the NWTSG and SIOP tumor staging systems are designed to stratify patients into low- and high-risk groups. The goal is to select out high-risk patients for more intense therapy while minimizing treatment and thus morbidity for low-risk patients. The NWTSG relies on surgical and pathologic staging reflecting the extent of disease at diagnosis. If one looks carefully at both NWTSG and SIOP data, the two groups are similar with respect to their attempts to decrease the number of patients that receive postoperative XRT (79).

The NWTSG continues to recommend primary surgical treatment of Wilms' tumor. This will allow precise staging of patients with modulation of treatment for each individual, thereby decreasing the intensity of treatment when possible while maintaining excellent overall survival. The current recommendations from the NWTSG are that preoperative chemotherapy is of benefit in patients with bilateral involvement (19), inoperable tumor at surgical exploration (162), and IVC extension above the hepatic veins (160). All other patients should undergo primary nephrectomy.

Bilateral Disease

Synchronous bilateral nephroblastoma occurs in about 5% of children, with metachronous lesions developing in only 1% (19,48,131). The importance of intraoperative examination of the contralateral kidney previously was addressed (164). In the past, bilateral Wilms' tumor patients were managed with a primary surgical approach. Review of NWTSG patients with bilateral Wilms' tumor found an increased incidence of renal failure, 9.1% of synchronous and 18.8% of metachronous bilateral Wilms' tumor (165). Therefore the preferred approach for patients with bilateral Wilms' tumor is initial biopsy followed by preoperative chemotherapy (19,43,116). With use of this approach, nephrectomy can be avoided entirely in almost 50% of patients (131,172). One area of controversy is the role of enucleation versus partial nephrectomy when renal salvage procedures are performed in these patients. Enucleation is more likely to result in positive surgical margins (98). For favorable histology tumors, adjuvant therapy results in a good outcome (42). However, if anaplasia is in the resected specimen, a positive margin will adversely affect survival.

Surgical Management of Bilateral Tumors

Radical excision of the tumor should not be done at the initial operation. Partial nephrectomy or wedge excision can be performed at the initial operation, only if all tumor can be removed with preservation of two-thirds or more of the renal parenchyma on both sides. Bilateral biopsies are obtained to confirm the presence of Wilms' tumor in both kidneys and define the histologic type. Suspicious lymph nodes should be biopsied and a surgical stage assigned. Patients are then given chemotherapy to reduce the tumor burden. Surgical exploration with definitive resection is deferred until tumor burden has been reduced significantly. A second-look operation should be performed following the completion of the initial course of chemotherapy, usually in 8 to 10 weeks (164). Preoperative CT should be obtained to assess the reduction in tumor volume and to assess the feasibility of partial resection. At the time of the second-look procedure, partial nephrectomies or wedge excisions of the tumors are performed. This should only be done if it will not compromise tumor resection and negative margins can be obtained. If tumor involvement is extensive, precluding partial resection, complete excision of tumor from the least involved kidney is performed. If this leaves a viable kidney, then nephrectomy of the other kidney is carried out.

Some patients may not have a measurable response to preoperative chemotherapy. Serial imaging evaluation is helpful to assess response, but radiographic evidence of persistent disease can occasionally be misleading. Failure of the tumor to shrink could be due to predominance of skeletal muscle or benign elements, and a second-look procedure to confirm persistent viable tumor is necessary (194). Patients with persistent viable tumor should be changed to a different chemotherapeutic regimen. The patient should be reassessed after an additional 12 weeks to assess feasibility of resection. If salvaging the remaining kidney is a possibility, partial nephrectomy or wedge excision of the tumor is performed. If tumor involvement is extensive, precluding partial resection in one kidney, complete excision of tumor from the least involved kidney is performed. If this procedure leaves a viable and functioning kidney, radical nephrectomy is performed to remove the kidney with extensive tumor involvement.

Bilateral nephrectomy and dialysis may be required if the tumors fail to respond to chemotherapy and radiation therapy (146,169). Patients with DDS often undergo bilateral nephrectomy both because of the increased risk of Wilms' tumor in the remaining kidney and the associated nephropathy. The most common cause of renal failure in NWTSG patients is bilateral nephrectomy for persistent tumor (165). The recommended interval between successful completion of treatment of the Wilms' tumor and renal transplantation varies, with a minimum of 1-year tumor-free survival after completion of chemotherapy (146,169). However, bilateral Wilms' tumor patients need long-term follow-up because relapses have occurred as late as 4 years' posttreatment (43).

Partial Nephrectomy for Unilateral Tumors

The success of renal preservation in bilateral Wilms' tumor has prompted some surgeons to recommend parenchymal-sparing procedures for unilateral tumors (50,128,132). The majority of Wilms' tumors are too large for a partial nephrectomy at initial presentation and therefore pretreatment

is necessary. Staging of the patient after chemotherapy could lead to inaccuracy as previously discussed. After preoperative chemotherapy, partial nephrectomy has been feasible in 10% to 15% of patients. Some advocate enucleation of the tumor to allow parenchymal-sparing procedures for even centrally located tumors for which partial nephrectomy with a rim of renal tissue would be inadvisable (50). A recent review of patients with bilateral Wilms' tumor found that the incidence of local recurrence was 7.5% following partial nephrectomy versus 14% local recurrence after enucleation (NS) (98). Although overall survival was comparable, patients with residual disease and recurrences receive added therapy to maintain this survival.

Those who advocate this approach cite concern about the late occurrence of renal dysfunction in children who have undergone unilateral nephrectomy (1,3). The risk of developing renal failure following treatment for unilateral Wilms' tumor appears to be quite low. There is a 0.25% incidence of renal failure in NWTSG patients after nephrectomy for unilateral tumors (165). Most of those were patients with DDS who have intrinsic renal disease and present with renal failure at diagnosis or generally progress to end-stage renal disease. One group of patients at increased risk of renal failure is those with the WAGR syndrome. A recent report found a 38% risk of renal failure in these children at 20 years' follow-up (34). The onset of renal failure was at a median of 14 years.

In summary, parenchymal-sparing procedures for patients with unilateral Wilms' tumor are controversial. The current recommendation of the NWTSG is to consider partial nephrectomy for patients with bilateral Wilms' tumor, solitary kidney, and renal insufficiency. Also, patients known to have an increased incidence of NRs (e.g., BWS, hemihypertrophy, aniridia) are at increased risk for the development of a metachronous tumor and should be considered for parenchymal-sparing procedures (27,48). The risk of undertreatment and potentially increased risk of local recurrence must be weighed against the possible benefit of decreasing the incidence of renal failure.

Inoperable Tumors

In some patients, the tumor cannot be resected primarily. The decision regarding unresectability should be made intraoperatively and not based on imaging studies. Radical en bloc resection of the tumor and surrounding organs is probably not justified in most children because this is associated with increased surgical morbidity. Nephroblastomas are large tumors that often compress and adhere to adjacent structures without frank invasion. The gross appearance of the tumor at the time of surgery can be misleading in interpreting tumor extent, and in the majority of cases tumor invasion is not confirmed after the adjacent visceral organs are removed (158). There may be circumstances when removal of other organs is justified. In a patient known to have extracapsular extension, resection of a small portion of liver or tail of the pancreas to avoid leaving residual tumor, for example, may eliminate the need for radiation therapy and allow a reduction in the amount of chemotherapy. Even if the tumor is confined to the kidney, en bloc resection of nonessential structures also may prevent violation of the tumor capsule and obviate tumor rupture or spill during nephrectomy. Therefore it is a trade-off between the added surgical morbidity of en bloc resection versus a potential reduction in long-term complications of adjuvant treatment if this can be limited by complete tumor removal.

Patients who are determined to have unresectable tumor should be considered stage III and treated accordingly (162). Once there is an adequate reduction in the size of the tumor to facilitate nephrectomy, then definitive resection should be completed. In general, the operative procedure can be performed within 6 weeks of initiating treatment. Serial imaging evaluation is helpful to assess response. Patients with progressive disease have a very poor prognosis, and these patients will require treatment with a different chemotherapeutic regimen (162).

Treatment of Relapses

Results from NWTS-3 demonstrate that the risk of tumor relapse at 3 years is 9.6%, 11.8%, 22%, and 22%, respectively, for stages I to IV. Relapses occurred in 36% and 45%, respectively, of unfavorable histology patients stage I to III and IV (53). Children with relapsed Wilms' tumor have a variable prognosis, depending on the initial stage, site of relapse, time from initial diagnosis to relapse, and prior therapy. Adverse prognostic factors include previous treatment that included DOX, relapse less than 12 months after diagnosis, and intraabdominal relapse in patients who had previously undergone abdominal irradiation (90). In the past, treatment of these patients has been highly individualized. NWTS-5 is treating children with relapsed Wilms' tumor with a more aggressive approach, particularly for those high-risk patients with adverse prognostic factors at the time of relapse.

Late Effects

As survival of Wilms' tumor patients has increased dramatically over the past 35 years, there has been an ever-increasing cohort of long-term survivors of therapy. NWTSG patients that survive 5 years after completion of therapy are asked to participate in a late effects study. Numerous organ systems are subject to the late sequelae of anticancer therapy. Clinicians must now become familiar with the spectrum of problems that face these children as they grow into adulthood. An early report of 608 NWTSG patients followed more than 5 years, found that musculoskeletal problems such as scoliosis were seven times more common in children treated with radiation (66). It should be noted that these were NWTS-1 and NWTS-2 patients for whom treatment

intensity was much greater than currently is recommended (75% of the children enrolled in NWTS-1 received XRT compared with 25% currently).

Damage to reproductive systems can lead to problems with hormonal dysfunction and or infertility. Gonadal radiation in males can result in temporary azoospermia and hypogonadism (110). The severity of damage to the testis is dependent on the dose or radiation. Female Wilms' tumor patients who received abdominal radiation have a 12% incidence of ovarian failure (179). In addition, women with prior abdominal radiation have the potential for adverse pregnancy outcomes. Perinatal mortality rates are higher, and infants are more likely to have low birth weights (123).

Congestive heart failure is a well-known complication of treatment with anthracycline, and the incidence is dose related (70). In addition to the acute cardiotoxicity, reports are surfacing of cardiac failure up to 20 years after treatment (178). In a preliminary review of patients entered on NWTS-1, NWTS-2, NWTS-3, and NWTS-4, the frequency of congestive heart failure was 4.4% among DOX-treated patients who received this drug as part of their initial chemotherapy regimen (89). The risk was increased if the patient received whole lung or left flank irradiation. In light of these findings, all children who undergo treatment with these modalities should undergo periodic reevaluation.

Children treated for Wilms' tumor are at increased risk for second malignant neoplasms. Alkylating agents have been implicated in chemotherapy-induced second tumors (93). Two studies in Wilms' tumor survivors have noted a 1% cumulative incidence at 10 years postdiagnosis and a rising incidence thereafter (30,122). All but 2 of 26 second malignant neoplasms in the two studies occurred in irradiated patients, most often in the radiation field. All children that developed hepatocellular carcinoma had received flank irradiation (115).

Other Renal Tumors

Clear Cell Sarcoma of the Kidney

CCSK accounts for 3% of renal tumors reported to the NWTSG. Although not currently considered a variant of Wilms' tumor, the age at diagnosis and location are the same as nephroblastoma. An extensive review of 351 cases of CCSK was completed recently (2). Important predictors of improved survival were lower stage, younger age at diagnosis, treatment with DOX, and absence of tumor necrosis. The addition of DOX improved both overall and relapse-free survival (2,53). Patients with stage I tumors had a 98% survival rate. This improved survival for stage I patients was attributed to the assignment of all tumors with renal sinus invasion as stage II. Long-term follow-up of CCSK patients is needed because 30% of relapses occurred more than 3 years after diagnosis and some as late as 10 years.

Rhabdoid Tumor of the Kidney

RTK is highly malignant and accounts for 2% of renal tumors registered to the NWTSG. RTK is now considered a sarcoma of the kidney and not of metanephric origin (53). CCSK and RTK both occur in renal and extrarenal locations, suggesting an origin from a non–organ-specific mesenchymal cell. Cytogenetic studies have shown that renal and extrarenal rhabdoid tumors may have a common genetic basis. Deletions and somatic mutations in the INII gene on chromosome 22 in the region of 22q11 have been found in renal and extrarenal rhabdoid tumors (18). Germ-line mutations of INI1 have been identified in renal rhabdoid tumors. Some mutations also have been found in extrarenal tumors suggesting that INI1 is a tumor suppressor gene and that germ-line mutations predispose children for development of rhabdoid tumors.

This tumor is typically seen in infants and very young children with a mean age of 13 months. RTK metastasizes to the brain, which is exceedingly uncommon for Wilms' tumor. Several cases of primary neuroectodermal tumors of the brain have occurred separately in children with RTK (25). The prognosis of RTK remains dismal with conventional chemotherapeutic regimens, and new treatment strategies are being developed for management of these children.

Congenital Mesoblastic Nephroma

Bolande and associates (22) first described CMN as a separate clinical and pathologic entity and they reported eight cases of the tumor (22). In CMN, tumor induction is postulated to occur at a time when the multipotent blastema is predominately stromagenic (176,182). No cytogenetic or molecular markers have been discovered that are unique to CMN. WT-1 and *N*-myc are not expressed in this tumor (182). Although CMN is the most common renal tumor in infants, with a mean age at diagnosis of 3.5 months, it has been reported in an adult (99,121). The tumor occurs more commonly in males and is usually unilateral. The typical presentation is a newborn with an abdominal mass, but the tumor can be detected prenatally (141). Fourteen percent of children with CMN have had other congenital anomalies, which is comparable to the incidence found in Wilms' tumor patients (99). Imaging studies cannot reliably distinguish CMN from other renal mass lesions. Abdominal CT shows a heterogeneous solid mass arising from the kidney (Fig. 54.7).

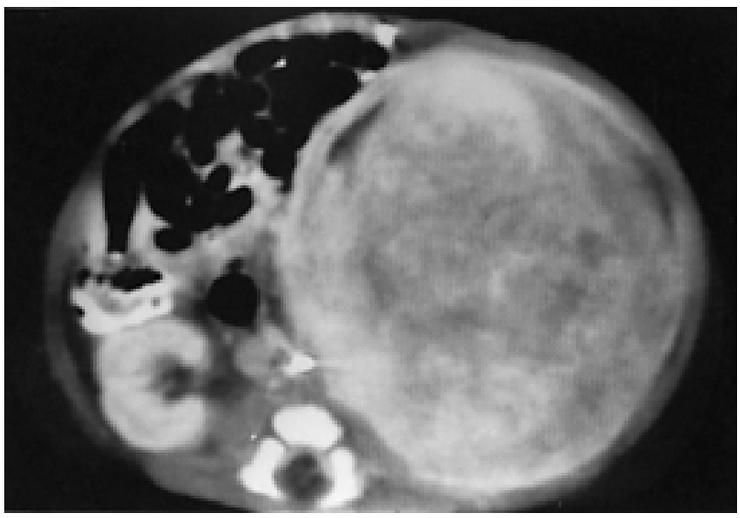

FIGURE 54.7. Computed tomography scan of a large congenital mesoblastic nephroma detected on antenatal ultrasound in a 2-day-old infant.

CMN is a very firm tumor on gross examination, and the cut surface has the yellowish gray trabeculated appearance of a leiomyoma. The tumor tends to demonstrate local infiltration into the surrounding perirenal connective tissue lacking the pseudocapsule typically seen in Wilms' tumor (Fig. 54.8). The neoplasm is histologically distinct from Wilms' tumor. The cell population is characterized by interlacing sheets of connective cells. An atypical or cellular variant has

been reported (76,105). This lesion is characterized by a high mitotic index and dense cellularity, but these features are present in 25% of CMN specimens (9).

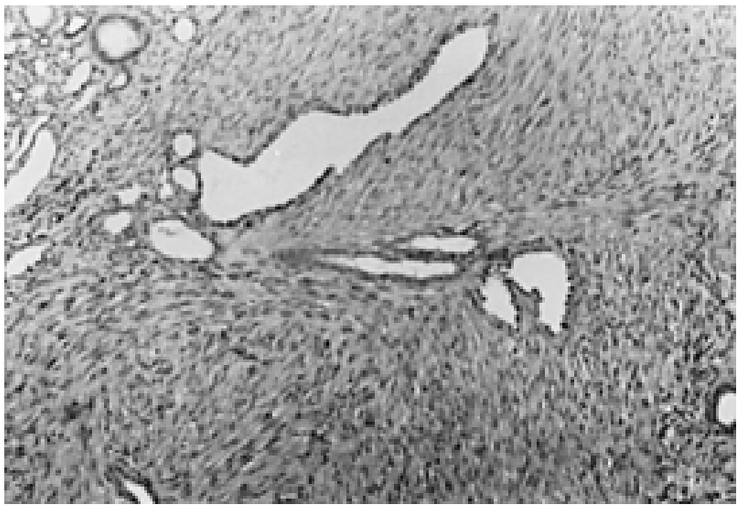

FIGURE 54.8. Microscopic view of typical congenital mesoblastic nephroma with interlacing sheets of mature connective tissue cells (hematoxylin and eosin, 100× magnification).

Complete excision is curative for most patients with CMN. The growth pattern is one of local invasion and extension through the capsule (99). Local recurrence has been reported in several patients with a cellular variant of CMN. Adequacy of surgical resection and age at diagnosis in these patients appear to be more important predictors of relapse than histology (9). The risk of recurrence is thought to be less in children younger than 3 months of age at diagnosis, but metastases have been reported in a few infants (95). Neither chemotherapy nor radiation therapy is routinely recommended (99), but consideration for adjuvant treatment should be given to patients with cellular variants that are incompletely resected (76).

Solitary Multilocular Cyst and Cystic Partially Differentiated Nephroblastoma

Solitary multilocular cyst, also known as multilocular cystic nephroma, is an uncommon, benign renal tumor with a bimodal incidence. Fifty percent of the multilocular cysts reported in the literature have been found in young children, usually boys. The second peak incidence occurs in adults, and unlike the pediatric cases, are usually in women (4,104). The most common presenting feature of multilocular cyst of the kidney is an abdominal or renal mass found on routine physical examination. All cases of multilocular cystic renal disease have been unilateral. The gross appearance of the tumor is its most distinguishing feature (Fig. 54.9). The cut surfaces reveal a well-circumscribed multilocular tumor composed of cysts ranging from several millimeters to several centimeters in greatest diameter. The tumor is well encapsulated, compressing the surrounding renal parenchyma. Wilms' tumors that are composed of only cysts with delicate septa are called cystic partially differentiated nephroblastoma. Within the septa are foci of blastema. Most of these lesions occur in the first year of life (106). These lesions are indistinguishable radiographically from solitary multilocular cysts.

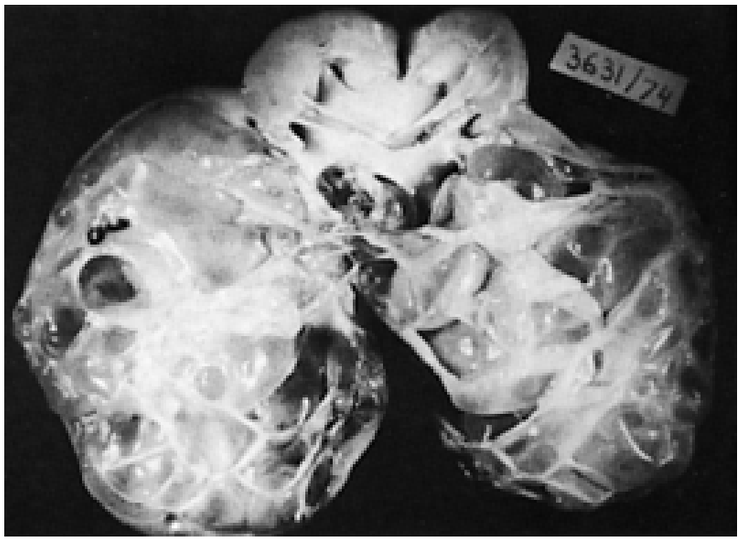

FIGURE 54.9. Gross nephrectomy specimen. Note well-circumscribed, predominantly cystic tumor. Cysts near hilus prolapse into renal pelvis but do not communicate with it. Small portion of remaining renal parenchyma is seen at upper pole. (From Joshi W, Banerjee AK, Yadav K, et al. Cystic partially differentiated nephroblastoma: clinicopathologic entity in the spectrum of infantile renal neoplasis. *Cancer* 1977;40:789, with permission.)

A recent review of the clinical and pathologic features of cystic renal tumors in children also was recently reviewed (65). These authors recommended that tumors in children previously identified as multilocular cystic nephroma and cystic partially differentiated nephroblastoma be considered the same entity. They are indistinguishable radiographically. Surgery is curative in almost all patients, with recurrence

the result of incomplete resection (65). Histologic examination reveals that blastemal cells or NRs may be found in the septa of both tumors. Some of the smaller lesions can be managed by partial excision, salvaging a portion of the kidney. If partial nephrectomy is considered, frozen section is indicated to ensure negative margins (106).

Renal Cell Carcinoma

RCC is the most common non–Wilms' renal tumor of childhood. Only 5% of RCCs occur in children (35,94). These patients generally present after age 5 years, and it is the most common malignancy in the second decade of life. It has been reported in infants younger than 1 year of age (148). There is no sex predilection in contrast to the male predominance seen in adult patients. The signs and symptoms are similar to that of other solid renal tumors, with an abdominal mass being the most common presentation in a child. Hematuria is more common in RCC than in Wilms' tumor (35). Imaging studies cannot differentiate RCC from other solid renal tumors.

Survival of children with RCC is dependent on the ability to completely resect the tumor. Raney and co-workers (152) found that all children with stage I lesions survived, and others have reported 64% to 80% survival for stage I and II tumors, respectively (38,58). Overall survival was about 50%. Age is also a prognostic factor, with improved survival in children younger than 11 years (153). These tumors do not appear responsive to chemotherapy or radiation therapy.

Miscellaneous Tumors

Renal *angiomyolipoma* is a hamartomatous lesion that is only rarely seen in childhood. There is a clear association with the tuberous sclerosis complex (TSC) and the lesion is more often bilateral in these patients (20). The renal lesions of the TSC include angiomyolipoma, simple cysts, polycystic kidney disease, and RCC. Angiomyolipoma develops in up to 80% of patients with the TSC. Two genes have been identified in the TSC on chromosome 9 (TSC1) and chromosome 16 (TSC2) (149). It has been postulated that these genes act as tumor suppressor genes and that the LOH of TSC1 or TSC2 may explain the progressive growth pattern of renal lesions seen in these patients.

The incidence of angiomyolipoma increases with age. Ewalt and others reported on 60 patients with TSC who were followed with periodic ultrasound. The average age at which a normal ultrasound became abnormal was 7.2 years. Angiomyolipomas were found in 45 children. Growth of the lesion was observed in 28 children. Girls were more likely to have an increase in the size of the lesion. All patients with lesions greater than 4 cm in diameter were postpubertal. Annual ultrasounds are recommended after puberty. Children with growing lesions (Fig. 54.10) can be managed with embolization or partial nephrectomy before they become symptomatic with bleeding (118). The risk of serious bleeding appears to correlate with a diameter of greater than 4 cm (20). Nephron-sparing approaches are recommended in children with TSC because of the presence of multiple, bilateral lesions and the risk of development of new lesions.

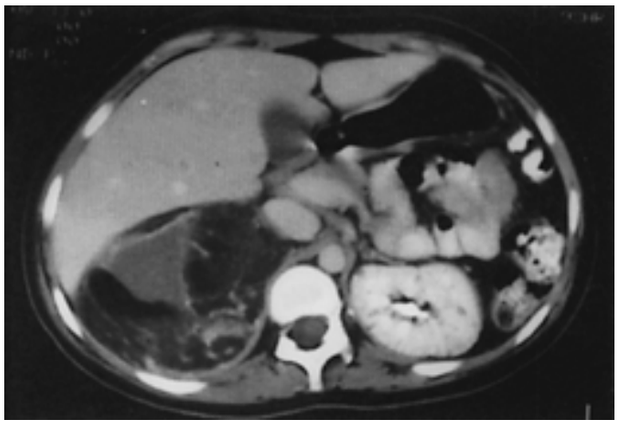

FIGURE 54.10. Angiomyolipoma of the right kidney in a patient with tuberous sclerosis.

Tumors of the renal collecting system also are very uncommon in childhood. *Transitional cell carcinoma* of the renal pelvis has been reported, and these lesions are managed with nephroureterectomy (100). Fortunately, most filling defects of the upper collecting system represent benign lesions. The most common lesion is a *fibroepithelial polyp* (72). These patients typically present with symptoms secondary to obstruction (Fig. 54.11). Management consists of segmental resection and reconstruction of the urinary tract.

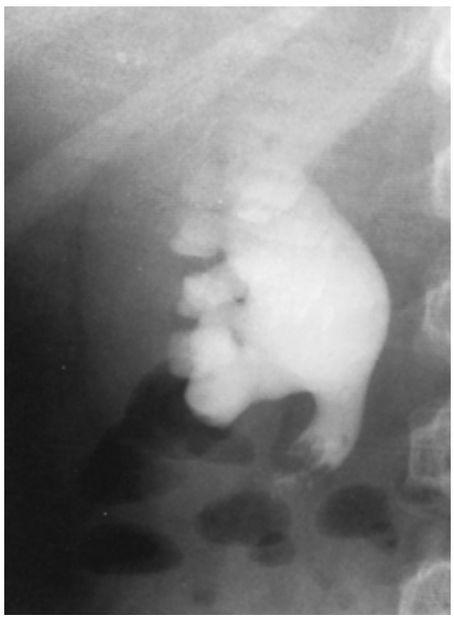

FIGURE 54.11. Fibroepithelial polyp at the ureteropelvic junction, causing intermittent obstruction of the right kidney.

NEUROBLASTOMA

Part of "54 - PEDIATRIC UROLOGIC ONCOLOGY "

Neuroblastoma is known to arise from cells of the neural crest that form the adrenal medulla and sympathetic ganglia. Tumors derived from the sympathetic nervous system are differentiated along two lines: the pheochromocytoma line and the sympathoblastoma line. The latter includes neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. Neuroblastoma and ganglioneuroblastoma are most notable for the potential to regress or mature spontaneously. The ability of neuroblastoma to transform into benign ganglioneuroblastoma and ganglioneuroma was first reported in 1927 (210). The incidence of spontaneous regression in childhood neuroblastoma has been reported to be 1% to 2% (216). Most cases of regression or maturation of neuroblastoma occur in the first year of life.

Genetics

It is suggested that 20% of neuroblastoma cases occur in patients with an inheritable mutation (245). The familial cases reported are postulated to represent an autosomal- dominant pattern of inheritance. The median age at diagnosis of unselected patients with neuroblastoma is 21 months, contrasting with the median age of 9 months in familial cases of neuroblastoma (248). Twenty percent of patients with familial neuroblastomas have bilateral or multifocal primary tumors. The risk of neuroblastoma developing in a sibling or offspring of a patient with neuroblastoma is less than 6% (248). Some of the difficulties in detecting the incidence and penetrance of an inheritable susceptibility to neuroblastoma are due to the frequent spontaneous regression and maturation of the tumor, the high mortality rate, and the complications of therapy, which preclude reproduction of multigenerational pedigrees for evaluation.

Numerous karyotypic abnormalities have been found in neuroblastoma. These changes occur in the forms of chromosomal deletions, translocations, and cytogenetic evidence of gene amplification. Deletion of the short arm of chromosome 1 is found in 70% to 80% of neuroblastomas (204). This deletion is thought to represent the loss of a gene, the putative neuroblastoma suppressor gene that prevents tumor development. Unlike the WT-1 gene associated with Wilms' tumor, there has been no evidence of constitutional deletions of this gene in neuroblastoma patients or of any chromosome 1p deletion syndrome.

Pathology

Ganglioneuroma

A ganglioneuroma is a histologically benign neoplasm that is quite rare compared with other benign neural tumors such as neurofibromas and schwannomas. Most ganglioneuromas are diagnosed in older children and usually are located in the posterior mediastinum and retroperitoneum, with only a small number arising in the adrenal glands (212). Because of their site of origin, the ganglioneuromas tend to have a paravertebral location. In the retroperitoneum, the presacral space is the most common site. Ganglioneuromas generally grow to a very large size before they cause symptoms due to compression of adjacent structures (199). Catecholamine excretion is elevated in 20% of patients and appears to increase as a function of tumor size (251).

The pathology of ganglioneuroma is that of a well-circumscribed tumor with a fibrous pseudocapsule. These tumors are very firm and rubbery in consistency on cross section. Careful examination of a ganglioneuroma is necessary to exclude ganglioneuroblastoma, which can have a similar gross appearance. On microscopic examination, mature ganglion cells with abundant cytoplasm are scattered throughout a mature Schwann cell matrix.

It is unclear whether a ganglioneuroma arises *de novo* or by maturation of a preexisting neuroblastoma or ganglioneuroblastoma. Cases of metastatic lesions that have been observed to develop the histology of mature ganglioneuromas support the latter theory (234). In rare cases, a ganglioneuroma has undergone malignant transformation into a malignant peripheral nerve sheath tumor or malignant schwannoma. Some of these patients have received antecedent abdominal radiation (242). Ganglioneuroblastoma is intermediate between neuroblastoma and ganglioneuroma. Distinguishing between neuroblastoma and ganglioneuroblastoma is often difficult.

Neuroblastoma

The gross morphology in neuroblastoma can vary considerably. Small adrenal tumors usually appear well encapsulated. The adrenal gland may be draped over the tumor, but larger tumors generally preclude precise identification of the anatomic site of origin. On cross section, the tumor will vary in appearance and consistency, depending on the degree of stromal elements. The tumor may rupture during removal, spilling out friable and hemorrhagic tumor. Cystic degeneration may be a prominent feature.

Neuroblastoma is the prototypical small “blue-cell” tumor of childhood (Fig. 54.12). The most common histologic

pattern is that of lobular growth, but it may have a more diffuse or solid pattern. Neuroblastoma can be confused with lymphoma, Ewing's sarcoma, or embryonal sarcoma. A characteristic feature of this tumor is the arrangement of the nuclei into pseudorosettes. The nuclei are separated by fibrils, which can appear as a meshwork. The nuclei vary in size and have a stippled nuclear chromatin pattern. Ganglion cell differentiation in neuroblastoma is evidence of maturation. Special staining may help characterize neuroblastoma cells. Neuron-specific enolase staining of the tumor is reported to be specific for neuroblastoma (265). Neuroblastoma usually lacks glycogen, which will help differentiate it from some of the sarcomas.

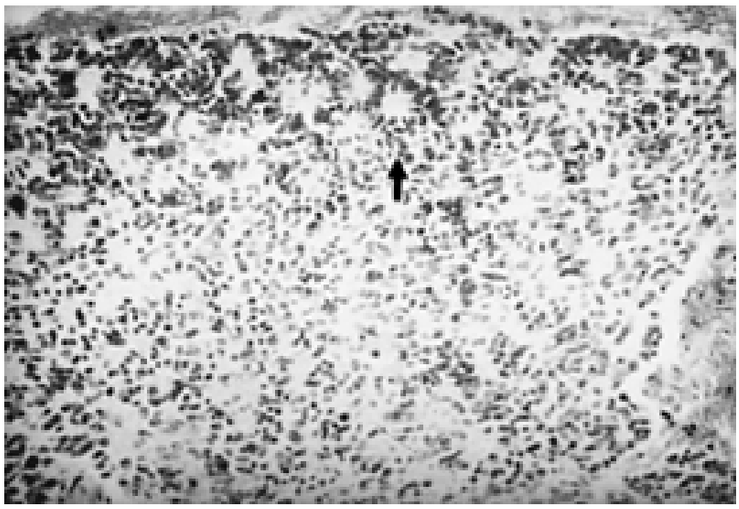

FIGURE 54.12. Microscopic (hematoxylin and eosin) view of neuroblastoma, demonstrating pseudorosette formation *(arrow).*

Various antibodies are used to detect the presence of certain structural products, cellular products, and membrane-associated antigens. Most antibodies used are monoclonal. Although no specific neuroblastoma monoclonal antibody is available, a battery of antibodies can be used in the diagnostic evaluation of neuroblastoma or a similarly appearing neoplasm (244). Although these immunohistochemical stains have some limitations, they can help differentiate neuroblastomas from other small blue-cell tumors of childhood.

In 1984, an age-linked histopathologic classification of neuroblastoma was introduced with definition of subtypes of ganglioneuroblastoma (278). One of the important aspects of the Shimada classification is determining whether the tumor is stroma poor or stroma rich. Stroma-rich tumors can be separated into three subgroups: nodular, intermixed, and well differentiated. The last category consisted of tumors that more closely resemble ganglioneuroblastomas or immature ganglioneuromas. The survival rates of stroma-rich patients were as follows: well-differentiated, 100%; intermixed, 92%; and nodular, 18%. The stroma-poor tumors can be divided into favorable and unfavorable subgroups based on the patient's age at diagnosis, degree of maturation, and the mitosis-karyorrhexis index (MKI). This index is based on a differential count of the mitoses in the tumor. Patients with stroma-poor tumors with unfavorable histopathologic features (higher MKI, higher age, undifferentiated histology) have a very poor prognosis, with less than 10% survival. Patients with stroma-poor favorable tumors have an excellent survival rate (greater than 90%) (278).

In addition to maturation of clinically evident cases of neuroblastoma, spontaneous regression of *"in situ"* neuroblastoma may occur far more often. Beckwith and Perrin (198) coined this term in 1963 for small nodules of neuroblastoma cells found incidentally within the adrenal gland that histologically are indistinguishable from neuroblastoma. In infants less than 3 months of age undergoing postmortem examination, neuroblastoma *in situ* was found in 1 per 224 infants. This represents an incidence of *in situ* neuroblastoma about 40 to 45 times greater than the incidence of clinical tumors. If these lesions clearly are neoplastic, then the majority undergoes spontaneous involution, mature, or remain clinically occult. Notably, no known instances of *in situ* neuroblastoma have been identified in an extraadrenal site. Neuroblastic nodules are considered a normal part of the fetal adrenal gland. In the developing fetus, the adrenal goes through a stage in which clusters of neuroblasts are seen that resembles neuroblastoma *in situ.* This reaches a peak level at 18 to 20 weeks of gestation (283). There is some difficulty in distinguishing *in situ* neuroblastoma from nodules of neuroblast cells that linger into early infancy. The relationship of neuroblastic nodules to *in situ* neuroblastoma is unclear.

Incidence

Neuroblastoma is one of the more common solid tumors, accounting for 7% to 8% of all childhood malignancies (286). In the United States, the annual incidence is 10 per 1 million live births. There are no sex-related differences in incidence rates. It is the most common malignant tumor of infancy, with 50% of cases occurring in children less than 2 years of age, and 75% are noted by the fourth year of life (221). Associated congenital anomalies are few, although an association with neurofibromatosis has been reported (246).

Clinical Presentation

The clinical manifestations of neuroblastoma vary widely with the site of the primary tumor, the presence of metastases, and secretion of biochemical products. More than one-half of neuroblastomas originate in the abdomen, and two-thirds of these arise in the adrenal gland (Fig. 54.13). Patients with an abdominal tumor may present with an abdominal mass, pain, or weight loss. The mass is typically hard and irregular, often extending across the midline. Pelvic neuroblastoma accounts for only 4% of tumors. Extrinsic compression of the bowel and bladder produces symptoms of urinary retention and constipation. Mediastinal

and paraspinal retroperitoneal tumors that arise from sympathetic ganglia have a propensity to grow into the intervertebral foramen in a dumbbell configuration. A presentation of extradural spinal cord compression is more common for thoracic neuroblastoma than other locations (194,195). Unilateral Horner's syndrome may develop in cervical or upper mediastinal tumors (Fig. 54.14). There may also be asymmetric coloration of the iris because the sympathetic nervous system is involved in iris pigmentation (240). About one-half of mediastinal tumors are diagnosed incidentally (194).

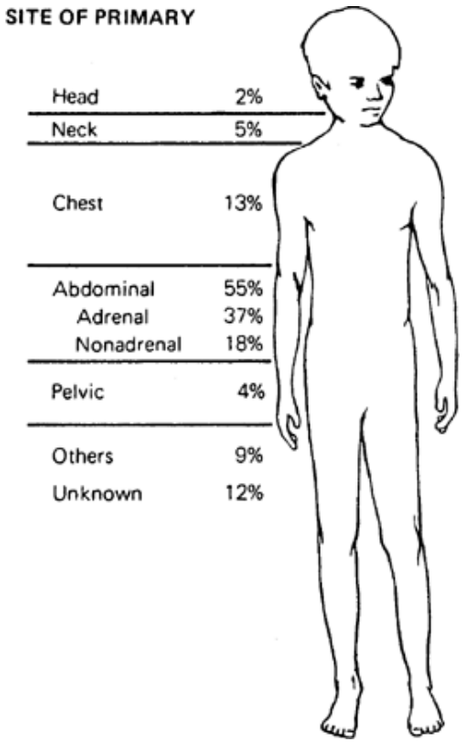

FIGURE 54.13. Anatomic sites of origin of neuroblastoma. (From Williams TE, Donaldson MH. Neuroblastoma. In: Sutow WW, Vietti TJ, Fernbach DJ, eds. *Clinical pediatric oncology.* St. Louis: Mosby, 1973:388, with permission.)

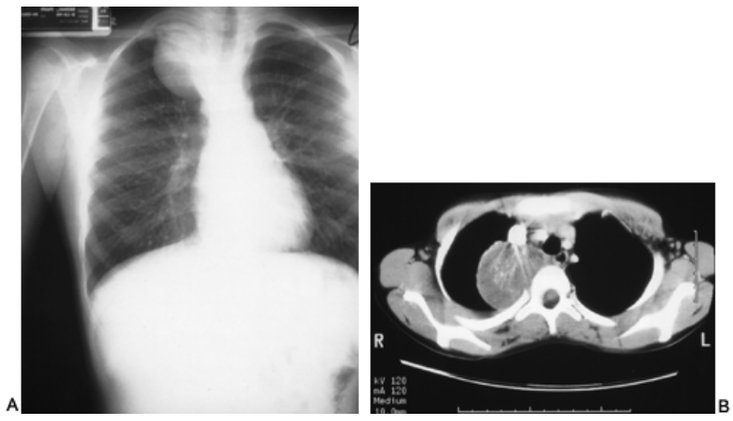

FIGURE 54.14. Neuroblastoma arising from the upper mediastinum. **A:** Chest radiograph. **B:** Computed tomography scan.

Metastases are present in 70% of neuroblastoma patients at diagnosis and can be responsible for a variety of the clinical signs and symptoms of presentation. Fever, lethargy, weight loss, and bone pain are among these findings. The skull and long bones are most commonly involved. Radiographs will reveal lytic lesions that are frequently bilateral and asymmetric. More than 50% of patients with neuroblastoma will have involvement of the bone marrow (218), and anemia is found in more than one-third of children.

Retrobulbar soft tissue involvement can result in another unique presentation of metastatic neuroblastoma. The tumor produces proptosis and periorbital ecchymosis. Subcutaneous nodules are common in infants with stage 4s disease (279). These have been described to have the appearance of blueberry muffins because of their bluish color.

Neuroblastoma is a biochemically active tumor with catecholamine secretion by over 90% of tumors. Symptoms may mimic pheochromocytoma, with paroxysmal hypertension, palpitation, flushing, and headache. Secretion of vasoactive intestinal peptide (VIP) by the tumor can produce

severe watery diarrhea and hypokalemia (209). Another unusual presentation of neuroblastoma is acute myoclonic encephalopathy (217,276). These patients develop myoclonus, rapid multidirectional eye movements (opsoclonus), and ataxia. The etiology of these symptoms is most likely antibodies against tumor antigens that cross-react with the cerebellum (219). These symptoms often do not resolve even with successful treatment of the primary tumor; however, tumors associated with this syndrome generally have a good prognosis.

Diagnosis

Laboratory Evaluation

A complete blood count is essential. Anemia is noted in children with widespread bone marrow involvement. Coagulation abnormalities may be present as a result of massive liver metastases. Bone marrow aspiration is performed in all children with suspected neuroblastoma. Metastatic tumor to the bone marrow can occur in the absence of skeletal metastases (218).

Twenty-four-hour urine collection will detect elevated levels of the two major metabolites of catecholamine production, vanillylmandelic acid (VMA) and homovanillic acid (HVA) in 90% of tumors (284). It is surprising that hypertension is not more common in neuroblastoma patients, but increased serum levels of norepinephrine are not present in neuroblastoma. This is attributed to breakdown of the catecholamines in the tumor. It has been noted that catecholamine storage vesicles are relatively lacking in patients with neuroblastoma as compared with patients with pheochromocytoma (267). Because these storage vesicles protect the catecholamines from degradative enzymes, norepinephrine and epinephrine concentrations are much higher in pheochromocytoma, leading to the clinical symptoms. Another explanation for the lack of clinical signs and symptoms related to catecholamines could be the absence of periodic massive catecholamine release by tumor vesicles in neuroblastoma patients.

Urinary levels of HVA and VMA can be monitored throughout treatment. Therapy with various modalities has been shown to produce a reduction in catecholamine metabolite excretion in the majority of patients (223). These metabolites also can be followed to detect tumor relapse. Biochemical evidence of relapse has been found before clinical evidence of a recurrent mass or other symptoms.

Imaging

Imaging studies play an important role in the evaluation of a child with neuroblastoma. The diagnosis is suggested on excretory urography, which reveals inferior displacement of the kidney by a suprarenal mass. The kidney generally lacks the calyceal distortion typically seen with Wilms' tumor. Currently, abdominal ultrasound and CT are used more commonly than excretory urography. Invasion of the renal parenchyma is not uncommon and can be detected radiographically by CT (196). A speckled pattern of calcification is noted in 50% of cases on plain abdominal films. An even greater percentage of patients will have calcifications noted on CT (Fig. 54.15). Ultrasound and CT both demonstrate the solid nature of the mass and the location of the tumor. Examination of the liver for metastases is accomplished with either of these studies. Ultrasound is not as helpful for defining anatomic relationships of the tumor, particularly in extraabdominal sites. Prenatal diagnosis of neuroblastoma is possible with ultrasound (241). MRI has advantages over CT in the evaluation of intraspinal tumor extension (197). MRI also can define involvement of the major vessels and central nervous system. Cystic forms of neuroblastoma are well delineated with CT imaging (Fig. 54.16).

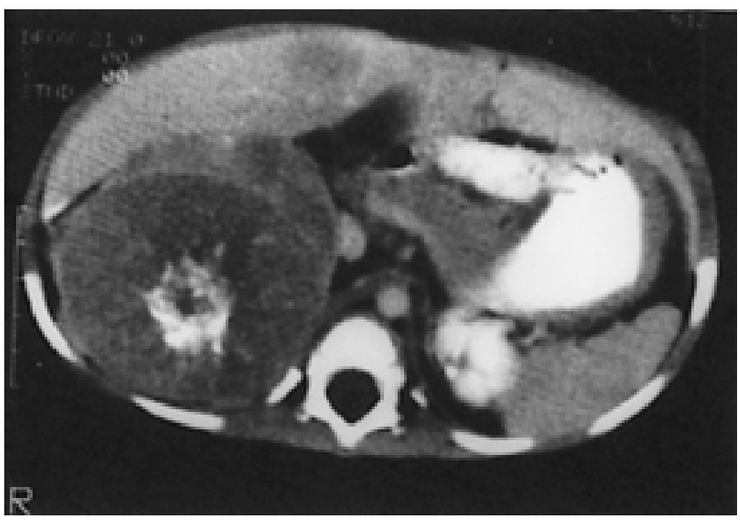

FIGURE 54.15. Computed tomography scan demonstrating calcifications within a neuroblastoma.

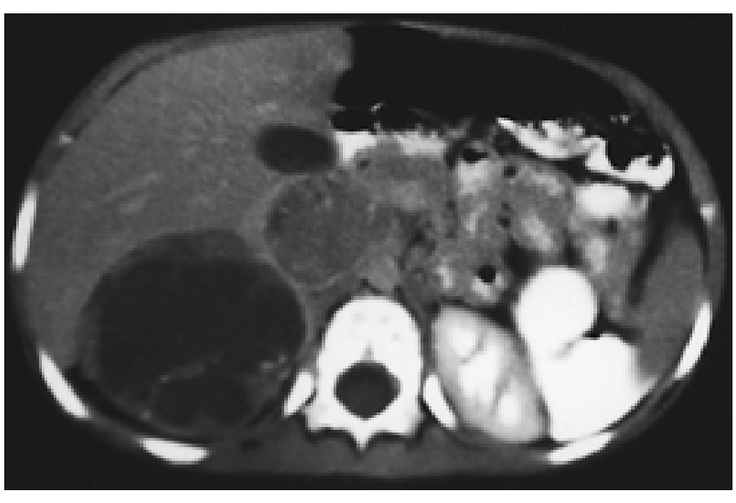

FIGURE 54.16. Cystic neuroblastoma.

A skeletal survey is routinely obtained to exclude metastases. These lesions are found most commonly in the long bones and skull. If the skeletal films are negative, a radionuclide bone scan may detect earlier metastases. Another

method of imaging both the tumor and metastatic sites is with radiolabeled ^{123}I metaiodobenzylguanidine (MIBG) (222,235). MIBG bears structural similarity to norepinephrine and is taken up by the adrenergic secretory vesicles of the tumor cells both in primary and metastatic sites. MIBG scintigraphy can be used to determine the extent of disease and also to detect recurrence of tumor after completion of therapy (222). Not all tumors have uptake of MIBG, and false negatives occur. It appears that maturation of the neuroblastoma to more mature forms such as ganglioneuroma also results in the loss of an ability to concentrate MIBG.

An interesting subset of patients is those diagnosed on prenatal ultrasound. As ultrasonography becomes more routine during pregnancy, the number of prenatally diagnosed neuroblastomas is increasing (241). In the Italian Neuroblastoma Registry, 17 patients were identified (224). Primary tumor site was most often adrenal (16 of 17). Thirteen were stage 1, one was stage 2a, one was stage 2b, and two patients were stage 4s. All patients had primary tumor resection at a mean age of 4 weeks. Only one patient had *N*-myc amplification. Two of these patients died, one of bleeding after tumor resection and one from progressive disease despite aggressive multimodal treatment. This mode of diagnosis may have future implications in the screening of patients for neuroblastoma.

Screening

Mass population screening for neuroblastoma has been advocated to detect disease at an earlier stage and thus improve survival. This was initiated in Kyoto, Japan, in 1974 (270) and has been used widely in Japan since 1985 (261). Screening is generally performed at 6 months of age. An increased number of infants younger than 1 year of age have been diagnosed with the mass screening program (238), and most of these patients have lower-stage tumors (271). Before mass screening started, 20% were diagnosed at less than 1 year of age, whereas after mass screening was instituted 55% were diagnosed at less than 1 year of age. A decrease in the percentage of primary adrenal gland tumors has been noted in the postscreening era. This suggests an increase in the diagnosis of tumors at other sites that could possibly have regressed undetected if screening had not been instituted.

An unanswered question is whether early detection of tumors will have an overall impact on survival (258). It is clear that patients less than 1 year of age when diagnosed with low-stage tumors have a better outlook (201). In addition, tumors diagnosed by screening have other striking biologic differences from tumors detected clinically (232). In a review of 48 cases discovered by screening, none were observed to have amplified *N*-myc oncogene expression (see Prognostic Factors) (239). In addition, 80% had a diploid chromosome pattern, which is associated with a favorable prognosis. All 48 patients were still alive without tumor. Altogether 357 patients from Kyoto have been diagnosed by mass screening, and the overall survival is 97% (271). Given the favorable biologic characteristics of tumors discovered by screening, it is possible that these patients would have the same excellent survival if they were discovered later in life as a result of clinical symptoms. There is also some concern that many of the unfavorable histology tumors destined to present clinically at an older age go undetected by mass screening (281). In a Canadian study, population screening was found to increase the incidence of neuroblastoma but did not decrease the incidence of unfavorable advanced-stage disease in older children (285). The optimal screening regimen for neuroblastoma has yet to be determined.

Staging

As with most solid tumors, staging of neuroblastoma patients is an important aspect of management because the stage of the disease is a significant prognostic variable. Currently four anatomic staging systems are used for neuroblastoma: the Evans classification (213); the St. Jude Classification (233); the TNM classification; and the International Staging System (INSS), which is most widely used currently (Table 54.6) (206). This system relies on anatomic

features of the tumor, its resectability, and also on histopathology of the resected specimen. As more knowledge of the biologic prognostic features of neuroblastoma is gained, it is apparent that staging systems based solely on anatomy of the tumor are inadequate and these factors must be considered in determining a risk-grouping system.

TABLE 54.6. STAGING SYSTEM FOR NEUROBLASTOMA

Stage	Characteristics
Stage 1	Tumors are confined to the organ or structure of origin. Complete gross excision with or without microscopic residual disease is recommended. Identifiable ipsilateral and contralateral lymph nodes are microscopically negative.
Stage 2a	Unilateral tumor with incomplete gross excision. Identifiable ipsilateral and contralateral lymph nodes are microscopically negative.
Stage 2b	Unilateral tumor with complete or incomplete gross excision, with positive ipsilateral regional lymph nodes. Identifiable contralateral lymph nodes are microscopically negative.
Stage 3	Tumors infiltrating across the midline with or without regional lymph node involvement. Or unilateral tumor with contralateral regional lymph node involvement. Or midline tumor with bilateral lymph node involvement.
Stage 4	Dissemination of tumor to bone, bone marrow, liver, distant lymph nodes, or other organs (except as defined in stage 4s).
Stage 4s	Localized primary tumor as defined for stage 1 or 2, with dissemination limited to liver, skin, and/or bone marrow.

Prognostic Factors

Many variables have an impact on the prognosis of neuroblastoma. The site of origin is of significance. Nonadrenal primary tumors are associated with better survival than are those that originate from the adrenal. Most children with thoracic neuroblastoma present at a younger age with localized disease and have an improved survival, even with correction for age and stage (194). Overall survival was 88% at 4 years in 96 patients with thoracic neuroblastoma studied by the Pediatric Oncology Group.

Age at diagnosis is another powerful prognostic indicator. Survival is inversely correlated with age at diagnosis. Children less than 1 year of age have a far better survival than those diagnosed later in life (201). This may be attributed to more favorable biologic parameters in tumors diagnosed at this age. Spontaneous regression also is more likely to occur in children less than 6 months of age.

Stage of the disease is also an important prognostic factor. Virtually all stage 1 patients with complete resection of the primary tumor will survive. Stage 2 patients also have a more favorable survival, even though excision may be incomplete (254). Advanced regional disease, stages 3 and 4, fares less well and requires more aggressive treatment. Clearly, tumors that can be completely resected have a more favorable prognosis. Whether this is independent of biologic factors is unclear.

DNA content of tumor cells and ploidy number have been reported to have prognostic value. Studies of DNA content measured by flow cytometry showed that DNA aneuploidy correlated with better prognostic factors (age younger than 1 year; stage 1, 2, or 4s) and a good outcome (247,250). Diploidy and tetraploidy were associated with poor prognostic indicators (age older than 1 year and advanced clinical stage) and decreased survival.

Several cytogenetic abnormalities have been identified in neuroblastomas, with the most consistent structural abnormalities noted on the short arm of chromosome 1 (207). Loss of heterozygosity for chromosome 1 is found in the majority of children with neuroblastoma but does not correlate as well as other prognostic factors with advanced stages of disease (220). Also noted in about one-third of neuroblastoma tumors was the presence of homogeneously staining regions (HSRs) and double minute chromosomes (DMs) (203). These abnormalities are cytogenetic manifestations of gene amplification that led to the investigation of tumor oncogenes in neuroblastoma. DMs and HSRs are found in approximately 30% of neuroblastomas, and it was subsequently found that the *N*-myc oncogene was mapped to these regions. Amplification of the *N*-myc oncogene has been recognized in approximately one-third of patients (205). The association of *N*-myc amplification with the pathogenesis of neuroblastoma is unclear, but the level of expression and amplification of the oncogene is important in determining prognosis (274). It has been noted that *N*-myc amplification is associated with high levels of expression of the gene for the multidrug-resistance protein (200), which account for the association between *N*-myc amplification and poor outcome (264).

N-myc amplification is associated with a poor prognosis independent of patient age or stage of disease at presentation, and appears to remain constant regardless of therapy or tumor status (274). Children with multiple copies or genomic amplification of the *N*-myc tumor oncogene generally present with clinically advanced tumors that progress rapidly and respond poorly to therapy. In a recent study of stages 1 and 4s tumors, not one of the patients was found to have multiple copies of *N*-myc and the tumors were associated with a good prognosis (229). On the other hand, 50% of patients with stage 3 or 4 disease have *N*-myc amplification (197). There was an 18-month progression-free survival of 70% when there was no genomic amplification, compared with 30% in those patients with 3 to 10 copies of *N*-myc and only 5% in those with more than 10 copies of the oncogene. However, many advanced-stage tumors lack *N*-myc amplification at diagnosis, and recurrence or progressive disease develops in the majority of these patients. Therefore it is important that other prognostic factors involved in the pathogenesis of neuroblastoma be identified.

Several other biologic markers have prognostic value. Elevated levels of serum ferritin have been found in patients with neuroblastoma (231). Serum ferritin levels are elevated in 40% to 50% of patients with stage 3 or 4 disease. Only 4% of stage 4 patients with levels above 140 ng/mL survive 2 years, compared with 30% survival in children with levels less than 75 ng/mL. If the serum ferritin is not elevated in stage 3 disease, survival is significantly better (76% versus 23% 2-year disease-free survival). Patients also can be subdivided based on age and serum ferritin levels. Patients with normal serum ferritin and age less than 2 years have a 93% 2-year survival; patients older than 2 years of age with normal serum ferritin levels have 38% 2-year survival; and patients of any age with abnormal serum ferritin levels have a 19% 2-year survival (231). Neuron-specific enolase (NSE) is elevated in more than 90% of patients with metastatic neuroblastoma at diagnosis (287). In infants younger than 1 year of age, the survival rate was only 25% with high NSE levels compared with almost 100% survival in those infants in whom NSE was less than 190 g/mL. However, NSE is more difficult to assay, which has limited its widespread application.

Another prognostic factor is the transmembrane glycoprotein tyrosine kinase receptor (TRK), which may be

critical in allowing the differentiation and regression of neuroblastoma (253). An association between high levels of the TRK gene and favorable outcome in patients with neuroblastoma has been observed (257).

Stage 4s

Stage 4s ("s" stands for special) comprises a distinct group of infants with distant liver, skin, and bone marrow metastases without radiologic evidence of bone metastases. Eight to 12% of all children with neuroblastoma present with this stage of disease. These children typically have a small intraabdominal adrenal primary, but in 10% of cases no primary can be identified. The median age of these infants is about 3 months, but occasionally they present after 1 year of age. This group of patients has an overall good prognosis, ranging from 80% to 87% (280). Many of these tumors undergo spontaneous regression (215,225). This regression can occur without treatment even in patients with a significant tumor burden. It is suggested that these patients do not have metastases but simply have collections of nonmalignant neural crest cells in these other sites. Studies of children with stage 4s neuroblastoma have not revealed significant cytogenetic abnormalities or other adverse prognostic findings, such as *N*-myc oncogene amplification or elevated serum ferritin typically seen in children with stage 4 neuroblastoma (229,230).

Treatment

It was not until an appropriate staging system was available that patients could be separated into groups for stratification of treatment (213). The identification of biologic and other prognostic factors has allowed further separation of patients into favorable and unfavorable categories of tumors. The INSS staging classification relies on anatomic features, resectability, and pathology of the tumor. Based on the INSS classification and on the biologic markers with known prognostic significance, patients can be grouped into low, intermediate, or high-risk populations (Table 54.7).

Risk Group	Factors
Low risk	INSS stage 1, 2, or 4s Age usually <1 yr No *N*-myc amplification Hyperdiploid/triploid with DNA index >1.25 No 1p LOH High TRK >90% cure
Intermediate risk	INSS stage 3 or 4 Age usually > 1 yr No *N*-myc amplification Near-diploid or tetraploid Low TRK Presence of 1p allelic loss or other structural change >25%–50% cure
High risk	INSS stage 3 or 4 Age 1–5 yr *N*-myc amplified Near-diploid or tetraploid Presence of 1p allelic loss Low TRK <5% cure

INSS, International Staging System; LOH, loss of heterozygosity; TRK, tyrosine kinase receptor.

TABLE 54.7. RISK LEVEL BASED ON INSS CLASSIFICATION AND BIOLOGIC MARKERS WITH KNOWN PROGNOSTIC SIGNIFICANCE

Low-risk Disease

Localized neuroblastoma can be treated by surgical excision alone with excellent results. Stage 1 patients with complete excision have an excellent prognosis (266). The Pediatric Oncology Group reviewed 101 children with localized neuroblastoma who had complete gross excision of the primary tumor (263). The overall disease-free survival rate at 2 years was 89%. Nine patients developed relapses, but six were salvaged with chemotherapy. Although chemotherapy is not used initially in stage 1 patients, it has a high rate of inducing remission and extending disease-free survival rates in patients who relapse following excision (286).

Stage 2 tumors, by definition, have residual disease either because of incomplete resection (stage 2a) or because of positive ipsilateral lymph nodes (stage 2b). Radical resection is probably not justified in this group of patients. Formal lymph node dissection is not necessary, but diagnosis of contralateral lymph nodes is an important aspect of staging. Radiation of the local tumor bed has been advocated for treatment of residual disease in stage 2 patients. A report of 156 patients with stage 2 neuroblastoma found a 90% 6-year progression-free survival whether or not radiotherapy was used (254). Therefore surgical excision alone may constitute adequate therapy for the majority of stage 2 tumors, and chemotherapy and radiation may be reserved for those with relapse. A recent study reports that children with stages 1 and 2 neuroblastoma have a 98% survival with surgery alone as primary therapy (269). This study found that *N*-myc amplification, age older than 2 years, and either unfavorable histopathology or positive lymph nodes were poor prognostic variables.

In stage 4s tumors, resection of the primary is not mandatory and is of unknown benefit. A retrospective review of 37 patients did demonstrate that removal of the primary can be safely accomplished (252), and after resection a 95% survival rate was noted. However, information regarding histologic prognostic factors was not available for

all of these patients. Others have found that stage 4s patients do very well whether or not their primary tumors are resected or they are given chemotherapy (215,259). Using the Shimada classification, all stage 4s neuroblastomas studied by Hachitanda and others were in a favorable-prognosis group of stroma-poor tumors (229). A recent study of 80 stage 4s patients found no *N*-myc amplification (58 of 80 tested) and favorable Shimada histopathology in 96% of patients (260). Supportive care only was provided for 55% of these 80 patients, and their 5-year survival was 100%. Patients with symptoms were treated with cyclophosphamide for 5 days, with or without hepatic irradiation, and their survival was 81%. Five of six deaths occurred in infants younger than 2 months at diagnosis and were due to complications of extensive abdominal involvement with respiratory compromise or disseminated intravascular coagulation. Patients with extensive metastatic disease who are *N*-myc positive represent a high-risk group (252). These patients should be considered for a more aggressive treatment with multimodal therapy. Treatment of symptomatic infants with massive hepatic involvement using radiation therapy or chemotherapy can initiate tumor regression (214). Temporary abdominal wall augmentation by surgical placement of a prosthetic patch also can be used to decrease intraabdominal pressure in these infants (214).

Intermediate-risk Disease

Among patients with INSS stage 3 or 4, additional factors determine whether they are intermediate of high-risk patients. Those without *N*-myc amplification, with low serum ferritin and neuron-specific enolase, and with negative bone marrow are at intermediate risk. Younger patients have more favorable outcomes as with other stage tumors. These patients usually require multiagent chemotherapy as primary therapy and often receive irradiation to metastatic sites. In one study, infants with INSS stage 4 tumors treated aggressively with chemotherapy, and irradiation to metastatic sites, had a survival of 75% (268).

A recent study evaluated the utility of treatment stratification based on biologic prognostic factors among patients with Evans stage 3 neuroblastoma (255). Risk stratification was performed using age, *N*-myc gene copy number, Shimada histopathologic classification, and serum ferritin level. Based on the presence or absence of these prognostic factors, patients were treated with either low-intensity chemotherapy or intensive multimodality therapy, including in some cases autologous bone marrow transplantation. Event-free survival was 100% at 4 years for patients with favorable biologic factors at any age, compared with 54% for patients older than 1 year of age with unfavorable biology. Only *N*-myc copy number and age were independent factors in multivariate analysis. Although the survival rate for the unfavorable patients is low, it is better than historical controls, indicating that intensive chemotherapy may be beneficial.

High-risk Disease

Older patients with INSS stages 3 and 4 tumors and those with *N*-myc amplification or other adverse biologic markers are at highest risk. These patients require aggressive multimodal treatment. There is some debate on the intensity of the surgical resection required for stage 3 lesions. A report of 58 patients with stage 3 disease found that 8 of 12 with initial complete excision and 12 of 14 with subsequent resection of the primary tumor were long-term survivors (226). This contrasts with only 9 of 32 survivors among patients in whom complete tumor excision could not be accomplished. Significant morbidity was reported in association with the surgical procedures, with 21 major complications. Nephrectomy also was required for complete excision in 6 of the patients. In a retrospective review, Kieley compared the results of radical tumor resection versus more conventional surgery (243). In a large group of stage 3 and 4 patients, he found no difference in survival of 46 patients treated with radical surgical procedures versus 34 patients treated with more conventional surgery. Both groups had 30% long-term survival rate. Biologic factors remain very important in patients with advanced-stage disease. In a recent Children's Cancer Group study, 134 patients with stage 4 disease were evaluated and found to have an overall survival of 71% (272). However, overall survival among patients without *N*-myc amplification had a 3-year event-free survival of 93%. Those with *N*-myc amplification had an event-free survival of only 10%.

Usually, the safest approach for advanced tumors is to defer tumor resection until after initial chemotherapy. There is no clear advantage to debulking or cytoreductive surgery in this disease. Neuroblastoma is a highly vascular tumor, but it does respond to chemotherapy. After chemotherapy, the tumors are smaller and firmer with less risk of rupture and hemorrhage. Timing of surgery is generally 13 to 18 weeks after initiation of chemotherapy (197). There is evidence that delaying surgical resection until after chemotherapy significantly reduces the risk of nephrectomy in these patients (277). Many children with bulky unresectable tumors or with widespread metastases at diagnosis can benefit from delayed attempts at surgery. This is particularly true in regard to debulking patients before bone marrow transplantation. Other attempts at local tumor control for unresectable diseases have included the use of intraoperative radiation therapy. This technique has the advantage of delivering a higher dose of radiation to the operative field while sparing normal adjacent tissues. Intraoperative radiation therapy has been used at Denver Children's Hospital in 30 children with neuroblastoma (228). Nine of 14 patients with advanced disease remain alive at a mean of 40 months.

Chemotherapy

Several different agents have been used in the treatment of neuroblastoma. However, the long-term survival in patients older than 1 year of age with metastatic disease remains poor. A reduced response of neuroblastoma to chemotherapy is believed to be due to a large number of nonproliferating tumor cells (249). Most regimens now use a combination of nonspecific and cell cycle–specific drugs. The most common agents used include cyclophosphamide, VCR, DOX, cisplatin, carboplatin, and etoposide. Although the initial response is often good, relapse continues to be a major problem, with 4-year overall-survival at 20% in stage 4 disease (227,237). Chemotherapeutic regimens are limited by dose-related toxicities and side effects, and much effort is now directed toward developing methods of increasing dosages to improve response while controlling toxicity to survivable levels.

Peripheral blood stem-cell infusion, augmented by hematopoietic agents such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, or the reinfusion of purged autologous bone marrow cells (ABMT) may allow increased delivery of chemotherapeutic agents while controlling potentially lethal neutropenia. Autologous bone marrow transplantation following sublethal chemotherapy or total body irradiation has resulted in complete remission in up to 50% of patients with recurrent stage 4 disease (211,228,275). A recent study found improved event-free survival in high-risk patients randomized to receive myeloablative chemotherapy, total body irradiation, and ABMT, when compared with those receiving conventional chemotherapy (256). One problem that is becoming apparent with this treatment, however, is the late risk of relapse. The presence of bulky disease results in increased failure. Tumor debulking with surgery or radiation therapy is warranted before ABMT. Toxicity of bone marrow transplantation can be lethal, but these risks are necessary given that long-term survival is difficult to achieve in these patients.

Another option in the treatment of metastatic neuroblastoma is the use of ^{131}I MIBG (236). The finding that both the primary tumor and metastatic areas take up this radiotracer suggested the possibility that therapeutic doses can be delivered to the tumor. Preliminary analysis indicates that objective responses do occur in terms of reduction of tumor volume. Little toxicity and few side effects have been reported.

TESTICULAR TUMORS

Part of "54 - PEDIATRIC UROLOGIC ONCOLOGY "

Malignant germ cell tumors occur in both gonadal and extragonadal sites. Testicular tumors account for 1% to 2% of all pediatric solid tumors. The peak incidence of childhood testicular tumors is 2 years of age (330). The incidence tapers after 4 years of age, but then begins to rise again at puberty. Benign testis lesions occur much more commonly in prepubertal children than in adults (Table 54.8). Germ cell tumors account for only 65% of prepubertal testicular tumors. Testis tumors are rare in African American and Asiatic children.

TABLE 54.8. CLASSIFICATION OF PREPUBERTAL TESTICULAR TUMORS

Germ cell tumors	Tumors of supporting tissues
Yolk sac	Fibroma
Teratoma	Leiomyoma
Mixed germ cell	Hemangioma
Seminoma	Lymphomas and leukemias
Gonadal stromal tumors	Tumorlike lesions
Leydig cell	Epidermoid cysts
Sertoli cell	Hyperplastic nodule secondary to congenital adrenal hyperplasia
Juvenile granulosa cell	
Mixed	Secondary tumors
Gonadoblastoma	Tumors of the adnexa

From Kay R. Prepubertal testicular tumor registry. *J Urol* 1993;150: 671, with permission.

Embryology and Classification

The gonads first become evident in the yolk sac by the fourth week of gestation. Primordial germ cells originating in the yolk-sac endoderm migrate to the genital ridge at 4 to 5 weeks of gestation. Arrested migration of these germ cells accounts for the development of extragonadal germ cell tumors. During the sixth week, the indeterminate gonads differentiate into testes under the influence of the Y chromosome. The movement of the germ cells is accompanied by the development of the sex cords derived from the celomic epithelium. These form the rete testis and seminiferous tubules. Sertoli cells are probably derived from the primitive sex cords.

The germ cell and non–germ cell tumors arise from the primordial germ cells and celomic epithelium, respectively. Embryonal carcinoma is capable of differentiating into extraembryonic (yolk-sac and choriocarcinoma) and embryonic (mature or immature teratomas). Yolk sac tumors account for the majority of prepubertal testicular tumors. Seminoma or dysgerminoma is a primitive germ cell neoplasm that lacks the capacity for further differentiation. These tumors are unusual in childhood except when related to gonadal dysgenesis. Teratomas represent the most common histologic type of pediatric germ cell tumor. Teratomas are defined by the presence of all three embryonic layers, although one layer may be predominant. The sacrococcygeal location is the most common site of all prepubertal teratomas and the testis accounts for 3% of cases.

Genetics and Risk Factors

The etiology of testicular cancer is unknown. There is clearly a link between cryptorchidism and germ cell tumors of the testis, but these are quite rare in childhood (323). Patients with intersex disorders have an increased incidence of gonadal tumors. These disorders include androgen insensitivity syndromes, such as complete testicular feminization and gonadal dysgenesis. The risk of tumor formation in gonadal dysgenesis is increased if there is a Y chromosome present, with the incidence of tumor development approximately 10% by age 20 years. Intratubular germ cell neoplasia has been noted in 6% of children with intersex disorders, with a higher incidence after puberty (346). The incidence of testicular cancer has been increasing in the past few decades (337). It is suggested that early or prolonged exposure to some carcinogenic stimuli might be implicated.

Testicular germ cell tumors of adolescents have the same chromosomal abnormalities seen in adult germ cell tumors. The most common chromosomal abnormality is the isochromosome of 12p or i(12p), characteristically composed of two copies of 12p. Other abnormalities include loss of chromosomes 11, 13, and 18, and gain of chromosomes 7, 8, and the X chromosome (296). Testis tumors of infants and young children fail to show the presence of i(12p). Endodermal sinus tumors have been noted to have a deletion of the short arm of chromosome 1, specifically 1p36 in 80% to 100% of cases (343). DNA ploidy analysis reveals that most infantile testicular endodermal sinus tumors are diploid or tetraploid, whereas adult germ cell tumors are typically aneuploid (351).

Clinical Presentation and Diagnosis

The most common presentation of patients with testicular tumors is a painless scrotal mass. The mass is typically nontender and does not transilluminate. Disorders that must be excluded are epididymitis, hernia, hydrocele, and torsion. The latter condition can present as a painless mass in the neonate with little scrotal wall inflammation if the event occurred prenatally. There is often a delay from first recognition of the scrotal swelling by the parents and initiation of treatment (295). Some patients with hormonally active tumors may have small intratesticular lesions that are not palpable on physical examination. Acute abdominal pain can be the presenting symptom with torsion of an abdominal undescended testicle containing a tumor (Fig. 54.17).

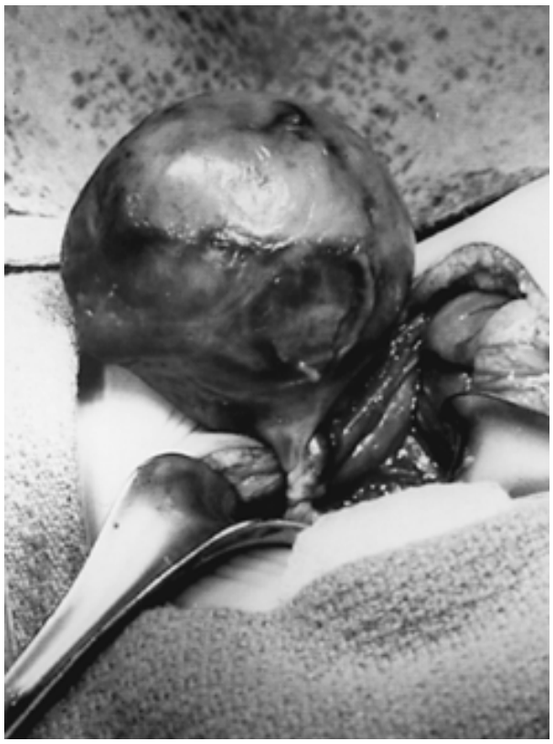

FIGURE 54.17. Teratoma arising from an abdominal undescended testis. The patient presented with acute abdominal pain.

Imaging

Ultrasound is very helpful in the evaluation of testicular abnormalities. Hydrocele fluid around the testicle may prevent palpation of the testes. Ultrasound can detect small lesions not palpable on examination and is particularly useful in identifying cystic components of a teratoma of the testis or epidermoid cyst (Fig. 54.18). If a benign lesion such as teratoma or epidermoid cyst is suspected preoperatively, a testicular-sparing procedure can be considered (313,349).

Color Doppler ultrasound has been reported to be more effective than gray-scale ultrasound in detecting intratesticular neoplasms in the pediatric population (331). Very small functioning Leydig cell tumors that are not evident on ultrasound have been detected with MRI (324).

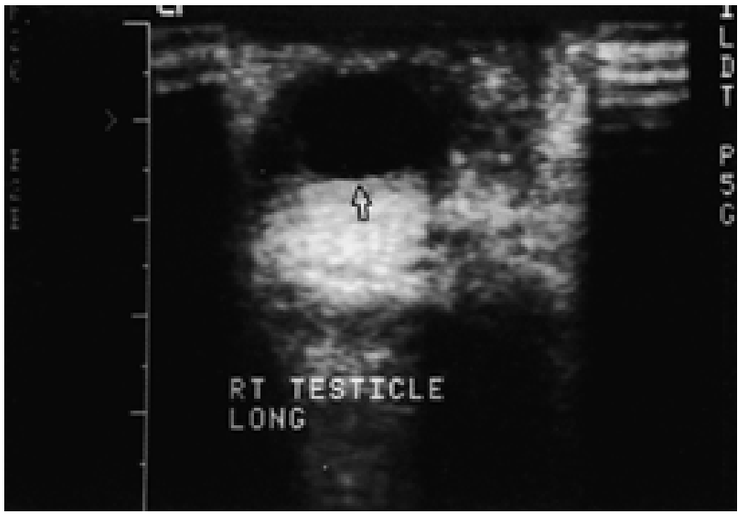

FIGURE 54.18. Testicular ultrasound demonstrating cystic lesion *(arrow)* that proved to be a teratoma of the testicle. The patient underwent a testis-sparing procedure.

Examination of the retroperitoneum for metastatic disease is indicated in patients with malignant tumors. Abdominal CT is most commonly used. Chest radiograph or chest CT is mandatory to exclude pulmonary metastases.

Tumor Markers

α-Fetoprotein (AFP) is a single-chain glycoprotein produced by the fetal yolk sac, liver, and gastrointestinal tract. Various benign and malignant conditions can produce elevations of AFP, including yolk sac tumors of the testis. AFP has a half-life of 5 days, and degradation curves can be followed after orchiectomy to assess for residual disease. One precaution is that the age of the patient must be taken into consideration when monitoring serum levels of AFP because the normal adult reference laboratory values do not apply to young children (294,328,362). AFP synthesis does not stop at birth, and some hepatocytes produce AFP in infancy. Reference normal values for infants have now been established (Table 54.9) (362). Normal adult levels (less than 10 mg/mL) are not reached until 8 months of age. Recognition of this may avoid unfounded concern regarding residual disease following orchiectomy for yolk sac tumor in a young infant. Levels are monitored to detect tumor recurrence.

TABLE 54.9. AVERAGE NORMAL SERUM α-FETOPROTEIN OF INFANTS AT VARIOUS AGES

Age	Number	Mean ± SD (ng/mL)
Premature	11	134,734 ± 41,444
New born	55	48,406 ± 34,718
Newborn–2 wk	16	33,113 ± 32,503
Newborn–1 mo	43	9,452 ± 12,610
2 wk–1 mo	12	2,654 ± 3,080
2 mo	40	323 ± 278
3 mo	5	88 ± 87
4 mo	31	74 ± 56
5 mo	6	46.5 ± 19
6 mo	9	12.5 ± 9.8
7 mo	5	9.7 ± 7.1
8 mo	3	8.5 ± 5.5

SD, standard deviation.
From Wu J, et al. Serum α-fetoprotein (AFP) levels in normal infants. *Pediatr Res* 1981;15:50, with permission.

The ß-subunit of human chorionic gonadotropin (ß-HCG) is a glycoprotein that is produced by embryonal carcinoma and mixed teratomas. The normal value for ß-HCG is less than 5 IU/L. The half-life of ß-HCG is approximately 24 hours.

Carcinoma *in situ*

Carcinoma *in situ* (CIS) occurs in the majority of adult patients with testicular tumors, suggesting that it is a precursor to the development of invasive germ cell tumor (352). An increased incidence of CIS has been noted in children with dysgenetic gonads and androgen insensitivity disorders (340,346). Jorgensen and associates (322) noted that CIS was frequently noted in adolescent cases of germ cell tumor. CIS has not been noted in children with endodermal sinus tumors of the testis. The seminiferous tubules adjacent to germ cell tumors in prepubertal children frequently contain cells with enlarged nuclei and clear cytoplasm. Staining of seminiferous tubules adjacent to germ cell tumor for CIS markers, c-kit, and placental alkaline phosphatase (PLAP), was negative in 28 prepubertal testes (317). These cells can be proliferating cell nuclear antigen (PCNA) positive suggesting that they are proliferative and not neoplastic in nature. These differences suggest that the etiology of germ cell tumor in infants is different than in adults.

The diagnosis of CIS is determined by histologic examination of the testis. Testicular biopsies in adults who have previously undergone orchidopexy reveal an incidence of 1.7% (308). In the prepubertal patient, identification of CIS is more difficult. Biopsies at the time of orchidopexy in prepubertal children only rarely have demonstrated CIS (316). The prepubertal patient with CIS should be followed with a repeat biopsy after puberty because the natural history of the disease in younger patients is unknown (307). An exception is the patient with androgen insensitivity or dysgenetic gonads.

Germ Cell Tumors

Yolk Sac Tumor

Yolk sac tumor is the most common prepubertal testicular tumor, accounting for 60% of all tumors (323). More than 75% of childhood yolk sac tumors occur in the first 2 years of life. It is known by several other eponyms, including *endodermal sinus tumor, embryonal adenocarcinoma, infantile adenocarcinoma of the testis, orchidoblastoma,* and *Teilum's tumor.* These tumors are believed to arise from the yolk sac elements. Grossly, the tumor is firm and yellow-white on cross section and hemorrhage is unusual. The characteristic histologic finding in yolk sac tumors is Schiller-Duval bodies (361). Eosinophilic cytoplasmic inclusions are common and specialized staining techniques demonstrate the presence of AFP.

The clinical behavior of yolk sac tumor is quite at variance with its adult counterpart, embryonal carcinoma, despite the histologic similarities. Unlike adult tumors, spread to the retroperitoneal lymph nodes is quite uncommon with an incidence of only 4% to 6% (293,295). Approximately 80% to 85% of prepubertal children present

with stage I disease. When distant metastases do occur, they are most likely to be hematogenous metastases to the lung, which are found in 20% of patients.

Radical inguinal orchiectomy is the standard initial therapy for all children with yolk sac tumors. The need for RPLND both for staging and treatment has been controversial. Historically, the addition of RPLND has been associated with increased survival. Staubitz and co-workers reported that patients with retroperitoneal disease could be cured with orchiectomy and RPLND (354). Hopkins and associates (319) found a better survival with orchiectomy and RPLND compared with orchiectomy alone (84% versus 50%). However, all of these patients were given adjuvant chemotherapy and radiation therapy if nodes were involved. Others reported similar survival advantage of node dissection plus orchiectomy in comparison to orchiectomy alone (302). Treatment options considered for retroperitoneal disease included radiation therapy and chemotherapy. A radiation dose of 2,000 to 3,000 cGy has achieved an 84% survival (320). Adjuvant chemotherapy also has been advocated to prevent relapse, but this has not been performed prospectively in a large number of patients.

The need for RPLND began to be questioned based on low incidence of metastases to the retroperitoneal lymph nodes, improved imaging of the retroperitoneum for staging purposes, and availability of a reliable tumor marker for the presence of residual or metastatic disease. It is interesting that most authors who reported improved survival with RPLND did not find evidence of nodal disease (319). CT imaging of the retroperitoneum can identify most patients that have lymph node metastases, but there is a 15% to 20% false negative rate (345). Another justification for omitting RPLND was the development of effective combination chemotherapy that allows salvage of relapsed patients with clinical stage I disease (315,325,332).

The current staging system used by the Children's Oncology Group is listed in Table 54.10 . AFP levels are determined at diagnosis and monitored after radical inguinal orchiectomy to determine whether there is an appropriate half-life decline. CT scans of the retroperitoneum and chest are obtained to exclude metastatic lesions.

Stage	Extent of Disease
I	Tumor is limited to the testis. If scrotal orchiectomy has been performed, all margins are negative after resection of proximal cord structures to the level of the internal inguinal ring. Tumor markers are negative after appropriate half-life decline.
II	Microscopic residual disease is present in the scrotum or spermatic cord. Tumor markers remain elevated after appropriate half-life interval. Tumor rupture or scrotal biopsy should occur before complete orchiectomy.
III	Presence of retroperitoneal lymph node involvement.
IV	Distant metastatic deposits.

COG, Children's Oncology Group.

TABLE 54.10. COG STAGING SYSTEM FOR TESTICULAR GERM CELL TUMORS

Clinical stage I patients do not receive additional adjuvant treatment after radical orchiectomy. Chest radiograph, CT, or MRI of the retroperitoneum is recommended monthly for 3 months and then once every 6 months. This surveillance is continued until the patient is 36 months posttreatment. Tumor markers and physical examination are performed at more frequent intervals. Scrotal orchiectomy with negative margins can be treated as stage I, but the proximal cord structures should be resected to the level of the internal ring.

Patients who have undergone prior scrotal biopsy are considered stage II. A completion orchiectomy with removal of all cord structures is performed. This approach has proven to be beneficial in adult patients with gross contamination during removal of germ cell tumors (297,306). All patients undergo abdominal CT to examine for retroperitoneal lymphadenopathy. Patients with enlarged lymph nodes should undergo lymph node sampling or biopsy. Patients that have persistent elevation of AFP and retroperitoneal adenopathy are presumed to have metastatic disease. These patients can be treated as stage III.

Chemotherapy regimens used for pediatric patients with advanced germ cell tumors are similar to those used in adults. Combination chemotherapy using platinum-based therapy is recommended (289). An intergroup study for the treatment of localized and advanced germ cell tumors in children conducted by the Children's Cancer Group and the Pediatric Oncology Group was recently completed (347). All stage II patients are given chemotherapy (cisplatin, etoposide, and bleomycin). At 12 weeks, patients with evidence of recurrent disease or elevation of tumor markers will undergo surgery. Residual retroperitoneal masses postchemotherapy are uncommon (357), but they warrant resection to establish a histologic diagnosis. Patients with persistent viable tumor are then switched to another treatment regimen.

Children with stage III and IV germ cell tumors initially undergo retroperitoneal lymph node sampling. Those patients that develop relapse after initial treatment of a stage I tumor also should undergo biopsy for histologic confirmation. All patients with stage III and IV germ cell tumors receive chemotherapy. Patients with elevated tumor markers or clinically evident retroperitoneal disease after chemotherapy undergo biopsy and/or resection. Radiation therapy is not a routine part of the protocol for treatment of yolk sac tumors. A similar regimen has been used by United Kingdom Children's Cancer Study Group (332). Carboplatin also has been used instead of cisplatin in the UK studies with equivalent success (344). Survival in stage III and IV germ cell tumors (all sites) was 83% and 67%, respectively.

However, overall survival for 68 patients with yolk sac testis tumors was 99%.

Mature Teratoma

Teratoma is a germ cell tumor with recognizable elements of more than one germ cell layer: endoderm, ectoderm, and mesoderm. The incidence of teratoma is lower than in adults, but it is the second most common testis tumor in children (295). Teratomas are classified as mature, immature, and malignant. Immature teratomas often have been considered to be malignant tumors, but in children they appear to be benign unless they have foci of malignant cells.

Mature teratomas generally appear well encapsulated on gross examination. Multiple cysts are present, but consistency on cross section varies with the amount of solid tissue present between the cysts. The microscopic appearance varies with the relative amounts of tissue derived from the different germ layers and the degree of maturation (339). Cartilage, bone, mucous glands, or muscle may be evident.

Prepubertal mature teratomas have a benign clinical course, which contrasts with the clinical behavior of teratomas in adults, which have the propensity to metastasize (309,312,315,339). In past years, the majority of these tumors have been managed with radical orchiectomy. However, ultrasound of the testis can demonstrate the cystic nature of this lesion, suggesting the diagnosis of teratoma. Other cystic lesions of the testis such as simple cysts or epidermoid cyst must be considered in the differential diagnosis. The latter lesions generally have a hyperechoic center surrounded by an outer hypoechoic rim (336). Teratoma appears more as complex hypoechoic areas surrounded by highly echogenic signals (326). If the preoperative evaluation suggests a benign intratesticular lesion, then a testicular-sparing procedure can be considered (290,314,334,349). Although only a limited number of patients have been treated with enucleation of the tumor, no recurrences have been reported to date (349). Theoretic concerns include tumor seeding, incorrect diagnosis, or multifocal microscopic disease within the testis. However, frozen section diagnosis of teratoma is possible because of the characteristic histologic features of the tumor. In addition, a detailed review of 21 cases of prepubertal teratoma at the Armed Forces Institute of Pathology did not reveal evidence of multifocal disease or CIS of the adjacent testis (349).

Immature Teratomas

A less common tumor of the testis is immature teratoma. The most common extracranial site is in the ovary, with only 10% occurring in the testes. Immature teratomas have a gross appearance similar to that of mature teratomas. Recently, the pathologic characteristics of immature teratomas in children were reviewed (318). The reviewers found that the incidence of foci of yolk sac tumor increased with the grade of the tumor teratoma, and these patients frequently had elevated serum AFP levels preoperatively (318). Evidence of yolk sac tumor was found in all but one testicular immature teratoma. Recurrence of immature teratomas after resection occurs almost exclusively in patients with elevated AFP or foci of yolk sac tumor in the initial resection specimens. Recurrent tumors typically are yolk sac tumors. Because most patients with recurrent tumor can be salvaged with platinum-based chemotherapy, observation alone is recommended for completely resected immature teratoma (309,335).

Gonadal Stromal Tumors

Leydig Cell Tumor

Gonadal sex-cord stromal tumors are the most common nongerminal testicular tumors in children (299,310). These tumors may show differentiation toward Leydig cells, Sertoli cells, or granulosa cells. Pathologic diagnosis can be difficult because of incomplete differentiation and the presence of some areas that can resemble other entities. *Leydig cell tumors* are the most common gonadal stromal tumor both in children and adults. The peak incidence is age 4 to 5 years. Leydig cells produce testosterone, and the tumor may continue production of the hormone, resulting in precocious puberty. Leydig cell tumors account for approximately 10% of all cases of precocious puberty in boys (358). In addition, the boys may have accelerated skeletal and muscle development, which may not resolve after removal of the tumor (338). Other hormones produced by Leydig cell tumors include estrogens, progesterone, and corticosteroids. These may cause gynecomastia, which occurs more often in adults with Leydig cell tumors (321).

Differential diagnosis of precocious puberty includes pituitary lesions that can be excluded by the finding of prepubertal LH and FSH levels with an increased serum testosterone. Leydig cell tumors also must be differentiated from large cell Sertoli cell tumors, Leydig cell hyperplasia, tumors of adrenal rest tissue, and hyperplastic testicular nodules that develop in boys with poorly controlled congenital adrenal hyperplasia (CAH) (Fig. 54.19) (300,353,359,360). Leydig cell hyperplasia can be distinguished by normal levels of urinary 17-ketosteroids. Testicular nodules in CAH often present in the second decade of life. These lesions tend to occur bilaterally, but bilateral Leydig cell tumors have been reported (292). A family history of CAH is helpful in making the diagnosis. The hyperplastic nodules that develop in CAH resemble Leydig cells histologically but behave biochemically like adrenal cortical cells. Urinary ketosteroids are elevated in patients with 21-hydroxylase deficiency and serum levels of 17-hydroxy progesterone are elevated. Urinary pregnanetriol levels are absent in patients with Leydig cell tumors. Glucocorticoid replacement in CAH generally produces regression of the hyperplastic nodules, but this is not universal (353,359). This may be due to the presence of fibrosis or calcification in the nodule.

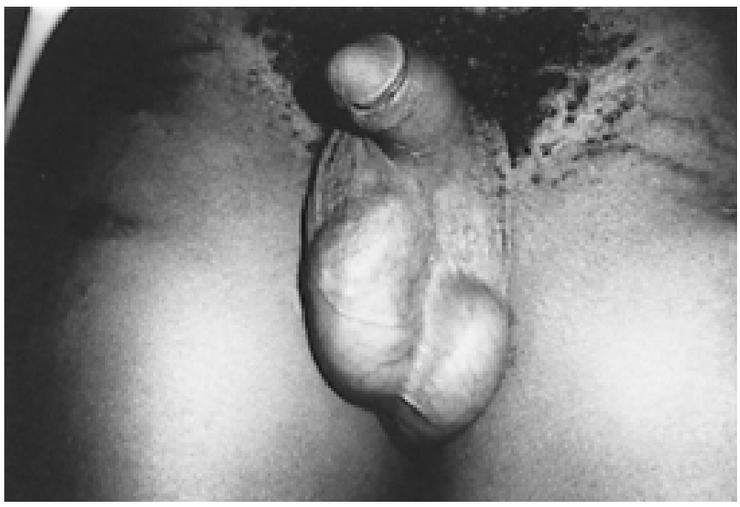

FIGURE 54.19. Precocious puberty in an 11-year-old boy due to hyperplastic Leydig cell nodules. (Photograph courtesy of Dr. David Bloom.)

Leydig cell tumors appear well encapsulated with compression of the adjacent testicular tissue. They appear yellow to brown on cross section, reflecting the steroid production by the tumor. The pathognomonic histologic feature of Leydig cell tumor, Reinke's crystals, is present in only about 40% of tumors (339). Increased mitotic figures or other features suggestive of malignancy are absent in prepubertal Leydig cell tumors. Because malignancy has not been reported in children, orchiectomy is adequate treatment (295).

Sertoli Cell Tumor

Sertoli cell tumors are the next most common gonadal stromal tumor in children. These tumors are not as metabolically active as Leydig cell tumors, but gynecomastia has been reported (305). The typical presentation is usually a painless testicular mass, and these tumors present at an earlier age than Leydig cell tumors. There are limited series of patients with Sertoli cell tumors in children (305,310). Most recommend observation in infants because metastases have not been reported. Histology does not correlate with outcome because they often have features of high mitotic rates, nuclear pleomorphism, and increased cellularity. Treatment is orchiectomy, but examination of the retroperitoneum is warranted to exclude retroperitoneal spread (348). Large cell Sertoli cell tumors have been noted with increased frequency in patients with Peutz-Jeghers syndrome and the Carney complex (298). Large cell Sertoli cell tumors can be confused with Leydig cell tumors. Both tumors are characterized by cells with abundant eosinophilic cytoplasm. The tumors of the adrenogenital syndrome are also another confusing entity in the differential diagnosis.

Gonadoblastoma

Gonadoblastomas occur in children with dysgenetic gonads and are associated with the presence of a Y chromosome in the karyotype (333). Gonadoblastomas are small benign tumors that are bilateral in up to one-third of cases. The tumor is composed of germ cells, sex cord derivatives resembling immature granulosa and Sertoli cells, and occasionally stromal elements. These are the most common tumors found in association with intersex disorders. The risk of tumor formation in patients with mixed gonadal dysgenesis is 25% (350), and the incidence increases with age (333). The germ cell component of gonadoblastoma is prone to malignant degeneration into seminoma and nonseminomatous tumors. It has been recommended that all streak gonads in patients with gonadal dysgenesis be removed (288). Patients with gonadal dysgenesis raised as females should have the gonads removed at diagnosis (311,342). In addition, all undescended testes should be removed, but scrotal testes can be preserved because they are less prone to tumor development. Early gonadectomy is advocated because tumors have been reported in children younger than 5 years of age (311,342). CIS has been demonstrated in gonadal biopsies of children with gonadal dysgenesis, and this has been suggested as a means of identifying those at risk for development of malignant germ cell tumors (340). However, recognition of CIS in prepubertal gonadal biopsies can be difficult, and a negative biopsy does not preclude the later development of a germ cell tumor.

Other Lesions

Leukemia and *lymphoma* are the most common malignancies to spread to the testicle in children. Patients with acute lymphoblastic leukemia who have bulky disease at diagnosis have up to a 20% incidence of testicular relapse (291). Routine biopsies of the testis to help determine further chemotherapy and the need for radiation to the testes are no longer recommended (356). Positive testis biopsies early in remission identify patients at a slightly higher risk for adverse events, but do not influence survival. Testicular involvement occurs in 4% of boys with Burkitt's lymphoma and may be the initial clinical presentation (329). Follicular lymphoma may occur as a primary tumor of the testis (303). The prognosis is favorable if the tumor is localized.

Testicular cystic dysplasia is a rare benign lesion in boys that has been reported with increasing frequency (341,355). It is distinguished by the presence of multiple small irregular cysts localized in the rete testis. More than half the cases are associated with renal agenesis or multicystic renal dysplasia. One proposed the etiology is a defective connection between the efferent ductules originating from the metanephros and the rete testis tubules originating from the gonad. Testis-sparing surgery has been possible in a few cases, and nonoperative treatment has been proposed (341). If the latter approach is used, follow-up with serial testicular ultrasound is advised.

Testicular microlithiasis has been reported in association with testicular tumors. It has been noted rarely in children.

Recommendations have been made for noninvasive ultrasound follow-up until adult age (301,304).

GENITOURINARY RHABDOMYOSARCOMA

Part of "54 - PEDIATRIC UROLOGIC ONCOLOGY "

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in infants and children. RMS accounts for approximately half of all pediatric soft tissue sarcomas and 15% of all pediatric solid tumors. RMS can arise from almost any site and has a peak incidence between the ages of 2 and 5 years. Genitourinary RMS accounts for approximately 20% of these tumors (400). The most common genitourinary sites are paratesticular, vagina, bladder, and prostate. Survival varies by site, and special sites such as vagina and paratesticular have a better prognosis than bladder/prostate primaries (372,413). There is a male predominance for genitourinary RMS (399).

The treatment strategy for RMS requires a multidisciplinary approach involving surgeons, oncologists, radiation-oncologists, and pathologists. As with most uncommon tumors, large clinical trials conducted by groups such as the Intergroup Rhabdomyosarcoma Study Group (IRSG), have led to improved outcomes. The protocols used by the IRSG include multiagent chemotherapy, radiotherapy, and surgical treatment, and have led to current long-term overall survival approaching 70% (373).

Molecular Biology and Genetics

The etiology of RMS is unknown, but subgroups of children with a genetic predisposition have been identified (408). The two major histologic subtypes, embryonal and alveolar, have each been demonstrated to have characteristic genetic alterations that may in part explain their clinical behavior. Evaluation of DNA content in RMS tumors has shown that hyperdiploid tumors are usually embryonal and those with hyperdiploid DNA content may be more sensitive to chemotherapy and irradiation than embryonal tumors without this feature (408). Tumors with tetraploid DNA content are almost always alveolar and may have a worse prognosis (415).

Embryonal and alveolar tumors can often be distinguished by structural chromosomal abnormalities. Alveolar tumors often have a translocation involving chromosomes 2 and 13, the +(2;13) (q35; q14), which affects the PAX3 and FKHR genes (378,416). The reciprocal translocation fuses the PAX 3 gene to the FKHR gene, and this may result in inappropriate activation of PAX3 transcriptional targets, resulting in dysregulation of cell growth. Several alveolar RMS tumors have had another translocation, +(1;13) (P36; q14) (370), which results in fusion of PAX7 to the FKHR gene, which may result in similar dysregulation of cell growth. Identification of these translocations by reverse-transcriptase polymerase chain reactions of fluorescence *in situ* hybridization techniques may allow improved identification of patients with poorer prognosis.

Other genetic abnormalities have been identified in RMS. Mutations of the p53 oncogene have been identified in both RMS and RMS cell lines and may be present in as many as 50% of tumors (377). Dias and co-workers showed amplification of *N*-myc in 4 of 6 alveolar RMS tumors but no embryonal tumors (375). No amplification of *C*-myc was identified in this study. Mutations of the N-ras and K-ras oncogenes have been reported in embryonal tumors (4/8).

The Li-Fraumeni syndrome associates childhood sarcomas with mothers who have an excess of premenopausal breast cancer and with siblings who have an increased risk of cancer (396). A mutation of the p53 tumor suppressor gene was found in the tumors in all patients with this syndrome (398). An increased incidence of RMS has been found in association with neurofibromatosis (401).

Pathology

RMS cells arise from indifferentiated mesodermal tissue and may appear in any part of the body, including tissues that do not ordinarily contain striated muscle. Histologically, it is classified within the category of small, round, blue-cell tumors of childhood, a category that also includes neuroblastoma, Ewing's sarcoma, small-cell osteogenic sarcoma, non-Hodgkin's lymphoma, and leukemia. It may be difficult to distinguish among these tumors by light microscopy alone, and other studies, including electron microscopy, cytogenetics, immunohistochemistry, and DNA flow cytometry may be needed (415).

Gross features of RMS are neither characteristic nor helpful in distinguishing it from other soft-tissue tumors, with the exception of sarcoma botryoides, which is a mass of grapelike clusters arising from within a hollow viscus. These RMS tumors are usually firm, nodular, and of varying size but may be of varying consistency and appearance. They tend to form pseudocapsules, but the tumor often extends outside the pseudocapsule.

There are several histologic variants of RMS. Embryonal RMS is the most common subtype seen in children and accounts for more than 60% of genitourinary tumors (399). When including the botryoid variant, more recent studies have reported that more than 90% of genitourinary tumors in children are embryonal (405).

The second most common subtype in children is alveolar, which occurs more commonly in extremity and trunk lesions, than genitourinary sites and has been reported to have a worse prognosis (382,405). Recent studies have suggested that site may be a more important predictor of prognosis than histology (365,404). A less common subtype in children is pleomorphic RMS. This tumor is no longer considered a separate entity, but rather an anaplastic variant of the more common embryonal or alveolar RMS (392).

Metastatic spread of RMS is usually through the lymphatics. Regional lymph node metastases may be fairly common and vary with the site of the primary tumor.

Clinical Grouping and Preoperative Staging

Clinical grouping has been used in all IRS studies and is based on the extent of disease and the operative outcome (Table 54.11). Initially, it was based on the premise that total tumor extirpation at the original operation offered the best hope for cure. As the treatment for RMS has evolved and the chemosensitivity and radiosensitivity of this tumor has been recognized, many patients with large tumors or difficult to resect tumors have had biopsy only as the initial operation. After chemotherapy, further resection is considered, and in some locations (i.e., vagina), chemotherapy may be the only form of treatment (364,367). This results in the shifting of more patients from group I to group III. This system depends on the surgical aggressiveness of the surgeon and may result in mutilating surgery. It does not take into account the biologic nature or the natural history of the tumor. A pretreatment staging system that relies on physical examination and imaging studies and examines tumor site, size, invasion, nodal involvement, and distant metastasis was devised (Table 54.12) (394). This pretreatment staging system has been shown to be more predictive of outcome and better reflects the risk by site (404). Low-risk (stage I), intermediate-risk (stage II, III), and high-risk groups are thus identified, and treatment can be tailored to the risk group.

Group I: Localized disease, completely removed
- a. Confined to muscle or organ of origin
- b. Infiltration outside organ or muscle of origin; regional nodes not involved

Group II: Total gross resection with evidence of regional spread
- a. Grossly resected tumor with microscopic residual
- b. Regional disease with involved nodes, completely resected with no microscopic residual
- c. Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node in the dissection

Group III: Incomplete resection, or biopsy with presence of gross disease

Group IV: Distant metastasis

IRS, Intergroup Rhabdomyosarcoma Study.

TABLE 54.11. IRS CLINICAL GROUPS OF RHABDOMYOSARCOMA

Stage	Sites	Tumor Size	Regional Nodes	Metastasis
I	Orbit Head and neck (superficial) Genitourinary (non-B/P)	a or b	N_0N_1 or N_x	M_0
II	B/P Extremity, trunk Parameningeal Other	a	N_0 or N_x	M_0
III	B/P Extremity, trunk Parameningeal Other	b N_0N_1 or N_x	N_1	M_0
IV	All	a or b	Any N	M_1

a, <5 cm in diameter; b, >5 cm in diameter; B/P, bladder/prostate; head and neck, entire area excluding nonparameningeal tumors; M_0, no distant metastasis; M_1, distant metastasis present; N_0, not clinically involved; N_1, clinically involved; N_x, clinical status unknown; other, all other sites; TNM, tumor/node metastasis.

TABLE 54.12. TNM PRETREATMENT STAGING CLASSIFICATION OF PATIENTS WITH RHABDOMYOSARCOMA IN IRV-IV TUMOR SIZE REGIONAL NODES METASTASIS

Treatment: General Principles

Radical surgical excision was the first effective treatment for RMS. For pelvic genitourinary tumors, this consisted of total pelvic exenteration. It was later noted that RMS was radiosensitive (417), but high doses were required for local tumor control. In the 1960s, following surgical excision, adjunctive chemotherapy and radiotherapy were used (409). These efforts showed that survival was significantly enhanced if chemotherapy was routinely administered after surgery (388).

Cooperative trials for RMS began in 1972 with IRS-I (399). This multimodal approach to treatment over the last 28 years has significantly improved survival at all sites in these children (373).

Once it was recognized that RMS was chemosensitive,

investigators explored the use of primary chemotherapy to avoid the exenterative surgery performed for genitourinary RMS (407,420). A major aim of these protocols for patients with genitourinary tumors in IRS-II (1978–1984) was the preservation of a functional distal urinary tract with maintenance of the high survival rates achieved in IRS-I (381,411). Unfortunately, primary chemotherapy with vincristine, dactinomycin, and cyclophosphamide (VAC) did not obviate the need for radiation therapy or radical surgery for patients with pelvic RMS. The percentage of patients alive after 3 years was the same for IRS-II as for IRS-I (23). In IRS-III (1985–1992), more intensive chemotherapy was used—VAC plus DOX and cisplatinum—and radiation therapy was initiated sooner. With intensification of treatment for pelvic RMS in IRS-III, there has been an increased rate of salvage of functional bladders with overall survival maintained (386). Bladder RMS was shown to be responsive to chemotherapy and fewer bladders had to be removed for residual tumors (390). It also was demonstrated that partial cystectomy after chemotherapy could be used with good survival (384,387).

The surgical treatment of RMS is site specific, and as mentioned, treatment is directed at the risk group, which is influenced by site and stage. Secondary excision after initial biopsy and readjuvant therapy has a better outcome than partial or incomplete resection and should be planned in cases in which primary excision is not possible. Second-look operations have been used for several types of pediatric tumors to evaluate therapeutic response and to remove any residual tumor after completing initial therapy (366,384).

Specific Sites

Bladder and Prostate Tumors

RMS of the bladder and/or prostate may present with urinary dysfunction, pain, constipation, or a mass, which may be quite large at presentation (Fig. 54.20). Tumors of the bladder usually occur as a botryoid form and grow intraluminally, usually at or near the trigone (381). Urachal and bladder dome RMS are seen less frequently and lend themselves to partial cystectomy. Prostatic RMS tends to present as a solid mass rather than the botryoid form seen in the bladder. Extension into the bladder neck or compression may lead to bladder outlet obstruction. The bladder may be displaced significantly to one side and ureteral obstruction, unilaterally or bilaterally can occur. Determining the actual site of the primary can be difficult. Contrast studies reveal bladder-filling defects within the bladder, or elevation or displacement of the bladder in prostatic RMS (Fig. 54.21). Ultrasound or CT may show the extent of the tumor and reveal evidence of ureteral obstruction and/or hydronephrosis. Biopsy via cystoscopy may establish the diagnosis.

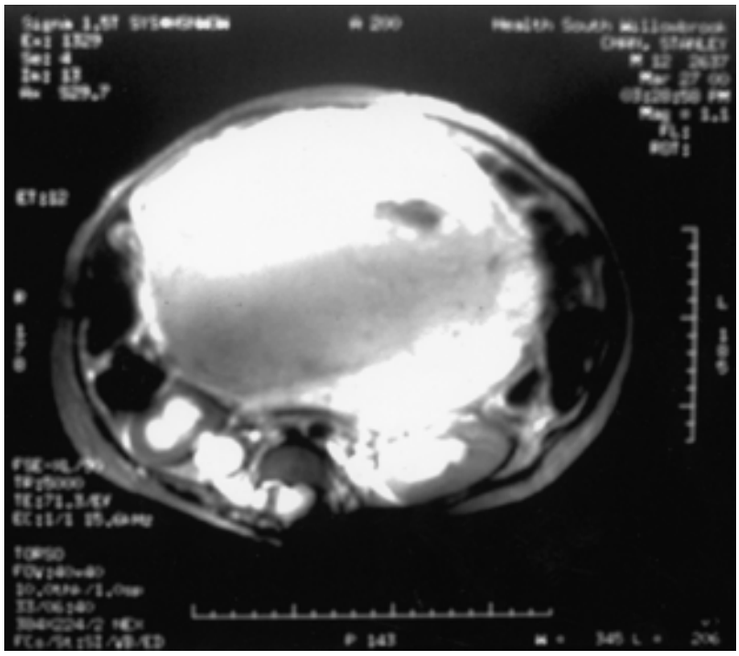

FIGURE 54.20. Computed tomography scan of a large prostatic rhabdomyosarcoma extending into the upper abdomen with bilateral hydroureteronephrosis.

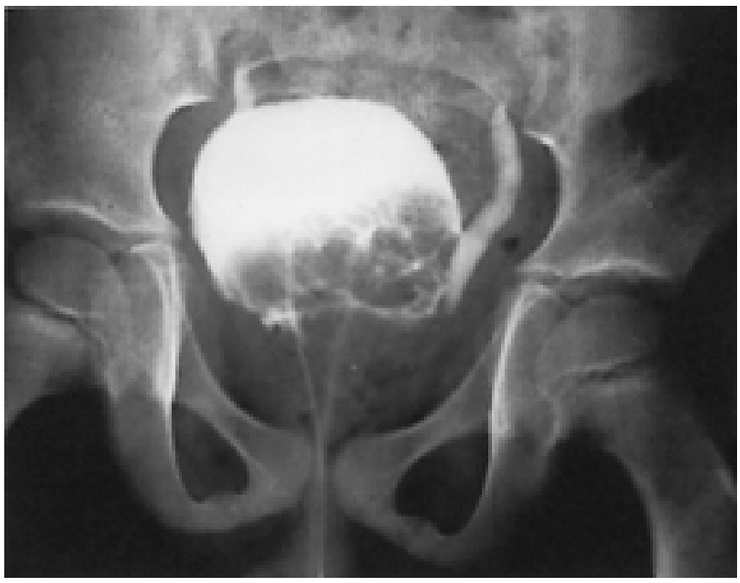

FIGURE 54.21. Excretory urogram demonstrating filling defects in the bladder due to rhabdomyosarcoma. (Photograph courtesy of Dr. Stanford Goldman.)

Historically, many bladder/prostate patients underwent anterior pelvic exenteration. This was associated with a high rate of serious complications (403) and is no longer recommended for initial therapy (412). Biopsy, chemotherapy, and attempts at bladder salvage are keys to surgical management today. This has led to increased bladder salvage while maintaining excellent survival (385,386). Partial cystectomy in 40 patients was reported to achieve a 78.5% survival compared with 79.5% of 131 patients treated with total cystectomy (387). This has been confirmed by others (368). Bladder augmentation or substitution has been used in some of these patients with good functional results (391).

Unfortunately, many of these tumors arise from the trigonal area and are not amenable to local or partial cystectomy. Pelvic exenteration has been used selectively in

relapsed tumors (386). Prostatectomy without cystectomy has been performed in selected patients with persistent disease or local relapse (386,402). Local recurrence, however, may be a problem (402).

Retention of the bladder may minimize some of the long-term problems of sexual dysfunction associated with cystectomy for bladder RMS. Cystoscopy and CT or MRI are used to follow and evaluate the tumor response to chemotherapy. If the primary tumor mass is decreasing in size and if histologic review of the biopsy specimens shows a decrease in cellularity, absence or reduction in tumor cells, presence of benign tissue (fibrosis, necrosis, or edema) as maturing rhabdomyoblasts, treatment should be continued with cystoscopic examinations at 1- to 2-month intervals. These favorable histologic findings at 6 months of therapy or later are consistent with a good long-term outcome or cure with a retained bladder. If cystectomy is warranted based on documented persistence of tumor by imaging studies or examination and verified by histologic sections, structures outside the bladder, particularly in the female, should not be removed unless directly invaded by the tumor itself. Thus few bladders will be removed unnecessarily, and few patients will escape tumor control without a needed surgical resection (390).

Exenteration is rarely required for RMS of the prostate. Delayed surgical excision after initial biopsy and chemotherapy can result in bladder salvage in most patients (397).

Paratesticular RMS

Paratesticular RMS arises in the distal portion of the spermatic cord and may invade the testis or surrounding tissues. The majority of paratesticular tumors are of the embryonal subtype, with a high percentage being of the favorable-histology spindle-cell variant. These tumors are generally stage I, low-risk tumors. They account for 70% of childhood RMS and 12% of childhood scrotal tumors (421,422).

Presentation is often a unilateral painless scrotal swelling or mass above the testis. On physical examination, a firm mass is found that is usually distinct from the testis. Ultrasound can confirm the solid nature of the lesion (Fig. 54.22).

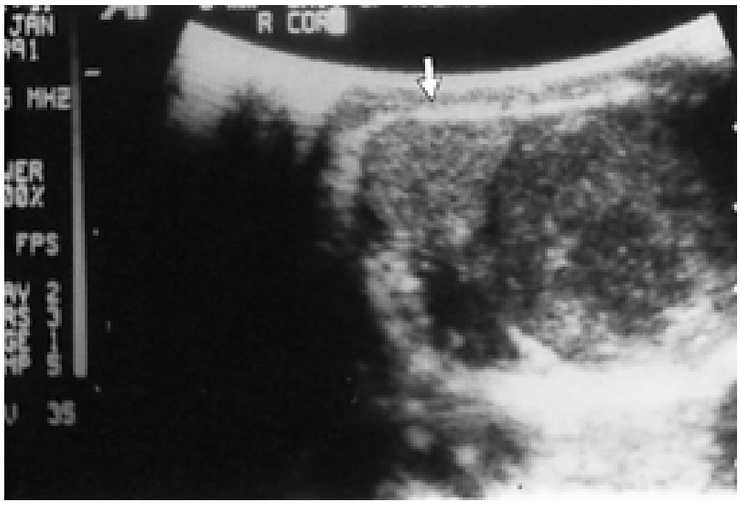

FIGURE 54.22. Scrotal ultrasound of a young boy presenting with a painless mass that shows compression of the testicular parenchyma *(arrow)* by the paratesticular rhabdomyosarcoma.

Initial management includes inguinal orchiectomy with high ligation of the cord structures as with any suspected scrotal tumor (Fig. 54.23). Frozen section of the proximal end of the cord resected should be clear of tumor. If positive, a higher resection should be attempted. Scrotal incisions for biopsy or orchiectomy should not be performed because they violate tissue planes and are associated with an increased risk of local recurrence and systemic lymphatic metastasis. If cord elements remain, removal of the spermatic cord and partial hemiscrotectomy should be considered. In a review of 14 hemiscrotectomy specimens at Memorial Sloan-Kettering Cancer Center, 29% had residual tumor identified (393).

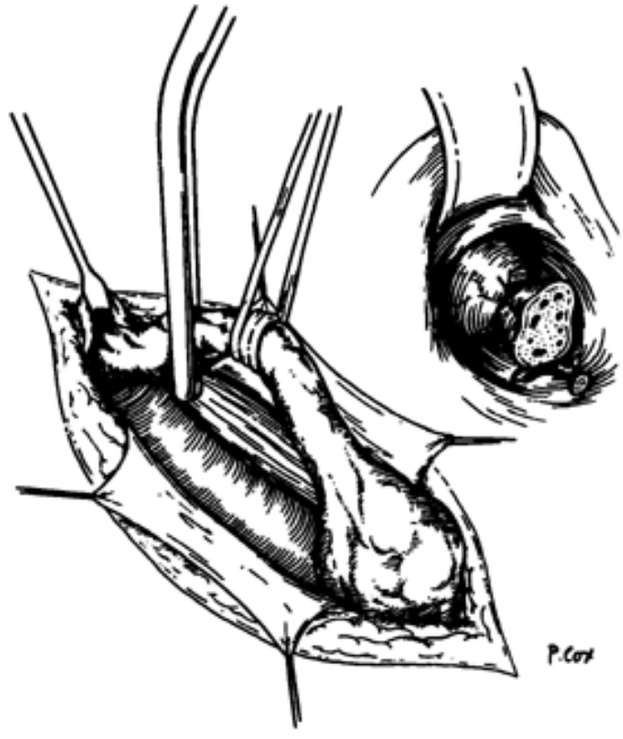

FIGURE 54.23. Drawing showing technique of high ligation of the spermatic cord with vascular occlusion of the cord vessels.

Before the advent of effective systemic therapy, surgery alone produced a 50% relapse-free survival at 2 years (419). With the introduction of multimodal treatment, chemotherapy and occasionally radiation therapy, the survival rates are over 90% (379,422). A metastatic evaluation is performed at diagnosis. CT imaging of the retroperitoneum evaluates the retroperitoneal nodes. Lymphatic spread has been reported to be as high as 28% to 40% in the past (395,410). CT may significantly underestimate nodal status

and should be used with caution. RPLND initially was recommended to stage the disease (369). Patients with positive nodes receive radiation therapy to the involved area.

The role of RPLND for paratesticular RMS is controversial (406,414,422). Significant morbidity has been reported with routine RPLND (389). This may be reduced by newer methods of dissection (376,393). Wiener and co-authors (422) reported on 121 patients in IRS-III with nonmetastatic paratesticular RMS who underwent RPLND. Of the patients who had clinically normal nodes, 14% were shown to have lymphatic metastases. Only two experienced regional node recurrence. It was initially felt that RPLND was not necessary in patients with clinically negative nodes and that CT surveillance would be adequate (414,422). IRS-IV revealed that CT underestimated the nodal status in patients and relapse was seen in patients not treated with radiation to the retroperitoneum. Patients over age 10 were particularly at risk and recommendations now include RPLND in patients over 10 years of age (423). Consideration of sentinel lymph node mapping has been discussed and appears feasible but there is little experience to date with this technique for paratesticular RMS (404). Survival of patients with paratesticular RMS with or without positive RPLNDs has been excellent.

Vaginal/Vulvar RMS

Vaginal RMS presents with vaginal bleeding, discharge, or a polypoid, grapelike mass (sarcoma botryoides) (Fig. 54.24). It most commonly originates from the anterior vaginal wall in the middle or distal third of the vagina. Embryologically, this is part of the urogenital septum that ultimately becomes the anterior wall of the vagina and the posterior wall of the bladder. The posterior bladder wall is the most common location for bladder RMS (364,366). Vaginal tumors may invade the vesicovaginal septum or bladder wall because of proximity. Cystoscopy and vaginoscopy are warranted during initial evaluation and at intervals during follow-up (364).

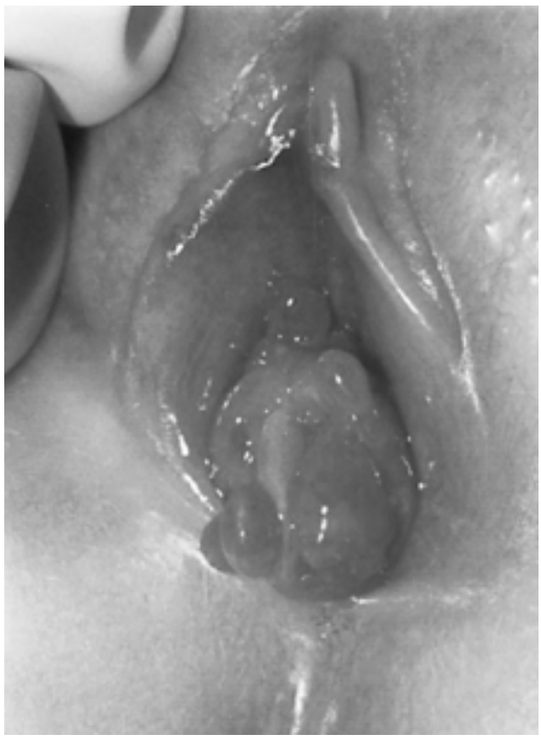

FIGURE 54.24. Mass protruding from the vaginal introitus in a young girl with vaginal rhabdomyosarcoma.

Before 1972, pelvic exenteration was the accepted surgical approach for vaginal RMS. Beginning in 1972, the IRS Group began to enter patients on prospective trials. The first eight patients entered with nonmetastatic vaginal RMS and all underwent primary surgical intervention followed by postoperative chemotherapy with VAC (380). Because vaginal RMS appeared to be responsive to chemotherapy, IRS-II (1978–1984) consisted of a primary chemotherapy regimen followed by delayed surgical intervention and selected radiation. Fourteen of 20 patients (70%) eventually underwent surgical resection. Primary chemotherapy consisted of VAC plus DOX (383).

During IRS-III (1984–1988), three patients were given primary chemotherapy consisting of VAC plus DOX and cisplatin after initial biopsy (clinical group III, stage 1). Only 7 of 23 patients (30%) underwent surgical resection after primary chemotherapy. Six of these seven patients had no viable tumor in the resected specimen and one had maturing rhabdomyoblasts. The presence of rhabdomyoblasts may not signify persistent active cancer. At M.D. Anderson Cancer Center, we have continued chemotherapy without resection when rhabdomyoblasts are found. No viable tumor or rhabdomyoblasts were found after further chemotherapy or subsequent biopsy in these patients. Only six patients in IRS-III underwent radiotherapy (367).

During IRS-IV (1988–1996), only 3 of 21 patients (13%) underwent surgical resection after primary chemotherapy. Three patients had rhabdomyoblasts only, whereas one patient who underwent early second-look surgery had rhabdomyoblasts and a small amount of viable tumor. The indications for these surgical procedures are unclear. No patient in IRS-IV had a cystectomy, and all but one patient are alive with no evidence of disease (NED) (367).

Thus the trend over 25 years of consecutive IRS trials is for less surgical resection, using primary chemotherapy as the means for both local and systemic control. Occasionally, surgeons continue to perform vaginectomy and hysterectomy, but currently there is evidence that this is unnecessary except for relapsed disease. Confusion regarding the significance of maturing rhabdomyoblasts at second-look surgery may encourage these physicians to pursue more radical intervention. Heyn and others found evidence of cellular maturation in tumors of the bladder on chemotherapy (390). They hypothesized that given adequate time, tumor cells increased maturation after therapy will further mature and ultimately disappear. d'Amore and co-workers also

found maturation in biopsy specimens after just 6 weeks of chemotherapy (374). They concluded that chemotherapy of RMS tumors causes tumor-cell maturation that follows the pathways of normal muscle cell development. Others have observed no progression of disease when maturing tumor cells were found (368).

Some lessons from review of these patients include the following: (a) Biopsy and primary chemotherapy constitute the initial treatment of choice; (b) resection of organs (vaginectomy or hysterectomy) rarely is required for vaginal RMS; (c) limited vaginal wall resection is acceptable if the tumor can be removed without significant surgical injury; (d) lymph node dissection for vaginal RMS usually is unnecessary unless the nodes are clinically positive, in which case a biopsy should be performed; and (e) the presence of rhabdomyoblasts may be evidence of response to chemotherapy, and continuing chemotherapy without resection appears to provide adequate treatment.

Vulvar RMS presents as a firm nodule embedded in the labial folds, or it may be periclitoric in location. Vulvar lesions may have alveolar histology, but because most are localized, they also have a good prognosis.

Uterine RMS

Previous studies have suggested that uterine RMS represents a distinct group of patients who present at an older age and have less response to treatment and thus poorer prognosis compared with vaginal RMS (380,383). A review of IRS III and pilot IRS IV treated by primary chemotherapy and delayed resection, suggests that these previously held beliefs may not be true (371). Patients with uterine RMS in recent studies also may present as younger patients and respond well to chemotherapy. With a primary chemotherapy approach and conservative surgical therapy, it may be possible to salvage the uterus in selected patients much like in vaginal RMS (371).

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55

OFFICE PEDIATRIC UROLOGY

Steven J. Skoog

Hal C. Scherz

S.J. Skoog: Department of Surgery and Pediatrics, Oregon Health Sciences University, Portland, OR 97201.

H.C. Scherz: Department of Urology, Emory University; Division of Pediatric Urology, Georgia Urology, Children's Healthcare of Atlanta, Atlanta, GA 30322.

Contents

Most patients seen by a pediatric urologist begin their care in the office, which may be academic or private practice based, and either closely tied to a children's hospital or geographically separate. The purpose of this chapter is to present some basic aspects of current office practice in pediatric urology. Patient problems and the structural components of office practice will be discussed. The physical plant, office personnel, documentation, and record-keeping pertaining to pediatric urology will be presented along with the basics of Current Procedural Terminology (CPT) and International Classification of Diseases (ICD) coding in pediatric urologic billing. Particular attention is given to establish compliance with federal regulations. Patient demographics based on ICD-9 codes and procedural codes will be reviewed. These data will provide insight into the day-to-day clinical practice of pediatric urology and the variety of outpatient services provided. The clinical practice, such as procedures presently performed in the office (e.g., neonatal circumcision, lysis of adhesions, meatotomy), are discussed as well as essentials of the pediatric office laboratory.

The “back office” organization, including the examination rooms and personnel necessary to complete the patient's evaluation and treatment, and the role of the pediatric urology nurse and medical assistant will be reviewed. Special attention to “compliant” record-keeping and documentation is stressed.

Eighty percent of children seen in the office will not require an operation. Patient diagnoses in this nonoperative group include voiding dysfunction, hematuria, enuresis, urinary tract infection (UTI), genital problems in the male and female, and some forms of urolithiasis and hydronephrosis. An extensive exposition on singular conditions or diagnoses is not attempted because they are addressed in other portions of this text, but an office-based methodology to all aspects of the management of children with ambulatory urologic problems is provided.

Office Practice of Pediatric Urology

Patients are referred to the pediatric urologist by their general practitioner, family practice physician, and pediatrician, and as secondary referrals from other urologists. In both rural and urban practices, an increased number of referrals will be from physician extenders such as nurse practitioners and physician's assistants. The referral is often in the form of a consultation, with limitations on the number of visits and procedures that are approved before the visit. These potential limitations must be realized by the treating physician to prevent adding expense to the patient or the office and associated institutions. Unfortunately, this process may work in opposition to the delivery of appropriate care.

The common problems referred to the pediatric urologist are recorded in the literature (Table 55.1). In this author's office practice, the most common problems seen are voiding dysfunction, enuresis, UTIs and vesicoureteral reflux, penile anomalies, scrotal anomalies, and hydronephrosis. Many patients have more than one urologic complaint. This most commonly is observed in patients with voiding dysfunction, UTI, and/or vesicoureteral reflux. The initial urinary tract infection often leads to the discovery of voiding dysfunction and vesicoureteral reflux (105). Overall, 42% to 45% of the new patients seen were sent for evaluation of urinary infection, wetting and voiding dysfunction, and vesicoureteral reflux (Table 55.2).

	Kroovand, 1981	Rabinowitz, 1982	Skoog, 1999	Scherz, et al., 1999[a]
Total patients seen	2,395	1,574	1,483	11,356
New patients	682	533	524	5,684
Voiding dysfunction and or UTI	297	256	192	3,374
Hypospadias	102	71	62	1,457
UDT/hernia/hydroule	109	82	79	2,553
Meatal stenosis	34	32	20	542
Surgical cases	694 (29%)	330 (21%)	306 (21%)	3,075 (27%)

[a]Includes patients of six pediatric urologists.
UDT, undescended testes; UTI, urinary tract infection.

TABLE 55.1. PATIENT DEMOGRAPHICS

		New Patient Visits (1999)	
Category	ICD-9	Skoog (%)	Scherz et al. (%)
Voiding dysfunction and wetting	596.54, 596.59, 788.1, 788.30, 788.36, 788.37, 788.39	23	26
UTI/VUR	590.1, 595.9	22	16
Scrotal abnormality	464.4, 550.9, 752.51, 752.52, 788.6	15	22
Penile abnormality	605, 752.61, 752.62, 752.63, 752.64, 752.65, 753.6	19	22
Hydronephrosis	753.29	8	8
Other		13	6

ICD, International Classification of Diseases; UTI, urinary tract infection; VUR, vesicoureteral reflux.

TABLE 55.2. DIAGNOSIS OF NEW PATIENTS BY PERCENTAGE

Penile anomalies run the gamut, with the largest number of patients referred for preputial issues. Questions relating to circumcision or complications of circumcision, such as inadequate resection, penile adhesions, and meatal stenosis, are most common, followed by hypospadias and issues related to repair.

Scrotal abnormalities constitute 15% to 22% of new patient visits. The diagnosis of undescended testis predominates, followed by inguinal hernia, hydrocele, and varicocele. Hydronephrosis, usually diagnosed prenatally, constituted 8% of all new patients. The etiology of the hydronephrosis varied, but most commonly was associated with posterior urethral valves, ureteropelvic junction obstruction, duplication anomalies, and vesicoureteral reflux. Complex problems (i.e., the “other” category), including bladder exstrophy, cloacal exstrophy, multicystic kidney, renal agenesis, urachal anomalies, vaginal abnormalities, myelodysplasia, sacral agenesis, ambiguous genitalia, urogenital sinus, and imperforate anus, were least commonly seen.

THE PEDIATRIC UROLOGY OFFICE

Part of "55 - OFFICE PEDIATRIC UROLOGY "

The pediatric urologist's office serves several functions, the most important being a site of patient evaluation and care. Other activities will depend on whether the practice is university-based or a private practice. In the former, data entry and evaluation may be emphasized, whereas in the latter, business activities may predominate.

The personnel are selected with focus on the needs of children and their parents. The average pediatric urologist employs 3.7 full-time equivalents in the office. Group practices may be able to economize on scale. The staffing for most offices might be something as follows:

Front office:	Check-in
	Check-out
	Receptionist/phone
Back office:	Nurse
	Operating room (OR) scheduler
	Physician extender
	Transcriptionist
Business office:	Billing
	Collections
	Office manager

The actual number of employees in the office may differ dramatically in a university-based practice, where many of the aforementioned jobs will be performed centrally. In smaller private-practice offices, some of these jobs may be

combined by multitasking. In larger offices, other employees may perform specialized tasks that are not listed, such as information-technology specialists, research coordinators, managed-care specialists, and the like.

Successfully running a medical practice has become increasingly difficult—many factors contribute to this. Managed care typically is cited as the chief reason for the difficulty, and that may be true. The reimbursement given to physicians for the work that they do has decreased steadily over the past two decades. Furthermore, effort expended to collect these payments has dramatically increased; reasons for this include increased paper work and "red tape" required to see patients, perform tests, and schedule surgery. This bureaucracy results in delays and/or reimbursement denial. All result in inefficiency and increased overhead.

Issues that also weigh heavily on most practicing physicians include concerns with federal and state regulations involving medical practices, adequate record-keeping and documentation, and precise coding of office medical services to ensure proper reimbursement. Unfortunately, the list of non–patient-related issues continues to expand, which tends to increase overhead and reduce time available for patient care.

There are two important related strategies for dealing with some of these issues: time management and standardization. An electronic medical record (EMR) seems to be the key to both. The greater the ability to integrate all demographic information with clinical information, the greater the ability of the practice to defend against all of the impediments. Information is power when it is accurate and easily accessible, and it now is vital to the practicing physician.

Standardized forms are the basis of data capture and ensure practice uniformity. This enables consistent collection of demographic information about patients, as well as clinical, coding, and billing information. EMRs obviate the need for forms because the information can be entered directly. In addition, specialized information can be scanned into the medical record. Patient identification and medical history forms can be sent to patients before their appointments to expedite flow through the office.

When an EMR is not available, standardized history and physical forms may improve efficiency and facilitate thorough documentation of the office visit as required by Medicare, Medicaid, and insurance carriers (Forms 1 to 3, Appendix 1). Compliance with the Health Care Financing Administration (HCFA) regulations ensures that claims are filed properly and maximizes the potential for reimbursement. The level of service is dictated by the documentation of the history, physical examination, and decision-making process (i.e., the three elements of the encounter). Without the proper documentation, justification for an appropriate level of service cannot be made. Therefore it is important to be thoroughly familiar with the grids that determine the level of service for evaluation and management (E/M) codes. A sample grid, which should be posted to assist in proper coding, is shown in Forms 4 to 8 in Appendix 1 (127).

The *superbill* is the critical form in the office. It is found in almost every office and lists the commonly seen diagnoses (ICD-9) and CPT codes. It is extremely important that the codes are accurate and current and that they reflect the services rendered. The superbill can be modified to suit a particular practice, but it is critical that the physician has a clear understanding regarding proper coding of services provided. Office personnel may check for errors, but errors in coding most often occur when this task is delegated to someone other than the physician. When communication between the physician and billing personnel breaks down, the result is usually undercharging of the patient. Unfortunately, if overcoding occurs, the physician is liable. Inefficiency in billing is a lose–lose situation for the physician and the office. Modifiers can be used to more accurately code procedures that are unique (4). These two-digit codes are added to the five-digit CPT designation, which informs the payer that a unique service was rendered. Numerous modifiers should be understood by the practicing physician to ensure appropriate potential for reimbursement (Table 55.3).

22	Unusual procedural services Service provided is greater than that usually required for the listed procedure.
24	Unrelated E/M service by the same physician during a postoperative period For service that is unrelated to the original procedure
25	Significant, separately identifiable E/M by same physician on the same day of other service or procedure
50	Bilateral procedures
51	Multiple procedures
52	Reduced services
57	Decision for surgery An E/M service that resulted in the initial decision to perform surgery.
62	Two surgeons: 270-7

E/M, evaluation and management.

TABLE 55.3. COMMON CODING MODIFIERS USEFUL TO THE PEDIATRIC UROLOGIST

Patients often request more information and appreciate educational materials. These may take the form of disease- or problem-specific pamphlets, reprints of articles that the physician has written, key general references, or reference to websites containing more information (some practices are developing their own websites with such information). When surgery is planned, standardized information (e.g., pamphlets or even videotapes) can be very useful. This information can include preoperative and postoperative instructions and can be individualized to the anticipated procedure. Such information can save time and save some telephone calls, as well as ease parental anxiety with specifics of postoperative care and expectations.

Back Office and Equipment

Examination Room

The examination room must be appealing, friendly, and comfortable for the parents and patients. It needs to be warm, not hot or uncomfortable. Every effort must be made to make the child relaxed and comfortable in the examination-room setting. Children frequently are resistant to hospital examination gowns, and the child's parent or caregiver is the first person to enlist to help get the child into the appropriate attire.

Plenty of distractions, such as a chalkboard, in-room toys, puzzles, and books, will keep the child and his or her siblings at ease and occupied. Caregiver involvement in playful activities while the physician obtains measurements and vital signs aids patient confidence and promotes acquisition of accurate data, especially the blood pressure (BP). If the child is old enough, he or she can be kept at ease by allowing him or her to participate in the history taking and allowing contact between the parent and child, especially if the child is between 2 and 5 years of age. Many children will look forward to returning to a well-planned and well-equipped office, because going there previously was a “fun” experience.

The examination room itself should have an examination table with potential for lithotomy positioning. A bright light source adjacent to the table will allow illuminated perineal examination. This is a necessity when inspecting female patients for interlabial masses, urethral prolapse, urogenital sinus, and ectopic ureteral orifices. An x-ray viewing box and an erasable chalkboard should be placed in the room. These are both indispensable in showing parents the “hydronephrotic kidney,” or for drawing the duplication anomaly so that they can better understand their child's condition and how it can be corrected. A well-stocked cabinet should contain tape, K-Y Jelly, povidone-iodine (Betadine) swabs, alcohol swabs, cotton swabs, tongue blades, sterile urine cups, 4 × 4's, adhesive remover, and adhesive liquid. Adjacent to the examination room are a scale to weigh the patient, sphygmomanometer with appropriately sized cuffs, and a stadiometer to measure height. The nurse or medical attendant will record these results on the patient's records and growth chart as necessary.

Equipment

A dedicated minor-procedure room is ideal, because all equipment can be located there. A good light source, examination table, and cautery are essential. Commonly performed procedures are listed in Table 55.4 . Basic operating instruments include a “circumcision tray” with scissors, fine hemostats (both straight and curved), a needle holder, surgical-knife handle, probe and director, and Gomco clamps with all three diameters available (1.1, 1.3, and 1.45 cm). This tray will provide most of the equipment needed for the majority of in-office procedures (Fig. 55.1). The infant/child “papoose board” is effective and well-tolerated in the restraint of small infants. Either an electrocautery device or disposable battery cautery also should be available.

Catheterization	Meatotomy
Circumcision	Meatal dilation
Lysis of adhesions	
Penile	
Labial	

TABLE 55.4. OFFICE PROCEDURES

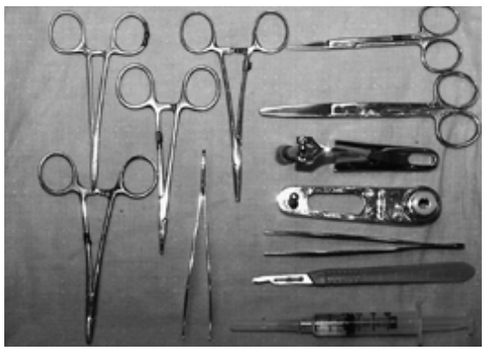

FIGURE 55.1. Basic in-office operative procedural tray.

Pain management is an extremely important aspect of office surgery. In general, topical anesthetics or locoregional nerve blocks (penile block) are used. For topical use, a cream containing lidocaine and prilocaine [eutectic mixture of local anesthetics (EMLA)] decreases the pain associated with a variety of minor procedures, such as lysis of adhesions and meatotomy (75). For topical analgesia to succeed, at least 1 hour must elapse between application and the time of the procedure. The analgesia may last 1 to 2 hours. Application of the EMLA cream under a Tegaderm transparent dressing keeps the cream in apposition to the operative site; the cream can be applied at home before the procedure. A single application of the cream is associated with few complications and has not been shown to cause clinically important methemoglobinemia in term neonates (56).

The two most commonly used local anesthetics for local regional penile blocks are lidocaine and bupivacaine, without epinephrine. The maximum dose of lidocaine is 4.5 mg/kg and for bupivacaine is 2.5 mg/kg. A ring block of local anesthetic placed into the skin at the base of the penis provides effective analgesia for circumcision (100), but does not necessarily provide analgesia for the glans. The classic dorsal penile nerve block (DPNB) with a subpubic injection under Buck's fascia provides effective total penile analgesia

but has the potential complications of bleeding, injury to the neurovascular bundle, and rarely, gangrene (60). *Epinephrine should not be used in any penile block.*

Patient catheterization to obtain a urine specimen or for teaching intermittent self-catheterization requires a supply of catheters available in the office. All catheters, gloves, and surgical stock supplies should be latex-free. The catheter assortment should include straight, coudé tipped, and Foley, and sizes from 3 to 16 Fr. Specialty catheters such as the hydrophilic “Lo-Fric” catheters also should be available. An assortment of small bougies from 6 to 12 Fr and meatal dilators can be used in a variety of clinical situations and sometimes obviate the need for surgical intervention for meatal stenosis.

In-office ultrasound for bladder-volume assessment is an absolute necessity. It can offer a noninvasive means of determining postvoid residuals and also can be used for behavior-modification teaching programs in children with voiding dysfunction. Formal in-office ultrasound is expensive and requires additional training. However, it can provide on-site evaluation of the kidneys and bladder, and is particularly useful in monitoring postoperative patients. Furthermore, patients with refractory day and/or nocturnal enuresis can be screened in the office for upper tract anomalies and effective bladder emptying. With special probes, the testes can be evaluated for size and lesions (185).

Urodynamic equipment varies considerably in its cost, complexity, and utilization. In a university-based practice, the equipment is integrated with the fluoroscopy unit in radiology. Complex cystometrograms with intraabdominal pressure manometry, electromyography (EMG), and voiding cystourethrography are recorded and monitored simultaneously. In this author's office space, a uroflowmetry measurement is available with remote monitoring so urination can be completed in an unobtrusive manner. In sensate patients, sedation may be necessary for complex studies. Consequently, complex urodynamics may be difficult to perform in an outside office setting unless a specific center for pediatric assessment (pediatric continence center) is established. This type of center can offer full urodynamic testing and biofeedback and behavior modification treatment of incontinence and voiding dysfunction (109).

The pediatric office laboratory is focused primarily on urine evaluation. The typical laboratory consists of a centrifuge, microscope, refrigerator, and urinalysis multisticks. The standard analysis includes pH, protein, blood, nitrites, leukocyte esterase, glucose, and specific gravity and sediment analysis for white blood cells (WBCs), red blood cells (RBCs), casts, crystals, and bacteria. All results are recorded in the patient's office record. Subsequent cultures may be performed in a central laboratory or the office. The federal government has provided clinical laboratory improvement amendments (CLIA), which regulate laboratory testing. A specific current list of provider-performed microscopic (PPM) procedures is available at www.phppo.cdc.gov/dis/clia/ppm.asp.

Medications are administered in the office setting by the physician and/or nurse. Testosterone injections to stimulate penile growth before hypospadias or epispadias repair occasionally are necessary. Testosterone cypionate 40 to 50 mg/m^2 given 2 and 5 weeks before surgery has been used (63). Pediatric dosage for transdermal testosterone is unavailable. Human chorionic gonadotropin (hCG) in various dosage schemes is used in patients with cryptorchidism (132). Sequential intramuscular (IM) administration is necessary. IM or intravenous (IV) antibiotics are administered to children at risk for infection at the time of tube removal or office procedures.

Minor Surgical Procedures

Most office procedures, such as circumcision, lysis of adhesions, and meatotomy, do not require general anesthesia. If a local regional anesthetic or topical anesthetic are judged inadequate after discussion with the patient's parents, the patient is better served in a formal outpatient operating-room setting.

Newborn Circumcision

Contraindications to circumcision include any penile abnormality. This includes hypospadias, epispadias, chordee, megalourethra, and webbed penis. A history of bleeding diathesis or recent acute illness precludes office circumcision.

The four guiding principles in the performance of circumcision include aseptic technique, removal of an appropriate amount of inner and outer preputial skin, hemostasis, and cosmesis.

All neonates undergoing circumcision experience pain from the procedure. Neuroanatomic components and neuroendocrine systems are sufficiently developed to allow transmission of painful stimuli in the neonate. A lack of behavioral responses (including crying and movement) does not necessarily indicate a lack of pain (5). Preterm and term infants demonstrate similar or exaggerated physiologic and hormonal responses to pain compared with those observed in older children and adults (30). Consequently, all patients undergoing penile procedures require an anesthetic. In studies comparing EMLA with locoregional nerve block, the nerve block was superior to EMLA as measured by changes in physiologic and behavioral monitors. Dorsal penile nerve block or penile ring block is preferred (100).

The infant is restrained on a papoose board, which inhibits movements of the extremities. His genital area is scrubbed with a warm Betadine scrub and painted with Betadine solution. The area is draped in a sterile fashion. A bilateral dorsal penile nerve block is performed by injection of a small amount of lidocaine or bupivacaine laterally

beneath Buck's fascia; alternatively, a ring block at the base of the penis is performed. At least 10 minutes should be allowed for anesthetic set-up.

The circumcision is performed with one of three devices: the Gomco, Plastibell, or Mogen clamps (Fig. 55.2). The Mogen clamp should be used only by individuals experienced with its use; it can result in serious injury to the glans penis. All of these devices rely on compression for hemostasis. The first step is to release the inner preputial skin from the glans penis. Failure to perform this simple task will leave too much inner preputial skin or remove too much skin from the shaft of the penis. On most occasions, a dorsal slit of the preputial skin is necessary for placement of the bell after takedown of the inner preputial skin adhesions. The surgeon must ensure that the inner skin is retracted proximal to the coronal sulcus.

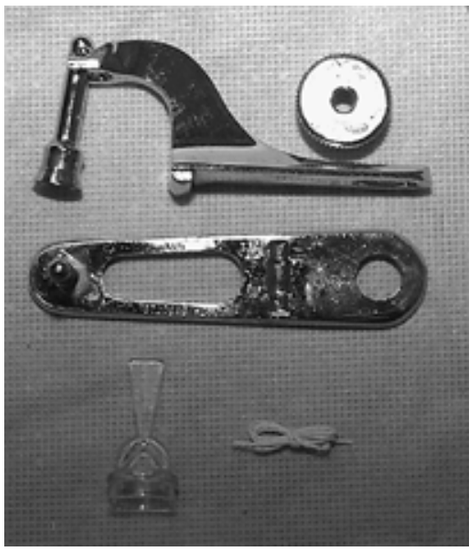

FIGURE 55.2. Gomco clamp *(top)* and Plastibell clamp *(bottom).*

At this time, the appropriate-size Plastibell clamp is positioned over the glans penis. A suture is tied over the ring to compress the skin edges. The distal prepuce is excised. The ring remains in place for 5 to 7 days as the edges heal. Using a ring that is too small should be avoided because it will compress the glans and lead to ischemia. If a Gomco clamp is used, the appropriate-sized bell is positioned over the glans penis. The bell over the glans penis is positioned in the clamp, and the prepuce to be excised is pulled distally through the hole in the clamp. Care is taken to ensure that an equal amount of inner and outer preputial skin is clamped onto the bell. The clamp is tightened and the prepuce distal to the clamp is excised. *Never excise with electrocautery with a metal bell in place* (124). The crushing of the vessels between the clamp and bell provides hemostasis. It is important to leave the tissue clamped for 5 to 7 minutes. The most common problem immediately seen with the compressive devices is bleeding. Use of cautery, direct pressure, or suture ligation usually is successful. Other methods include topical thrombin, Gelfoam, dilute epinephrine sponges (1:10,000), and silver nitrate.

The overall complication rate is 0.2% to 5% for neonatal circumcision. Complications range from simple bleeding to Fournier's gangrene. In a large series of patients, Gee and Ansell noted the Plastibell to have a higher rate of infectious complications than Gomco circumcision (65). Bleeding complications are similar between the two methods. Wound separation is more common with a Gomco clamp (41,62,65).

Lysis of Adhesions

Penis.

Penile adhesions are of two varieties: those resulting from inadequate takedown of the inner preputial skin at circumcision, and the dense attachment of penile shaft skin to the coronal sulcus or glans penis (Fig. 55.3). The latter is caused by a skin bridge between the crushed shaft skin and the denuded corona or glans penis. It can be prevented by retraction of the shaft skin following neonatal circumcision. Problems arise resulting from the accumulation of smegma under the bridge and infection.

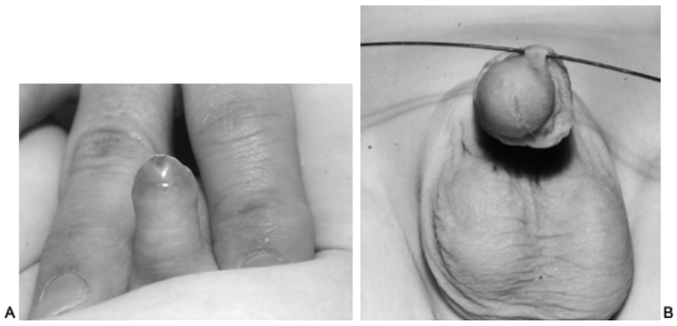

FIGURE 55.3. A: Loose penile adhesion. **B:** Dense penile adhesion.

In the office, EMLA cream is applied to the penis under a Tegaderm occlusive dressing. It is left in place for 60 minutes. The filmy adhesion caused by previous inadequate lysis can be pushed back easily with a gauze or gentle blunt dissection. The “thick” skin bridge requires a good aseptic cleansing followed by application of a hemostat across the bridge. If pain is noted, a local injection of lidocaine is necessary. The clamp is removed and the skin bridge is incised with scissors. An absorbable suture on the shaft and coronal sulcus may be necessary. Topical bacitracin ointment is applied until healing has occurred.

Labia.

Labial adhesions are estimated to occur in 0.6% to 3.0% of prepubertal girls. The peak incidence is at 13 to 23 months of age (103). The cause of labial adhesions is not known, but probably is related to low estrogen levels in prepubertal children. Local irritation results in a denuded labia minora edge. Contact between the edges result in reepithelialization and midline fusion.

Children with labial adhesions usually are asymptomatic, but many have dysuria, UTIs, or recurrent vulva or vaginal infections (102,164). Urinary retention rarely has been present. Labial adhesions can be a result of sexual abuse. This should be considered when treating a child with this condition (92,108,117).

Topical treatment with conjugated estrogen has been the mainstay of therapy, with a success rate of up to 88% (7). Conjugated estrogen (Premarin) vaginal cream 1% applied to the area of adhesion with a cotton swab and gentle pressure twice daily for 2 to 4 weeks usually results in separation. Slight vulvar pigmentation and increased vascularity

will be noted. Topical treatment should not exceed 8 weeks.

When symptoms persist and topical estrogen therapy does not work, surgical lysis of adhesions is indicated. Topical application of EMLA cream under a Tegaderm transparent dressing provides adequate local anesthesia (75). The diaphanous adhesion usually is separated easily with a moistened cotton swab or sterile probe with midline pressure. The thicker, nontransparent adhesion may require a hemostat to spread the adhesion. Postoperatively, the application of conjugated estrogen cream to the perineum with a cotton applicator twice a day for 1 week will allow reepithelialization of the edges of the labia without refusion in the midline.

Meatotomy

Meatal stenosis is the most common long-term complication of circumcision (30). It likely results from recurring meatitis with epithelial loss at the meatal edge and side-to-side adherence. A pinpoint meatus develops, which deflects the urinary stream dorsally and can cause dysuria or blood spotting in the underwear (Fig. 55.4).

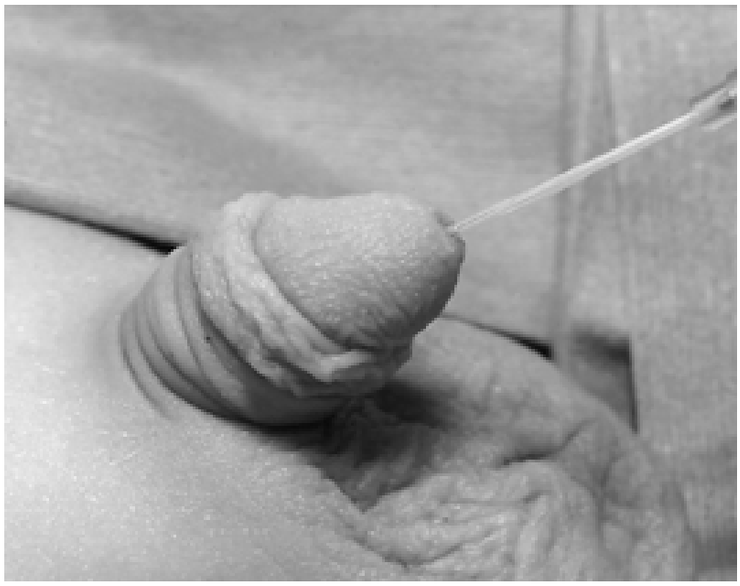

FIGURE 55.4. Meatal stenosis with only a 24-gauge intracatheter able to enter the meatus.

Office meatotomy using EMLA cream has proved to be effective, simple, and cost-effective (26,157). The cream is applied generously to the glans penis and held in place with an occlusive transparent membrane (Tegaderm). The patient remains quiet for 60 minutes as the local anesthetic takes effect. Home application may streamline this process. After the dressing is removed, a prong of a straight hemostat is placed within the urethral lumen on its ventral surface and an appropriate amount of tissue is clamped in the hemostat. The clamp is left in place for 1 minute then released. The crushed tissue is cut with sharp scissors. It usually is not necessary to use any other form of hemostasis. A small amount of antibiotic ointment is applied to the edges of the meatus; this application is repeated at least twice a day for 1 week after surgery.

History and Physical Examination: General Principles

In spite of all the technologic advances in medicine, a well-performed history and physical examination remain the clinician's most important tools. The physician's initial

entry into the examination room sets the stage for the encounter. Knowledge of the patient's name and a cordial greeting to the parents and/or caregivers will alleviate some of the tension of a first visit. The clinician should take the time to preview available patient information. An obviously informed physician instills confidence in the patient and family.

History

An older child should participate in the interview process. The clinician should listen carefully to the parent because they usually provide the information that is critical to making an accurate diagnosis. In the younger patient prenatal history, including the results of antenatal ultrasound studies, should be addressed. The birth history and possible complications should be elicited. The results of the postnatal physical examination may provide clues in patients with cryptorchidism, hernias, hydroceles, and neonatal torsion. Family history of genitourinary abnormalities is important because many of the encountered abnormalities are inherited. This is particularly true in hypospadias, renal disease, cryptorchidism, and vesicoureteral reflux (24). Before the patient's visit, screening of relevant medical records and imaging studies will direct the subsequent interview and imaging needed in the patient's evaluation.

Physical Examination

Skilled physicians begin their observations of physical characteristics, dexterity, coordination, and mental aptitude during the interview. An active child climbing over the examination table or hiding under the sink demonstrates normal coordination and gross motor ability. The patient's interactions with surrounding objects and people, response to sounds, and speech pattern give clues about mental development. The age of the child dictates the different techniques to employ to gain patient cooperation. For infants and toddlers, a parent should be close at hand or holding the child, which will provide a comfortable setting for evaluation. Toys, picture books, or food will distract a 2- to 4-year old. Asking the patient's mother for advice is invaluable. Patients who have had previous poor experiences in the physician's office offer the greatest challenge. This situation is common in patients with voiding dysfunction, urinary infections, and ambiguous genitalia. Undue or inappropriate acting out may be a sign of significant psychosocial stress or personality disorder and should be recognized before examination. In severe cases, several visits may be necessary before physical examination is possible. The physician should ask the child's permission and be gentle.

Standard measurements of height, weight, pulse, and BP should be taken. Patients who will be followed for a lifetime (e.g., for exstrophy or posterior urethral valves) should have their growth and weight charted on standardized growth charts. This allows assessment of normal development. Pulse varies with age; up to 3 months, the range is 90 to 200 beats per minute; from 3 months to 2 years of age, it is 100 to 190 beats per minute; from 2 years to 10 years of age, pulse ranges from 60 to 140 beats per minute; and older than 10 years of age, from 60 to 100 beats per minute (169). A heart rate that is higher than normal may indicate primary cardiac disease, an underlying systemic or metabolic disorder, infectious disease, or fever. The BP is an important measurement because a variety of abnormalities treated by the pediatric urologist may be the cause of hypertension. A normal BP is defined as systolic and diastolic BP below the ninetieth percentile for age and sex. Hypertension is defined as average systolic or diastolic BP greater than or equal to the ninety-fifth percentile for age and sex measured on at least three separate occasions. The keys to accurate BP measurement are proper cuff size; a controlled environment; and a resting, quiet patient. The age- and sex-related normal values, as well as specific recommendations for the measurement of BP, are published in the National Institutes of Health (NIH) publication no. 96-3790 (171).

The general physical examination and single organ system examinations must have specific content documented in the medical record. This documentation allows for compliance with billing of evaluation and management services. The highest level of a physical examination is the comprehensive examination, defined as a general multisystem examination or a complete examination of a single organ system. (The elements of the genitourinary system are listed in Appendix 2 .) Unfortunately, this examination is geared toward adults and not children; however, it provides the government's view of appropriate content.

The skin should be inspected for color, turgor, lesions, masses, and defects. Essentially all lesions originating in the skin of children are benign. A mass that moves freely over the underlying fascia is likely benign. A lesion fixed to the underlying tissues is possibly malignant and requires appropriate referral. Pigmented lesions of interest to the pediatric urologist are hypopigmented ash-leaf spots seen with tuberous sclerosis. Light-brown macular lesions (café au lait spots) greater than 10 cm in size or more than five in number are consistent with neurofibromatosis. Diffuse neonatal hemangiomas with cutaneous and visceral lesions may result in urinary tract bleeding (79). Perineal genital condylomata or herpetic lesions should alert the examiner to possible sexual abuse.

Low-set ears, where the superior rim of the pinnae is below a line drawn posteriorly from the superior orbital rims, may be associated with renal anomalies.

Breast examination is important in precocious puberty and normal sexual development. Up to age 8, there is no discernible difference between boys and girls in size and shape of the nipples and the chest wall. In early adolescence, a tender subareolar nodule develops in boys and girls. In males, this can be the precursor of adolescent male gynecomastia.

Gynecomastia can result from adrenal and gonadal lesions as well as renal disease (55). In females, the mean age for the start of breast development is 8.5 to 10 years of age (70).

Examination of the chest and heart is performed to ensure absence of acute respiratory illnesses or signs of congenital heart disease such as gallops, extra heart sounds, or murmurs.

Abdominal examination is an integral aspect of the genitourinary evaluation. The abdomen is observed for laxity as seen in prune-belly syndrome and cutis laxa. Umbilical abnormalities include hernias, masses, or drainage. In the neonate, drainage from the umbilicus may be a result of a patent urachus, omphalomesenteric duct, or urachal sinus. Auscultation allows assessment of bowel activity and bruits. Palpation for organ enlargement, masses, kidneys, costovertebral angle tenderness, and location of the bladder should be performed. The back should be inspected for occult midline spinal lesions as lipomas, hairy patches, dermal sinus, or signs of spina bifida occulta. Flattened buttocks with shortened gluteal cleft is indicative of sacral malformation or agenesis. Having the patient stand, bend at the waist, and touch his or her toes allows detection of scoliosis.

Genitourinary examination requires a cooperative, trusting patient. The male patient, especially the adolescent, should be examined supine and upright to detect varicoceles. The penis should be inspected and prepuce retracted, if possible, to expose the meatus. The prepuce is fully retractable in 90% of 5-year-old boys (34). The location and size of the meatus is noted. The meatal size may be difficult to assess, and the ability to gently evert mucosa at the meatal edge suggests normal anatomy. Observing the patient void can be critical to the assessment of meatal anatomy. The location of the meatus and urethra should be noted clearly, as well as the location of the median raphe along the shaft of the penis and completeness of the prepuce. The stretched length of the penis and its width are measured in cases of ambiguity or microphallus. Standards for penile length based on gestational age are established (44).

The scrotum and its contents should be inspected and palpated. Scrotal development and degree of rugation is noted. Palpation of each scrotal half between the thumb and index finger with occlusion of the internal ring will assist in testicular palpation. The location of each testis, its size, and consistency is recorded. The Prader orchidometer, a series of comparative ovoids, is used to measure testicular size, especially if a size difference is noted on palpation (ultrasound also can be used to obtain testicular measurement, particularly in the patient with a hydrocele). A ballotable mass should be transilluminated and assessed for communication of the fluid with the abdominal cavity. Hernias and communicating hydroceles should be reducible, whereas hydroceles do not decompress easily. Infants and children can be examined in the squatting or knee–chest position to enhance scrotal and testicular evaluation.

Genitourinary examination of young girls is accomplished with the patient in the supine position and the legs in the froglike position. Gentle separation of the labia majora will expose the introital anatomy. The size of the clitoris is noted, as well as the location of the urethral meatus and the hymenal ring. Labial adhesions prevent visualization of these structures. A bifid clitoris suggests female epispadias. Occasionally, an ectopic ureteral orifice will be seen leaking clear urine near the urethral meatus or from the vagina. Anatomy of the hymen should be established. The location of any interlabial mass and its characteristics are noted. A lesion exiting the meatus may be urethral prolapse, urethral caruncle, a protruding ectopic ureterocele, inclusion cyst, or sarcoma botryoides. Vaginal masses include imperforate hymen, Gartner's duct cyst, vaginal cysts, and sarcoma botryoides.

PROBLEM SOLVING

Part of "55 - OFFICE PEDIATRIC UROLOGY "

Hematuria

Hematuria can be described as asymptomatic microscopic hematuria, symptomatic microscopic hematuria, gross (macroscopic) hematuria, blood spotting on diapers or underwear, and traumatic hematuria (which is discussed in other parts of this text). The clinical approach to each is different.

Asymptomatic Microscopic Hematuria

The source of hematuria in children is most often the kidney (28). It usually is found incidentally during a school or sports physical examination. The definition of microscopic hematuria is more than five RBCs per high-power field on a centrifuged specimen, and it is preferred that two subsequent urinalyses show the same results.

Frequently, the hematuria is detected by dipstick analysis for hemoglobin on the basis of a pseudoperoxidase reaction. This methodology is very sensitive and can detect insignificant hematuria. False-positive results can be caused by the presence of other oxidizing agents in the urine. Free hemoglobin and myoglobin also are detected. Therefore the positive dipstick finding requires microscopy to confirm the presence of erythrocytes (31). Furthermore, microscopy offers other information that may lead to a specific diagnosis, including WBCs, casts, epithelial cells, bacteria, and crystals.

Once the presence of hematuria has been documented, its source is sought. In general, if the microscopic hematuria is associated with proteinuria, cellular casts, and brown-tea discoloration of the urine, a glomerular origin is likely (122). Phase-contrast microscopy can be used to

distinguish glomerular from nonglomerular bleeding based on finding dysmorphic RBCs (139).

Children with asymptomatic microscopic hematuria have been studied longitudinally in two large population studies. These studies suggest that (a) if three samples are required to demonstrate the hematuria, the prevalence falls from 4.0% to less than 0.5%; (b) of those children with three positive samples, only 37% had hematuria 1 year later, and 7.6% had it 5 years later; (c) significant renal disease was almost nonexistent when microscopic hematuria was the only abnormality found (48,174). Based on the natural history described, the first step is to repeat the urinalysis to confirm the finding and follow the child with repetitive examinations to detect new, if any, signs and symptoms. With persistent microhematuria, one should exclude idiopathic hypercalciuria, especially if a family history of nephrolithiasis is present. A random urine for a calcium-to-creatinine ratio is recommended (162). The other entity that needs to be addressed is familial or hereditary hematuria, because it can present with microscopic hematuria without proteinuria. This can be assessed by dipping the urine of family members and, if positive, confirming with microscopy (16,142).

If the patient has microscopic hematuria combined with proteinuria, he or she is more likely to have significant renal disease. Microscopic hematuria does not cause proteinuria. The presence of proteinuria strongly suggests a renal glomerular origin of the hematuria. The amount of protein excreted is quantified by either determining the ratio of protein to creatinine in a random sample or quantification in a timed urine collection. The significance of renal involvement is, in most cases, proportional to the degree of proteinuria (46). These patients benefit by referral to a pediatric nephrologist.

Symptomatic Microscopic Hematuria

Children with symptomatic microscopic hematuria present with signs or symptoms of systemic or renal/urologic disease and their urine contains RBCs. The clinical manifestation may be general (e.g., fever, malaise, pain, hypertension), unrelated specifically to the urinary tract [e.g., rash, arthritis, gastrointestinal (GI)], or urinary tract specific (e.g., dysuria, urgency, frequency, enuresis, flank pain). The role of the pediatric urologist is to exclude anatomic, structural, and functional causes of the patient's symptoms and hematuria.

The history and physical examination provide important information to direct the urologic evaluation. Dysuria, urgency, frequency, and enuresis suggest an inflammatory process. Stranguria, intermittency of the urinary stream, and dribbling urination suggest an obstructive process. Flank pain may indicate a stone, ureteropelvic junction obstruction, or symptomatic vesicoureteral reflux. A history of recent upper respiratory infection followed within a few days by hematuria suggests a renal parenchymal cause, such as immunoglobulin A (IgA) nephropathy. A family history of renal disease, renal cysts, nephrolithiasis, deafness, and sickle cell disease may suggest a cause in the child. A history of recent athletic endeavors may indicate exercise hematuria related to distance running and strenuous workouts. Avoiding the activity for 48 to 72 hours usually will solve the problem, and further work-up is unnecessary (119).

Physical examination should include a well-taken BP, because hypertension is a frequent finding in glomerulonephritis and tubulointerstitial disorders. The skin should be evaluated for rashes, a frequent finding in Henoch-Schönlein purpura and systemic lupus erythematosus. The abdomen should be inspected for flank masses and a palpable bladder. The urethral meatus needs to be assessed for obstructive lesions and, in the female, the vaginal introitus evaluated for masses.

Gross Hematuria

Gross hematuria is alarming to the child and the parent. Initial gross hematuria suggests a urethral origin, whereas total hematuria implies a more proximal origin. Trying to distinguish bright-red bleeding from tea-colored urine is important, because it suggests a different origin as its cause. The most common cause will be a UTI, which is suggested by the finding of pyuria and bacteriuria. As mentioned previously, the history and physical examination will direct the subsequent evaluation, because the differential diagnosis will not change from the symptomatic patient with microscopic hematuria. This includes bleeding of glomerular, nonglomerular, urinary tract, and systemic origins.

Urethrorrhagia

Blood spotting the underwear of prepubertal boys, also known as *idiopathic urethritis,* is associated with dysuria and the finding of microscopic hematuria on urinalysis. The condition is self-limited and has a benign course (120). If the urine culture is normal and the patient has a normal history and physical examination, no further evaluation is necessary.

The etiology of the “urethritis” remains obscure. Urine cultures for bacteria, mycoplasma, and chlamydia have been negative (59). Reiter's syndrome should be considered in those boys with arthritis or conjunctivitis (86). In patients who underwent cystoscopy, a circumferential inflammation was found in the bulbar urethra, which may be associated with a “stricture.” The stricture has been attributed to the trauma induced by dilation and endoscopy (47).

The course of the disease is variable and often protracted. Dysuria and spotting lasting up to 3 years or more is seen in 39% of patients (43). Most patients have resolution of their symptoms as puberty progresses, which has suggested that the prepubertal hormonal milieu combined with an inflammatory source is the etiology of this obscure condition (47). In general, the symptoms are specific, and caring observation is the best treatment. Cystoscopy and voiding cystourethrograms

have been of low yield unless a stricture is suspected. Antibiotics are not useful, because cultures are normal.

Evaluation

The evaluation is tailored to the individual patient and the type of hematuria. In patients with asymptomatic microscopic hematuria, repetitive urinalyses, calcium-to-creatinine ratio, and family screening for hematuria is all that is necessary. Follow-up examination to exclude changes in history, physical findings, and urinalysis findings are essential. Screening of the urinary tract with ultrasound and/or voiding cystourethrography is not necessary if the child remains asymptomatic.

Patients with symptomatic microscopic hematuria and gross hematuria should have a urine culture performed and, if it is normal, a renal and bladder ultrasound with prevoid and postvoid bladder assessment is needed. This will exclude masses, hydronephrosis, and other structural causes of hematuria. Bladder emptying ensures a functional normal lower urinary tract. The urine should be sent for a calcium-to-creatinine ratio. Hypercalciuria is the most frequent cause of noninfectious, nonglomerular hematuria in Caucasian children (161,163). Approximately 30% of children whose hematuria is isolated will be hypercalciuric. Hypercalciuria can be associated with episodic gross hematuria in the absence of demonstrable renal calculi. The mechanism of bleeding probably is irritation or damage to the renal tubule by calcium crystals.

A calcium-to-creatinine ratio of more than 0.21 is indicative of hypercalciuria. If the ratio is elevated, a 24-hour urine collection for quantitative measurement of calcium should be performed. Calcium excretion of more than 4 mg/kg per day should be treated with hydration and a low-sodium diet. Hydrochlorothiazide may be necessary if initial treatment does not lower urinary calcium (135).

If the urinalysis demonstrates red cell casts or more than 5% dysmorphic RBCs, laboratory measurement should include complete blood count (CBC) with platelet counts, serum electrolytes, creatinine, blood urea nitrogen (BUN), ASO titer, C_3,C_4, antinuclear antibodies (ANA), and sickle cell screen in selected patients. If total serum protein and albumin globular ratios are evaluated, referral to a pediatric nephrologist is appropriate (120).

Those patients who have a positive urine culture will need a voiding cystourethrogram (VCUG) following a course of antibiotics. A VCUG will be necessary in those patients with abnormal screening ultrasounds, gross hematuria, or symptoms suggestive of obstruction. If a stone is suspected, a flat plate of the abdomen followed by spiral computed tomography (CT) is indicated. The results of the sonogram and VCUG will determine the need for subsequent imaging studies such as CT scans, nuclear scans, and magnetic resonance imaging (MRI).

Cystoscopy is not indicated in the evaluation of asymptomatic microscopic hematuria (59). Children with symptomatic microscopic hematuria, but normal renal ultrasound, intravenous pyelography (IVP), and VCUG, usually do not require cystoscopy. Patients with gross hematuria that persists or symptoms suggestive of lower urinary tract abnormalities undergo cystoscopy that usually confirms the normal imaging studies. Infrequently, a bladder lesion, bladder hemangioma, bulbar stricture, or urethral polyp will be recognized. In general, cystoscopy must be tailored to the individual patient based on interpretation of his or her history, physical examination, and imaging and laboratory findings. Cystoscopy ideally would be performed at a time of bleeding.

The well-performed history and physical examination guide the investigation of hematuria. This investigation should never be allowed to pose a greater risk to the child than does the problem itself. Consequently, cystoscopy, angiography, and renal biopsy rarely, but selectively, are performed. The urinalysis with microscopic examination of the urinary sediment is the cornerstone of the evaluation process. Red cell casts are the hallmark of glomerulonephritis and obviate further urologic evaluation. Subsequent imaging is specific to the individual patient's needs.

Urinary Tract Infection

Patients sent for evaluation of UTIs constitute 15% to 22% of all patient referrals (Table 55.2). Most of these patients are on antibiotics or have finished antibiotics for their acute infection. They often have poor documentation of the UTI, have not been imaged, and may have suffered more than one infection. It is important to obtain all documentation of the urinary infection and any imaging studies before the visit.

Patients frequently are referred based on symptoms alone, which may be unreliable in establishing the diagnosis of true infection (21). Frequency, urgency, dysuria, and enuresis may be caused by vulvitis, urethritis, or dysfunctional voiding, for example. Usually, urine samples obtained in the primary care physician's office are from a “bag” specimen or voided urine, and subsequent diagnosis of a UTI is based on an enzymatic assessment of leukocyte esterase and nitrite. When both tests are positive, they have a sensitivity of 78% to 92% and a specificity of 60% to 98% of predicting a UTI (125). Unfortunately, not all of these urines are sent for culture. The potential for contamination with bag urine collections due to preputial, vaginal, and/or stool is high. Midstream-voided samples in older girls, circumcised boys, and boys with retractable foreskins are fairly reliable for culture; however, these same specimens from young girls and uncircumcised boys may reflect periurethral and preputial skin bacterial colonization. When cultures are difficult to interpret, especially in the setting of voiding dysfunction and incontinence, reliable specimens obtained by catheterization or suprapubic aspiration are

necessary to proceed with appropriate evaluation and management. A diagnosis of significant bacteriuria from a voided specimen is defined as greater than 10^5 colony-forming units (CFU)/mL (87). Colony counts of less than 10^4 CFU/mL in children may be significant, regardless of the method used in collection.

Once the diagnosis of a significant UTI is ascertained, it is important to establish whether it represents a first infection or recurrence. Reinfection with the same organism may be a result of inadequate treatment, acquired bacterial resistance, or an unrecognized anatomic site of persistent infection (e.g., stone). Most recurrent infections represent a reinfection with or without the same organism.

The natural history of UTIs predicts that 25% of patients will suffer a second infection within 1 year; the risk increases as the number of documented infections increases so that after three infections the risk is 75% (179). In school-aged girls, recurrence of UTI within 18 months was 80% for Caucasian girls and 60% for African American girls (98). The risk of recurrent infection in infant males is related to preputial bacterial colonization, which is highest immediately after birth and decreases after 6 months. This explains the tenfold increased incidence of UTI in uncircumcised versus circumcised boys. The added risk for UTIs in uncircumcised boys persists until age 5 (17). Periurethral colonization in female infants is associated with a 0.57% incidence of UTIs (152). The risks for increased colonization in older children is unclear but likely is related to the presence of certain blood group antigens on uroepithelial cells that serve as bacterial receptors and allow bacterial adherence, colonization, and subsequent UTI (85).

In children with asymptomatic infections, the majority will have normal radiologic studies (82,110). Twenty-five percent of children with renal scarring have normal VCUGs (82). Twenty-five to fifty percent of children with culture-documented UTIs will have vesicoureteral reflux, whereas only 0.4% to 1.8% of children without UTIs have vesicoureteral reflux (152). When carefully interviewed, children with “covert” or asymptomatic bacteriuria frequently have lower urinary tract symptoms such as enuresis or urgency, and 20% have a history of previous UTI. Approximately 50% of these children will have normal urinary tract imaging (154).

Evaluation

It is important to discover if the patient had previously undiagnosed infections. Mothers are quick to remember if a fever was “poorly explained” by an upper respiratory infection or the flu, which may have prompted use of an antibiotic and masked the diagnosis of a UTI. A detailed bowel and bladder history to discern voiding dysfunction and constipation are critical. An “elimination diary” (Table 55.5) kept for a few days before the appointment will greatly facilitate identifying these children. Most children between 3 and 12 years old void five to six times per day and have a bowel movement each day (14). The age at toilet training and problems encountered need to be elicited. Toilet training ages range from 9 months to 5 years, with a mean of 2.4 years (14). A family history of recurrent UTIs and vesicoureteral reflux are conditions with strong heredity implications for the patient.

Date				
Time	Day 1	Day 2	Day 3	Day 4
7 AM				
8 AM				
9 AM				
10 AM				
11 AM				
12 AM				
1 PM				
2 PM				
3 PM				
4 PM				
5 PM				
6 PM				
7 PM				
8 PM				
9 PM				
10 PM				
11 PM				
12 PM				
Overnight				

Codes: BM = bowel movement or “poop”
I = wet panties or underwear
II = wet outside clothes
P = urinate or void or pee
S = poop in underwear
WB = wet bed

TABLE 55.5. VOIDING LOG

The physical examination of children with UTIs should include palpation of the abdomen for masses, bladder distention, or fecal impaction. The meatus should be examined to rule out stenosis. The circumcision status should be noted. In the female, important findings of vulvovaginitis and labial adhesions predispose the patient to perineal colonization and potential contamination of voided urine specimens. The spine should be inspected for signs of occult dysmorphism. A rectal examination needs to be performed if constipation or encopresis is present.

All children 5 years of age or younger with a culture-documented UTI should undergo imaging of their urinary tract (144). Prepubertal males with symptomatic infections and older females with recurrent or febrile UTIs should be imaged. Evaluation should identify those patients at risk for

renal damage or conditions that predispose to recurrent infections.

Initial studies should include a renal bladder ultrasound and a VCUG. In the office setting, the acute infection has likely been treated. The VCUG can be performed as soon as the urine is sterile. It does not require a delay of 4 to 6 weeks after the infection (128). The sonogram evaluates renal size, hydronephrosis, masses, and duplication anomalies. A prevoid and postvoid bladder volume measurement assesses bladder emptying. A significant renal size discrepancy on ultrasound or low-grade hydronephrosis can be associated with vesicoureteral reflux. In girls, either a contrast or isotope cystogram may be obtained. In boys, a contrast study is necessary to visualize the urethra. In general, an initial contrast VCUG will provide anatomic information and grade of vesicoureteral reflux if present. The VCUG is evaluated for capacity and emptying. The volume instilled is compared with estimated bladder capacity. This will provide information concerning voiding dysfunction.

Any subsequent imaging is dictated by the finding of the VCUG and sonogram. Children with higher grades of vesicoureteral reflux should have a dimercaptosuccinic acid (DMSA) scan to evaluate for renal scarring (165). The presence of hydronephrosis and/or hydroureter requires assessment by a mercapto acetyl triglycine (MAG-3) renal furosemide (Lasix) scan. In children with a normal VCUG and ultrasound, there is no indication for cystoscopy.

Management

Acute infections encountered in the office are classified as complicated or uncomplicated. Uncomplicated UTIs include cystitis, recurrent UTIs, and asymptomatic bacteriuria. Complicated UTIs include structural abnormalities, pyelonephritis, and operatively reconstructed patients.

If an infection is diagnosed in a neonate or ill infant, hospitalization for parenteral broad-spectrum antibiotics is recommended. These agents include an aminoglycoside plus ampicillin or a cephalosporin, or a third-generation cephalosporin such as ceftriaxone (Table 55.6). Treatment of acute infections depends on the child's age and severity of symptoms. Regardless of age, if the child is acutely ill with fever, pain, and poor hydration, or infected with a highly resistant organism, parenteral antibiotics are indicated and hospitalization is needed. The duration of parenteral therapy is guided by the clinical course of the child. Generally, it is continued until the patient is afebrile for 24 to 48 hours (4a).

Antimicrobial	Dosage	Interval
Antibiotics for Parenteral Treatment of UTIs		
Ceftriaxone	75 mg/kg/day	Divided q12h
Cefotaxime	150 mg/kg/day	Divided q6h
Ceftazidime	150 mg/kg/day	Divided q6h
Gentamicin	7.5 mg/kg/day	Divided q8h
Ampicillin	100 mg/kg/day	Divided q6h
Antibiotics for Oral Treatment of UTIs		
Amoxicillin	20–40 mg/kg/day	Divided q8h
Cefixime	8 mg/kg/day	Divided q12h
Cephalexin	50–100 mg/kg/day	Divided q6h
TMP-SMX	6–12 mg TMP, 30–60 mg SMX per kg/day	Divided q12h
Antibiotics for Prophylaxis of UTIs		
TMP-SMX	2 mg TMP, 10 mg SMX per kg	Once daily
Nitrofurantoin	1–2 mg/kg/day	Once daily
Sulfisoxazole	10–20 mg/kg/day	Divided q12h
TMP	2 mg/kg/day	Once daily

TMP-SMX, trimethoprim-sulfamethoxazole; UTIs, urinary tract infections.

TABLE 55.6. ANTIBIOTICS FOR TREATMENT OF UTI

Oral antibiotics follow IV therapy; the choice is based on the sensitivity analysis of the cultured bacteria. Oral therapy should continue for 10 to 14 days. Prophylactic antibiotics are recommended until imaging studies are complete.

For children with uncomplicated UTIs, treatment will depend on the child's age and severity of symptoms. The majority will have bladder irritative symptoms and cystitis. The optimal duration of treatment of acute uncomplicated infection is controversial. The range is from a single dose of IM aminoglycoside to 10 days of an oral agent (144). A 3- to 5-day course of an appropriate agent with sensitivity confirmed by the culture results is this author's method of treatment.

If the child has two or more documented UTIs within 6 months, prophylactic antibiotics may be considered, because the child has established his or her propensity for recurrent infections. Table 55.6 lists some of the agents of value for prophylaxis. These drugs have high urinary concentrations and avoid antimicrobial resistance patterns in the gut at the prescribed dosage. These same antibiotics should be avoided as primary treatment agents when used prophylactically, because the higher dosages will result in bacterial resistance (154).

Prophylactic antibiotics are the mainstays of medical treatment in children who are discovered to have vesicoureteral reflux. In children with recurrent infections and voiding dysfunction, prophylaxis is combined with specific treatment of their voiding disorder that may include timed voiding, anticholinergics, and behavior modification (94). It also is important to treat constipation, which often coexists with urinary infection and infrequent voiding (123).

Voiding Dysfunction and Wetting

Children with inappropriate wetting and voiding habits are common, constituting 20% to 25% of new patients seen in the pediatric urology office setting (Table 55.2). A myriad of structural, neurogenic, and functional disorders can result in

a wet child. In the office setting, the majority of these children will have functional abnormalities without overt neuropathies or anatomic disease. A thorough history, physical examination, and an understanding of the normal development of urinary control direct the evaluation of these children. In the absence of associated urinary infection, invasive or complex procedures or imaging rarely are necessary. The focus of this discussion is on the normal child who presents with wetness after an age when toilet training should have been accomplished.

Acquisition of Bladder Control

The neurophysiologic mechanisms resulting in continence are discussed elsewhere in this text. These processes result in various observed developmental stages of urinary control. In newborns, micturition is a reflex occurring 20 or more times per day (67). Bladder filling to an appropriate degree stimulates the efferent response of emptying, with detrusor contraction preceded by relaxation of the sphincteric mechanism with complete bladder emptying. By 6 months of age, a noticeable increase in voided volume and decrease of urinary frequency is seen. This is attributed to unconscious inhibition of the voiding reflex (184). Between 1 and 2 years of age, the child develops a conscious sensation of bladder fullness that sets the stage for voluntary control of voiding. Volitional voiding and inhibition of voiding at any degree of bladder fullness develops in the second and third years of life. By the age of 4 or 5 years, most children have developed an adult pattern of urinary control. The usual sequence of attainment of bowel and bladder control is (a) nocturnal bowel control, (b) daytime bowel control, (c) daytime urinary control, and (d) nocturnal urinary control (145). Children between 3 and 12 years of age void five to six times per day and have a bowel movement each day (14). Normal voiding volume is more difficult to define, but bladder capacity can be approximated by the following formula: age (years) + 2 = volume (ounces) (93). Comparison of expected bladder capacity with measured bladder volumes provides insight into voiding dysfunction patterns and treatment.

Involuntary voiding beyond the age of anticipated control is called *enuresis. Diurnal enuresis* is daytime wetting and *nocturnal enuresis* is nighttime wetting. Primary enuresis implies no interval of dryness, whereas secondary enuresis implies a 6- to 12-month dry interval. Twenty percent of wet children have diurnal enuresis, and children with secondary enuresis comprise 25% of all wet children, but their evaluation, treatment, and response to therapy are no different than for primary enuresis (76).

Evaluation

The patient's history combined with the voiding log are the mainstays in separating patients with functional enuresis from those with anatomic and neurogenic incontinence. Most parents have poor knowledge of the specifics of their child's bowel and voiding habits. Sending a voiding log to keep for a few days before an appointment will clarify the frequency of voids, the degree of wetness, and bowel accidents (Table 55.5).

Continuous wetness between normal voiding episodes is a classic history in the female patient with an ectopic ureter. Continuous wetness without voiding is seen in patients with neurogenic bladders and in female and male epispadias.

Children with episodic wetness are questioned regarding frequency of voiding, urgency, and posturing. Leg crossing, squirming, or heel sitting (Vincent's curtsy) is used to suppress the urgency associated with uninhibited bladder contractions. A small spot on the underwear immediately after voiding in females may signal pseudoincontinence caused by vaginal voiding. This also is seen in boys with urine trapped in the bulbar urethra and prepuce. Infrequent voiders usually will not empty their bladders upon awakening. The quality of the voiding effort is questioned. A dribbling urination may signify obstruction, a staccato character implies intermittent contraction of the external sphincter, and the use of Valsalva maneuver may suggest overflow incontinence or detrusor decompensation.

Other historic features important to note are the birth history and other conditions such as imperforate anus, vesicoureteral reflux, neurologic disease, and duplication anomalies. A history of a normal prenatal ultrasound suggests structural integrity of the urinary tract. A history of UTI and constipation will need to be considered in the treatment program (105).

How the family has dealt with the child's wetting and their immediate and future concern will help guide subsequent treatment. A family history of nocturnal enuresis in the parent, and when the parent stopped wetting the bed, assist in helping the child.

The physical examination usually is normal. However, abdominal examination and assessment of a palpable bladder, flank masses, or stool will help typify the elimination dysfunction. Careful examination of the spine for signs of occult spinal dysraphism includes inspecting for cutaneous lesions, dimples, lipomas, hairy tufts, and asymmetry of the gluteal cleft. Anal sphincter tone and anal wink are assessed. The gait is observed with testing of lower-extremity reflexes. A high-arched foot or slight leg length discrepancy are significant signs of a tethered cord. The external genitalia are inspected for epispadias, ectopic ureters, labial adhesions, and interlabial masses such as a ureterocele.

A urinalysis and culture are performed. If infection is present, it is managed as previously discussed. If no infection is present and the child is older than 5 years with daytime wetting, a screening renal bladder ultrasound with prevoid and postvoid bladder assessment is performed (180). This will assess volitional voiding efficiency, residual urine, and the integrity of the upper urinary tract. A VCUG is performed on those children with a prior history of UTI and daytime incontinence. A kidneys, ureters, and bladder

(KUB) examination as part of the VCUG detects vertebral abnormalities and constipation. The VCUG rules out vesicoureteral reflux and urethral abnormalities.

If a spinal abnormality is detected, a neurologic origin is suspected, or the VCUG depicts an abnormal bladder, then formal urodynamics are performed. The results of urodynamics may confirm a neurologic origin and assist with management. These patients usually are studied with an MRI of the spine and referred to the pediatric neurosurgeon.

Management

The intent, interests, and cooperation of the child and family must be determined as treatment is planned. The length of treatment and commitment to various programs, such as behavior modification with an alarm system, needs to be explained.

Diurnal Enuresis

Patients with urge incontinence are wet day and night. They may posture and, when urine volume is assessed, have a low functional bladder capacity. They may have a staccato type of urination due to contraction of the external sphincter during voiding. Many have concomitant UTIs. Initial treatment consists of a timed voiding schedule, emptying the bladder every 2 to 3 hours. If this is not successful, anticholinergic medication to treat the unstable bladder is helpful. Parents are instructed to listen to the child's voided stream and alert the child to intermittency and staccato urination. Overall, 87% of children with isolated overactive bladders will improve over a mean of 2.7 years (39). It is important that the child and parents understand this time commitment. Biofeedback training with reflex inhibition of detrusor contractions also has shown success in this group of patients (109).

Infrequent Voiding

As stated previously, children with wetting and infrequent voiding are placed on a timed voiding schedule. These children frequently do not void upon awakening and have associated UTIs and constipation, which require ongoing treatment. A voiding log documenting time, wetting episodes, and volume of urine is kept by the child under parental supervision (Table 55.5). The ultrasonic bladder scan to assess emptying has been used in the office and at home, providing immediate feedback on bladder emptying to the patient (185).

Hinman Syndrome

The extreme form of dysfunctional voiding is the nonneurogenic neurogenic bladder or *Hinman syndrome* (72,73). These patients have upper and lower urinary tract involvement resulting from detrusor instability and significant learned detrusor sphincter dyssynergia (145). The lack of coordination results in high-pressure inefficient voiding. High-pressure voiding leads to bladder decompensation, vesicoureteral reflux, residual urine, UTI, and in the worst-case scenarios, renal failure. Most of these patients also have constipation and encopresis. They often come from families with abusive or overbearing parents. Treatment ranges from that previously discussed to adjunctive medications such as α-blockers to relax the bladder neck, clean intermittent catheterization, behavior modification, and psychologic assistance (8). Help from the pediatric gastroenterologists to develop a good bowel program is sought (183). Behavior modification to teach relaxation of the external sphincter with voiding also is successful (126). Occasionally, construction of a continent stoma (Mitrofanoff) to facilitate clean intermittent catheterization for bladder emptying or even urinary diversion is necessary.

Giggle Incontinence

Complete loss of urinary control precipitated by laughter during the daytime is the hallmark of this voiding dysfunction. It usually is not associated with UTIs or anatomic abnormalities. Giggle incontinence is not stress related, because there is not urinary loss with coughing, sneezing, or straining. It often is seen in adolescent girls and is a source of great embarrassment. Its cause is unknown. Giggle incontinence is very difficult to treat with behavior modification, and expedient bladder emptying is the most effective therapy (178). Anticholinergic agents usually are not efficacious. Methylphenidate (Ritalin, 0.3 to 0.5 mg/kg every 4 to 6 hours while awake) has been successful in some patients with this disorder (153). Fortunately, the incontinence abates spontaneously in some girls.

Nocturnal Enuresis

Control of urination at night is the last step in the development of acquiring social continence. The standard for acquisition of nocturnal continence is 5 years of age in our society. Fifteen to twenty percent of 5-year-old children wet the bed. Of these, 75% have always done so and 25% have secondary nocturnal enuresis. Fifteen percent of these children become dry at night each year, attesting to its developmental nature (74). It is important to remember that nocturnal enuresis is a symptom and not a disease. The family history is one key, because if one parent wet the bed, 44% of his or her children will do so and if both parents wet the bed, 77% of their children will do so (9). The age of attainment of nocturnal control will be similar to that of the parent.

The etiology of nocturnal enuresis is likely multifactorial. Conceptually, the triad of relatively small bladder capacity,

poor sleep arousal, and increased urine volume are the determinants of wetness at night (74). In simple terms, the bladder capacity is exceeded. The child is not aroused in response to the full bladder. Thus the bladder empties while the child continues to sleep. The pattern of sleep as measure by electroencephalogram (EEG) is normal; however, all of the parents of these children will attest to how difficult it is to awaken the child. The daytime functional bladder capacity is decreased in some of these children (143). In addition, a group of these children have increased nocturnal urine production resulting from a deficiency in the amount of antidiuretic hormone (ADH) secreted at night. This loss of a normal diurnal increase in nocturnal ADH secretion combined with poor arousal results in a wet bed (121).

The evaluation of children who wet the bed has been outlined previously. Most require a good history, physical examination, and urinalysis; no further imaging or studies are necessary if the history, examination, and urinalysis are normal. The decision to treat these children is based on the family's and child's perception of the social and personal consequences of the bedwetting. If it prevents normal socialization or affects the child's self-esteem, then treatment is warranted. Many of the families just want to know that the condition will improve, and reassurance is all that is necessary.

The mainstay of treatment of primary nocturnal enuresis is behavior modification because it provides the best long-term success (115). Motivational therapy, consisting of positive reinforcement and active patient involvement, is combined with conditioning therapy with an alarm. The alarm, which is positioned on the pajamas, is triggered by urine contact with a sensor in the underwear. When wetting occurs, the alarm sounds and the patient must awaken, which sometimes initially requires the assistance of his or her parents. The patient will stop urination upon awakening and voids into the toilet. This process results in awakening in response to a full bladder and a dry bed. The conditioning may take up to 15 weeks to occur. This author requires 25 consecutive dry nights before removal of the device. Numerous studies have reported a 65% to 100% cure rate after 4 to 6 months of treatment (88,115,166). Relapse may occur in up to 30% of children, but re-treatment is successful if relapse occurs. Unfortunately, many families and patients are not willing to put in the time and effort to ensure success with conditioning therapy (145).

The primary pharmacologic agents used in treating nocturnal enuresis are anticholinergics, tricyclic antidepressants, and desmopressin acetate (DDAVP). Anticholinergics, specifically oxybutynin, decrease or abolish uninhibited bladder contractions and increase functional bladder capacity. Oxybutynin is of particular help in the child with both day and night wetting. However, its use in children with nocturnal enuresis only rarely is beneficial (88). In children with small functional bladder capacity, anticholinergics with an alarm system has proven successful (27). In children 6 years of age or older, the dose of oxybutynin is 5 mg taken two to three times daily (0.2 mg/kg two to three times a day). Parents need to be alerted to the facial flushing, dry mouth, and heat intolerance associated with its use.

Imipramine, a tricyclic antidepressant, has success in the treatment of nocturnal enuresis. Its pharmacologic actions appear to be multiple because it acts centrally to effect arousal from sleep and it has weak anticholinergic effects on the bladder and mild α-adrenergic effects to close the bladder neck. It also may stimulate the secretion of ADH from the posterior pituitary. The dose of imipramine given 1 to 2 hours before bedtime should not exceed 50 mg in children 6 to 12 years of age, nor exceed 75 mg in children 12 to 14 years of age. On a weight basis, the usual recommended dose is 0.9 to 1.5 mg/kg per day (145). Initial success with imipramine is as high as 50%; however, only 25% of patients have a long-term cure. Imipramine works best in older children who have minimal daytime wetness. Its effects are immediate and it can be used on an as-needed basis for a dry night. Side effects include anxiety, insomnia, dry mouth, and personality changes. The medicine must be safely guarded and administered by the parents because fatal overdoses have occurred, with death due to cardiac arrhythmias, conduction blocks, and hypotension (115).

DDAVP, a synthetic analog of arginine vasopressin, is the only other medication with U.S. Food and Drug Administration (FDA) approval to treat nocturnal enuresis. In some patients with decreased nocturnal secretion of ADH, it is used as replacement therapy. In theory, the use of DDAVP combined with fluid restriction will result in a reduction in nocturnal urine output to a volume less than bladder capacity, resulting in a dry bed. It does not explain the sleep arousal–related problem in enuretic children. DDAVP is available as a spray or tablet. The spray delivers 10 μg per spray; the initial dose is 20 μg (one spray in each nostril). This can be titrated to a total of 40 μg (two sprays in each nostril). The tablet contains 200 μg of DDAVP. Treatment begins with 1 tablet and can be titrated to a total of 3 tablets per night (600 μg). In a number of blinded controlled studies, a significant improvement (defined as greater than 50% reduction in wet nights) is attained in greater than 50% of patients (114,156). Improved response to DDAVP is noted in older patients, with fewer wet nights per week, and in patients with greater than 70% of predicted bladder capacity for age (143). This medication, like imipramine, has a high relapse rate when discontinued. It acts swiftly and can be used on an as-needed basis. The side effects of taking DDAVP have been negligible when strict fluid restriction is performed. Rare cases of hyponatremia and seizures have been seen (140). Fluid restriction beginning at least 2 hours before bedtime and voiding before going to bed are a important aspects of treatment with DDAVP. Patients with refractory nocturnal enuresis persisting into adulthood have been treated with various combinations of alarm system with pharmacotherapy (19,20).

A recent study using hyoscyamine and DDAVP reported success in 78% of patients (27). Combining the alarm system with oral DDAVP is particularly effective in children with the most severe bed wetting, which is defined as in excess of 6 wet nights per week (19).

Genital Problems in the Male

Prepuce

The prepuce begins to form at 10 to 12 weeks of gestation. The inner epithelial layer of the fold of skin is fused with the glans epithelium and will not retract in most newborns. Complete development of the prepuce occurs after formation of the urethra. Abnormalities in urethral formation result in ventral deficiency of the prepuce as seen in boys with hypospadias. Issues related to the prepuce concerning removal and care constitute many patient visits to the office. The intention of this section is not to discuss the pros and cons of circumcision, but rather to review the normal process of preputial retraction and problems related to the circumcised and uncircumcised phallus.

Many observers have recorded the timing of complete separation of the inner preputial skin from the glans penis. It is variable and may not be complete well into adolescence (30). It is not pathologic to have an incompletely retractable prepuce. Forceful separation as frequently advocated in the primary care office is the harbinger of future phimosis and penile adhesions. The accumulation of desquamated epithelium recognized as keratin pearls (i.e., infant smegma) is part of the natural process of separation of the two layers. The most frequent reason for visits related to the prepuce is phimosis. The vast majority is “physiologic” phimosis with incomplete separation. The meatus is clearly visible and there is no ballooning of the prepuce with voiding. Circumcision is not medically necessary under these circumstances. The care of the uncircumcised phallus should be clearly presented to the parents. This includes common sense hygiene and a hands-off approach without forceful retraction of the prepuce, and normal bathing. Explaining to the parents how the process occurs completes the visit. A fact sheet provided by the American Academy of Pediatrics entitled “Care of the Uncircumcised Penis” can be given to the parents.

Patients with pathologic phimosis have experienced previous balanoposthitis and/or traumatic scarring as a result of previous forceful attempts at preputial retraction. At times, a dense, white cicatrix forms at the outlet of the prepuce, resulting in ballooning of the prepuce with voiding. Obstructive uropathy resulting from phimosis is rare (173). This condition has been treated with variable results with topical steroids (116,181). Circumcision is generally felt to be the treatment of choice.

Paraphimosis develops when the prepuce is retracted behind the corona of the glans penis and left in place. Subsequent swelling and edema prevent easy return of the prepuce to its covering position. Initial treatment with compression and manual distraction usually is successful. Penile compression with an elastic bandage or pediatric BP cuff maintained at diastolic pressure for 10 minutes makes reduction easier (11). Dorsal band traction with Adson forceps has proved useful (170). Rarely, performance of a dorsal slit is necessary to release the constricting band. Subsequent circumcision can be performed on an elective basis if desired.

The performance of in-office circumcision has been discussed previously. The issues involved with this decision will not be further addressed. However, many visits to the office will be with patients who were circumcised elsewhere. These procedures have resulted in a number of cosmetically less-than-perfect results. The most common of which is too little skin removed, resulting in a partially circumcised phallus. The parents are unhappy with the result and the referring physician is concerned about his unhappy parents. The surplus of retained prepuce is of consequence only if it results in problems with hygiene. Readherence of the retained inner preputial skin to the glans penis can occur. Many of these patients require recircumcision.

Separation of the skin edges following circumcision results from removal of too much skin from the shaft of the penis. The uncovered shaft of the penis alarms the parents and physician. Fortunately, conservative management with wet to dry dressings and antibiotic ointment allows for healing by secondary intention without resultant chordee. Skin grafting or suture reapproximation is not necessary.

Circumcision can result in the shaft and glans of the penis becoming buried under the penile skin. This is distinguished from the unoperated “buried or concealed” penis that results from an abnormally large suprapubic fat pad and dense dysgenetic dartos fascial bands that tether and retract the penis inward, but may be related to the same pathophysiology (52). When the buried penis results from circumcision, there may be a tight band in the proximal prepuce similar to that of the buried penis anatomy. Surgical repair is indicated to release the penis from the circumferential scar and resurface the shaft of the phallus. Usually, a variety of Z-plasties are necessary and, rarely, a full-thickness skin graft is required. If the buried penis is not caused by prior circumcision, then its surgical correction combines removal of the suprapubic fat pad and release of the dysgenetic dartos fascial bands, and release of the proximal preputial stenosis. In both conditions, the penile shaft skin is tacked to the corporal bodies.

The most common complication of circumcision is meatal stenosis, which is seen rarely, in uncircumcised males. The lesion can result in hematuria, dysuria, urethral irritation, urinary infection, and rarely, hydronephrosis. It is best diagnosed by observation of a thin, upward deflection of a high-velocity urinary stream, because many boys referred for meatal stenosis have a normal meatal caliber. See the previous discussion in this chapter for treatment.

Balanoposthitis

Acute infection of the prepuce and glans penis is seen most commonly in toilet-trained, uncircumcised preschool boys. The cause usually is infectious but may be a result of contact irritation or contact dermatitis. Infectious causes include candida, ß-hemolytic streptococcus, and Gram-negative pathogens (1). The preschool male often complains of dysuria and penile pain and tenderness. Purulent material is visible at the preputial meatus. A Gram stain of the exudate may be helpful, but a culture of the material will disclose the pathogen.

Treatment consists of application of a topical antibiotic ointment such as bacitracin zinc or Neosporin. In more severe cases with localized cellulitis, an oral second-generation cephalosporin is prescribed (61,149). Penile cellulitis in its most severe form can lead to necrotizing fasciitis and should be treated with hospitalization and IV antibiotics. In general, however, mild forms can be treated with oral antibiotics and penile cleansing with soap and water combined with parental and patient education concerning penile hygiene. Most boys suffer a single episode only. Recurrent balanoposthitis with or without ballooning of the prepuce and/or associated phimosis is an indication for circumcision.

Hypospadias and Chordee

Hypospadias, usually recognized at birth, is the most common penile anomaly referred to the urologist's office (see Chapter 52B). Parental anxiety is high because the defect in urethral location and abnormal curvature is visibly apparent. Hypospadias is usually an isolated abnormality with a low incidence of associated upper tract anomalies; screening the kidneys is not necessary (141). Most pediatric urologists restrict x-ray evaluation to those patients who would otherwise undergo radiographs for other indications, such as a UTI. If the patient has proximal hypospadias, an enlarged utricle may be present. This can cause problems with catheter placement at the time of surgical correction (29). Patients with proximal hypospadias and undescended testes, especially if nonpalpable, may have an intersex condition, and a complete evaluation including karyotype is necessary (84).

Abnormal curvature of the penis or chordee may be present with or without hypospadias. Chordee without hypospadias usually is associated with a spongiopenile urethral deficiency, but can be seen with normal urethral anatomy. Penile curvature associated with hypospadias or abnormal urethra is in a ventral direction, whereas the curvature with a normal urethra noted early in life may improve spontaneously. Chordee has three potential causes: (a) abnormal development of the urethral plate, (b) fibrosis of the dartos fascia, and (c) growth disproportion between the normal corporal tissue and abnormal urethral plate (51).

A family history of hypospadias is important, and potential risk to future male infants needs to be discussed. The surgical correction should be detailed with diagrams and drawings. The need for urinary drainage with a tube through the penis and its postoperative care must be taught. The “double diaper” open drainage technique should be discussed. The timing of surgery is key. Surgery on the genitalia is optimally performed from 6 to 18 months of age. This avoids anxiety separation, allows correction before the child perceives his genital defect, and diminishes any recollection of the surgical experience. This age window for surgery is recommended by the Section on Urology of the American Academy of Pediatrics as providing the greatest benefit and minimizing the psychologic effects of surgery and anesthesia (5a).

Inguinal and Scrotal Problems

Hernia and Hydroceles

Scrotal swelling or bulges in the groin are among the most common types of problems seen in the pediatric urologist's office. Inguinal hernias are one of the most common problems seen in children; the vast majority of which occur in boys. They result when the processus vaginalis fails to close, an event typically observed in the third trimester of gestation (151); hence the high incidence of hernias in premature infants. Hernias also are commonly found in association with undescended testes (54).

Office evaluation of the child who presents with an enlarged scrotum first requires a thorough history. Many babies with hydroceles at birth will present to the office with a tense, enlarged scrotum (Fig. 55.5). Parents will report that their baby appears irritable, and it may be difficult to differentiate scrotal enlargement due to an incarcerated hernia from other causes of irritability, such as colic. This may cause crying, then increased abdominal pressure, resulting in scrotal enlargement from peritoneal fluid being forced through the open processus vaginalis. The same phenomenon

may be seen in babies with constipation. Calming the baby by offering a pacifier often is helpful to allow reassessment to determine whether the problem is in fact acute.

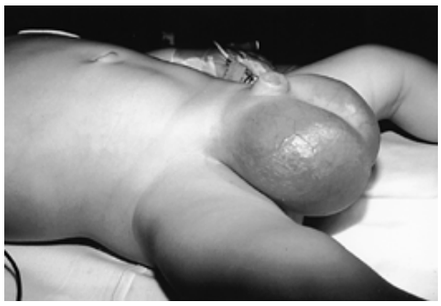

FIGURE 55.5. Communicating hydroceles. Scrotum is tense and enlarged. This often is indistinguishable from an incarcerated hernia.

Examination is important to differentiate a hernia from more serious problems. Transillumination of the scrotum using a penlight in a darkened room will determine whether the mass is fluid filled or is solid. The testis often is difficult to palpate in a tense hydrocele, but can be identified by transillumination, or better with scrotal ultrasound. Not infrequently, a child will present with an inguinal mass along the spermatic cord, and differentiation between an incarcerated hernia and a hydrocele in the cord can be difficult. Transillumination again may help establish the diagnosis, but if this is equivocal, auscultation with a stethoscope may pick up bowel sounds. Ultrasound may be useful in this clinical situation as well. Fluid seen without internal echoes in the mass is characteristic of a hydrocele.

The age at which the child presents influences management. Neonates and infants with very large hernias may have symptoms that warrant early surgery, such as irritability or feeding problems. An incarcerated or strangulated hernia is a medical emergency that requires urgent reduction. Successful reduction of an incarcerated hernia allows time to prepare the baby for an urgent, but more elective, operation rather than emergency surgery. In children with asymptomatic hernias, observation is reasonable; however in neonates and children younger than 1 year of age, repair on an urgent but not necessarily emergent basis is indicated because of the increased potential for incarceration in this group. Children with communicating hydroceles may be followed for the first year of life in anticipation of closure of the processus vaginalis. Should this fail to occur by age 1 year, the likelihood of closure is slim (150). If the hydrocele is large and shows no sign of diminution in size by 6 months of age, surgery is justified. It is at this age that the anesthetic risk has reached its nadir.

Undescended Testes

Many boys are referred to the pediatric urologist because of suspected cryptorchidism, or undescended testes. This can be a difficult diagnosis to make, because retractile testes and undescended testes may be indistinguishable clinically. Yet it is critical to attempt to make this distinction (57,99,133).

The diagnosis of cryptorchidism is made on physical examination. Many children referred for consultation have already had some imaging studies (e.g., sonogram, CT scan, MRI scan) in attempts at either identifying or localizing a testis that the primary care physician could not identify. Unfortunately, these studies have low specificity and sensitivity and consequently are of little use. The overall accuracy of radiologic testing has been reported to be 44% compared with 53% accuracy of physical examination by the referring physician and 84% by the pediatric urologist (77). The diagnosis is made during a thorough and carefully performed physical examination. First, the child should be relaxed. Attempts should be made to gain the patient's trust and to convince him that there will be no pain. The room should be warm to minimize the cremasteric reflex. Observation of the scrotum is the most important part of the examination. The testes should lie in a dependent position. Next, bimanual examination with one hand over the inguinal region and the other on the scrotum will allow the examiner to palpate the testis and “milk” it into the scrotum. The undescended testis usually will not be able to be manipulated into the scrotum, and if it can, it will not remain there, springing back into its original position.

In situations where the diagnosis is not clear, other diagnostic measures should be undertaken. Examination of the child should not be limited to the supine position. For example, the patient can be examined standing, sitting on the examination table with legs crossed or with the legs hanging from the end of the table, or resting on the examiner's lap. All are ways of minimizing the cremasteric reflex and therefore facilitating the differentiation between a true cryptorchid testis and retractile testis. Valsalva maneuver, initiated by having the patient bear down, also can dampen the cremasteric reflex. Another helpful diagnostic trick is to put liquid soap on the examining fingers to enhance tactile sensation, which often is useful in palpating a testis high in the inguinal canal or buried in fat. Scrotal hypoplasia may indicate true cryptorchidism, but also may be associated with peripenile adipose.

When the diagnosis is still inconclusive (mobile versus true undescended testis), the use of hCG can be of further diagnostic assistance (133). Many protocols have been described for administration of hCG for such purposes (81). Presumably, a retractile testis will descend after a course of hCG, but an undescended testis will not. This is based on the empiric observation that at puberty, a retractile testis previously not palpable in the scrotum will indeed be in the correct position (131). This is not true of undescended testes. One distinguishing feature of puberty is testosterone production, which establishes the rationale behind giving hCG as a diagnostic test. It is safe, and any virilizing side effects usually are mild and reversible after discontinuation of hCG. When giving the hormone in this manner, strict criteria should be used when interpreting the clinical results. After a course of hCG, the testis should be in a dependent position at the base of the scrotum. If this is not the case, the diagnosis of retractile testis cannot be made with assurance.

In patients with bilateral, nonpalpable testes, the diagnosis of bilateral anorchia needs consideration. If serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are elevated in boys younger than 9 years of age, no further evaluation is necessary to make this diagnosis (80). If gonadotropins are not elevated, hCG administration of 2,000 IU daily for 3 days, with measurement of preinjection and postinjection serum testosterone will determine the presence of testicular tissue (68,176). Some caution should be exercised in the interpretation of this test because testes

have been reported in cases where there has been no testosterone response to hCG (158,175). This is presumed to be so in cases in which the testis fails to recognize hCG, such as 5-α-reductase deficiency. Treatment in such cases is controversial. There has been some enthusiasm for the use of hCG in patients with unilateral, nonpalpable testes, in an attempt to stimulate some descent, effectively making them palpable, undescended testes and obviating the need for more extensive surgical procedures. Therapeutic options are simpler in such cases, and it has been reported that the testosterone effect on the spermatic vessels makes them less apt to suffer from trauma during surgery (15).

Undescended testes may occur in association with other problems of the external genitalia, such as hypospadias. When these two conditions occur together, there should be concerns of ambiguous genitalia and intersex. Consequently, a karyotype analysis is essential (84,134).

Once the diagnosis of cryptorchidism has been established, treatment needs to be instituted. Orchiopexy is the treatment of choice in North America, whereas in Europe, hormonal treatment with hCG and gonadotropin-releasing hormone (GnRH) is quite popular. The choice of surgical procedure depends in large part on the location of the testis; the other decision is the timing of surgery. Currently, surgery is recommended before age 2 years, in attempts to prevent damage to the primary spermatogonia, an observation made with increasing frequency the later the surgery is performed after 2 years of age (112). Over the past decade, the trend has been to operate at an even earlier age if the diagnosis is obvious, and it appears unlikely that the testis will descend with further observation (95). Consequently, it is not unreasonable to perform surgery as early as 6 months of age in selected cases.

The surgical options depend on a variety of factors. Testes that are palpable can easily be approached inguinally, and generally are easy to bring down into the scrotum. Intraabdominal testes, especially if solitary, pose greater challenges. Many approaches have been described, including stages 1 and 2 Fowler-Stephens orchiopexy, laparoscopic-assisted orchiopexy, and microvascular orchiopexy. Detailed descriptions of these operations are beyond the scope of this chapter.

The Acute Scrotum

The child who is referred to the office with a painful scrotum needs prompt evaluation in the event that the cause of the pain is torsion of the spermatic cord (33). Testicular torsion is the most common pediatric urologic emergency. However, this is not the most common reason for scrotal pain or swelling. Time is critical in establishing the diagnosis and instituting treatment, because testicular viability is measured in hours once the blood supply to the testis is compromised. The likelihood of testicular salvage is greater if the duration of the torsion is less than 6 hours (96,168).

As in all cases, evaluation begins with a careful history. Pain is the typical symptom and is sudden in onset, often awakening the patient from sleep. Nausea and vomiting are common. The scrotum often becomes erythematous and enlarges, and a reactive hydrocele often is encountered. A history of trauma should be excluded, as should other signs and symptoms such as irritative voiding symptoms, fevers, or rashes. It is not uncommon to learn that patients have had previous painful episodes of less severity, suggesting intermittent torsion.

Physical examination obviously is important in making an accurate diagnosis. The earlier in the course of the event the examination takes place, the easier it will be to establish the diagnosis without any ancillary diagnostic studies. Once edema and induration occur, the reliability of the physical examination alone diminishes. A reactive hydrocele also may occur, further obscuring the examination. When present, it usually is bloody. Testicular position in the scrotum is an important diagnostic criterion. The testis may appear “high riding,” because as the spermatic cord twists, it draws the testis up out of the scrotum (Fig. 55.6). The orientation of the testis likewise may be abnormal. The epididymis may be located in a position other than its typical posterior location; however, this may be variable, because the torsion can occur 360 or 720 degrees. The testis may assume a horizontal lie in the scrotum, also suggestive of torsion. The testis typically is extremely tender to palpation, often with extension into the inguinal canal. The cremasteric reflex usually is absent, but this is not a reliable finding because it may still be present in early torsion, or may be absent in conditions other than torsion.

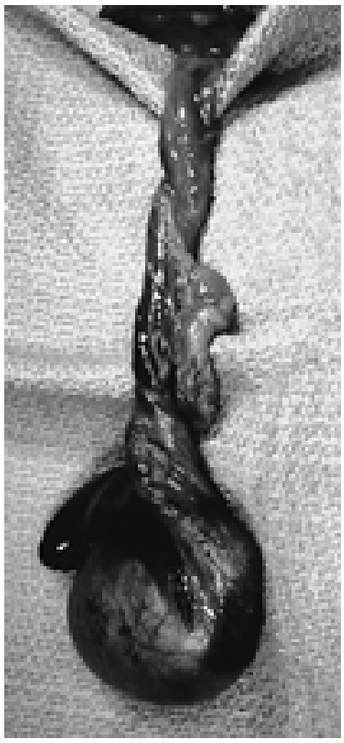

FIGURE 55.6. Torsion of spermatic cord. Note that there are several twists in the spermatic cord, elevating it into a “high-riding” position in the scrotum.

Laboratory tests usually are unnecessary in most patients presenting with an acute scrotum, with the exception of a urinalysis to exclude pyuria and bacteriuria, typically found in patients with epididymitis. However, an abnormal urinalysis is not pathognomonic for epididymitis. Crystals in the urine should make one suspicious of a stone, with the testicular pain being referred. In such cases, there is usually no erythema or edema of the testis or scrotum.

The etiology of the acute scrotum often can be determined in the office, and if testicular torsion is present, detorsion can be attempted to temporize the situation until definitive surgery can be performed. Rotating the testis outward from the midline when viewing the patient from his feet does this, because torsion usually occurs inward. In the small child with an acute scrotum, these maneuvers rarely are successful. If the diagnosis is equivocal, emergency scrotal exploration should be performed as soon as possible to reestablish blood flow to the testis. However, if further evaluation does not appear to pose much risk regarding the eventual outcome, scrotal sonography with Doppler has proven to be a useful diagnostic tool in the hands of experienced examiners (91,182). Flow to the interior of the testis rules out testicular torsion and usually saves the child an emergency operation. Nuclear testicular scan is another reliable testicular imaging study that can determine whether blood flow is present, but it usually is more time consuming than sonography, and involves some radiation exposure (42). False-positive and false-negative findings have been reported with both studies (18). Furthermore, these studies should be used only in the clinical situation where a nonoperative approach seems most likely, and these studies serve as justification of this approach. If surgery is seriously considered (i.e., if testicular torsion seems a real possibility), neither test is indicated. The patient should be taken to the operating room as soon as possible.

Torsion of the appendix testis is the most common cause of the acute scrotum and testicular pain, and is a self-limited condition. In most cases of an acute scrotum, torsion of the appendix testis is a diagnosis of exclusion in all but the most obvious cases. Early in the course of torsion of the appendix testis, point tenderness may be elicited over the anterosuperior pole of the testis, the area where the appendix testis is expected to be found (Fig. 55.7). Before scrotal edema ensues, the necrotic appendix can be visualized through the skin, giving the blue dot sign (50).

FIGURE 55.7. Torsion of appendix testis. The testis and epididymis are normal, but the appendix testis demonstrates hemorrhagic infarction.

Once acute testicular torsion and torsion of the appendix testis have been excluded, other etiologies for testicular pain need to be considered. Intermittent testicular torsion is a difficult diagnosis to prove, and a high index of suspicion is necessary to make this diagnosis. Intermittent torsion usually occurs in adolescents and teens. The most obvious cases are those in which there is sudden-onset scrotal pain and swelling, which can last several minutes or longer, and then completely revert back to normal just as quickly as it came on. A transverse orientation of the testis in the scrotum further supports this diagnosis. This may be the cause of longstanding intermittent, transient pain in the scrotum but it is very difficult to prove. The problem may be one of degree and may be related to the extent of torsion of the cord. When the cord twists 360 degrees, there is little doubt about the diagnosis, but if the testis partially twists, symptoms will vary accordingly.

The differential diagnosis of acute scrotal pain also includes epididymitis and other inflammatory processes of the testes. The epididymal inflammation may be bacterial, viral, or chemical. Epididymitis is uncommon in prepubertal boys, and when found should suggest some anatomic abnormality involving the urinary tract (155). In the evaluation of the acute scrotum, a urinalysis consistent with infection is strongly suggestive of this diagnosis, but epididymitis may occur with a normal urinalysis. This has been observed when there is urethral obstruction, resulting in increased voiding pressure and reflux of urine into the ejaculatory ducts. Hemophilus influenza has been reported to cause epididymitis in association with otitis media. The presence of a prepuce has been reported as a possible risk factor for epididymitis (13). The onset of symptoms in children with epididymitis is typically more insidious than in those with testicular torsion, and may be associated with fever, urethral discharge, or other constitutional symptoms. These patients often have pyuria, leukocytosis, and bacteriuria. Indwelling urethral catheters are a risk factor for epididymitis. Viral orchitis most commonly seen with mumps and testicular/epididymal vasculitis, such as is seen with Henoch-Schönlein purpura, also can present as an acute scrotal processes and often results in unnecessary scrotal exploration. Thorough history and physical examination usually will help in making these diagnoses, however.

Antenatal Torsion

The clinical presentation of a child with antenatal torsion depends on when the event took place. If torsion occurred weeks before delivery, it is likely that the testis will have atrophied already and the scrotum may be relatively normal in appearance. If the event was perinatal, the examination may be similar to that of an acute scrotum in an older child. Unlike torsion in older children that is intravaginal, antenatal torsion typically is extravaginal. The likelihood of testicular salvage in antenatal torsion is remote because the event usually occurs well before delivery, and irreversible ischemia is likely (Fig. 55.8). Consequently, early surgery is controversial (101). Some have speculated that an immunologic effect on the contralateral testis may warrant removal of the ischemic testis (2). Others have argued that approximately 10% of antenatal torsion is intravaginal (40), increasing the risk of contralateral torsion and justifying early surgery to remove the affected testis and for contralateral orchiopexy. The risk of contralateral metachronous torsion is highest in the first 4 to 8 weeks of life.

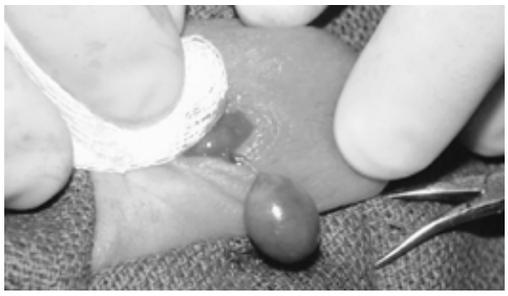

FIGURE 55.8. Antenatal torsion. Testis has completely twisted extravaginally.

Most cases of torsion in infants are antenatal, but approximately 30% have been reported perinatally. These have a greater chance of being salvaged if they are recognized promptly.

Varicocele

Varicoceles are rare in prepubertal males (12). The incidence of varicoceles in adolescents is between 15% and 20%, which is the same as has been reported in adults (22). They often first present in the teenage years, and occasionally in prepubertal males. They represent dilated veins in the pampiniform plexus and almost always are found on the left, because of the anatomy of the left spermatic vein draining into the left renal vein. The characteristic clinical description is a “bag of worms” appearance (Fig. 55.9).

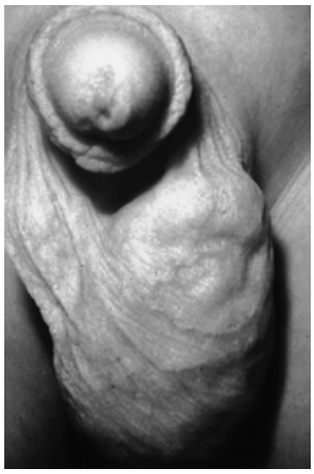

FIGURE 55.9. Left varicocele. Scrotum has a “bag of worms” appearance.

Most varicoceles in adolescents are discovered by a parent or on a routine physical examination. Most varicoceles are asymptomatic, but data strongly suggest that varicoceles can result in testicular damage in some adolescent boys. As many as 75% of boys presenting with a varicocele have testicular atrophy (107), and 90% have abnormal testicular biopsies. Careful measurement of testicular size rather than simple estimation is very important. Although the orchidometer is of some use, sonography is much more reliable in assessing testicular volume (37,45).

There is no consensus regarding the appropriate management of adolescent varicoceles. In asymptomatic boys with normal testes, the treatment should be individualized, and those boys not undergoing surgery should be followed with an annual examination to measure testicular growth. Surgery should be performed in boys who either complain of discomfort or have testicular growth retardation (90). When testicular atrophy is observed, surgery to correct the varicocele usually results in catch-up growth of the affected testis (89). It has been reported that ipsilateral testicular hypertrophy occurs in a substantial number of adolescents following varicocele ligation (66). Semen analysis should not be performed in the adolescent, but is reserved as a study to be used in adults as a criterion for surgery.

Spermatocele

Spermatocele is one of the more common scrotal masses seen in adolescents. It typically is cystic and nontender, and is paratesticular in location, most commonly in the head of the epididymis. Trauma, infection, or obstructions in the epididymal tubules all have been proposed as etiologies for spermatoceles. They occur in postpubertal boys, they transilluminate on physical examination, and they are filled with spermatozoa. Sonography confirms the diagnosis if there is

any doubt on examination. No treatment is necessary unless there is significant discomfort, although in the teenage boy, any scrotal mass may arouse anxiety and warrant surgical excision. Spermatoceles are not associated with more serious problems.

The Red Scrotum

Many children will present to the office with a red scrotum, sometimes with associated pain, but usually fairly easy to distinguish from torsion of the testis or the testicular appendages. Conditions that should be considered in the differential diagnosis include Henoch-Schönlein purpura, idiopathic scrotal edema, orchitis, cellulitis, insect bites, and trauma including sexual abuse.

Henoch-Schönlein purpura is a systemic vasculitis characterized by nonthrombocytopenic purpura with involvement of the genitourinary and GI systems, skin, and joints (Fig. 55.10). The etiology is unknown and is associated with pain and swelling in the spermatic cord and scrotum in up to one-third of affected patients. Seventy-five percent of the patients are younger than age 7 years. The problem may persist for more than 4 weeks. Other symptoms include purpura, arthralgias, hematuria, hematemesis, and abdominal pain. The problem is self-limited, requiring no specific treatment. The diagnostic dilemma is distinguishing Henoch-Schönlein purpura from testicular torsion because of the similarity of the clinical presentation in some cases. In 25% of patients, both problems occur concomitantly (106). Doppler ultrasound usually will exclude torsion by confirming flow to the testis.

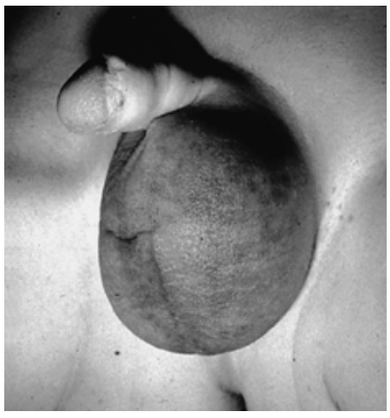

FIGURE 55.10. Henoch-Schönlein purpura. Note the petechial hemorrhages over the scrotum and thighs. The erythema is confined to the scrotum.

Acute idiopathic scrotal edema often is difficult to diagnose because it may mimic testicular torsion. However, close inspection will disclose no testicular swelling or tenderness. Scrotal edema is a diagnosis of exclusion. The onset usually is sudden and may be unilateral or bilateral. The erythema is confined to the scrotum. Boys with this condition usually are afebrile, but many may have a low-grade fever. The average age of presentation is between 4 and 7 years, with most younger than age 10. Urinalysis and WBC count usually are normal, but eosinophilia may be seen. Many etiologies have been suggested including insect bites, allergic reactions, contact dermatitis, and angioneurotic edema. The condition is self-limited, but supportive treatment involves analgesia, rest, and reassurance. Antihistamines may be of some help.

Orchitis is an unusual, isolated finding in boys. It may be seen in association with some viral conditions such as mumps, which is rare in boys younger than 10 years of age. It usually occurs as a sequela of some other condition, such as bacterial epididymitis or inflammation, seen as a result of torsion of a paratesticular appendage (Fig. 55.11). The testis appears swollen and may be very painful, and there may be an associated hydrocele. Treatment is supportive with analgesics, scrotal elevation, and ice packs.

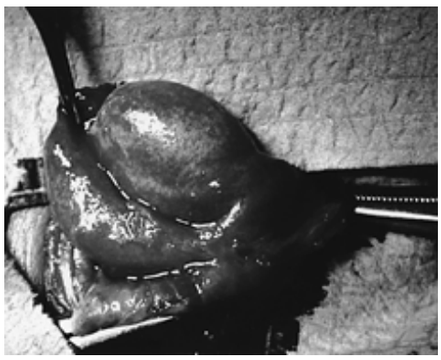

FIGURE 55.11. Epididymoorchitis. There is diffuse erythema and edema of testis and epididymis.

Tumors

The finding of a firm, nontender scrotal mass strongly suggests a tumor. Although not sudden in onset, it may be perceived as a new onset mass, and consequently present as an acute scrotal mass. A testicular tumor needs to be differentiated from a paratesticular tumor. Seventy-five percent of testis tumors in prepubertal boys are germ cell tumors, the majority of which are yolk sac, followed by teratoma. Non–germ cell tumors include gonadal stromal tumors, adnexal tumors, and metastatic tumors. Testicular tumors in older boys are unusual until the late teens, when

adult-type germ cell tumors predominate. Rhabdomyosarcoma is the most common paratesticular tumor, usually occurring in the spermatic cord. This tumor may present with scrotal erythema and induration. Tumors in the epididymis are virtually never seen in children.

Genital Problems in the Female

The pediatric urologist typically is relied upon to evaluate genital problems in girls, because other specialists lack the experience or interest in treating these problems. There is also a close relationship between the female genital and urinary tracts, making it quite natural and appropriate for the pediatric urologist to address these problems because of the intimate knowledge of the anatomy and problems encountered.

Labial Adhesions

Labial adhesions are the most common of all the problems associated with the female genitalia. These are acquired adhesions of the labia minora. They usually occur during the first 2 years of life and the etiology is multifactorial. The withdrawal of maternal estrogens renders the skin in the perivaginal area thin and very easily irritated. Contact of this skin with wet diapers or other irritants such as soaps or bubble baths results in erythema and rashes resulting in damage to the epithelial layer. When such surfaces are in contact for prolonged periods of time, they “heal” together (Fig. 55.12).

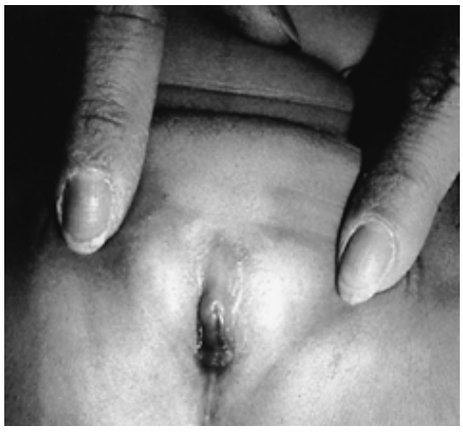

FIGURE 55.12. Labial fusion.

Girls with labial fusion may present with voiding complaints, incontinence, or postvoid dribbling of urine, or may be referred because of UTIs (102). The latter diagnosis may be dubious depending on the extent of the adhesions. When the labial fusion is almost complete, the urine specimen is questionable because of introital contamination due to urine trapping. Many girls with labial adhesions are referred because of the inability to catheterize them.

The most difficult issue regarding labial fusion is preventing recurrences. Educating the parents is very important, reviewing with them the elements of perineal care, which entails prevention of erythema and rashes in the perineum. Liberal use of diaper rash creams may help. Sitz baths using baking soda or oatmeal may help stabilize the fragile perivaginal skin.

Vulvovaginitis

Vulvovaginitis is the most frequent pediatric gynecologic problem. This, like labial fusion, occurs because the skin of the introital area is thin, delicate, and easily traumatized. Irritants such as urine and feces come in contact with this area in children wearing diapers or soiling themselves after toilet training. Some common chemical irritants include soaps, shampoo, bubble baths, and laundry detergents. Parasites such as pinworms, fungal infections especially after antibiotic therapy, and foreign bodies can all result in vulvovaginitis (10).

The typical presentation of vulvovaginitis is erythematous introital skin; a yellowish, thin discharge; and dysuria. It often is misdiagnosed as a yeast infection, and it is not uncommon to find that many of these girls have been on multiple courses of antifungal agents or antibiotics. Often, a UTI will be diagnosed based on symptoms and an abnormal urinalysis, which commonly is found when the urine collection is a voided specimen. A catheterized specimen in girls with vulvovaginitis must be performed to establish a diagnosis of UTI.

The treatment of vulvovaginitis consists of warm sitz baths, often with the addition of baking soda or oatmeal; liberal application of diaper rash creams that contain zinc oxide; and occasionally, short courses of estrogen cream. The recurrence rate of vulvovaginitis is high.

Vaginal Foreign Bodies

Vaginal foreign bodies should be considered in children with recurrent or persistent vaginal discharge or bleeding, and especially if it is associated with a foul odor. Many objects commonly are inserted into the vagina by little girls, such as cotton, toilet paper, tips of cotton swabs, beans, peas, BBs, twigs, pencils, crayons, and pebbles. Initial efforts should be made to culture the vaginal drainage. If the cultures do not reveal a single pathogen, or if the drainage or bleeding persists after antibiotics, the diagnosis of a foreign body should be strongly suspected, and sometimes can be made by careful examination.

If the foreign body is large enough, it may at times be detectable on rectal examination. However in most cases, examination under anesthesia and vaginoscopy are required to make the diagnosis and to remove the foreign body. The vagina should be lavaged out with irrigating fluid.

Interlabial Masses

Young girls often present with a mass in the interlabial area. These masses often are similar in appearance but must be distinguished to implement appropriate and timely treatment.

Urethral Prolapse

Urethral prolapse generally is seen in prepubertal girls, and occurs more often in African American girls than in Caucasian girls. It has been proposed that poor attachments between smooth muscle layers of the urethra in association with increased intraabdominal pressure results in eversion of the urethral epithelium. Urethral prolapse often is misdiagnosed as sexual abuse (83). Girls with urethral prolapse often present with introital bleeding (6). They may complain of pain, especially when the prolapse is large, and it often results in dysuria or perineal discomfort. These lesions are not obstructive. The diagnosis is established by putting a catheter into the urethra to demonstrate a symmetric protrusion circumferentially around the tube (Fig. 55.13). Once the diagnosis is made, initial therapy should be sitz baths and estrogen cream twice a day for 2 to 3 weeks to reduce the inflammation and to ameliorate the symptoms (136). Medical management rarely is definitive treatment, and surgical excision will be necessary.

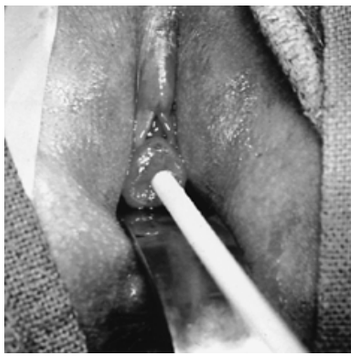

FIGURE 55.13. Urethral prolapse. Note circumferential eversion of edematous urethral mucosa around urethral catheter.

Introital Cysts

Introital cysts typically are seen in neonates and represent obstruction of either Gartner's ducts or Skene's glands (Fig. 55.14). When large, these cysts need to be differentiated from a prolapsed ectopic ureterocele, which is best accomplished with sonography. These rarely, if ever, cause urethral obstruction or infection. Once the diagnosis is established, the cysts can be observed, because most will resolve once estrogen levels, which are of maternal origin, decrease over the first few months of life. If the introital cysts do not regress, the preferred treatment is marsupialization.

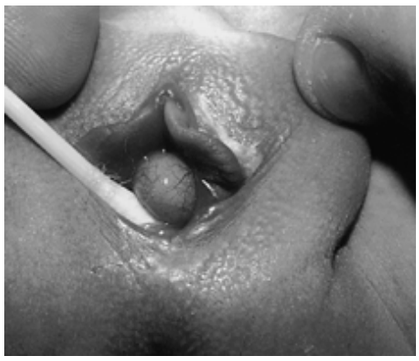

FIGURE 55.14. Introital cyst. Cyst is located at urethral meatus or superior to it.

Prolapsed Ectopic Ureterocele

Ectopic ureteroceles may extend into the urethra and protrude through the meatus. They appear as a cystic mass and can be distinguished from urethral prolapse because they are located eccentrically relative to the lumen, and the vagina appears to be normal relative to the urethra. This is the presenting symptom in 10% of girls with ureteroceles (25). Ectopic ureteroceles may be erythematous and can be associated with irritative voiding symptoms. They tend to be very tender, and sometimes can be reduced manually. The diagnosis is confirmed with sonography and on VCUG. These studies almost always will demonstrate an obstructed upper-pole ureter, and rarely, bladder outlet obstruction. Treatment involves either an intravesical approach or a supravesical procedure. All treatments involve decompression of the ureterocele. Transurethral resection rarely is employed and when it is, it is as an adjunct procedure to remove an obstructing lip of tissue left behind from either upper-pole heminephrectomy or intravesical treatment of the ureterocele (i.e., resection or marsupialization) (148).

Imperforate Hymen

An imperforate hymen usually is detected at birth as a bulging mass at the introitus (Fig. 55.15). The typical blue hue to the mass represents fluid in the vagina. It may be associated with an abdominal mass secondary to hydrometrocolpos and/or mucocolpos. It has been suggested that there may be an autosomal-recessive mode of inheritance and therefore may be familial. If these masses are very large,

venous return from the lower extremities may be obstructed. The treatment is a simple hymenotomy, which can be performed in the office. Ultrasound should be performed first to confirm the diagnosis. If this condition is missed at birth and is allowed to persist, many of these girls present at puberty because of amenorrhea and distention of the imperforate hymen by menstrual blood (hematometrocolpos).

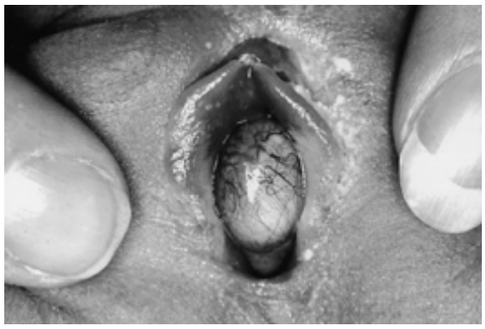

FIGURE 55.15. Imperforate hymen. Bulging mass completely obscures urethral meatus.

Rhabdomyosarcoma (Sarcoma Botryoides)

Rhabdomyosarcoma is the most common primary malignancy involving the vagina, uterus, or bladder within the first 5 years of life. It has the appearance of a cluster of grapes protruding from the introitus (Fig. 55.16). Girls with this lesion often present with vaginal bleeding or passage of sloughed tissue fragments. Rectal examination is mandatory to gauge the extent of the mass. Metastatic spread to lymph nodes, lung, liver, and bones are late manifestations. Treatment involves a combination of chemotherapy, radiation therapy, and surgery.

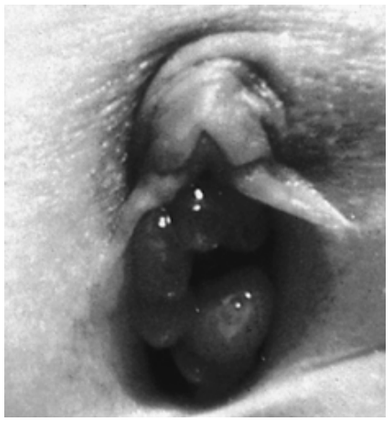

FIGURE 55.16. Vaginal rhabdomyosarcoma. Sarcoma botryoides, or “cluster of grapes,” originating from vagina.

Trauma

Trauma to the introital area can be accidental or intentional (i.e., sexual abuse). Typical examples of accidental trauma are straddle injuries, accidental penetration, and forced stretching (e.g., from falls or gymnastics). Injuries can involve any and all areas in the introitus: the mons, clitoris, urethra, labia majora and minora, and even the rectum. It is important to try to determine the mechanism of injury and to exclude sexual abuse (71). Many cases are associated with severe bleeding; therefore examination under anesthesia often is necessary, although small lesions can be examined and treated in the office. Traumatic hematomas of the vulva can be managed with ice and bed rest if they are not expanding. When very large, a Foley catheter may be necessary for bladder drainage. Suspected cases of sexual abuse need to be reported promptly to the proper agency or law enforcement, and examination under anesthesia with sampling of secretions and cultures, and with photographic documentation, are mandatory.

Urolithiasis

It generally has been assumed that urolithiasis is rare in children in industrialized nations. When present, they often are associated with metabolic disorders, anatomic abnormalities, infection, or obstruction. In developing nations, stone formation is quite common, with bladder stones composing a large percentage of the cases. However, it appears that the incidence of stones in the United States has likely been underreported (177) and that metabolic factors play a far greater role in stone formation than was previously suspected (49).

The age of the patient is an important factor influencing the clinical presentation. The older child often will have the typical symptoms seen in adults with calculus disease, such as flank pain, hematuria, and emesis. In younger children, the symptoms may be more subtle, such as vague abdominal pain or feeding problems. In any case, a high index of suspicion is necessary so that appropriate evaluation is initiated. The presence of fever should be considered serious and UTI should be suspected until proven otherwise, because obstruction from a stone and infection together put a child at higher risk of sepsis and renal damage. Other historic information important in considering the possibility of stones is a history of prematurity often associated with the use of diuretics such as furosemide. The risk of nephrocalcinosis

and urolithiasis is increased significantly with this history.

The evaluation of the patient with suspected stone disease is twofold. First, imaging studies are necessary to make the diagnosis and to plan appropriate treatment. Second, after successful treatment, evaluation of the patient is important to determine the etiology of the stone formation so that subsequent stone formation is prevented, if possible. The initial imaging study depends on the office capabilities. Renal sonography is very easy to perform, if available, and depending on the resolution of the probe used, stones 0.5 cm or larger usually can be identified easily, as can associated problems such as hydronephrosis. Unfortunately, small renal stones or ureteral stones are very difficult to image, which means that even when ultrasound is used, some other imaging study will still be necessary. Intravenous urography (IVU) has been the standard in the evaluation of renal colic. One of the best features of the study is the usual excellent visualization of the entire collecting system, but it also has some shortcomings. Small stones and radiolucent stones can be missed. These studies typically are performed in an unprepped patient and, as a result, there are often large amounts of fecal material and gas that hinder visualization. Finally, IV contrast must be given for the study, and problems such as contrast allergies are not rare. In light of these problems, spiral CT is considered by some as the procedure of choice in the evaluation of suspected stones (159). It is rapid (less than 2 minutes) and requires no contrast, although it may be combined with contrast after initial noncontrast images are obtained, to exclude obstruction. Small stones, often as small as 1 mm, can be identified, and radiolucent stones are seen better on CT scan than on IVU.

Once the correct diagnosis has been established, decision making is shifted to treatment, which again varies depending on many factors. Patients who are septic or who are in severe pain will require different management from a patient with mild intermittent colic. Other factors that are important in the decision-making process include age of the patient, size of the stone, location of the stone, composition of the stone, and anatomy of the urinary tract. Large stones, a large stone burden, or a staghorn calculus may make one treatment modality appear more favorable over another. Stone composition influences which treatment to recommend, as in the case of known cystine stones that are typically resistant to extracorporeal shock wave lithotripsy (ESWL). The anatomy of the urinary tract in children is probably the most important factor that influences treatment decisions. The incidence of stone formation is higher in patients with congenital malformation of the urinary tract. Furthermore, the small size of the pediatric urinary tract often makes treatment of stones a very challenging exercise. The limiting factor in the past typically has been the size of the instrumentation available. The surgical management of stone disease in children is now similar to that in the adult (32,97,104).

The various treatment modalities available in children are identical to those in adults. Of course with some, extreme modifications other than just size alone need to be made to accommodate patients who are very small or who may have significant associated congenital problems, such as spina bifida and severe kyphoscoliosis. The specific treatments are well-known to all urologists experienced in treating stones and have been employed successfully in children. These include ESWL (58,118), percutaneous lithotripsy (PCL), ureteroscopy (3,113), laser lithotripsy (137,146), ultrasonic lithotripsy, and electrohydraulic lithotripsy (EHL). Open surgical stone extraction is another reasonable treatment modality in children, especially when there are associated congenital problems, such as ureteropelvic junction obstruction, that need correction.

As previously mentioned, there are differences that need to be considered when employing these stone treatment modalities in children. ESWL, for example, generally cannot be performed in children without general anesthesia. Technical factors such as modifying the table so that the shock heads are adequately positioned also are involved when the patient is very small or has skeletal deformities. Passage of stone fragments may be less likely to occur through small ureters. In a recent series of 33 children, no stone in excess of 3 mm passed spontaneously (172). Excessive shock waves or high-intensity shock waves need to be avoided because of the sensitivity of the immature kidney, and in doing so, the treatment of the stone may be rendered inadequate. When PCL is being considered, the pediatric kidney is much more difficult to access adequately; consequently, an experienced pediatric interventional radiologist is a very important part of the team. The size of the tract that is established is usually the limiting factor for this procedure, along with the size and length of the instruments. Infusion of irrigating fluid needs to be monitored carefully, because the margin for error is much less in children than in adults (78). Multiple procedures are not uncommon with this approach, which is unappealing to most children and parents. Tubes required after PCL are more apt to fail either because of stone fragments and debris occluding the small lumen of the tube or because they are more tenuous and get pulled out accidentally. Ureteroscopy is excellent for stones below the true pelvis and has become more available to the pediatric endoscopist since the development of smaller, rigid telescopes that often can be passed without dilation of the ureteral orifice. Flexible ureteroscopes and the holmium laser also have contributed to the improvements in ureteroscopy.

The etiology of the stone is relevant both in treatment considerations acutely, and in terms of prevention subsequently. Stones may be either infectious or metabolic. The most common metabolic stones are typically calcium, oxalate,

uric acid, or cystine. Other types of stones may be seen as part of underlying metabolic problems, such as xanthinuria, or xanthopurine stones found in Lesch-Nyhan disease. Calcium stones may be found in patients with hypercalciuria or normocalciuria.

Infection stones, also called *struvite stones* (magnesium–ammonium phosphate) typically are made in alkaline urine. Urease produced by bacteria produces large amounts of ammonium that buffers the urine to a constant alkaline pH. This leads to crystallization of magnesium and phosphorus. Antibiotics are unsuccessful in addressing these stones because causative bacteria are encased in the stone. Treatment involves complete stone removal and then subsequent antibiotics for sterilization of the urine. *Proteus, Providencia, Pseudomonas, Klebsiella, Streptococcus,* and *Mycoplasma* all have been implicated in struvite stone formation.

Calcium oxalate stones are the most common stones in children, and hypercalciuria is the most common etiology. Hypercalciuria most commonly occurs because of a renal leak, because of increased absorption from the gut, or resulting from the acidic form of renal tubular acidosis (i.e., distal RTA). Prolonged immobilization also can result in calcium stone formation.

In renal leak hypercalciuria, there is a high urinary calcium-to-creatinine ratio (Ca:Cr) in fasting patients in both spot and 24-hour urine specimens. The 24-hour urinary calcium exceeds 4 mg/kg per day, and the urinary Ca:Cr exceeds 0.21 (160). In absorptive hypercalciuria, there is increased absorption of calcium from the GI tract. It is detected on 24-hour urine by measuring Ca:Cr on a standard diet and then repeated. Finally, a third measurement is taken after a 14-day period of dietary sodium and calcium restriction (129,160). Normal children excrete less than 4 mg/kg per day of calcium in all three samples. Distal RTA is determined by checking voided urinary pH throughout the day. If the pH is ever less than 5.3, the diagnosis of RTA can be excluded (49). If this test is equivocal, an acid-loading test may be necessary to establish this diagnosis.

Two forms of hyperoxaluria exist: a primary type and a secondary type. The primary form is an autosomal-recessive trait, and children with this develop calcium oxalate stones early in life, often before 5 years of age. Oxalate excretion that exceeds 50 mg per day should call this diagnosis into question (147). Secondary hyperoxaluria almost always is associated with enteric disease such as malabsorption, irritable bowel disease, cystic fibrosis, or bowel resection (short gut). It also is seen in patients with high-oxalate diets or excessive vitamin C intake (i.e., greater than 4 g per day) (129).

Patients with calcium stones who have normocalciuria often form stones because of a deficiency of stone inhibitors such as magnesium or citrate. No studies show that the addition of magnesium or citrate in patients with low urinary levels of these stone inhibitors will decrease the incidence of subsequent stone formation.

Uric acid stones are formed in acid urine. Urinary pH less than 5.8 will promote crystallization of uric acid. Elevated serum uric acid will result in elevated urinary levels and is seen in familial hyperuricemia, bowel disease, certain inborn errors of metabolism (Lesch-Nyhan disease), or dietary abnormalities.

Cystine stones also are formed in acid urine. Cystine precipitates in urine with a pH of less than 7. Cystinuria is inherited, as an autosomal-recessive trait in which there is failure of the renal tubules to absorb four amino acids: *c*ystine, *o*rnithine, *l*ysine, and *a*rginine (COLA). Only cystine has poor solubility in the pH range of urine and consequently stones will form.

Once the patient has been rendered stone free, the emphasis is placed on prevention of further stone formation. If a specific cause for stone formation is determined, there is a possibility that specific treatment can be instituted. This may entail the use of drugs such as thiazide diuretics, or dietary modifications to attempt a reduction in the excretion of the offending substance. When no specific reason for stone formation is detected, the mainstay of treatment is to significantly increase fluid intake to increase urine output.

Antenatal Assessment

The widespread use of screening ultrasonography of the pregnant female detects anomalies in 1% of pregnancies, of which 20% occur in the genitourinary tract (69,138). When an anomaly of the urinary tract is identified, multiple specialists including the perinatologist, primary care physician, ultrasonographer, and pediatric urologist are involved in the assessment and subsequent management. The vast majority of anomalies are those causing antenatal hydronephrosis. The obvious stress and uncertainty this brings to the family requires close coordination with all physicians involved to provide the best care.

The pediatric urologist should provide counseling on specific urologic conditions such as exstrophy and hydronephrosis. A balanced view can be presented to the parents to minimize the ongoing stress. The physician should provide specific information and answer questions about the condition with the parents. The postnatal imaging and management need to be discussed in detail, because this knowledge will decrease anxiety after the baby is born. It is important to provide all requested information to the parents so they can make informed decisions in conjunction with the perinatologist.

Before the office visit, it is incumbent upon the pediatric urologist to talk to the perinatologist and ultrasonographer. Specifics of the pregnancy and testing already performed should be ascertained. Sex of the fetus, other anomalies, results of amniocentesis, and any genetic testing are obtained.

If the fetal bladder urine has been sampled for electrolyte content, these results are requested. The mother's prior obstetric history and urologic history also are obtained.

The prenatal ultrasounds are reviewed with the perinatologist and radiologist. The urinary tract measurements, including renal size, anteroposterior diameter of the renal pelvis, calyectasis, renal echogenicity, corticomedullary differentiation, ureterectasis, and amount of amniotic fluid on serial measurements are reviewed (53). Bladder filling and emptying should be present. Abdominal wall defects and penile anomalies, if detected, combined with absent bladder filling and emptying indicate exstrophy of the bladder (23,64). Currently, a renal pelvic diameter of greater than 4 mm *before* 33 weeks of gestation and greater than 7 mm *after* 33 weeks of gestation is considered significant hydronephrosis (36). Serial fetal ultrasounds demonstrating increased renal pelvic diameter imply increased severity of the process. The main considerations in determining the management of the fetus are overall fetal well-being, gestational age, amniotic fluid volume, and unilateral versus bilateral hydronephrosis (36).

If hydronephrosis is unilateral with normal amniotic fluid, no special delivery is required. The pediatrician is contacted concerning postnatal antibiotic prophylaxis. On rare occasions with unilateral hydronephrosis, predelivery renal pelvic aspiration is necessary to prevent dystocia (38). The primary life-threatening anomalies are those causing bilateral hydroureteronephrosis and bladder distention. These include posterior urethral valves, urethral atresia, and prune-belly syndrome. Urethral atresia is nearly always fatal, resulting from coexistent renal dysplasia. When oligohydramnios is present, normal pulmonary development does not occur and is a severe adverse prognostic sign. Neonatal demise in these circumstances results not from renal failure but from pulmonary hypoplasia. The fetus with bilateral hydronephrosis is at high risk and should be delivered at a center specializing in the care of high-risk pregnancies and with infant intensive care and surgical specialists.

Fetal intervention continues to evolve and includes termination of pregnancy, placement of a vesicoamniotic shunt, and open or fetoscopic surgery. Prenatal interventions to improve renal function and pulmonary development remain experimental and, although technically feasible, are associated with significant fetal and maternal risk. Complications occur in up to 45% of fetuses. There are few clinical data to prove that *in utero* intervention improves postnatal renal function or minimizes renal dysplasia. At present, the selection of patients for fetal intervention are based on the following fetal prognostic factors:

1. Renal cystic dysplasia
2. Fetal urinary electrolytes
3. Reduced lung area
4. Elevated $ß_2$-microglobulins
5. Prolonged oligohydramnios

The best case scenario for fetal intervention is the male patient with bilateral hydronephrosis with distended bladder, no other anomalies, normal chromosomal analysis, second trimester onset of oligohydramnios, and “favorable” serial fetal urine electrolyte measurements. This fetus would have a poor prognosis, but theoretically has improvable renal parameters and renal outcome (35).

In summary, prenatal imaging alerts the physician to urinary tract abnormalities before the onset of symptoms. Postnatal evaluation allows for timely intervention if necessary. Prenatal intervention based on present knowledge rarely is indicated. This information needs to be given to the parents in a coordinated caring fashion to diminish their anxiety and fears.

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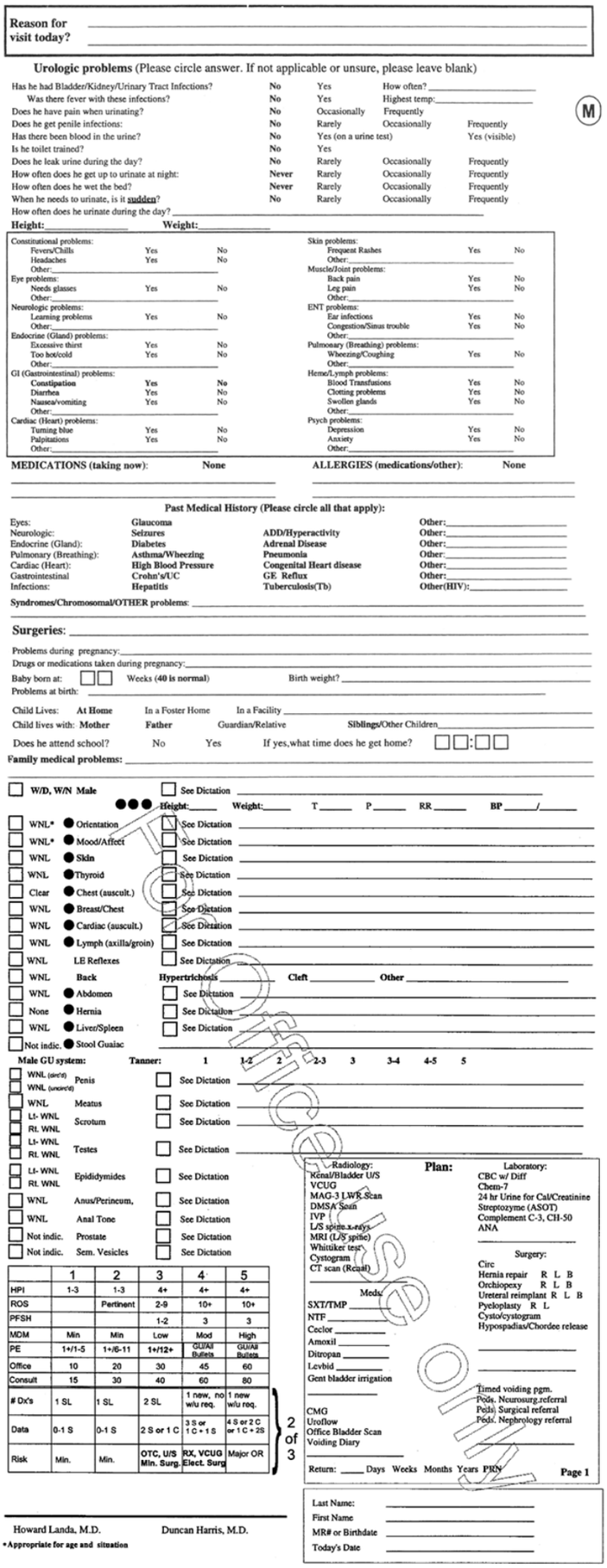
APPENDICES

APPENDIX 1



Reason for visit today? _____

Urologic problems (Please circle answer. If not applicable or unsure, please leave blank)

Has he had Bladder/Kidney/Urinary Tract Infections?	No	Yes	How often? _____	
Was there fever with these infections?	No	Yes	Highest temp: _____	
Does he have pain when urinating?	No	Occasionally	Frequently	
Does he get penile infections:	No	Rarely	Occasionally	Frequently
Has there been blood in the urine?	No	Yes (on a urine test)		Yes (visible)
Is he toilet trained?	No	Yes		
Does he leak urine during the day?	No	Rarely	Occasionally	Frequently
How often does he get up to urinate at night:	Never	Rarely	Occasionally	Frequently
How often does he wet the bed?	Never	Rarely	Occasionally	Frequently
When he needs to urinate, is it sudden?	No	Rarely	Occasionally	Frequently

How often does he urinate during the day? _____

Height:_____ **Weight:**_____

Constitutional problems:			Skin problems:		
Fevers/Chills	Yes	No	Frequent Rashes	Yes	No
Headaches	Yes	No	Other:		
Other:			Muscle/Joint problems:		
Eye problems:			Back pain	Yes	No
Needs glasses	Yes	No	Leg pain	Yes	No
Other:			Other:		
Neurologic problems:			ENT problems:		
Learning problems	Yes	No	Ear infections	Yes	No
Other:			Congestion/Sinus trouble	Yes	No
Endocrine (Gland) problems:			Other:		
Excessive thirst	Yes	No	Pulmonary (Breathing) problems:		
Too hot/cold	Yes	No	Wheezing/Coughing	Yes	No
Other:			Other:		
GI (Gastrointestinal) problems:			Heme/Lymph problems:		
Constipation	**Yes**	**No**	Blood Transfusions	Yes	No
Diarrhea	Yes	No	Clotting problems	Yes	No
Nausea/vomiting	Yes	No	Swollen glands	Yes	No
Other:			Other:		
Cardiac (Heart) problems:			Psych problems:		
Turning blue	Yes	No	Depression	Yes	No
Palpitations	Yes	No	Anxiety	Yes	No
Other:			Other:		

MEDICATIONS (taking now): **None**

ALLERGIES (medications/other): **None**

Past Medical History (Please circle all that apply):

Eyes:	**Glaucoma**		Other: _____
Neurologic:	**Seizures**	**ADD/Hyperactivity**	Other: _____
Endocrine (Gland):	**Diabetes**	**Adrenal Disease**	Other: _____
Pulmonary (Breathing):	**Asthma/Wheezing**	**Pneumonia**	Other: _____
Cardiac (Heart):	**High Blood Pressure**	**Congenital Heart disease**	Other: _____
Gastrointestinal	**Crohn's/UC**	**GE Reflux**	Other: _____
Infections:	**Hepatitis**	**Tuberculosis(Tb)**	Other(HIV): _____

Syndromes/Chromosomal/OTHER problems: _____

Surgeries: _____

Problems during pregnancy: _____

Drugs or medications taken during pregnancy: _____

Baby born at: ☐☐ Weeks (**40 is normal**) Birth weight? _____

Problems at birth: _____

Child Lives: **At Home** In a Foster Home In a Facility _____

Child lives with: **Mother** **Father** Guardian/Relative **Siblings**/Other Children _____

Does he attend school? No Yes If yes,what time does he get home? ☐☐:☐☐

Family medical problems: _____

☐ **W/D, W/N Male** ☐ See Dictation _____

Height:_____ **Weight:**_____ **T**_____ **P**_____ **RR**_____ **BP**_____/_____

☐ WNL*	● Orientation	☐ See Dictation	_____
☐ WNL*	● Mood/Affect	☐ See Dictation	_____
☐ WNL	● **Skin**	☐ See Dictation	_____
☐ WNL	● Thyroid	☐ See Dictation	_____
☐ Clear	● Chest (auscult.)	☐ See Dictation	_____
☐ WNL	● Breast/Chest	☐ See Dictation	_____
☐ WNL	● Cardiac (auscult.)	☐ See Dictation	_____
☐ WNL	● Lymph (axilla/groin)	☐ See Dictation	_____
☐ WNL	LE Reflexes	☐ See Dictation	_____
☐ WNL	**Back**	**Hypertrichosis** _____ **Cleft** _____ **Other** _____	
☐ WNL	● Abdomen	☐ See Dictation	_____
☐ None	● Hernia	☐ See Dictation	_____
☐ WNL	● Liver/Spleen	☐ See Dictation	_____
☐ Not indic.	● Stool Guaiac	_____	

Male GU system: **Tanner:** 1 1-2 2 2-3 3 3-4 4-5 5

☐ WNL (circ'd) ☐ WNL (uncirc'd)	Penis	☐ See Dictation	_____
☐ WNL	Meatus	☐ See Dictation	_____
☐ Lt. WNL ☐ Rt. WNL	Scrotum	☐ See Dictation	_____
☐ Lt. WNL ☐ Rt. WNL	Testes	☐ See Dictation	_____
☐ Lt. WNL ☐ Rt. WNL	Epididymides	☐ See Dictation	
☐ WNL	Anus/Perincum,	☐ See Dictation	
☐ WNL	Anal Tone	☐ See Dictation	
☐ Not indic.	Prostate	☐ See Dictation	
☐ Not indic.	Sem. Vesicles	☐ See Dictation	

	1	2	3	4	5
HPI	1-3	1-3	4+	4+	4+
ROS		Pertinent	2-9	10+	10+
PFSH			1-2	3	3
MDM	Min	Min	Low	Mod	High
PE	1+/1-5	1+/6-11	1+/12+	GU/All Bullets	GU/All Bullets
Office	10	20	30	45	60
Consult	15	30	40	60	80
# Dx's	1 SL	1 SL	2 SL	1 new, no w/u req.	1 new w/u req.
Data	0-1 S	0-1 S	2 S or 1 C	3 S or 1 C + 1 S	4 S or 2 C or 1 C + 2S
Risk	Min.	Min.	OTC, U/S Min. Surg.	RX, VCUG Elect. Surg	Major OR

2 of 3

Plan:

Radiology:
Renal/Bladder U/S
VCUG
MAG-3 LWR Scan
DMSA Scan
IVP
L/S spine x-rays
MRI (L/S spine)
Whitaker test
Cystogram
CT scan (Renal)

Laboratory:
CBC w/ Diff
Chem-7
24 hr Urine for Cal/Creatinine
Streptozyme (ASOT)
Complement C-3, CH-50
ANA

Surgery:
Circ
Hernia repair R L B
Orchiopexy R L B
Ureteral reimplant R L B
Pyeloplasty R L
Cysto/cystogram
Hypospadias/Chordee release

Meds:
SXT/TMP _____
NTF _____
Ceclor _____
Amoxil _____
Ditropan _____
Levbid _____
Gent bladder irrigation

Timed voiding pgm.
Peds. Neurosurg.referral
Peds. Surgical referral
Peds. Nephrology referral

CMG
Uroflow
Office Bladder Scan
Voiding Diary

Return: ____ Days Weeks Months Years PRN

Page 1

Last Name: _____
First Name _____
MR# or Birthdate _____
Today's Date _____

Howard Landa, M.D. Duncan Harris, M.D.

*Appropriate for age and situation

Reason for visit today? _____

Urologic problems (Please circle answer. If not applicable or unsure, please leave blank)

Has she had Bladder/Kidney/Urinary Tract Infections?	**No**	Yes	How often? _____	
Was there fever with these infections?	**No**	Yes	Highest temp: _____	
Does she have pain when urinating?	**No**	Occasionally	Frequently	
Has there been blood in the urine?	**No**	Yes (on a urine test)	Yes (visible)	
Is she toilet trained?	**No**	Yes		
Does she leak urine during the day?	**No**	Rarely	Occasionally	Frequently
How often does she get up to urinate at night:	**Never**	Rarely	Occasionally	Frequently
How often does she wet the bed?	**Never**	Rarely	Occasionally	Frequently
When she needs to urinate, is it **sudden**?	**No**	Rarely	Occasionally	Frequently

How often does she urinate during the day? _____

Height:_____ **Weight:**_____

Constitutional problems:			Skin problems:		
Fevers/Chills	Yes	No	Frequent Rashes	Yes	No
Headaches	Yes	No	Other:		
Other:			Muscle/Joint problems:		
Eye problems:			Back pain	Yes	No
Needs glasses	Yes	No	Leg pain	Yes	No
Other:			Other:		
Neurologic problems:			ENT problems:		
Learning problems	Yes	No	Ear infections	Yes	No
Other:			Congestion/Sinus trouble	Yes	No
Endocrine (Gland) problems:			Other:		
Excessive thirst	Yes	No	Pulmonary (Breathing) problems:		
Too hot/cold	Yes	No	Wheezing/Coughing	Yes	No
Other:			Other:		
GI (Gastrointestinal) problems:			Heme/Lymph problems:		
Constipation	**Yes**	**No**	Blood Transfusions	Yes	No
Diarrhea	Yes	No	Clotting problems	Yes	No
Nausea/vomiting	Yes	No	Swollen glands	Yes	No
Other:			Other:		
Cardiac (Heart) problems:			Psych problems:		
Turning blue	Yes	No	Depression	Yes	No
Palpitations	Yes	No	Anxiety	Yes	No
Other:			Other:		

MEDICATIONS (taking now): **None**

_____

_____

ALLERGIES (medications/other): **None**

_____

_____

Past Medical History (Please circle all that apply):

Eyes:	**Glaucoma**		**Other:**_____
Neurologic:	**Seizures**	**ADD/Hyperactivity**	**Other:**_____
Endocrine (Gland):	**Diabetes**	**Adrenal Disease**	**Other:**_____
Pulmonary (Breathing):	**Asthma/Wheezing**	**Pneumonia**	**Other:**_____
Cardiac (Heart):	**High Blood Pressure**	**Congenital Heart disease**	**Other:**_____
Gastrointestinal	**Crohn's/UC**	**GE Reflux**	**Other:**_____
Infections:	**Hepatitis**	**Tuberculosis(Tb)**	**Other(HIV):**_____

Syndromes/Chromosomal/OTHER problems: _____

_____

Surgeries: _____

Problems during pregnancy: _____

Drugs or medications taken during pregnancy: _____

Baby born at: ☐☐ Weeks **(40 is normal)** Birth weight? _____

Problems at birth: _____

Child Lives: **At Home** In a Foster Home In a Facility _____

Child lives with: **Mother** **Father** Guardian/Relative **Siblings/Other Children**_____

Does she attend school? No Yes If yes,what time does she get home? ☐☐:☐☐

Family medical problems: _____

_____

☐	**W/D, W/N Female**	☐	See Dictation _____
	Height:_____ **Weight:**_____ T_____ P_____ RR_____ **BP** _____/_____		
☐ WNL*	● Orientation	☐	See Dictation _____
☐ WNL*	● Mood/Affect	☐	See Dictation _____
☐ WNL	● **Skin**	☐	See Dictation _____
☐ WNL	● Thyroid	☐	See Dictation _____
☐ Clear	● Chest (auscult.)	☐	See Dictation _____
☐ WNL	● Cardiac (auscult.)	☐	See Dictation _____
☐ WNL	● Lymph (axilla/groin)	☐	See Dictation _____
☐ WNL	LE Reflexes	☐	See Dictation _____
☐ WNL	**Back**	**Hypertrichosis** _____ **Cleft** _____ **Other** _____	
☐ WNL	● Abdomen	☐	See Dictation _____
☐ None	● Hernia	☐	See Dictation _____
☐ WNL	● Liver/Spleen	☐	See Dictation _____
☐ Not indic.	● Stool Guaiac		_____

Female GU system: **Tanner:** 1 1-2 2 2-3 3 3-4 4-5 5

☐ WNL	Ext. Genit.	☐	See Dictation _____
☐ WNL	Meatus	☐	See Dictation _____
☐ WNL	Bladder	☐	See Dictation _____
☐ WNL	Anus/Perineum	☐	See Dictation _____
☐ Not indic.	Urethra	☐	See Dictation
☐ Not indic.	Vagina	☐	See Dictation
☐ Not indic.	Cervix	☐	See Dictation
☐ Not indic.	Uterus	☐	See Dictation
☐ Not indic.	Adnexa	☐	See Dictation
☐ Not indic.	DRE	☐	See Dictation
☐ Not indic.	Breast	☐	See Dictation

	1	2	3	4	5
HPI	1-3	1-3	4+	4+	4+
ROS		Pertinent	2-9	10+	10+
PFSH			1-2	3	3
MDM	Min	Min	Low	Mod	High
PE	1+/1-5	1+/6-11	1+/12+	GU/All Bullets	GU/All Bullets
Office**	10	20	30	45	60
Consult**	15	30	40	60	80
# Dx's	1 SL	1 SL	2 SL	1 new, no w/u req.	1 new w/u req.
Data	0-1 S	0-1 S	2 S or 1 C	3 S or 1 C + 1 S	4 S or 2 C or 1 C + 2S
Risk	Min.	Min.	OTC, U/S Min. Surg.	RX, VCUG Elect. Surg	Major OR

} 2 of 3

Plan:

Radiology:
Renal/Bladder U/S
VCUG
MAG-3 LWR Scan
DMSA Scan
IVP
L/S spine x-rays
MRI (L/S spine)
Whittiker test
Cystogram
CT scan (Renal)

Meds:
SXT/TMP _____
NTF _____
Ceclor _____
Amoxil _____
Ditropan _____
Levbid _____
Gent bladder irrigation

Return: ____ Days Weeks Months Years **PRN**

Laboratory:
CBC w/ Diff
Chem-7
24 hr Urine for Cal/Creatinine
Streptozyme (ASOT)
Complement C-3, CH-50
ANA

Surgery:
Hernia repair R L B
Ureteral reimplant R L B
Pyeloplasty R L
Cysto/cystogram

CMG
Office Bladder Scan
Voiding Diary

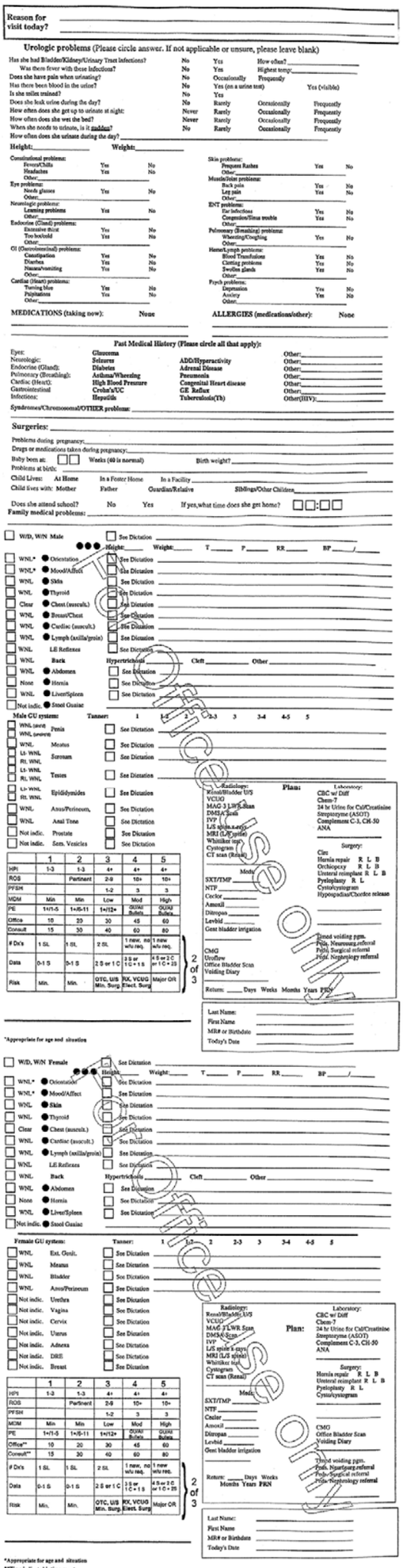
Timed voiding pgm.
Peds. Neurosurg.referral
Peds. Surgical referral
Peds. Nephrology referral

Last Name: _____
First Name _____
MR# or Birthdate _____
Today's Date _____

Howard Landa, M.D. Duncan Harris, M.D.

***Appropriate for age and situation**

****Time indicated is time spent**



Reason for visit today? _____

Urologic problems (Please circle answer. If not applicable or unsure, please leave blank)

Has she had Bladder/Kidney/Urinary Tract Infections? No Yes How often? _____
Was there fever with these Infections? No Yes Highest temp: _____
Does she have pain when urinating? No Occasionally Frequently
Has there been blood in the urine? No Yes (on a urine test) Yes (visible)
Is she toilet trained? No Yes
Does she leak urine during the day? No Rarely Occasionally Frequently
How often does she get up to urinate at night: Never Rarely Occasionally Frequently
How often does she wet the bed? Never Rarely Occasionally Frequently
When she needs to urinate, is it sudden? No Rarely Occasionally Frequently
How often does she urinate during the day? _____

Height: _____ **Weight:** _____

Constitutional problems:
Fevers/Chills Yes No
Headaches Yes No
Other: _____

Eye problems:
Needs glasses Yes No
Other: _____

Neurologic problems:
Learning problems Yes No
Other: _____

Endocrine (Gland) problems:
Excessive thirst Yes No
Too hot/cold Yes No
Other: _____

GI (Gastrointestinal) problems:
Constipation Yes No
Diarrhea Yes No
Nausea/vomiting Yes No
Other: _____

Cardiac (Heart) problems:
Turning blue Yes No
Palpitations Yes No
Other: _____

Skin problems:
Frequent Rashes Yes No
Other: _____

Muscle/bone problems:
Back pain Yes No
Leg pain Yes No
Other: _____

ENT problems:
Ear Infections Yes No
Congestion/Sinus trouble Yes No
Other: _____

Pulmonary (Breathing) problems:
Wheezing/Coughing Yes No
Other: _____

Hemet/Lymph problems:
Blood Transfusions Yes No
Clotting problems Yes No
Swollen glands Yes No
Other: _____

Psych problems:
Depression Yes No
Anxiety Yes No
Other: _____

MEDICATIONS (taking now): None

ALLERGIES (medications/other): None

Past Medical History (Please circle all that apply):

Eyes: **Glaucoma** Other: _____
Neurologic: **Seizures** **ADD/Hyperactivity** Other: _____
Endocrine (Gland): **Diabetes** **Adrenal Disease** Other: _____
Pulmonary (Breathing): **Asthma/Wheezing** **Pneumonia** Other: _____
Cardiac (Heart): **High Blood Pressure** **Congenital Heart disease** Other: _____
Gastrointestinal **Crohn's/UC** **GE Reflux** Other: _____
Infections: **Hepatitis** **Tuberculosis(Tb)** Other(HIV): _____

Syndromes/Chromosomal/OTHER problems: _____

Surgeries: _____

Problems during pregnancy: _____
Drugs or medications taken during pregnancy: _____
Baby born at: ☐☐ Weeks (40 is normal) Birth weight? _____
Problems at birth: _____
Child Lives: At Home In a Foster Home In a Facility _____
Child lives with: Mother Father Guardian/Relative Siblings/Other Children _____
Does she attend school? No Yes If yes,what time does she get home? ☐☐:☐☐
Family medical problems: _____

☐ W/D, W/N **Male** ☐ See Dictation _____

●●● **Height:**____ **Weight:**____ T____ P____ RR____ BP____/____

☐ WNL*	● Orientation	☐ See Dictation	
☐ WNL*	● Mood/Affect	☐ See Dictation	
☐ WNL	● Skin	☐ See Dictation	
☐ WNL	● Thyroid	☐ See Dictation	
☐ Clear	● Chest (auscult.)	☐ See Dictation	
☐ WNL	● Breast/Chest	☐ See Dictation	
☐ WNL	● Cardiac (auscult.)	☐ See Dictation	
☐ WNL	● Lymph (axilla/groin)	☐ See Dictation	
☐ WNL	LE Reflexes	☐ See Dictation	
☐ WNL	**Back**	Hypertrichosis _____ Cleft _____ Other _____	
☐ WNL	● Abdomen	☐ See Dictation	
☐ None	● Hernia	☐ See Dictation	
☐ WNL	● Liver/Spleen	☐ See Dictation	
☐ Not indic.	● Stool Guaiac	_____	

Male GU system: **Tanner:** 1 1-2 2 2-3 3 3-4 4-5 5

☐ WNL (uncir) ☐ WNL (circ)	Penis	☐ See Dictation	
☐ WNL	Meatus	☐ See Dictation	
☐ Lt- WNL ☐ Rt. WNL	Scrotum	☐ See Dictation	
☐ Lt- WNL ☐ Rt. WNL	Testes	☐ See Dictation	
☐ Lt- WNL ☐ Rt. WNL	Epididymides	☐ See Dictation	
☐ WNL	Anus/Perineum,	☐ See Dictation	
☐ WNL	Anal Tone	☐ See Dictation	
☐ Not indic.	Prostate	☐ See Dictation	
☐ Not indic.	Sem. Vesicles	☐ See Dictation	

	1	2	3	4	5
HPI	1-3	1-3	4+	4+	4+
ROS		Pertinent	2-9	10+	10+
PFSH			1-2	3	3
MDM	Min.	Min	Low	Mod	High
PE	1+/1-5	1+/5-11	1+/12+	DDX/2 Bullets	DDX/3 Bullets
Office	10	20	30	45	60
Consult	15	30	40	60	80
# Dx's	1 SL	1 SL	2 SL	1 new, no w/u req.	1 new w/u req.
Data	0-1 S	0-1 S	2 S or 1 C	3 S or 1 C + 1 S	4 S or 2 C or 1 C + 2S
Risk	Min.	Min.	OTC, U/S Min. Surg.	RX, VCUG Elect. Surg	Major O/R

2 of 3

Plan:

Radiology:
Renal/Bladder U/S
VCUG
MAG 3 L/WR Scan
DMSA Scan
IVP
L/S spine x-rays
MRI (L/S spine)
Whitaker test
Cystogram
CT scan (Renal)
_____ Meds
SXT/TMP _____
NTF _____
Cocior _____
Amoxil _____
Ditropan _____
Levbid _____
Gent bladder irrigation _____
_____
CMG
Uroflow
Office Bladder Scan
Voiding Diary
_____
Return: ____ Days Weeks Months Years PRN

Laboratory:
CBC w/ Diff
Chem-7
24 hr Urine for Cal/Creatinine
Streptomyme (ASOT)
Complement C-3, CH-50
ANA
_____
Surgery:
Circ
Hernia repair R L B
Orchiopexy R L B
Ureteral reimplant R L B
Pyeloplasty R L
Cystor/cystogram
Hypospadias/Chordee release
_____
_____
_____
Timed voiding pgm.
Peds. Neurosurg.referral
Peds. Surgical referral
Peds. Nephrology referral
_____

Last Name: _____
First Name _____
MR# or Birthdate _____
Today's Date _____

*Appropriate for age and situation

☐ W/D, W/N **Female** ☐ See Dictation _____

●●● **Height:**____ **Weight:**____ T____ P____ RR____ BP____/____

☐ WNL*	● Orientation	☐ See Dictation	
☐ WNL*	● Mood/Affect	☐ See Dictation	
☐ WNL	● Skin	☐ See Dictation	
☐ WNL	● Thyroid	☐ See Dictation	
☐ Clear	● Chest (auscult.)	☐ See Dictation	
☐ WNL	● Cardiac (auscult.)	☐ See Dictation	
☐ WNL	● Lymph (axilla/groin)	☐ See Dictation	
☐ WNL	LE Reflexes	☐ See Dictation	
☐ WNL	**Back**	Hypertrichosis _____ Cleft _____ Other _____	
☐ WNL	● Abdomen	☐ See Dictation	
☐ None	● Hernia	☐ See Dictation	
☐ WNL	● Liver/Spleen	☐ See Dictation	
☐ Not indic.	● Stool Guaiac	_____	

Female GU system: **Tanner:** 1 1-2 2 2-3 3 3-4 4-5 5

☐ WNL	Ext. Genit.	☐ See Dictation	
☐ WNL	Meatus	☐ See Dictation	
☐ WNL	Bladder	☐ See Dictation	
☐ WNL	Anus/Perineum	☐ See Dictation	
☐ Not indic.	Urethra	☐ See Dictation	
☐ Not indic.	Vagina	☐ See Dictation	
☐ Not indic.	Cervix	☐ See Dictation	
☐ Not indic.	Uterus	☐ See Dictation	
☐ Not indic.	Adnexa	☐ See Dictation	
☐ Not indic.	DRE	☐ See Dictation	
☐ Not indic.	Breast	☐ See Dictation	

	1	2	3	4	5
HPI	1-3	1-3	4+	4+	4+
ROS		Pertinent	2-9	10+	10+
PFSH			1-2	3	3
MDM	Min	Min	Low	Mod	High
PE	1+/1-5	1+/5-11	1+/12+	DDX/2 Bullets	DDX/3 Bullets
Office**	10	20	30	45	60
Consult**	15	30	40	60	80
# Dx's	1 SL	1 SL	2 SL	1 new, no w/u req.	1 new w/u req.
Data	0-1 S	0-1 S	2 S or 1 C	3 S or 1 C + 1 S	4 S or 2 C or 1 C + 2S
Risk	Min.	Min.	OTC, U/S Min. Surg.	RX, VCUG Elect. Surg	Major O/R

2 of 3

Plan:

Radiology:
Renal/Bladder U/S
VCUG
MAG 3 L/WR Scan
DMSA Scan
IVP
L/S spine x-rays
MRI (L/S spine)
Whitaker test
Cystogram
CT scan (Renal)
_____ Meds
SXT/TMP _____
NTF _____
Cocior _____
Amoxil _____
Ditropan _____
Levbid _____
Gent bladder irrigation _____
_____
CMG
Office Bladder Scan
Voiding Diary
_____
Timed voiding pgm.
Peds. Neurosurg.referral
Peds. Surgical referral
Peds. Nephrology referral
_____

Laboratory:
CBC w/ Diff
Chem-7
24 hr Urine for Cal/Creatinine
Streptomyme (ASOT)
Complement C-3, CH-50
ANA
_____
Surgery:
Hernia repair R L B
Ureteral reimplant R L B
Pyeloplasty R L
Cystor/cystogram
_____
_____
_____
_____
Return: ____ Days Weeks Months Years PRN

Last Name: _____
First Name _____
MR# or Birthdate _____
Today's Date _____

*Appropriate for age and situation
**Time indicated is time spent

Observation or Hospital Inpatient Care Services

(Initial)

(Admission and Discharge)

	Level 1	Level 2	Level 3
Observation Care	99218	99219	99220
Hospital Inpatient	99221	99222	99223
Admission & Discharge	99234	99235	99236

■ KEY COMPONENTS

MUST SATISFY ALL THREE KEY COMPONENTS

History	Content of Services		
History of Present Illness	4+*	4+*	4+*
Review of Systems	2–9	10+	10+
PFSH—Family and Social	1–2	3	3

*An extended can also be reached by documenting the status of at least 3 chronic or inactive conditions

Physical	System/Element	System/Element	System/Element
Single Organ System	1+/12+ 1+/9+ for eye & psych	shaded/all unshaded/1	shaded/all unshaded/1
Multisystem—General	1+/6–11	9+/x2 each	9+/x2 each

Medical Decision Making

MUST SATISFY TWO OF THE THREE ELEMENTS

Number of Diagnoses	Min.–Lim.	Multiple	Extensive
Amount of Data	Limited	Moderate	Extensive
Amount of Risk	Min.–Low	Moderate	High

■ CONTRIBUTORY COMPONENTS

Time

BECOMES KEY COMPONENT AND OVERRIDES OTHER COMPONENTS IF OVER 50% OF SERVICE IS COUNSELING OR COORDINATING [TIME IN MINUTES ONLY APPLIES TO CODES 99221, 99222 AND 99223]

Time	30	50	70

Problem

PROBLEM MUST JUSTIFY TREATMENT

Risk of Morbidity	Low	Moderate	High
Risk of Mortality		Moderate	Mod–High

Consult/Follow-Up Inpatient Subsequent Hospital Care

	Level 1	Level 2	Level 3
Subsequent Hospital Care	99231	99232	99233
Consults/Follow-Up Inpatient	99261	99262	99263

■ KEY COMPONENTS

MUST SATISFY TWO OF THE THREE KEY COMPONENTS

History	Content of Services		
History of Present Illness	1-3	1-3	4+*
Review of Systems		Pertinent	2-9
PFSH—Family and Social			

*An extended can also be reached by documenting the status of at least 3 chronic or inactive conditions

Physical	System/Element	System/Element	System/Element
Single Organ System	1+/1-5	1+/6-11	1+/12+ 1+/9+ for eye & psych
Multisystem—General	1+/1-5	1+/6-11	2+/12+

Medical Decision Making

MUST SATISFY TWO OF THE THREE ELEMENTS

Number of Diagnoses	Minimum	Multiple	Extensive
Amount of Data	None-Min	Moderate	Extensive
Amount of Risk	Minimum	Moderate	High

■ CONTRIBUTORY COMPONENTS

Time

BECOMES KEY COMPONENT AND OVERRIDES OTHER COMPONENTS IF OVER 50% OF SERVICE IS COUNSELING OR COORDINATING

Subsequent Hospital Care	15	25	35
Consult/Follow-Up	10	20	30

Problem

PROBLEM MUST JUSTIFY TREATMENT

Risk of Morbidity	Low	Moderate	High
Risk of Mortality		Moderate	Mod-High

Emergency Room

	Level 1	Level 2	Level 3	Level 4	Level 5
Emergency Room	**99281**	**99282**	**99283**	**99284**	**99285**

■ KEY COMPONENTS

MUST SATISFY ALL THREE KEY COMPONENTS

History	Content of Services				
History of Present Illness	1–3	1–3	1–3	4+*	4+*
Review of Systems		Pertinent	Pertinent	2–9	10+
PFSH—Family and Social				1	2–9

*An extended can also be reached by documenting the status of at least 3 chronic or inactive conditions

Physical	System/Element	System/Element	System/Element	System/Element	System/Element
Single Organ System	1+/1–5	1+/6–11	1+/6–11	1+/12+ 1+/9+ for eye & psych	shaded/all unshaded/1
Complete or Complete spec. exam	1+/1–5	1+/6–11	1+/6–11	2+/12+	9+/x2 each

Medical Decision Making

MUST SATISFY TWO OF THE THREE ELEMENTS

Number of Diagnoses	Minimum	Limited	Multiple	Multiple	Extensive
Amount of Data	Minimum	Limited	Moderate	Moderate	Extensive
Amount of Risk	Minimum	Low	Moderate	Moderate	High

■ CONTRIBUTORY COMPONENTS

Problem

PROBLEM MUST JUSTIFY TREATMENT

Risk of Morbidity		Low–Mod	Moderate	High	High
Risk of Mortality		Zero–Mod	Moderate	Mod–High	Mod–High

This product was developed in cooperation with Physician Reimbursement Systems as a compliment to their speciality specific books and coding course(s) and Relative Value Studies, Inc.'s publication Passport to E/M Coding.

New Patient, Outpatient, and Consults

	Level 1	Level 2	Level 3	Level 4	Level 5
New Patient, Outpatient	99201	99202	99203	99204	99205
Outpatient Consults	99241	99242	99243	99244	99245
Inpatient Consults	99251	99252	99253	99254	99255
Confirmatory Consults	99271	99272	99273	99274	99275

■ KEY COMPONENTS

MUST SATISFY ALL THREE KEY COMPONENTS

History	Content of Services				
History of Present Illness	1–3	1–3	4+*	4+*	4+*
Review of Systems		Pertinent	2–9	10+	10+
PFSH—Family and Social			1–2	3	3

*An extended can also be reached by documenting the status of at least 3 chronic or inactive conditions

Physical	System/Element	System/Element	System/Element	System/Element	System/Element
Single Organ System	1+/1–5	1+/6–11	1+/12+ 1+/9+ for eye & psych	shaded/all unshaded/1	shaded/all unshaded/1
Multisystem—General	1+/1–5	1+/6–11	2+/12+	9+/x2 each	9+/x2 each

Medical Decision Making

MUST SATISFY TWO OF THE THREE ELEMENTS

Number of Diagnoses	Minimum	Minimum	Limited	Multiple	Extensive
Amount of Data	Minimum	Minimum	Limited	Moderate	Extensive
Amount of Risk	Minimum	Minimum	Low	Moderate	High

■ CONTRIBUTORY COMPONENTS

Time

BECOMES KEY COMPONENT AND OVERRIDES OTHER COMPONENTS IF OVER 50% OF SERVICE IS COUNSELING OR COORDINATING

Office/Outpatient	10	20	30	45	60
Outpatient Consults	15	30	40	60	80
Inpatient Consults	20	40	55	80	110
Confirmatory Consults	—	—	—	—	—

Problem

PROBLEM MUST JUSTIFY TREATMENT

Risk of Morbidity		Low	Moderate	Mod–High	Mod–High

Established Patient

	Level 1	Level 2	Level 3	Level 4	Level 5
Office/Outpatient	**99211**	**99212**	**99213**	**99214**	**99215**

■ KEY COMPONENTS

MUST SATISFY TWO OF THE THREE KEY COMPONENTS

History	Content of Services				
History of Present Illness	Chief	1–3	1–3	4+*	4+*
Review of Systems			Pertinent	2–9	10+
PFSH—Family and Social				1	2–3

*An extended can also be reached by documenting the status of at least 3 chronic or inactive conditions

Physical	System/Element	System/Element	System/Element	System/Element	System/Element
Single Organ System	None–Min	1+/1–5	1+/6–11	1+/12+ 1+/9+ for eye & psych	shaded/all unshaded/1
Multisystem—General		1+/1–5	1+/6–11	2+/12+	9+/x2 each

Medical Decision Making

MUST SATISFY TWO OF THE THREE ELEMENTS

Number of Diagnoses	Minimum	Minimum	Limited	Multiple	Extensive
Amount of Data		Minimum	Lt-Mult	Moderate	Extensive
Amount of Risk		Minimum	Low	Moderate	High

■ CONTRIBUTORY COMPONENTS

Time

BECOMES KEY COMPONENT AND OVERRIDES OTHER COMPONENTS IF OVER 50% OF SERVICE IS COUNSELING OR COORDINATING

Time	5	10	15	25	40

Problem

PROBLEM MUST JUSTIFY TREATMENT

Risk of Morbidity			Low–Mod	Mod–High	Mod–High
Risk of Mortality			Zero–Mod	Mod–High	Mod–High

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APPENDIX 2

Genitourinary Examination

System/Body Area	Elements of Examination	
Constitutional	• Measurement of **any three of the following seven** vital signs: a) sitting or standing blood pressure, b) supine blood pressure, c) pulse rate and regularity, d) respiration, e) temperature, f) height, g) weight (may be measured by ancillary staff) • General appearance of patient (e.g., development, nutrition, body habitus, deformities, attention togrooming	
Head and face		
Eyes		
Ears, nose, mouth, and throat		
Neck	• Examination of neck (e.g., masses, overall appearance, symmetry, tracheal position, crepitus) • Examination of thyroid (e.g., enlargement, tenderness, mass)	
Respiratory	• Assessment of respiratory effort (e.g., intercostal retractions, use of accessory muscles, diaphragmatic movement) • Auscultation of lungs (e.g., breath sounds, adventitious sounds, rubs)	
Cardiovascular	• Auscultation of heart with notation of abnormal sounds and murmurs • Examination of peripheral vascular system by observation (e.g., swelling, varicosities) and palpation (e.g., pulses, temperature, edema, tenderness)	
Chest (breasts)	[See genitourinary (female)]	
Gastrointestinal (abdomen)	• Examination of abdomen with notation of presence of masses or tenderness • Examination for presence or absence of hernia • Examination of liver and spleen • Stool sample obtained for occult blood test when indicated	
Genitourinary	**Male:**	• Inspection of anus and perineum Examination (with or without specimen collection for smears and cultures) of genitalia including: • Scrotum (e.g., lesions, cysts, rashes) • Epididymides (e.g., size, symmetry, masses) • Testes (e.g., size, symmetry, masses) • Urethral meatus (e.g., size, location, lesions, discharge) • Penis (e.g., lesions, presence or absence of foreskin, foreskin retractability, plaque, masses, scarring, deformities) Digital rectal examination including: • Prostate gland (e.g., size, symmetry, nodularity, tenderness) • Seminal vesicles (e.g., symmetry, tenderness, masses, enlargement) • Sphincter tone, presence of hemorrhoids, rectal masses
	Female:	• Inspection and palpation of breasts (e.g., masses or lumps, tenderness, symmetry, nipple discharge) • Digital rectal examination including sphincter tone, presence of hemorrhoids, rectal masses Pelvic examination (with or without specimen collection for smears and cultures) including: • External genitalia (e.g., general appearance, hair distribution, lesions) • Urethral meatus (e.g., size, location, lesions, prolapse) • Urethra (e.g., masses, tenderness, scarring) • Bladder (e.g., fullness, masses, tenderness) • Vagina (e.g., general appearance, estrogen effect, lesions, pelvic support, cystocele, rectocele) • Cervix (e.g., general appearance, lesions, discharge) • Uterus (e.g., size, contour, position, mobility, tenderness, consistency, descent or support) • Adnexa/parametria (e.g., masses, tenderness, organomegaly, nodularity) • Anus and perineum
	Includes **at least seven of the following eleven** elements identified by bullets:	
Lymphatic	• Palpation of lymph nodes in neck, axillae, groin, and/or other location	
Musculoskeletal		
Extremities		
Skin	• Inspection and/or palpation of skin and subcutaneous tissue (e.g., rashes, lesions, ulcers)	
Neurologic	Brief assessment of mental status including:	
psychiatric	• Orientation (e.g., time, place, and person) and • Mood and affect (e.g., depression, anxiety, agitation)	

Content and Documentation Requirements

Level of Examination	Perform and document
Problem focused	**One to five** elements identified by a bullet
Expanded problem focused	**At least six** elements identified by a bullet
Detailed	**At least twelve** elements identified by a bullet
Comprehensive	Perform **all** elements identified by a bullet, and document every element in a box with a shaded border and at least one element in a box with an unshaded border.

56

PEDIATRIC ENDOUROLOGY

William R. Strand

David A. Bloom

W.R. Strand: Department of Urology, UT Southwestern Medical Center at Dallas; Department of Pediatric Urology, Children's Medical Center, Dallas, TX 75235.

D.A. Bloom: Department of Urology, University of Michigan, Ann Arbor, MI 48109.

Contents

PEDIATRIC ENDOSCOPIC SURGERY

Part of "56 - PEDIATRIC ENDOUROLOGY "

The pursuit of endourology (from the Greek word *endon* meaning “within”) exploits controlled manipulations within the urinary tract, often aided by either fluoroscopic or ultrasonographic imaging. Principles in this practice date back to urethral catheterization for relief of urinary retention due to bladder stone. For centuries, this treatment has been considered a preferable alternative to the terror and significant mortality of perineal lithotomy (25). Percutaneous nephrostomy, the cornerstone technique of endourology, also has a long history born of necessity. Dr. Thomas Hillier (1865), of Great Ormand Street Hospital for Sick Children, intermittently aspirated urine over a 4-year interval from the massively hydronephrotic right kidney of a young boy to ease the boy's suffering (27). The urge to comfort and help the sick by formulating rational methods of therapy are traits at the heart of human civilization (25)

that have served as the muse for development of pediatric endourology.

HISTORY OF PEDIATRIC ENDOSCOPY

Part of "56 - PEDIATRIC ENDOUROLOGY "

Evolution of the Pediatric Cystoscope

More than 120 years have passed since the first practical light cystoscope was constructed in Germany. Nitze (1879) combined the basic structure (candle holder in a box with a hollow tube used for viewing) proposed in 1806 by Philipp Bozzini (37) with an internal glowing platinum wire at the inner tip of the endoscope developed by Trouvé (375), and added an optical lens near the light source to provide magnification (283,326). The incandescent platinum wire became easily fused, requiring frequent exchange, and also could burn the bladder and urethra on removal of the cystoscope (280). After Edison invented the light bulb, the Mignon lamp was rapidly incorporated into cystoscope design and provided more reliable illumination. This eliminated the need for the complex and expensive internal cooling system developed by Nitze, and changed the cystoscope to an inexpensive and readily usable instrument (326).

Nitze developed a cystoscope for use in children, but its relatively large size (17 Fr) and standard adult length greatly limited its use. Edwin Beer constructed and promoted the first pediatric cystoscope (1907) with a shorter length and acceptable caliber (15 Fr). This design included a detachable catheterizing apparatus (195). In 1911, he reported on a large series of cystoscopic examinations in children as young as 14 months in girls, and 5 years in boys (15). Hugh Hampton Young performed the first endoscopic examination on a patient (17 years old) with posterior urethral valves in 1912. He also managed to pass the extra-long child's cystoscope (12 Fr) through a patulous right ureteral orifice (1.5 cm) and up a dilated ureter into the renal pelvis, thereby completing the first ureteropyeloscopy (75). When McCarthy (1931) added a movable lever controlling a cutting loop (252) to the resectoscope design first constructed by Stern (1926) (359), routine instrumentation for lower urinary tract pathology became possible (326).

In 1960, Hopkins patented the revolutionary rod lens system, which substituted solid glass rods with intervening air spaces for the delicately positioned glass lenses previously used (170). This design proffered enhanced light transmission from a higher refractive index and greater durability because these new cystoscope lenses were constructed primarily of glass. By 1961, the McCarthy miniature and infant cystoscopes had become a distinct asset in evaluating children with urinary infection for structural derangements of the lower urinary tract (353). An interchangeable fiber-optic light source available for both of these instruments was considered a very marked advance over the standard incandescent light source. Pediatric resectoscope sheaths ranging from 11 to 14 Fr using interchangeable telescopes and a variety of working elements were widely available by 1979 (345).

Development of Percutaneous Nephroscopy

The development of nephroscopy necessarily followed refinements in percutaneous renal access. Initial reports of percutaneous access for evaluation of renal cysts (394) led to the landmark article by Goodwin and others (1955) detailing temporary percutaneous nephrostomy drainage in 16 patients with severe hydronephrosis (145). Although intraoperative nephroscopy with a rigid endoscope through a pyelotomy incision was first reported in 1948 (374), the utility of nephroscopy was extended greatly when it could be performed through an existing nephrostomy tract (62). The 16-Fr flexible fiber-optic nephroscope, introduced in 1979, allowed enhanced renal access for electrohydraulic nephrolithotripsy (68).

Evolution of Flexible and Rigid Ureteroscopes

Breakthroughs in fiber optics and a perceived requirement to follow the contour of the ureter initially promoted the development of flexible rather than rigid ureteroscopes. However, enthusiasts found it hard to rally around early models because of limited visibility (no irrigation port, and limited flexibility) (8,80). Once a 39 cm long, rigid ureteroscope with an irrigation channel was used for ureteropyeloscopy (1980) (298), rapid advances for rigid and later flexible ureteroscopes were made, extending their use to therapeutic interventions (8). Flexible ureteroscopes currently offer working diameters of 6.8 Fr with large working channels (3.6 Fr), and active tip deflection in two directions, suitable for use in children.

As technical improvements in optics become rapidly accepted and adopted for use, traditional endoscopic boundaries blur. Percutaneous endoscopic fulguration of posterior urethral valves in a 22-week-gestation fetus has been demonstrated to be technically possible. A 2.5-mm steerable endoscope with a 1.3-mm operating channel was passed through a 10-gauge trocar placed under ultrasonographic guidance through the maternal abdomen into the fetal bladder, and advanced over a soft-tip 0.025-inch guidewire into the prostatic urethra. Posterior urethral valves were fulgurated under visual guidance using a 2-Fr ball-tip monopolar flexible electrode. Although ablation of the obstructing valves was noted on postnatal examination, in this case the child succumbed to complications of pulmonary hypoplasia at 31 weeks of gestation (318). Specific indications for evaluation and intervention continue to be refined as more advanced endoscopic equipment becomes available.

CYSTOSCOPY

Part of "56 - PEDIATRIC ENDOUROLOGY "

Historical Indications

Lyon and Smith (244) described a consistent narrowing of the distal urethra in the majority of female children studied for urinary infection and invoked distal urethral stenosis as the cause of their malady. Cystoscopy with urethral dilation thus became routine practice in the evaluation and treatment for both recurrent urinary infection (148), and diurnal and nocturnal enuresis (7). Cystoscopic examination also was used to detect vesicoureteral reflux (VUR) evident visually after first filling (and then emptying) the bladder to capacity with indigo carmine (6).

Smith and Lattimer (353) recorded 4,088 endoscopic procedures in children over a 10-year interval from 1961 to 1971. Johnson and associates (187) noted that more than 95% of cystoscopies were performed independent of other open urologic procedures. Although some authors detected distal urethral stenosis in up to 96% of children with recurrent urinary infection (393), others found similarity in urethral calibration for groups of recurrently infected and normal children (148,174). Govan and Palmer (146) suggested that this finding merely represented "a normally narrowed area in the distal region of the urethra." Recognition that routine correction of this perceived bladder outlet obstruction in girls failed to afford any protection from recurrent urinary infection (198,388) caused the pervasive use of cystoscopy in these children to wane. Other accepted indications besides voiding dysfunction also were reviewed, and some were discarded. Routine cystoscopy for initial evaluation of VUR, primary enuresis, and most cases of hematuria was and still is considered unnecessary (187,390).

Current Indications

Children with microscopic hematuria and normal radiographic studies (sonography and voiding cystourethrogram [VCUG]) most commonly have normal cystoscopic examinations (59). Although bloody urethral spotting (urethrorrhagia) in children does not mandate cystoscopy (196), urethral stricture should be suspected (26). Urethrorrhagia lasting longer than 6 months, and gross hematuria in the absence of infection, trauma, or stone disease should be evaluated (39). Children with recurrent gross hematuria and normal radiographic studies may require cystoscopy and ureteropyeloscopy to identify small vascular abnormalities, typically associated with the renal papilla (12,203).

Over the last two decades, cystoscopy has remained most useful in evaluating suspected urinary obstruction (urethral valves or strictures, congenital or postoperative ureteral obstruction) and severe congenital defects (intersex and cloacal anomalies) (187). Diagnostic cystoscopy also may be helpful in select cases in which urinary undiversion is planned, or to facilitate placement of a suprapubic cystostomy before urodynamic assessment. When massive VUR is present, cystoscopy should still be considered and may prove invaluable in identifying an unsuspected ureterocele (ureterocele disproportion), by allowing ureterocele puncture and opacification of the otherwise undetectable upper-pole moiety (81,347).

Instrumentation and Technique

Impressive technologic improvements in optics and size of instrumentation have further altered pediatric practice. Traditional pediatric cystoscopes with conventional lens telescopes are available in sizes ranging from 7 Fr up to 13.5 Fr and are accompanied by various accessories, such as grasping and biopsy forceps. Ureteral stents and guidewires, cauterizing electrodes, or laser fibers also can be passed through the cystoscopic working ports. Flexible cystoscopes ranging from 7 to 9 Fr outer diameters with steerable distal tips are available and may be especially helpful for use in children that have undergone urinary tract reconstruction. Neonatal and pediatric resectoscopes as small as 8.5 Fr have a variety of interchangeable cutting blades and cautery electrodes available to facilitate treatment for conditions such as posterior urethral valves or urethral strictures. Use of these instruments allows early and effective ablation of posterior urethral valves in infants.

Despite the small size of these instruments, it is critical that they be well lubricated, passed under direct visualization and that extreme caution be exercised during their use. The urethra is so fragile and delicate that minimal trauma may easily result in injury and subsequent urethral stricture formation. Passage of a cystoscope blindly with an obturator in place is rarely indicated. Pediatric cystoscopy usually requires general anesthesia. Infants can be placed in a frog-leg position, whereas older children are placed in a standard dorsal lithotomy position. In addition to the endoscopic evaluation, the anesthetized child presents an opportunity for careful examination of the lower abdomen, the genital area (including vaginoscopy) and rectum.

Each age group has a normal range of urethral calibers. The infant male urethra will usually accept a 9 Fr instrument, whereas preadolescent boys can accept instruments of 13 to 14 Fr. The urethral meatus is usually the narrowest portion of the male urethra (4,237). Inspection of the entire urethra from the lacuna magna to the bladder neck is important and may identify an unsuspected distal urethral diverticulum or polyp. The anatomic configuration of the external sphincter, verumontanum, and bladder neck also should be appreciated. Inspection of the prostatic urethra with irrigant flowing may aid in the diagnosis of a significant prostatic utricle or ectopic ureter. In males, inspection for urethral valves should be performed with both retrograde and antegrade flow of irrigant. In females, larger diameter instruments generally can be used because of the inherent elasticity and distensibility of the female urethra (174,175). A systematic examination of the bladder should include all

surfaces, with the bladder in a full and partially emptied condition. The appearance of the epithelium, configuration of the trigone, and position of the ureteral orifices deserve specific attention. Careful examination for possible duplex ureteral orifices and identification of urine efflux from the orifices should be a routine part of cystoscopy.

Complications of cystourethroscopy are generally uncommon; however, urinary infection and urethral injury can certainly occur. Urethral stricture formation can present early with stranguria, split urinary stream or decreased force and caliber of urinary stream. Symptoms also may not become apparent until several months following cystoscopy. Bladder perforation from direct injury from cystoscope passage or overdistention of the bladder is rare but may represent a greater risk in children with augmented bladders. Irrigant fluid pressure should not exceed 60 cm of water. Furthermore, bladder overdistention in small children has been associated with arrhythmias and oxygen desaturation.

ENDOSCOPIC MANAGEMENT FOR LOWER URINARY TRACT PROBLEMS

Part of "56 - PEDIATRIC ENDOUROLOGY "

Transurethral Incision of Posterior Urethral Valves

Transurethral incision of posterior urethral valves remains one of the most common indications for endoscopic surgery in infant and young boys. Open surgical excision of obstructing valves has now been entirely supplanted by the endoscopic approach, first demonstrated by Young (414) using a miniature punch, and Randall (319) using transurethral fulguration. After introduction of the fiber-optic light source allowed adequate illumination, use of the transurethral approach to posterior urethral valves was limited primarily by the relatively small caliber of the urethra in infant boys. Even as recently as 20 years ago, introduction of the (13 Fr) resectoscope often required use of a perineal urethrostomy. Alternatively, incisions could be made in the valve leaflets using a Bugbee electrode through a smaller cystoscope (10 Fr) (345). Even premature infants can now undergo transurethral incision of posterior urethral valves using either an 8-Fr resectoscope, or a 6.9-Fr cystoscope with a cold hook or 3-Fr Bugbee electrode (355). A neodymium:yttrium-aluminum-garnet (Nd:YAG) laser fiber also can be passed easily through a small working channel, and has proven effective in disrupting posterior urethral valves (107).

A cutaneous vesicostomy may be helpful in managing some premature infants with small-caliber urethras. This also offers a valuable opportunity to inspect the obstructing valve leaflets from proximal to the bladder neck. Antegrade disruption of the posterior urethral valves through the vesicostomy is an option (416), but complete disruption of the valve leaflets is often more easily performed using a retrograde approach. Because the valve represents a membrane with the perforation based posteriorly (adjacent to the verumontanum), incision of the posterior urethral valves should be performed at three points (at 12, 5, and 7 o'clock) (144). Antegrade valve incision also can be performed via percutaneous access (Fig. 56.1)(418,419). A flexible ureteroscope may be helpful in negotiating the angle beneath the symphysis pubis leading into the bladder neck region. This approach recently has been extended to *in utero* percutaneous fetal cystoscopy with antegrade fulguration of posterior urethral valves (318).

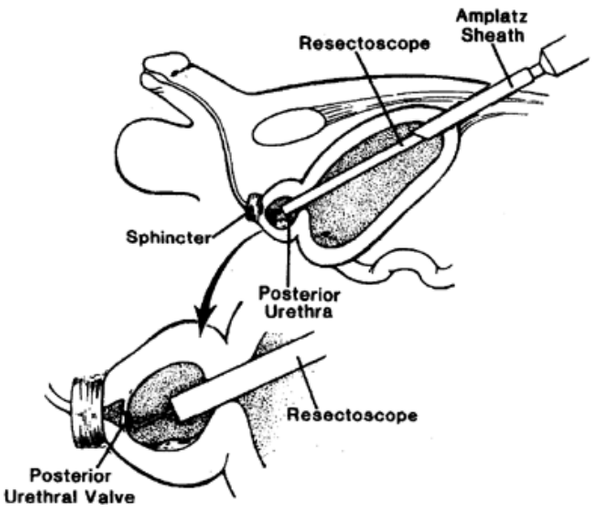

FIGURE 56.1. Percutaneous antegrade approach to posterior urethral valves. This method is preferred in neonates with very narrow urethras through which urethroscopy is not possible.

Endoscopic Incision of Urethral Stricture

Urethral strictures in children were only rarely reported before availability of the McCarthy miniature and infant cystoscopes (1961) (224). Subsequently, many more cases have been reported (284,285,338). Endoscopic urethrotomy using the cold-knife has become the preferred choice for initial treatment of discreet, short, and translucent urethral stricture disease in boys. Thermal injury secondary to electrosurgical urethrotomy is thought to be responsible for a high stricture recurrence rate (338). The Nd:YAG laser allows more precise and bloodless incision of the urethral stricture, and has proven effective (83% success) in treatment of boys failing cold-knife internal urethrotomy (120). However, recurrent strictures have developed following use of both the cold-knife and the Nd:YAG laser (120,197,285). More extensive stricture disease may require a combination of endoscopic incision and intermittent urethral dilation (284). Although adjunctive steroid injection has been thought to improve success following endoscopic urethrotomy (285), long-term benefit remains suspect (338).

Flexible cystoscopy performed through a suprapubic cystostomy tract can aid in localizing the proximal urethral segment in cases of complete traumatic disruption (328). Endoscopic Nd:YAG laser urethrotomy also can be considered in managing obliterative bulbar urethral strictures in children, yielding success in 7 of 8 adult men treated. This approach has been limited to strictures less than 2 cm in length, judged to have good urethral alignment (98).

Transurethral Incision of Ureterocele

Although endoscopic incision and unroofing of ureteroceles was recognized effective in alleviating obstruction, this procedure was not often advised because it consistently caused high-grade VUR in the affected ureter (52,356,397). Monfort and associates (264) described using a small horizontal meatotomy in the ureterocele positioned just above the bladder neck, and reported effective decompression without new VUR in six infants with intravesical ureteroceles, and one infant with a duplex ectopic ureterocele. One additional male infant with bilateral duplex ectopic ureteroceles was left with bilateral high-grade VUR following similar incisions. Transurethral incision of ureteroceles designed to relieve obstruction was then further popularized by Tank (370), who noted remarkable improvement in upper-pole renal function in half (20) of the infants and children in his series (40 duplex systems in 39 children). Improvement in function was based on the change in appearance of excretory urograms performed before and at least 6 months after incision of the ureterocele. Only 6 of 40 children subsequently required early reconstructive surgery to correct VUR and breakthrough urinary infection (370). Interestingly, Tank used an incision high and lateral on the ureterocele away from the bladder neck and willingly accepted VUR in nearly every case (370).

A low transverse puncture incision was later shown to effectively decompress intravesical ureteroceles (single and duplex) in more than 90% of cases, without creation of VUR in up to 85% of infants and children treated (28,77,329). Presumably, this minimal incision creates a better flap valve from the ureterocele remnant. Upper-pole renal function was preserved on nuclear renography in more than 95% of children undergoing endoscopic puncture of intravesical ureteroceles, including all 13 with single systems and 13 of 14 with duplex systems (28). Since then, endoscopic incision has proven successful and definitive for treatment of the vast majority of intravesical ureteroceles, especially those associated with single collecting systems (28,161,305).

The triumph achieved with endoscopic incision of intravesical ureteroceles has prompted renewed interest in endoscopic management for duplex ectopic ureteroceles. This may potentiate preservation of renal function by relief of obstruction and prevention of urinary infection. Employment of a limited incision also is expected to lower the risk for creation of new VUR following treatment. Unfortunately, neither objective can consistently be met.

Upper-pole renal function is often not actually quantitated in reports dealing with ureteroceles (5,28,370). When measured, function in upper-pole renal segments associated with duplex ectopic ureteroceles is often nominal (3,354,383). Blythe and co-workers (28) reported detectable upper-pole renal function in only half of their 24 cases following endoscopic incision of duplex ectopic ureteroceles. In 9 children treated by Smith and others (354), upper-pole renal function accounted for an average of 8.4% on preoperative nuclear renography and did not change significantly after endoscopic ureterocele incision. Vates and associates (383) also showed that upper-pole partial nephrectomy failed to significantly change renal function in 8 children when preoperative and postoperative nuclear renograms were compared. Because preoperative renograms are performed while the upper-pole system is actively obstructed, recovery of renal function after ureterocele incision may be better estimated by considering the sonographic appearance of the upper-pole system (184).

Urinary infection poses the greatest risk for damage to the normally functioning lower-pole renal segments. A large ectopic ureterocele obstructs its upper-pole renal segment, but also can obstruct the bladder neck, and thereby jeopardize additional renal segments (58). VUR into a lower-pole ureter partially obstructed by a large ureterocele further raises the risk of urinary infection and renal damage. Although a significant percentage of infants with duplex ectopic ureteroceles are diagnosed following antenatal ultrasonography (50% to 90%), urosepsis also remains a relatively common presentation (161,305). Endoscopic incision of the ureterocele is especially useful for emergency decompression of an infected and obstructed ureter (either upper or lower pole) blocked by an ectopic ureterocele. Occasionally, emergency decompression also is required in an infant with a solitary functioning kidney subtended by an ectopic ureterocele or with bilateral ectopic ureteroceles. Early postnatal radiographic evaluation and antibiotic therapy are mandatory. Husmann and co-workers (173) reported that only 1 of 33 infants receiving antimicrobial prophylaxis sustained a urinary infection while awaiting surgical treatment.

The endoscopic appearance of ectopic ureteroceles varies with bladder fullness. This impression ranges from a large diverticulum to a small mucosal fold to an obstructing promontory as the bladder changes from full to partially full to empty. Compression of the ipsilateral flank during the examination also may distend the ureterocele. The contralateral ureteral orifice may appear perched upon the ureterocele when that system is distended and may appear to recede laterally as the bladder is filled and the ureterocele collapses. It is occasionally difficult to discern which system gives rise to the ureterocele. Furthermore, identification of the ureteral orifice draining the ureterocele may not be possible.

Transurethral puncture of the ureterocele with a 23-gauge needle wedged onto a 4-Fr ureteral catheter (after breaking off the hub of the needle) allows injection of contrast material and opacification of the ureterocele and contiguous ureter (77). A technically simpler alternative uses percutaneous puncture of the ureterocele under cystoscopic guidance using a 25-gauge spinal needle.

Incision of the ureterocele can be completed using a 3-Fr Bugbee electrode and the cutting electrocautery current. Complete decompression requires sufficient energy delivery to attain a clean cut through both surfaces of the ureterocele. Repeat endoscopic incision is required in 10% to 25% of ectopic ureteroceles incised endoscopically (28,184,354), and the presence of a “thick wall” may further increase this risk up to 35% (161). It is more difficult to preserve an effective nonrefluxing flap valve following endoscopic incision of an ectopic ureterocele, presumably because of its larger surface area, which forms a wedge defect across the bladder neck. Postoperative bladder neck incompetence may be suspected when the ureterocele remnant distorts the bladder neck radiographically, and stress urinary incontinence occurs after toilet training. These uncommon cases may obligate ureterocelectomy with bladder neck reconstruction and ureteral reimplantation.

Primary endoscopic decompression of ectopic ureteroceles creates new VUR in 30% to 46%, and requires secondary open surgery in 50% to 86% (28,161,173,305,354). Husmann (173) showed that endoscopic incision and puncture are equally efficacious, each creating new VUR in approximately 10% of intravesical, and 50% of ectopic ureteroceles. This rate of new VUR remains relatively stable despite modification of the endoscopic technique. Employment of a longitudinal incision in the ureterocele across the bladder neck (or alternatively, punctures of both the urethral and intravesical segments) yielded VUR in 46% of cases (28). More recently, a single puncture of only the intravesical segment of the duplex ectopic ureterocele has been advocated, which led to a slightly lower rate of VUR (38%) (161). This single intravesical puncture effectively decompresses the ectopic ureterocele (161), and avoids creation of an obstructing flap from the urethral portion of the ureterocele in the majority (90%) of cases (Fig. 56.2) (354). Precise placement of this perpendicular puncture along the lateral edge of the ectopic ureterocele away from the bladder neck (Fig. 56.3) can be facilitated by either using an angled Bugbee electrode (161) or pinning the ureterocele in position with a percutaneously placed 25-gauge spinal needle. New onset, recurrent, or progressive VUR may develop with extended surveillance over an interval as long as 48 months (184).

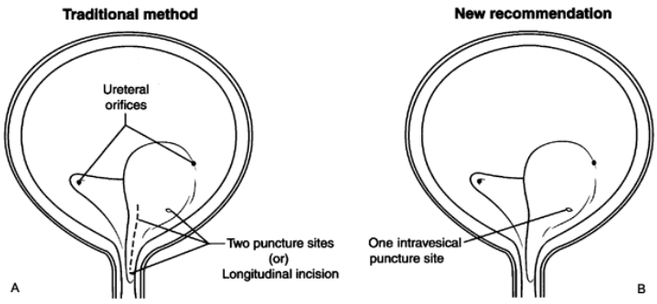

FIGURE 56.2. A: Traditional approach to transurethral incision of duplex ectopic ureteroceles uses either a longitudinal incision traversing the bladder neck or separate punctures of the urethral and intravesical portions of the ureterocele. **B:** A single puncture of only the intravesical portion of the duplex ectopic ureterocele also effectively decompresses the ureterocele and avoids creation of an obstructing flap from the urethral portion of the ureterocele in most cases.

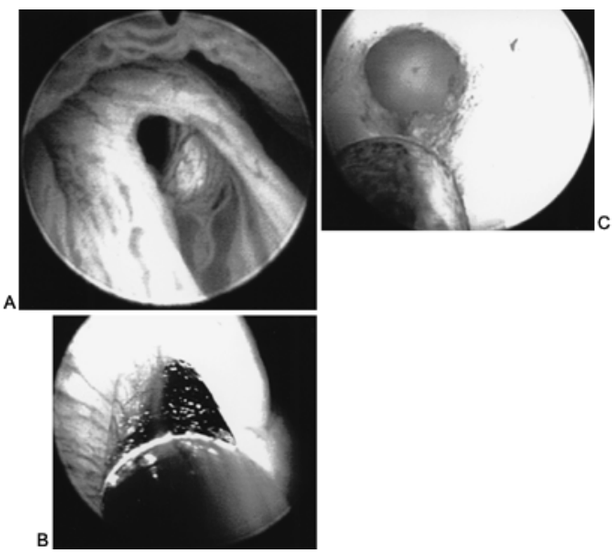

FIGURE 56.3. Duplex ectopic ureterocele. **A:** Cystoscopic view of an ectopic upper-pole ureterocele orifice within the urethra **B:** View of a 3-Fr Bugbee electrode positioned along the lateral edge of the ureterocele within the bladder **C:** Transurethral puncture through both surfaces of the ureterocele has been completed using electrocautery cutting current.

Some authors continue to advocate endoscopic decompression of all antenatally detected ectopic ureteroceles as initial therapy (161,305). However, endoscopic incision of duplex ectopic ureteroceles not associated with VUR is definitive therapy in only 36% of cases. In contrast, partial nephrectomy alone is definitive therapy in 85% of cases (173). Endoscopic incision in these select infants results in an increased risk for additional and probably unnecessary lower urinary tract reconstructive procedures. When initial radiographic studies demonstrate VUR, additional surgery is usually necessary regardless of the initial treatment modality. VUR present on initial radiographic studies resolves in only 16% of these children following either partial nephrectomy or endoscopic incision, presumably because of an intrinsic muscular defect of the trigonal region (173).

Treatment of duplex ectopic ureteroceles should be individualized according to patient age, clinical presentation, and presence of VUR. All patients should be treated with prophylactic antibiotic therapy while awaiting surgical intervention. Infants and children with ectopic ureteroceles and without VUR are best treated with partial nephrectomy. Endoscopic incision is especially appropriate for young infants (less than 6 months of age) with VUR, who either demonstrate bladder outlet obstruction from a large ectopic ureterocele or present with urosepsis. Because older children with duplex ectopic ureteroceles and VUR achieve equal and disappointing results with either partial nephrectomy or endoscopic incision, total urinary tract reconstruction by heminephroureterectomy, ureterocelectomy, and ureteroneocystostomy should be considered as a definitive surgical treatment (173,348).

Subureteric Injection for Vesicoureteral Reflux

Subureteric injection therapy (STING) has remained an option over the last two decades whenever surgical correction of VUR in children is considered (250), offering a very brief general anesthetic requirement on an outpatient basis. Although the STING procedure itself has become accepted as safe and effective (199,200,314), the implant materials chosen to effect this therapy have remained under continuous scrutiny. Teflon paste has been used most commonly, but significant experience also has been achieved using glutaraldehyde cross-linked (GAX) bovine collagen and dextran microspheres (Deflux). Injection of an autologous chondrocyte-alginate gel suspension recently has been used clinically in children (91). Success rates after a single injection (56% to 75%) (85,91,131,171,227,261,316,317,358) have so far fallen short of those achieved with extravesical ureteroneocystostomy (90% to 100%) (41,222,387,417), which currently allows release from hospitalization predictably on the day after surgery (Table 56.1).

Injectable Agent	No. of Patients	No. of Ureters	Single Injection Success Rate (%)
Teflon paste (316)	8,332	12,251	75
Collagen (47,85,130,131, 227,325)	617	953	71
Deflux (358)	75	101	68
Autologous chondrocytes (91)	29	46	56

TABLE 56.1. SUBURETERIC INJECTION FOR VESICOURETERAL REFLUX

A recent review of economic costs (in Sweden) associated with treatment of VUR comparing antibiotic prophylaxis, subureteric injection, and ureteroneocystostomy concluded that injection therapy was less expensive than ureteroneocystostomy (281). Although, subureteric injection therapy was performed as an outpatient, open ureteroneocystostomy required hospitalizations ranging from 6 to 11 days (four different hospitals studied). When the costs are adjusted for increased rates of failure with subureteric injection, and for an overnight hospitalization with ureteroneocystostomy, expense incurred for ureteroneocystostomy would actually have been less than subureteric injection at one of the two

hospitals in the report (Hospital B). Length of hospitalization following ureteroneocystostomy was not documented in a similar report that also concluded the subureteric injection with glutaraldehyde cross-linked bovine dermal collagen was more cost-effective for treatment of VUR when single hospital treatment episodes were compared. Although intraoperative supplies were more expensive, very brief operative times and outpatient surgery for subureteric injection significantly reduced expense (229). However, cure was achieved in only 56% after a single subureteric injection, with an overall cure rate of 78% reported in 27 children after treatment failures received one to three additional injections.

Endoscopic correction of VUR relies on placement of a sufficient volume of submucosal bulking material in a position that effectively lengthens the course of the intramural ureter and promotes coaptation of the ureteral orifice during bladder filling and emptying. To be durable and effective, the injectable material must conserve its volume indefinitely and must not extrude or migrate. To be safely usable, the material must be biocompatible, nonantigenic, and noncarcinogenic. Unfortunately, no injectable material is currently available that meets all these requirements.

Subureteric Injection Technique

Endoscopic subureteric injection is performed with the child in the dorsal lithotomy position for cystoscopy, under general anesthesia. Preoperative antibiotic prophylaxis is indicated. A 14-Fr angled cystoscope was typically required during earlier series (199), but 9.5- or 11.5-Fr models are now available (131). After the position of the ureteral orifice is identified, a 22-gauge cystoscopic needle is advanced through the working channel of the angled cystoscope. When Teflon is used, the barrel of the injection gun and the needle are primed with glycerin and then filled with the Teflon paste. The needle tip is precisely inserted with a single puncture just caudal to the subureteric space approximately 5 mm distal to the ureteral orifice, and then advanced with the bevel up until it is positioned posterior to the ureteral orifice. Placement of a 3-Fr catheter into the ureter may facilitate proper needle placement.

As the bulking material is injected, the flattened orifice should appear as if it is on top of a volcano (the bead of material) (199). The needle should remain in position for approximately 2 minutes to minimize release of material through the injection site. The orifice is then viewed with the bladder full to identify incomplete support (229). Alternatively, fluoroscopic cystography can be performed after subureteric injection is complete, leaving the contrast material within the bladder as the child awakens. Repeat subureteric injection can then be pursued if VUR is detected during monitoring. Operative time is generally brief (less than 30 minutes), and children return home the same day as their surgery.

Correct needle positioning is critical to achieve correction of VUR. Rupture of the epithelium can occur during injection if the needle is too superficial, and migration of implant material outside the bladder can result when the needle is placed too deeply. Multiple injection sites must be avoided because they promote extrusion of the bulking material. Precise placement of the bead of injectable material is somewhat more difficult for children with duplex ureters or neuropathic bladder dysfunction, which may in part account for lower success rates reported (115,219,325). Subureteric injection of Teflon paste also has been used in three adults after endoscopic puncture of ureteroceles to prevent VUR, with its utility limited to only intravesical ureteroceles (384,403).

Injectable Materials

Teflon Paste

Teflon paste consists of a 50% suspension of polytetrafluoroethylene particles in glycerin, which acts as a vehicle and is rapidly absorbed (219). Polytetrafluoroethylene particles in the paste may vary in size from 5 to 100 microns, with more than 90% of particles less than 40 microns. Local migration of these particles can occur directly or as they are engulfed by phagocytes. These smaller particles also may be injected directly into capillaries and embolized to distant organs (1,89,219). Distant particle migration and resultant granuloma formation in pelvic lymph nodes and distant organs (lungs, brain, kidney and spleen) has been documented after periurethral injection in male monkeys and female dogs (246). Subsequently, distant particle migration has been reported in both experimental animals (1,89) and humans (61,90,219,260), including an ischemic stroke occurring in a previously healthy 6-year-old girl 1 year after subureteric injection of Teflon paste (35). Notably, no clinically adverse effects were reported in any patient from the endoscopic injection of Teflon paste for correction of VUR in the multicenter (41 centers) survey reporting results in more than 8,000 children (316).

Injection of Teflon paste was first introduced for correction of VUR for adults (1981) (250) and was later adopted for use in children (1986), achieving success rates of approximately 85% in more than 150 ureters (286,287). Larger series typically report resolution of VUR on cystography performed within 3 months of the last treatment in 75% to 85% of ureters after one injection, and 90% to 95% after additional subureteric injections (97,219,317,335). The most recent multicenter survey for endoscopic subureteric injection of Teflon paste reported that VUR resolved in 75% of more than 12,000 ureters treated after one injection. VUR resolved after two injections in 12%, and after three or four injections in 2% of ureters. No further treatment was administered when VUR improved to grade I in 6%, but ureteral reimplantation was performed for higher-grade VUR in treatment failures (4.5%). Ureterovesical junction obstruction required ureteral reimplantation in 41 additional ureters (316).

Cross-linked Bovine Collagen

Injectable collagen is composed of highly purified sterile bovine corium collagen (95% type I and 5% type III) that is cross-linked with glutaraldehyde to slow its degradation by endogenous collagenases (208,219). Fibroblast migration and neovascularization lead to endogenous collagen production (types I and III) at the injection site (132). Although mild inflammatory reactions may be evident, there are no reports of granuloma formation or migration of the cross-linked collagen (132,382). Skin testing is required before subureteric injection because the foreign bovine protein can provoke cellular and humoral responses in humans (76). New serum antibodies to bovine collagen were detected in 3 of 10 children within 2 years of subureteric collagen injection. No seroconversion to antibodies cross-reacting with human collagen occurred, and no systemic symptoms were reported (228). However, anaphylactic reactions have been reported with negative skin tests (236).

Initial success rates with subureteric injection of glutaraldehyde cross-linked collagen in children compare favorably with those reported for Teflon paste. Success rates within 3 months after subureteric injection of collagen in children range from 62% to 82% (average 71%) (47,85,130,131,229), with improvement to more than 90% after additional injections (325). However, recurrence of VUR was detected in 10% to 20% of ureters during the next year (47,229,236,325). Similar results can be achieved with subureteric collagen injection with duplex ureters (325). Haferkamp and others (159) reported an initial VUR resolution rate of 93% 1 month after subureteric collagen injection in 36 children with 58 refluxing ureters. After 1 year, this dropped to 35% VUR resolution and to 13% resolution at 3 years after the initial injection. Biodegradation and contraction of the injected implant results in higher VUR recurrence with time, despite apparent initial successful treatment (208,219).

Deflux System

Dextranomer microspheres (80- to 120-micron diameter) suspended in a 1% molecular weight sodium hyaluronan solution, called Deflux, forms a highly viscous solution that causes neither allergic nor immunogenic reaction when used for subureteric injection (219). These microspheres are made up of a network of cross-linked dextran polysaccharide molecules that prevents fragmentation and migration after subureteric injection (spherical shape and particles larger than 80 microns) (208,219). Sodium hyaluronan is a glucosaminoglycan present in human tissues that serves as a degradable carrier for the microspheres (absorbed within 2 weeks after injection). Contraction of the Deflux is balanced by a bulking effect from ingrowth of fibroblasts and production of endogenous collagen between the microspheres, effectively maintaining most of the original size of the injected implant (75%) (219,358).

Deflux is easily injectable through a 3.5-Fr polytetrafluoroethylene-coated needle passed through a 10-Fr cystoscope using a standard injection technique. Initial clinical trials with 75 consecutive patients (101 ureters) with grade III or IV VUR indicated success in correcting VUR in 68% of the ureters at 3 months following treatment. Recurrence of VUR occurred in 10% of children treated by 1 year. Treatment results were better for children with grade III VUR when compared with grade IV VUR. The response rate in duplex ureters was 60% (10/16) (208,219,358).

Autologous Injectable Materials

Subureteric injection of alternative autologous materials is being investigated experimentally because of concern for the long-term safety and effectiveness of the currently available materials. Use of autologous fat (249), collagen (53), chondrocytes (9) and bladder muscle cells (10) all have been investigated in laboratory animals. When used clinically, injection of autologous fat corrected VUR in only 3 of 19 ureters (16%) (54,293). Diamond and Caldamone (91) recently reported subureteric injection of autologous chondrocytes grown from a small cartilage specimen initially harvested from the child's own left ear in conjunction with a diagnostic cystoscopy. The alginate-cartilage paste could be injected through a 5-Fr needle passed through a 10-Fr cystoscope. Chondrocyte injection corrected VUR in 57% of ureters after a single injection, and 83% after additional injections in the 46 ureters studied (29 children) (91). Although an ideal material for use in children during subureteric injection has not yet been identified, many of the substances currently under development seem promising and deserve further attention (208).

Role in Neuropathic Bladder

Subureteric injection of Teflon paste has been used with more limited success (56% to 86%) for children with neuropathic bladder dysfunction (115,194,262,315). In the

largest series of 53 children with neuropathic bladder dysfunction and VUR undergoing the STING procedure with Teflon paste, success in correcting VUR was achieved in 56% of ureters after a single injection. Although efficacy diminished with higher grades of VUR, it did not correlate with preinjection urodynamic parameters (115). A 70% success rate had previously been reported for the first 13 children in this group (199). An excellent initial success rate (92%) for correction of VUR also was achieved for 20 patients (26 ureters) with neuropathic bladder dysfunction using GAX-35 collagen. However, success rates fell to only 15% with ongoing surveillance over the next 2 years (160). Although others have suspected that late failure results from poor bladder compliance (411), Haferkamp and co-workers (160) showed that patients in this study failing subureteric injection had favorable bladder storage characteristics.

Endoscopic Injection for Urinary Incontinence

Stress urinary incontinence in children is most often due to intrinsic sphincter deficiency resulting from either congenital spinal dysraphism or from the exstrophy-epispadias complex. The risk for urinary incontinence may be further compounded by detrusor hyperreflexia or diminished bladder capacity and compliance. When anticholinergic therapy coupled with clean intermittent catheterization fails to control stress incontinence in a child with low bladder outlet resistance, surgical options include bladder neck reconstruction, placement of an artificial urinary sphincter, fascial bladder neck sling (or wrap), and bladder neck closure. Endoscopic injection therapy is an alternative, which can be used as an independent procedure to achieve continence or to recruit additional bladder capacity.

Vorstman (385) reported cure or improvement in 8 of 11 (73%) children (mean follow-up of 5 years) treated with endoscopic injection of Teflon paste at the bladder neck. Five of the children had previously undergone extensive bladder neck surgeries and were incontinent, while the remaining children had either spinal dysraphism (4) or exstrophy-epispadias complex (2) as their primary diagnosis. The only complication was a perineal abscess requiring incision and drainage (385). Concern for particle migration and granuloma formation after injection curtailed further use of Teflon (1,61,89,90,219,246,260).

Wan and associates (391) later reported on the endoscopic injection of glutaraldehyde cross-linked collagen in six children with urinary incontinence due to neuropathic bladder dysfunction. They recognized that this therapy works best within the first two injections, when the bladder neck and urethral epithelium are flexible enough to expand and retain the injected collagen material. At 1-year follow-up after injection, three were cured and two were improved (83% success) (391). Continence rates for children with neuropathic bladder dysfunction in other series ranged from 0% to 55%, with improvement reported in an additional 10% to 72% of children, generally resulting from more than one treatment session (33,47,230,299). Definitions for dry and improved status varied between reports, such that children reported as dry in some studies (44,47) would be categorized as improved in others (33,230,299,391). Stable detrusor function on urodynamic evaluation preoperatively is recognized to be important for achievement of urinary continence (299); however, detrusor hyperreflexia may develop after bladder outlet resistance is enhanced with periurethral collagen injection. Although resting leak point pressures changed little with collagen injection and did not correlate with response (33,299), Valsalva leak point pressures nearly doubled for those children with neuropathic bladder dysfunction that achieved improvement after periurethral collagen injection (33) (Table 56.2).

Reference	Boys	Girls	Range of Follow-Up (Months)	# Children Treated (Dry:Improved) Exstrophy/Epispadias		
				Neurogenic Bladder	With BNR	Without BNR
Wan[391]	4	4	6–33	6(3:2)	1(1:0)	0
Caione[44]	3	13	18–48	0	10(7:2)	6(0:5)
Capozza[47]	(30 total)		9–36	9(5:4)	16(8:2)	5(0:4)
Ben-Chaim[16]	15	4	9–84	0	15(1:6)	4(1:2)
Pérez[299]	23	9	3–19	25(5:7)	6(3:1)	1(0:0)
Bomalaski[33]	28	12	3–75	25(0:18)	3(2:1)	11(6:5)
Leonard[230]	12	6	5–21	10(3:1)	6(2:2)	0

BNR, bladder neck reconstruction.

TABLE 56.2. PERIURETHRAL COLLAGEN INJECTION FOR INCONTINENCE

Achievement of continence and improvement were reported more consistently for children with exstrophy-epispadias complex than for those with neuropathic bladder

dysfunction (16,33,44,47,230,299,391). Although injection of collagen into the submucosal space of a previously operated bladder neck (Young-Dees-Leadbetter procedure) increases the risk for extrusion of collagen on injection, the more tubular and narrow urethra presumably promotes luminal coaptation (299). Persistence of the collagen implant may be aided by use of a temporary suprapubic cystostomy (33). Children with intrinsic sphincter deficiency and neuropathic bladder dysfunction typically have a patulous proximal urethra, which leads to lower rates of success. Failure also may be more likely in these patients because intermittent urethral catheterization may cause extrusion or deformation of the collagen implant (33).

ENDOSCOPIC RENAL SURGERY

Part of "56 - PEDIATRIC ENDOUROLOGY "

Endopyelotomy

Open pyeloplasty remains standard treatment for correction of primary ureteropelvic junction (UPJ) obstruction in infants and young children (126). However, endopyelotomy has proven to be an effective alternative for treatment of the failed pyeloplasty (128,176,204) and can be considered in conjunction with percutaneous nephrolithotripsy (PNL) when renal calculi also are present. Success rates of endopyelotomy for primary UPJ obstruction in children (62%) are considerably lower than for open pyeloplasty, with possible late failure of treatment (128). Endopyelotomy can be performed using a retrograde ureteroscopic technique (324), but visualization of the UPJ is optimized using an antegrade nephroscopic approach.

Control of the renal pelvis with a percutaneous guidewire is essential before endoscopic incision of the stricture is performed. Successful retrograde passage of a 5-Fr angiographic catheter through the obstruction into the renal pelvis is required for further progress to be made. After the patient is turned prone and percutaneous access established, the catheter is grasped and brought out through the flank. Two guidewires can then be placed traversing the obstruction. This splays the UPJ, clearly defining the level of obstruction, and allows accurate endoscopic incision between the guidewires, preferably using the hook knife. Electrocautery or laser incision can cause thermal injury, increasing the risk for recurrent stricture formation. A posterolateral incision avoids injury to the hilar vessels and ureteral branches that emanate anteromedially from basilar branches of the renal artery. The incision should be made away from any visible pulsations, and deep enough to reveal periureteral fat, thereby fashioning a funnel-shape appearance of the UPJ.

Alternatively, a low-profile (10-Fr) Acucise cutting balloon catheter (Applied Urology, Laguna Hills, California) can be passed up the ureter over the guidewire exiting the urethra. After proper positioning of the balloon and the cutting wire are confirmed, both by fluoroscopy and direct visualization, the balloon is inflated with contrast material and the cutting wire is electrified. The balloon is left inflated for 10 minutes to tamponade any small bleeding vessels (126). An antegrade nephroureteral stent (either a graduated 14/7-Fr endopyelotomy stent, or a 7-Fr single-J ureteral catheter passed through a 16-Fr council-tip nephrostomy catheter) is then positioned across the UPJ, and extravasation of contrast material is confirmed using fluoroscopic guidance. If no further extravasation is evident when a nephrostogram is completed 48 to 72 hours postoperatively, then the council-tip catheter can be removed, leaving only the percutaneous ureteral stent for 2 to 4 more weeks (217). Preliminary placement of the endopyelotomy stent also has been suggested to allow a more precise endopyelotomy incision using a Bugbee electrode passed directly over the stent (336).

Complications of endopyelotomy may include persistent or recurrent obstruction, bleeding, arteriovenous fistula, and urinary leakage resulting in fistula or urinoma. Risk factors for failure include a crossing renal vessel, long strictures (more than 2 cm), large pelvicaliceal volumes, and poor preoperative renal function (126,380). Because a crossing renal vessel may be present even after prior open pyeloplasty (233), a spiral computed tomography (CT) scan should be considered before endopyelotomy in all cases (119). Alternative treatment is preferable when crossing renal vessels are identified because of an increased risk for endopyelotomy failure and intraoperative hemorrhage associated with their presence (380).

PEDIATRIC STONE DISEASE

Part of "56 - PEDIATRIC ENDOUROLOGY "

Selection of Treatment Modality

Although most renal and proximal ureteral calculi in children are currently treated with extracorporeal shock wave lithotripsy (ESWL), specific treatment for individual patients often depends on multiple factors, including the size and position of the stone, the presence of anatomic abnormalities, the severity of obstruction, and the level of renal function present in the affected kidney. Proximal ureteral stones can be treated in the supine position, and generally do not require pretreatment manipulation. Stones in the distal ureter can be effectively treated in the prone position (186), but ureteroscopic laser lithotripsy is often more efficient treatment, especially for stones smaller than 5 mm (300). Larger distal ureteral stones are more easily visualized fluoroscopically, but require an increased number of shocks (20). Although deleterious effects from shock waves on developing bone or ovaries have not been recognized in experimental animals, their effects in children are unknown (216,253,406). Stones associated with a horseshoe kidney, UPJ obstruction, or caliceal diverticula are often poorly treated with primary ESWL. Stone burdens greater than 2 cm in size, or composed primarily of cystine, calcium

oxalate monohydrate, or calcium phosphate also may be problematic.

Stones smaller than 5 mm may be difficult to image fluoroscopically and often require either intravenous or retrograde ureteral contrast administration for localization. An acute infundibulopelvic angle or narrow infundibular neck may significantly limit passage of lower pole caliceal fragments after ESWL, making either PNL or flexible ureteropyeloscopy more optimal therapy (111). Cystine stones or ESWL failures are effectively treated with PNL, using either a standard or a minipercutaneous technique. Ureteropyeloscopy is generally reserved for ESWL failures with a stone burden less than 1 cm, or for small recurrent cystine stones to avoid a more morbid percutaneous approach. In addition, Jordan and co-workers (191) recently reported successful completion of a laparoscopic extended pyelolithotomy in a 16-month-old child with a large cystine stone filling the renal pelvis.

Staghorn Calculi

Struvite calculi in children typically fragment easily with ESWL; however, the larger stone burden present in these staghorn calculi can create ureteral obstruction and lead to urosepsis. PNL is often preferred over ESWL because it offers optimal upper tract drainage, and more efficient clearance of stone burden. Nonetheless, ESWL maintains a role in treatment of these special complex patients. Placement of a ureteral stent before ESWL may be helpful in preventing ureteral obstruction, especially for staghorn calculi involving the upper-pole renal segment. In these cases, placement of an urgent percutaneous nephrostomy following ESWL is more likely to be complicated by pneumothorax. Children with staghorn calculi involving the lower-pole renal segment, or associated with a dilated collecting are best treated with initial PNL followed by ESWL (344). Although partial and complete staghorn calculi have been treated effectively by ESWL monotherapy in children (greater than 70% stone resolution rate), the majority of children required multiple treatment episodes. Administration of shock waves at the pelvic portion of the stone initially was credited with enhanced passage of stone fragments, obviating the need for ureteral stent placement in all 15 children treated (291). Success rates for ESWL monotherapy in adults drop sharply as the surface area of the stone increases (221).

Pediatric Extracorporeal Shock Wave Lithotripsy

ESWL is effective in treating renal calculi in infants and children, with stone-free rates ranging from 50% to 95% (32,133,214,241,248,278,282,349,396). Complications are rare, and radiation exposure is comparable to routine diagnostic radiographic studies (214). Because pediatric ureters accommodate stone passage well after ESWL, preplacement of a ureteral stent in children with stones less than 1.5 cm in diameter is not recommended (313). Steinstrasse formation in children may require percutaneous nephrostomy when symptoms of pain, vomiting, or fever develop. Nijman and associates (282) noted that steinstrasse developed in only 8 of 86 renal units treated with ESWL (9%), and that only 2 of these children required nephrostomy drainage.

General anesthesia is required during ESWL in children to ensure patient cooperation and comfort because the shock waves produced by the spark gap electrode in the Dornier HM-3 lithotripter (Dornier Medical Systems, Kennesaw, Georgia) are painful. Use of newer-generation electromagnetic lithotripters with smaller focal zones like the Siemens Lithostar (Siemens Medical Systems, Iselin, New Jersey) may allow intravenous sedation to be used during ESWL in adolescent patients (291). Retreatment rates and shock requirements are generally higher with these less powerful units in adults (235). However, Van Horn and others (381) detected no difference in success rates when comparing ESWL performed with the Dornier HM-3 and the Siemens Lithostar in similar groups of children. Cass and associates (50) actually achieved greater stone-free rates using the Medstone STS (Medstone International, Aliso Viejo, California) (100%) compared with the Dornier HM-3 (71%). However, this difference was attributed to a larger number of children with abnormal urinary tract anatomy in the HM-3 treatment group (50). Modifications in lithotripter treatment regimen previously required for treatment of children on the HM-3 unit (flattening the gantry, lowering water levels and shielding the lungs with polystyrene to prevent lung contusion) also have been greatly simplified using these newer machines. A modified infant car seat with a hole cut in the back, and with polystyrene plastic pads affixed to the back affords both security and lung protection for small children treated on an unmodified Dornier HM-3 lithotripter (185).

Although both bruising at the shock wave exit site and hematuria are common in children undergoing ESWL, the incidence of clinically significant hematoma is rare (133,278). Neither hypertension, nor significant alteration in renal parenchymal function have been reported after ESWL in children (78,134,240,248,372). However, apparent growth impairment for both the treated and untreated kidney was reported in a recent series of 29 children undergoing ESWL (232). For ESWL in children, most authors use relatively low power settings (15 to 20 Kv), with the fewest shocks for effect (less than 2,000) (32,133,214,241,248,278,282,349,396). Multiple ESWL treatments on the same kidney should not be performed over a short interval, and bilateral ESWL at the same setting is not recommended.

Percutaneous Nephrolithotripsy

The first report of percutaneous stone removal in children (1985) (400) followed development of this technique in adults by almost 10 years (124). Woodside and associates (400) described successful direct removal of small or multiple stones, and lithotripsy fragmentation (electrohydraulic and ultrasonic) and removal of larger stones in 7 children, between the ages of 5 and 18. PNL offers safe and effective treatment when ESWL fails or is contraindicated. PNL should be considered for initial therapy in children with lower-pole renal calculi larger than 1 cm, especially when the lower-pole calix is drained by a long, narrow infundibulum, or exhibits an acute infundibulopelvic angle (111).

Some authors advocate a staged approach with percutaneous access and tract dilation followed by stone retrieval to optimize visibility and to limit blood loss (215). Others have performed the procedure in a single stage without excessive blood loss (270). Dilation of the nephrostomy tract to 24 or 26 Fr allows use of standard adult instrumentation to fragment or retrieve the stones (46,88,270). Both rigid nephroscopes with an offset lens (17 to 24 Fr), and flexible nephroscopes (15 Fr) are available, but flexible ureteroscopes also can be engaged to obtain access through a narrow infundibulum.

Hollow-core ultrasonic lithotrite probes are efficient at stone clearance because they aspirate stone fragments as they are created. Both the rotating ultrasonic burr-tip probe, and the ballistic probe (Lithoclast, Lausanne, Switzerland) can fragment extremely hard stones, but are limited to use through rigid nephroscopes (87). Electrohydraulic lithotripsy (EHL) probes are available in smaller sizes appropriate for use in flexible nephroscopes, but demand accurate positioning of the probe tip when used in small spaces. The EHL probe must be placed just off the stone to maximize the benefit of the cavitation bubble and shock waves produced with discharge. Because the energy is delivered spherically from the tip of the EHL probe, extreme caution must be exercised to avoid damage to the nephroscope lens, the guidewire, or the urothelium. Enhanced flexibility of the holmium:YAG laser allows its use through any percutaneously placed endoscope (322,399). Although most large renal stones (greater than 3 cm) can be removed with PNL, a second session may be required in up to half of the patients treated (88).

Technique of Percutaneous Nephrolithotripsy

Cystoscopic placement of a ureteral occlusion balloon at the beginning of the PNL procedure facilitates establishment of the percutaneous nephrostomy tract. Although this step generally requires a change in position from the dorsal lithotomy position (for cystoscopy) to the prone position (for PNL) in younger children, passage of the ureteral catheter through a flexible cystoscope with adolescent patients in the prone position is often possible. A urethral catheter is placed to decompress the bladder. Appropriate padding for protection of pressure points and for preservation of diaphragmatic excursion is critical. First air and then contrast material are introduced through the ureteral balloon catheter to outline the posterior and anterior collecting system, respectively. This allows percutaneous access to be secured, and eventually leads to establishment of both a working wire and a safety wire. Nephrostomy tract dilation is then completed over a Super-Stiff working guidewire using either a series of graduated coaxial dilators, or a fascial dilating balloon. The working sheath (18 to 26 Fr) is positioned inside the collecting system. Progress is monitored fluoroscopically at intervals to ensure proper alignment of the dilators and instruments with the renal parenchyma and collecting system.

Use of an adequate-sized percutaneous sheath ensures low working pressures within the renal pelvis during nephroscopy (333). Only warmed saline should be used as irrigant to avoid hypothermia, and dilutional hyponatremia. Injury to the renal pelvis also can require prolonged nephrostomy drainage (88) or cause UPJ obstruction (46). Although perioperative bleeding with PNL is usually controllable with gentle technique (88,215), significant blood loss requiring transfusion in up to 20% of children treated has been reported (46). Excessive torque on the nephroscope must be guarded against, because it can lead to parenchymal tearing and serious hemorrhage. Kaye and Clayman (206) described use of a tamponade nephrostomy catheter with a large-diameter occlusive balloon (36 Fr) carried on a 14-Fr nephrostomy tube. This can prove invaluable for temporary control of parenchymal bleeding, since it tamponades the entire nephrostomy tract as it drains the renal pelvis and maintains ureteral access (206). Intraoperative bleeding can sometimes be controlled merely by placement of a large nephrostomy tube, but significant bleeding presenting after nephrostomy removal may require percutaneous arteriography and embolization (297). The possible need for blood transfusion should be considered in all children undergoing PNL and prepared for by obtaining at least a type and screen for packed red blood cells and parental informed consent preoperatively.

A “mini-percutaneous” technique, with dilation of the nephrostomy tract to only 11 Fr (178) or 15 Fr (168), can be used in a small child with a lesser stone burden. This may limit the risk for significant bleeding or injury to the collecting system. Jackman and co-workers (178) achieved a stone-free rate of 85% and sustained no complications in children with a mean stone burden of 1.2 cm. No tube was left in place postoperatively in one of the 7 kidneys, in which the stone was removed intact. This approach requires use of either an offset 7-Fr pediatric cystoscope (5-Fr working channel) or a 7.5-Fr flexible ureteroscope

(3-Fr working channel) to fit within the smaller sheath. Either a 3-Fr electrohydraulic lithotripsy probe (86), or a holmium:YAG laser fiber (399) must be used to fragment the stones, which can then be removed through the sheath using a 3-Fr 3-prong grasper.

Ureteropyeloscopy

Ritchey and associates (329a) reported the first successful ureteroscopic lithotripsy and removal of a distal ureteral calculus in a 4-year-old boy using an 8.5-Fr ureteroscope in 1988. Ureteroscopic laser lithotripsy has subsequently become standard treatment for distal ureteral calculi in children, but only limited experience exploiting ureteropyeloscopy for treatment of renal calculi in children has been described (151,218,331,399). Ureteropyeloscopy in children follows the development of small, actively deflectable ureteroscopes (149) and of laser fibers small enough to pass within their working channels. A primary ureteropyeloscopic approach may be best suited for treatment of lower-pole renal caliceal stones because of limited fragment clearance achieved following ESWL (111,150,218). Grasso and Ficazzola (151) reported complete fragmentation rates greater than 90% for renal stones smaller than 2 cm in diameter using the 7.5-Fr flexible ureteroscope, and the 200-micron holmium:YAG laser fiber in their 79 patients (including one 10-year-old child). Larger stones required a second-look endoscopy to increase fragmentation rates from 45% to 82%. In their series, a narrow lower-pole infundibulum or stricture could prohibit access to lower-pole renal calculi, but an acute infundibulopelvic angle was not problematic (151). Wollin and co-workers (399) reported holmium:YAG laser lithotripsy using a similar ureteropyeloscopic technique in six children with renal stones, including three with lower-pole caliceal stones. Russell and others (331) included 4 children with renal calculi in their series of 32 children undergoing ureteroscopy for treatment of upper tract calculi. An overall stone-free rate of 100% was achieved, including a second session in four patients.

Access to most pediatric upper tract stones is now possible using small caliber ureteroscopes and working instruments. Associated risk for ureteral perforation (0%) or stricture formation (0.5%) is small (152). Ureteral perforation and retroperitoneal migration of stone fragments occurs only rarely (less than 2%). Because aggressive attempts at retrieval of extravasated stone fragments generally are unsuccessful and can cause ureteral injury with stricture formation, these injuries are best managed with ureteral stent placement to allow the ureteral perforation to heal (117). The risk for postoperative VUR should now be negligible because dilation of the intramural ureter beyond 10 Fr is only rarely necessary. VUR had developed previously in up to 20% of adults undergoing dilation of the ureteral orifice to 24 Fr (136). Apprehension over a potentially prolonged ureteropyeloscopic procedure to fragment or retrieve renal calculi in children may limit its widespread use. However, its utility in managing lower-pole caliceal stones, or residual fragments after ESWL makes it a valuable addition to the pediatric endourologic armamentarium.

Technique of Ureteropyeloscopy

Effective ureteropyeloscopy requires an understanding of the ureteral and renal anatomy and strict adherence to endoscopic principles. Placement of the endoscopic and fluoroscopic monitors adjacent to each other is critical for efficient visual integration during ureteroscopy. Expected areas of anatomic or functional narrowing occur at the UPJ, iliac vessels, and intramural ureter. Ureteroscopy generally begins with passage of a guidewire into the collecting system. A hydrophilic guidewire can be substituted when a standard guidewire cannot be passed through a tortuous ureter or beyond an impacted stone. Use of a gauze sponge or a torque vise at the end of the guidewire aids in rotation of the slippery wire when necessary. Combining an angled hydrophilic guidewire with an angiographic catheter provides further control in negotiating the guidewire tip beyond an obstruction. After access to the upper collecting system has been attained, the hydrophilic guidewire should be replaced with a standard guidewire to minimize the risk for inadvertent dislodgement of the wire. Periureteral scarring from previous surgical procedures may limit ureteral distensibility and impede endoscopic access. Percutaneous access in line with the ureteral orifice may even be required if transtrigonal ureteral reimplantation with a long tunnel has been performed (334).

Ureteral stones located distal to the iliac vessels are best approached with a semirigid ureteroscope, whereas, use of a flexible ureteroscope provides safer and easier access to stones at or proximal to the iliac vessels. The semirigid ureteroscope is passed into the ureter adjacent to a single guidewire, which tends to straighten the ureteral course. Inverting the ureteroscope aligns the beveled tip along the floor of the ureter, aiding passage beyond the dorsal lip of the ureteral orifice. The lumen of the ureter should be visible at all times to prevent bowing of the ureteroscope or perforation of the ureter. Although a semirigid ureteroscope may be safely passed into the proximal ureter in select cases, the versatility of the flexible ureteroscope and the ability to advance safely into the kidney clearly favors its use for treatment of proximal ureteral stones.

Two guidewires should be used when passing a flexible ureteroscope. The flexible ureteroscope is passed in a monorail fashion over the working wire under fluoroscopic guidance, while the other is left as a safety wire to guarantee access to the collecting system. Introduction of the second guidewire is readily accomplished during dilation of the intramural ureter to 10 Fr using an 8/10-Fr coaxial safety wire introducer, which accommodates two guidewires. Use of a ureteral access sheath may be helpful if repeated entry

and exit from the ureter is anticipated for retrieval of multiple stone fragments. Careful fluoroscopic monitoring during passage of the access sheath (12 Fr) is essential to prevent perforation of the ureter. An extrastiff guidewire with flexible tips at both ends may be helpful, both in preventing damage to the ureteroscope as the wire is introduced and angulation of the ureteroscope as it is passed up the ureter.

Flexible ureteroscopes with two working channels are preferred, because instruments can be passed without interruption of irrigant flow. Optimal visualization still depends on use of pressurized irrigation fluid, which can usually be accomplished by applying pressure to the irrigant bag with a pneumatic cuff or by using a piston irrigation syringe. Continuous or periodic bladder drainage helps lower intrarenal pressure during ureteroscopy. Inspection of the proximal ureter and renal pelvis during flexible ureteroscopy should be monitored fluoroscopically. Intermittent fluoroscopic imaging promotes accurate orientation of the ureteroscope within the collecting system. Instillation of dilute contrast material through the ureteroscope also creates a fluoroscopic map of the collecting system, allowing inspection of specific calices to be confirmed.

Introduction of the flexible ureteroscope into lower-pole calices with a shallow infundibulopelvic angle may often be accomplished through only active deflection. However, entry into a dilated lower-pole calix with an acute infundibulopelvic angle will generally require a combination of both active and passive deflection of the ureteroscope, and must be attentively monitored by fluoroscopy (Fig. 56.4). Passive deflection occurs when a portion of the flexible ureteroscope (approximately 5 cm from the tip) is allowed to bank off the upper-pole infundibulum, effectively redirecting the ureteroscope inferiorly toward the lower-pole calices. Maximal active deflection may not be possible when an instrument is present within the working channel.

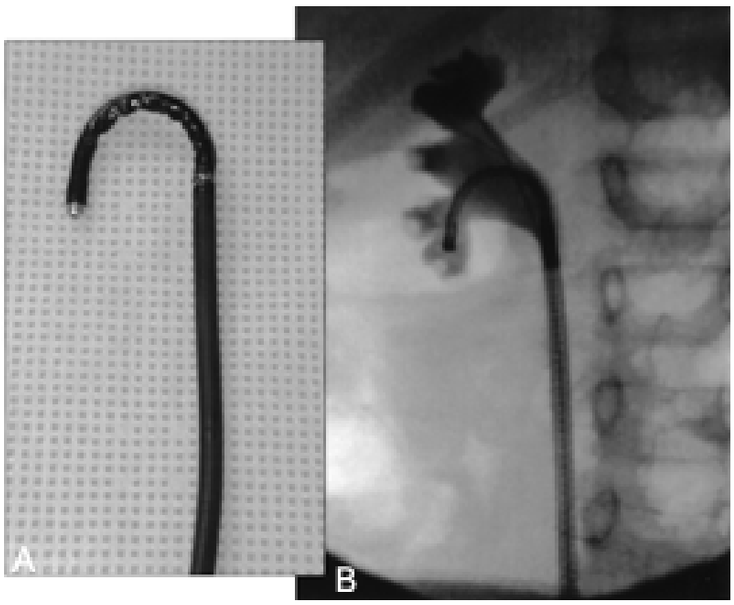

FIGURE 56.4. Actively deflectable, flexible, 7.5-Fr ureteroscope with 3.6-Fr working channel. **A:** Flexible ureteroscope with maximal retrograde deflection. **B:** Passage of flexible ureteroscope into a lower-pole calix (containing a 4-mm stone) with an acute infundibulopelvic angle is achieved by using a combination of active and passive deflection.

Use of a ureteral stent at the completion of ureteroscopy avoids ureteral obstruction from transient edema. Stenting is generally unnecessary following simple diagnostic ureteroscopy using either a semirigid or flexible ureteroscope. If more aggressive dilation of the intramural ureter is required or if significant ureteral edema results from multiple passes with the ureteroscope, then ureteral stenting will likely minimize the risk for postoperative flank pain from ureteral obstruction. When use of this stent is expected for only a few days, the attached string can be affixed externally to ease removal in the office setting. If a second ureteroscopy or prolonged ureteral stenting is anticipated, the string should be removed to minimize both discomfort and the risk for inadvertent stent dislodgement.

Transurethral Cystolithotripsy

Endoscopic lithotripsy in children is most commonly used for treatment of stones forming in augmented bladders (29,209). Both electrohydraulic and laser lithotripsy can effectively fragment stones larger than 2.5 cm in diameter. Some bladder stones consist of a calcified shell surrounding a core of mucus. However, most of the larger stones are extremely dense and require much higher energy settings for fragmentation (Fig. 56.5). A larger laser fiber (550 or 1,000 microns) can be passed easily through a pediatric cystoscope (14 Fr) and lends additional rigidity and surface area for energy delivery. The holmium:YAG laser initially should be set at a low energy setting (0.5 Joules) with a slow pulse rate (5 Hz), but settings may be safely tripled for larger and denser stones. Drawing the laser fiber across the stone surface promotes vaporization of the stone in layers and minimizes formation of large fragments. Injury to the bladder urothelium can result if the stone is pinned against the bladder wall, but then “dances” away from the fiber as the energy is delivered. Large numbers of stone fragments can be efficiently irrigated from the bladder through a cystoscope sheath using the Ellik evacuator. However, a percutaneous suction sheath can be placed, which can be very efficient in aspirating smaller to moderate-sized stone fragments under direct endoscopic control. Use of a percutaneous nephroscope with an angled lens as a cystoscope allows passage of the more rigid ultrasonic lithotripsy probe for controlled fragmentation and suction evacuation of bladder stones. This approach also can be used through percutaneous access after closure or reconstruction of the bladder neck (118). Access through a catheterizable bladder entry constructed from appendix, ureter, or reconfigured bowel significantly limits the size of usable instruments and may compromise the continence mechanism. Initial ESWL, followed

immediately by endoscopic evacuation of stone debris also has proven effective for treatment of bladder stones larger than 3.5 cm (172). Although this combination of modalities may be effective, it is not likely to be more efficient than endoscopic lithotripsy alone. Open removal of larger stones in such cases may ultimately be the most efficient approach.

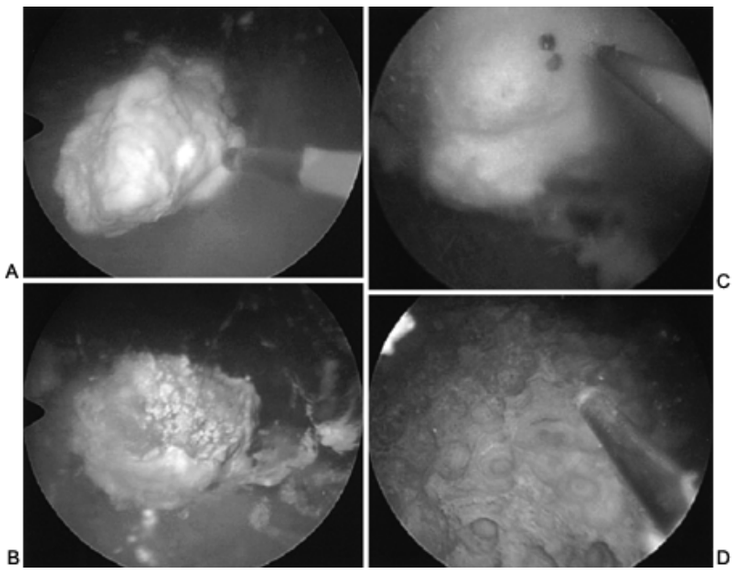

FIGURE 56.5. Transurethral cystolithotripsy of bladder stones in children with augmented, neuropathic bladders. **A:** Intact 3-cm bladder stone with adjacent 360-micron laser fiber (holmium:YAG laser) **B:** Fragmented bladder stone demonstrates a core predominantly composed of mucus. **C:** Intact 5-cm bladder stone with adjacent 550-micron laser fiber (holmium:YAG laser) **D:** Partially fragmented bladder stone demonstrates extremely dense core with surface scarred from laser lithotripsy.

LAPAROSCOPIC SURGERY IN PEDIATRIC UROLOGY

Part of "56 - PEDIATRIC ENDOUROLOGY "

Development of Urologic Laparoscopic Surgery

Use of peritoneoscopy (laparoscopy) in children was introduced contemporaneously by two groups in 1973 (70,135). These two series included 20 infants and children with intersex abnormalities, who underwent diagnostic laparoscopy, and gonadal biopsies when necessary (biopsy technique not described). In their report, Gans and Berci (135) declared that open laparotomy for evaluation of intersex problems was an obsolete procedure. Then in 1976, Cortesi (79) moved the focus directly into the province of urology as they described the location of bilateral intraabdominal testes near the common iliac vessels in an 18-year-old man. Silber and Cohen (352) described intraabdominal, inguinal and vanished testes in three different patients (two adults and one 5-year-old boy) and suggested that laparoscopy should become a valuable tool in the surgical management of nonpalpable cryptorchid testes. Soon thereafter, laparoscopy was enthusiastically adopted as the preferred investigation for routine localization of nonpalpable testes by several groups (30,243,247,343,402). Further surgical exploration was considered unnecessary when a blind ending vas deferens and spermatic vessels were found above the internal inguinal ring at laparoscopy (30,243).

Diagnostic Laparoscopy

Diagnostic laparoscopy also was recognized as valuable in planning the location of the incision and the preferred surgical technique (microvascular autotransplantation,

Fowler-Stephens orchiopexy, or the Jones approach) when an intraabdominal testis was discovered (112,138,163,188,275,371,386). Diamond and Caldamone (93) reported identification of testicular absence in 26% and detection of intraabdominal testes in 21% of 100 impalpable testes undergoing diagnostic laparoscopy. Blind-ending cord structures also were found above the internal inguinal ring in four boys after previous negative inguinal exploration. In their series, roughly half (51 testes) of the laparoscopic examinations were of significant value (93). Although laparoscopy suggested that an atrophic inguinal or canalicular testis was present in the remaining cases, an inguinal incision was still required for definitive management. Seminiferous tubules with occasional germ cells have been identified in roughly 5% to 10% of these testicular nubbins (147,306,371,376). In another large series, Moore and others (267) showed that an inguinal testis was present in 48% of cases when the vas deferens and spermatic vessels entered the internal inguinal ring. Similarly, Cisek and co-workers (60) found a salvageable testis in 45% of cases when normal appearing vas and vessels entered the internal ring, but found only atrophic testes when these structures were atretic. An absent testis was much more likely to be found when one, rather than both, testes were impalpable (60,93,267), and when the processus vaginalis was closed rather than patent (113).

Laparoscopy has largely supplanted radiographic imaging for evaluation of nonpalpable testes. Although use of scrotal and inguinal ultrasonography has recently been advocated to obviate the need for laparoscopic examination, only 7 of 21 atrophic inguinal testes could be identified with this modality (43). Gadolinium-enhanced magnetic resonance angiography offers a higher rate of diagnostic sensitivity. It is capable of localizing intra-abdominal, canalicular, and atrophic inguinal testes (409). Because surgical exploration continues to be indicated regardless of the outcome, this test may be most useful in rare cases in which spermatic vessels cannot be identified during laparoscopy.

After two decades of advancement, identification of nonpalpable testes and diagnosis of intersex problems continued to be the only widespread clinical applications of laparoscopy in pediatric urology. Clayman (67) recognized the great potential value that laparoscopic surgery could offer this specialty because more than 80% of the procedures are performed through an open surgical approach. He noted the preponderance of anecdotal experience in ablative and reconstructive surgical procedures (nephrectomy, orchiopexy, varicocelectomy, ureteroneocystostomy, autoaugmentation cystoplasty, appendicovesicostomy, and pyeloplasty), and called for careful studies comparing the surgical and laparoscopic outcomes for each procedure in patients of similar age, evaluating efficacy, cost, and patient morbidity. Subsequent comparisons of laparoscopic and open procedures have revealed higher operating room expenses for laparoscopic procedures, but also have suggested that overall expenses can be constrained by a shorter and simpler hospitalization (108,162,310). Operating room expenses also may be further limited by use of sterilizable (reusable) equipment (122). Although Peters (302) cautioned that judicious application of laparoscopic techniques in children is essential, he also predicted that its potential in pediatric urology practice is limited only by imagination and technology. In that spirit, Yeung and others (408) recently have extended the utility of laparoscopy to include investigation for and resection of suspected dysplastic kidneys associated with ectopic ureters in children with urinary incontinence (238).

Laparoscopic Orchiopexy

Vasal-pedicle Orchiopexy

Surgical treatment for intraabdominal testes has long been recognized as more exigent than treatment for palpable inguinal testes. Bevan (19) described a radical orchiopexy method for treatment of nonpalpable, intraabdominal undescended testicles almost a century ago, which involved ligation and division of the spermatic vessels. He recognized that the spermatic and vasal arteries anastomose freely, and that the spermatic vessels can be sacrificed without endangering the vitality of the testicle, but advised that this approach be used sparingly (18,19). Some of his contemporaries embraced this technique without reservation (271) and had dismal long-term surgical outcomes with almost complete atrophy of all testes treated (18). Fowler and Stephens (129) radiographically verified communication between the spermatic and vasal arteries, and also described the “bleeding test” using a vascular clamp to occlude the spermatic vessels temporarily during the surgical procedure. Bleeding after incision of the testicular tunic signaled a viable vasal-pedicle orchiopexy. Ransley and associates (320) introduced a staged Fowler-Stephens procedure involving preliminary ligation of the spermatic vessels, followed by orchiopexy several weeks to months later. Successful orchiopexy was reported for all 13 testicles in 10 boys (including 8 prune-belly patients) treated with this approach, in contrast to a recognized atrophy rate greater than 30% achieved with a concurrent procedure (96,129,223,273).

Primary Orchiopexy

Over the last decade, laparoscopic orchiopexy emerged as a practicable surgical option and progressed from continued technical refinement. Bloom (24) reported laparoscopic application of vascular clips to the spermatic vessels as the first stage of a two-step vasal-pedicle orchiopexy in ten boys with high intraabdominal testes. The second-stage was completed through an open incision in seven of the boys, and atrophy was detected in only one testicle. In this case,

the vasal artery was suspected to have been inadvertently ligated consequent to a previous inguinal exploration. Jordan and others (189) later described an entirely laparoscopic (except for creation of the subdartos pouch) single-stage orchiopexy with preservation of the spermatic vessels in a 10-year-old boy using a 10-mm scrotal laparoscopic port to facilitate testicular transfer. Further mobilization of the spermatic vessels and vas deferens was then possible because pneumoperitoneum was preserved with this five-port technique. Soon thereafter, Bogaert (31) successfully performed a similar single-stage orchiopexy in two boys, and a two-stage vasal-pedicle orchiopexy in three additional boys, again using entirely laparoscopic techniques. Dissection of the spermatic vessels to the level of the renal hilum was achieved using 3 laparoscopic ports. Primary orchiopexy was feasible when mobility of the spermatic leash allowed transposition of the testicle to the contralateral internal inguinal ring (31,189).

Further experience with laparoscopic orchiopexy demonstrated that primary orchiopexy with preservation of the spermatic vessels was possible for the majority of intraabdominal testes (55,60,95,125,154,192,234,276,308,310,330) (Table 56.3).Vasal-pedicle orchiopexy was selected as an alternative when spermatic vessels were judged to tether the testicle high in the abdomen (31,45,55,60,192,234,310). Cumulative success rates reached 86% (19 of 22) for single-stage (55,234,310) and 95% (25 of 27) for two-stage (31,45,55,192,234,310) vasal-pedicle orchiopexy. The internal inguinal ring has been managed in various ways, including closure with laparoscopic clips (154,192,310) or endoloops (234). However, it is clear that no specific attention other than dissection of the processus vaginalis from the canal is required (95,125,308,330). In most cases, the testicle was transferred using a canula into the scrotum through a newly constructed canal, medial to the epigastric vessels (55,95,125,154,192,234,310) as Jordan and co-workers (189) originally described. However, the testicle was actually passed down the existing inguinal canal into the scrotum using a laparoscopic grasper in two series (45,276). Passage of a surgical clamp through the scrotal incision into the abdomen to accomplish transfer of the testicle can save one laparoscopic port (31,330), but risks loss of pneumoperitoneum and effective exposure. Use of smaller 2-mm instruments allows even less noticeable laparoscopic port scars (125,330). Poppas and others (308) recently described an ingenious “concealed” laparoscopic orchiopexy using only an umbilical and a scrotal port, using the operating laparoscope with its 5-mm working channel through the umbilical port to facilitate testicular dissection.

Reference	# Pts	Age Range (Years)	Primary	Vasal Pedicle	Closure Int. Ring	Testis Transfer	Mean Hospital Stay	Compl.
Bogaert[31]	5	0.5–16	2	3	Open[a]	Clamp	outpt	Major[b]
Jordan[192]	14	1.5–15	13	3	Clips	Canula	outpt	None
Caldamone[45]	5	2–15		5	Used[c]	Grasper	23H	Major[d]
Docimo[95]	9	1–13	12		None	Canula	outpt	Minor[e]
Nassar[276]	3	1.5–11	3		Used[c]	Grasper	23H	None
Gaur[154]	3	6–14	3		Clip	Canula	23H	None
Poppas[310]	11	0.5–9	10	3	Clips	Canula	23H	Minor[f]
Lindgren[234]	32	0.8–11	33	6	Endoloop	Canula	outpt	Minor[e]
Cisek[60]		50	19					
Ross[330]	6	0.7–7	8		None	Clamp	outpt	None
Poppas[308]	3	0.8–4	3		None	Canula	outpt	None
Ferrer[125]	16	(mean 4)	18		None	Canula	outpt	None
Chang[55]	80	0.5–12	72	29		Canula	outpt	Minor[g]

[a]Inguinal incision if patent processus vaginalis detected.
[b]Bladder perforation (repaired through suprapubic incision)—1.
[c]Testis passed through inguinal canal using grasper.
[d]Bowel perforation with Veress needle—1 (stage-1).
[e]Readmission for intravenous hydration.
[f]Postoperative size discrepancy noted—3.
[g]Atrophy noted following vasal-pedicle orchiopexy—4.

TABLE 56.3. CLINICAL SERIES OF LAPAROSCOPIC ORCHIOPEXY IN CHILDREN

Most children undergoing laparoscopic orchiopexy can be treated as outpatients (31,55,95,125,192,234,308,330). Reported complications have been limited to single episodes of bladder perforation (during creation of a new inguinal channel) (31), and bowel perforation (Veress needle injury) (45).

In a recent multiinstitutional analysis of laparoscopic orchiopexy involving 310 nonpalpable testes studied at 10 different pediatric centers, the success rate with primary laparoscopic orchiopexy exceeded 97%. A two-stage vasal-pedicle orchiopexy offered an 89% success rate (13). Clearly, laparoscopy will continue to play an important role in the surgical management of nonpalpable undescended testes.

Technique of Laparoscopic Orchiopexy

A careful physical examination under general anesthesia may detect a previously nonpalpable testicle and encourage completion of a standard inguinal orchiopexy. Bladder drainage and nasogastric decompression as well as abdominal and scrotal antiseptic preparation are routine. A 5-mm laparoscopic camera port is introduced directly into the peritoneum through an infraumbilical incision using an open access technique. Although use of this technique can seem more cumbersome when compared with insertion of the Veress needle, the minimal additional time requirement is more than justified by the safety margin attained. In this way, the laparoscopic camera port can be accurately placed even in children that have undergone previous transperitoneal surgical procedures. A figure-of-eight suture capturing the anterior rectus fascia ensures an adequate seal for pneumoperitoneum (10 mm Hg) to be maintained. Alternatively, a box-type suture pattern can be used to ensure adequate pneumoperitoneum (307,308). A radially dilating port introduction system (125,342) passed directly into a small peritoneotomy simplifies open port placement and creates a secure seal. Tethering each port to the skin with a stay suture passed around the insufflation valve limits excursion and prevents inadvertent removal during manipulation.

Although smaller laparoscopic cameras are available, optical transmission through a 5-mm camera seems optimal and only minimal cosmetic advantage is achieved from using a 2-mm port within the umbilicus. The position and condition of the undescended testicle is then evaluated laparoscopically with the operating table rolled toward the surgeon, and with the patient in the Trendelenburg position. When the vas deferens and spermatic vessels end blindly within the abdomen, no further intervention is required. If the testis appears viable and is judged to be within 2 cm of the internal inguinal ring, then a primary laparoscopic orchiopexy can likely be completed successfully. Laparoscopic orchiopexy is still appropriate when the spermatic vessels and vas deferens enter the internal inguinal ring if pressure on the inguinal canal delivers a peeping testicle. A staged vasal-pedicle orchiopexy should be considered for more cephalad intraabdominal testicles. Microvascular autotransplantation is clearly indicated when the integrity of the vasal artery has been compromised by prior surgical exploration (Fig. 56.6).

FIGURE 56.6. Management of the intraabdominal undescended testicle based on laparoscopic findings.

When proceeding with laparoscopic orchiopexy, two working ports (either 2 mm or 5 mm) are placed under laparoscopic guidance, just medial to the anterior superior iliac spines (Fig. 56.7). Transillumination of the abdominal wall allows identification and avoidance of the epigastric vessels. The peritoneum is incised with endoshears on either side of the spermatic vessels, extending cephalad to the renal hilum if necessary. The lateral incision is carried around the internal inguinal ring and then passes medial to the inferior epigastric vessels (Fig. 56.8). Elevation of the spermatic vessels then creates a flap of tissue, which includes the testicle. The gubernaculum is mobilized from within the internal inguinal ring and divided as far caudally as possible, as the processus vaginalis is everted. Both peritoneal incisions are then extended medially, flanking the vas deferens, to complete the dissection. Adequate mobility is achieved when the testis can be transferred intraabdominally to the contralateral internal inguinal ring, grasping the gubernaculum for traction. A new inguinal canal medial to the epigastric vessels can then be created. Passage of a laparoscopic dissector through the abdominal wall and out a scrotal incision allows retrograde loading of a laparoscopic port over this instrument (Fig. 56.9). Alternatively, passage of a mosquito clamp or a dissecting instrument (loaded with a laparoscopic port) allows direct access to the abdomen for transfer of the testicle. The testicle must be monitored laparoscopically during transfer to preclude torsion of the spermatic vessels and then can be secured routinely to the subdartos pouch.

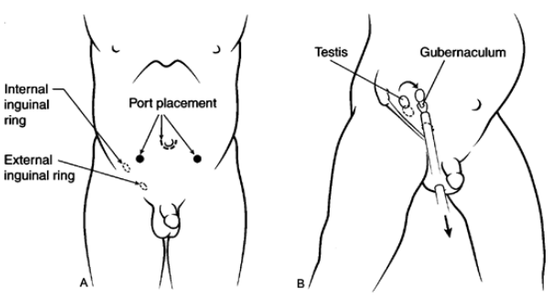

FIGURE 56.7. Port placement for laparoscopic orchiopexy. **A:** A 5-mm camera port is placed through an infraumbilical incision using an open access technique. Two working ports (either 2 or 5 mm) are positioned medial to the anterior superior iliac spines. **B:** Use of a 10-mm scrotal port facilitates testicular transfer, and preserves pneumoperitoneum, allowing additional intraabdominal dissection of the spermatic vessels if necessary.

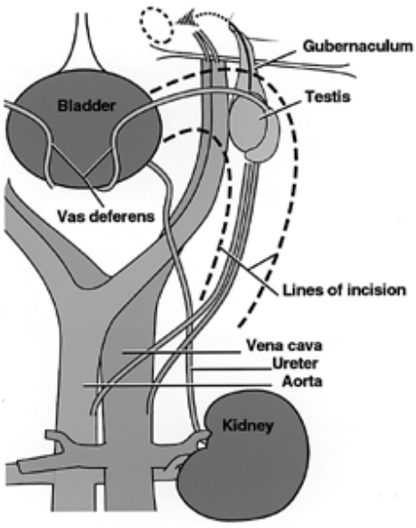

FIGURE 56.8. Lines of peritoneal incision for laparoscopic orchiopexy. The gubernaculum is mobilized from within the internal inguinal ring, divided distally, and transposed to a newly created inguinal canal medial to the inferior epigastric vessels.

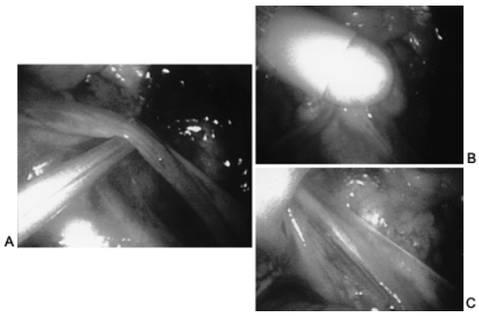

FIGURE 56.9. Laparoscopic orchiopexy. **A:** Spermatic vessels elevated with a 2-mm laparoscopic forceps after peritoneal incisions and mobilization have been completed **B:** Testicle fits within a 10-mm scrotal laparoscopic port passed intraabdominally through a newly created inguinal canal. **C:** View of spermatic vessels and vas deferens as they enter the newly created inguinal canal after testicular transfer to the scrotum.

If adequate spermatic vessel length is not attained for scrotal placement of the testicle after initial mobilization, further dissection of the peritoneum cephalad is often possible with the caudal traction now imparted on the testicle. Division of the spermatic vessels still can be considered if the spermatic vessels remain too short for a tension-free orchiopexy, because the vasal pedicle has not been compromised. However, reliance on a single-stage vasal-pedicle orchiopexy yields testicular atrophy in a troubling percentage of patients even with significant surgical experience (55). Best results are attained when insufficient length of the vessels is suspected early during dissection, allowing a staged vasal-pedicle orchiopexy to be selected. Intraabdominal testicles found medial to the umbilical artery typically have foreshortening of both the spermatic vessels and vas deferens, which makes them especially problematic. Staged laparoscopic orchiopexy with preservation of the spermatic vessels should be considered because all other options are limited. After completion of the laparoscopic orchiopexy, intraabdominal pressure should be lowered (below 4 mm Hg) to aid identification of existing bleeding. Closure of the internal inguinal ring with clips, suture, or an endoloop can be considered, but is generally unnecessary. Each working port site should then be observed laparoscopically as the port is removed. Bleeding can be controlled by placement of a figure-of-eight ligature through the fascia using a port

closure device. All port sites (especially the umbilical port) should be closed to prevent herniation of the omentum.

Laparoscopy for Intersex States

Laparoscopy has a limited, but significant role in evaluation and treatment of children born with intersex conditions. A specific clinical diagnosis is often suspected after a thorough physical examination, and confirmed with karyotype, biochemical studies, and a genitogram (304). In select cases, laparoscopy may be necessary to discern internal anatomy, including the configuration of a uterus or müllerian duct remnant, and the appearance of intraabdominal gonads (71). Laparoscopy is most often helpful in the evaluation of true hermaphrodites or male pseudohermaphrodites. Although laparoscopy is generally not required to confirm the diagnosis of congenital adrenal hyperplasia, it may prove indispensable in rare cases with normal biochemical studies (304). Laparoscopic bilateral adrenalectomy also has been reported in a 14-year-old girl with 11ß-hydroxylase deficiency refractory to medical adrenal suppression (274).

Gonadal biopsy can be performed laparoscopically when an ovotestis or gonadal dysgenesis is suspected. Because these biopsies must generally be longitudinal and deep to permit an accurate histologic diagnosis, a greater degree of surgical control and skill is required to complete the biopsy, close the biopsy site, and avoid injury to the remaining gonad. The biopsy can be completed using conventional

methods and tactile control when the gonad is mobile enough to be exteriorized through a 10-mm port placed directly anterior to it. After closure of the biopsy site, the gonad can then be placed back into the abdomen through the laparoscopic port (Fig. 56.10). This method also allows accurate removal of discordant tissue when an ovotestis is detected. Gonadal biopsies also can be safely performed laparoscopically (22,415) using three ports in the lower pelvis, similar to those used for laparoscopic orchiopexy (304). Laparoscopic gonadectomy has been reported for patients with complete androgen insensitivity syndrome (256,377,415) and gonadal dysgenesis (213,245,346,415).

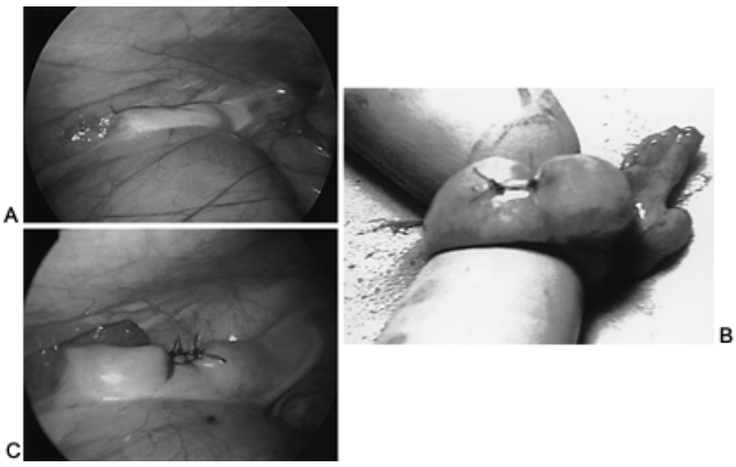

FIGURE 56.10. Laparoscopic-assisted gonadal biopsy. **A:** Intraabdominal gonad overlying a pelvic kidney in a child with intersex abnormality **B:** Gonad has been transferred through the abdominal wall using a 10-mm laparoscopic port placed anteriorly, and a longitudinal biopsy has been completed using standard techniques. **C:** Gonad has been replaced within the abdomen.

Orchiopexy in boys with failure of müllerian inhibiting substance (hernia uteri inguinalis) is problematic because the vas deferens and vasal artery are incorporated into the lateral aspects of their uterus (Fig. 56.11). Preservation of testicular function and possible fertility potential most often requires preservation of these persistent müllerian structures. A laparoscopic approach provides enhanced visualization of the shared vascular supply and allows assessment of the mobility of the uterine structures. Sufficient mobility for standard laparoscopic orchiopexy is present when the testis can be drawn over to the contralateral internal inguinal ring. Both the testis and associated müllerian structures can be removed laparoscopically when the testis is atrophic (395). Müllerian remnants usually are adherent to the vas deferens or seminal vesicles at their confluence with the prostate. McDougall and associates (255) described laparoscopic dissection of a müllerian duct cyst and separation of its attachments to the ureter and seminal vesicle in a symptomatic adult. The cyst was then transected using the gastrointestinal stapler where it joined the prostate. Yeung and co-workers (407) performed laparoscopic excision of large prostatic utricles in three boys using coincident cystoscopic illumination and manipulation to promote complete distal dissection.

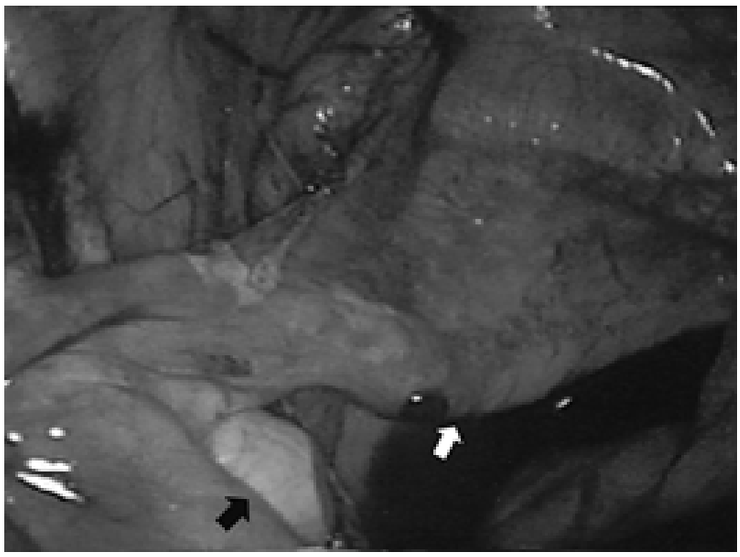

FIGURE 56.11. Failure of müllerian inhibiting substance (hernia uteri inguinalis). Intraabdominal testicle *(black arrow)* tethered by uterine structure *(white arrow)* encroaching on vas deferens.

Laparoscopic Varicocelectomy

Palpable varicoceles should be corrected in adolescent boys when they are very large, or when they are accompanied by ipsilateral testicular hypotrophy (337). Atrophy of the affected testis indicates thermal injury or growth retardation, and correlates with impaired motile sperm counts in adulthood (350). Testicular injury also may be inferred by an exaggerated gonadotropin response to a luteinizing hormone–releasing hormone stimulation test (201). Varicocelectomy performed during early adolescence offers reversal of testicular growth arrest, and rapid catch-up growth of the ipsilateral testis (202,225,292,337). Correction of a varicocele in patients with early changes (atrophy) in Leydig cell morphometry on testis biopsy leads to significant improvement in the postoperative spermiogram. This is not observed, however, in patients undergoing correction of varicocele after late changes (proliferation and hyperplasia of Leydig cells) are evident (158). Varicoceles can be effectively corrected using either percutaneous embolization or surgery. Although a percutaneous approach may be preferred for ablation of unilateral varicoceles (327), laparoscopic varicocelectomy generally is recommended when varicoceles are bilateral (2,116). Antegrade scrotal sclerotherapy can be performed in adolescent males under local anesthesia with excellent success reported (272). However, technical and anatomic obstacles may preclude placement of coils or sclerosing agent in up to 19% of boys (251,373). Success rates determined by telethermography are improved when the sclerosing agent is introduced into the caudal portion of the internal spermatic veins at the level of the internal inguinal ring (82%), rather than more cranially (68%) (351).

Varicocelectomy may involve division of both the spermatic artery and veins (295). However, preservation of the spermatic artery can offer the theoretic advantage of optimizing fertility potential. Furthermore postoperative hydrocele is less common when the spermatic artery and adjacent lymphatic vessels are left intact (116,225,364). Optical magnification and intraoperative Doppler ultrasonography aid identification of the spermatic artery (401). Venography to identify undivided spermatic veins intraoperatively offers little benefit, with varicocele persistence rates reported up to 9% despite its use during suprainguinal varicocelectomy (164,294). Microsurgical repair of the adolescent varicocele yields the lowest rates of recurrent varicocele and hydrocele formation postoperatively (225). Similar results (persistence rates less than 2%) can be obtained by experienced surgeons using a laparoscopic approach (99,183). The benefit of optical magnification obtained through laparoscopy is offset somewhat by increased difficulty incurred during dissection of small veins adherent to the spermatic artery. Persistence of these vessels likely accounts for the higher varicocele recurrence rate associated with spermatic artery preservation in a recent, large multicenter study of laparoscopic varicocelectomy (116).

Laparoscopic varicocelectomy is performed with the patient under general anesthesia in the supine position, with a single video monitor placed at the foot of the operating table. Unilateral or bilateral varicocelectomy then can be completed using an umbilical camera port and two working ports placed laterally (similar to the arrangement used for orchiopexy). Use of a curved scissor and a curved grasper promotes precise dissection of the spermatic vessels, and allows preservation of the spermatic artery. Electrocautery should only be used during longitudinal dissection of the peritoneum, to avoid injury to the spermatic artery. Spermatic veins are occluded using either 5-mm hemoclips (99) or permanent sutures passed through a working port and ligated with an extracorporeal knot-pusher. Mere fulguration of spermatic vessels with electrocautery or with the Nd:YAG laser is not recommended because it leads to higher varicocele recurrence rates and increases the risk for delayed bleeding associated with thermal injury to the spermatic artery (100,226). Diminutive venules adjacent to the spermatic artery must be delicately dissected and divided if complete venous ablation is to be achieved.

Eventually the spermatic artery remains the only intact vessel within the spermatic cord. Preservation of small lymphatic channels adjacent to the artery will likely reduce the risk for postoperative hydrocele. Although its pulsation generally allows visual identification of the spermatic artery, arterial spasm during the course of dissection may cause confusion and delay. Papaverine dripped onto the spermatic vessels through a percutaneously passed 25-gauge spinal needle restores a bounding pulse to the artery. The laparoscopic Doppler probe (5 mm) may further expedite identification of the artery because it can demonstrate an arterial pulse even when blood flow is reduced (242).

Laparoscopic Adrenalectomy

Although laparoscopy has dramatically changed the surgical approach to the adrenal gland in adults (362,369,413), laparoscopic adrenalectomy only occasionally has been reported in children (69,72,84,123,369,389,413). Laparoscopic adrenalectomy yields smaller incisions with less postoperative pain, less intraoperative blood loss, and diminished pulmonary and wound complications (69,362), and it can be performed using either transperitoneal or retroperitoneal access. Each approach has inherent advantages related to the exposure of the adrenal gland and its blood supply. Both are comparable in terms of operative time, intraoperative blood loss, and hospital course (362,365). The more commonly reported transperitoneal approach has generally been used for resection of pheochromocytomas in children (69,72,369,389). This approach also offers exposure to both adrenal glands and has been used to perform bilateral laparoscopic adrenalectomies in two children with congenital adrenal hyperplasia refractory to medical therapy (274,339). A retroperitoneal approach

may be preferable for patients with previous abdominal surgery (123).

Laparoscopic adrenalectomy for pheochromocytoma in children was first reported in 1999 (69,72). Anesthetic management for one of these two boys was described in a separate report and indicated that the most significant intraoperative catecholamine release occurred during induction of pneumoperitoneum (312). Others have shown that intraoperative hemodynamic values during open and laparoscopic adrenalectomy for pheochromocytoma are comparable (369), with less severe and less frequent hypotensive episodes accredited to the laparoscopic approach (357). Regardless of the surgical approach for pheochromocytoma, intraoperative hemodynamic instability is most anticipated with right adrenal tumors (short adrenal vein) (369) and tumors secreting predominantly noradrenaline (72). Walther and associates (389) recently described partial adrenalectomy in a 16-year-old boy with von Hipple-Lindau disease manifesting multiple right adrenal and extraadrenal pheochromocytomas. Hemodynamic parameters remained stable following preoperative phenoxybenzamine and metyrosine blockade, despite an inability to selectively ligate the adrenal vein with this approach (389). Bilateral partial laparoscopic adrenalectomy, with preservation of adrenocortical function also has been reported in a 9-year-old child with familial pheochromocytoma (277). Although laparoscopic adrenalectomy generally is contraindicated for malignant adrenal lesions, laparoscopic adrenalectomy also has been reported in three infants found to have small neuroblastomas during a mass-screening program in Japan (404).

LAPAROSCOPIC RENAL SURGERY

Part of "56 - PEDIATRIC ENDOUROLOGY "

Laparoscopic Nephrectomy

Laparoscopic nephrectomy has developed rapidly over the last decade, since Clayman and others (63,65) performed the first transperitoneal procedure in an 85-year-old woman with a 3-cm oncocytoma (1990). Shortly thereafter, the first retroperitoneal laparoscopic nephrectomy also was performed by Clayman and associates (64), but the transperitoneal approach was favored because it afforded a larger working space (207). Clayman and co-workers (66) described division of the distal ureter with a cuff of bladder using the laparoscopic GIA stapler. With this maneuver, he completed the first transperitoneal laparoscopic nephroureterectomy. The patient was an 82-year-old man with transitional cell carcinoma of the renal pelvis (1991). The first laparoscopic partial nephrectomy removed a lower-pole caliceal diverticulum containing a stone. This procedure used a novel adjustable renal tourniquet and a composite probe for electrocautery and argon beam coagulation (Birtcher Medical Systems, Irvine, California) (398).

Two groups completed the first laparoscopic nephrectomy procedures in children almost simultaneously (103,212). Koyle and Kavoussi (212) removed a multicystic kidney from an 8-month-old infant using three laparoscopic ports and a LapSac (Cook Inc., Spencer, Indiana) for retrieval. Ehrlich and others (103) removed a 15-cm multicystic kidney from a 3-year-old girl laparoscopically, by first establishing pneumoperitoneum with the Veress needle in the supine position, and then converting to a modified flank position. For subsequent cases, pneumoperitoneum was created using an open technique with the child already in a modified flank position (104). Included in this series of 17 procedures is an attempted retroperitoneal laparoscopic nephrectomy in an 11-month-old infant; however, limited working space thwarted the procedure, which was then completed transperitoneally (104).

Diamond and co-workers (92) reported the first series of retroperitoneal laparoscopic nephrectomy procedures using three ports placed in the posterior flank. The retroperitoneal space was developed with either a balloon fabricated from the finger of a glove [as described by Guar (153)], or with blunt digital dissection and placement of a balloon distention trocar (92). Improved visualization of the renal hilar vessels and elimination of the risk for intraabdominal adhesions were both cited as advantages for the retroperitoneal approach (92). Valla and associates (379) placed the camera port directly within the retroperitoneal space, and then created the working space by moving the tip of the telescope systematically (aided by insufflation pressure). A purse-string suture around the posteriorly placed camera port provided a secure seal. Both the balloon dilation method (34,169,211) and direct expansion of the retroperitoneum (108,109,156,379) provide excellent exposure. Peritoneal perforation has been reported with both techniques (108,109,156,169,211,379). Although no specific complications result from peritoneal transgression, some of the exposure to the renal hilum afforded by this retroperitoneal approach is lost, and an additional port may be required to achieve adequate retraction. Borer and others (34) advocated prone patient positioning to optimize access to the renal hilum as the kidney settles ventrally, and they adopted 2-mm instrumentation to more effectively maneuver within the limited retroperitoneal space available in infants and children.

Laparoscopic Nephroureterectomy

Das and others (82) reported the first laparoscopic nephroureterectomy in a child. A refluxing kidney and ureter in an 11-year-old girl was dissected using a 5-port transperitoneal laparoscopic technique. The distal ureter was transfixed with an intracorporeal suture at the ureterovesical junction, and then transected. The specimen was retrieved intact through the 10-mm umbilical port. Suzuki (363) laparoscopically resected an atrophic pelvic kidney with an ectopic ureteral insertion into the vagina in a 4-year-old girl, using five ports and a fiber-optic endoscope within the ureter. Five additional cases in children with hydroureteronephrosis

were reported by two groups contemporaneously, using the laparoscopic gastrointestinal anastomosis (GIA) stapling device to transect the distal ureter with a cuff of bladder (104,127). Current series advocate transection of the ureter at the ureterovesical junction, recognizing that preservation of the intramural ureter poses little risk (162). Although this can be accomplished using a hemoclip (169,181,311), suture ligation (intracorporeal or extracorporeal) of the distal ureter is a more reliable method (361,405). Resection of the distal ureter also has been completed through an open incision, either routinely (83) or when concomitant ureteroneocystostomy is required (34,83,181).

Access to the distal ureter is limited when a posterior retroperitoneal laparoscopic approach is used. Kobashi and co-workers (211) relied on cystoscopy with fulguration of the intramural ureter and ureteral stump when reflux nephropathy was present, but found and endoscopically re-treated persistent VUR in one of five children managed with this method. Furthermore, Borzi and others (36) noted that recurrent urinary infection occurred following incomplete resection of the ureter in two of their 58 children undergoing laparoscopic nephrectomy by a posterior retroperitoneal approach. The entire distal ureter can be accessed either by adding a fourth port placed anteriorly (108), or by positioning the array of three ports laterally on the flank (Fig. 56.12). Selection of approach (transperitoneal or retroperitoneal) for laparoscopic nephroureterectomy remains at the discretion of the operating surgeon. However, a transperitoneal approach favors cases where massive hydroureteronephrosis is present because it allows more space for dissection. Traction on the renal pelvis and aspiration of urine also can be accomplished by drawing the redundant renal pelvis through the abdominal wall via a 10-mm midaxillary port. A retroperitoneal approach should be chosen for children managed by peritoneal dialysis, or when extensive peritoneal adhesions are anticipated from prior abdominal surgery (Fig. 56.13).

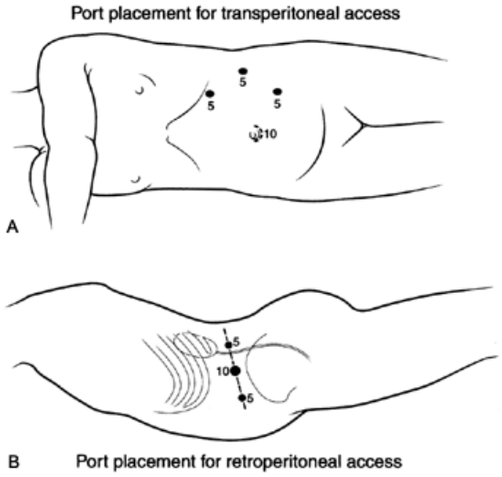

FIGURE 56.12. Port placement for laparoscopic nephroureterectomy. **A:** With the patient in a modified flank position, a 10-mm umbilical camera port and three 5-mm working ports are placed (two at the anterior axillary line, and one at the midaxillary line). **B:** With the patient in the flank position, one 10-mm camera port and two 5-mm working ports are placed on a line that would create a subcostal incision. The medial 5-mm working port facilitates manipulation of the distal ureter for ligation and transection.

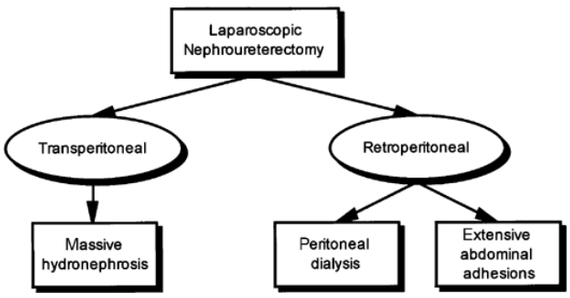

FIGURE 56.13. Proposed scheme for laparoscopic nephroureterectomy. A transperitoneal approach allows adequate space for dissection when massive hydroureteronephrosis is present. A retroperitoneal approach is ideally suited for children maintained on peritoneal dialysis or those with extensive intraabdominal adhesions. Either approach can be used for routine cases.

Laparoscopic Partial Nephroureterectomy

Jordan and Winslow reported the first laparoscopic partial nephroureterectomy in a child. They performed bilateral upper-pole partial nephroureterectomy procedures asynchronously in a 14-year-old girl, using four transperitoneal laparoscopic ports, and divided the renal parenchyma using a combination of electrocautery and the argon beam coagulation probe (190). Ehrlich (104) included four partial nephroureterectomy procedures in his initial series, and divided the renal parenchyma using three passes of the laparoscopic GIA stapling device. Before division of the renal parenchyma, individual vessels supplying the hydronephrotic pole of the kidney are dissected and controlled with hemoclips. More recently, atrophic upper-pole systems have been resected using bipolar electrocautery (181), the microwave coagulator (165), or the harmonic scalpel (143,162,405). Transection of the kidney in pigs using the harmonic scalpel (LaparoSonic Coagulating Shears, Ethicon Endo-Surgery, Cincinnati, Ohio) without first controlling segmental vessels caused a high incidence of significant hemorrhage (179). Only limited intraoperative complications have been reported with laparoscopic partial nephrectomy, through either a transperitoneal (104,143,181,311,368,405) or retroperitoneal (108,379) approach. However, two duodenal perforation injuries have occurred while retroperitoneoscopically dissecting the upper-pole renal vessels (108,379).

Although experience with laparoscopic nephrectomy in children is mounting (Table 56.4), the margin of benefit over an open surgical approach can be very slim. Elder and co-workers (114) reported a series of 34 infants and children that underwent open nephrectomy for either multicystic-dysplastic or nonfunctioning hydronephrotic kidneys as an outpatient through a small (2.5 to 3.0 cm) incision. Operative times were minimal (mean of 45 minutes), and all children did well postoperatively. However, one infant required appendectomy and hospitalization because the appendiceal artery was ligated during a search for the diminutive right kidney, this presumably linked to minimal surgical exposure offered by such a small incision.

Reference	# Pts	Age Range (Years)	Surgical Approach		Laparoscopic Procedure			#MCDK	Mean Hospital Stay	Compl.
			TP	RP	N	NU	PNU			
Ehrlich[104]	16	0.3–11	16		10	4	2	6	23H	None
Diamond[92]	3	6–14		3	3			0	2.6D	None
Tan[368]	23		23		17		6	5		Minor
Valla[379]	18	0.4–14		18	16		2	6	2.3D	Major[a]
Guillonneau[156]	3	3–9		3	3			0	2.6D	None
Janetschek[181]	14	0.6–14	14				14[b]	0	4.8D	None
Fahlenkamp[122]	6	6–10	6		1	5		0	4.2	None
El-Ghoneimi[108]	39	0.4–14		39	31		8	8	2.5D	Major[c]
Davies[83]	24	1–15	23		23[b]			6	2D	Minor
Kobashi[211]	20	0.8–17		19	14	5		8	23H	Major[d]
Prabhakaran[311]	6	0.4–5	6			4	2	0	3.3D	Minor[e]
Borer[34]	14	0.4–10		14	14[b]			4	1.2D	None
Hemal[169]	11	4–16		11	9[f]	2			2.3D	Minor
El-Ghoneimi[109]	19	0.6–13		22	22			5	5.2D[g]	None
York[412]	9	1–16	11		11			0	2.6D	None
Yao[405]	26	0.3–11	26		14[f]	6	6	6	1.5D	None
Hamilton[162]	10	0.3–12	8	2	3	4	3	2	23H	Minor
Glassberg[143]	13	0.4–9	14				14	0	2.5D	None
Strand[361]	33	0.5–13	30	3	3	30		1	23H	None

[a]Duodenal perforation requiring open repair—1 (PNU case).
[b]Distal ureter resected through an open incision—12 (Davies), 2 (Janetschek), 6 (Borer).
[c]Duodenal perforation and renal vein injury requiring complete open nephrectomy—1 (PNU case).
[d]Vena caval laceration.
[e]Bleeding requiring transfusion—1.
[f]Division of isthmus of horseshoe kidney—1.
[g]Included 12 nephrectomies in 9 children with end-stage renal disease.
N, nephrectomy; NU, nephroureterectomy; PNU, partial nephroureterectomy; RP, retroperitoneal; TP, transperitoneal.

TABLE 56.4. CLINICAL SERIES OF LAPAROSCOPIC NEPHRECTOMY IN CHILDREN

Combined benefits of improved visualization and small incision size remain the most appealing aspect for laparoscopic

nephrectomy in children (34,92,109,156,405). These advantages are especially evident for laparoscopic nephroureterectomy, which traditionally requires both a flank and lower abdominal incision to allow complete resection of the kidney and the entire ureter (73,102,361). In a direct comparison of laparoscopic (10 patients) with open (10 patients) nephrectomy or nephroureterectomy procedures in children, operative times were consistently longer (175 versus 120 minutes), but postoperative hospital stays were shorter (22 versus 41 hours) (162). With greater experience, operative times can decrease to less than 60 minutes for either a transperitoneal or retroperitoneal laparoscopic nephrectomy (211,368,405). Hospital stays can safely be reduced to 23 hours or less following laparoscopic nephrectomy or nephroureterectomy (104,162,211,361,405). Just as for open surgery, operative times, and hospitalization following laparoscopic partial nephrectomy are expected to remain longer. Even so, a laparoscopic approach to partial nephrectomy in infants or children has recently yielded excellent results with a mean operative time of 100 minutes (range of 70 to 135 minutes), and a mean hospitalization of 2.5 days (143).

Technique of Laparoscopic Nephroureterectomy

Transperitoneal Approach

The patient is placed in the modified supine position, with a pad placed under the appropriate flank. The operating table is rotated to allow placement of the 10-mm infraumbilical camera port using an open access technique with the patient roughly supine. Peritoneal insufflation with carbon dioxide to a pressure of 10 mm Hg is established. The table is then rotated the opposite direction to elevate the flank and allow the bowel to settle dependently. Two 5-mm working ports are then placed along the anterior axillary line under laparoscopic guidance. A fourth 5-mm port placed midway between these on the midaxillary line aids in dissection of both the renal hilum and the distal ureter. After the colon has been reflected medially, the ureter is readily identifiable as it crosses the iliac vessels. The ureter is dissected distally using the endoscopic scissors, and then doubly ligated at the ureterovesical junction using absorbable suture and the extracorporeal knot-pusher. Proper positioning of these sutures can be confirmed by filling the bladder through an indwelling urethral catheter accessible to the surgical field (Fig. 56.14). Division of the ureter distally then facilitates exposure of the renal hilum by upward traction on the proximal ureter using a grasper through the midaxillary port. Renal vessels are secured separately with endoscopic clips (two clips proximally) and divided. After transferring a 5-mm videocamera to one of the working ports, the distal ureter is grasped and removed along with the kidney through the 10-mm umbilical port. Removal of the entire port often aids in delivery of the atrophic kidney through the existing incision. When necessary, fragmentation of the kidney can be achieved by placing the kidney within an endoscopic confinement bag and disrupting the parenchyma using a large clamp passed through the umbilical port into the bag. Port sites are monitored laparoscopically as they are closed. The urethral catheter is removed the following morning, and the patient is discharged home.

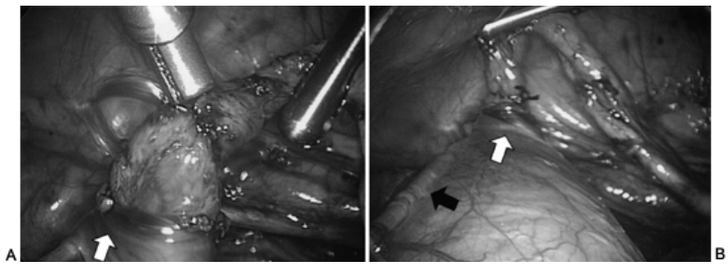

FIGURE 56.14. Transperitoneal laparoscopic nephroureterectomy. **A:** Distal ureter is ligated at the ureterovesical junction with a 3-0 absorbable suture secured using an extracorporeal knot-pusher. Position of the vas deferens is indicated *(white arrow)*. **B:** Proper placement of the sutures on the distal ureter can be confirmed by filling the bladder using a urethral catheter accessible to the surgical field. Position of the obliterated umbilical artery *(black arrow)* and the vas deferens *(white arrow)* is indicated.

Retroperitoneal Approach

With the patient in the modified flank position, direct placement of the 10-mm camera port through a 1.5-cm incision (positioned midway between the costal margin and the anterior superior iliac spine) into the retroperitoneum follows blunt dissection using two surgical clamps. A purse-string suture is placed to secure an adequate seal, and insufflation is initiated (10 mm Hg) with the port traversing the flank musculature. The retroperitoneal working space is then easily dissected by systematic separation of loose connective fibers using the tip of the camera itself. After the peritoneum has been mobilized medially, two additional 5-mm working ports are placed in a line that would create a subcostal incision. Again, the distal ureter is easily identifiable as it crosses the iliac vessels, and can be dissected distally to the ureterovesical junction using the endoscopic scissors. Lateral placement of the laparoscopic ports offers enhanced access to the distal ureter and allows the ureter to be ligated and divided as it joins the bladder (Fig. 56.15). After the lateral attachments of the kidney are separated, exposure of the renal hilum is improved (under adequate insufflation) as the kidney follows the peritoneum medially. Renal vessels are again secured separately with endoscopic clips (two clips proximally) and divided. The ureter also is grasped and drawn out through the 10-mm port to complete delivery of the entire kidney and ureter.

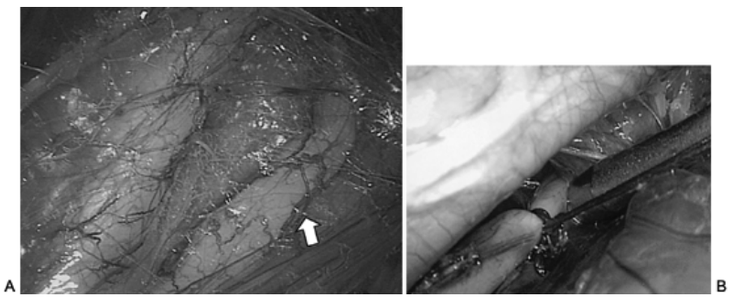

FIGURE 56.15. Retroperitoneal laparoscopic nephroureterectomy **A:** Visual identification of the distal ureter *(white arrow)* medial to the external iliac artery is easily accomplished after the retroperitoneal space has been expanded by systematic dissection with the tip of the camera. **B:** View of the distal ureter as it is secured with an extracorporeal ligature.

Laparoscopic Pyeloplasty

Laparoscopic pyeloplasty was first reported by Schuessler and others (341) using a transperitoneal approach in five adults with UPJ obstruction due to crossing renal vessels (two patients), a redundant renal pelvis (two patients), or a previously failed open pyeloplasty (one patient). Soon thereafter, Peters and associates (303) reported the first laparoscopic dismembered pyeloplasty in a child (7-year-old boy), again using a transperitoneal approach with four ports and interrupted sutures tied intracorporeally. Since then, laparoscopic pyeloplasty has remained an intriguing alternative to open pyeloplasty, with anticipated success rates greater than those achieved by endopyelotomy. Improved technical outcomes are projected for cases involving crossing renal vessels, large pelvicaliceal volumes, or diminished renal function (157,380) when using a laparoscopic approach.

Optical magnification promotes excellent visualization of renal pelvic anatomy, allowing crossing renal vessels to be preserved and transposed after the obstructing UPJ segment is divided (17,56). When renal calculi are present, flexible nephroscopy with stone retrieval can be performed through one of the laparoscopic ports (268). UPJ obstruction in kidneys with abnormal anatomy such as a pelvic or horseshoe kidney also is amenable to laparoscopic pyeloplasty (180). However, perinephric scarring resulting from either previous surgical procedures, or pyelonephritis may interfere with dissection of the UPJ region, thereby prolonging operative time or necessitating conversion to an open surgical pyeloplasty (17,268,367).

The main disadvantage of laparoscopic pyeloplasty is the longer operative time required, predominantly a function of technical difficulty with manual laparoscopic suturing. Janetschek and co-workers (180) reported laparoscopic pyeloplasty procedures using both a transperitoneal and retroperitoneal approach, but suggested that dismembered pyeloplasty is too difficult and demanding to compete with either endopyelotomy or open surgery. Use of a nondismembered

repair (Fenger-plasty) was considered preferably, especially with retroperitoneoscopy because of limited space available for suturing or knot tying. Although 8 hours was required to complete one of the first laparoscopic dismembered pyeloplasty procedures reported (205), operative times have steadily declined most notably because of systematic procedural refinements and acquired proficiency in laparoscopic suturing (56,57,366,410).

McDougall and associates (257) created unilateral UPJ obstruction in 16 pigs and then performed laparoscopic dismembered pyeloplasty, using either intracorporeal suturing and a suture clip knot (Lapra-Ty, Ethicon Endo-Surgery, Inc., Cincinnati, Ohio) or a semiautomatic suturing device (Endostitch, U.S. Surgical Corporation, Norwalk, Connecticut). Success and healing were similar with these two methods, and the time required to perform the pyeloplasty anastomosis was less than 40 minutes for both groups. Routine use of this suturing device (4-0 suture) is prevalent in adult laparoscopic pyeloplasty series (57), whereas manual intracorporeal suturing with finer suture material (5-0 or 6-0 suture) is preferred in series with infants and children (366,367,410).

Tan (367) has accumulated the largest experience with laparoscopic dismembered pyeloplasty in children, initially reporting clinical and radiographic improvement in 4 of the 5 children (2 to 15 years of age) undergoing transperitoneal laparoscopic pyeloplasty (1996). Operative times ranged from 90 to 160 minutes using either three or four ports, and a running sutured anastomosis over a double pigtail ureteral catheter introduced percutaneously. Additional experience with transperitoneal laparoscopic dismembered pyeloplasty was later recorded in 18 total children, including two infants only 3 months old (366). Operative times improved to a mean of 89 minutes, still using manual intracorporeal suturing of the anastomosis. The only treatment failures (2 patients) occurred in the 3-month-old infants. Both subsequently underwent successful reoperative laparoscopic pyeloplasty. Presumably because of these failures, Tan (366) advised against laparoscopic pyeloplasty in infants younger than 6 months of age. Yeung (410) more recently reported successful retroperitoneoscopic dismembered pyeloplasty in six infants and children (ages 3 months to 10 years), with operative times ranging from 140 to 245 minutes (mean of 175 minutes). Either three or four laparoscopic ports (5 mm) were used, and a running sutured anastomosis was again completed over a double pigtail ureteral catheter.

Retrospective comparison of laparoscopic (12 patients) and open (11 patients) pyeloplasty, with endopyelotomy (22 patients) in adults, demonstrated improved success rates overall with pyeloplasty, and a more rapid resumption of all normal activities with laparoscopic (2.3 weeks) versus open (10.3 weeks) pyeloplasty (40). A direct comparison of laparoscopic (70 patients) and open (35 patients) pyeloplasty primarily in adults concluded that long-term pain relief, improved activity level, and correction of obstruction was similar for the two groups (14). Although similar comparisons have not yet been made in children, laparoscopic dismembered pyeloplasty has become a feasible alternative to open surgery that should soon supplant endopyelotomy as alternative therapy for management of pediatric UPJ obstruction.

LAPAROSCOPIC BLADDER SURGERY

Part of "56 - PEDIATRIC ENDOUROLOGY "

Vesicoureteroplasty

Laparoscopic vesicoureteroplasty for correction of VUR was first performed in pigs by Atala and others (11) using a modified Lich (231) extravesical technique. After a detrusor trough was created with endoscopic scissors and electrocautery, the ureter was placed within the trough, and the trough was closed over the ureter with metal staples. Correction of VUR without obstruction was reported in all four animals studied (11). McDougall and associates (258) subsequently used either staples or a running intracorporeal suture to close the seromuscular incision proximal to the ureter in their pig model. One of five animals studied 6 months postoperatively had persistent grade I VUR present. Schimberg and others (340) added ureteral advancement with suture fixation [detrusorrhaphy (417)] and used a running suture for closure of the detrusor trough routinely in six pigs. Ureteral obstruction occurred in one of their initial cases with this approach.

Ehrlich (106) applied extravesical vesicoureteroplasty to two children younger than 5 years, with operative times recorded at 135 and 195 minutes, respectively. At about the same time, laparoscopic ureteral reimplantation was performed to correct ureterovesical junction obstruction in a 74-year-old obese man. After distal ureteral transection, the ureter was reapproximated to the bladder over a percutaneously placed nephrostent using interrupted absorbable sutures, without any attempt to tunnel the ureter. Renal function was preserved at 1-year follow-up (321). Janetschek and others (182) subsequently reported laparoscopic correction of VUR in six girls (three bilateral cases). Postoperative ureteral obstruction developed in one child, but resolved after ureteral stent placement for 6 weeks. Laparoscopic vesicoureteroplasty was considered a technically demanding procedure, offering little benefit over conventional open ureteral reimplantation (182).

In an effort to simplify correction of VUR, endoscopic trigonoplasty using two percutaneously placed intravesical trocars, and a cystoscope in the urethra was then reported independently by Okamura and others (289), and Cartwright and co-workers (48). Following the Gil-Vernet principle (141), a transverse incision is made through the mucosa of the interureteric ridge. After undermining the mucosal edges, the lateral extent of the incision is approximated with a horizontal mattress suture. This anchoring suture converts the previously transverse incision into a vertical orientation and advances the ureteral orifices toward the midline. Ureteral catheters may be placed temporarily

after trigonal incision to facilitate proper placement of the anchoring suture and removed after midline approximation has been completed (289).

Okamura and others (288) reported 100% success in correction of VUR using percutaneous endoscopic trigonoplasty in their initial 12 patients, including one child. However, a review of 28 of their patients (six children) with at least 1-year follow-up indicated only 79% correction of VUR (290). Delayed separation of the midline incision, allowing lateral migration of the ureteral orifices, has been implicated in failure of trigonoplasty (290). Cartwright reported 62.5% resolution of VUR in 22 children (10 with bilateral VUR preoperatively) at 1- to 6-month follow-up, with further decrease in successful correction of VUR to 47% by 37 months (137). Insufflation of the bladder with carbon dioxide was well tolerated, but significant intraperitoneal extravasation of irrigant, and resultant hyponatremia occurred after using sterile water in one initial case (48). This percutaneous endoscopic procedure was revised to include formal ureteral dissection and transtrigonal ureteral advancement in six children (all with bilateral VUR). Operative time was doubled, and a 1-year success rate of 83% was realized (137).

Laksmanan and Fung (220) have recently resurrected laparoscopic vesicoureteroplasty using a modified extravesical approach with one umbilical camera port and three lower abdominal working ports. In this approach, ureteral advancement is not performed. The ureter remains secured distally and an inverted-Y detrusor incision is made with laparoscopic scissors and electrocautery at the ureterovesical junction. The detrusor trough is closed with interrupted sutures tied intracorporeally. Successful correction of VUR without obstruction is reported in all 71 refluxing ureters (24 bilateral patients) in their series. However, two initial cases required open ureteral reimplantation because of ureteral injury. The authors stress careful handling of ureters during laparoscopic dissection and advocate use of a 3-mm adjustable Diamond-Flex retractor (Snowdon Pencer, Tucker, Georgia) for atraumatic ureteral retraction (220). Operative times were not mentioned.

LAPAROSCOPIC URINARY TRACT RECONSTRUCTION

Part of "56 - PEDIATRIC ENDOUROLOGY "

Laparoscopic-assisted Appendicovesicostomy

Urinary tract reconstruction for children with neuropathic bladder dysfunction often involves augmentation cystoplasty using ileum, sigmoid colon, or stomach. Such urinary tract reconstruction and intermittent catheterization also may be necessary occasionally for children with bladder exstrophy, posterior urethral valves, and bilateral ectopic ureteroceles. Compliance with a prescribed intermittent urinary catheterization regimen is promoted by creation of a continent catheterizable bladder entry in children who have urethral stricture disease or intact urethral sensation. Children who are wheelchair-confined, or entirely caregiver dependent also should be considered good candidates for creation of alternative bladder access.

Appendicovesicostomy remains the preferred surgical approach because of limited perioperative morbidity (101,263). Mobilization of the cecum and appendix during appendicovesicostomy generally has been completed through a lower midline abdominal incision, which may then be extended cephalad when more extensive surgical exposure is required (42,101,166,167). Positioning of the appendicovesicostomy stoma in the right lower quadrant of the abdomen or preferably at the umbilicus demands extensive mobilization of the cecum and often the entire right colon (166). Abnormal fixation of the cecum and appendix high in the right upper quadrant of the abdomen or extensive intraperitoneal adhesions consequent to a ventriculoperitoneal (VP) shunt frequently makes access to the appendiceal mesentery remarkably difficult through a small incision. Under these circumstances, the catheterizable urinary conduit can be fashioned from bowel (51), or alternatively, the appendix can be pursued through an extended midline incision.

A laparoscopic approach provides direct access to the entire right colon without the need for a large abdominal incision (Fig. 56.16). The first laparoscopically assisted appendicovesicostomy was completed (1993) in a 15-year-old girl born with bilateral ectopic ureteroceles who had undergone extensive prior surgical reconstruction, including right ureteroneocystostomy, left nephrectomy, and multiple bladder neck reconstructions (193). Laparoscopic creation of a cutaneous ureterovesicostomy also was reported in a 13-year-old girl with a similar history (360). The majority of other laparoscopically assisted appendicovesicostomy

procedures have been accomplished in children with spina bifida, either as an isolated procedure (42), or in combination with augmentation cystoplasty (166). Limited formation of intraperitoneal adhesions with this approach was both suspected (269) and observed (166). Continence in four adults undergoing entirely laparoscopic nontunnelled appendicovesicostomy procedures (239) may be attributed to intrinsic appendiceal peristalsis, which creates a sufficient functional profile length (392).

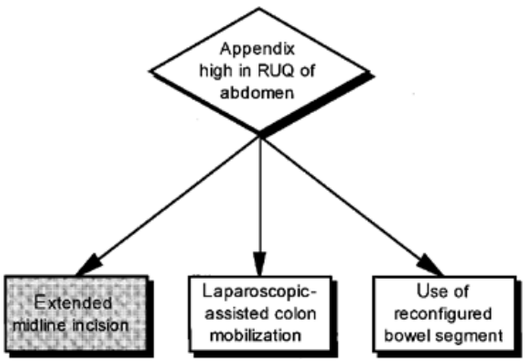

FIGURE 56.16. Proposed scheme for creation of a catheterizable urinary conduit for children with neuropathic bladder dysfunction. RUQ, right upper quadrant.

Twenty children (14 boys and 6 girls) ranging in age from 5 to 17 years old with neuropathic bladder dysfunction resulting from spina bifida have undergone laparoscopic-assisted urinary tract reconstruction at our institution. Appendicovesicostomy with an umbilical stoma was successful after laparoscopic mobilization of the right colon and appendix in 10 children. In the remaining 10 children, there was tethering of the appendiceal mesentery that could not be corrected with colon mobilization. Therefore an alternative catheterizable bladder entry was created using either the primary (51,265) or extended Monti (Casale) technique (49) (using ileum in 6 and sigmoid colon in 4). All 19 children with a VP shunt were noted to have intraperitoneal adhesions present in the right lower quadrant. Port placement (including creation of the umbilical U-shaped flap) and laparoscopic dissection time generally required 40 minutes. Augmentation cystoplasty also was performed through a Pfannenstiel incision in all 20 children (using ileum in 16, and sigmoid colon in 4), and 9 children also had a concomitant suspended bladder neck wrap procedure performed. No intraoperative or postoperative complications occurred, and intraoperative blood loss was negligible. Morbidly obese children were not considered for this laparoscopic approach because of the limited likelihood that the appendix could span the distance from the umbilicus to the bladder. Rather, the Casale technique (49) using reconfigured bowel was preferred in these children.

Postoperative pain control was subjectively improved using a laparoscopically assisted approach because the Pfannenstiel incision was often entirely below the sensory level for the child undergoing surgery (in contrast to a lower midline abdominal incision, which typically causes discomfort at its cephalad extent). Median postoperative hospitalization was 5 days (range of 4 to 6 days). Redman and Barthold noted that a Pfannenstiel incision is cosmetically superior to a midline incision for augmentation cystoplasty, and may be less prone to dehiscence. Return of bowel function and duration of hospitalization also are improved for children undergoing bladder augmentation through a Pfannenstiel incision (323). These benefits also are manifested when a laparoscopic-assisted approach through a Pfannenstiel incision is used (166). Use of laparoscopic dissection during appendicovesicostomy allows rapid assessment of the utility of the appendix, and provides unencumbered exposure for expeditious appendiceal mobilization.

Technique of Laparoscopic-assisted Appendicovesicostomy

A 10-mm camera port is initially placed using an open access technique through a semilunar incision within the inferior aspect of the umbilicus. Once pneumoperitoneum is established, two additional 5-mm working ports are placed under laparoscopic guidance. The most cephalad working port is placed in the midline approximately midway between the xiphoid and the umbilicus, and the caudal working port is placed to allow later incorporation into the planned Pfannenstiel incision (Fig. 56.17). The right colon is then mobilized along the white line of Toldt from the cecum to the hepatic flexure under laparoscopic guidance using endoshears and dissecting forceps. Laparoscopic portion of the case is concluded when the cecum can be brought dependently into the pelvis.

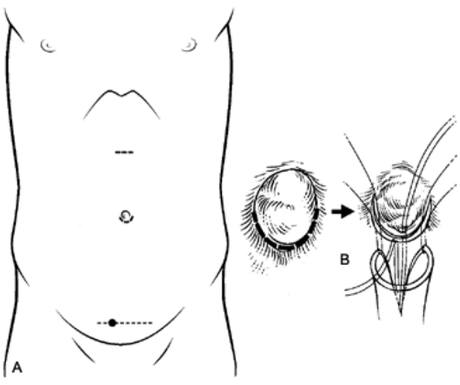

FIGURE 56.17. Port placement for laparoscopic-assisted appendicovesicostomy. **A:** A 10-mm camera port is placed through a semilunar incision within the inferior aspect of the umbilicus, using an open access technique. Two 5-mm working ports are utilized (one midway between the xiphoid and the umbilicus and one incorporated into the line for the Pfannenstiel incision). **B:** The semilunar umbilical flap is approximated to the spatulated appendix to create a widely patent, but concealed umbilical stoma.

Laparoscopic Autoaugmentation

Laparoscopic autoaugmentation was first described by Ehrlich and Gershman (105) using a transperitoneal approach, and later by McDougall and co-workers (259) using an extraperitoneal technique. Both reports used electrocautery to incise the detrusor muscle and to create the bladder diverticulum. The first case was complicated by a delayed intraperitoneal leak that was managed successfully by catheter drainage (105). McDougall and others (259) described

use of a novel intravesical balloon. This is created from a 5-Fr angiographic catheter passed through an 18-Fr council-tip catheter coupled with the small finger of a size 8 surgical glove. It is used to aid in recognition of the plane separating bladder muscle and mucosal layers. Braren and Bishop (38) noted improved urodynamic parameters and relief of incontinence in 6 of 7 girls undergoing laparoscopic bladder autoaugmentation using electrocautery. Poppas (309) later used the KTP laser equipped with an angled backstop device to safely complete the detrusor incision while protecting mucosal integrity. Although adequate bladder capacity and compliance can be achieved with laparoscopic autoaugmentation (259), long-term results may be unacceptable and formal enterocystoplasty may be required (309).

Laparoscopic Augmentation Cystoplasty

Laparoscopic enterocystoplasty has the potential to become a viable alternative to open enterocystoplasty. Gill and others (142) described a primarily laparoscopic approach in three adults in whom mobilization of the bowel and then anastomosis to the bladder were completed laparoscopically. The interim steps of harvesting and reconfiguring the bowel segment and reapproximating bowel continuity were completed with the intestine exteriorized through a 2-cm infraumbilical incision. Previously, Hedican and associates (166) reported laparoscopic-assisted enterocystoplasty in six patients, using laparoscopic techniques for bowel mobilization, and then completing the bladder augmentation using either ileum (four patients) or sigmoid colon (two patients) through a Pfannenstiel (three patients) or low midline (three patients) incision. Although an entirely laparoscopic gastrocystoplasty had previously been completed in one of these patients (94), the gastrocystoplasty patch was resected when she developed the hematuria-dysuria syndrome (166). Development of a hand-assisted approach to gastrocystoplasty would allow use of a Pfannenstiel incision and should be feasible in children with abdominal cavities large enough to accept the surgeon's hand.

Pneumoperitoneum and Ventriculoperitoneal Shunts

Gas insufflation is performed at pressures greater than those normally present under physiologic conditions, and these pressures are transmitted equally to all intraperitoneal organs and structures. Distention of the peritoneum and displacement of the diaphragm further transmits this pressure to surrounding structures. Carbon dioxide is the most commonly used insufflating gas because of its ready availability and because of its rapid absorption and clearance with respiration. Although insufflation with carbon dioxide gas can increase the central venous pressure and mean arterial pressure, these changes are not clinically important in healthy individuals (140). In infants maintained at insufflation pressures of 10 mm Hg, transient cardiovascular impairment (decrease in aortic blood flow and increase in systemic vascular resistance) had no clinical consequences and was completely reversed after desufflation (155). The negative respiratory effect of carbon dioxide insufflation can be effectively monitored by pulse oximetry and capnography, and controlled by increasing respiratory rate and tidal volume during general anesthesia (139). Transient alterations in renal function causing oliguria are commonly observed with elevated insufflation pressures. These intraabdominal pressures are suspected to cause central venous compression and resultant renal vascular insufficiency (210). Insufflation pressures must be greater than 15 mm Hg in pigs for this effect to be observed (254), but only 10 mm Hg in rats (210). Oliguria is reversible after desufflation and is not associated with any persistent renal abnormalities (254).

Despite apprehension that intracranial hypertension may result from establishment of pneumoperitoneum in children with VP shunts (378), neurologic sequelae were neither detected in any published reports (42,166,167) nor observed in the 19 children with VP shunts in our experience. Review of intraoperative monitoring of 18 children with VP shunts undergoing laparoscopic surgery failed to detect any episodes of intraoperative bradycardia and hypertension during pneumoperitoneum and indicated that no specific neurologic deterioration associated with pneumoperitoneum occurred in any patient. Routine monitoring of intracranial pressure was therefore not recommended for children with VP shunts undergoing laparoscopic surgical procedures (177). Insufflation pressure limits should be set as low as feasible (generally 10 mm Hg) when operating on children with VP shunts, and laparoscopic operative times should be limited to minimize risk.

LAPAROSCOPIC COMPLICATIONS

Part of "56 - PEDIATRIC ENDOUROLOGY "

As diagnostic and operative laparoscopy becomes firmly established in pediatric urology practice, complication rates are expected to reach a marginal baseline level, reflecting the experience of the surgeon and the complexity of the procedures performed. In a recent survey of complications sustained during laparoscopic procedures performed by pediatric urologists, overall complications were reported in approximately 5% of cases (301). However, when inadequate insufflation (primarily associated with use of the Veress needle) was excluded, the complication rate dropped to almost 1%, with surgical repair necessary in less than 0.4%. Limited laparoscopic experience (fewer than 20 cases) was the strongest predictor for occurrence of operative complications (301).

Intraoperative complications specific to laparoscopy are primarily associated with either port manipulation or use of laparoscopic instruments. Complications associated with access and insufflation are diminished significantly when the initial laparoscopic port is placed under direct vision into the peritoneal space (74,296). However, open access to the peritoneum remains difficult in obese children, and injury to adjacent bowel has been reported even using this open technique (332). Transillumination of the abdominal wall should be performed routinely to avoid injury to the epigastric vessels. This complication is more likely to occur in obese patients in whom transillumination is inadequate (296). Compression of an injured vessel can be accomplished by passage of a transfascial (but subcutaneous) figure-of-eight suture adjacent to the port site using either a 14-gauge angiocatheter or a port closure device (110). Removal of working ports and placement of port closure sutures should be monitored laparoscopically at the completion of the procedure to ensure hemostasis. After all the carbon dioxide gas is evacuated, the camera port is removed with the camera still in the abdomen to prevent migration of bowel or omentum through the channel. The last port site can then be sutured closed with previously placed fascial sutures (monitored laparoscopically from another port site), or under visual guidance. All laparoscopic port sites should be sutured closed in children because omental evisceration has been observed even using 4-mm ports (23). Closure also may prevent formation of adhesion at port sites (266).

Children must be properly grounded with an appropriate sized grounding pad during laparoscopic surgical procedures. Insufficient contact of the grounding pad can cause thermal injury, either at a local or distant site, during electrodissection using unipolar cautery. Inadvertent contact of intraperitoneal structures with uninsulated portions of electrified laparoscopic instruments must be avoided by constant vigilance and use of instruments with extensively insulated tips (21). This is especially important in small infants when working space is limited. Although reusable metal laparoscopic ports safely dissipate electrical current if applied transiently, port site burns can occur following prolonged exposure to electrocautery (121). Contact of the uninsulated portion of the instrument with the metal port should be considered immediately when electrocautery fails. Switching to bipolar cautery limits thermal injury to the tissue captured between the prongs of the forceps (121).

Laparoscopic bowel perforation occurs in only 0.2% of cases. Most often, they are recognized only postoperatively (69%) after symptoms of abdominal distention, severe trocar site pain, or diarrhea develop (21). Progression to leukopenia, sepsis, and cardiopulmonary collapse can occur within 96 hours of surgery. More than half result from inadvertent thermal injury to the bowel during laparoscopic dissection (21). Thermal injuries typically become apparent only postoperatively (21,121). Although most bowel injuries require laparotomy for repair, laparoscopic repair is possible when the injury is recognized early, and the patient has undergone preoperative mechanical and antibiotic bowel preparation (279). Major colonic injury to unprepped bowel mandates a diverting colostomy. Careful examination of adjacent structures must be performed to avoid missing additional subtle injuries. Abscess formation also can occur in areas near supposed insignificant serosal abrasions. Consequently, even relatively minor bowel injuries should be managed with caution and repaired to protect from fistulization or abscess formation (21).

Vascular injuries to the aorta or iliac vessels during trocar placement require immediate open surgical exploration and repair. Unfortunately, delayed recognition of vascular injury is a very real risk because of elevated intraperitoneal pressures and a Trendelenburg position, even after perforation of the aorta with the Veress needle (121). Intraperitoneal pressure should be lowered intermittently during the procedure and before final removal of the laparoscope to allow timely identification of significant bleeding. Bleeding during dissection of major vessels (renal hilum) resulting from injury to an unrecognized posterior branch often can be controlled by temporary occlusion with a laparoscopic instrument, and systematic dissection and control of all vessels present. Uncontrollable bleeding requires conversion to an open surgical procedure. This situation must be planned for preoperatively, and appropriate instruments must always be readily available.

The laparoscopic approach to many of the urologic problems in children is in still in its infancy. However, it is already clear that application of this new technology to testicular, renal and bladder surgery is a very real probability. The surgeon of the future will need to be facile with open, endoscopic, and laparoscopic technology.

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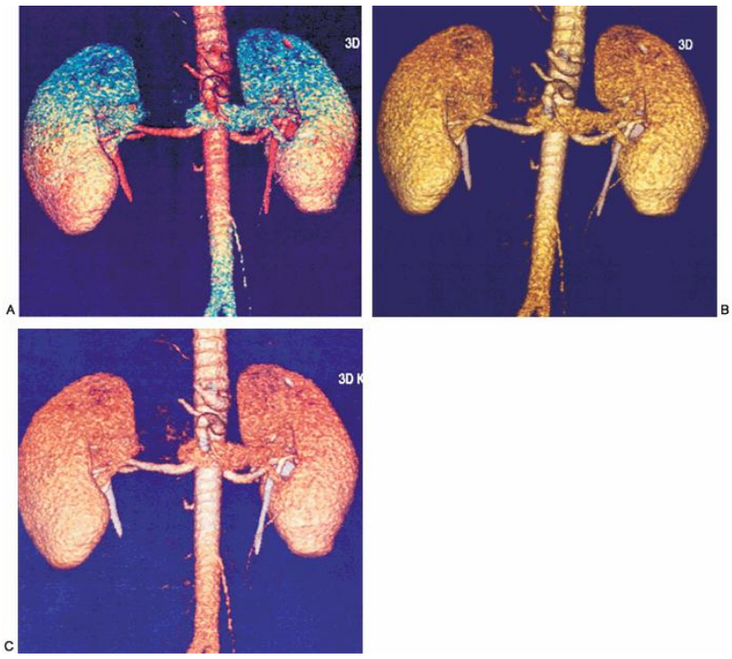
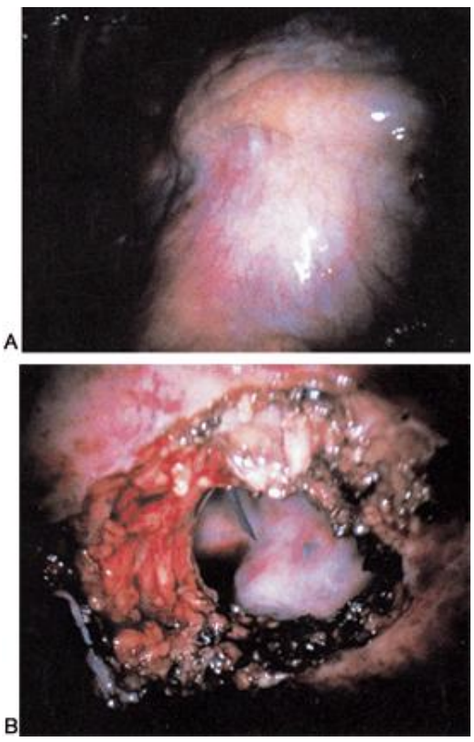
RESOURCES

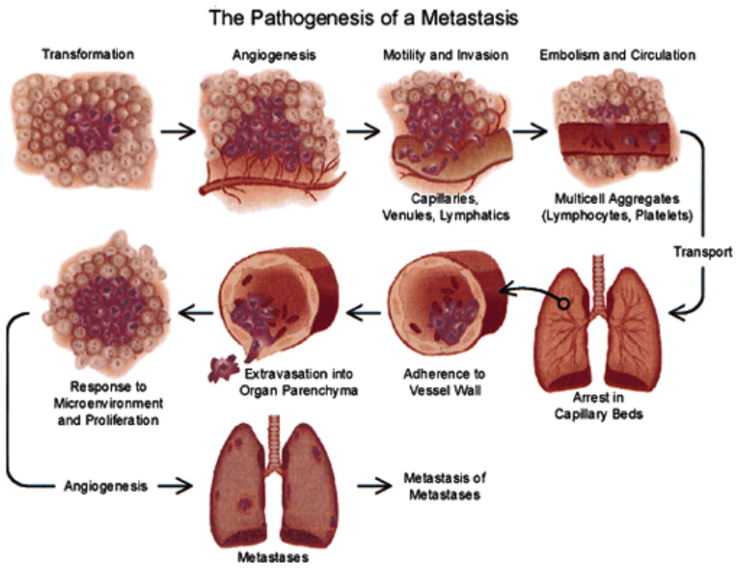
COLOR FIGURES



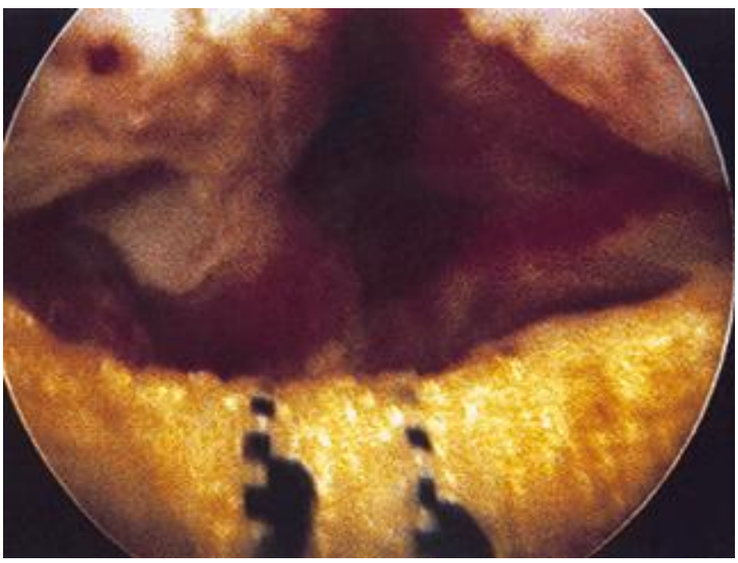
Color Figure 3F.4. Living renal donor computed tomography angiogram shows single arteries to each kidney and left renal vein passing anterior to the aorta. Different color schemes can be used depending on the preference of the viewing physicians. See also Figure 3F.4, page 178.



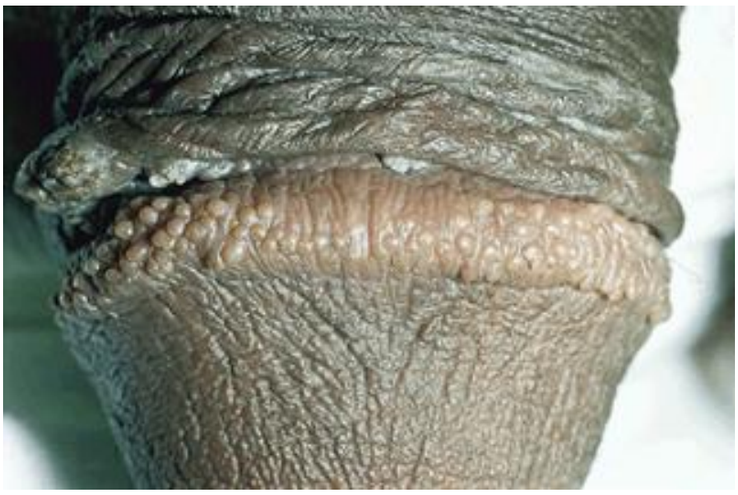
Color Figure 18.12. A: Laparoscopic inspection revealing the bluish-gray bulge of the lymphocele in the pelvis. **B:** Unroofed lymphocele with percutaneously placed needle visible within. See also Figure 18.12, page 685.



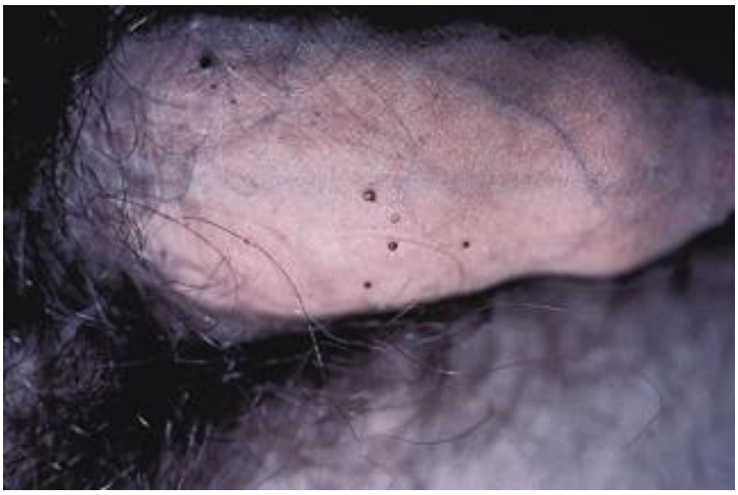
Color Figure 33.90. Successful completion of the metastatic process involves more than simply anatomic or "mechanistic" issues. It is now believed that an affinity exists between the tumor cell and the host microenvironment that is ultimately colonized. This phenomenon has been described as the "seed and soil" hypothesis. It should be emphasized that the process of metastasis consists of multiple sequential steps. All of these must be successfully completed to produce a clinically relevant metastasis. Angiogenesis must be induced to support the growth of both the primary neoplasm and its metastasis. See also Figure 33.90, page 1603. (From Fidler IJ, Kumar R, Bielenberg DR, et al. Molecular determinants of angiogenesis in cancer metastasis [Review]. *Cancer J Sci Am* 1998;4[Suppl 1]:S58, with permission.)



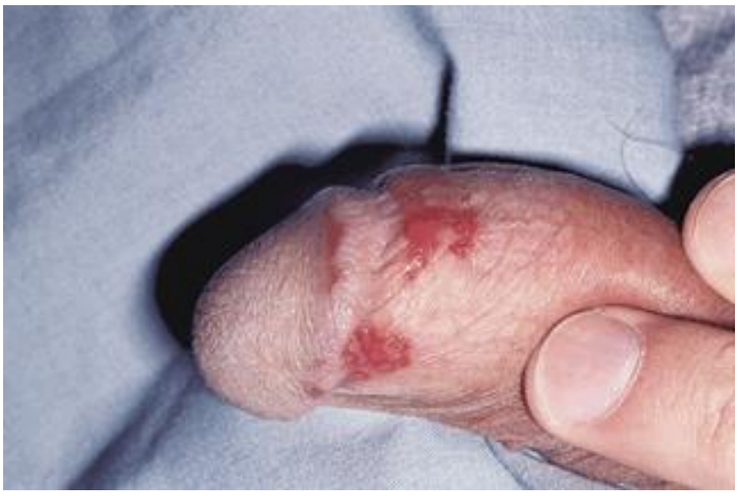
Color Figure 38.15. Cystoscopic view from urethra demonstrating entire eroded polyester sling within urethral lumen. See also Figure 38.15, page 1837.



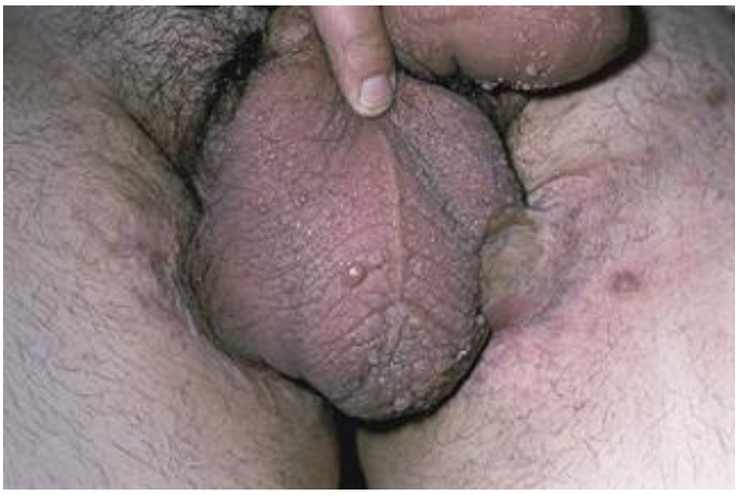
Color Figure 44.1. Pearly penile papules are dome-shaped on the coronal margin and sulcus. See also Figure 44.1, page 2012.



Color Figure 44.3. Violaceous and erythematous papules with variable scaling located on the scrotum. See also Figure 44.3, page 2012.

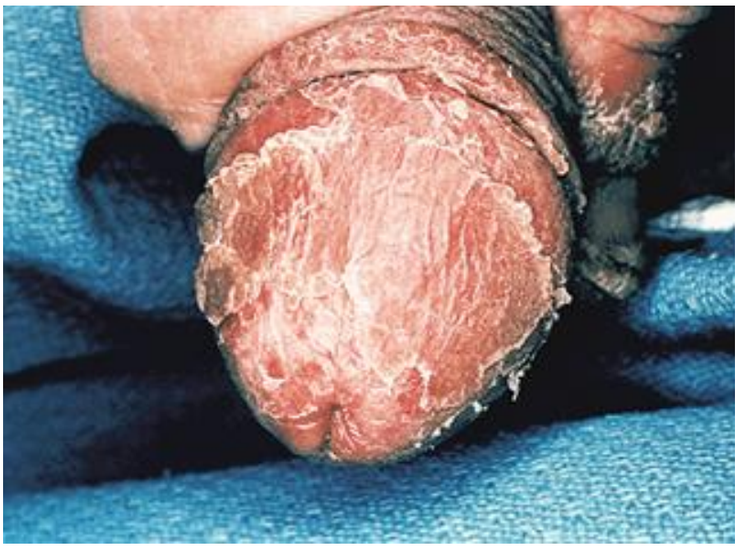


Color Figure 44.4. *Candida albicans* as a secondary infection on moist papules on the glans penis. See also Figure 44.4, page 2012.

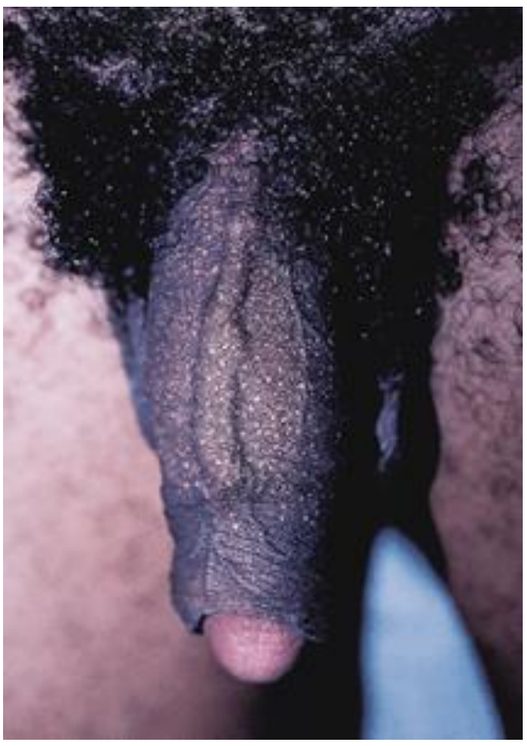


Color Figure 44.5. Lymphangioma resembling papules of Fox-Fordyce. Erythematous papules on the shaft and scrotum. See also Figure 44.5, page 2013.

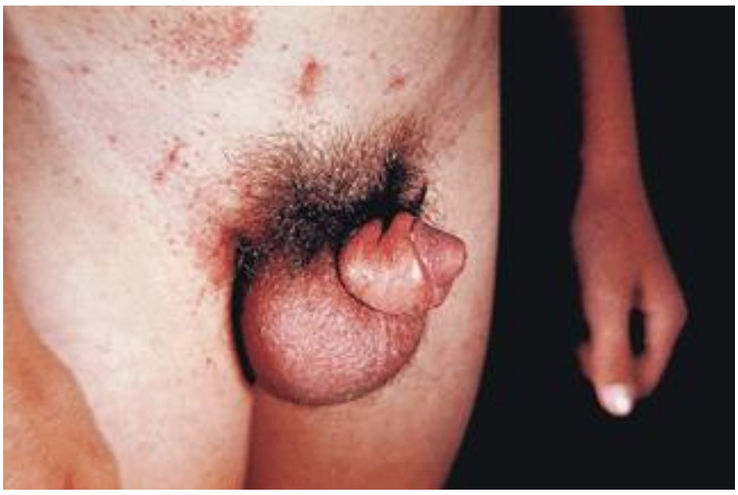
Color Figure 44.6. Progressive circumferential sclerosis at the meatus in lichen sclerosus et atrophicus (can lead to stenosis). See also Figure 44.6, page 2013.



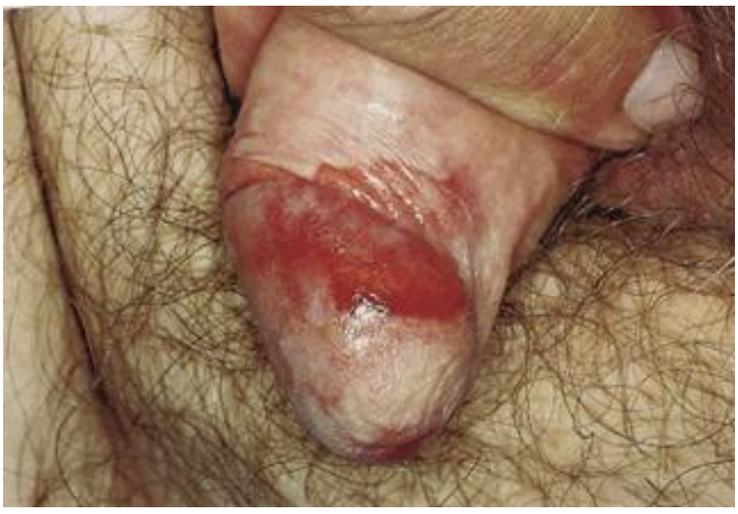
Color Figure 44.8. Typical erythematous psoriatic papules on the glans penis and sulcus. See also Figure 44.8, page 2014.



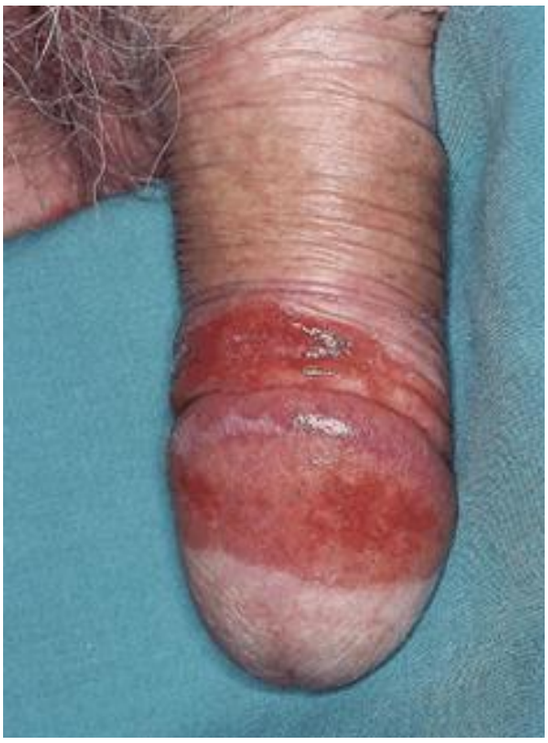
Color Figure 44.11. Numerous flat-topped papules typical of lichen nitidus on the glans penis. See also Figure 44.11, page 2015.



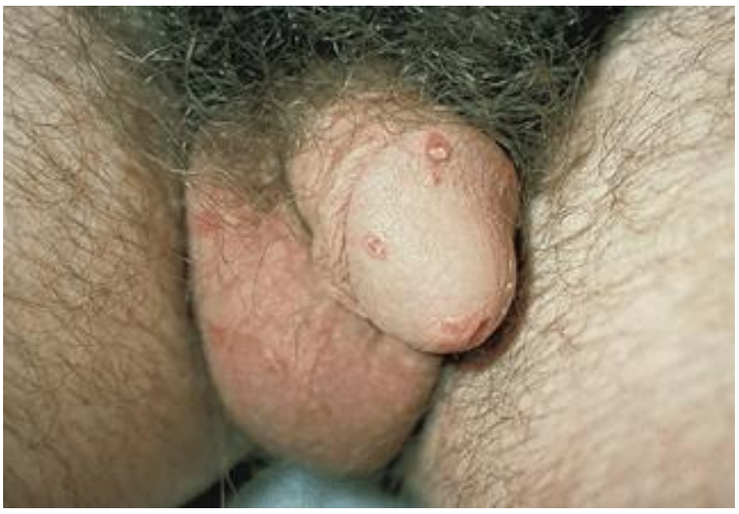
Color Figure 44.12. Contact dermatitis of the glans and shaft of the penis and the scrotum. See also Figure 44.12, page 2015.



Color Figure 44.16. A moist plaque found in nonspecific balanitis on the glans penis. See also Figure 44.16, page 2016.

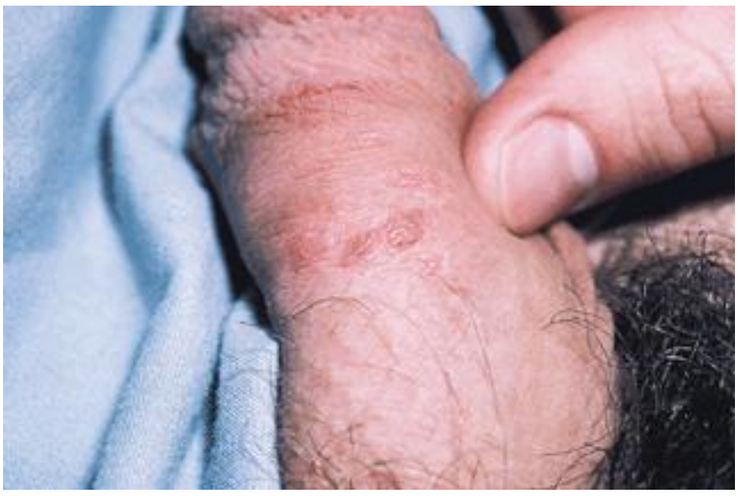


Color Figure 44.17. Zoon's balanitis occurs more typically on the glans and prepuce of the penis. See also Figure 44.17, page 2016.

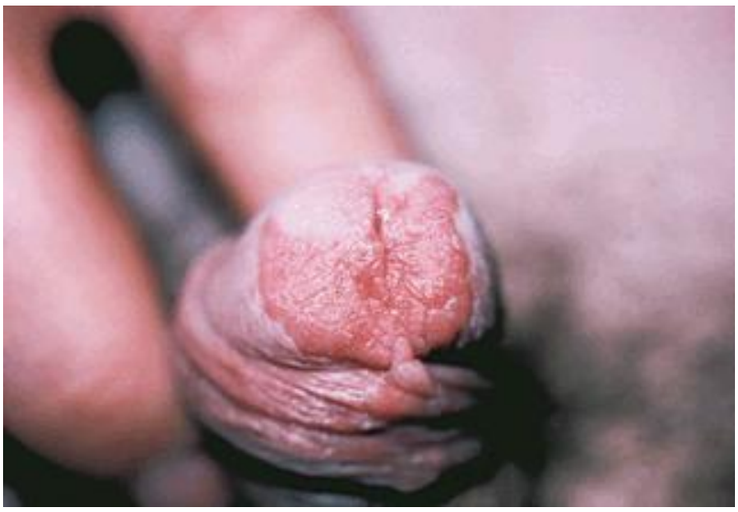


Color Figure 44.23. Scabies with papules on the glans and shaft of the penis. See also Figure 44.23, page 2019.

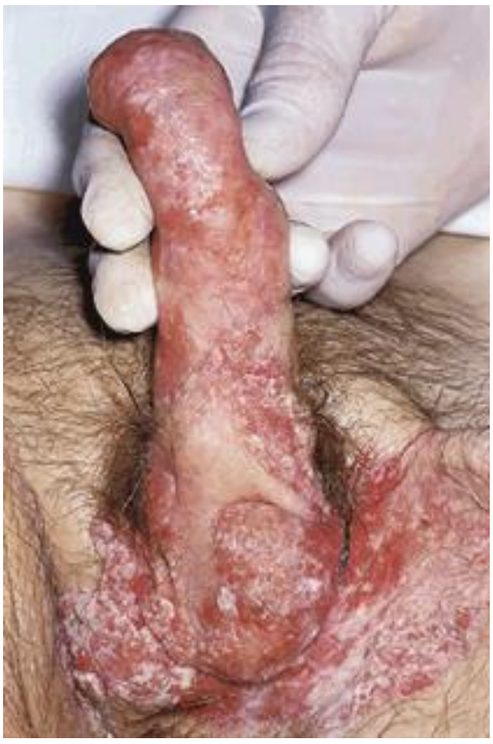
Color Figure 44.24. Condyloma acuminatum with hyperkeratotic papules on the glans penis and sulcus. See also Figure 44.24, page 2019.



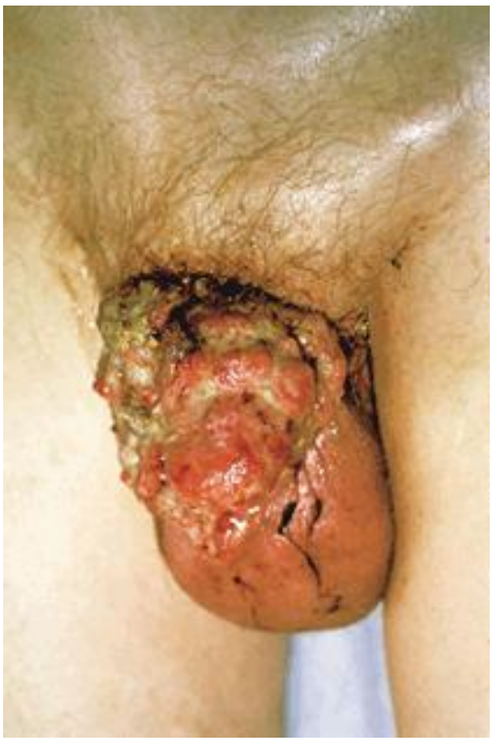
Color Figure 44.25. Papular Bowes's disease on the shaft of the penis. See also Figure 44.25, page 2020.



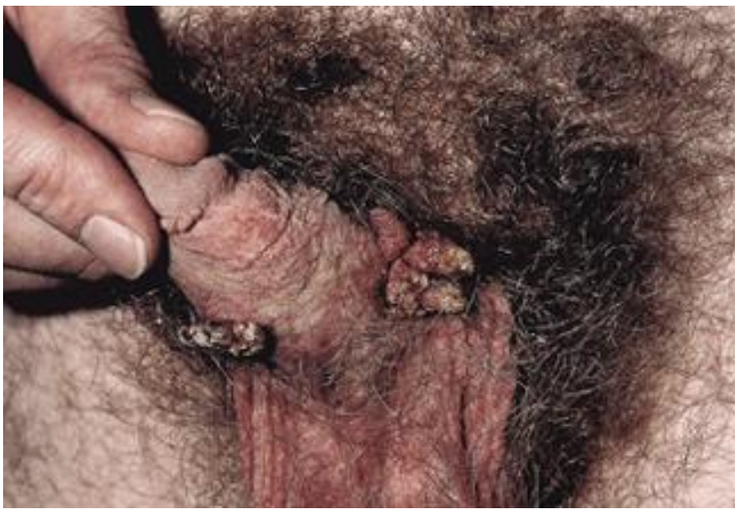
Color Figure 44.26. Bowen's disease with an erythematous localized patch on the shaft of the penis. See also Figure 44.26, page 2020.



Color Figure 44.27. Bowen's disease extends from the scrotum to the shaft of the penis. See also Figure 44.27, page 2021.



Color Figure 44.28. Papular Bowen's disease suggestive of condyloma is on the shaft near the sulcus. See also Figure 44.28, page 2021.



Color Figure 44.30. Early papules of condyloma acuminatum. See also Figure 44.30, page 2021.

Index

W

X

Y

Z